Antidepressant medications and other treatments of depressive disorders: a CINP Task Force report based on a review of evidence

Members of the Task Force:
Norman Sartorius¹ (Chairperson), Thomas C. Baghai², David S. Baldwin³, Barbara Barrett⁴, Ursula Brand⁵, Wolfgang Fleischhacker⁶, Guy Goodwin⁷, Heinz Grunze²,³, Martin Knapp⁸, Brian E. Leonard⁹, Jeffrey Lieberman¹⁰, Yoshibumi Nakane¹¹, Roger M. Pinder¹², Alan F. Schatzberg¹³, Jaromír Švestka¹⁴

This text was written by:
Thomas C. Baghai², David S. Baldwin³, Barbara Barrett⁴, Pierre Baumann¹⁵, Kareem Ghali¹⁶, Guy Goodwin⁷, Heinz Grunze²,³, Martin Knapp⁸, Brian E. Leonard⁹, John C. Markowitz¹⁷, Frank Padberg⁵, Roger Pinder¹² and Norman Sartorius¹.

Substantial contributions to some of the chapters were made by Ursula Brand⁵, Max Fink¹⁸, Toshiaki Furukawa¹⁹, Konstantinos N. Fountoulakis²⁰, Peter Jensen¹⁶, Shigenobu Kanba²¹, Anita Riecher-Rössler²².

The text was edited by:
Thomas C. Baghai², Heinz Grunze²,³ and Norman Sartorius¹.

The names of the persons who produced the first draft of the chapters are given in the table of contents.

Website: www.cinp-antidepressant-task-force.de

Address for correspondence: Thomas C. Baghai, M.D., Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Nussbaumstr. 7, D-80336 Munich, Germany.
Tel.: +49-89-5160-5711 Fax: +49-89-5160-5718
E-mail: Baghai@med.uni-muenchen.de

With copy to:
Norman Sartorius, M.D., Ph.D., Chairperson of CINP Task Force, 14 chemin Colladon, 1209 Geneva, Switzerland.
Tel.: +41-22-788 23 31 Fax: +41-22-788 23 34
E-mail: sartorius@normansartorius.com

Heinz Grunze, M.D., School of Neurology, Neurobiology and Psychiatry, Newcastle University, UK.
Tel.: +44-191-28-25765 Fax: +44-191-222-6162
E-mail: Heinz.Grunze@newcastle.ac.uk

Affiliations:
¹ 14 chemin Colladon, 1209 Geneva, Switzerland
² Dept. of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Nussbaumstr. 7, D-80336 Munich
³ School of Neurology, Neurobiology and Psychiatry, Newcastle University, Leazes Wing, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, United Kingdom
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1 Foreword

According to the World Health Organization, depression is one of the most debilitating disorders affecting humankind. The social and economic costs of chronic ill health resulting from untreated or inadequately treated depression are considerable and frequently underestimated.

The CINP established the Task Force on Antidepressant Medications in 2004 to examine all aspects of therapy with antidepressant drugs. This was considered necessary as, despite the availability of effective antidepressants for the past 50 years, a substantial minority of depressed patients either remains untreated or under treated. As the only international organization devoted to the promotion of research, education and the applications of neuropsychopharmacology to the clinic, the main task of the CINP is to extend the knowledge of the drugs that are available with the aim of improving the management of mental disorders. The purpose of this Task Force document was not to produce an academic monograph nor a set of guidelines, but to provide mental health and other professionals with comprehensive and objective information about the different aspects of the use of antidepressants important in clinical practice.

The Task Force consisted of 15 experts in psychiatry, psychopharmacology, public health, economics and family care. The majority of its members are senior members of the CINP. The Task Force was also advised to rely in the course of its work on advisors in different countries selected because of their outstanding expertise in the matters covered by the review. The report presented here was approved by the Executive Committee and the Council of the CINP at its meeting in Chicago in July 2006.

As a service to those engaged in mental health care and to ensure maximum impact, the Task Force review is being published as a supplement to the CINP’s journal, the International Journal of Neuropsychopharmacology. In addition, the information will later be made available on the CINP website. To facilitate access to the review for non-English-speakers, we also intend for it to be published in Chinese, French, Russian and Spanish.

It is the intention of the CINP to provide, in the future, other task force publications dealing with other major groups of medications used for the treatment of mental disorders. We hope in this way to enhance the effectiveness of the CINP as a major international organization committed to improving knowledge worldwide of the appropriate use of psychotropic drugs for the optimal treatment of psychiatric disorders.

BRIAN E. LEONARD
President, CINP
January 2007

2 Note from the Editors

This review is the result of the work of many. The names of those who contributed the first drafts of the text are given in the table of contents: in their present form, however, the chapters often differ significantly from their original version. This is because they have been revised – often more than once – to do justice to the numerous comments and suggestions concerning additional evidence received from the Advisory Group and the members of the CINP Task Force. In selecting the members of the Advisory Group the Task Force made every effort to include experts from different countries and with outstanding expertise in a manner that was to make it possible to obtain advice and guidance in the relevant areas of knowledge and disciplines. Their contribution is acknowledged in the acknowledgements chapter 16. In addition, we would like to express our thanks for the particularly useful comments and suggestions, as well as additional materials, contributed by Profs. Baumann, Blier, Burrows, Dunn, Furukawa, Halaris, Kutcher, Remschmidt and Möller.
The method used to produce the first draft of the chapters of this review and the sources of data used are described in chapter 4.1. What makes this effort different from similar documents are the steps that were taken after the review of the literature was completed. First, as soon as the Task Force approved the text, the review was submitted for comments and review to an advisory group composed of experts from the countries the world over. At the same time the review was translated into Chinese, French, Russian and Spanish, and these versions of the text were then presented to experts in regional meetings held in Caracas, Munich, Paris, Shanghai and St. Petersburg. Present at each of these meetings were experts from the host country and from other countries that use the same language or share scientific traditions. The participants in these meetings undertook to organize national meetings in their countries to review the materials presented and to examine the facts in the light of the experience, special circumstances and evidence that may not have been available in international databases. The national meetings have been taking place during the year 2007 and will continue in 2008. The results of these meetings will be examined by the CINP and may be published, possibly together with results of new studies that become available or of studies that have been missed by those who drafted the chapters, by the members of the Advisory Group and the CINP Task Force. It would have been desirable to make the regional meetings coincide with CINP regional meetings: this however was not possible because of the need to complete the production of the review within a year which imposed serious time constraints on the work plan. However, the regional and national meetings included a number of members of the CINP.

After lengthy discussions and some hesitation the Task Force decided to supplement the description of antidepressant medications with chapters that provide information about the diagnosis of depression (chapter 5.1) and its epidemiology (chapter 5.3), as well as about principles of caring for people with depression (chapter 6) and treatment that can be used in combination with antidepressants or alone (chapters 9.1 and 12). In view of the many discussions and differences of opinion over whether to include description of other treatment methods, the Task Force finally decided to provide a brief description of these methods in the text of the review and to place more detailed information in the annexes (19.3–19.8). An important argument in this respect was that the main task of the Task Force was to produce a review of evidence (and experience) and not guidelines for treatment that should be produced at the national or even subnational level, taking evidence as well as local circumstances into account.

In reviewing the evidence, we paid particular attention to results obtained in randomized control trials of antidepressant medications. The results of these trials are important, and their statistical significance is often put forward as being sufficient for recommendations about clinical practice. A statistically significant difference, however, is not always equal to a clinically meaningful difference; nor is the evidence obtained in research the only evidence to consider in making treatment decisions. For that reason, this review was developed in consultation with leading mental health experts, representatives of family organizations and specialists in medical disciplines other than psychiatry. These consultants generously provided advice, spoke from experience and contributed information published in non-English languages. We hope that this intensive process of consultation has helped the review to reflect evidence from research as well as from experience and clinical wisdom.

3 Introduction

The criteria used to assess whether a problem is of public health importance (and therefore should be a priority for health services) include the prevalence of the problem, the severity of its consequences, the likelihood that it will remain stable or grow if unattended and the availability of effective means of intervention to resolve or significantly reduce the problem.

Depressive disorders satisfied the first three criteria long ago. These disorders are among the most frequent mental illnesses, and their prevalence matches that of many serious physical illnesses given priority in public health action. The consequences of depression, if left untreated, are grave and include increased morbidity and mortality from various physical illnesses as well as significant impairment that produces more disability than many common chronic disorders such as diabetes and chronic collagenoses. Reports of the World Health Organization (WHO) show that depressive disorders rank very high in number of life years lost due to illness, premature death and disability. Depressive disorders also significantly increase the risk of suicide and of suicidal attempts.
Depressive illness is likely to become even more prevalent in the decades to come for a variety of reasons. These include increased life expectancy both among the general population in many countries (with a concomitant increase in groups that are at particularly high risk for depressive disorders) and among people with chronic physical illness often accompanied by depressive disorders (e.g., chronic gastrointestinal disorders, cardiovascular disorders and stroke); greater numbers of iatrogenic mental disorders, including depression; and, in both developed and developing countries, continuously increasing levels of stress that parallel the weakening of social support. WHO has predicted that unipolar depression alone will be the second most important contributor to disability by the year 2020, not only in Europe and northern America, but worldwide (World Health Organization, 2001).

The fourth criterion for public health importance, and for consequent action, is the availability of an effective intervention that can reduce or eliminate the problem and is suitable for widespread application. Until recently that criterion had not been satisfied for the majority of mental disorders. Although public health authorities succeeded in preventing some mental disorders (e.g., cretinism in areas where iodine deficiency was eliminated, and of progressive paralysis in areas where infection with syphilis was brought under control), treatment of mental disorders was, by and large, not very effective. Electroconvulsive therapy (ECT) helped in treating people with certain forms of depressive disorders and schizophrenia, but the number of those who could not benefit from ECT vastly surpassed the numbers of those who could. Thus this intervention did not fit the criterion of wide applicability. Psychotherapy helped many, but the number of experts qualified to apply it were – and still are – small in most parts of the world. Psychotherapeutic strategies and techniques have become sufficiently well defined to be candidates for study in undergraduate medical education and in-service training of non-psychiatrists. Moreover, psychotherapies may have widespread utility, even in countries in which the purchase and regular distribution of medications are different (Bolton et al., 2003).

The introduction of antidepressant medications changed the public health importance of depressive disorders and their priority in health care services. In addition, recognizing that depressive disorders are frequent and severe, that they are likely to multiply in the years to come and that they complicate treatment of many physical disorders, it gradually became evident that antidepressant medications could help a significant proportion of people with depressive disorders even when applied by general medical staff in primary care and non-psychiatric health services. It also became possible to speak publicly about depression because society accepted that depression was a disease that could be effectively treated by medical means – medicinal drugs – like many other diseases.

Since the introduction of imipramine we know that antidepressant medications are not a miracle cure. They do help approximately two thirds of the people with depression if appropriately used (Klerman and Cole, 1965): although this is considerably better than the response to placebo, which helped approximately one third of the people to whom it had been given in clinical trials, it still leaves one third of the patients with depression in whom the prescription of an antidepressant medication will not improve the condition. The addition of psychotherapy, better social support and the use of other, additional medications will help some of those who did not respond to the treatment with the first prescribed antidepressant, but some others will still remain unwell. There is thus considerable room for further improvement of the effectiveness and safety of antidepressants and it is to be hoped that future research will result in still better medications and other methods of treatment of depressive disorders. Meanwhile, imperfect as they may be, the currently available antidepressant medications are a powerful tool that can be used in general and specialized mental health services.

The lessened stigma of depression and the growing conviction that antidepressant medications are effective emboldened patients to seek help from health workers and motivated non-psychiatrists to deal with depression, to prescribe antidepressants and in general to see patients with depression as having a manageable health problem. The number of patients and doctors with this mindset grew over time, supported by an increase in the array of available medications, and the encouraging results of studies showing their usefulness and ever milder side effects. The general public and the media supported this notion as well. In several countries, direct advertisements to consumers

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1 Despite a greater number of depressive symptoms requiring treatment in old age, the prevalence of major depressive disorder has not been reported to correlate with age (Patten et al., 2001; Steffens et al., 2000). One explanation may be the inappropriateness of the diagnostic criteria for depression which are valid for depressive disorders in adults but not for those in the elderly.
may have played a role (Berndt, 2005). The Prime Minister of Norway took a few weeks off to treat his depression and came back in good health. Famous artists and other stars described their depression and how they got better. Although this change of public opinion – from seeing depressive disorders as an intractable form of madness to being a physical illness that could be treated by pills prescribed by the general practitioner – was positive because it changed the way patients and medical staff thought about depression, it was also a step towards a different interpretation of depression. Increasingly, reports appeared claiming that depressive disorders are no more than variations of mood that do not warrant medical attention. Psychiatric epidemiologists published studies showing that the lifetime prevalence of depressive disorders was nearly 80%, a figure that can easily be interpreted by the lay public as evidence that depressive disorders are part of normal life. This banalization of depressive disorders came about partly spontaneously and partly owing to promotion by various sects and anti-psychiatry movements. Depressive disorders, it was proclaimed, were most often not really diseases: rather, they were conditions that everyone had. Medications that had previously been hailed as miraculous cures were declared by some as an expensive and unnecessary form of placebo. Worse, they were reported as dangerous because they affected people’s personality and made them dependent on drugs. According to these arguments, it was only the coalition between doctors and drug manufacturers that kept alive the myth of depressive illness and its medical solution.

Studies showing that successful treatment of depressive disorders not only helps people who suffer from them but also benefits society and patients’ families were neither widely known nor sufficiently publicized. What received much greater airing and prominence was the high cost of many medications and the large amounts of money made by producers and distributors of medications. To some extent, the idea that drugs used to treat mental disorders are expensive stems from the stigma that accompanies mental illness and the disregard for people who have these disorders. Even when psychiatric medications are inexpensive – a month’s supply of a drug such as chlorpromazine costs no more than US$1 – governments do not buy them, and the general public accepts that even a dollar a month is too much to spend for a person whom most of the population considers not worth it.

Developments in research and technology have increased the number of active substances that could be used to treat depression, and the knowledge about their mechanisms of action continued to advance, which has enhanced possibilities of adjusting the treatment with psychopharmacological medications to the clinical needs of individual patients (see Table 1).

The results of studies carried out to assess the effectiveness of the new substances showed that newly discovered medications are at least as good as their predecessors and that they have some advantages over other drugs.

Studies comparing medications have increased, but they are frequently sponsored by drug companies, and their results are not always in harmony. Government-sponsored studies, which might help to resolve some of the contradictory results, are still far too few in numbers. There are also still far too few investigations of the effects of new drugs for patients in populations outside the major industrialized countries.

Some studies did show differences in dosage and effects of medications given to patients living in countries with varying climate, nutrition and general morbidity patterns, but definitive studies of the effect of drugs on patients from different populations are still lacking. The scarcity of studies on psychotropic drugs in the third world is part of the larger problem of the predominance of research in a few highly developed countries. One recent study showed that only 6% of the articles on mental health in the scientific literature come from other than high-income countries. The US and UK alone contribute 50% of the accessible scientific literature on mental health matters (Saxena et al., 2006).

In the light of these considerations, it is not surprising that the CINP, aware of its obligation to facilitate clinical interpretation of neuropsychopharmacological findings (Ban, 2006a), felt that it would be useful to carry out a detailed technical review of antidepressant medications.

Antidepressants are now used to treat many conditions, even if the justification for their use reflects more of clinical experience and consensus instead of evidence (see Table 3) – but it was decided that this review would concentrate on the use of antidepressants for the treatment of depression as defined in ICD-10 (World Health Organization, 1992)

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2 More recently, studies sponsored by international pharmaceutical companies have included patients from India and other countries in the third world; the results of these investigations usually do not report results obtained in such countries separately and mix the data from those countries with data obtained in other countries.
Table 1. Commonly used antidepressants\(^3\), including their primary mode of action and influence on other receptor systems

<table>
<thead>
<tr>
<th>Pharmacological group</th>
<th>Generic name</th>
<th>Primary pharmacodynamic mode of action</th>
<th>Secondary pharmacodynamic actions</th>
<th>Additional effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>Citalopram</td>
<td>SRI (++)</td>
<td>5-HT(_{2c})</td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>Escitalopram(^4)</td>
<td>SRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>Fluoxetine</td>
<td>SRI (++)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>Fluvoxamine</td>
<td>SRI (+++)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>Paroxetine</td>
<td>SRI (+++)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>Sertraline</td>
<td>SRI (+++)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRI</td>
<td>Venlafaxine</td>
<td>SRI/NRI (+/+)</td>
<td>DRI</td>
<td></td>
</tr>
<tr>
<td>SNRI</td>
<td>Duloxetine</td>
<td>SRI/NRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRI</td>
<td>Milnacipran</td>
<td>SRI/NRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NARI</td>
<td>Reboxetine</td>
<td>NRI</td>
<td></td>
<td>(M(_1))</td>
</tr>
<tr>
<td>(NARI)</td>
<td>Viloxazine</td>
<td>(NRI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaSSA</td>
<td>Mirtazapine</td>
<td>(\alpha_2)</td>
<td>5-HT(_{2c}); + 5-HT(_1)</td>
<td>H(_1), (\alpha_v), (\alpha_2)</td>
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<tr>
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<td>Agomelatine(^5)</td>
<td>MT1/MT2</td>
<td>5-HT(_{2c})</td>
<td></td>
</tr>
<tr>
<td>RIMA</td>
<td>Moclobemide</td>
<td>MAI</td>
<td></td>
<td>(M(_3))</td>
</tr>
<tr>
<td>MAOI</td>
<td>Selegiline(^6)</td>
<td>MBI</td>
<td>MAI, APD</td>
<td></td>
</tr>
<tr>
<td>MAOI</td>
<td>Phenelzine</td>
<td>MAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAOI</td>
<td>Isocarboxacid</td>
<td>MAI/MBI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAOI</td>
<td>Tranylcypromine(^7)</td>
<td>MAI/MAI</td>
<td>APD</td>
<td></td>
</tr>
<tr>
<td>MAOI</td>
<td>Pirasidol(^8)</td>
<td>MAI/MAI</td>
<td></td>
<td></td>
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<tr>
<td>SMA</td>
<td>Nefazodone(^9)</td>
<td>SMA (+)</td>
<td>5-HT(_{2\alpha}); SRI</td>
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</tr>
<tr>
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<td>Trazodone</td>
<td>SMA</td>
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</tr>
<tr>
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<td>Buproprion</td>
<td>DNRI (+)</td>
<td>NRI</td>
<td></td>
</tr>
<tr>
<td>DA</td>
<td>Trimipramine</td>
<td>DA</td>
<td>5-HT(_2)</td>
<td>H(_1), (\alpha_m), (\alpha_v), (\alpha_2)</td>
</tr>
<tr>
<td>GM</td>
<td>Tianeptine</td>
<td>GM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-TCA</td>
<td>Clomipramine</td>
<td>SRI</td>
<td>NRI, D(_3)</td>
<td>M(_1), (\alpha_1)</td>
</tr>
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<td>S/N-TCA</td>
<td>Amitriptyline</td>
<td>SRI/NRI (+/++)</td>
<td>5-HT(_2)</td>
<td>H(_1), (\alpha_m), (\alpha_v), (\alpha_2)</td>
</tr>
<tr>
<td>S/N-TCA</td>
<td>Amitriptyline oxide</td>
<td>SRI/NRI</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Dibenzepine</td>
<td>SRI/NRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/N-TCA</td>
<td>Dosulepine/Dothiepin</td>
<td>SRI/NRI (+/+)</td>
<td>5-HT(_2)</td>
<td></td>
</tr>
<tr>
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<td>Doxepin</td>
<td>SRI/NRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/N-TCA</td>
<td>Imipramine</td>
<td>SRI/NRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S/N-TCA</td>
<td>Melitracen(^{10})</td>
<td>SRI/NRI</td>
<td>(\alpha_1)</td>
<td>(\alpha_1)</td>
</tr>
<tr>
<td>S/N-TCA</td>
<td>Protriptyline</td>
<td>SRI/NRI</td>
<td></td>
<td>(\alpha_1)</td>
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<tr>
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<td>Desipramine</td>
<td>NRI (+++)</td>
<td></td>
<td>(M(_1))</td>
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<tr>
<td>N-TCA</td>
<td>Lofepramine</td>
<td>NRI (++)</td>
<td></td>
<td></td>
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<td>Nor-tripryline</td>
<td>NRI</td>
<td></td>
<td></td>
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<tr>
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<td>Mianserin</td>
<td>(\alpha_2)</td>
<td>NAR</td>
<td>H(_1), (\alpha_1)</td>
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<tr>
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<td>Amoxapine</td>
<td>NRI</td>
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<td></td>
</tr>
<tr>
<td>N-TetraCA</td>
<td>Maprotiline</td>
<td>NRI</td>
<td></td>
<td>H(_1), (\alpha_1), (\alpha_2)</td>
</tr>
</tbody>
</table>

For abbreviations see p. 9.

\(^3\) St. John’s wort is not included in the list of antidepressants because of it has no proven efficacy in severe depression.

\(^4\) In addition to its serotonin reuptake-inhibiting properties, escitalopram also binds to the allosteric site on the serotonin transporter. A new class of SSRIs has been proposed (allosteric serotonin reuptake inhibitors, ASRIs).

\(^5\) Not yet available; currently under review by European authorities (EMEA).

\(^6\) In some countries selegiline has only been approved as a drug against Parkinson’s disease, not as an antidepressant.

\(^7\) In some countries irreversible MAOIs are not longer available (e.g. Czech republic, Spain and others).

\(^8\) The use of pirasidol is limited to Russia and other eastern countries of the same geographical region. In the Russian literature it can also be found also under other names, such as pirlindol, pyrazidol, pirazidol and pirazidolum (for review see Mosolov, 1998).

\(^9\) Nefazodone has been withdrawn from the market in some countries.

\(^10\) Melitracen has activating properties in low dosages and is predominantly used in Asian countries in a combined formulation (Deanxit) with the antipsychotic drug flupentixol.
and DSM-IV (American Psychiatric Association, 1994).

Later, it became obvious that it would be necessary to add chapters on the use of antidepressants for anxiety and chronic pain because these conditions are frequently associated with depression and possibly rely on the same pathophysiological mechanisms and pathways.

The review is based on published evidence; however, it also incorporates advice and comments of leading experts in the fields of psychiatry, pharmacology and public health. Additional sources of expertise consulted include regulatory agencies, patient and family organizations, representatives of the pharmaceutical industry and public health authorities. Our hope was that combining a review of the literature with the outcome of a wide-ranging discussion involving people whose experience usually is not published (or is published in places that are difficult to access) might produce a solid body of facts on which the CINP could reach consensus and make its opinion widely known. The particular aim of the consensus was to provide evidence and other information that would help to answer to at least the following questions:

- Are antidepressant medications effective in alleviating symptoms of depression and in preventing relapses of depressive illness? (predominantly chapters 9 and 7)
- Are the side effects of antidepressant drugs currently in use so severe that they outweigh the benefits of these drugs? (chapters 7.3 and 9.1.1.3)
- Is the treatment of depressive disorders with antidepressant drugs cost-effective for individuals and societies? (chapter 14)

- What areas of scientific investigation related to antidepressant medications and their use deserve priority? (chapter 8)
- Are there depressive disorders that do not require treatment with antidepressant drugs? (chapter 12)

This review presents evidence and experience that should help to answer these questions and facilitate the process of reaching a consensus that will guide public health action and the education of health workers, of the general public and of those who suffer from depressive illnesses.

4. Method used to produce the review

4.1 Consensus process

The challenge for the CINP Task Force created in May 2005 was to review the evidence on the use, effectiveness and safety of antidepressant medications and to assemble experience that clinicians using them and carers (e.g. family members) have accumulated. This challenge was to be met by preparing a review of published evidence and exposing it to a process of consultation with experts in different parts of the world.

Thus, after an initial meeting with some members of the Task Force, Dr T. C. Baghai and Dr H. Grunze, with the assistance of Dr F. Padberg, prepared a review of pharmacological and therapeutic evidence on

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**Table 1 abbreviations:** (primary modes of action are explained in the text): (+) = modest receptor binding affinity; (+++) = appreciable receptor binding affinity; (++++) = strong receptor binding affinity; + 5-HT_1_ = serotonin 1 receptor stimulation; 5-HT_2_ = serotonin 2 receptor antagonism; 5-HT_3_ = 5-HT_3_ receptor antagonist; 5-HT_4_ = serotonin 3 receptor antagonist; α_1_ = α_1_-receptor antagonism; α_2_ = α_2_-receptor antagonism; all. 5-HTT = binding to the allosteric site of the serotonin transporter; APD = amphetamine prodrug; DA = dopamine (D_2_) receptor antagonist; DNRI = dopamine and noradrenaline reuptake inhibitor; DRI = dopamine reuptake inhibition; GM = glutamatergic modulator; H_1_ = blockade of histamine 1 receptors; M_1_ = blockade of cholinergic muscarinic receptors; MAI = monoamine oxidase A inhibition; MBI = monoamine oxidase B inhibition; MAOI = irreversible inhibitor of monoamine oxidase A and B; MAOBI = irreversible inhibitor of monoamine oxidase B; MT = melatonergic antidepressant; MT_1_/MT_2_ = melatonin 1 and melatonin 2 receptor agonist; NARI = noradrenaline-releasing properties; NAR = noradrenaline-sparing properties; NARI = selective noradrenaline (norepinephrine) reuptake inhibitor; NaSSA = noradrenergic and selective serotonergic antidepressant; NRI = noradrenaline (norepinephrine) reuptake inhibition; N-TCA = tricyclic antidepressant with primary noradrenergic effects; N-TetraCA = tetracyclic antidepressant with primary noradrenergic effects; RIMA = reversible inhibitor of monoamine oxidase A ; SMA = serotonin-modulating antidepressant; SNRI = selective serotonin and noradrenaline reuptake inhibitor; S/N-TCA = tricyclic antidepressant with similar serotonergic and noradrenergic effects; SRI = serotonin reuptake inhibition; SRS = serotonin reuptake stimulation; SSRI = selective serotonin reuptake inhibitor; S-TCA = tricyclic antidepressant with primary serotonergic effects; S-TetraCA = tetracyclic antidepressant with primary serotonergic effects.

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11 For example, the NICE (National Institute for Clinical Excellence, UK) recommendations acknowledge a role for antidepressants in primary care in moderate and severe, but not mild depression. For these patients, NICE recommends observation or psychological intervention as first-line treatment, and antidepressants only in the case of refractoriness (National Institute for Health and Clinical Excellence, 2004).
antidepressants. This initial review was supplemented with a review of evidence on the economic aspects of the treatment of depression prepared by Prof. Dr M. Knapp and Dr B. Barrett. That version of the review was presented to the CINP Task Force in January 2006 and revised in the light of comments received during the meeting. Several chapters were added with the involvement of experts in the relevant fields, such as the chapter on psychopharmacotherapy of children (first draft contributed by Dr K. D. Ghalib) and the chapter on psychotherapy (drafted by Dr J. C. Markowitz).

The main purpose of the technical review is to reflect the actual scientific evidence on the use and usefulness of antidepressants in the treatment of depression. But it also deals with other major indications for antidepressant medications (Table 3).

Severity: 12

Severity of disease according ICD-10 does not necessarily include ratings of disability and impairment.

Table 2. Classification and criteria of major depressive disorder (DSM-IV; American Psychiatric Association, 1994) and depressive episode (ICD-10; World Health Organization, 1992) (adapted from Bauer et al., 2002c)

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive disorder</td>
<td>A. Depressive episode (F32)</td>
</tr>
<tr>
<td>A. Single episode (296.2x)</td>
<td>B. Recurrent depressive disorder (F33)</td>
</tr>
<tr>
<td>B. Recurrent (296.3x)</td>
<td>Severity: 12</td>
</tr>
<tr>
<td></td>
<td>• Mild (F−0): at least 2 main symptoms, plus at least 2 accessory symptoms; none of the symptoms intense</td>
</tr>
<tr>
<td></td>
<td>• Moderate (F−1): at least 2 main symptoms, plus at least 3 accessory symptoms; some symptoms marked</td>
</tr>
<tr>
<td></td>
<td>• Severe (F−2): all 3 main symptoms, plus at least 4 accessory symptoms; some symptoms severe with intensity</td>
</tr>
<tr>
<td>Criteria major depressive episode (abridged):</td>
<td>Criteria of depressive episode (abridged):</td>
</tr>
<tr>
<td>A. Over the last 2 weeks, 5 of the following features should be present most of the day, or nearly every day (must include 1 or 2):</td>
<td>Minimum duration of episode: about 2 weeks</td>
</tr>
<tr>
<td>1. Depressed mood</td>
<td>Main symptoms:</td>
</tr>
<tr>
<td>2. Loss of interest or pleasure in almost all activities</td>
<td>1. Depressed mood</td>
</tr>
<tr>
<td>3. Significant weight loss or gain (more than 5% change in 1 month) or an increase or decrease in appetite nearly every day</td>
<td>2. Loss of interest and enjoyment</td>
</tr>
<tr>
<td>4. Insomnia or hypersomnia</td>
<td>3. Reduced energy, increased fatigability</td>
</tr>
<tr>
<td>5. Psychomotor agitation or retardation (observable by others)</td>
<td>Accessory symptoms:</td>
</tr>
<tr>
<td>6. Fatigue or loss of energy</td>
<td>1. Reduced concentration and attention</td>
</tr>
<tr>
<td>7. Feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach about being sick)</td>
<td>2. Reduced self-esteem and self-confidence</td>
</tr>
<tr>
<td>8. Diminished ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others)</td>
<td>3. Ideas of guilt and unworthiness</td>
</tr>
<tr>
<td>9. Recurrent thoughts of death (not just fear of dying), or recurrent suicidal ideation, or a suicide attempt or a specific plan for committing suicide</td>
<td>4. Agitation or retardation</td>
</tr>
<tr>
<td>B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.</td>
<td>5. Ideas or acts of self-harm or suicide</td>
</tr>
<tr>
<td>C. The symptoms are not due to a physical/organic factor or illness</td>
<td>6. Sleep disturbances</td>
</tr>
<tr>
<td>D. The symptoms are not better explained by bereavement (although this can be complicated by major depression)</td>
<td>7. Loss of appetite</td>
</tr>
</tbody>
</table>
Table 3. Indications other than depressive disorders for antidepressant medication (based on clinical experience, consensus and evidence)

<table>
<thead>
<tr>
<th>Main categories of diseases</th>
<th>Specific condition</th>
</tr>
</thead>
</table>
| Anxiety disorders (see chapter 19.9) | • Generalized anxiety disorder  
• Panic disorder  
• Social phobia  
• Post-traumatic stress disorder  
• Obsessive-compulsive disorder |
| Pain conditions (see chapter 5.2.1.3.5) | • Chronic pain  
• Somatoform disorders  
• Schizophrenia  
• Schizoaffective disorders  
• Postschizophrenic depression |
| Schizophrenic spectrum disorders | • Adjustment disorders  
• Personality disorders  
• Akathisia  
• Eating disorders  
• Impulse control disturbances  
• Insomnia |

The revised draft was sent to the group of advisors listed on p. 199 (Annex 13: List of Advisors) and further revised based on comments received. In April 2006, translation of the text into Chinese, French, Russian and Spanish began so translations would be ready for the next phase of the project.

That phase commenced with a series of regional meetings that brought together 8–12 experts from the country in which the meeting was held and 8–10 representatives of other countries of the region who agreed to critically review the document and to organize a national meeting similar to the one they attended. By the time that this review went to press national meetings similar to the one they attended were held in the following countries: Argentina, Australia, Austria, Brazil, Chile, China, Croatia, Czech Republic, Denmark, Dominican Republic, Ecuador, France, Hong Kong, Japan, Kazakhstan, Korea, Philippines, Serbia, Singapore, Slovakia, Taiwan, Ukraine.

A list of countries represented at the regional meetings held in St. Petersburg, Munich, Shanghai, Caracas and Paris is given in Annex 10. Comments and suggestions as well as references to local studies published in English and other languages received from the participants at these meetings served to re-draft the review. The results of the examination of the review at national level will be published locally and may subsequently be brought together in a summary paper. In July 2006 the review was examined by the Executive Committee and Council of the CINP, which recommended its publication and adopted the Consensus Statement presented in chapter 15.

4.2 Data sources

The data considered in the development of this technical review have been extracted from different sources: the Medline database (up to October 2007), the Cochrane Library, review articles from Medline-indexed journals, meta-analyses (see Box 1), textbook chapters known to the authors of the draft or brought to their attention by members of the Task Force or the Advisory group and material supplied by pharmaceutical companies. Several national and international treatment guidelines were also examined, including the American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Major Depressive Disorder (American Psychiatric Association, 2000), the Canadian Psychiatric Association and Canadian Network for Mood and Anxiety Treatments (CANMAT), Clinical guidelines for the treatment of depressive disorders (Canadian Psychiatric Association and Canadian Network for Mood and Anxiety Treatments (CANMAT), 2001), the guidelines by the German Psychiatric Society (Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde, DGPPN), Praxisleitlinien in Psychiatrie und Psychotherapie, Behandlungsleitlinie affektive Erkrankung edited by van Calker and Berger (2000), and the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, parts 1 and 2 (Bauer et al., 2002c; Bauer et al., 2002b) as well as the Textbook of Mood Disorders (Stein et al., 2006).

The review is mostly, but not exclusively, based on papers published between 1990 and 2007 – not least also because of time constraints – because over the past two decades the methodology of studies became more uniform and comparable, and consistent and full information became easier to retrieve since papers from this period are usually available electronically.

14 When using meta-analyses as the primary source of evidence, the authors were aware of the methodological limitations of the approach (Anderson, 2000b). Only when properly conducted can meta-analyses bring out possible subgroup differences (heterogeneity) and publication biases (funnel plot analysis and others) (Sterne et al., 2000; Thompson, 1994). Meta-analyses performed according to the Cochrane method usually have the largest acceptance and best scientific ranking (see Box 1).
4.3 Additional sources of information

In addition to scientific experts, families and carers are represented on the Task Force group by EUFAMI – the European Federation of Association of Families of People with Mental Illness

15 EUFAMI is a not-for-profit organization registered in Belgium that currently represents 48 member associations from 1 non-European and 26 European countries. It was founded in 1992 by members of a several family and carer organizations. Family organization activities include advocating for better services, equal and housing rights, raising awareness at the national and local level, and countering stigma.

4.4 Limitations

As the previous section makes clear, this technical review is based on publicly available materials obtained via a Medline database search and other evidence that was brought to the attention of the authors. For that reason, the review may be subject to several biases.

For example, modern medicine requires decision making on the basis of hard data, i.e. data that come mainly from randomized controlled trials (RCTs). But even these data are not flawless, and translating RCT results to everyday clinical practice is sometimes problematic. One major cause may be that the population of patients included in RCTs differs significantly from the ‘natural’ population of the ‘real world’. To avoid this bias, in recent years the US National Institute of Mental Health (NIMH) designed and independently sponsored a clinical trial known as Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (Menza, 2006). Results from the initial phase of this trial are touched on in this review.

Owing to the current technical and legislative climate16, patients who are included in randomized trials (RCT), tend to be chronic, refractory and closely affiliated with doctors or with institutions and associations. This situation has a number of consequences, including lower response to active drugs and higher response to placebo. Moreover, a continuous increase in placebo response and simultaneous drop in the active compound response rate has been observed in RCTs over the past few decades. For this reason, it is now essentially impossible to interpret results of studies that do not include a placebo group.

15 EUFAMI is a not-for-profit organization registered in Belgium that currently represents 48 member associations from 1 non-European and 26 European countries. It was founded in 1992 by members of a several family and carer organizations. Family organization activities include advocating for better services, equal and housing rights, raising awareness at the national and local level, and countering stigma.

16 A variety of attributes of clinically routine patients, such as psychiatric comorbidity, concomitant somatic disease, concomitant use of most psychopharmacologic and other medications, suicidality, pregnancy and others represent exclusion criteria in RCTs and induce the selection of a subgroup of patients. Also, in some countries the fact that treatment in RCTs is sponsored causes the predominant inclusion of specific social subgroups of patients without health insurance.
Statistical significance and clinical effectiveness are not synonymous (for a definition, see Box 6) and not always closely correlated. The so-called efficacy gap between outcomes in clinical trials and in primary care may be influenced by patient compliance, family and social supports, and negative media reporting on antidepressants (Wade, 2006). Another source of confusion is the use of refined statistical methods to demonstrate the therapeutic efficacy and effectiveness of antidepressants without a re-evaluation of the psychiatric nosology employed and without additional research in psychopathology. In addition it may be relevant to the interpretation of study results that by the 1990s single-center clinical investigations were replaced by multi-center centrally coordinated clinical investigations in which individual contributions are restricted to a small proportion of the total sample. Moreover, education and research in pharmacotherapy are controlled predominantly by the pharmaceutical industry (Ban, 2006b). In fact, most studies utilized for this report are from recent years and may shift the overall impression on the efficacy of antidepressants into the direction of limited efficacy, and thus may impact treatment related considerations, potentially underestimating the efficacy of antidepressants in a clinical cohort. It is therefore also important to keep in mind that the outcome of industry-sponsored phase III studies often cannot be taken at face value. The overt and covert influence of the vested interests of study sponsors on results (sponsorship bias) has recently received a fair amount of attention (Healy, 2006; Heres et al., 2006; Lexchin et al., 2003; Lexchin and Light, 2006; Montgomery et al., 2004a; Perlis et al., 2005; Procyshyn et al., 2004).

On the other hand, failed trials are usually not published or are published only with low priority and after an extensive delay, as publication is usually not in the interest of the sponsor and may interfere with marketing strategies. For a complete assessment of the utility of antidepressants it would be helpful to take all those studies into account. But because it is not possible to report in full about unpublished studies, the Task Force decided to base its work only on peer-reviewed, published papers and information from book chapters. Unpublished studies have not been considered in the main review, except within the chapter on treatment of children and adolescents (chapter 10.2.1), which includes some unpublished data available on Internet sites of pharmaceutical companies. Some, but not all companies have now committed themselves to an open database policy of supplying information regarding all controlled, company-sponsored trials on their Internet site. However, using this information from some companies but not from others would also unfairly bias the results and views expressed here. Hence, the Task Force's decided to base its report only on peer-reviewed, published papers and information described in chapter 4.2 above. Unpublished materials, papers not available using a Medline database search and abstracts (posters and lectures) were considered only if they were presented at major conferences or explicitly supplied as additional information by a company (e.g., on the company's freely accessible Web page). Overall, those materials had no major impact on the technical review.

The CINP Task Force is also well aware that most evidence quoted in this technical review originated from clinical studies carried out in Europe and North America. Results may therefore not be representative of populations living elsewhere and under different cultural and climatic conditions. Biological differences, e.g., in metabolism, differences in food intake, different patterns of physical morbidity as well as cross-cultural differences in concepts of health and in the expression of depressive episodes all lead to differences in treatment outcome. The use of medication may differ from culture to culture with consequences for both compliance and treatment outcome. For example, Sugahara reports an adherence rate of 66.8% over 13 weeks of antidepressant treatment in a non-psychiatric outpatient clinical setting in Japan (Sugahara et al., 2005), whereas in Western European countries and North America compliance is usually worse (Brown et al., 2005; Demyttenaere, 1998).

Most RCTs include patients who have been diagnosed as suffering from major depression or depressive disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th revision (DSM-IV), or the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). By defining specific subgroups of patients suffering from depressive disorders, both operationalized diagnostic systems may influence treatment outcome. In addition, as mentioned above, a relatively high placebo response rate in patients suffering from depressive disorders has an impact on efficacy studies of substances with possible antidepressant effects by reducing the likelihood of separating them from placebo. Finally, because the vast majority of RCTs deal with major depressive disorder, it remains unclear whether one can extrapolate from these studies to other (minor) forms of depression or depression comorbid with other mental or somatic illnesses.

Another important, yet often forgotten, methodological issue is that the fact that just because two
studies are significantly positive in favor of a specific medication does not mean that both drugs are equal in efficacy. Variations in sample sizes make it hard to compare trials due to the related statistical power of the study. When including a large number of subjects, a drug-placebo difference in the Hamilton Rating Scale for Depression (HAMD) of 2 may still be significant, but not clinically meaningful. On the other hand, if the power calculation was too optimistic and only a small number of patients have been included, even a HAMD difference of 6 may lack statistical significance. In the case of superiority in comparison with placebo treatment, both statistical significance and effect size are very important factors influencing clinical effectiveness. However, it would clearly be beyond the scope of a review to detail the methodology of each trial mentioned and the Task Force decided that it would refer the reader to the original publications. Also, placebo response rates may differ substantially from study to study due to different allowances of rescue medication, settings, severity of illness and so on. Thus, relevant findings may be obscured by high placebo responses and may also lead to the perception that placebo could be an adequate antidepressant. Again, it would be difficult within the scope of a review to give more detailed information for every single trial concerning all these potentially confounding factors.

Nevertheless, the introduction of RCTs was a great step forward in clinical psychopharmacology, simply by the fact that they replaced testimonials (consensus of experts), contaminated by many other factors, in the demonstration of efficacy of antidepressants. Therefore, proving efficacy in RCTs remains the key issue for regulatory approval; for instance, the European Medicines Agency (EMEA) recommends for the approval of an antidepressant medication both multiple arm short-term studies, including at least three dosages of the agent to be tested, an active comparator and placebo, and a randomized withdrawal study, proving maintenance of effect, with an observational period of at least six months (Dokument cpm/ewp/ 518/97, Committee for Proprietary Medicinal Products, 2002.). However, even these sophisticated designs have their inherent short comings, and some experts would give preference to non-placebo controlled comparator trials proving superiority of the new compound (Barbui et al, 2001). Also between regulatory agencies there is no clear consensus what kind of evidence has to be considered sufficient to support an antidepressant claim, or, to express it in the words of a title of this review, what makes an antidepressant ‘useful’. EMEA, for example, dedicates several chapters on specific recommendations for safety and the use of an antidepressant in geriatric patients, adolescents and special groups, e.g. treatment-refractory patients.

Table 4 supplies a comparative overview about the regulatory requirements in three selected regions.

The limitations noted in this chapter have to some extent been corrected by the process of collaboration described in chapter 4.1. No review can in itself be an unbiased and conclusive piece of evidence, but can only direct readers to the original publications. Clearly, responsible treatment decisions should never be based on reviews, no matter how comprehensive, but on one’s own critical reading of the sources. The Review should help readers in this respect and serve as support to the development of treatment guidelines at national level in which the knowledge of local conditions and experience can help to produce useful instructions for the practicing health professionals.

5. Diagnosis and epidemiology

5.1 Diagnosis of depressive disorders

Despite decades of intensive biologically oriented psychiatric research, the etiology of depressive disorders is not yet fully understood. A multifactorial genesis is supposed. Besides psychological and social factors, biological variables, too, apparently play a major role, and lead in aggregate to disturbed central nervous system homeostasis. The so-called catecholamine- and serotonin-deficiency hypothesis (Burke and Preskorn, 1995), which postulates a dearth of monoamines (noradrenaline and serotonin) within the synaptic cleft, is essential in understanding the pathophysiology of depression.

Depressive syndromes responsible to specific antidepressant therapies are classified within diagnostic entities using operationalized diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders, 4th revision (DSM-IV) (American Psychiatric Association, 1994) and the International Classification of Diseases, 10th revision (ICD-10) (World Health Organization, 1992). Table 5 lists the variety of symptoms that characterize depressive disorders.

To diagnose a major depressive disorder (MDD), according to the DSM-IV five main criteria of depression must be met, and according to ICD-10 a minimum of two main symptoms and two accessory symptoms must be present (see Table 2 adopted from Bauer et al., 2002c).

Sometimes, owing to standardized diagnostic procedures, subsyndromal depression in elderly patients...
Table 4. Requirements for licensure of a medication as an antidepressant in three exemplary regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| EU (EMEA) (The European Agency for the Evaluation of Medicinal Products, 2002) | A: Acute treatment <br> EMEA gives specific recommendations for an antidepressant claim: 
Superiority vs. placebo in a three arm trial including both placebo and an active control to check internal validity, recommended duration 6 weeks. At least three different fixed doses of the test substance should be used to determine the lower end of the effective dose range as well as the optimal dose. <br> Note: For a claim for acute treatment, it is mandatory to fulfill both A and B |
| US (FDA) (U.S. Food and Drug Administration, 2006) | A: Maintenance of effect 
(Relapse prevention) 
Randomized withdrawal study after acute response on test substance with re-randomization either to test substance or placebo, recommended duration up to 6 months. 
B: Prevention of recurrence 
(Prophylaxis) 
Double-blind comparison against placebo, minimum duration 1 year. |
| South Africa (MCC) (Medicines Control Council, 2007) | MCC gives no specific recommendations for an antidepressant claim, but 
the following general recommendations: 
Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs' 
FDA demands no specific design for antidepressants, but recent licensures had the following characteristics: 
Superiority vs. placebo in two pivotal studies (randomized, double-blind, adequate number of patients and statistical power). Studies may include an active treatment control or a dose-comparison control 
No specific recommendations are supplied for a separate prophylactic claim |

EMEA = European Medicines Agency; FDA = US Food and Drug Administration; MCC = Medical Control Council of South Africa.

does not fulfill the complete diagnostic criteria according to DSM-IV or ICD-10 even when antidepressant therapies are clearly needed (see chapter 10.2.2). In addition, differences in the clinical picture of depressive disorders influence both the choice and outcome of specific antidepressant treatment. The tendency of patients to stop eating and lose weight may also alter the clinical presentation of depressive disorders. These patients are more often referred to general practitioners or specialists in internal medicine than to psychiatrists.

The PRIME-MD Patient Health Questionnaire (PHQ-9) (Nease and Maloin, 2003) and even simpler screening questions (Arroll et al., 2005) have been suggested as appropriate instruments for accurately identifying depressed patients in primary care settings because there is good evidence that screening helps to identify persons in need of treatment (Berg, 2002).
The use of operationalized diagnostic systems such as ICD-10 and DSM-IV may cause an inclusion of larger populations in diagnostic categories in comparison to the former used categories based on psychopathology and psychiatric nosology e.g. introduced by Kurt Schneider or Emil Kraepelin. Distinguishing vital depression, depressive psychopathy and reactive depression according Schneider may influence also therapeutic outcome during antidepressant therapies. Nevertheless the diagnostic systems help to compare similar populations suffering from depressive disorders and to evaluate treatment effects worldwide.

In this chapter the effects of diagnostic categories and subgroups on treatment outcome are described not only on basis of scientific evidence, but also based on a broad clinical consensus within the CINP antidepressant task force. The review of the subgroups of depression is selective, based on the relevance of clinical features to treatment choices.

### 5.2 Features of particular relevance to the treatment of depressive disorders

The basis of the following chapter 5.2 are rarely RCTs but predominantly a clinical consensus of the CINP antidepressant task force predominantly based on clinical experience, open studies, case series and case reports. The information provided in this chapter should serve as a contribution to the actual knowledge base, not as a guideline for treatment. Table 6 summarizes diagnostic indications including diagnostic subgroups and psychiatric comorbidities for specific classes of antidepressants.

#### 5.2.1 Unipolar depression

A significant proportion of depressive disorders show an episodic course. With the exception of the recurrent brief depressive episodes singled out in the ICD, the threshold for reaching a diagnosis is that symptoms be present for at least 2 weeks. Shorter duration places the episodes into a ‘subthreshold’ group. The differences between threshold and subthreshold depression are discernible but not very helpful in clinical work since it has been shown that subthreshold depression (for which treatment may not be reimbursable in some countries) causes disability and often requires treatment. Especially in children and adolescents, as well as in the elderly, depressive disorders comprise a variety of inherently difficult diagnostic problems. These difficulties may be further aggravated by the presence of other conditions such as anxiety or personality disorders. The following sections describe specific subtypes of depressive symptoms that may influence antidepressant therapy. For other subtypes of depression that respond similarly to treatment, no differentiation appears to be warranted.

##### 5.2.1.1 Severity of the disease

Depressive episodes can be classified as mild, moderate or severe (ICD-10). Subsyndromal depression may enhance the risk of developing a syndromal depressive disorder according to ICD-10 and DSM-IV, and treatment may be necessary. In addition to clinical judgment, e.g. using ICD-10 diagnostic criteria or the Clinical Global Impressions scale (CGI-S, Item I, severity of disease) (National Institute of Mental Health, 1976), severity groups can be distinguished using instruments such as the Hamilton (Hamilton, 1960) or Montgomery–Åsberg rating scales for depression (Montgomery and Åsberg, 1979).

This subdivision is of clinical importance because there is some consensus in the literature that mild depressive syndromes should be treated by

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### Table 5. Symptomatology of depressive disorders (American Psychiatric Association, 1994; World Health Organization, 1992; World Health Organization, 2005b)

<table>
<thead>
<tr>
<th>Category of depressive symptoms</th>
<th>Symptom list</th>
</tr>
</thead>
</table>
| Affective symptoms             | ● Depressed mood*  
|                                | ● Anhedonia*  
|                                | ● Anxiety17  
| Psychomotor disturbances       | ● Retardation  
|                                | ● Agitation  
|                                | ● Loss of energy and activity*  
| Disturbances of cognition and memory | ● Feelings of guilt  
|                                | ● Feelings of worthlessness  
|                                | ● Mood-congruent and -incongruent delusions  
|                                | ● Concentration deficits  
|                                | ● Memory deficits  
| Psychovegetative disturbances and somatic complaints | ● Sleep disturbances (insomnia, early morning awakening)  
|                                | ● Diurnal changes  
|                                | ● Loss of appetite and weight  
|                                | ● Sexual dysfunction  
|                                | ● Constipation  
|                                | ● Pain syndromes  
|                                | ● Hypertonia  
|                                | ● Tachycardia  

* Core symptoms of depression.

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17 Anxiety is not included in the diagnostic systems of ICD-10 and DSM-IV, but there is a broad clinical consensus that anxiety symptoms are accompanying depression frequently.

18 ‘Psychopathy’ here is used as a historical term, not as a diagnostic category.
psychotherapy without additional biological therapies such as pharmacotherapy or electroconvulsive therapy (ECT). In moderate depression non-biological treatments are also the first choice in some guidelines, although, moderately depressed patients respond equally well to antidepressant medication. Moreover,
there is a distinct probability that patients with mild to moderate depression may respond to phytotherapeutics such as St. John’s wort (Kasper, 2001; Laakmann et al., 1998) or benzodiazepines without antidepressants (though this option is not recommended) (Laakmann et al., 1996). There is also some evidence that very severe depressive syndromes show a better response to ECT, tricyclic antidepressants (TCAs) and dual-action substances such as venlafaxine, duloxetine and mirtazapine.

5.2.1.2 Depression with psychotic symptoms

Psychotic features of depression such as hallucinations and delusions, e.g. delusional hypochondria, feelings of guilt or nihilistic thoughts, are predominantly mood congruent, but may also be non-congruent with depressed mood. Depressive episodes with psychotic symptoms are in most cases an indicator of the particular severity of the disease, including high risk of suicide. This additional risk factor must be taken into account in planning treatment. In patients suffering from psychotic symptoms, a combination of antidepressant therapy with antipsychotic medication is usually recommended (Coryell, 1996). It has, however, been reported that this combination confers no benefit for some patient subgroups, e.g. elderly patients (Mulsant et al., 2001). TCAs and selective serotonin reuptake inhibitors (SSRIs) in combination with antipsychotics are recommended, and amoxapine has been shown to exert somewhat lower but likewise significant efficacy (Anton and Burch, 1990; Rothschild et al., 1993). SSRI monotherapy reportedly is efficacious during acute and maintenance treatment (Zanardi et al., 1996; Zanardi et al., 1997). ECT has been recommended as a possible first-line treatment because of its high effectiveness during acute episodes (Coryell, 1998) and more favorable long-term outcome (Birkenhager et al., 2004) in this subgroup of patients, especially in comparison with pharmacotherapy (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). Finally, early consideration of lithium augmentation is recommended in this patient group especially in the case of antidepressant treatment failure (Bauer et al., 2003; Price et al., 1983).

5.2.1.3 Other clinical features with a possible impact on antidepressant therapies

5.2.1.3.1 Severe psychomotor agitation and retardation

Severe psychomotor retardation, stupor, immobility or, in contrast, severe agitation (called catatonic features by some authors) are also seen in depressed patients (Fink, 1992; Starkstein et al., 1996; Taylor and Fink, 2003). ECT has been reported to have an excellent effect in these cases (Fink, 1990; Rohland et al., 1993). Administration of benzodiazepines (lorazepam) during acute-phase treatment can lead to immediate relief of catatonic symptoms. For routine clinical cases, sedating antidepressants or combinations of non-sedating antidepressants with sedating benzodiazepines are used in agitated patients, whereas activating substances such as SSRIs or noradrenalin reuptake inhibitors (NARIs) are used in patients with predominantly psychomotor inhibition.

5.2.1.3.2 Melancholic features

Melancholic forms of depression are characterized by a higher age of occurrence, a loss of the ability to feel pleasure, depressive delusions and a variety of often severe somatic symptoms (Table 2 and Table 5), as well as major psychomotor symptoms. The treatment of depression with melancholic features is similar to that recommended for severe depression. Patients frequently respond to augmentative strategies, such as addition of lithium and sleep deprivation.

5.2.1.3.3 Atypical features

There is no clear agreement about the features that characterize atypical depression (Fountoulakis et al., 1999). In French-speaking countries the term ‘atypical’ is used for depressed patients with psychotic features. According to DSM-IV, a diagnosis of atypical depression requires meeting two of the following criteria: increase in appetite and weight gain, hypersomnia, leaden paralysis and a long-standing pattern of interpersonal rejection sensitivity. The Inventory of Depressive Symptomatology – Clinician Rating (IDS-C30) is also suitable for diagnosing atypical depression, and includes earlier age at onset, greater comorbidity with anxiety symptoms and greater symptom severity compared with non-atypical depression (Novick et al., 2005). Empirical data support the hypothesis that monoamine oxidase inhibitors (MAOIs) and SSRIs represent a first-line treatment option that is superior to other pharmacological treatment (Andrews and Nemeroff, 1994; Henkel et al., 2006; Sogaard et al., 1999). Owing to the special precautions they require, in some countries irreversible MAOIs are not recommended as a first-line treatment.

5.2.1.3.4 Seasonal features

Patients suffering from depression that recurs on a regular, annual basis during fall or early winter
and spring often show subsequent symptoms of bipolar disorder (chapter 5.2.2.1). In addition, depressive syndromes are frequently characterized by features listed as atypical in DSM-IV (see chapter 5.2.1.3.3).

If depressive symptoms are of moderate severity, seasonal forms of depression are treated like other recurrent episodes. Bright light therapy (phototherapy; see also chapter 19.7) can be used as an early augmentation strategy (chapter 12.3.8). Because of its proven efficacy (Kasper et al., 1990; Rosenthal et al., 1985), bright light therapy can even be used as monotherapy in the case of mild depression during a limited treatment trial. But the possibility of occurrence or enhancement of suicidal ideation during phototherapy must be taken into account (Praschak-Rieder et al., 1997).

5.2.1.3.5 Depressive syndromes in pain conditions

Depressive disorders and predominantly chronic pain are frequent comorbid conditions. Approximately 70% of patients with major depression present with physical complaints (Fava, 2002; Simon et al., 1999b). Severe pain caused by somatic diseases comorbid with depression makes the treatment of depression difficult. Somatoform disorders, fibromyalgia and similar conditions characterized by pain are often accompanied by depressed mood. Effective treatment of neuropathic pain requires the application of antidepressants with a mixed serotonergic and noradrenergic mode of action, such as the TCA amitriptyline (Saarto and Wiffen, 2005, 2007). Newer antidepressants have been shown to be useful in the treatment of pain conditions with and without comorbid depression. Various pharmacodynamic classes, such as SSRIs, NARIs, noradrenergic and selective serotonergic antidepressants (NaSSAs) (Mattia et al., 2002) and selective serotonin and noradrenaline reuptake inhibitors (SNRIs) (Barkin and Barkin, 2005; Gendreau et al., 2005) have shown efficacy in anecdotal reports, only SNRI and TCA have proven efficacy according a recent Cochrane review (Saarto and Wiffen, 2007). It seems plausible that antidepressants with both serotonergic and noradrenergic properties could be particularly effective in treating pain and painful physical symptoms. Higher remission rates in these subgroups of depressed patients have recently been discussed (Fava, 2003c). Antidepressants are now seen by many as an essential supplement in a variety of therapeutic regimes for pain control.

5.2.1.3.6 Depressive syndromes in adjustment disorders

Because symptoms of adjustment disorders and depressive disorders may be identical, and also because depressive episodes often occur after exposure to severe stress, there is no reason to offer patients suffering from adjustment disorder therapeutic regimes other than those that offered to patients with depressive disorders. This is especially true during the period of acute treatment. Although controlled efficacy trials in adjustment disorders are rare, both clinical experience and retrospective studies (Hameed et al., 2005) suggest no difference between depression and adjustment disorder in response rates to treatment. The use of psychosocial therapies in adjustment disorders may begin earlier and be more intense.

5.2.2 Other forms of depressive disorders

5.2.2.1 Bipolar depression

Diagnostic criteria for a depressive episode due to bipolar I disorder are the same as already described for cases of unipolar depression (see chapter 5.1). In addition, a diagnosis of bipolar disorder must be based on at least one previous manic or mixed episode, including a period of abnormally and persistently elevated, expansive or irritable mood lasting at least 1 week (even shorter, if hospitalization is necessary). During this time, grandiosity or inflated self-esteem are normally present together with decreased need for sleep, hyperactivity, psychomotor agitation, racing thoughts with flight of ideas, distractibility and a drive to keep talking that causes marked impairment in social functioning. In the case of a mixed episode, these symptoms occur simultaneously with depressive symptoms for at least 1 week. In the case of bipolar II disorder, the patient’s history must include at least one episode of hypomania (a period of manic symptoms of lesser severity that lasts at least 2-4 days). However, shorter hypomanic bleeps may also justify treating a patient according to criteria for bipolar depression, not unipolar depression (Akiskal et al., 2000; Cassano et al., 1988). Finally, continuity between bipolar II disorder and unipolar severe (major) depression has been suggested (Akiskal and Benazzi, 2006).

Because the symptoms of bipolar depression are identical to those of unipolar depression, and because at the time of the initial depressive episode it is not

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19 There exists no clear cut definition for ‘mild depression’ in the literature. In addition to the severity of disease mentioned in the ICD-10 (World Health Organization, 1992) the subdivision of depressive syndromes can be done with rating scale cut off values using the CGI or HAMD scale (e.g. as done in Laakkann et al., 1996 and 1998).
possible to make a diagnosis of bipolar disorder, up to 50% of younger patients suffering from depression at the first index episode later receive a diagnosis of a bipolar disorder (Angst, 2006; Goldberg, 2003). These rates are, however, controversial (Patten, 2006). Although the evidence for the efficacy and effectiveness of antidepressant treatment of bipolar depression is less compelling than that for treatment of unipolar depression, the same substances that lead to clinical improvement in unipolar depression can be used in bipolar depression. Because of a lower switch risk from depression to hypomania or mania and given their good efficacy, predominantly SSRIs or MAOIs (Gijssman et al., 2004) and bupropion (Sachs et al., 1994) in combination with mood stabilizers are considered to be the treatment of choice (Grunze et al., 2002). In addition monotherapies using mood stabilizers such as lithium or lamotrigine or atypical antipsychotics (e.g. quetiapine) are possible. Because there is no uniform definition of ‘switch’, the switch rates in scientific publications vary widely. Nevertheless, a threefold higher switch rate during TCA therapy in comparison with SSRI treatment has been reported (Peet, 1994). It has thus been suggested that all antidepressants, but especially TCAs and dual-action antidepressants such as SNRIs, be recommended in combination with mood stabilizers to prevent an enhanced switch risk.

It should be mentioned that for bipolar depression there is also reasonably good evidence for monotherapy with the mood stabilizers lithium and lamotrigine as well as with the atypical antipsychotics olanzapine and quetiapine (Yatham, 2005). Moreover, the use of adjunctive antidepressant medication in was not associated in with increased efficacy in comparison to treatment with mood stabilizers alone (Sachs et al., 2007). However, to date there is no proof that these treatment regimens work any better than antidepressants (Möller et al., 2006).

5.2.2.2 Dysthymia and depressive disorder in combination with dysthymia

Diagnostic criteria for dysthymia and depressive disorders differ in the severity and duration of symptoms. Dysthymia constitutes a chronic depressive syndrome of lower intensity of symptoms than severe depression, although it produces very similar levels of disabilities. Also, an additional and superimposing major depressive episode can occur in patients already suffering from dysthymia, diagnosed then as a ‘double depression’ or ‘double major depressive disorder’. When a dysthymic episode follows a depressive episode, the differential diagnosis of both disorders is difficult because the symptoms of dysthymia are then indistinguishable from the (reduced) symptoms of depressive disorder with only partial remission, which should be diagnosed in this case. Only after full remission lasting at least 6 months can the subsequent dysthymic symptoms be diagnosed as dysthymia.

Because both diagnostic entities respond to the same antidepressant, identical acute treatment plans can be prescribed for depressive disorders, dysthymia and double depression. In addition, antipsychotic treatment such as amisulpride (Rocca et al., 2002; Zanardi and Smeraldi, 2005) may be of use. Due to the chronic nature of dysthymic disorders, earlier implementation of psychotherapy can help. Treatment goals should be formulated somewhat more cautiously because dysthymia appears to have less likelihood of complete recovery (Judd et al., 1998a). The combination of pharmacotherapy and an empirically supported psychotherapy may be optimal for chronically depressed patients (Keller et al., 2000; Rush and Thase, 1999; Markowitz, 1993).

5.2.2.3 Recurrent brief depression

Recurrent brief depression (RBD) is characterized by depressive episodes that occur at least once a month and last only a few days (Pezawas et al., 2001). The combination of depressive disorders and RBD exhibits a relatively high prevalence. The substantially higher risk for suicidal ideation in such cases presents a special concern. Most trials investigating antidepressant therapies were designed to judge therapeutic efficacy in major depressive disorders. Different study designs are needed to properly investigate the combination of depressive disorders and RBD. The literature contains a variety of negative results concerning RCTs of SSRIs in the treatment and prophylaxis of RBD (e.g. Angst and Dobler-Mikola, 1985; Montgomery et al., 1994),

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22 Amisulpride is not available in the US, and for the time being, the use of other antipsychotics for dysthymia is not recommended.

23 According to DSM-IV, recurrent brief depression can only be diagnosed as subthreshold major depressive disorder (MDD). According to ICD-10, it is a diagnostic category of recurrent depressive disorder (RBD). The combination of severe depressive disorders and RBD is sometimes called combined depression (CD) (Pezawas et al., 2001).
but methodological problems and highly selective patient samples may account for the results (Pezawas et al., 2001). There are as yet no efficacious treatment algorithms for RBD (Pezawas et al., 2005).

5.2.3 Depressive disorders with comorbid psychiatric disorders

Comorbidity of depressive disorders with other psychiatric disorders is common (Pincus et al., 1999) and significantly affects treatment outcomes. The greater the number of concurrent comorbid conditions, the greater the severity, morbidity and chronicity of depressive disorders (Rush et al., 2005c). Treatment of depression that occurs with other conditions thus calls for special attention and reflection in treatment plans.

5.2.3.1 Other psychiatric disorders

5.2.3.1.1 Anxiety disorders

A lifetime prevalence of more than 40% for the comorbid depression and anxiety disorders, such as panic disorder, phobias and generalized anxiety disorder, has been reported in patients suffering from depressive disorders (Hasin et al., 2005). Up to now, however, it has not been sufficiently clear whether the two diagnostic conditions are distinct or represent a single mixed anxiety-depression syndrome (or a ‘spectrum disorder’). Patients with depressive disorders and comorbid panic disorder show differences in the clinical course and severity of disease compared with patients suffering from depressive disorders alone (Grunhaus et al., 1994).

Because comorbid conditions can diminish the clinical effectiveness of antidepressant pharmacotherapy (Grunhaus et al., 1986), they should be considered in treatment plans. Administering antidepressants with demonstrated efficacy for both diagnostic entities (e.g. in the case of depressive and anxiety disorders, SSRIs such as paroxetine (Montgomery, 1992)), together with implementing specific psychotherapeutic options for depression and anxiety, seems to be a useful strategy (see also chapters 13 and 19.9).

5.2.3.1.2 Substance abuse

Disorders related to the use of alcohol, nicotine and other drugs often occur together with depression, and in the US have a lifetime comorbidity of 40, 30 and 17%, respectively (Hasin et al., 2005). Depressed patients with comorbid substance abuse are more likely to have an earlier age of onset of depression, greater depressive symptomatology, greater functional impairment and more previous suicide attempts than patients with depression alone (Davis et al., 2006). Because pharmacokinetic and -dynamic drug interactions, as well as psychosocial consequences of drug abuse, all influence response and recovery rates from depressive disorders, a combined therapeutic approach should address both the depressive disorder and the comorbid condition. This is especially true for psychotherapeutic and psychosocial approaches, but it holds as well for pharmacological treatment plans, e.g. in choosing antidepressants of lower pharmacological interaction potential, as is the case for some SSRIs, NARIs and dual-action antidepressants.

5.2.3.2 Personality disorders

About one-third of depressed patients also have a personality disorder. The most common forms are obsessive-compulsive (16%), paranoid (10%) and schizoid (7%) personality disorder (Hasin et al., 2005). In such instances, the effects of biological antidepressant therapies are less impressive, and treatment takes longer. Depression may be a positive predictive factor in the treatment of persons who have personality disorders (Shea et al., 1992). Early implementation of psychotherapeutic approaches in treatment may be helpful.

5.2.4 Depressive disorders with comorbid somatic disorders

5.2.4.1 Physical disorders

Depressive syndromes are frequently present in people with severe and chronic physical disorders. Somatic disorders or their treatment may be directly responsible for depressive symptoms (Patten and Barbui, 2004). The choice of treatment will depend on the severity of depression, comorbid somatic risks and somatic treatment.

If an organic factor is the source of the depressive syndromes (‘organic depression’), treating the organic disease first must be considered when it can be done directly (e.g. substitution of thyroid hormones in case...

24 Axis I disorders according to DSM-IV.
25 Axis II disorders according to DSM-IV.
26 The concept of comorbidity does not necessarily include known causal interdependencies between somatic diseases and depression. Nevertheless, in some cases of comorbidity these may be known, and in others they may exist without precise knowledge. In addition, different somatic and psychiatric phenotypes of the same disease may exist.
27 The treatment of depression during chronic pain conditions is described in chapter 5.2.1.3.3.
of hypothyroidism) and when depression is of mild to medium severity. When depression is severe or there is risk of suicide, an additional symptomatic antidepressant treatment is obligatory. The same is true if the organic factor cannot be treated owing to other conditions (e.g. immune system suppressors in the case of transplantation) or if recovery is unlikely (e.g. stroke). Table 7 lists possible organic causes for depressive syndromes.

5.2.4.1.1 Cardiovascular disorders

A variety of studies confirm the interdependency of medical disorders and the risk for developing depressive symptoms caused by comorbid depressive disorders or adjustment disorder (Glassman et al., 2003; Glassman, 2005; Glassman et al., 2006). An exceptionally high comorbidity of depressive symptoms and cardiovascular disorders (CVDs) has been described (Purebl et al., 2006), but the detection of depression in patients suffering from CVD is relatively low. Moreover, the comorbidity of depressive disorders and CVD significantly influences the medical outcome of coronary artery disease and myocardial infarction (Fraseure-Smith et al., 1993; Musselman et al., 1998), especially when depressive symptoms are refractory (Carney et al., 2004). Knowledge about differential risk factors or predictors of adverse events in patients suffering from myocardial infarction and depression is still limited (Jaffe et al., 2006). Depression enhances cardiovascular mortality independent of other cardiovascular risk factors (Penninx et al., 2001) and appears also to be an independent additional risk

Table 7. Examples of organic factors that may cause depressive disorders (see also Evans et al., 2005; Katona, 1997; World Psychiatric Association, 2006)

<table>
<thead>
<tr>
<th>Category of organic disease</th>
<th>Organic illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological disorders</td>
<td>● Stroke&lt;br&gt;● Dementia&lt;br&gt;● Epilepsy&lt;br&gt;● Huntington’s chorea&lt;br&gt;● Hydrocephalus&lt;br&gt;● Central nervous system (CNS) infectious diseases&lt;br&gt;● CNS neoplasias&lt;br&gt;● Parkinson’s disease&lt;br&gt;● Narcolepsy&lt;br&gt;● Sleep apnea&lt;br&gt;● Trauma&lt;br&gt;● Wilson’s disease</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>● Adrenal disorders (Cushing’s disease, Addison’s disease)&lt;br&gt;● Hyperaldosteronism&lt;br&gt;● Hyper- or hypoparathyroidism&lt;br&gt;● Hyper- or hypothyroidism&lt;br&gt;● Postpartum hormonal changes</td>
</tr>
<tr>
<td>Other medical disorders</td>
<td>● Neoplasias and paraneoplastic syndromes&lt;br&gt;● Cardiopulmonary diseases&lt;br&gt;● Autoimmune disorders (e.g. lupus erythematoses)&lt;br&gt;● Porphyria&lt;br&gt;● Uremia&lt;br&gt;● Avitaminoses (vitamins B₁₂, C, folate, niacin or thiamine)</td>
</tr>
<tr>
<td>Pharmacogenic depression&lt;sup&gt;28&lt;/sup&gt;</td>
<td>● Analgesics (ibuprofen, indometacin, opiates, phenacetin)&lt;br&gt;● Antibiotics (streptomycin, sulfonamides, tetracyclines)&lt;br&gt;● Antihypertensives (reserpin, clonidine, digitalis)&lt;br&gt;● Chemotherapeutics (asparaginase, azathioprine, bleomycine, trimethoprim, vincristine)&lt;br&gt;● Hormones (high-estrogen oral contraceptives)&lt;br&gt;● Immune system therapy/suppression (corticosteroids, interferons, mycophenolate mofetile, tacrolimus)</td>
</tr>
</tbody>
</table>

<sup>28</sup> It is presently not clear whether depressive syndromes following treatment with classical antipsychotics represent symptoms of the disease or a side effect of treatment.
factor for cardiovascular disease (Wulsin and Singal, 2003). The most important influencing factor may be the severity of the depressive syndrome (Penninx et al., 2001) or the presence of a major depressive disorder (Schulz et al., 2000). Less severe forms of depression seem to be less deleterious. Another apparently important influencing factor is activation of central stress regulation systems, predominantly hypothalamic-pituitary adrenal (HPA)-axis activation present in the majority of depressed patients (Lederbogen et al., 1999).

There is consensus that it is important to treat depression in this patient subgroup sufficiently, although, both a significantly lowered risk of death or recurrent myocardial infarction in patients taking selective SSRIs (Taylor et al., 2005) and a failure to prove lowered cardiac risk due to antidepressant treatment (Berkman et al., 2003; Shimbo et al., 2005) have been reported. Antidepressant pharmacotherapy stimulates using drugs that have as low a drug-drug interaction risk as possible and exert no negative influence on cardiac conductance, rhythm or output. Most modern antidepressants fit this profile, including SSRIs, NARIs and dual-action substances. In addition, because depression may worsen coronary blood flow (Lederbogen et al., 2001), it seems plausible to make use of the diminishing effects of SSRIs on platelet aggregation (Maurer-Spurej et al., 2004) to achieve further benefit for patients suffering from depression and cardiovascular disease.

5.2.4.1.2 Endocrinological disorders and diabetes mellitus

Depression has been shown to be a risk factor for type II diabetes mellitus (Eaton et al., 1996); a bidirectional positive association has been assumed (Eaton, 2002; Evans et al., 2005). Endocrinological disturbances known to be present during depressive states, such as hypercortisolism, may facilitate the development of diabetes. A negative influence of depression on therapeutic adherence and the risk of vascular complications and disability have been described. The effectiveness of antidepressant treatments in diabetic patients has been shown, but the potential benefit for blood glucose and HbA1c levels remains unclear (Evans et al., 2005). Antidepressants and antipsychotics with sedating properties due to antihistaminergic effects also facilitate weight gain and the development of metabolic syndromes, worsen diabetes mellitus or abet a switch from prediabetic syndrome to frank diabetes (American Diabetes Association, 2005).

5.2.4.1.3 Renal disorders

Severe acute and chronic renal diseases can cause depressive syndromes (Kimmel and Peterson, 2005) within adjustment disorders. They also represent a psychosocial burden capable of initiating episodes of depressive disorders. Both cases call for an antidepressant treatment plan. In addition to psychotherapeutic counseling, antidepressant pharmacotherapy may be necessary. Renal failure can complicate antidepressant pharmacotherapy because diminished renal clearance can provoke increased side effects and toxic effects of antidepressants. Increased responsiveness to antidepressant drugs (Finkelstein et al., 2002) along with greater unpredictability and inter-patient variability (Dawling et al., 1982) have been reported.

Dose adjustment is often necessary, e.g. half the standard does at the outset of treatment. Antidepressants with a lower likelihood of interacting with other drugs via the cytochrome P-450 system (see chapter 9.1.1.1), such as the SSRIs sertraline or citalopram, are suggested. Frequent evaluation of side effects and blood level monitoring are useful tools to prevent overdoses. If renal failure progresses to end-stage renal disease and hemodialysis, hemoperfusion or hemofiltration are necessary, lower antidepressant plasma levels are possible, and dose adjustment may be required considering blood levels, efficacy and side effects.

5.2.4.1.4 Hepatic disorders

Patients suffering from chronic hepatitis may develop enhanced risk for depression, especially in the case of treatment with interferon (Asnis and De La Garza, II, 2006), and some may even require prophylactic antidepressant treatment (Schaefer et al., 2002; Schaefer et al., 2003). Comorbidity of depression and hepatic diseases demands specific precautions. Antidepressant drugs are metabolized in the liver, and only a small proportion of some substances (e.g. 2% of paroxetine) can be secreted unchanged in the urine (Tossani et al., 2005). Antidepressants rank 5th on the list of drugs that cause liver injury (Andrade et al., 2005). The hepatotoxic properties of antidepressants can lead to transient increases in liver enzymes, but also to fulminant liver failure. For that reason, in depression accompanied by liver disease it is necessary to start treatment using substances that have a lower probability of causing additional liver damage. TCAs, MAOIs and nefazodone appear to have higher hepatotoxicity compared with newer agents such as SSRIs (Lucena et al., 2003). But SSRIs and other modern
substances also require dose adaptation in patients suffering from liver disease to prevent side effects and intolerable toxicity which may occur because of a lower clearance of antidepressants and metabolites, and consequently prolonged elimination times (Demolis et al., 1996; Joffe et al., 1998; Suri et al., 2005). Milnacipran may be an exception: because it is metabolized outside the liver, it appears possible to use milnacipran in the case of liver impairment without having to adapt the dose (Montgomery et al., 1996; Puozzo et al., 1998).

5.2.4.2 Neurological disorders

Depression is a relatively common psychiatric comorbidity of most neurological disorders, with prevalence rates ranging between 20 and 50% among patients with epilepsy, stroke, dementia, Parkinson’s disease and multiple sclerosis (Kanner, 2005b). In addition, a side effect of treatment of neurological disorders (e.g. with corticosteroids) enhances risks for depression. Antidepressant pharmacotherapy is therefore mandatory in most cases of medium to severe depression. Antidepressant pharmacotherapy may however worsen the neurological condition of patients. For example, in patients taking high doses of antidepressants, the incidence of seizures rises markedly. This is particularly important if TCAs, especially maprotiline, are used.

5.2.4.2.1 Epilepsy

A bidirectional relationship between the incidence of epilepsy and depression has been described (Kanner, 2005a). In addition, patients with treatment-resistant epilepsy who have undergone temporal lobectomy often experience post-surgical depression following temporal lobectomies (Kanner, 2003), and antidepressant pharmacotherapy may be necessary. Lifting of depression after resective surgical treatment for epilepsy has also been reported (Spencer et al., 2003).

Because lower therapeutic doses of antidepressants may also trigger seizures in patients suffering from epilepsy, cautious treatment using the lowest efficacious doses is mandatory, especially with TCA treatment, because TCAs may diminish the threshold for seizures. But SSRIs, too, have the potential to prolong epileptic seizures, e.g. during ECT treatment (Curran, 1995), or to cause lower sodium levels, which lower the seizure threshold. Fluoxetine and fluvoxamine seem to exhibit the lowest risk for seizures (Pisani et al., 1999). In addition, pharmacokinetic interactions between antidepressants and antiepileptic drugs are to be expected, especially with carbamazepine.

5.2.4.2.2 Stroke and dementia

Patients suffering from severe depression who need hospitalization are at an increased risk of developing cerebrovascular disorders (Nilsson and Kessing, 2004). Patients hospitalized after stroke very often not only suffer from neurological disturbances but also show depressed mood, requiring treatment. A concept of a vascular or ‘arteriosclerotic depression’ has been proposed (Krishnan and McDonald, 1995). Symptoms of depression in Alzheimer’s disease (AD) (Derouesne and Lacomblez, 2004) and other forms of dementia are often seen but are rarely distinguishable from apathy, loss of drive and affective disturbances that are among the symptoms of Alzheimer’s disease. Moreover, depressive symptoms seem to be an independent risk factor for later development of AD (Green et al., 2003; Ownby et al., 2006). A history of depression is associated with a more rapid cognitive decline in patients with AD and pronounced neuropathological changes in the hippocampus (Rapp et al., 2006). It has been suggested that AD and depression are associated with shared risk factors such as sex, age, vascular function and apolipoprotein E4 (APOE4) (Gallarda, 1999).

This connection notwithstanding, meta-analyses show no improvement in cognitive function or disability following treatment for post-stroke depression (Anderson et al., 2004), although relief of depression in itself may justify pharmacologic treatment (Hackett et al., 2004). Moreover, good efficacy of the NaSSA mirtazapine in preventing post-stroke depression has been reported (Niedermaier et al., 2004; Ween, 2005). Also SSRI or NARI in the treatment of post-stroke depression have shown to be superior to placebo (Rickards, 2005), moreover SSRI or TCA treatment during the first 6 months poststroke significantly increased the survival of both depressed and nondepressed patients (Jorge et al., 2003). The recovery after stroke appeared to be enhanced by the use of antidepressant medication if treatment was started within the first month after stroke (Narushima et al., 2003b). In addition, on the long term, an improved cognitive function after remission of post-stroke depression is likely to remain stable if no additional cerebrovascular events occur (Narushima et al., 2003a) and also an improvement of executive functioning following stroke seems to be enhanced due to antidepressant treatment (Narushima et al., 2007).
Treatment of depression must not be allowed to contribute to a worsening of dementia, e.g. due to anticholinergic side effects. For this reason SSRIs, NARIs, SNRIs and NaSSAs would appear to compare favorably with TCAs.

5.2.4.2.3 Parkinson’s disease

The risk for depressive disorders in patients suffering from Parkinson’s disease (PD) (Hantz et al., 1994) is controversial. A high prevalence of depression in PD (20–40%) has been reported (Lieberman, 2006), and even up to 50% (McDonald et al., 2003). In addition, depression may precede the diagnosis of PD (Schuurman et al., 2002). Although published controlled studies are lacking it seems that antidepressant treatment is beneficial for patients and improves the overall quality of life (Anon., 2002; Weintraub et al., 2005). Both SSRIs and SNRIs are generally well tolerated and efficacious (Lemke, 2002; Menza et al., 2004). Selegiline can be integrated into MAO-B inhibitor treatment plans for PD (Bodkin and Amsterdam, 2002), even though its therapeutic effect on depression may in some cases be only modest (Amsterdam, 2003). The potential benefit of the anticholinergic properties of TCAs in PD should be considered. Given that concomitant heart disease, prostatic enlargement and acute angle-closure glaucoma are frequent comorbid conditions in elderly patients suffering from PD, TCAs should be used with caution in this patient group (Cummings and Masterman, 1999). A moderate association of SSRI use and extrapyramidal motor side effects has been reported in susceptible patients (Schillevoort et al., 2002). These effects include acute dystonia, akathisia and aggravation of parkinsonism (Anon., 2001). They may be caused by an interaction between serotonergic and dopaminergic pathways (Lambert et al., 1998).

5.2.4.2.4 Encephalitis disseminata/multiple sclerosis

Even though patients suffering from multiple sclerosis often show affective disturbance without depression, such as pathological laughing and crying (Feinstein et al., 1999), anxiety and euphoria (Diaz-Olavarrieta et al., 1999), an association between multiple sclerosis and depression has also been reported (Patten and Metz, 1997). In these cases, antidepressant pharmacotherapy should be considered.

5.2.4.2.5 Migraine

Depression is one of the most frequent comorbid disorders in chronic migraine (Mercante et al., 2005). Comorbid migraine significantly influences the quality of life of depressed patients (Hung et al., 2006). When migraine accompanies depressive disorder, antidepressant pharmacotherapy not only ameliorates depressive symptoms but can also prevent migraine attacks. Both TCAs (amitriptyline) and SSRIs (fluoxetine) have shown effectiveness in this indication, in the usual antidepressant doses (Campo-Arias, 2004), but exacerbation of migraine attacks during SSRI treatment has also been described (Bickel et al., 2005). Patients prescribed triptans for migraine who are also taking SSRIs, MAOIs or lithium may be at enhanced risk of developing serotonin syndrome. Because the number of serotonin syndromes reported is low, and their severity mild to moderate, combined use of triptans and SSRIs or lithium appears to be only a relative contraindication. But owing to the limited results published to date, MAOIs should be strictly avoided (Gardner and Lynd, 1998).

5.2.4.3 Infectious disorders

Infectious diseases are often accompanied by psychiatric syndromes such as depression. This may be true not only during the acute state of the disease but also after adequate treatment of the medical condition. For example, mixed anxiety-depression syndrome has been reported to follow medical recovery from falciparum malaria (Dugbartey et al., 1998). Also, patients infected with hepatitis C are more likely to suffer psychiatric comorbidities such as depressive disorders (Butt et al., 2006). In addition, specific somatic therapies such as interferones or antibiotics may increase the risk of developing severe depressive symptoms. Infectious diseases affecting the nervous system, such as Lyme disease (Fallon and Nields, 1994) or neurosyphilis (neuro-lues) (Pavlovic and Milovic, 1999), have been associated with psychiatric disorders, including major depression.

A particular interdependency has been described between infection with the human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS) and depressive disorders: depression is believed to be associated with HIV risk behaviors (Hutton et al., 2004), and HIV infection is associated with depression and suicidal behavior (Jin et al., 2006; Porche and Willis, 2006). For further details see (Maj et al., 1993).

Both the infection and the depressive syndrome should be adequately treated, considering all options, including antidepressant pharmacotherapy. Possible interactions between antidepressants and medical treatments such as antibiotics must also be taken into account.
5.2.4.4 Neoplasias and paraneoplastic syndromes

Stressful life events including severe physical illness including neoplasias have been linked to depressive symptoms and to major depressive disorder (Monroe and Simons, 1991). Depression occurs at an increased rate in patients suffering from cancer (Rodin et al., 2007). Recently in cancer patients rates of 19% for depressive symptoms and 8% for major depressive disorder have been reported (Wedding et al., 2007). Moreover most chemotherapeutics used in the pharmacological treatment of cancer (see Table 10) may cause a pharmacogenic depression.

Oncologists play a key role in screening for psychiatric disorders including anxiety and depression in patients with cancer (Miovic and Block, 2007). The treatment should include the available pharmacologic and psychotherapeutic approaches and improves quality of life substantially (Miovic and Block, 2007). Of course potential interactions of antidepressant medications with somatic disturbances due to cancer, e.g. renal (see chapter 5.2.4.1.3) or liver (see chapter 5.2.4.1.4) failure and pharmacological interactions with chemotherapeutics (see chapter 9.1.1.1) have to be taken into account and substances with low interaction potential e.g. citalopram, sertraline or venlafaxine may be advantageous. In addition mianserin has shown good efficacy in a RCT (van Heeringen and Zivkov, 1996).

5.3 Epidemiology of depressive disorders

Depressive disorders are very common. They are among the main causes of disability due to disease, and the World Health Organization (WHO) estimates that they will be the second most important cause of disability by the year 2020 (World Health Organization, 2002). Chronic depressive episodes are common and are associated with greater illness burden and socioeconomic disadvantage (Gilmer et al., 2005). Throughout Europe, 25% of years of healthy life is lost due to brain disorders; they cause approximately one-third of all burden of disease (Olesen and Leonardi, 2003). Among these disorders, depression plays a predominant role. In Europe depression is the major cause of disability, with a prevalence of around 5% per year (Paykel et al., 2005), a still present widespread underrecognition and undertreatment of depressive disorders has been reported recently (Lecrubier, 2007). Epidemiological studies of depression show considerable variation across and within countries (see Figure 1), to a large extent on account of imperfect assessment instruments. One recent estimate put prevalence at 16% (Ebmeier et al., 2006). In a study carried out by the International Consortium of Psychiatric Epidemiology (ICPE), 37000 adults in 10 countries (in the Americas, Europe and Asia) were interviewed with the WMH-CIDI (World Health Organization Composite International Diagnostic Interview; Kessler et al., 2003; Robins et al., 1988; Wittchen, 1994). The lifetime prevalence of depression varied widely from 3% in Japan to 16.9% in the US, with most countries in the range between 8% and 12% (Andrade et al., 2003). Across the Asia-Pacific region, lifetime rates ranged from 1.1 to 19.9% (Chiu, 2004). In an extended WHO household survey with the WMH-CIDI of more than 60000 adults in 14 countries (Americas, Europe, Middle East, Africa and Asia), the 12-month prevalence of mood disorders ranged from 0.8% (Nigeria) to 9.6% (US) (Demyttenaere et al., 2004). A South American study that focused not on the diagnosis of depression but on depressive symptoms found prevalence rates up to 72.6% (Rodriguez and Puerta, 1997). The prevalence of depression in Venezuela is reported to vary between different parts of the country. Only 1 out of 10 depressed patients receives care and treatment. Similar numbers hold true for Mexico. With a lifetime prevalence of 9.1% for affective disorders, there is a wide variance between urban and rural areas. However, use of services for any psychiatric disorder is low: 11.7% for those with one psychiatric diagnosis and 19.4% for those with two diagnoses (Medina-Mora et al., 2003).

These results and the ICPE study demonstrate the potential impact of psychosocial and cultural factors on the manifestation and diagnosis of depression as well as the methodological difficulties of studies of depression. The European Study of the Epidemiology of Mental Disorders (ESEMEd), which used methods similar to those of the WHO study, found a 12-month prevalence rate of 4.2% for mood disorders across six European nations, comparable to the results of the WHO study (Alonso et al., 2004) and to earlier WHO estimates of the prevalence of depression (Sartorius et al., 1993; Sartorius, 1993). Other publications describing the prevalence of depression in northern Africa are currently in preparation.

The low rates in Nigeria, however, might be explained by the fact that most diagnostic criteria for depression and the scales used in developed countries may be not appropriate for assessing functional impairment in rural African communities, and that many features of depression, e.g. fatigue, could be misinterpreted as signs of HIV infection. Another possible explanation may be that depression occurs at a later age in Africa (Gureje et al., 2007). The Nigerian survey sample had a mean age of onset of about 30 years, but
the median age of onset of major depressive disorder in the sample was about 45 years. In other words, most of the respondents had lived through the mean age of onset. Another survey among the elderly in Nigeria confirms a much later age of onset (compared with what is commonly reported in the literature) and yields a much higher prevalence of depression. Correcting for these confounders by using appropriate scales and symptom criteria, Bolton et al. found the point prevalence as high as 21% for depression in Uganda (Bolton et al., 2004).

The fact that older prevalence studies reported lower prevalence rates in comparison to newer studies has been reported early: The lowest figures in studies performed between 1961 and 1978 are at least 9 times greater than the highest figures in surveys between 1931 and 1961 (Hoenig, 1980). Because the second period corresponds with the introduction of antidepressants, it could be argued that the presence of effective treatments may enhance the awareness for now better treatable diseases. But in addition the postulated increasing prevalence or changing diagnostic systems including a higher sensitivity for depressive disorders may serve as an explanation.

The average age of onset is reported to be between 20 and 30 years (Ebmeier et al., 2006). Marked gender differences have been reported; women are affected twice as often as men (Kessler, 2003). In addition, women are twice as likely as men to report a positive family history of mood disorder, which is associated with a younger age of onset of depression (Nierenberg et al., 2007). In addition not only the prevalence but also the consequences of depressive disorders, such as impairment and suicidality, are affected by age and gender of patients (see also chapter 10). The mean duration of depressive episodes was 16 weeks. About 90% of patients are suffering from at least moderate up to very severe forms of depression, causing severe impairment in their daily activities (Kessler et al., 2003).

The particular health importance of depression is further heightened by the prediction that the prevalence of depressive disorder will increase in the years to come (Sartorius, 2001). The rationale for this prediction includes demographic factors (e.g. increased life expectancy at all ages), better chances of survival of people with chronic diseases often comorbid with depression, iatrogenic effects (e.g. because the widespread use of drugs is likely to increase rates of depression), passive risks inherent in social changes (such as diminishing family care and increased numbers of people living alone) and rising levels of stress observable in many countries. While depressive disorders in most, but not all studies appear to be within the same range worldwide (2–7%), estimates of rates of suicide attempts and completed suicides vary greatly among countries. The recent increases in suicide rates in eastern European countries are a particularly good example of the impact of changes in society on rates of suicide (Sartorius, 1995).

6. Standards of care

According to WHO, fewer than 25% (in some countries less than 10%) of depressed patients receive adequate care:

Barriers to effective care include the lack of resources, lack of trained providers, and the social stigma associated with mental disorders, including depression.

Primary care-based quality improvement programs for depression have been shown to improve the

- quality of care
- satisfaction with care
- health outcomes
- functioning
- economic productivity
- and household wealth at a reasonable cost.

(World Health Organization, 2005b).

To achieve these goals, as put forward by WHO, education of the population and those who deliver health care is crucial to increase the number of patients being diagnosed correctly and early. When a diagnosis
of depression has been established, patients and caregivers should gain unrestricted access to mental health and complementary services. Even in highly industrialized countries, there is a large gap between the relatively high prevalence of depressive disorders and the less frequent use and late onset of the use of antidepressant treatments (Henkel and Möller, 2005). In the case of treatment-resistant depressive disorders, further enhancement of therapeutic approaches should be provided as well (see also chapter 9.1.12) to attain the ultimate treatment goal of full remission.

Unfortunately, these standards are realized for only a minority of patients. On a global scale, the primary diagnosis is more often made and treatment supplied by other resources, e.g. traditional healers.

6.1 Diagnosis

In comparing recommendations and clinical practice in different countries, there seems to be no general consensus on who should establish the diagnosis of depression. Whereas most European guidelines, including the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines (Bauer et al., 2002c), explicitly or implicitly refer to a trained psychiatrist for establishing a diagnosis of depression, several review papers by US experts acknowledge a role for primary care physicians in establishing diagnosis and initiating initial treatment. In the US, a majority of patients suffering from depressive disorders are diagnosed and treated by general practitioners or well-trained clinical psychologists. The screening instruments for GPs therefore should include a screening for the main core symptoms of depression (see chapter 5.1). Other countries take a different approach, e.g. China, where most depressed patients are treated by psychiatrists and in some extend by neurologists and internal specialists, or some South-East Asian, e.g. Philippines, and South American countries, e.g. Bolivia, where traditional healers play a prominent role (Seguin, 1986). Their contribution to the management of depression should not be underestimated, as non-specific aspects, including beliefs and trust, are important variables for any treatment success (Alarcon et al., 1999; Shepherd and Sartorius, 1989).

Nevertheless, psychiatric consultation is recommended when a patient has not shown marked improvement within 8 weeks of initial treatment or when the primary care physician is concerned about the complexity of the case (Wittchen and Pittrow, 2002), and also when collaboration between psychiatrists and clinical psychologists is needed. In some countries guidelines recommend also shorter intervals, e.g. 6 weeks in China. Aside from considerations of cost-effectiveness, the main argument is that the primary care physician is generally in a better position to diagnose and treat depression if he or she is responsible for the overall medical care of the patient, which may include other ongoing medical diseases and the potential for drug-drug interactions. In addition, patients tend to see the primary care physician first because somatic complaints are part of the depressive syndrome. The important role of primary care physicians is also shown in a German survey (Wittchen and Pittrow, 2002), which found that 10.9% of unselected patients visiting their primary care doctor suffer from depression. However, only 55% of them were recognized by their doctors as having depression, despite the fact that 72% of the primary care physicians participating considered their competence in diagnosing depression to be good.

To study the degree to which primary care physicians recognize depression as a mental health problem, Dutch researchers looked at accuracy of diagnosis and treatment in accordance with clinical guidelines for depression. The researchers found that non-recognition, misdiagnosis and inadequate treatment were not limited to patients with relatively mild and brief depression but were also prominent in patients with persistent depression who consulted their general practitioner 8.2 times on average during the year their depression persisted (Van Os et al., 2006). Standardized training programs are obviously needed and can be helpful in improving management of depression by primary care physicians (Van Os et al., 1999).

Thus, arguments in favor of early consultation with a psychiatrist include the complexity of a differentiated diagnosis and treatment of depressive disorders, including all the considerations mentioned above and – of utmost importance – expertise in assessing the risk of suicide and, in rare cases, homicide.

If health resources are limited, e.g. in developing countries where both psychiatrists and clinical psychologists are often in very short supply, patients should have access to personnel with sufficient knowledge and experience to diagnose depression, e.g. general practitioners or at least trained nurses. If resources allow, identification of the core symptoms of depression should be considered against a checklist, such as the Diagnostic and Statistical Manual of Mental Disorders, 4th revision (DSM-IV) (American Psychiatric Association, 1994), or the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (World Health Organization, 1992), to improve confidence in and reliability of diagnosis of depression. Structured interviews, such as the Structured Clinical Interview...
for DSM-IV (SCID), may be helpful tools, especially if in doubt. Due to the time-consuming nature of the SCID in primary care settings, the shorter Mini International Neuropsychiatric Interview (MINI) can help to generate reliable DSM-IV and ICD-10 diagnoses. Note, however, that though such instruments may be very sensitive, their validity could be low. In non-specialist settings, the value of routine administration of simple questionnaires to detect and measure depression remains unclear. A review by Gilbody et al. found it unreliable in the majority of studies (Gilbody et al., 2003b). In contrast, the US Preventive Services Task Force (US Preventive Services Task Force, 2002) and the Canadian Task Force on Preventive Health Care (MacMillan et al., 2005) report on good evidence that screening instruments improve accurate identification of depression in adults in primary care settings, although evidence for children and adolescents is insufficient. Of the multitude of screening instruments available, the PRIME-MD Patient Health Questionnaire (PHQ-9) is considered the best available screening tool for depression in primary care (Nease and Maloin, 2003).

Comorbidity, especially with anxiety disorders or substance abuse, may often mask the underlying depressive illness. On the other hand, after establishing the diagnosis of depression, patients should routinely be interviewed for other major psychiatric disorders, as their presence will impact the choice of treatment. Organic conditions such as neurological illnesses, e.g. multiple sclerosis or any other lesions involving subcortical or cortical areas and other limbic circuits, should always be excluded.

However, when discussing the potential under-diagnosis of depression, someone should also be aware of the caveat of overdiagnosing. As demonstrated by Beck (Beck, 1967) in a sample of 486 probands, ranging from non depressed controls to severely depressed patients, there is still a fair amount of clinical features of depression even in normal controls (see Table 8). With increasing public and specialist awareness of depression, strict diagnostic criteria should be followed, the diagnosis should not be based on one or few features, and the diagnosis should be regularly rechecked to avoid overdiagnosis and at least unnecessary, if not harmful, treatment.

Once a diagnosis of major (unipolar) depression has been established, keeping all potential caveats in mind, the level of symptom severity, functional impairment and impact on quality of life should be determined. If possible, this should be done not only on the basis of patients’ reports but also on the basis of the history supplied by relatives and objective data, e.g.

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**Table 8. Frequency of Clinical features of patients varying in depth of depression, based on a sample of n = 486 probands (adapted from Beck, 1967)**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>None (%)</th>
<th>Mild (%)</th>
<th>Moderate (%)</th>
<th>Severe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sad facies</td>
<td>18</td>
<td>72</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>Stooped posture</td>
<td>6</td>
<td>32</td>
<td>70</td>
<td>87</td>
</tr>
<tr>
<td>Crying in interview</td>
<td>3</td>
<td>11</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Speech: slow, etc.</td>
<td>25</td>
<td>53</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>Low mood</td>
<td>16</td>
<td>72</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Diurnal variation of mood</td>
<td>6</td>
<td>13</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Suicidal wishes</td>
<td>13</td>
<td>47</td>
<td>73</td>
<td>94</td>
</tr>
<tr>
<td>Indecisiveness</td>
<td>18</td>
<td>42</td>
<td>68</td>
<td>83</td>
</tr>
<tr>
<td>Hopelessness</td>
<td>14</td>
<td>58</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>Feeling inadequate</td>
<td>25</td>
<td>56</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>Conscious guilt</td>
<td>27</td>
<td>46</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>Loss of interest</td>
<td>14</td>
<td>56</td>
<td>83</td>
<td>92</td>
</tr>
<tr>
<td>Loss of motivation</td>
<td>23</td>
<td>54</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Fatigability</td>
<td>39</td>
<td>62</td>
<td>89</td>
<td>84</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>31</td>
<td>55</td>
<td>73</td>
<td>88</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>17</td>
<td>33</td>
<td>61</td>
<td>88</td>
</tr>
<tr>
<td>Constipation</td>
<td>19</td>
<td>26</td>
<td>38</td>
<td>52</td>
</tr>
</tbody>
</table>

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recent periods on sick leave. To characterize the depressive syndrome as well as to choose the appropriate treatment and treatment setting, any psychotic symptoms and – most important – suicidal thoughts or plans must be assessed at the first visit. Especially suicidality, the outstanding threat of depressive disorders, determines the further treatment plan, since in some instances it may be necessary to hospitalize a patient against his or her will. Given that more than 10% of depressed patients commit suicide (Angst et al., 2005; for patients who received no inpatient psychiatric treatment, lower rates have been reported (Simon and Von Korff, 1998)), acute suicidality constitutes a medical emergency that calls for immediate and consequent action. In addition it is essential to optimize the awareness of suicidal ideations and attempts. Predictors of elevated suicide risk include greater severity of depression, suicidal ideation, hopelessness, unemployment, comorbid psychotic disorder, substance abuse, personality disorder, a family history of mental disorders, history of attempted suicide, male gender, or being widowed or divorced (Brown et al., 2000; Moscicki, 1999). Thus, it is crucial to be aware of the patients’ history and evaluate signs of suicidality, e.g. hopelessness (Goldston et al., 2006; Sinclair et al., 2005), on a regular basis.
To obtain a full clinical picture prior to treatment, patients and, if available, relatives should be interviewed about previous illness and treatment history, and other concurrent psychiatric and somatic disorders, including non-psychiatric medication. Because psychosocial stress factors may both contribute to the onset of a depressive episode and interfere with treatment success, recent life events should be documented and may lead to early psychotherapeutic intervention in addition to medication.

Especially for patients who do not respond to treatment, diagnosis should be rechecked regularly for correctness. Treatment success could, for example, be confounded by ongoing substance abuse or underlying personality disorder. In addition, because in most cases bipolar disorder first manifests with a depressive episode, patients and relatives should be questioned for emerging (hypo)manic symptoms both at the initial taking of the patient’s history and also during treatment. Emergence of (hypo)manic symptoms usually leads to changes in treatment plans, e.g., discontinuing antidepressants and switching to mood stabilizers.

6.2 Access to mental health services

The following principles of access to services are adapted from the British Association for Psychopharmacology (BAP) guidelines for treating bipolar disorder (Goodwin, 2003) but also apply to unipolar depression (see Box 2).

Whether diagnosis and treatment initiation should be done by a primary care physician, a health professional or a trained psychiatrist has been discussed above. While WHO has recommended general practitioners and World Psychiatric Association (WPA) psychiatrists as primary care suppliers, CINP currently has no position of its own. With respect to easy access to a trained psychiatrist, including the possibility of direct hospital admission, health and insurance policies in different countries may not yet reflect this standard; elsewhere, a lack of resources makes it difficult. Nevertheless, considering the consequences of inadequate diagnosis and treatment (including treatment settings) for prolonged illness, chronicity and finally potential suicide, measures must be taken to ensure these standards worldwide.

6.3 Enhanced care

Guidelines (e.g. APA (American Psychiatric Association, 2000), WFSBP (Bauer et al., 2002c; Bauer et al., 2002b)) embody a uniform consensus that, independent of the choice of the specific medical treatment intervention, general components of psychiatric management and psychotherapeutic support should be initiated and continued throughout the entire treatment (Bauer et al., 2002c). As a first step, a therapeutic alliance must be established. This includes the psychiatrist or physician taking full responsibility for diagnosis, physical examination, other investigations and explanation of the medical plan of management to the patient and his relatives. The therapist should take his time to listen to the patient’s complaints and always communicate clearly, understandably and honestly what he thinks. He should determine together with the patient a treatment plan and the appropriate treatment setting, and, for outpatients, ensure regular visits. During acute phase treatment, weekly or biweekly visits are recommended (Bauer et al., 2002c); during the continuation phase and after syndromal recovery, a frequency of one visit per month appears to be adequate (Bauer et al., 2002c). In the case of concurrent psychotherapy supplied by a psychotherapist, frequent communication between the physician and therapist about the patient’s status should be ensured. In addition, a good communication between the treating psychiatrist and the GP about the patients general health status and the recommended laboratory controls during antidepressant treatment is essential.
Box 3 presents an example for enhanced care adapted from Goodwin et al. (Goodwin, 2003). Other aspects of enhanced care, e.g. therapeutic drug monitoring, will be addressed more specifically in the next chapter (see also chapter 9.1.1.1.3).

In primary care settings, integrated quality improvement strategies involving combinations of clinician and patient education, nurse case management, enhanced support from specialist psychiatric services and monitoring of drug concordance have been shown to be clinically and cost-effective in the short term, but this effect disappears in longer-term follow-up. However, simple and relatively cheap telephone support, counselling and medication monitoring delivered by counsellors or nurse practitioners are clinically effective and likely to be cost effective (Gilbody et al., 2003a; Gilbody et al., 2003b).

7. Goals of treatment: response, remission, recovery

Traditionally, treatment is divided into acute, continuation and maintenance (prophylactic) phases (Kupfer, 2005) (see Figure 2).

Clinical trials focus on symptomatic relief measured by specific scales, e.g. the HAMD score (Hamilton, 1967), and define response and remission in relation to these scores (usually 50% reduction of the baseline score as ‘response’ and a specific cut-off as ‘remission’, see Box 4). It should be kept in mind that remission as defined in clinical trials does not necessarily correspond to remission in clinical terms.

Box 3. Principles of enhanced care (adapted and modified according to Goodwin, 2003)

- Educate yourself and then the patient and his relatives about the disorder.
- Ensure that you are always up to date regarding the latest developments in diagnosis and treatment through continuing medical education.
- Try to base the treatment decision on evidence and not on beliefs.
- Use the evidence also to address the acute treatment modalities of the illness, the risk of relapse and the benefit of psychotherapeutic engagement to the patient.
- Educate the patient and his relatives about the treatment for the illness to enhance adherence.
- In addition, inform the patient and his relatives about possible side effects of medication and potential symptoms that may question the original diagnosis, e.g. emergence of (hypo)manic symptoms.
- Inform the patient and his relatives that enhanced drive before the onset of antidepressant action in the initial antidepressant treatment phase could lead to increased risk of suicide.
- Make the patient aware of stressors, the impact of sleep disturbance, the importance of regular patterns of activity and early signs of relapse.
- Educate the patient about the poor outcome associated with alcohol and substance abuse and, if required, give appropriate advice and offer treatment.
- Evaluate and manage functional impairment and supply the patient and his family with a realistic view about his capacity to work and function within the family. Identify potential sources of psychosocial support in the community and help the patient to contact them.

Figure 2. Long-term treatment of depression (modified from Kupfer, 1991).

Clearly, clinical management of depression goes far beyond these criteria, which are meant to establish evidence for efficacy of treatment. Although remission is recognized as the optimal outcome of treatment for depression, remission lacks a universally accepted definition (Israel, 2006).

- Goals of clinical management can be divided into acute, intermediate and long-term goals. The ultimate goal of acute treatment is to achieve remission, in other words not only being asymptomatic (in the sense of not meeting the criteria for diagnosis of the disorder and having no or only minimal residual symptoms) but also showing improvement in psychosocial and occupational functioning. The intermediate goal is further stabilization and preventing relapse, eliminating subsyndromal symptoms and restoring the prior level of functioning. The long-term goal is full recovery (Rush et al., 2006a) to prevent further episodes, maintain functioning and ensure a satisfactory quality of life (AHCPR (Agency for Health Care Policy and Research), 1999;
Box 4. Definition of response and remission (Thase, 2003)

- **Response** is defined as the absence of depressive symptoms and a full return to premorbid levels of functioning. In most randomized controlled studies, an absolute rating scale threshold is defined as remission (e.g. HAMD score ≤ 7).
- **Remission** is defined as the nearly complete absence of depressive symptoms (which can be defined as the nearly complete absence of depressive symptoms) should be the goal of the acute phase of pharmacotherapy (Thase and Hirschfeld, 2000). To regain social and occupational functioning therefore is one of the major treatment goals.
- **Full Recovery** is defined as the absence of depressive symptoms and a full return to premorbid levels of functioning. In most randomized controlled studies, an absolute rating scale threshold is defined as remission (e.g. HAMD score ≤ 7).
- **Remission** is defined as the full regain of social and occupational functioning without residual symptoms of depression.

Box 5. Choice of a specific drug

The availability of different antidepressants may vary from country to country (see chapter 14). Among the antidepressants available, proven efficacy must be the first consideration. In the next step, the choice of a specific drug should take into account not only the subtype of depression but also previous experience with antidepressants, especially potential tolerability problems in conjunction with contraindications due to medical comorbidity, and finally the preference of the patient after explaining potential advantages and disadvantages of candidate medications.

- From the patient’s perspective, the most important criteria for remission are the presence of features of positive mental health such as optimism and self-confidence, self-satisfaction and a return to one’s usual, normal self and level of functioning (Zimmerman et al., 2006). Therefore, while the patient is still depressed, the therapist should facilitate the maintenance of social activities and prevent stigmatization. This includes the use of psychotherapeutic and sociotherapeutic approaches.
- Depressive disorders are frequently associated with significant impairments in social functioning due to a long persistence of residual symptoms after remission of depressive symptoms (Fava et al., 2007; Hirschfeld et al., 2000). To regain social and occupational functioning therefore is one of the major treatment goals.
- Depression is associated with marked suffering, morbidity, and a high risk of recurrence and/or chronicity. Treating patients with depression to a state of remission is associated with a significantly improved long-term outcome, including reduced risk of relapse (Ramana et al., 1995; Rush et al., 2006b) and improved functioning. Thus, remission (which can be defined as the nearly complete absence of depressive symptoms) should be the goal of the acute phase of pharmacotherapy (Thase and Ninan, 2002).
- However, an important goal in all phases of the illness is to prevent suicide as the most deleterious, and unfortunately still frequent outcome of depression (Angst et al., 2005), as well as to prevent death from somatic disorders associated with depression, e.g. cardiovascular disease (Angst et al., 2002a).

Optimal clinical effectiveness of the treatment should also include optimized safety and tolerability. Assessing and documenting the achievement of these treatment goals on a regular basis is of utmost importance because it guides further treatment decisions.

7.1 *Acute treatment*

Initiation of antidepressant treatment should be a first step of an overall treatment plan. If antidepressant treatment with medication is the choice, it may be combined with varying degrees of psychosocial intervention ranging from basic psychoeducation to formal augmentation with an empirically supported psychotherapy, if necessary in combination with psychosocial support. The decision which medication to choose depends on several factors (see Box 5).

Depending on the setting (inpatient or outpatient), the medical constitution of the patient and previous experience, the rate of titration may vary considerably. The usual recommendation for outpatients is to start with the lowest effective dose to ensure good tolerability. If no side effects occur or if side effects fade within a few days, further stepwise dosage increases up to the usual standard dose (see Table 11) can be made until relief of symptoms is observed.

Especially when specialist care is not available, e.g. in a general hospital, and ease of use, high tolerability and low drug-drug interaction potential are of importance, the recommended first choice of antidepressant is a selective serotonin reuptake inhibitor (SSRI) or other, newer antidepressant with a favorable side effect profile (Voellinger et al., 2003). Regardless of the drug chosen, during antidepressant pharmacotherapy one must reckon with a delay of several weeks until sufficient antidepressant effects can be seen. Up to now no definite response prediction using

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30 Response and remission are usually measured using instruments such as the Montgomery–Åsberg Depression Rating Scale (MADRS) or the HAMD rating scale. In comparing RCTs, it is important to be aware of the time interval after which response or remission was achieved.
biological variables can be used during an antidepressant pharmacotherapy. Nevertheless behavioral changes such as an early improvement in motor retardation or a reduction of anxiety have been reported to be dependent of the clinical profile of the class of the prescribed antidepressant and may be clinically useful to predict the later treatment response (Katz, 2004). This has also been true in the case of a comparison of the effects of TCA and psychotherapy – whereas Amitriptyline had early effects on vegetative symptoms of depression psychotherapy showed more delayed effects on mood, suicidal ideation, work, and interests (DiMascio et al., 1979). In addition also an overall early onset of improvement has been shown to be highly predictive of later outcome (Stassen et al., 1996, 1997; Stassen and Angst, 1998). An absence of any change (improvement <20%) during the first two weeks of treatment is highly predictive of clinical non-response during the following weeks of treatment (Stassen et al., 1996; Stassen and Angst, 1998). Therefore the prior postulated lag of clinical response to antidepressants has been questioned during the last years due to the fact that an effective antidepressant treatment initiates clinical changes even during the first week of antidepressant treatment (Stassen et al., 1999; Taylor et al., 2006).

If a treatment is not the first medication trial and a patient has previously been on fluoxetine or irreversible monoamine oxidase inhibitors (MAOIs), a washout period of at least 2 weeks (up to 5 weeks in the case of a switch from fluoxetine to irreversible MAOIs) must be observed, especially when treatment with a serotonergic acting drug is planned. Otherwise, serotonin syndrome – a potential lethal complication may, rarely, occur (Boyer and Shannon, 2005; Haddad, 2001). Serotonin syndrome is not specific only to SSRIs but may also occur with other serotonergic acting substances, e.g. venlafaxine in combination with MAOIs (Phillips and Ringo, 1995). When switching to reversible MAOIs, e.g. moclobemide, a few (2–3) days of pausing medication is sufficient (Dingemanse et al., 1995; Dingemanse et al., 1998). For details of MAOI tolerability, see also chapter 9.1.3.2.

On the other hand, sudden discontinuation of antidepressant treatment usually cannot be advised, but the possibility of immediate switching has been proposed (Wohltreich et al., 2005b; Wohltreich et al., 2005a). When switching from one medication to another, overlapping tapering is recommended unless a specific medication, e.g. an irreversible MAOI, requires a washout phase (Larsen, 1988).

Sudden cessation of treatment can lead to discontinuation symptoms (see chapter 9.1.1.3.2), which have been described for numerous classes of antidepressant drugs (particularly common with MAOIs, venlafaxine and SSRIs, especially paroxetine, and less common with fluoxetine and escitalopram) (Baboolal, 2004; Haddad, 1998; Rosenbaum et al., 1998; Schatzberg et al., 2006). The reported frequency of antidepressant discontinuation syndromes varies widely from 10–60% depending on the class of medication and study methodology, with an estimated average of 20% (Warner et al, 2006). A survey of the French pharmacovigilance database revealed that SSRIs are clearly associated with a higher risk of discontinuation syndrome than other antidepressants (OR 5.05, 95% CI 3.81–6.68) and in particular venlafaxine and paroxetine (OR 12.16, 95% CI 6.17–23.35 and OR 8.47, 95% CI 5.63–12.65, respectively) (Trenque et al., 2002). Discontinuation syndrome may also affect newborns of mothers who are taking SSRIs. A database analysis revealed a total of 93 suspected cases of SSRI-induced neonatal discontinuation syndrome. These were regarded as sufficient to suggest a possible causal relation. Sixty-four of the cases were associated with paroxetine, 14 with fluoxetine, 9 with sertraline and 7 with citalopram (Sanz et al., 2005a). It is also worth noting that the novel pharmacological compound agomelatine has not been on the market sufficiently long enough for a final judgement regarding discontinuation symptoms, but the substance was not associated with discontinuation symptoms in one, specially designed, randomized, double blind, placebo-controlled, discontinuation study (Montgomery et al., 2004c). Antidepressant discontinuation syndrome presents as a flu-like syndrome and is to some degree similar to the well-known activation syndrome that can occur when starting a serotonergic drug. Symptoms of discontinuation syndrome include agitation, sleep disturbances, sweating, gastrointestinal discomfort and headache, and may take up to 2 weeks to subside. Symptoms may put the patient at risk for an early relapse (Fava, 2003a; Harvey et al., 2003) and may stress the therapeutic alliance (Garner et al., 1993). Abruptly stopping TCA treatment may put susceptible patients at risk for cholinergic syndrome, especially older patients or patients with pre-existing neurological conditions (Garner et al., 1993). Where there is doubt whether the symptomatology is related to drug discontinuation, reintroducing the previous medication with consequent cessation of symptoms may clarify the issue.

Expectations regarding the potential efficacy of a given treatment differ according to expert reviews and guidelines. For acute treatment, recommendations vary regarding how long the drug of first choice...
should be tested and when to alter treatment depending on time and degree of improvement. All available antidepressants are estimated to produce treatment responses of 50–75% in moderately to severely depressed patients, which means that despite sufficient dosage, 25–50% of patients do not respond sufficiently to the initial treatment selection. However, of those responding, the estimated likelihood that they would have also responded to placebo is 25% to 50%. This has also been outlined by Davis et al.’s meta-analysis, in which, response rates with active drugs, ranged from 45% to 79%, and, with placebo, from 23% to 48%. (Davis et al., 1993). Higher levels of pain and somatization predict a longer time to remission. Higher levels of pain correlates with severity of depression as shown in a Swedish population study (Andersson et al, 1993). Pain especially may be a marker for depression that is more difficult to treat as demonstrated by a secondary analysis of an imipramine/interpersonal psychotherapy combination study (Karp et al., 2005). The investigators of this study concluded that patients with recurrent depression should thus be screened for painful physical symptoms. They also suggest these symptoms may require a more aggressive treatment or the use of dual-mechanism antidepressants, although the usefulness of this approach still needs to be proven.

The decision regarding whether a response is sufficient can be guided by administration of established rating scales. As outlined by Rush and Kupfer (Bauer et al., 2002c; Kupfer and Rush, 1983), non-response would be defined as a $\leq 25\%$ decrease in baseline symptom severity, partial response as a $26–49\%$ decrease and response as a $\geq 50\%$ decrease. According to World Federation of Societies of Biological Psychiatry (WFSBP) guidelines, an acute-phase medication trial should last at least 6 weeks, and 8–10 weeks to define the full extent of symptom reduction (Bauer et al., 2002c). This contrasts with a recommendation from a round-table consensus published by Hirschfeld et al. calling for a switch of antidepressant in the case of non-response after 4 weeks of treatment. Patients remaining as partial responders after 6–8 weeks should receive a dose escalation, followed by augmentation or switching strategies (Hirschfeld et al., 2002; Quitkin et al., 2005).

These recommendations are based, among others, on the findings of Nierenberg et al. (2000) showing that in patients who had not received at least 30% reduction of symptom severity by 4 weeks on fluoxetine, the likelihood of a response at 8 weeks was only about 12–27%. Similarly, Stassen and Angst (1998) reported that in a controlled study comparing moclobemide and fluoxetine, onset of improvement occurred in more than 70% of patients within the first 3 weeks. There was no evidence for pronounced improvement rates thereafter. Also, during mirtazapine and paroxetine treatment early improvement was a highly sensitive predictor of later stable response or remission (Szegedi et al., 2003). By the same token, evidence suggests that older patients especially may take longer to show a full response to antidepressant medication (up to 12 weeks) (Furukawa et al., 2000). To bridge the time until onset of symptomatic improvement and for acute relief of symptoms, e.g. agitation and sleep disturbance, short-term addition of benzodiazepines may be considered, as they have been shown to accelerate response (Furukawa et al., 2000; Furukawa et al., 2001a; Furukawa et al., 2001b; Smith et al., 2002). Bear in mind, however, that depressed patients treated in mental health settings often receive long-term treatment with benzodiazepines, which is inconsistent with guideline recommendations (Clark et al., 2004; Valenstein et al., 2004). Additional augmentation therapies such as sleep deprivation and light therapy may also be considered.

To establish true refractoriness in the case of non-response or suspected insufficient dosage, if available, therapeutic drug monitoring (TDM) may be helpful (see also chapter 9.1.1.1.3). TDM is based on the hypothesis that a well-defined relationship exists between drug plasma concentration and its clinical effects (therapeutic effects, adverse effects and toxicity). This hypothesis is generally well accepted for lithium and for the TCAs nortriptyline, amitriptyline, desipramine and imipramine (Baumann et al., 2005). But results are inconsistent for other tricyclics, SSRIs and several more recently introduced antidepressants, with the exception of venlafaxine (Corruble and Guelfi, 2000). Due to the economic aspects of TDM (measuring plasma levels for a single psychoactive drug, including its metabolites, costs between €20 and €80) (Baumann et al., 2005), TDM should be reserved for cases where a relationship can be demonstrated between serum concentration effectiveness and side effects and in conjunction with a clinical question, e.g. insufficient treatment response, side effects due to overdosing and so on. Moreover, serum level measurements should only be performed under steady-state conditions (at least five half-lives, in most drugs 1 week after a dosage increase or decrease) and when the concentration of a drug is at a minimum (trough level). Several factors may interfere with antidepressant serum concentration, including absorption and excretion of the drug, bioavailability and binding to plasma proteins. These factors determine the plasma half-life of the
drug, e.g. a short (about 2–10 hours) plasma half-life for venlafaxine, trazodone, tranylcypromine and moclobemide, or a very extensive plasma half-life, e.g. 3–15 days, for fluoxetine and its metabolite norfluoxetine.

Several potential pharmacokinetic interactions between antidepressants and other medications are due to common metabolism by cytochrome P-450 (CYP) enzyme isoforms and/or enzyme inhibition (see also chapter 9.1.1.1.2, Table 12). Genetically determined polymorphisms of CYP2D6 and CYP2D19 are of high clinical relevance for antidepressants that are substrates of these enzymes, including tricyclic antidepressants (TCAs), some SSRIs, venlafaxine and mirtazapine. Roughly 5–8% of Caucasians are considered to be poor metabolizers (PM) and 1–7% are ultrarapid metabolizers (UM) (Baumann et al., 2005); the first leads to increased serum levels and the latter to insufficient buildup of serum concentrations. In Asian populations, the PM type may be less prevalent (about 1% among Thai, Chinese and Japanese populations, and up to 4.8% among Indians (Kitada, 2003)). But other enzymes may show variabilities that require further investigation in populations other than Caucasians (Morrison and Levy, 2004).

Concomitant medication processed by the same enzymes influences the metabolic rate of other substances. For example, some SSRIs that inhibit CYP2D6, especially fluoxetine and paroxetine, but also bupropion, may result in clinically significant inhibition with a consequent increase in serum levels of other substrates, e.g. antiarrhythmics, β-receptor antagonists such as propanolol and metoprolol, and opioids, e.g. codeine. Other antidepressants, including imipramine, nefazodone, venlafaxine and reboxetine\(^{31}\), are metabolized by the CYP3A4 pathway; some antidepressants, e.g. norfluoxetine, the metabolite of fluoxetine and fluvoxamine, also show potent inhibition of this enzyme (Baumann et al., 2005). Thus, TDM may also be an important tool in monitoring interactions when augmentation or combination treatments are considered (Baumann et al., 2005).

When the chosen antidepressant treatment is effective and symptomatic remission has been achieved, the usual recommendation is to continue the antidepressant in unchanged dose unless side effects require tapering down. It is also recommended to continue the full dose of acute treatment during the maintenance phase. Frank et al. and Franchini et al. demonstrated that patients on maintenance therapy who received only half the acute phase dose of imipramine or paroxetine, respectively, rather than the full dose showed a significantly higher rate of recurrence (Franchini et al., 1998; Frank et al., 1990). Thus, the frequent clinical practice of reducing dosage for maintenance treatment lacks an evidential base and may increase the patient’s risk of relapse. The situation may be different when full response during acute treatment has already been achieved with low-dose antidepressants; in this case, it may be reasonable to continue treatment in the lower-dose range (Furukawa et al., 2003).

7.2 Continuation and maintenance treatment

Following initial remission from acute depression, continuation treatment should ensure stabilization, prevent early relapses, improve further functionality and foster reintegration. It is generally recommended to continue with the effective antidepressant monotherapy or combination treatment for at least another 3–6 months (Hirschfeld, 2000, see also Table 9), but patients with a history of long previous episodes may be candidates for longer continuation phase treatments (Ramana et al., 1995). Although relapse or recurrence may be prevented with long-term pharmacotherapy, this approach is only suited to patients at high risk of relapse or recurrence (Nierenberg et al., 2003). In a prospective 15-month follow-up study in depressed patients strong predictors of subsequent early relapses were residual symptoms. Relapses occurred in 76% (13/17) of patients with residual symptoms and 25% (10/40) of patients without (Ramana et al., 1995). It is thus strongly recommended to continue treatment until all symptoms have totally subsided (Prien, 1990).

However, for patients whose history includes a previous, untreated episode, the individual duration of continuation treatment can be determined by asking about the time elapsed until spontaneous recovery occurred. For example, if a previous untreated episode lasted 9 months, continuation treatment of this episode should now last at least for the same time period. In general, treatment durations of between 6 months and 2 years have been recommended (Burrows, 1992; Burrows et al., 1993).

If a decision for long-term maintenance treatment (prophylaxis against new depressive episodes) has been made, the transition from continuation to prophylaxis is not clear-cut. However, if there is no indication for prophylaxis or if the patient refuses to continue on medication, slow tapering off at the end of continuation is strongly advised. It has been suggested that the tapering phase should last at least 4–6 months (Bauer et al., 2002c).

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\(^{31}\) As of this writing, reboxetine is marketed in Europe but not in the US.
Maintenance treatment is most commonly appropriate for patients with recurring episodes, especially when more than one episode prior to the present one has occurred during the last 5 years or when remission has been difficult to achieve. Other factors that influence the decision in favor of maintenance treatment include the number as well as the severity of previous episodes, the duration of previous symptom-free intervals, and comorbidity with other psychiatric or medical illnesses as well as the presence of suicidal ideation. Combining an antidepressant with lithium may not only improve relapse prevention (Sackeim et al., 2001a) but also be more protective against suicide (Müller-Oerlinghausen et al., 2006). Once a patient has stabilized on the combination, it is unwise to withdraw lithium for at least a year (Bauer et al., 2000; Bschor et al., 2002). However, there are no controlled studies for assessing the optimal length of maintenance treatment in general or how to identify clear predictors for choosing an individual time span. In patients with more than two or three relapses, year-long or sometimes lifelong prophylactic treatment has been recommended, e.g. the WFSBP Guidelines recommend maintenance treatment of 5–10 years in recurrent patients not at special risk. They consider lifelong maintenance in patients at greater risk, e.g. with more severe episodes, and especially when two or three attempts to withdraw medication have been followed by another episode within a year (Bauer et al., 2003).

Risk factors for recurring depression have also been summarized by Nierenberg et al. (Nierenberg et al., 2003) based on evidence from several studies (Doogan and Caillard, 1992; Judd et al., 1998b; Keller, 1999; Keller and Boland, 1998; Kupfer et al., 1992; Montgomery et al., 1988; Nelson, 2006; Ramana et al., 1995; Rush et al., 2006b) (Table 10).

Analysing recent randomized, controlled maintenance studies, Fakra et al found that treatment prevents roughly 50% of the recurrences that occur under placebo, regardless of the duration of the study or the pharmacological nature of the antidepressant drug (Fakra et al, 2006). Of special interest for daily practice, dealing with refractory patients, are the recent

### Table 9. Selected guidelines for duration of antidepressant treatment following acute treatment response (adapted from Geddes et al., 2003 and extended)

<table>
<thead>
<tr>
<th>Recommended duration of continuation after medical management of the acute episode (months)</th>
<th>Number of episodes that would indicate that longer ‘maintenance’ treatment is appropriate</th>
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<tr>
<td><strong>UK Defeat Depression Consensus Statement (Paykel and Priest, 1992)</strong></td>
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<td><strong>US Agency for Health Care Policy and Research (Agency for Health Care Policy and Research, 1993)</strong></td>
<td>4–9</td>
</tr>
<tr>
<td><strong>British Association for Psychopharmacology (Anderson et al., 2000)</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>American Psychiatric Association (American Psychiatric Association, 2000)</strong></td>
<td>4–5</td>
</tr>
<tr>
<td><strong>Korean Guidelines (Lee et al., 2006)</strong></td>
<td>6–12</td>
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</tr>
<tr>
<td><strong>Brazilian Guidelines (Fleck et al., 2003)</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Australian and New Zealand Guidelines (Ellis, 2004)</strong></td>
<td>12</td>
</tr>
</tbody>
</table>

Maintenance treatment is most commonly appropriate for patients with recurring episodes, especially when more than one episode prior to the present one has occurred during the last 5 years or when remission has been difficult to achieve. Other factors that influence the decision in favor of maintenance treatment include the number as well as the severity of previous episodes, the duration of previous symptom-free intervals, and comorbidity with other psychiatric or medical illnesses as well as the presence of suicidal ideation. Combining an antidepressant with lithium may not only improve relapse prevention (Sackeim et al., 2001a) but also be more protective against suicide (Müller-Oerlinghausen et al., 2006). Once a patient has stabilized on the combination, it is unwise to withdraw lithium for at least a year (Bauer et al., 2000; Bschor et al., 2002). However, there are no controlled studies for assessing the optimal length of maintenance treatment in general or how to identify clear predictors for choosing an individual time span. In patients with more than two or three relapses, year-long or sometimes lifelong prophylactic treatment has been recommended, e.g. the WFSBP Guidelines recommend maintenance treatment of 5–10 years in recurrent patients not at special risk. They consider lifelong maintenance in patients at greater risk, e.g. with more severe episodes, and especially when two or three attempts to withdraw medication have been followed by another episode within a year (Bauer et al., 2003).

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findings of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study. With two or more acute treatment trials needed to achieve remission, the probability of a relapse increases: 33.5% after the first treatment step, 47.4% after the second, 42.9% after the third and 50% after the fourth (Rush et al., 2006b).

On the other hand, chances of relapse decrease and prognosis improves depending on the time elapsed since discontinuing medication. The risk of a depressive relapse is 60% on placebo (compared with 29% on antidepressants) after 1 year. For the second and third year, the risk to relapse on both antidepressants and placebo is reduced by 50% compared with the first year (29% for placebo) and may continue to decline (Geddes et al., 2003). Thus, decisions regarding long-term treatment must be made on an individual basis, taking into account the patient's past experience with longer medication-free intervals, if any.

In selected patients, long-term treatment may be not favorable. A literature review by Fava (Fava, 2003a) raised the question whether at least a substantial subgroup of depressed patients may not benefit from maintenance medication and may experience a worsening of the long-term course of the illness. According to Fava, the mechanism of this paradoxical effect may include growing tolerance to antidepressants, onset of resistance upon each challenge with the same antidepressant and withdrawal symptoms on sudden discontinuation of antidepressants, leading to destabilization. Fava speculates that continued drug treatment may initiate biological processes that counteract the initial acute effects of a drug and may result in loss of clinical effectiveness. When drugs are withdrawn abruptly, these processes may operate unopposed at least for some time and increase vulnerability to relapse. Whereas a multitude of clinical studies (e.g., Frank et al, 1990, Robinson et al, 1991, Terra and Montgomery, 1998), including a meta-analysis of long-term treatment (Geddes et al., 2003), clearly support the efficacy of antidepressant maintenance in clinical trial subjects, the role of long-term antidepressant continuation in less severely depressed patients still requires further clarification.

7.3 Managing side effects

This section focuses on general management of side effects. Medication-specific side effects are detailed in the specific sections on patients (see chapters 9.1.2 up to 9.1.11).

Patients' complaints about side effects of medications should always been taken seriously to forestall non-adherence and uncontrolled discontinuation. But patients do not always report side effects spontaneously, so active probing is recommended. Therapists must be familiar with drug side-effect profiles.

7.3.1 Frequency of the occurrence of side effects

Minor side effects are common and are associated with most medication trials. They differ depending on the class of drug, e.g., SSRIs may produce more agitation, anxiety, diarrhea, insomnia, nausea and vomiting, whereas TCAs produce more dry mouth, dizziness and constipation. A meta-analysis of Trindade reports on an equal number of side effects in controlled studies comparing SSRIs and TCAs, though different in their nature (Trindade et al., 1998). However, more recent metaanalyses express a tendency for a better overall tolerability of newer antidepressants when compared with older one's (Anderson, 2000; Anderson, 1998; Peretti et al., 2000; Wilson and Mottram, 2004), also reflected by a slightly higher adherence to SSRIs in controlled studies (Anderson, 2000; Anderson, 1998; Peretti et al., 2000; Wilson and Mottram, 2004). The patient interview must clarify whether somatic symptoms are true side effects or part of the depressive syndrome. For patients taking SSRIs, symptoms may also be due to an activation syndrome including restless and agitation or to unreported discontinuation (Fava, 2006).

7.3.2 Consequences for treatment

If side effects are tolerable and the patient is responding either completely or at least partially and is willing to continue with a drug despite side effects, careful tapering of the medication is a reasonable first step. If side effects are already occurring at unusually low

<table>
<thead>
<tr>
<th>Table 10. Risk factors that influence the probability of recurrence of a depressive episode (modified from Nierenberg et al., 2003)</th>
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<tbody>
<tr>
<td>Risk factors for depressive recurrence</td>
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<tr>
<td>Residual symptoms</td>
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<tr>
<td>More than three prior depressive episodes</td>
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<tr>
<td>Chronic depression (episode ≥ 2 years)</td>
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<tr>
<td>Family history of mood disorders</td>
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<tr>
<td>Comorbidities (e.g. anxiety disorder, substance abuse)</td>
</tr>
<tr>
<td>Late onset (age &gt; 60 years)</td>
</tr>
<tr>
<td>Two or more acute medication trials to achieve remission</td>
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</tbody>
</table>
doses, TDM and potential identification of a poor metabolizer status may be helpful (Baumann et al., 2005). If, after tapering medication, side effects do not subside or efficacy is lost, switching drugs with slow tapering off, stopping and then titration of a new antidepressant is advised. In general, SSRIs and mixed serotonergic/noradrenergic antidepressants have a more favorable side-effect profile than older TCAs or irreversible MAOIs (Preskorn, 1995, Kahn and Halbreich, 2005). But newer antidepressants may also not be as well tolerated as generally assumed, and an activation syndrome, observed especially with SSRIs, may have implications for their use, e.g. in adolescents (see chapter 10.2.1.5). The frequency of these side effects may be underestimated because clinical trials often only disclose spontaneously reported side effects, and in natural settings they may be much more common. In the context of managing side effects, psycho-education of the patient plays an essential role. Experience of side effects is less frightening if the patient is aware about their possibility, especially when they may subside after some days, e.g. increased sleepiness. Informed patients may be more likely to tolerate a drug and to stay on it.

When side effects are severe, stopping an antidepressant and restarting with another is advised, provided the patient is willing.

8 Mechanisms of action and future directions in the development of antidepressants

8.1 The development of antidepressants based on the monoamine hypothesis of depression

Following the accidental discovery of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) some 50 years ago (Slattery et al., 2004), the use of opium and some former alternatives (e.g. dinitrile succinate, hematoporphyrin, reserpine) in the treatment of depression was fortunately promptly abandoned (Ban, 2001). Further information on the development of psychopharmacology can be seen in a CINP monograph (Ban et al, 1998). The pharmaceutical industry has developed numerous antidepressants that had similar therapeutic and adverse side effects. In the process, the mechanisms underlying the actions of effective drugs have been defined. These relate to blocking the re-uptake of transmitters, reducing their enzymatic break down or acting pre-synaptically to prolong their release. The observation that imipramine reduced the transport of tritiated noradrenaline and serotonin into rat brain slices in vitro, whereas iproniazid, the first clinically effective MAOI, inhibited the intraneuronal metabolism of these biogenic amines, gave support to the emerging monoamine hypothesis of depression (Ban, 2001). However, despite the refinement of the pharmacology of antidepressants, which led to the synthesis of drugs that were highly selective in blocking either the reuptake of noradrenaline (noradrenaline reuptake inhibitors, NRIs, as exemplified by maprotiline and reboxetine) or serotonin (selective serotonin reuptake inhibitors, SSRIs, as exemplified by fluoxetine) (Brunello et al., 2002; Nutt, 2002), it soon became apparent that not all antidepressants blocked the monoamine transporters. Indeed, mianserin, a tetracyclic compound, was the first effective antidepressant to act on neither monoamine transporters nor on monoamine oxidase (Tatsumi et al., 1997). Later it was found that mianserin had a unique mode of action in that it increased the release of noradrenaline by blocking the presynaptic, inhibitory, \( \alpha_2 \)-adrenoceptors. As these receptors, on stimulation by intersynaptic noradrenaline, normally reduce the influx of calcium ions and thereby reduce the calcium-dependent release of noradrenaline, drugs that specifically block the presynaptic \( \alpha_2 \)-adrenoceptors would be expected to increase the intraneuronal concentration of calcium and thereby increase noradrenaline release. This is how mianserin was thought to act. More recently mirtazapine, a structural relative of mianserin, has been developed, which combines enhanced release of noradrenaline with increased release of serotonin, leading to enhanced activation of postsynaptic 5-HT_{1A} receptors and an antagonism of 5-HT_{3} and 5-HT_{4} receptors (Haddjeri et al., 1998). Thus, a slight modification of the tetracyclic structure of mianserin has led to the development of a dual-action antidepressant that lacks the gastrointestinal and neurological side effects of the SSRIs, adverse effects that are the result of activation of serotonin receptors (5-HT_{1C}, 5-HT_{3}) in the gastrointestinal tract and on blood vessel walls. Also pharmacotherapies for depression with dopaminergic activity predominantly developed as antipsychotic agents have shown efficacy in the treatment of depression (Amore and Jori, 2001; Papakostas, 2006).

Moreover the positive influence of antidepressants on monoamine neurotransmitter systems is not limited to the treatment of depressive disorders. Therapeutic effects are also observed in the treatment of anxiety disorders such as panic disorder or generalized anxiety disorders (Kahn et al, 1979) leading to the hypothesis that influence on specific neurotransmitters may influence the regulation of behavior...
and moods such as impulsive aggression (Linnoila et al., 1983) independently of disease categories (for review see Morilak and Frazer, 2005).

It is interesting to note that following 2 decades of emphasizing the specificity of action of antidepressants on noradrenaline, serotonin or even dopamine (e.g. bupropion), there is now a renewed interest in antidepressants with dual action, in other words, tricyclic-like antidepressants that lack cardio- toxicity and other adverse side effects. Venlafaxine and to a far lesser extent duloxetine are examples of monoamine reuptake inhibitors that, at normal therapeutic doses, show a greater potency in inhibiting serotonin rather than noradrenaline reuptake, whereas milnacipran is more selective in inhibiting noradrenaline reuptake at normal doses. These dual-action antidepressants (Briley, 1998) enhance both noradrenaline and serotonin. While venlafaxine exerts its dual action at higher therapeutic doses, both duloxetine and mirtazapine do so across the therapeutic dose range (Briley, 1998).

Recent developments also show differences between different subtypes of SSRIs. For example, escitalopram, which binds to both the primary binding site and to the allosteric site on the serotonin transporter, seems to be different from other SSRIs (Chen et al., 2005; Sanchez et al., 2004; Thase, 2006).

Despite the plethora of different types of antidepressants that have been marketed over the past 30 years (Table 11) (for review see Richelson, 2001), the main advance has been made not in terms of efficacy but safety. Modern antidepressants are no more effective than the first tricyclics, such as imipramine or amitriptyline.

While it is generally assumed that all effective antidepressants enhance monoaminergic function in some way, their common mode of action remains an enigma. It has long been realized that there is a disparity between the qualitative and quantitative effects of these drugs on monoamine transport and the onset of their therapeutic action (Nestler, 1998). In addition to the delay in onset of therapeutic action, acute depletion of tryptophan from the diet, an event that significantly decreases the concentration of brain serotonin, results in either no effect or a mild dysphoria in healthy volunteers and does not affect the mood state of untreated depressed patients (Delgado, 2004; Nestler, 1998). Nevertheless, tryptophan depletion is able to acutely reverse therapeutic action in long-term SSRI treatment and to cause acute relapse in recovered unmedicated patients who have responded to SSRIs (Bell et al., 2001; Delgado et al., 1999; Smith et al., 1997). These effects show that in vulnerable individuals, acute lowering of 5HT function can contribute to depressive states.

The discovery that chronic antidepressant treatment produces adaptive changes in postsynaptic β-adrenoceptors that approximately correlated with the onset of the antidepressant effect (Sulser et al., 1978) stimulated new ideas regarding the mode of action of antidepressants by directing research away from presynaptic to postsynaptic events. It soon became apparent that the changes in postsynaptic monoamine receptors were coupled to changes in intracellular signal transduction molecules. This stimulated research into the effects of chronic antidepressants on neuropeptides, neurotrophic factors and intracellular signaling molecules (Manji et al., 2001; Wong and Licinio, 2004). A variety of recent studies support the hypothesis that possibly a decreased expression of brain-derived neurotrophic factor (BDNF) contributes to the development of depressive disorders and that upregulation of BDNF plays a role in the action of antidepressant treatments (Duman and Monteggia, 2006).

Thus, the monoamine hypothesis of depression, and the explanation of how antidepressants work, has gradually evolved into a molecular hypothesis. This hypothesis is based on the view that adverse environmental factors, such as stress, acting on a genetic vulnerability, cause maladaptive changes in a range of neurotransmitters among which the monoamines are presumed to play a significant role. Effective antidepressant treatments normalize the disturbed neurotransmitter networks that are assumed to be responsible for the clinical features of depression (Castren, 2005). The monoamine hypothesis has stimulated the search for genes that are altered in depression or by chronic application of antidepressants in the hope that the molecules encoded by these genes could provide targets for novel types of antidepressants (Knuuttila et al., 2004; Wong and Licinio, 2004).

In spite of the rapidly increasing knowledge about antidepressants up to now there is no established relationship between the pharmacological profile of antidepressants and their therapeutic effects.

### 8.2 Developments leading to new understanding of the mechanism of action of antidepressants

Despite the advances that have been made in the treatment of depression over the past 50 years, a number of major problems remain. These include a lack of response or only a partial response to treatment by a substantial proportion of patients. In addition, the
diagnosis of depression, and the different types of depression, is dependent on the symptoms; these are frequently complicated by comorbidity with other psychiatric disorders. Clearly, the development of specific diagnostic tests for depression would be a major advantage, but to date, no such tests have been reliably devised. It would also be a help if there were reliable animal models of depression, but again, those that are available have been of limited value for detecting novel compounds or in elucidating the mechanisms whereby antidepressants work. Most animal models of depression rely on stress-induced abnormalities in behavior and in the subsequent changes in neuroendocrine and neurotransmitter (mainly monoamine) function.

In the past, animal models of depression have largely been based on acute observations of the effects of drugs that either reduce the functional activity of brain monoamines that are assumed to be responsible for the symptoms of depression (for example, reserpine) or that reverse the behaviors that simulate some of the symptoms of depression (for example, learned helplessness induced by unavoidable foot-shock). While such models have been useful in the development of new antidepressants that largely resemble those already available, they have been less successful in identifying novel agents. This situation has stimulated research into models (in rats) that not only exhibit behavioral changes that may be relevant to depression (anhedonia, decreased libido, changes in locomotor activity and in the sleep profile, cognitive and memory deficits) but also in neurotransmitter function (particularly in the monoamines), in the hypothalamic-pituitary-adrenal (HPA) axis and in the immune axis. A relevant animal model should fulfill at least 3 criteria, namely predictive validity (an ability to detect all treatments that are therapeutically effective), face validity (an ability to produce behavioral changes that are similar to those seen in depressed patients) and construct validity (by exhibiting psychobiological changes that may underlie depression). While several rodent models of depression fulfill the first two criteria, it is more difficult to validate the third criterion until the precise causes of depression are known. Nevertheless, the olfactory bulbectomised rat model and the gestational stress models probably fulfill these criteria better than others.

The olfactory bulbectomised rat (OBX) model is now widely accepted as a model that bears similarities to the agitated form of depression (Harkin et al., 2006; Jesberger and Richardson, 1988; Leonard and Song, 2002; Willner, 1990). Thus surgical removal of the olfactory bulbs results in changes in the behavioural, endocrine, immune and neurotransmitter systems that are largely reversed by chronic, but not acute, antidepressant treatment, including electroconvulsive seizures (ECS) (Leonard and Song, 2002; Zhou et al., 1998).

Dysfunction of the brain serotonergic system has been shown to relate to the mood changes in depression and bipolar disorder (Spoont, 1992) and there is evidence that the changes in serotonin are widespread and linked to the depression-like behaviour in the OBX model (Hasegawa et al., 2005; Watanabe et al., 2006). The OBX model has been shown to be particularly suitable for studying the complex relationships between the brain, behaviour, the neuroendocrine and immune systems, in addition to detecting putative antidepressants that do not act primarily on brain monoamine systems (Breivik et al., 2006).

The gestational stress (GS) model is based on the observation that pre-natal stress, in both animals and humans, as associated with an increased risk of depression in later life (Huizink et al., 2004). Such changes are associated with an increased incidence of depression and anxiety particularly in female offspring (Weinstock, 2007).

When pregnant rats undergo daily restraint stress for one week during the mid-gestational period, the offspring show increased immobility in a stressful environment (such as the open field apparatus) and in the forced swim test, a test that simulates learned helplessness and depressed mood. This suggests that rats stress in utero display depressive-like behaviours post partum, changes that are reduced by chronic antidepressant treatment.

Despite the limitations of these rodent models of depression, they have been beneficial in providing possible links between the main symptoms of depression and changes in monoamines, endocrine and immune systems (Leonard and Song, 1999). As these models, like depressed patients, only respond effectively to chronically administered antidepressants, they also give some insight into the possible mechanisms of action of these drugs.

Recent reports describe alterations in the expression of numerous genes, notably those coding for neurotrophic factors such as BDNF and nerve growth factor (NGF) (Alfonso et al., 2006) as well as structural modifications in the areas of the brain related to mood disorders in such animal models submitted to those paradigms. This has led to depression research being focused on the hippocampus, amygdala, cortex and related neuronal circuits (LeDoux, 2000). The importance of these regions in the pathophysiology of depression has gained support from brain-imaging.
Effective antidepressant treatments have also identified the importance of these brain regions (Tamminga et al., 2002).

Clearly, the application of neuroscience to understanding brain function and psychopathology has resulted in novel insights into the psychobiology and biological subtypes of depression (Hasler et al., 2004), and possibly how antidepressants work. This raises the question, ‘Is mood chemistry?’, the subject of an important review by Castren (Castren, 2005). This new concept suggests that depression results from a malfunction of neuronal networks and that antidepressants work by improving information processing in the affected networks. At the basis of such disordered networks lies a failure of neuroplasticity. Thus, some antidepressants seem to increase the development of new neurons in the hippocampus (Malberg et al., 2000). This increase in neurogenesis in the hippocampus associated with long-term antidepressant treatment correlates with behavioral changes caused by chronic antidepressant treatments in animal models of depression (Santarelli et al., 2003). Note that numerous alterations other than a decrease in the rate of neurogenesis or in neuronal turnover in the hippocampus have been reported in depression, such as modifications in neuronal architecture. Very few publications have reported the effect of antidepressants on them.

Such observations are particularly pertinent to the mode of action of antidepressants, as for the first time, a cellular explanation has been proposed that identifies a possible reason for the delay in onset of response to treatment independent of the nature of that treatment. This hypothesis has led to the further observation that elimination of neurons through apoptotic cell death increases simultaneously with increased neurogenesis, events that are linked to antidepressant-induced increases in neurotrophic factors such as BDNF. It may be hypothesized that, in the hippocampus, antidepressants increase neuronal turnover rather than neurogenesis per se (Sairanen et al., 2005).

What are the implications of such findings for the development of future antidepressants? Clearly, the conventional approach whereby specific monoamine neurotransmitters are targeted must be reconsidered. It can be argued that such an approach has failed to bring about any major benefits to the depressed patient in terms of therapeutic efficacy. Further targets, while they may include monoamine receptors such as the 5-HT_{1A}, 5-HT_{2C}, 5-HT_{4}, and 5-HT_{1B} (Pauwels, 2000), have certainly produced some potentially interesting possibilities in rodent models of depression, but so far they have not yet been validated clinically. There is evidence that 5-HT_{1A} and 5-HT_{1B/D} antagonists augment the antidepressant response, but the clinical evidence that such drugs are effective antidepressants when administered alone is equivocal (Bosker et al., 2004). Similarly, the α_{2}-adrenoceptor has been targeted following the discovery that the tetracyclic antidepressants mianserin and mirtazapine act as antagonists at the pre-synaptic α_{2}-adrenoceptor (Blier, 2001) and block certain 5HT_{2} receptors. Therefore, both drugs influence noradrenergic and serotonergic neurotransmission.

Recently, it was shown that a peptide that is a member^{22} of the S100 protein family interacts with the 5-HT_{1B} receptor; there is experimental evidence that the function of this receptor depends on expression of the p11 peptide (Sanacora et al., 2000). The concentration of the p11 peptide was shown to be low in post-mortem brains from depressed patients. In knockout mice lacking the p11 peptide, depressive-like behavior was noted, whereas overexpression of p11 increases 5-HT_{1B} receptor function in cells and recapitulates behaviors seen after antidepressant treatment. Chronic antidepressant treatments, including electroconvulsive therapy (ECT), increased p11 expression and counteracted the depression-like phenotype (Svenningsson et al., 2006). These results serve to emphasize the potential importance of the 5-HT_{1B} receptor in animal models for depression and suggest that the 5-HT_{1D} receptor, the analogous serotonin receptor in humans, may play a role in antidepressant therapies.

Non-monoamine approaches have included antagonists of tachykinin receptors. The endogenous agonists include the peptide substance P, which is physiologically involved with pain perception, but experimental studies have demonstrated that NK_{1} receptors may function to modulate serotonergic transmission (Santarelli et al., 2001). Antagonists of these receptors would therefore be expected to exert the opposite effect upon serotonergic transmission and

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^{22} S100 is a protein characterized by two calcium binding sites. There are at least 21 different types of S100 proteins in the so-called S100 protein family.
enhance function (Culman et al., 1997). While considerable excitement was generated regarding the antidepressant potential of the first NK1 antagonist to be developed some years ago (Schwarz and Ackenheil, 2002), further clinical studies have proved disappointing. Nevertheless, with three known types of NK receptors, the search continues for antagonists with potential therapeutic properties (Kramer et al., 1998).

Among the amino acid neurotransmitters, attention has been directed to the N-methyl-D-aspartate (NMDA) receptor complex. Experimental findings have shown that most classes of antidepressants decrease the affinity of the glycine site on the NMDA receptor complex (Grundemar and Hakanson, 1994) following chronic antidepressant treatment. This modulation of the NMDA receptor complex may prove to be a novel approach to drug development, as the NMDA antagonist ketamine has been shown to cause a rapid but transient improvement in mood in depressed patients (Paul et al., 1994). At the cellular level, NMDA antagonists block the atrophy of hippocampal CA3 pyramidal neurons and the inhibition of neurogenesis caused by stress (Berman et al., 2000a). Another possible approach to modulating the glycine site on the NMDA receptor involves σ(sigma)-receptor antagonists. Igmescine was the first σ1-receptor antagonist shown to have antidepressant activity (Manji and Lenox, 1999; Roman et al., 1990), but it could not subsequently be confirmed in randomized controlled trials (RCTs) (Volz and Stoll, 2004). Therefore, and due to marketing reasons, it has not been developed further (Volz and Stoll, 2004). An exploratory RCT using the antibiotic drug d-cycloserine (DCS), which acts as a partial agonist at the NMDAR-GLY site, showed a reduction in depressive symptoms but no statistically significant advantage in comparison to placebo adjunct treatment (Heresco-Levy et al., 2006). The antidepressant tianeptine has been demonstrated to counteract the stress-induced increase in the NMDA/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) ratio (Kole et al., 2002). Recently the idea that influence on the regulation of glutamatergic neurotransmission may contribute to the development of new substances with antidepressants (Krystal, 2007; Witkin et al., 2007) has been supported by the publication of case reports (Goforth and Holsinger, 2007; Liebrenz et al., 2007) and one RCT (Zarate et al., 2006) showing a rapid antidepressant efficacy of ketamine treatment.

Of the other amino acid receptors that are possible targets, the observation that the concentration of γ-aminobutyric acid (GABA) is decreased in the brains of depressed patients (Sanacora et al., 2000) suggests that GABA receptor agonists, particularly those targeting the G protein-coupled GABA-B receptor that are prominently located in limbic regions of the brain, may be of interest. For a detailed review of new hypotheses on antidepressant modes of action, see (Slattery et al., 2004).

A novel antidepressant, agomelatine, was recently developed. It acts as an agonist at melatonergic receptors MT1 and MT2 and as an antagonist at 5-HT1c receptors (Audinot et al., 2003; Descamps-Francois et al., 2003; Millan et al., 2003; Millan et al., 2005; Pevet, 2002; Yous et al., 1992). Melatonin is secreted by the pineal gland and, via the suprachiasmatic nucleus in the hypothalamus, acts as the endogenous circadian rhythm oscillator. Circadian rhythms are known to be altered in depression (Darcourt et al., 1992). Consequently, it has been hypothesized that a drug acting as an agonist at melatonin receptors and as an antagonist at 5-HT1c receptors (which have been implicated as being oversensitive in anxiety and depression) could facilitate resynchronization in circadian rhythms (Krauchi et al., 1997; Leproult et al., 2005) and have useful antidepressant properties (Kennedy and Emsley, 2006; Loo et al., 2002).

The close interrelationship between the endocrine and immune systems has stimulated research into the role of pro-inflammatory cytokines into the etiology of depression. Thus, the observation that inflammatory mediators, such as the pro-inflammatory cytokines interleukin (IL)-1 and IL-6, tumor necrosis factor-α, γ-interferon and prostaglandin E2, are elevated in the blood of depressed patients has led to the macrophage hypothesis of depression (Smith, 1991). In addition, the treatment of non-depressed persons suffering from hepatitis with α-interferon often results in severe depression (Wichers and Maes, 2002). Furthermore, many of the symptoms that occur in depression (e.g. altered sleep profile, mood, memory, appetite, libido, cognitive function, endocrine function) may also be caused by pro-inflammatory cytokines that are increased in the blood and cerebrospinal fluid (CSF) of depressed patients (Dantzer, 2004). Conversely, chronic treatment with antidepressants attenuates the release of pro-inflammatory cytokines from activated macrophages both in the blood (Xia et al., 1996) and in the brain (Obuchowicz et al., 2006). These findings suggest that antagonists of pro-inflammatory cytokines, and possibly cyclo-oxygenase (COX)-2 inhibitors that reduce the synthesis of prostaglandin E2 in the brain, could act as novel antidepressants (Leonard, 2001). There is some clinical evidence that COX inhibitors have antidepressant-like activity (Collantes-Estevez and Fernandez-Perez, 2003).
Epidemiological studies show that there is a correlation between chronic depression and the likelihood of dementia in later life (Geerlings et al., 2000; Visser et al., 2000). Inflammatory changes in the brain are pathological features of both dementia and depression (Steffens et al., 1997). It would appear that an increase in inflammation-induced apoptosis, together with a reduction in the synthesis of neurotrophic factors caused by a chronic increase in brain glucocorticoid concentrations (Leonard and Myint, 2006b; Sapolsky, 2000), may play a major role in the pathology of these disorders. In addition, a reduction in the neuroprotective components of the tryptophan-kynurenine pathway in the brain (such as kynurenic acid) further contribute to the neurodegenerative changes seen in chronic depression (Leonard and Myint, 2006a). Such changes have been postulated to cause neuronal damage and thereby predispose the depressed patient to dementia (Leonard and Myint, 2006b). How do antidepressants counteract the neurodegenerative changes that underlie chronic depression? There is now experimental evidence that antidepressants increase the development of new neurons in the hippocampus (Malberg et al., 2000), an effect that may account for delay in the therapeutic response. New neuronal networks are thus established in response to chronic antidepressant treatment (Sairanen et al., 2005). In support of this view, antidepressants are known to enhance axonal and dendritic sprouting (Vaidya et al., 1999). Thus, in chronic depression, glucocorticoids and inflammatory mediators are responsible for increasing neuronal apoptosis and preventing repair of damaged neuronal networks. Effective antidepressant treatment appears, at least partly, to reverse such changes.

Whereas neurotransmitter receptors would appear to be the most accessible targets for the development of new antidepressants, there is now considerable research interest in intracellular signal transduction mechanisms. These are targets for neurosteroids, neurotrophic factors and enzymes that are linked, directly and indirectly, to postsynaptic receptors that reflect the action of both neurotransmitters and other physiologically active molecules such as the cytokines. To date, only one drug has been developed that appears to act by inhibiting a component of the post-receptor signaling pathway, rolipram, a phosphodiesterase inhibitor that is presumed to act by inhibiting breakdown of the second messengers cyclic adenosine and guanosine monophosphates. As a consequence, the postsynaptic response to receptor stimulation is increased. Nonetheless, compared with TCAs, rolipram has shown inferior therapeutic efficacy in RCTs (Hebenstreit et al., 1989; Scott et al., 1991). In the future, it seems likely that other postsynaptic targets will be investigated, including mitogen-activated protein (MAP) kinase agonists that indirectly increase the synthesis of BDNF, a key neurotrophic factor for repairing damaged neurons (Altar, 1999). Other possible targets include protein kinase C (PKC), an enzyme involved in regulating neuronal excitability, neurotransmitter release and long-term synaptic events (Manji and Lenox, 1999). Finally, in view of the importance of mechanisms that reduce apoptosis, and thereby assist in neurogenesis, antidepressants may be developed that act as promoters of anti-apoptotic proteins such as Bcl-2. This protein attenuates apoptosis by sequestering the pro-apoptotic caspase enzymes (Altar, 1999).

Dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) system is well known and one of the major neuroendocrine abnormalities in major depressive disorder. This dysregulation includes elevated levels of corticotropin-releasing hormone (CRH) (Nemeroff et al., 1984), corticotropin (ACTH) and cortisol (Linkowski et al., 1987) during depressive episodes, which normalize after clinical remission. Nevertheless, newer, more recent contributions to our knowledge about depression have also been made. Higher HPA activity during the first weeks of antidepressant pharmacotherapy seems to be associated with lower rates of early treatment response (Hatzinger et al., 2002). Furthermore, and significantly, persisting cortisol hypersecretion indicates lower remission rates (Ising et al., 2006) and a higher risk for recurrence of depression, even when a reduction of depressive symptoms or even clinical remission has been achieved (Zobel et al., 1999). Moreover, during the long-term course of depression, increasing HPA system deterioration is highly correlated not only with severity of disease, indicated by higher psychometric depression scores, but also with the number of previous episodes (Hatzinger et al., 2002). However, both molecular investigations and animal studies show that classical antidepressants, e.g. TCAs, modulate regulation of the HPA system by enhancing expression of glucocorticoid receptors, thereby improving the feedback mechanism of the HPA system (Barden et al., 1995; Holsboer and Barden, 1996). Thus, regulation of the HPA system appears to play a major role in the pathophysiology of depressive episodes. As such, it opens a variety of new pharmacotherapeutic approaches to depression that differ fundamentally from antidepressants available up to now.

The HPA and immune axis has become an important target for antidepressant development due to
the key role of stress in initiating depression. In the development of novel drugs that target the HPA axis, one approach involves antagonists of the CRF (=CRH)-1 receptors. Clinical studies have shown that the concentration of CRF is increased in the cerebrospinal fluid (CSF) of both suicide victims and in depressed patients (Nemeroff, 1996). However, despite initial promising clinical experience, so far CRF antagonists have shown no efficacy in treating depression in RCTs. More success has been reported in developing glucocorticoid type-2 receptor antagonists. This approach was based on the observation that hypersecretion of cortisol is a frequent occurrence in patients with chronic depression in which melancholic features are prominent. Preliminary clinical evidence suggests that novel glucocorticoid receptor antagonists may be beneficial in such subgroups of depressed patients (Gallagher and Young, In Press).

In conclusion, there are many possibilities for the future development of antidepressants. Microarray technology should enable candidate genes to be identified and targeted, and undoubtedly such methods will play an increasingly important role in drug discovery in years to come. However, it seems that the more conventional approach involving the identification of malfunctioning neurotransmitters and their signaling systems, and correcting their defects with novel molecules, offers the greater chance of success in the near term.

8.3 The role of pharmacogenetics in understanding how antidepressants work

Pharmacogenetics, a term proposed by Vogel in 1959, is the study of genetically based, inter-individual variability in response to drugs and their side effects. It is now realized that polymorphisms of the cytochrome P-450 microsomal oxidase system in the liver are responsible for many of the genetic differences that affect drug responsiveness and metabolism.

An important area that is related to pharmacogenetics is pharmacogenomics. Whereas pharmacogenetics is concerned with the individual patient and how differences in metabolism and drug response are a reflection of genetic makeup, pharmacogenomics involves the structure of the genome and how targeting compounds to it may lead to novel drugs that can be used to treat specific psychiatric disorders.

Classical genetics of human disease concentrate on monogenic disorders in which a single mutation or gene is the cause of the disorder. However, complex medical disorders such as diabetes, coronary artery disease and hypertension, and psychiatric illness are polygenic and therefore influenced by multiple factors linked to the genetic substrate and the environment.

Recent research has tended to focus on genes that encode neurotransmitter receptors together with enzymes involved in monoaminergic transmission. So far, the results of studies have been equivocal in their findings, with multiple claims for gene associations that could not be replicated. The limitations of the studies include small sample sizes coupled with the small magnitude of the genetic effect. Nevertheless, meta-analyses have identified several genetic variants of candidate genes. In bipolar disorder, for example, a variant of the MAO-A gene has been identified (Furlong et al., 1999), although other investigators have been unable to confirm this finding (Schulze et al., 2000).

There have been several studies of the promoter polymorphism of the serotonin transporter gene. The type of polymorphism is functionally important, as there appears to be an association between depression and anxiety and the short allele (Lesch et al., 1996). In addition, the short allele of this functional polymorphism in the promoter region of the serotonin transporter gene was found to enhance the influence of stressful life events on depression (Caspi et al., 2003). However, once again, not all investigators have been able to replicate this finding (Serretti et al., 1999). Polymorphisms of other receptors and enzymes of the biogenic amines have also been investigated. These include the tyrosine and tryptophan hydroxylase genes, the catechol-O-methyl transferase gene, as well as genes for the serotonin and dopamine receptors (Kato, 2001). To date these studies have yielded inconclusive or negative results.

In addition, functional polymorphisms in the angiotensin converting enzyme (ACE) gene seem to influence the risk for developing depressive disorders (Arinami et al., 1996; Baghai et al., 2006a), HPA axis activity (Baghai et al., 2002) and the clinical effectiveness of antidepressant therapies (Baghai et al., 2001; Bondy et al., 2005). Also, the glucocorticoid receptor-regulating co-chaperone FKBP5 has been shown to influence both the susceptibility to depression and response to antidepressant treatment (Binder et al., 2004).

The conventional view that unipolar depression is under the control of the same genes irrespective of the age of onset of the disorder has been challenged by studies of late-onset depression (Hickie et al., 2001). Thus, Hickie et al. (2001) have shown that late-onset depression is associated with a mutation in the methylene tetrahydrofolate reductase gene, which controls...
an important cofactor in monoamine biosynthesis; this mutation was not found in patients whose depression occurred at an earlier stage. It appears that this same mutation predisposes patients to cerebrovascular disease and is associated with increased plasma homocysteine and folate deficiencies, which frequently occur in late-onset depression. Such observations serve to emphasize the difficulties that exist in attempting to identify specific genetic factors that may predispose to depression. Moreover, operationalized diagnostic systems such as ICD-10 and DSM-IV, actually in use, promote only relatively fuzzy distinctions between subgroups of depressed patients who suffer from potentially biologically different diagnostic entities. This confusion may contribute to reported difficulties in association studies. In future, better diagnostic systems or investigation of endophenotypes may help to define genetically different subgroups of depressive disorders.

Only a few small studies have been published in which pharmacogenetics has been used to predict therapeutic response in individual patients. These studies have investigated genetic variations in the serotonin receptors (Lesch and Gutknecht, 2004), serotonin transporter and their promoter regions, and their associations with poor response to treatment with SSRI antidepressants (Joyce et al., 2003; Zanardi et al., 2001). Again, other investigators have been unable to replicate the observations that these parameters are associated with poor antidepressant response (Kim et al., 2000). For a more extensive update on recent findings, we refer to published reviews on pharmacogenetics and pharmacogenomics (Holsboer, 2001; Kirchheiner et al., 2004; Malhotra et al., 2004; Mancama and Kerwin, 2003; Serretti et al., 2005).

The current lack of knowledge of susceptibility genes for depression seems unlikely to discourage further research aimed at identifying the genetic basis of mood disorders by the application of DNA genotyping and genome-wide case-control studies (Risch, 2000).

9 Pharmacological treatment options

9.1 The use of medication in the acute treatment of depressive disorders

9.1.1 Introduction

This section provides general information regarding benefits and risks during the pharmacotherapy of depression, followed by further discussion regarding mechanism of action and specific drugs. General considerations during antidepressant acute and maintenance therapies are described in chapter 7. The treatment of depressive disorders consists of complex multimodal therapy that is determined by the current state of the illness. The main modalities are pharmacotherapy, psychotherapy and sociotherapy. Although they are often used in combination, here we will predominantly describe pharmacotherapeutic options. Pharmacotherapy is not always mandatory for less severe forms of depression, but severe depression usually requires medication or electroconvulsive therapy (ECT). In addition, a variety of other biological interventions, such as sleep deprivation and bright light therapy, may be helpful in certain patient subgroups. The discovery of tricyclic antidepressants (TCAs) was a milestone in the treatment of depression, and the TCA amitriptyline has consistently been included in the World Health Organization’s (WHO’s) list of essential drugs (World Health Organization, 2005a), updated biennially, although information about antidepressants has remained unchanged over the last few years. In developing countries or in other countries in which TCAs are preferred antidepressants it may also be reasonable to consider drugs with proven efficacy that are better tolerated than amitriptyline such as SSRIs but that are sometimes not prescribed because of their cost. However, despite the undoubted effectiveness of TCAs, it soon became apparent that the anticholinergic and antihistaminergic side effects of TCAs such as Imipramine or Amitriptyline can cause problems. New antidepressants, both TCAs such as desipramine and newer classes such as SSRIs, NARIs or SNRIs were developed with a more selective mode of action. The results were lower rates of anticholinergic and antihistaminergic side effects in most of the published studies. But interestingly also antidepressant effects of selectively anticholinergic acting substances have been reported (Furey and Drevets, 2006).

For historical reasons, currently available antidepressants are usually classified according to their chemical structure and mode of action. This classification seems sensible, e.g. to separate TCAs and tetracyclic antidepressants from modern substances to describe safety and tolerability properties and to follow widespread habits and to follow a scientific and historical classification. Nevertheless it may be useful to use a different ordering scheme in evolving treatment plans and algorithms. Classification according to

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33 Sociotherapy designates non-medical, social and work-related components of the care process.
the predominant mode of action, which is already applied to modern antidepressant substances, is more logical and practical. We thus suggest describing different classes of modern antidepressants according to their main mode of action, and recommend subdividing the older tri- and tetracyclic substances according to their predominant influence on serotonergic and noradrenergic neurotransmission. In this review, we present the classes of antidepressants in their approximate chronological order.

Currently, tri- and tetracyclic antidepressants with predominant serotonergic (S-TCA), noradrenergic (N-TCA) or mixed serotonergic/noradrenergic (S/N-TCA) action are available. To simplify things for more practicable treatment plans, tri- and tetracyclic antidepressants are summarized within the TCA group in a historical sequence. Additional agents on the market include selective and reversible inhibitors of monoamine oxidase A (RIMA); an irreversible MAO-B inhibitor (MAOBI); non-selective and irreversible inhibitors of MAO-A and MAO-B (MAOIs); selective serotonin reuptake inhibitors (SSRIs); selective noradrenaline reuptake inhibitors (NARIs); antidepressants with a dual mode of action, such as selective serotonin and noradrenaline reuptake inhibitors (SNRIs); and noradrenergic and specific serotonergic antidepressants (NaSSAs) acting via blockade of α2C and 5-HT2 receptors and enhanced release of noradrenaline and serotonin (Blakely, 2001; Frazer, 2001; Haddjeri et al., 1998; Kent, 2000; Pacher et al., 2001; Stahl, 1998b). In addition, a dopamine and noradrenaline reuptake inhibitor (DNRI) and serotonin modulating antidepressants (SMAs) are available. The most recently developed mechanism of action is agonism at melatonergic MT1 and MT2 receptors and selective antagonism at serotonergic 5-HT2C receptors, represented by the antidepressant agomelatine (Audinot et al., 2003), which is currently under review by authorities in Europe. Other developments include the use of single enantiomers instead of racemic compounds.

A consistent trend towards increased use of generic antidepressants over the last few years has been reported (Bruck et al., 1992). In addition, it remains unclear whether pharmacogenetic differences in populations of different countries play a major role in clinical trials investigating efficacy and tolerability. Moreover, outsourcing of clinical trials may cause difficulties in interpreting study results; caution is recommended, especially in cases where study results from different countries are pooled. In particular, there is concern that the practice by pharmaceutical companies of comparing the results of multicenter studies carried out in many different countries could raise doubts about the findings.

A summary of commonly used antidepressants, including their primary mode of action and influence on other receptor systems, is shown in Table 1. According to the review from Sanchez et al. (1999) semiquantitative information about receptor affinities concerning the main pharmacodynamic mode of action of the antidepressants and their major metabolites has been included (Sanchez and Hyttel, 1999). Similar information about receptor affinities concerning secondary and additional pharmacodynamic profiles may not be helpful in clinical routine due to a huge interindividual variation in the sensitivity of depressed patients. Therefore, this detailed information has been omitted. Possible adverse events can be deduced from chapter 7.3 and Table 16, the magnitude of adverse events due to secondary pharmacodynamic actions has to be evaluated in each individual patient and may vary during the treatment course.

44 For educational purposes it could be justified to use only a pharmacodynamic classification model of antidepressants. Due to historical reasons and after a consensus process in addition the classification according the chemical structure was retained.

45 Antidepressants such as fluoxetine, trimipramine, mirtazapine, mianserin, venlafaxine and reboxetine are generally marketed as racemic compounds. Both the pharmacological and pharmacokinetic profiles of these substances may differ between the enantiomers, e.g. of citalopram (Baumann et al., 2002; Baumann and Eap, 2001) or fluoxetine. In the case of the latter, a different pharmacological profile of the two enantiomers may cause differences in cardiac tolerability (Magyar et al., 2003).

46 Original brand-name antidepressants and generic substances are assumed to exert similar efficacy and tolerability, but we do not know whether that is true for each country. Direct comparisons between brand-name formulations and generics and between different generic substances have not yet been published.
Despite the development of a variety of new antidepressants with different pharmacodynamic profiles, to date the hope of better efficacy and clinical effectiveness (see Box 6) over older antidepressants has not been fulfilled.

In contrast to efficiency, the focus of effectiveness is achievement as such, not the resources spent, so anything that is effective is not necessarily efficient, but anything that is efficient also has to be effective. In psychiatry, the distinction between efficacy (ideal use) and clinical effectiveness (typical use) is often drawn. Whereas efficacy may be shown in clinical trials, clinical effectiveness has to be demonstrated in clinical practice.

Some reports of better efficacy for some recently developed antidepressants require further confirmation. Up to now there is no consensus that any of the recently developed antidepressants showed superiority in head-to-head comparisons with older antidepressants such as TCA or irreversible MAOI’s concerning their clinical effectiveness. But even in the case of a proven efficacy of antidepressants the clinical effectiveness may be diminished due high discontinuation rates. These seem to be influenced by noncompliance due to side effect profiles of antidepressants (Hotopf et al., 1997). In addition, it is necessary to evaluate the clinical relevance of small mean differences in depression rating scales between active substances or antidepressant and placebo treatment, even in the case of statistical significance. Moreover, the results of failed trials, e.g. due to high placebo response rates, and the probable huge amount of still unpublished data from clinical trials, should be evaluated before recommendations for specific substances can be made (see chapter 4.4).

The usual recommended daily dosages for starting and maintaining antidepressant treatments are presented in Table 11.

A further problem is the lack of information about both efficacy and tolerability of antidepressants for large portions of the world population. Predominantly genetic, but also cultural differences, may contribute to a differential responsiveness of ethnic groups during antidepressant treatment. In interpreting the existing literature it is particularly important to consider the lack of information about the treatment effects of most and especially newer antidepressants, e.g. in the black African population.

Nevertheless, the main advantages of newer antidepressants are the overall better tolerability and safety in comparison with older substances. Although newer antidepressants are better tolerated and cause fewer and less serious side effects, their specific

| Table 11. Commonly used antidepressants, including dosage recommendations37 |
|-----------------|-----------------|
| Generic name    | Dose recommended by the producer |
|                 | Starting dose (mg) | Dosage range (mg/day) |
| Agomelatine     | 25               | 25–50               |
| Amitriptyline   | 25–75            | 150–300             |
| Amitriptylin oxide | 30–60           | 180–300             |
| Amoxapine       | 50               | 100–400             |
| Bupropion       | 100              | 200–300             |
| Citalopram      | 20               | 20–60               |
| Clomipramine    | 25–50            | 100–250             |
| Desipramine     | 25–75            | 100–300             |
| Dibenzerine     | 120–180          | 240–720             |
| Dosulepine/Dothiepin | 75            | 75–150              |
| Doxepin         | 25–75            | 150–300             |
| Duloxetine      | 40/60            | 60–120              |
| Escitalopram    | 5–10             | 10–20               |
| Fluoxetine      | 20               | 20–80               |
| Fluvoxamine     | 50–100           | 100–300             |
| Imipramine      | 25–75            | 150–300             |
| Isocarboxacid   | 20               | 20–60               |
| Lofepramine     | 70               | 140–210             |
| Maprotiline     | 25–75            | 150–225             |
| Melleran        | 20               | 20–30               |
| Mianserin       | 30               | 60–120              |
| Milnacipran     | 50               | 100–200             |
| Mirtazapine     | 15               | 30–45               |
| Moclobemide     | 150–300          | 300–600             |
| Nefazodone      | 100              | 300–600             |
| Nortriptiline   | 25–50            | 75–300              |
| Paroxetine      | 20               | 20–60               |
| Phenerzine      | 15               | 30–90               |
| Protriptyline   | 10               | 20–60               |
| Reboxetine      | 4                | 8–12                |
| Selegiline      | oral: 30         | oral: 30–60         |
|                 | transdermal: 6–12| transdermal: 6–12   |
| Sertraline      | 50               | 50–200              |
| Tianeptine      | 37.5             | 37.5                |
| Tranylcypromine | 10               | 20–40               |
| Trazodone       | 50–100           | 200–600             |
| Trimipramine    | 25–50            | 150–400             |
| Venlafaxine     | 75               | 75–375              |
| Viloxazine      | 100              | 200–500             |

37 Different dosages are used on different continents and in different countries (Patten et al., 2005; Sartorius, 1986). For some populations, e.g. Japanese patients, the dose recommendations presented above are usually too high. In addition, marketing aspects may influence dosage recommendations owing to calculation of the lowest possible daily treatment costs. Indication-adjusted dose recommendations may also be important. Finally, indications for antidepressants vary from one country to another.

38 Recommended starting dose in the US is 40 mg; in Europe it is 60 mg.
side-effect profile still must be taken into account during treatment. In addition, the latency of several weeks until the onset of sufficient therapeutic effects remains a serious and clinically relevant problem. This principle holds true for each antidepressant and each class of antidepressant mechanisms. There are some reports of a faster onset of response for newer dual-acting compounds, e.g. mirtazapine (Benkert et al., 2000; Benkert et al., 2006; Leinonen et al., 1999; Montgomery, 1999) and venlafaxine (Benkert et al., 1996; Montgomery, 1999) in comparison to other antidepressants e.g. SSRIs or TCAs, but the clinical relevance of these findings remains controversial (Blier, 2003; Nierenberg, 2001). In addition early drug-specific behavioral changes which may be predictive for the clinical response (Katz et al., 2004) are not recorded sufficiently in all RCTs. Moreover, demographic factors and treatment settings appear to influence antidepressant choice more than clinical factors and evidence (Sim et al., 2006). The only methods of achieving more rapid acting, but unfortunately in most cases not sustained, antidepressant effects are wakefulness therapy (Wu and Bunney, 1990) (see chapter 12.3.6) and in some patients, in a more potent and enduring way, ECT (ECT review group, 2003; Gangadhar et al., 1982) (see chapter 12.3.1).

A further general problem in the pharmacotherapy of depression is the possible non-response to initial antidepressant treatment (Charney et al., 2002; Nierenberg and Amsterdam, 1990; Sackeim, 2001). The problem of inconsistencies in defining treatment resistant/refractory depression (see the definition in Box 8) has been described in a recent review (Berlim and Turecki, 2007).

About 50% of depressed patients do not respond adequately to a first course of an adequate antidepressant treatment (about 30% do not show satisfactory improvement, and about 20% drop out due to problems of tolerance). Adequacy of treatment includes treatment with proven efficacy during a time interval of at least 4–6 weeks in a sufficient therapeutic dose range, including reliable patient adherence to therapy (Fava, 2003a; Kupfer and Charney, 2003; Sackeim, 2001). Half of these patients fail to respond to a second antidepressant treatment trial. If several antidepressant treatment trials have been ineffective, even lower response rates after switching to another drug may be observed (Fava et al., 2006). Some authors include the use of augmentation strategies in the definition of treatment resistance or non-response to antidepressant treatment. In addition to obvious biological hypotheses for therapy resistance, such as occult medical conditions causing depression, substance abuse interfering with antidepressant treatments or abnormal metabolism (Rush et al., 2003b), psychosocial factors, too, may be responsible for failed treatment trials (Grote and Frank, 2003). As described further below, even given the difficulty in predicting the most effective solution for any one patient, the range of appropriate pharmacological treatment strategies includes adjustment of dosage, switch to an antidepressant of another class, switch to an antidepressant of the same class, combination therapies with more than one antidepressant, and pharmacological and non-pharmacological augmentation strategies. Strategies such as lithium augmentation (Bauer et al., 2003; Zullino and Baumann, 2001) or augmentation using thyroid hormones (Bauer et al., 1998) and other available methods are described in chapter 9.1.12. In addition, the concomitant use of benzodiazepines, e.g. lorazepam for the treatment of agitation in depressive disorder or alprazolam for the treatment of anxiety in depression (Möller, 2002), can be a clinically useful addendum. Prescription of anxiolytics as a monotherapy is barely effective in severe depression (Laakmann et al., 1996). Nevertheless, in the case of persistent non-responsiveness, the UK ECT review group and other authors consider the use of ECT in comparison with all of these strategies as clinically more effective and still the method of choice for treatment-resistant depression (Davidson et al., 1978; ECT review group, 2003; Folkerts et al., 1997; Kroessler, 1985) even if not all of these patients respond well to ECT.

**Box 7. Definition of pharmacotherapy-resistant depression (modified according to Berlim and Turecki, 2007; Burrows et al., 1994; Fava, 2003b; Fava and Davidson, 1996; Helmchen, 1974; Leonard, 1988; Nierenberg and Amsterdam, 1990; Rush et al., 2003b; Sackeim, 2001; Souery et al., 1999; Thase et al., 1997)**

**Therapy resistance or non-response to treatment** in depression are terms used to describe the lack of reaction to appropriate treatment.

The definition of appropriate treatment varies among experts. While some consider that appropriate treatment must include at least two courses of pharmacotherapy with antidepressants of different groups in sufficient doses and duration (Burrows et al., 1994), others believe that, in addition, pharmacotherapeutic augmentation therapy and treatment with cognitive-behavioral therapy and interpersonal psychotherapy must precede the decision that the condition is therapy resistant (Thase et al., 1997).
Non-response to pharmacotherapy (see Box 7) used as primary treatment implies that sufficient treatment attempts have been made with efficacious psychotherapies such as cognitive-behavioral therapy (CBT) or interpersonal psychotherapy (IPT) (Thase et al., 1997). The following chapters introduce the intravenous use of antidepressants, pharmacogenetics and therapeutic drug monitoring, and general side effects, then describe all presently available antidepressants according their mode of action, clinical effectiveness and main side-effect and risk profile.

### 9.1.1.1 Introduction

The pharmacological effect of an antidepressant depends on its presence in the target organ, i.e. the brain. Metabolites may contribute to its overall activity (Hendset al., 2006; Rudorfer and Potter, 1997). Therefore, the consequences of its absorption, distribution, metabolism and elimination (ADME), which are the fundamental parameters defining its pharmacokinetics, must be considered at a level of importance similar to that of its pharmacodynamics at receptor and transporter sites. Cytochrome P-450 and conjugating enzymes are the main enzyme systems involved in the metabolism of antidepressants. The study of their individual roles helps to understand pharmacokinetic interactions and their clinical consequences, even though, especially in the case of TCAs, a clear correlation between clinical response and plasma levels of antidepressants cannot be drawn (Burrows et al., 1972; Burrows et al., 1977). Many isozymes of cytochrome P-450 and glucuronidating enzymes present a genetic polymorphism, which result in important interindividual differences in drug metabolism in patients. Thus it may be assumed that drug plasma concentrations, rather than dose, reflect concentration in the brain, and this assumption has prompted numerous studies on the relationship of drug plasma concentrations and clinical effects and the introduction of therapeutic drug monitoring (TDM).

### 9.1.1.2 Metabolism and pharmacogenetics of antidepressants

Most antidepressants are metabolized by a phase I reaction implicating one or several isozymes of cytochrome P-450 to more polar metabolites. Then, via a phase II reaction, they undergo conjugation (Table 12) (Liston et al., 2001). Drugs such as tertiary amine TCAs and SSRIs such as fluoxetine, citalopram and escitalopram, but also venlafaxine are converted to active metabolites that may also be eliminated by phase I and phase II enzymes.

As both environmental and genetic factors determine the fate of the drug in the organism, pharmacogenetic tests represent a useful tool for diagnosing the metabolic status of the patient. The first case report on the clinical consequences of impaired hydroxylation of nortriptyline, due to a genetically determined poor metabolizer status (CYP2D6) and high plasma concentrations of this antidepressant in a depressed patient (Bertilsson et al., 1981), prompted rapid development of research in the field of pharmacogenetics of psychotropic drugs. Most forms of cytochrome P-450 implicated in the metabolism of antidepressants present a genetic polymorphism (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A5 and CYP2B6), or their activity varies highly among individuals (CYP3A4) for as yet unknown reasons. The genetic polymorphism of CYP2D6 is the most relevant for the metabolism of psychotropic drugs (Table 12). Generally, gene deletion or a defective gene leads to poor metabolizer (PM) status, and gene duplication or multiplication results in ultrarapid drug metabolism (ultrarapid metabolizer, UM). These patients differ from extensive (EM) or intermediate (IM) metabolizers, who are carriers of two or one active genes, respectively. The proportion of PMs, EMs, IMs and UM differs among different ethnic groups. From a clinical point of view, PMs have a higher risk of experiencing adverse effects as a consequence of impaired drug metabolism, whereas UM are at risk of non-response to a treatment due to the fact that even at high doses, steady-state drug concentrations may not reach therapeutic levels. This situation is illustrated by case studies of UMs who responded to tricyclic drugs only after very high drug doses (Bertilsson et al., 1985) or after comedication with a cytochrome P-450 inhibitor (Baumann et al., 1998; Conus et al., 1996).

Genotyping and phenotyping represent certain ‘trait markers’ and ‘state markers’, respectively (Steimer et al., 2001). Phenotyping is available for most of the above-mentioned CYP isozymes. It is generally carried out by administering one or several (‘cocktail’) test probes to patients and subsequently collecting blood or urine, followed by analyzing the parent compound and the metabolite formed by the particular enzyme (Clement Jerdi et al., 2005). Clearly, the result of phenotyping is influenced by comedication,
Table 12. Antidepressants as substrates of cytochrome P-450 (CYP)

<table>
<thead>
<tr>
<th>Class of antidepressants</th>
<th>Drug</th>
<th>Active (and clinically non-relevant) metabolites</th>
<th>Drug (and/or metabolite) substrate of CYP2D6</th>
<th>Drug (and/or metabolite) substrate of CYP2C19</th>
<th>Other forms of CYP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic and structurally related antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
<td>nortriptyline (10-OH-amitriptyline) (10-OH-nortriptyline)</td>
<td>+ (+) +</td>
<td>CYP3A4, CYP1A2, CYP2C9</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline N-oxide</td>
<td></td>
<td>amitriptyline and others (cf. amitriptyline)</td>
<td>(+) (+)</td>
<td>(CYP3A4, CYP1A2, CYP2C9)</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td></td>
<td>desmethyliclomipramine (2- and 8-OH-clomipramine)</td>
<td>+ (+) +</td>
<td>CYP1A2, CYP3A4, CYP2C19</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td></td>
<td>(2-OH-desipramine)</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dothiepine</td>
<td></td>
<td></td>
<td>§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxepin (a)</td>
<td></td>
<td>desmethyldoxepin (a)</td>
<td>+ +</td>
<td>CYP2C9, CYP1A2</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td></td>
<td>desipramine (2-OH-imipramine) (2-OH-desipramine)</td>
<td>+ (+) +</td>
<td>CYP1A2, CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Lofepramine</td>
<td></td>
<td>desipramine (2-OH-desipramine)</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maprotiline</td>
<td></td>
<td>(N-desmethyimaprotiline) (3-OH and 2-OH-maprotiline)</td>
<td>+</td>
<td>CYP1A2</td>
<td></td>
</tr>
<tr>
<td>Mianserin (b)</td>
<td></td>
<td>N-desmethylianserin (mianserin N-oxide) (8-OH-mianserin)</td>
<td>+ +</td>
<td>CYP3A4, CYP2B6, CYP1A2</td>
<td></td>
</tr>
<tr>
<td>Milnacipran</td>
<td></td>
<td>§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine (b)</td>
<td></td>
<td>N-desmethyliertazapine (8-OH-mirtazapine) (10-OH-nortriptyline)</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td></td>
<td></td>
<td>+</td>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Trimipramine (b)</td>
<td></td>
<td>desmethytrimipramine (OH-metabolite)</td>
<td>+ (+) +</td>
<td>CYP3A4</td>
<td></td>
</tr>
</tbody>
</table>

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### Table 12. (cont.)

<table>
<thead>
<tr>
<th>Class of antidepressants</th>
<th>Drug</th>
<th>Active (and clinically non-relevant) metabolites</th>
<th>CYP2D6</th>
<th>CYP2C19</th>
<th>Other forms of CYP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram (b)</td>
<td></td>
<td>desmethylcitalopram</td>
<td>+ (+)</td>
<td>+</td>
<td>CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(didesmethylcitalopram)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(citalopram propionic acid derivative)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
<td>S-desmethylcitalopram</td>
<td>+ (+)</td>
<td></td>
<td>CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(S-didesmethylcitalopram)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(S-citalopram propionic acid derivative)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (b)</td>
<td></td>
<td>norfluoxetine</td>
<td>+ (+)</td>
<td>+</td>
<td>CYP2C9, CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
<td></td>
<td>+</td>
<td>-</td>
<td>CYP1A2</td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
<td>norsertraline</td>
<td>-</td>
<td>+</td>
<td>CYP3A4, CYP2B6</td>
</tr>
<tr>
<td><strong>Other antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>CYP2B6</td>
</tr>
<tr>
<td>Dibenzepine</td>
<td></td>
<td></td>
<td>$\frac{%}{\text{new}}$</td>
<td></td>
<td>CYP1A2</td>
</tr>
<tr>
<td>Duloxetine</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>CYP2B6</td>
</tr>
<tr>
<td>Milnacipran</td>
<td></td>
<td>(desmethylduloxetine)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
<td>3-OH-nefazodone</td>
<td>- (+)</td>
<td></td>
<td>CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>m-CPP</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reboxetine (b)</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Trazodone</td>
<td></td>
<td></td>
<td>+ (+)</td>
<td></td>
<td>CYP3A4, CYP1A2</td>
</tr>
<tr>
<td>Venlafaxine (b)</td>
<td></td>
<td>m-CPP</td>
<td>+</td>
<td>+</td>
<td>CYP2C9, CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O-desmethyvenlafaxine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(N-desmethyvenlafaxine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(N,O-didesmethyvenlafaxine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viloxazine</td>
<td></td>
<td></td>
<td>$\frac{%}{\text{new}}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s wort</td>
<td></td>
<td></td>
<td>$\frac{%}{\text{new}}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MAOIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moclobemide</td>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td></td>
<td></td>
<td>$\frac{%}{\text{new}}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* From Baumann (in preparation), (cf. also Wilkinson, 2005).

§ No studies available.

(a) A mixture of geometric isomers: the isomers differ in their pharmacological and pharmacokinetic profile.

(b) Chiral drugs: the isomers (of the drug and of their chiral metabolites) may differ in their pharmacological and pharmacokinetic profile.
which inhibits the test enzyme. Guidelines are available for the optimal use of pharmacogenetic tests (De Leon et al., 2006).

Because their clinical relevance has not yet been demonstrated in studies with psychiatric patients, we will mention only briefly that transport proteins such as P-glycoprotein may regulate the transport of many drugs, including antidepressants, from the intestine into the blood and through the blood-brain barrier (Fromm, 2000; Kim, 2006; Lin, 2003; Marzolini et al., 2004). Some but not all antidepressants are substrates of this transport protein, which displays a genetic polymorphism (Uhr et al., 2000; Uhr and Grauer, 2003).

9.1.1.1.3 TDM of antidepressants

TDM of antidepressant drugs is widely practiced to optimize the pharmacotherapy of depression (Baumann et al., 2004; Brøsen, 1996; Burke and Preskorn, 1999; Mitchell, 2000; Mitchell, 2004). Table 13 lists indications for TDM of antidepressants and other psychotropic drugs. Bear in mind that, unfortunately, poor compliance is observed not only in patients treated with antidepressants (Meijer et al., 2001). Treating physicians also induce underuse or inappropriate use of TDM for antidepressants (Mann et al., 2006b). Only for some antidepressant drugs, such as TCAs (and lithium), in contrast to former publications (Burrows et al., 1972; Burrows et al., 1977) now there is reasonably good evidence for a relationship between drug plasma concentration and clinical effectiveness (Baumann et al., 2004). Table 14 represents the result of a consensus among experts with regard to recommended plasma concentration ranges (‘therapeutic windows’) for antidepressants. The concomitant analysis of the active metabolite is mandatory for some drugs, as indicated in Table 14. This consensus guideline includes a comprehensive list with drugs with a recommended TDM level for each one, as well as numerous recommendations for treating physicians and laboratories about how to use TDM optimally. It also contains tables summarizing the literature data on drug plasma concentrations measured at fixed doses and they may inform about the reliability of the drug plasma concentration measured in a patient treated with a particular dose.

9.1.1.1.4 Pharmacogenetics and TDM

It is now generally acknowledged that pharmacogenetic tests represent a useful tool in finding an optimal drug dose (Bertilsson et al., 2002; Ensom et al., 2001; Ingelman-Sundberg et al., 1999; Steimer et al., 2001), but clearly tests should be combined with TDM (Baumann et al., 2004; Kirchheiner et al., 2001; Kirchheiner et al., 2004). Pharmacogenetic tests are also recommended in elderly patients as part of an approach aimed at avoiding adverse effects (Egger et al., 2005). The main advantage of these tests is to explain unexpected plasma concentrations of drugs and their metabolites.

A few pharmacoepidemiological studies confirm that, indeed, the CYP2D6 genotype determines the plasma concentration of some antidepressants (Grasmäder et al., 2004; Mulder et al., 2006), and one

Table 13. Indications for TDM of antidepressants (according to Baumann et al., 2004)

<table>
<thead>
<tr>
<th>Suspected non-compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs for which TDM is mandatory for safety reasons (e.g. lithium)</td>
</tr>
<tr>
<td>Lack of clinical response, or insufficient response even if doses considered adequate</td>
</tr>
<tr>
<td>Adverse effects despite the use of generally recommended doses</td>
</tr>
<tr>
<td>Risk for drug interactions in comedicated patients</td>
</tr>
<tr>
<td>Situations involving problems of pharmacovigilance</td>
</tr>
<tr>
<td>Relapse prevention in long-term treatment, prophylactic treatment</td>
</tr>
<tr>
<td>Recurrence despite good compliance and adequate doses</td>
</tr>
<tr>
<td>Presence of a genetic particularity concerning drug metabolism (genetic deficiency, gene multiplication)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Children and adolescents</td>
</tr>
<tr>
<td>- Elderly patients (≥65 years)</td>
</tr>
<tr>
<td>- Patients with somatic comorbidities (hepatic or renal insufficiency, cardiovascular disease)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Forensic psychiatry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems occurring after switching from an original preparation to a generic form (and vice versa)</td>
</tr>
</tbody>
</table>
may conclude that CYP2D6 genotyping before starting pharmacotherapy could help to prevent increased drug plasma concentrations and concentration-dependent adverse effects. There is some preliminary support for the hypothesis that pharmacogenetic tests may also be advantageous from an economic point of view, as they may help to avoid adverse effects and rehospitalization, and reduce the duration of hospitalization (Chen et al., 1996). A recent analysis of the literature demonstrates the advantage of including TDM and pharmacogenetic tests in pharmacovigilance programs (Jaquenoud Sirot et al., 2006) (cf. also Phillips et al., 2001). However, despite a 25-year history of pharmacogenetics in psychiatry, these tests are still rarely routinely used, as shown in a recent study carried out in New Zealand and Australia (Gardiner and Begg, 2005), in spite of some recommendations to introduce pharmacogenetic testing into clinical practice (De Leon, 2006; De Leon et al., 2006a; De Leon et al., 2006b; Gardiner and Begg, 2006; Zourkova and Hadasova, 2003).

9.1.1.1.5 Pharmakokinetic interactions

Many patients are comedicated with other psychotropic and/or somatic drugs as a consequence of comorbidities or non-response to monotherapy. Patients suffering from recurrent depression are submitted to long-term treatment. This increases the lifetime risk of comorbidities, which necessitate simultaneous treatment with several drugs. Adverse effects are then to be expected as a consequence of pharmacokinetic interactions between drugs or when a pharmacokinetic interaction results in an increase in drug plasma concentrations, which may reach toxic levels.

Several drugs (fluoxetine, paroxetine, fluvoxamine, trimipramine etc.) and metabolites (norfluoxetine) are known to be clinically relevant inhibitors of some forms of cytochrome P-450 (Table 12). As a consequence, pharmacokinetic interactions between antidepressants and other drugs (including antidepressants) may have important clinical consequences, as they may act as substrates and/or inhibitors of cytochrome P-450 (Table 12). Classical examples are the interaction between fluvoxamine (Bertschy et al., 1991) or fluoxetine (Aranow et al., 1989) and tricyclic drugs.

Table 15 lists some of the most potent inhibitors and inducers of the cytochrome P-450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 (Armstrong and Cozza, 2000; Baxter, 2006; Bonnabry et al., 2001; Cozza and Armstrong, 2005; Jaquenoud Sirot et al., 2006; Wilkinson, 2005) (cf. also medicine.iupui.edu/flockhart/table.htm (14-8-2006), www.pharmacoclin.ch (14-8-2006)). It is striking to observe that authors differ in their appreciation of the inhibiting and inducing properties of some compounds (cf. also Armstrong and Cozza, 2000). Regrettably, some therapists tend to avoid ‘risky’ co-medications, which per se could be extremely useful for the patient. TDM should be recommended to allow concomitant treatments that, a priori, seem to present a risk but that could be highly beneficial for some patients.

9.1.1.2 Galenic forms of antidepressants

9.1.1.2.1 Oral antidepressants

Antidepressant medication used for oral application is delivered as immediate release (IR) and extended release (ER, XR) formulations. In addition quick dissolving tablets are available from some manufacturers possibly enhancing the convenience by the

<table>
<thead>
<tr>
<th>Drug and active metabolite</th>
<th>Recommended therapeutic range (consensus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline plus nortriptyline</td>
<td>80–200 ng/ml</td>
</tr>
<tr>
<td>Citalopram</td>
<td>30–130 ng/ml</td>
</tr>
<tr>
<td>Clomipramine plus norclomipramine</td>
<td>175–450 ng/ml</td>
</tr>
<tr>
<td>Desipramine</td>
<td>100–300 ng/ml</td>
</tr>
<tr>
<td>Doxepin plus nordoxepin</td>
<td>50–150 ng/ml</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>15–80 ng/ml</td>
</tr>
<tr>
<td>Fluoxetine plus norfluoxetine</td>
<td>120–300 ng/ml</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>150–300 ng/ml</td>
</tr>
<tr>
<td>Imipramine plus desipramine</td>
<td>175–300 ng/ml</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>125–200 ng/ml</td>
</tr>
<tr>
<td>Mianserin</td>
<td>15–70 ng/ml</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>40–80 ng/ml</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>300–1000 ng/ml</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>70–170 ng/ml</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>70–120 ng/ml</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>10–100 ng/ml</td>
</tr>
<tr>
<td>Sertraline</td>
<td>10–50 ng/ml</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>&lt;50 ng/ml</td>
</tr>
<tr>
<td>Trazodone</td>
<td>650–1500 ng/ml</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>150–350 ng/ml</td>
</tr>
<tr>
<td>Venlafaxine plus</td>
<td>195–400 ng/ml</td>
</tr>
<tr>
<td>O-desmethylvenlafaxine</td>
<td></td>
</tr>
<tr>
<td>Viloxazine</td>
<td>20–500 ng/ml</td>
</tr>
</tbody>
</table>
patients (Behnke et al., 2003). While there is common consensus that no differences concerning the clinical effectiveness can be observed, tolerability advantages of ER formulations in comparison to IR formulations have been reported e.g. in case of the SNRI venlafaxine (DeVane, 2003; Entsuah and Chitra, 1997; Norman and Olver, 2004; Olver et al., 2004).

9.1.1.2.2 Transdermal antidepressants

To date only one antidepressant, the MAOBI selegiline is available in some countries as a transdermal patch (see chapter 9.1.2). The patients’ acceptance seems to be good and it has been described that the transdermal system possibly may exert a better efficacy in comparison to orally administered selegiline (Morgan, 2007).

9.1.1.2.3 Intravenous antidepressants

Parenteral administration of antidepressants during the first 2 weeks of an acute depressive episode is common practice in several countries, particularly in continental Europe. However, the advantages of parenteral over oral administration of antidepressants, if any, have not been clearly demonstrated, neither from a pharmacological nor from a clinical viewpoint. It is reasonable to suggest that intravenous (i.v.) administration avoids intermediate stages and thus may result in higher plasma levels of TCAs. Unfortunately, most of the relevant literature is published in languages other than English, and access to it is limited. There has been, however, published, that intravenous administration of Clomipramine and Maprotiline may have a faster onset of action in comparison with oral therapy (Gastpar et al., 1986).

The drugs that are currently available for i.v. administration are clomipramine, doxepine, maprotiline, citalopram and mirtazapine. Note that clomipramine is not approved by the FDA for treatment of depression but only for obsessive-compulsive disorder (OCD). In continental Europe, however, i.v. clomipramine infusions are common practice, although research that supports the treatment is lacking. Eight studies have been published on the treatment of refractory depression (Bogdanowicz et al., 1991; Ceskova et al., 1983; Fountoulakis et al., 2004; Laux and Reimer, 1979; Nahunek et al., 1983; Ravizza, 1979; Sallee et al., 1997; Zapletalak et al., 1982), only three on the treatment of OCD (Fallon et al., 1998; Koran et al., 1998; Mundo et al., 1999), whereas another three studies use i.v. clomipramine as a challenge test (Golden et al., 1990; Kupfer et al., 1991; Sallee et al., 1998). Open studies are confirming a fast onset of treatment response with parenteral clomipramine and desipramine in drug resistant depression within one week (Ceskova et al., 1983; Nahunek et al., 1983).

Table 15. Typical inhibitors and inducers of cytochrome P-450

<table>
<thead>
<tr>
<th>Antidepressants and other CYP-450 substrates</th>
<th>CYP inducing (+) and inhibiting (–) properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broccoli (Brassica oleracea)</td>
<td>CYP1A2+</td>
</tr>
<tr>
<td>Caffeine</td>
<td>CYP1A2–</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>CYP2C9+, CYP3A+</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>CYP1A2–, CYP2D6–</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>CYP1A2–</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>CYP2C9–</td>
</tr>
<tr>
<td>Dihydralazine</td>
<td>CYP1A2–</td>
</tr>
<tr>
<td>Diliazem</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>CYP3A+</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>CYP2C19–, CYP2D6–</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>CYP1A2–, CYP2C9–, CYP2C19–</td>
</tr>
<tr>
<td>Grapefruit juice (Citrus paradisi)</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>CYP2D6–</td>
</tr>
<tr>
<td>Indinavir</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Intraconazone</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>CYP2D6–</td>
</tr>
<tr>
<td>MDMA (‘ecstasy’)</td>
<td>CYP2D6–</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>CYP3A+</td>
</tr>
<tr>
<td>Norfluoxetine</td>
<td>CYP1A2–</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>CYP2D6–</td>
</tr>
<tr>
<td>Panoxetine</td>
<td>CYP2D6–</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>CYP2C9+, CYP3A+</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>CYP2C9+, CYP3A+</td>
</tr>
<tr>
<td>Primidone</td>
<td>CYP2C9+</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>CYP1A2+, CYP2C9+, CYP3A+</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>CYP1A2+, CYP3A–</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>CYP1A2–</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>CYP3A–</td>
</tr>
<tr>
<td>St. John’s wort (Hypericum perforatum)</td>
<td>CYP2C9+, CYP3A+</td>
</tr>
<tr>
<td>Tobacco smoking (Nicotiana)</td>
<td>CYP1A2+</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>CYP3A–, CYP2C9–</td>
</tr>
<tr>
<td>Verapamil</td>
<td>CYP3A–</td>
</tr>
</tbody>
</table>
The usual practice of infusions suggests starting with $\frac{1}{2}$ ampoule (amp) of clomipramine (1 ml, 12.5 mg) and adding 1 amp (2 ml, 25 mg) every day to reach a maximum of 5–6 amp (125–150 mg). Anecdotal data report higher doses up to 8–9 amp per day (200–225 mg), but this is considered to be a highly aggressive strategy not supported by the literature. Close monitoring of cardiac function and blood pressure is essential because of side effects. Maprotiline is also available in i.v. form (Drago et al., 1983; Kissling et al., 1985; Zapletalek et al., 1982), but data regarding its efficacy are few. Intravenous citalopram was recently introduced (Kasper and Muller-Spahn, 2002). In one double-blind study i.v. citalopram showed superior response rates over oral (p.o.) citalopram (79 vs. 63%) in severely depressed patients at 8 weeks (Guelfi et al., 2000; review: Moukaddam and Hirschfeld, 2004). It has also been shown to be effective in the treatment of OCD in an open trial (Pallanti et al., 2002). Even more recently, i.v. mirtazapine was introduced and was reported to be effective in the treatment for depressed patients in open naturalistic studies (Konstantinidis et al., 2002; Muhlbacher et al., 2006).

Overall, the practice of i.v. administration has not been adequately shown to be superior to oral administration in the majority of depressive patients, but it may be recommended for treatment of refractory cases. In these refractory cases, it seems that at least some of these patients benefit from the bypassing of the gastrointestinal tract and achieve better and faster drug levels.

9.1.1.3 Summary of side effects

Antidepressant drugs can produce common side effects according their receptor profiles. In addition, possible discontinuation symptoms and the potential for allergic reactions and blood dyscrasias must be taken into consideration.

The use of TCAs appeared to be problematic in some cases due to their inherent side-effect profile. Anticholinergic and antihistaminergic side effects are of particular concern, and possible cardiovascular complications, especially in case of overdose, have consequently limited their use (Burrows et al., 1981; Vohra et al., 1975; Vohra and Burrows, 1974). New antidepressants have a more selective mode of action and are therefore more frequently used as a first-line therapy due to their favorable tolerability profile (Burrows and Norman, 1997). Despite their fewer anticholinergic effects, however, it is important to pay attention to the specific side-effect profiles of the newer substances. In particular, the activating properties of NARIs can cause tremor and restlessness together with sleep disturbances. SSRIs raise serotonin levels at multiple sites and at multiple receptors throughout the brain (Stahl, 1998a), and can lead to nausea, headache, agitation and a general ‘activation syndrome’, sexual dysfunction and sometimes sleeplessness. Substances with additional antihistaminergic properties, such as mianserin, mirtazapine and doxepin, may induce drowsiness, especially during the beginning of the treatment. Later, increased appetite and weight gain often emerges as a problem that markedly influences compliance (Kent, 2000). Especially during the first days of use of antihistaminergic antidepressants, patients must be informed about possible effects on their driving performance (see chapter 9.1.1.3.4). But untreated depression, too, usually worsens patients’ driving due to prolonged reaction times and concentration deficits. After the first week of treatment (Ramaekers, 2003) and during long-term treatment driving ability generally normalizes. This normalization may depend on the applied daily dosage. In addition, differences in driving performance based on treatment with sedating or non-sedating antidepressants have been reported (Ridout et al., 2003; Wingen et al., 2005).

Table 16 presents specific side-effect profiles based on the effect of antidepressants on receptors and neurotransmitters. Using this table in combination with Table 1, one can deduce the specific side-effect profile to be expected for a specific antidepressant.

9.1.1.3.1 Blood dyscrasias and disturbance of erythro- and leucopoiesis during the use of antidepressants

Neutropenia and thrombocytopenia have been observed during treatment with mood stabilizers like carbamazepine (Sheehan and Shelley, 1990), lamotrigine (LeDrew et al., 2005; Ural et al., 2005) and valproate (Vesta and Medina, 2003). During

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39 The subdivision in different classes of antidepressants including additional effects on specific receptors can be seen in Table 1. Together with Table 16 an individual side effect profile of each single antidepressant can be deduced. In addition to that profile also the used dose and the individual sensitivity of a patient influences the probability and magnitude of side effects.

40 Also, antipsychotics such as clozapine or olanzapine (Duggal et al., 2004), used in augmentation therapies (see chapter 9.1.12), may cause leukopenia culminating in agranulocytosis.
antidepressant monotherapy using a variety of substances, including TCA (Gibson, 1974; Gravenor et al., 1986) and tetracyclic substances such as mianserin (Thomas and Read, 1990), neutropenia has been reported. Divergent reports about newer antidepressants such as SSRIs (Ozcanli et al., 2005; Trescoli-Serrano and Smith, 1996), venlafaxine (Angelescu et al., 2002; Lucht et al., 2000) and mirtazapine (Anon., 2004; Ozcanli et al., 2005) have been published. They have also been reported to have negative effects on leucopoiesis, but due to rare reports and frequent combination therapies the causal interdependencies are not clear. As a therapeutic or even prophylactic option additional lithium therapy should be owing to its potential not only to augment antidepressant therapies (Bauer et al., 2003) but also to stimulate leucopoiesis (Hager et al., 2002).

Table 16. Modes of action and receptor profiles, and direct and indirect effects of antidepressants possibly associated with clinically relevant and compliance-influencing side effects

<table>
<thead>
<tr>
<th>Influenced receptors or neurotransmitters</th>
<th>Mode of action</th>
<th>Typical side effects (receptor)(^{a1})</th>
</tr>
</thead>
</table>
| M\(_1\) receptor                         | Antimuscarinic/anticholinergic | • Dry mouth  
• Accommodation disturbances  
• Constipation  
• Miction disturbances  
• Worsening of angle-closure glaucoma  
• Hyperhidrosis  
• Cognitive disturbances  
• Delirium  
• Cardiac arrhythmias |
| H\(_1\) receptor                         | Antihistaminergic | • Sedation  
• Drowsiness  
• Daytime tiredness  
• Increased appetite  
• Weight gain  
• Metabolic syndrome |
| \(\alpha_1/\alpha_2\)-receptor             | Antiadrenergic | • Hypotension |
| NA transporter                           | Noradrenalin reuptake inhibition/noradrenergic effects | • Tremor  
• Dry mouth  
• Tachycardia  
• Restlessness  
• Sleep disturbances  
• Hypertonia |
| 5-HT transporter blockade/5-HT receptor agonism | Serotonin-reuptake inhibition/serotonergic effects | • Headache (5-HT\(_1\)D)  
• Restlessness, agitation, akathisia (5-HT\(_2\))  
• Anxiety, panic (5-HT\(_2\))  
• Decreased appetite (5-HT\(_2\))  
• Weight reduction (5-HT\(_2\))  
• Sleep disturbances (5-HT\(_2\))  
• Sexual dysfunction (5-HT\(_2\))  
• Nausea (5HT\(_3\))  
• Diarrhea (5-HT\(_4\))  
• Serotonin syndrome (all 5-HT receptors; predominantly in combination)  
• Lack of emotion  
• SIADH\(^{a2}\)  
• Enhanced bleeding risk\(^{a3}\) |

\(^{a1}\) The sorting order represents grading from common and less serious to more serious but predominantly rare side effects.  
\(^{a2}\) Syndrome of inappropriate secretion of antidiuretic hormone, possibly resulting in hyponatremia and generalized epileptic convulsions  
\(^{a3}\) Due to decreased platelet concentration or diminished platelet aggregation.
Dependence potential of antidepressants and demarcation from a discontinuation syndrome

Haddad identified 21 English-language case reports of antidepressant addiction (Diagnostic and Statistical Manual of Mental Disorders, 4th revision (DSM-IV) ‘substance dependence’ criteria) published since 1963 (Haddad, 1999). Sixteen of these reports involved tranylcypromine or amineptine, which have atypical dopaminergic and stimulant properties, but have been withdrawn from the market in most countries. Subject characteristics included male sex (14/21), personality problems (10/21) and prior substance misuse (14/21). Signs of addiction such as increasing tolerance and compulsive use are not a feature of antidepressants. Accordingly, addiction in the currently accepted sense of the term is not clinically associated with antidepressants. Only bupropion, used as an antidepressant and for smoking cessation, has been controversial. But the compound has been shown not to be amphetamine-like, and its potential for human abuse is very unlikely (Griffith et al., 1983; Miller and Griffith, 1983). DSM-IV, whatever its limitations, does seem accurately to capture the real hazards of addiction, and on that basis, antidepressants are not, as a class, substances of misuse and hence should not be described as addictive.

Still, the addictive potential of antidepressants is a popular, widely held belief. It is promoted by reports in which individuals claim to have had severe withdrawal symptoms and to have extreme difficulties in stopping taking antidepressants. Moreover, authors such as Charles Medawar nourish the belief by painting it as part of a broader conspiracy (Medawar and Haron, 2004): ‘Both literally and metaphorically, all the drugs in this story cause some degree of dependence. People get hooked not only on the drugs, but also on the idea of drugs as solutions for mental distress. Subtle interplays of power and dependence nurture this process of medicalisation, as if through a ‘Conspiracy of Goodwill’.’ On this basis, addiction becomes equated with the side effects of drugs, and even ideas about drugs. When it is reasonable to use the emotive term ‘addictive’ and when it is not appears to be a matter of debate.

It would, however, be surprising if, on discontinuation, psychotropic drugs did not produce some withdrawal effects. Clearly they are often taken for relatively long periods of time, and receptors adapt in significant ways to their presence. Once the drug is removed, these changes will be expressed as imbalances in neurotransmitter function and subjective adverse effects. Typically, these effects may include agitation, sleep disturbances, sweating, gastrointestinal discomfort and headache, and may take up to 2 weeks to subside. In addition several reports about a ‘flu-like syndrome’ after sudden cessation of antidepressants such as SSRIs, MAOIs, or SMAs have been published (Belloeuf et al., 2000; Curtin et al., 2002; Lejoyeux et al., 1992; Rajagopalan and Little, 1999; Schatzberg et al., 1997). In a prospective survey of 97 patients stopping an SSRI treatment (Bogetto et al., 2002), the onset of symptoms occurred within 2 days on average. Discernible effects were more likely with high doses and prolonged treatment. With less than 5 weeks’ exposure, withdrawal effects are very unusual and would be unexpected. When a discontinuation syndrome occurs, it is particularly dramatic in newborns whose mothers were treated with serotonergic drugs until delivery (Isbister et al., 2001; Misri and Kostaras, 2002; Nijhuis et al., 2001; Wen et al., 2006).

Differences in the rates of discontinuation syndrome have been reported after patients stabilized on fluoxetine, sertraline or paroxetine had their maintenance therapy interrupted with double-blind substitution for 5–8 days. The incidence of discontinuation syndrome was lower in fluoxetine than in sertraline or paroxetine groups (14, 60 and 66%, respectively) in accordance with the half-life of the substance (Rosenbaum et al., 1998). The symptom categories seen with SSRIs and venlafaxine are disequilibrium (giddiness or even vertigo), sensory abnormalities (e.g. headache, ‘pins-and-needles’ sensation), gastrointestinal upset (e.g. nausea), general somatic distress (e.g. lethargy), sleep disturbance and affective symptoms (Fava et al., 1997; Haddad, 1998; Schatzberg et al., 2006). In a database analysis, a total of 93 suspected cases of SSRI-induced neonatal withdrawal syndrome were reported and were regarded as sufficient information to confirm a possible causal relation. Sixty-four of the cases were associated with paroxetine, 14 with fluoxetine, 9 with sertraline and 7 with citalopram (Sanz et al., 2005b). A survey of the French pharmacovigilance database revealed that SSRIs are clearly associated with a higher risk of withdrawal syndrome (OR 5.05, 95% CI 3.81–6.68) and in particular with the SNRI venlafaxine and the SSRI paroxetine.

44 The definition of ‘dependence potential’ varies among different systems of classification. DSM-IV defines ‘substance dependence’ in relation to a mixed picture of tolerance, withdrawal effects and compulsive drug-taking behavior, usually accompanied by a craving for the positive effects of the drug.

45 In addition, antidepressants have no market value for drug abusers, an authentic measure of abuse potential.
the addiction potential of antidepressants has been use of antidepressants has also been reported, and misuse of nonpsychotropic medications, excessive pounds (Judge et al., 2002). In addition, similar to the treatment due to the different half-lives of the constituents a serious barrier to discontinuation in the majority of patients (Bogetto et al., 2002). When clinician and patient ratings are compared under double-blind conditions, there is also a high level of agreement (Rosenbaum et al., 1998). This finding is important because the claim is sometimes made that companies and clinicians are in a conspiracy to deny how severe these symptoms are.

Just as it would be surprising not to have some withdrawal effects, odd physical effects as a result of individual differences on discontinuing a drug are also to be expected. About 50 comments on paroxetine withdrawal, from discussion boards posted between January 1999 and May 2002, were provided to the ‘Seroxat users’ website (http://www.seroxatuser-group.org.uk). There is in fact a reasonable concordance with the symptoms described in the literature, although the effects are often described as very severe and unexpected. Discontinuation symptoms and treatment interruption-emergent events were more frequent after paroxetine compared with fluoxetine treatment due to the different half-lives of the compounds (Judge et al., 2002). In addition, similar to the misuse of nonpsychotropic medications, excessive use of antidepressants has also been reported, and the addiction potential of antidepressants has been discussed (Dean, 2002; Haddad, 1999). Withdrawal symptoms have even (though rarely) been described following discontinuation of herbal antidepressants such as St. John’s wort (Beckman et al., 2000).

The apparent absence of appropriate notification that such effects can occur runs consistently through the messages. There is also a pervasive hostility to the doctors (usually general practitioners, it would appear) who prescribe the drug. It is a real challenge to know how to evaluate this evidence in a quantitative sense as well as qualitatively, in relation to the motivation and needs of people who use Internet discussion boards. There is clearly a remarkable opportunity to harness patient experience through the Internet, but a qualitative free-for-all could well be self-perpetuating and ultimately uninformative because it is very likely to suffer from a variety of confounding biases. There is also the complication that there appears to be a prospect of secondary gain from suing multinational drug companies who own patents on individual drugs. This issue is related to a much broader challenge, which is to improve current methods of post-marketing surveillance.

Finally, aside from the issues of addiction, but important from the point of view of management, it is certainly possible that on discontinuation patients may relapse with the original anxiety or depressive symptoms that promoted the use of antidepressants (Geddes et al., 2003). To prevent discontinuation symptoms a slow tapering of antidepressant medication in case of a planned discontinuation has been recommended (Rosenbaum and Zajecka, 1997; Shelton, 2001; Warner et al., 2006). Clearly, when this occurs, a clinical decision must be made whether to continue with the medication and accept the benefit of symptom control or discontinue medication and see the return of symptoms. There is no convincing evidence that the use of antidepressants makes returning anxiety or low-grade depressive symptoms worse, but obviously the costs and benefits of long-term use of any medication must be weighed on an individual basis.

In conclusion, the consensus view among experts is that antidepressant drugs are not addictive (Nutt, 2003) in the normally understood sense of the word and as regularly applied, e.g. to opiates. However, as with all medicines, their benefit comes at the potential cost of adverse effects. These adverse effects are somatic symptoms on withdrawal. Extending prescription for minor symptoms or syndromes runs the risk of the harm being perceived as greater than the benefit. There are undoubtedly some problems with the use and, particularly, the discontinuation of...
of that and partly because of other adverse effects. Some countries in Europe have discontinued its use, partly because one of its metabolites is an amphetamine (Briggs et al., 1990).

47 Definitions of dependence and addiction are still controversial (O’Brien et al., 2006). ‘Physical dependence’ is characterized by symptoms of withdrawal after discontinuation of a substance; ‘addiction’ is most commonly defined as the compulsive need and repeated use of a substance despite clear evidence of morbidity secondary to such use leading to tolerance and craving beyond voluntary control.

The dependence potential of tranylcypromine is related to the fact that one of its metabolites is an amphetamine (Briggs et al., 1990). Some countries in Europe have discontinued its use, partly because of that and partly because of other adverse effects.

46 The dependence potential of tranylcypromine is related to the fact that one of its metabolites is an amphetamine (Briggs et al., 1990). Some countries in Europe have discontinued its use, partly because of that and partly because of other adverse effects.

9.1.1.3.3 Use of antidepressants during pregnancy, post-partum depression and breast feeding

The pregnancy and post-partum periods are considered to be relatively high risk times for developing depressive symptoms as well as depressive episodes in women (see also chapter 10.1) (for review see Cohen et al., 2004; Nonacs and Cohen, 2003). Both acute and prophylactic treatment of depressive disorders during pregnancy may pose a difficult-to-solve therapeutic problem and require individual risk-benefit analysis. Untreated depression is associated with impaired feto-placental function, premature delivery, miscarriage, low fetal growth and perinatal unwanted effects, whereas use of antidepressant drugs during pregnancy might entail risk of teratogenesis, neonatal toxicity, discontinuation symptoms and neuropsychological-behavioral impairment (Bellantuono et al., 2006). In addition, during antidepressant pharmacotherapy after birth, each available antidepressant is excreted in the milk (approximately 1% of plasma levels can be seen) and may influence infants during breast feeding (for review see Burt et al., 2001; Dodd et al., 2000; Suri et al., 1998). Therefore, the risk of untreated depressive disorders causing maternal stress that also influences the fetus and birth outcomes, as well as enhanced risk for suicide, must be evaluated together with a possible increased risk for fetal malformation, growth impairment, fetal and neonatal toxicity, and behavioral teratogenicity caused by antidepressant treatment (Wisner et al., 2000).

These benefits and risks of antidepressant pharmacotherapy must also be assessed and compared with other non-pharmacologic treatment alternatives, e.g. ECT (chapter 12.2), which can safely be administered during pregnancy and breast feeding (Rabheru, 2001; Walker and Swartz, 1994). Sleep deprivation (chapter 12.3.7) (Parry et al., 2000) and bright light therapy (chapter 12.3.8) (Oren et al., 2002) should be considered. Because RCTs during pregnancy are not ethically acceptable and no controlled studies of the use of antidepressants during pregnancy have been published, all knowledge on the subject is anecdotal. Single case reports, case series and epidemiological data must be analyzed carefully, including patients’ individual histories. In addition to concerns about malformations and neonatal complications, the risk of influence on behavioral development, e.g. abnormal emotional behavior in offspring, cannot to date be excluded. Accordingly, recent studies in new born mice have shown an effect of serotonin and SSRI (Fluoxetine) treatment on behavioral phenotypes, leading to the hypothesis that these effects may indicate a critical role of serotonin in the maturation of brain systems that modulate emotional function (Ansorge et al., 2004).

Enhanced risk of intrauterine death or congenital malformation has generally not been reported in conjunction with TCAs and fluoxetine or other SSRIs (Wisner et al., 1999). Nevertheless, more neonatal complications were seen. Children of mothers treated with fluoxetine during the first trimester of pregnancy showed lower maternal weight gain during pregnancy.
(which is also associated with untreated depression) together with decreased birth weight of neonates and a higher rate of premature birth (Chambers et al., 1996). Moreover, infants of mothers treated with fluoxetine during breast feeding showed reduced growth (Chambers et al., 1999). The overall development of children of mothers receiving TCAs or SSRIs during pregnancy did not differ from that of controls (Wisner et al., 1999). A meta-analysis reported that use of newer antidepressants such as SSRIs, SNRIs, NARIs, NaSSAs and DNRIs is not associated with an increased risk of major malformations above the baseline of 1–3% in the population (Einarson and Einarson, 2005). Nevertheless, a recently published case-control study that has been somewhat contested by experts (Blier, 2006) reported an association between the maternal use of SSRIs in late pregnancy and persistent pulmonary hypertension in newborns as a probable cause of substantially enhanced infant mortality (Chambers et al., 2006). In addition, a warning has been published not to use paroxetine within the first trimester of pregnancy owing to a twofold increase in the rate of cardiovascular malformation (GSK Clinical Trial Register; http://ctr.gsk.co.uk/Summary/paroxetine/epip083.pdf). Recently published reports confirm the potentially increased risk of congenital malformation following paroxetine treatment (Cuzzell, 2006), therefore its use during pregnancy should be avoided. Also, the manufacturer of bupropion has established a ‘Pregnancy Registry program’ primarily to collect safety data regarding the use of this substance during pregnancy (White and Andrews, 1999). Newer compounds whose teratogenic risks are unknown or incomplete should not be used as first-line agents in the pharmacological treatment of depression during pregnancy and breast-feeding (Gentile, 2005). Even agents considered so far to be safe for mother and child during breast feeding, such as mirtazapine (Aichhorn et al., 2004) and escitalopram (Rampono et al., 2000), should be evaluated carefully as they have not been available for sufficiently long time for a final risk evaluation. The Health Research Group therefore even suggests to wait at least seven years from the start of the marketing of a new drug until reliable statements about the safety of this drug can be published, because the numbers of probands and patients receiving new drugs in RCTs may be too small to detect even life threatening rare adverse events (Wolfe et al., 2005). Although published studies show that plasma levels in babies are often below detectable levels (Blier, 2006), data from large prospective studies are lacking. Finally, the specific safety profiles of maintenance and continuation therapies during pregnancy and the postpartum period must also be considered (Ernst and Goldberg, 2002).

9.1.1.3.4 Antidepressants and fitness to drive

Most patients treated with antidepressants are not hospitalized, but continue to live in their community. It is therefore important to know whether antidepressants influence activities such as car driving, which requires intact psychomotor functioning. Some antidepressants produce side effects that include dizziness, sedation, blurred vision, sleepiness, and difficulty concentrating on tasks and making decisions. Some of these symptoms must be assumed to be similar to those observed in untreated depressed patients, and therefore the driving capacity of each patient must be examined individually, independently of his or her treatment (Laux, 2002).

One of the main tests used in this context is the same as that introduced for testing driving behavior in subjects who have ingested alcohol: the standard deviation of lateral position (SDLP) is an index of road-tracking precision or ‘weaving’, as described in detail by Van Laar et al. (1992). This test is carried out in real conditions, where the subjects are driving a test car (on-the-road driving test), but other methods have also been used, where car driving is only simulated (Brunnauer et al., 2006; Laux, 2002). This means that comparisons between different studies are sometimes difficult. The literature is surprisingly thin with regard to studies regarding the influence of antidepressants on driving behavior, and most of them were carried out with healthy volunteers treated with a single dose of an antidepressant drug (Table 17).

In healthy subjects, tricyclic drugs such as imipramine (van Laar et al., 1995) or amitriptyline (Louwerens et al., 1984) and others generally impair driving behavior after acute medication, but some tolerance my develop after prolonged administration (Table 17). According to Laux et al., most tricyclic drugs (amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, opipramol and trimipramine) and the tetracyclic antidepressants maprotiline and mianserin clearly decrease driving capacity, especially during the first 10–14 days following initiation of treatment (Laux, 2001). A retrospective cohort study showed that elderly patients treated with TCAs represent a higher risk group for traffic accidents in comparison to a group of control subjects (Ramaekers, 2003; Ray et al., 1992). Tricyclic drugs are increasingly used in low doses for the treatment of neuropathic pain (Sindrup et al., 2005). In a small group of patients...
suffering from this disease, a first dose of 25 mg amitriptyline significantly impaired driving performance, in comparison to placebo. After a 2-week treatment with 25 mg/day amitriptyline, tolerance had developed as the differences between placebo vs verum were not any more significant (the drug was always administered in the evening, about 13h before the test).

These effects of the TCA appear to be related to their pharmacological properties as $\alpha_1$, muscarinic and/or $H_1$ antagonists. As expected, due to their pharmacological profile, the $H_1$ antagonists mianserin (15 mg/day) and mirtazapine (30 mg/day) impaired slightly driving performance on day 2 in healthy volunteers (Ramaekers et al., 1998) (Table 17). However, tolerance apparently developed as on day 8, the effect was gone for mirtazapine, and strongly decreased for mianserin. Dose was then increased to 30 mg/day and 60 mg/day, respectively: on day 16 of treatment, there was some impairment of the driving performance with both antidepressants. This indicates that tolerance was not complete. In a similar study carried out by the same research group with healthy volunteers treated for one week with 30 mg/day mirtazapine confirmed that this drug impairs car driving performance on day 2, but not later on (Wingen et al., 2005). As concluded also from other studies, mirtazapine should be administered in the evening and the physician should inform the mirtazapine treated patient that car driving represents some risks, especially at the beginning of the treatment. A naturalistic clinical study with depressive patients treated chronically with mirtazapine nevertheless demonstrated that this drug did less impair driving performance than TCAs, SSRIs and venlafaxine (Brunnauer et al., 2006), but it also confirms that depressive illness per se represents a risk factor.

In contrast, escitalopram (Wingen et al., 2005), fluoxetine (Ramaekers et al., 1995), paroxetine (Robbe and O’Hanlon, 1995), sertraline (Warrington, 1991) and moclobemide (Ramaekers et al., 1992), which are mostly devoid of the properties mentioned above for TCA ($\alpha_1$, muscarinic and/or $H_1$ antagonists), do not

### Table 17. Fitness to drive during application of antidepressants in healthy volunteers

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Study details</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Healthy volunteers, 75 mg</td>
<td>SDLP elevation, adaptation after 1 week</td>
<td>Louwerens et al., 1984</td>
</tr>
<tr>
<td>Dothiepin</td>
<td>Healthy volunteers, 75–150 mg</td>
<td>SDLP not different from placebo</td>
<td>Ramaekers et al., 1995</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Healthy volunteers, 75 mg</td>
<td>SDLP elevation, adaptation after 1 week</td>
<td>Schoenmakers et al., 1989</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Healthy volunteers, 10–20 mg</td>
<td>Driving and psychomotor performance not affected</td>
<td>Wingen et al., 2005</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Healthy volunteers, 20 mg</td>
<td>Reduced attention, driving performance not affected</td>
<td>Ramaekers et al., 1995</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Healthy volunteers, 50 mg</td>
<td>SDLP elevation, adaptation after 1 week</td>
<td>van Laar et al., 1995</td>
</tr>
<tr>
<td>Mianserin</td>
<td>Healthy volunteers, 30–60 mg</td>
<td>Impaired driving performance, adaptation after 1 week</td>
<td>Louwerens et al., 1984; Ramaekers et al., 1998</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Healthy volunteers, 15–30 mg</td>
<td>SDLP elevation, impaired driving performance, adaptation after 1 week</td>
<td>Ramaekers et al., 1995; Ramaekers et al., 1998; Wingen et al., 2005</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Healthy volunteers, 200 mg</td>
<td>Driving performance not different from placebo</td>
<td>Ramaekers et al., 1992</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Healthy volunteers, 200 or 400 mg</td>
<td>Highway driving performance not impaired, slight impairment of lateral position control after 400 mg per day</td>
<td>van Laar et al., 1995</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Healthy volunteers, 20–40 mg</td>
<td>Impaired psychomotor performance, road tracking not affected</td>
<td>Robbe and O’Hanlon, 1995</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Healthy volunteers, 100–200 mg</td>
<td>Simulated car driving not affected</td>
<td>Warrington, 1991</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Healthy volunteers, 37.5–75 mg</td>
<td>No effect on SDLP or psychomotor performance</td>
<td>O’Hanlon et al., 1998</td>
</tr>
</tbody>
</table>

SDLP, Standard deviation of lateral position.
significantly influence driving behavior (Table 17). However, the information that sertraline does not impair simulated car driving in healthy volunteers is only mentioned in an abstract of a review paper (Warrington, 1991), but no comprehensive experimental report is available (Table 17). With regard to escitalopram, an already mentioned study (Wingen et al., 2005) (Table 17) shows that a one week treatment with 20 mg/day escitalopram did not result in an impairment of the driving capability of the healthy subjects, whether after acute nor after a 1-week treatment. This is in line with the low affinity of escitalopram for histamine receptors.

Conflicting results were obtained for venlafaxine. While it is considered relatively safe by some authors when tested in healthy volunteers (Ramaekers, 2003; O’Hanlon et al., 1998) (Table 17), others observed that depressive patients treated with venlafaxine performed less well than those treated with mirtazapine, but no data are available about the doses used (Brunnauer et al., 2006).

It has to be considered that patients may have comedictions such as benzodiazepines, either prescribed or as a self-medication. They certainly impair driving ability much more than antidepressants (Bramness et al., 2003; Van Laar and Volkerts, 1998, Van Laar et al., 1992). This effect can be even more pronounced in situations where such a drug is a substrate of CYP3A4 (e.g. alprazolam) or CYP2C19 (e.g. diazepam) and where it is administered to subjects comedicated with other drugs (see also chapter 9.1.1.1.5) which per se do not impair driving behavior but which are known inhibitors of one of these enzymes (e.g. fluoxetine, moclobemide) (Ramaekers, 2003).

The effect of an antidepressant can be be directly compared with that of alcohol, at a particular blood alcohol concentration (BAC: 0.5, 0.8, …, mg/ml) (Ramaekers, 2003). It is clinically important that some tricyclic drugs (and benzodiazepines) enhance the impairing effect of alcohol on skills related to driving behavior (Landauer et al., 1969), while generally SSRIs do not modify these alcohol effects (Baxter, 2006).

In conclusion, depressed patients must be informed that, owing to their illness, driving performance may definitely decrease, and that the risk of traffic accidents is increased by alcohol or benzodiazepine consumption. Moreover, the decision to medicate with an antidepressant must be made based on the patient’s situation with regard to his daily occupations, including car driving. However, it must be considered that, as shown by a recent study, patients often ignore warning labels on packages indicating that these drugs may impair driving capability (Veldhuijzen et al., 2006).

9.1.2 Monoamine oxidase inhibitors48

9.1.2.1 Efficacy

A comparable efficacy profile for all available irreversible MAOIs similar to that of TCAs has been reported, but this is true only for outpatients (Thase et al., 1995), even if they have been TCA treatment failures. For inpatients, TCAs have been reported to be more effective than phenelzine and isocarboxazid (for review see: Thase et al., 1995). In other studies a similar efficacy of phenelzine in comparison to the TCAs imipramine in inpatients (Davidson et al, 1981), nortriptyline (Georgotas et al., 1986) and amitriptyline in outpatients (Ravaris et al., 1980) has been reported. Responsivity to MAOI treatment is highest in patients suffering from depression with anergic or atypical features49 (Henkel et al., 2006; Himmelhoch et al., 1991; Thase et al., 1992; Thase et al., 1995), but anergic features were predominantly investigated in bipolar depression. Despite this efficacy profile, there is a broad consensus that irreversible MAOIs are considered predominantly as a second-line treatment strategy because of their potential to cause serious adverse events (see below, chapter 9.1.2.2) (Bauer et al., 2002c). Especially with depression resistant to TCAs, MAOI monotherapy or the combination of MAOIs and TCAs or mood stabilizers has been suggested based on promising results of case reports and retrospective data analyses (Amsterdam and Shults, 2005; Feighner et al., 1985; Schmauss et al., 1988). Tranylcypromine treatment has shown no significant advantage in terms of remission rates compared with venlafaxine and mirtazapine combination therapy in outpatients with treatment-resistant depression (McGrath et al., 2006). Due to the lower side-effect burden of the SNRI/NaSSA combination compared with irreversible MAOIs, combination therapy may also be suitable for patients suffering from highly treatment resistant depression (McGrath et al., 2006), but comparative RCTs up to now are missing.

48 The following sections describe the efficacy and safety profile of all available antidepressants. Substances are classed in groups according to their main mode of action. Because frequency of prescription varies among different countries, the group order corresponds to a more neutral and approximately historical chronology.

49 See chapter 5.2.1.3.3 for a detailed description of the concept of atypical depression. In France the term ‘atypical depression’ is synonymous to depression with psychotic symptoms (see chapter 5.2.1.2).
Dose-escalating strategies with MAOI therapy have also been suggested, but very few clinical data indicate that ultra-high-dose treatment with tranylcypromine is effective in refractory depression (Adli et al., 2005). As described in chapter 5.2.4.2.3, the preferential MAO-B inhibitor selegiline, which is mainly used in combination therapy for Parkinson’s disease, may also exert significant antidepressant effects (Amsterdam, 2003; Bodkin and Amsterdam, 2002). This is especially true at higher doses (>10 mg/day), which possibly also inhibit MAO-A activity (Mann et al., 1989). Selegiline transdermal system has shown superiority in comparison to placebo in several short-term (Feiger et al., 2006) and long-term RCTs (Amsterdam and Bodkin, 2006). In addition it has been described that the transdermal system possibly may exert a better efficacy in comparison to orally administered selegiline (Morgan, 2007). To date only a selegiline transdermal system has been approved as an antidepressant by the US Food and Drug Administration (FDA). The approval process in Europe is still ongoing. Actual data have been summarized in a recently published review (Frampton and Plosker, 2007). The reversible inhibitors of monoamine oxidase A (RIMAs) are considered to be as effective as TCAs and SSRIs, but somewhat less effective than irreversible MAOIs (Lotufo-Neto et al., 1999; Sogaard et al., 1999). It has been reported that there is evidence from meta-analyses that higher doses of moclobemide may sometimes enhance efficacy in treating depressive disorders (Lotufo-Neto et al., 1999).

9.1.2.2 Safety and tolerability

Interactions of predominantly irreversible MAOIs with sympathomimetic medication or tyramine-containing food carry a risk of hypertensive crisis of potentially fatal outcome (Amsterdam and Shults, 2005; Brown and Bryant, 1988). For this reason, there is broad clinical consensus that MAOIs are considered only as second-line antidepressants. Moreover, they entail dietary restrictions that prevent ingestion of tyramine-rich food (see Box 9).

MAOI ultra-high-dose therapy can cause delirium. In addition, following discontinuation of irreversible MAOI therapy, withdrawal phenomena such as agitation, anxiety, sleeplessness or drowsiness and even hallucinations and delirium have been described (Dilsaver, 1988). For more information concerning a possible dependence potential of MAOIs, see chapter 9.1.1.3.2 and Box 8. The risk of serotonin syndrome due to the concomitant use or accidental combination of other serotonin-enhancing antidepressants, such as SSRIs, S-TCAs, SNRIs or SMAs, must be taken into account. Depending on the half-life of the substances used, a drug-free time interval of at least 2 weeks in the case of serotonergic medication before or after irreversible MAOIs is necessary to minimize the risk of severe adverse events. Prescribing MAOIs following fluoxetine requires lengthening the time interval to 5–6 weeks. In the case of serotonergic substances following the RIMA moclobemide, the time interval can be shortened to 3 days. Restricted intake of tyramine-rich foods is not necessary when using RIMAs; however, in dose ranges above 900 mg/day, e.g. for moclobemide, the risk of interactions with tyramine might again become clinically relevant (Bonnet, 2003). Moreover, RIMAs interact with concomitantly used serotonin-enhancing drugs (Livingston and Livingston, 1996), and have the potential to cause severe serotonin syndrome (Dardennes et al., 1998; Guma et al., 1999; Roxanas and Machado, 1998). Prescribing the selegiline transdermal patch in higher dose ranges (9 or 12 mg/day) requires dietary modifications. Moclobemide may be suitable, particularly in the treatment of bipolar depression, due to a low switch risk (Silverstone, 2001).

During the licencing process, from a clinical point of view, overly low doses have been recommended possibly due to marketing or pricing strategies. In the UK, in comparison with other countries, a 200% dose has been proposed. The same recommendation was made in Germany several months after introduction of the drug onto the market.
9.1.3 Non-selective monoamine reuptake inhibitors/tricyclic antidepressants

Ever since the introduction of the first antidepressant, imipramine, and for a long time, tricyclics were the primary pharmacotherapeutic option in the treatment of depression. The TCA amitriptyline is even mentioned in the World Health Organization’s (WHO’s) list of essential drugs (World Health Organization, 2005a). Nevertheless, in recent years tri- and tetracyclic antidepressants have lost their status as first-line treatment for depression in several developed countries due in part to their particular side-effect profile and the introduction of newer antidepressants in these countries.

Even absent sufficient scientific justification for this approach, from a clinical point of view in preparing antidepressant treatment plans it may be useful to subdivide TCAs not only according their sedating and activating properties but also according to their influence on serotonergic, noradrenergic and dopaminergic neurotransmission.

In the event of treatment failure and pharmaco-therapy resistance, switching from serotonergic to noradrenergic or mixed action TCAs seems to be plausible. But unfortunately, controlled studies supporting this method are still lacking.

9.1.3.1 Efficacy

As described previously, TCA treatment is effective in depressive disorders, independent of subtype or severity of depression. Controlled studies comparing TCAs with other classes of antidepressants are provided within chapters 9.1.2 to 9.1.10. Especially in severely depressed, hospitalized patients mixed S/N-TCAs compare favorably with SSRIs (Anderson, 1998; Anderson, 2000a; Danish University Antidepressant Group, 1986; Danish University Antidepressant Group, 1990) and the RIMA moclobemide (Danish University Antidepressant Group, 1993), whereas SSRIs and MAOIs appear to be superior in depressive disorders with anergic or atypical features (see chapters 9.1.2.1 and 9.1.5.1). The influence of gender and depression subtype on antidepressant response is unclear, but higher age does seem to predict a better response to TCAs (Parker, 2002; Parker et al., 2003). From a clinical point of view, but again without sufficient support in the literature (Sartorius, 1974), TCAs with lesser sedating effects, such as clomipramine or desipramine, appear superior in retarded and anergic depression. TCAs with inherently stronger antihistaminergic effects, such as doxepin, amitriptyline and dosulepine, have advantages in agitated patients with significant sleep disturbances.

9.1.3.2 Safety and tolerability

The main concerns in using TCAs as a first-line treatment are anticholinergic and antihistaminergic side effects possibly influencing substantially tolerability and therapy adherence. Sedating properties may help in the treatment of depression-related sleep disturbance, but daytime drowsiness and sedation often lead to discontinuation of treatment. In the long term, increased appetite, resulting weight gain and in some cases even risk of enhancing the high rate of metabolic syndromes in depression also play a crucial role. Treatment safety can be increased by using modern antidepressants with greater specificity and a tolerability profile that includes a lower risk of cardiovascular and neurological side effects.

Suicidal behavior may be a further reason to be cautious in prescribing TCAs as first-line treatment. Whereas SSRIs, NaSSAs and SNRIs are associated with fewer completed suicide attempts in cases of drug overdose, a positive association between TCAs and fatal suicide attempts has been reported (Frey et al., 2002; Gibbons et al., 2005; Jonsson et al., 2004). One reason may be that despite the efficacy of TCAs in treating depression, they have greater toxicity compared with the newer antidepressants. This is especially true in case of overdose due to the electrocardiographically measured QTc time prolongation and enhanced cardiotoxicity caused by some, but not all TCAs.

9.1.4 Other modes of action not directly involving monoamines: the modified TCA tianeptine

Despite its modified tricyclic structure, initial studies showed that tianeptine did not share pharmacological properties with TCAs, MAOIs or SSRIs (Wilde and Benfield, 1995). Although acute in vitro and in vivo studies suggest that tianeptine enhances [3H]5-HT re-uptake into rat cortical and hippocampal synaptosomes (Fattaccini et al., 1990; Mennini et al., 1987), more recent studies assessing the release of serotonin

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51 TCAs are available in both oral and i.v. forms. There is no scientific evidence for a differential efficacy profile between them. See chapter 9.1.1.2.3 for a more detailed description of i.v. administration of antidepressants.

52 In chapter 11 (Suicidality and antidepressants: depression and suicide) the discussion about the postulated potential of SSRIs to induce suicidal ideations or suicide attempts has been evaluated in detail.
by microdialysis following chronic (14-day) administration clearly demonstrate that there is no significant change in serotonin release (Malagie et al., 2000). Previous studies had shown that, following chronic administration, tianeptine induces adaptive changes in cortical, but not hippocampal serotonin transporters (Pineyro et al., 1995a; Pineyro et al., 1995b).

Experimental studies now indicate that tianeptine has neuroprotective effects that contribute to its antidepressant properties (Defrance et al., 1988; McEwen and Olie, 2005). In this respect it resembles other classes of antidepressants (see chapter 8 for details). Thus, changes in neurogenesis and neuroplasticity of the hippocampus, cortex and amygdala may play a prominent role in the efficacy of tianeptine. In addition, tianeptine has been shown to change the neuronal architecture of the hippocampus and amygdala, and the rate of apoptosis in the hippocampus and temporal cortex, and to restore hippocampal volume following exposure to chronic stress (McEwen and Olie, 2005). Such effects have been explained in terms of modulation of glutamatergic transmission (see also chapter 8.2) (Kole et al., 2002; Reagan et al., 2004). In other words, experimental evidence suggests that changes in glutamatergic function reflect adaptive changes to stress of the glutamate transporter that are located on glial cells; any change in serotonergic function following tianeptine is therefore likely to be indirect.

9.1.4.1 Efficacy

The efficacy of tianeptine in most published studies was comparable to SSRIs (Kasper and Olie, 2002); only one RCT showed an advantage of fluoxetine in elderly patients (Guelfi et al., 1999). Comparison with other antidepressants such as amitriptyline (Guelfi et al., 1989; Invernizzi et al., 1994) and mianserin (Brion et al., 1996) also turned up no significant differences in efficacy.

9.1.4.2 Safety and tolerability

Tianeptine does not appear to be associated with severe anticholinergic or cardiovascular side effects (Loo and Deniker, 1988). Specific advantages in the case of comorbidities such as cardiovascular disorders (Pogosova et al., 2004) and Parkinson’s (Levin, 2006) disease have been described. The overall tolerability profile compared with SSRIs has been shown to be favorable, especially in the case of paroxetine (Kasper and Olie, 2002; Lepine et al., 2001). Nor have any detectably significant differences (in comparison with fluoxetine) been reported (Loo et al., 2001).

9.1.5 Selective serotonin reuptake inhibitors

9.1.5.1 Efficacy

Today, in many countries, SSRIs are the antidepressant substances prescribed most frequently as a first-line treatment (Ostacher et al., 2005). Good efficacy has been described for each of the currently available substances, regardless of the etiology or severity of depression. Although several reports suggest that some drugs may be superior to SSRIs (venlafaxine (Cipriani et al., 2005b; Cipriani et al., 2006; Smith et al., 2002; Thase et al., 2001), milnacipran (Puech et al., 1997), mirtazapine (Thase et al., 2006a)), it is difficult to interpret what these results mean clinically. For example, escitalopram has been shown to have comparable efficacy to venlafaxine (Kennedy et al., 2006). Escitalopram also demonstrates a statistically significant, but clinically speaking minimal superiority over the other SSRI, citalopram (Bech et al., 2004; Lepola et al., 2004; Moore et al., 2005). Consequently, use of escitalopram has been recommended (Montgomery, 2006), especially in severe depression (Llorca et al., 2005). Another RCT reports the superiority of escitalopram over both citalopram and paroxetine (Boulenger et al., 2006). Prior meta-analyses showed neither significant nor clinically relevant differences in efficacy (Edwards and Anderson, 1999). But a recently published pooled analysis of all available study data to date found significant advantages of escitalopram in comparison with several SSRIs, e.g. citalopram, fluoxetine and sertraline, and in comparison with the SNRI venlafaxine (Kasper et al., 2006). Nevertheless, more RCTs are needed to evaluate the clinical relevance of these findings, draw final conclusions and make specific recommendations.

Despite of the fact that SSRIs have shown no overall relevant inferiority compared with TCAs in a variety of randomized controlled trials (Möller et al., 1998) and meta-analyses (Geddes et al., 2000), there is some evidence of better efficacy and clinical effectiveness of TCAs in the subgroup of inpatients compared with outpatients (Anderson, 1998; Anderson, 2000a). This is especially true in comparing the TCA amitriptyline with SSRIs, taking into account that in most cases inpatients show a higher severity of the disease and a higher proportion of patients suffer from melancholic features of depression.

SSRIs and irreversible MAOIs also show an overall similar efficacy in the treatment of depression. Indeed, except among outpatients suffering from depression with atypical features (chapter 5.2.1.3.3), MAOIs give better results (Thase et al., 1995). In
addition, MAOIs show advantages during ultra-high-dose treatment in patients suffering from treatment-resistant depression, whereas increasing the SSRI doses has no substantial beneficial effect (Adli et al., 2005).

Despite their similarities, various SSRIs do have specific differences (Table 18).

### 9.1.5.2 Safety and tolerability

Different SSRIs show different safety profiles. Nevertheless, the safety and tolerability profile of SSRIs as a pharmacological group of compounds compares very favorably with TCAs (Mace and Taylor, 2000). Specifically, anticholinergic side effects especially are more common during TCA therapy. Therefore, lesser cardiovascular toxicity together with a lower risk for constipation and reduction of urinary flow can be expected. Also, anticholinergic side effects on the visual system, such as enhanced risk for worsening of angle-closure glaucoma and accommodation disturbances, are rare with SSRIs. Only paroxetine shows greater anticholinergic side effects and more adverse events, e.g. compared with the more selective escitalopram (Boulenger et al., 2006). The result is a lower discontinuation rate (Peretti et al., 2000) during SSRI treatment. In addition, SSRIs have proven safer than TCAs in cases of overdose (Barbey and Roose, 1998; Cheeta et al., 2004; Mason et al., 2000), which is beneficial during antidepressant treatment, especially in suicidal patients. In addition, a simplified dose regimen compared with TCA therapy diminishes the danger of antidepressant therapies being below therapeutic dose ranges. These factors all contribute to an efficacious and cost-effective first-line therapy in depression vis-à-vis TCAs despite higher prescription costs (Goldstein and Goodnick, 1998).

Nevertheless, clinicians need to be aware of the particular side-effect profile of SSRIs (Ferguson, 2001; Lader, 1996). The most frequent side effects following short-term treatment are gastrointestinal disturbances such as nausea, diarrhea and emesis. Also common are restlessness and agitation, sleep disturbances, dizziness and headache. During long-term SSRI

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**Table 18. Clinical highlights and differences among SSRIs based predominantly on clinical experience and consensus (modified according to Stahl, 1997; Stahl, 2006)**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Specific clinical features of SSRIs</th>
</tr>
</thead>
</table>
| Citalopram (Bezchlibnyk-Butler et al., 2000) | One of the most selective SSRIs  
Possibly lower incidence of sexual dysfunction  
Possibly better tolerability in the elderly  
Low interaction potential |
| Escitalopram (Baldwin, 2002) | One of the most selective and best-tolerated SSRIs  
Possibly rapid onset of action and high effect size during antidepressant treatment; good effect in anxious depression and comorbid anxiety disorders |
| Fluoxetine (Calil, 2001) | Good effect in atypical depression  
Good effect in patients with fatigue and low energy  
Long half-life, weekly administration possible |
| Fluvoxamine (Ware, 1997) | Good effect in anxious depression and comorbid anxiety disorders; potential advantages in psychotic depression  
Possibly lower incidence of sexual dysfunction  
Discontinuation effects after rapid tapering |
| Paroxetine (Green, 2003) | Good effect in anxious depression and comorbid anxiety disorders  
Mild anticholinergic action  
Discontinuation effects more likely than for other SSRIs |
| Sertraline (Khouzam et al., 2003) | Good effect in atypical depression; least selective over dopamine  
Low interaction potential  
More gastrointestinal side effects, but best documented cardiovascular safety |

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33 All possible interactions of antidepressants with other pharmacotherapeutics are beyond of scope of this review; the interactions described represent a selection and are not exhaustive.

34 In cases of acute angle-closure (closed-angle, narrow-angle) glaucoma, paroxetine is contraindicated due to greater anticholinergic side effects compared with other SSRIs (Bennett and Wyllie, 1999).
treatment sexual dysfunction, including loss of libido, anorgasmia and disturbances of erectile or ejaculatory function in men, are significant limitations of SSRI therapy. Some studies show these aspects to be less prominent with fluvoxamine therapy than with other SSRIs (Waldinger et al., 1998). Delayed ejaculation appears to occur more with paroxetine (Montego-Gonzalez et al., 1997). Discontinuation, restlessness and myoclonus together with hyperreflexia, tremor and pain syndromes together with unstable vital signs represent the potentially fatal serotonin syndrome (Boyer and Shannon, 2005). It may occur predominantly as an interaction of combining SSRIs with MAOIs or other serotonergic substances (e.g. S-TCAs or triptans used during acute therapy of migraine attacks), even during time intervals before and after treatment in dependency of the half-life of the substances, but also during SSRI monotherapy. In most cases, therefore, a washout period of 2 weeks (fluoxetine; 6 weeks before MAOI therapy) is recommended, and combining SSRIs and MAOIs is contraindicated. But there are published reports of good tolerability of combined therapy with SSRIs and triptans, possibly due to the fact that some triptans do not cross the blood-brain barrier after oral administration (Blier and Bergeron, 1995; Goldberg et al., 1999).

Rare side effects are weight gain, anticholinergic effects and extrapyramidal motor side effects (EPMSs). Caution must be exercised in prescribing SSRIs for patients suffering from Parkinson’s disease (Lemke, 2002), but there is no good evidence that SSRIs are associated with a worsening of motor features in Parkinson’s (Burn, 2002; Lemke et al., 2004). A very rare adverse event during SSRI therapy of younger patients, though not uncommon in the elderly, is inappropriate secretion of antidiuretic hormone (ADH) with possible electrolyte imbalance and hyponatremia leading to increased risk of seizures (Arinzon et al., 2002; Degner et al., 2004; Finkgeld, 2003). In addition, combined use of SSRIs and substances that increase the risk of bleeding events is discouraged owing to blockade of serotonin reuptake in platelets and subsequent platelet dysfunction (Serebruany, 2006). Risk of gastrointestinal hemorrhage in particular may be enhanced if nonsteroidal antiphlogistics or aspirin are combined with SSRIs (Weinrieb et al., 2005). Discontinuation symptoms can occur after SSRI treatment (Haddad, 2001) but seem to be rare events following treatment with fluoxetine, due to its long half-life, and some other SSRIs, e.g. sertraline (Sir et al., 2005) and escitalopram (Baldwin et al., 2005) (see also chapter 9.1.1.3.2).

9.1.6 Selective serotonin and noradrenaline reuptake inhibitors
9.1.6.1 Efficacy
SNRIs represent a group of newer antidepressants that act dually on serotonin and norepinephrine reuptake. Today, three substances of this group are available: venlafaxine, milnacipran and duloxetine. Compared with venlafaxine, duloxetine more potently blocks serotonin and noradrenaline transporters in vitro and in vivo (Bymaster et al., 2001). This is especially true for the noradrenaline reuptake-inhibiting effect after application of lower doses. Judging the comparative efficacy and clinical effectiveness is difficult because overall, newer antidepressants probably do not differ substantially with respect to these parameters for treatment of major depressive disorder (Hansen et al., 2005). Moreover, the available three SNRIs have been suggested to have similar efficacy (Stahl et al., 2005). Response rates during venlafaxine and duloxetine treatment were comparable, but patients treated with venlafaxine show a favorable trend in reaching remission (Vis et al., 2005). In comparison with the SSRIs sertraline (Sir et al., 2005) and escitalopram (Bielski et al., 2004; Montgomery et al., 2004b), venlafaxine demonstrated comparable efficacy effects in treatment of depressive disorders and quality of life. Venlafaxine has also proved to significantly reduce depressive symptoms compared with fluoxetine (Clerc et al., 1994). Several meta-analyses have also suggested superior efficacy of venlafaxine over SSRIs (Cipriani et al., 2005b; Cipriani et al., 2006; Smith et al., 2002), but because most of the studies investigated the efficacy of fluoxetine and paroxetine in comparison with SNRIs, the results must be evaluated carefully before conclusions about the efficacy of SSRIs as a pharmacological class can be drawn. The described superiority is reported to be enhanced when not only treatment response but also remission is used as an efficacy criterion (Stahl et al., 2005; Thase et al., 2001), but to date no sufficient evidence for a faster response of SNRIs in comparison to SSRIs has been published. In addition, better efficacy and tolerability of escitalopram over venlafaxine have been reported in the context of remission rates (Montgomery and Andersen, 2006), whereas a meta-analysis found no significant differences (Kennedy et al., 2006) (for review see Friedli et al., 2000; Miller et al., 2003; Scott and Freeman, 1992; Thase, 2004). Meta-analyses have shown milnacipran to have an antidepressant efficacy similar to that of imipramine and significantly superior to that of SSRIs (Puech et al., 1997). Direct comparisons between duloxetine and paroxetine in
RCTs showed, controversially, both superiority of the SNRIs (Goldstein et al., 2004) and no significant differences (Detke et al., 2004). Studies show duloxetine to have effectiveness similar to escitalopram (Hirschfeld and Vornik, 2004).

In contrast, direct comparisons between SNRIs (venlafaxine and milnacipran) and TCAs turned up no significant or clinically relevant differences in efficacy (Samuelian and Hackett, 1998; Van Ameringen et al., 2002). Direct comparison of venlafaxine and mirtazapine showed only trends in favor of mirtazapine but no significant differences (Guelli et al., 2001).

Besides its efficacy in treating depression, duloxetine has also been reported to significantly reduce painful physical symptoms (Detke et al., 2002).

### 9.1.6.2 Safety and tolerability

SNRI treatment has a favorable tolerability profile compared with TCAs; most adverse events occur early in treatment and tend to decrease or disappear with continued treatment (Stahl et al., 2005). Venlafaxine is similar to sertraline in terms of treatment efficacy and quality of life, but sertraline showed a more favorable tolerability profile with respect to discontinuation symptoms and the risk of elevated blood pressure (Sir et al., 2005). This risk seems to be less prominent in newer SNRIs such as duloxetine and milnacipran (Stahl et al., 2005). Nevertheless, duloxetine tends to have more adverse events than paroxetine (Detke et al., 2004; Goldstein et al., 2004). An extended release (ER) formulation of venlafaxine has tolerability advantages over the immediate release (IR) formulation (Norman and Olver, 2004; Olver et al., 2004) (see chapter 9.1.1.2). Hypertension may occur more frequently with high doses of venlafaxine than with low doses (Thase et al., 2006b). Discontinuation of the SSRI escitalopram results in a lower rate of reported discontinuation symptoms (Baldwin et al., 2005). In most studies SNRIs proved more efficacious than SSRIs and had better tolerability than TCAs, which at least in the case of milnacipran probably has a positive impact on the cost-effectiveness of treatment (Dardennes et al., 1999) (for more details on the cost-effectiveness of SNRIs see chapter 14.4.2). The fatal toxicity index for venlafaxine in cases of overdose seems to be in between that of SSRIs and TCAs (Koski et al., 2005), leading to the recommendation that venlafaxine be reserved as a second-line treatment after SSRIs (Medicines and Healthcare products Regulatory Agency, 2006; National Institute for Health and Clinical Excellence, 2004).

### 9.1.7 Selective noradrenaline reuptake inhibitors

#### 9.1.7.1 Efficacy

Controlled data directly comparing the single available NARI reboxetine 56 with other antidepressants are rare. One study looking at reboxetine and sertraline found no difference in response after 5 weeks of treatment, whereas reboxetine was found to be advantageous for remission between weeks 2 and 4, and at week 5 (Eker et al., 2005). Reboxetine was found to be similar to fluoxetine in efficacy for depressive disorders, and more effective in a subgroup of severely depressed patients (Massana et al., 1999). Among patients suffering from post-stroke depression, reboxetine was less efficacious in anxious depressed patients than citalopram, but more efficacious in retarded depressed patients (Rampello et al., 2004). In addition, reboxetine is reported to be at least as effective as other classes of antidepressants, including TCAs, and again in a subgroup of patients, in depressed patients with melancholic features, TCA was found to have advantages over reboxetine (Montgomery, 1998).

#### 9.1.7.2 Safety and tolerability

In all published studies, reboxetine showed a good safety and tolerability profile (Burrows et al., 1998). Reboxetine is safer and more tolerable than TCAs. NARI use was not associated with an increased risk of seizures, orthostatic hypotension or cardiovascular side effects. In addition, sexual dysfunction appears to be less common with reboxetine than with the SSRI fluoxetine (Clayton et al., 2003). Reboxetine has a different side effect profile than SSRIs, with advantages in terms of agitation, nervousness, anxiety and gastrointestinal events (Montgomery, 1998). Patients treated with reboxetine sometimes experience agitation and sleep disturbances; they may also be troubled by hyponidrosis. Despite the low anticholinergic activity of reboxetine, its α-receptor agonistic effects may affect micturation. In that event concomitant treatment with tamsulosin, an α1A-adrenoceptor antagonist, may prevent such patients from discontinuing reboxetine. Increased heart rate and blood pressure have also been reported. Weight loss occurs only rarely.

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55 The Medline database contains the wrong spelling ‘Van Ameringen’.

56 Reboxetine is available in Europe and Australia, but as mentioned above, to date it has not been marketed in the US.
9.1.8 α-Receptor-blocking tetracyclic antidepressants

9.1.8.1 Efficacy

To date the structurally similar tetracyclic antidepressants mianserin and mirtazapine represent the group of α2-receptor-blocking antidepressants. Mianserin was developed before mirtazapine and shows a higher affinity for the α2-adrenoceptor and more influence on noradrenaline (NA) reuptake (Kelder et al., 1997). Mianserin exerts only weak NA reuptake-inhibiting effects. Mirtazapine is characterized as its own class of antidepressant with noradrenergic and specific serotonergic properties (NaSSA). The α2-antagonistic effect of mirtazapine results in serotonergic activation, whereas the α1-antagonistic effect of mianserin counteracts the α2-antagonistic effect.

Both mianserin (Möller et al., 1995) and mirtazapine (Benkert et al., 2002) are described as being at least as effective as TCAs and have some advantages over other newer antidepressants (Szegedi and Schwertfeeger, 2005). In addition to its antidepressant effects, mirtazapine significantly improves sleep parameters associated with insomnia (Thase, 1999a). Mirtazapine also shows much more rapid onset of action than SSRIs (Benkert et al., 2000; Benkert et al., 2002; Blier, 2001; Blier, 2003; Quitkin et al., 2001; Tran et al., 2003). But owing to the retrospective character of some of these studies, further clarification is required of the hypothesis that these effects are caused not only by the sedating properties of mirtazapine but also its specific effects on other symptoms of depression. An RCT in elderly patients showed mirtazapine to have an earlier onset of action compared with the SSRI paroxetine (Schatzberg et al., 2002). It is better at reducing depressive symptoms than fluoxetine (Wheatley et al., 1998). Compared with other recently developed antidepressants, such as dual-action SNRIs and selective NARIs, mirtazapine shows no convincing differences in terms of overall efficacy or speed of onset (Möller, 2000; Olver et al., 2001). Nevertheless, from a clinical point of view, a significant advantage (and simultaneously a disadvantage, as described in chapter 9.1.8.2) of NaSSAs is their pharmacodynamic profile, including antihistaminergic properties, which are useful in treating depression-related sleep disturbances without the use of additional hypnotic substances. Mirtazapine is also available in the galenic form of fast dissolving tablets (see chapter 9.1.1.2).

9.1.8.2 Safety and tolerability

NaSSAs have a substantially better side-effect profile than a variety of TCAs (Blier, 2003; Montgomery, 1995; Tran et al., 2003). The safety of NaSSAs is similar to that of SSRIs (Olver et al., 2001), but typical serotonergic side effects such as sexual dysfunction and gastrointestinal complaints are less frequently present in mirtazapine-treated patients (Montgomery, 1995). The most frequently reported adverse events during mirtazapine therapy are antihistaminergic effects, such as initial somnolence and dizziness, together with increased appetite and cumulative weight gain over the long term (Tran et al., 2003). The weight gain often reduces patients’ compliance and may sometimes even facilitate development of a metabolic syndrome. Serious and potentially fatal side effects are rare, but clinicians need to be aware of the potential of both antidepressants to cause or enhance severe neutropenia (Ozcanli et al., 2005). In addition, mianserin is reported to carry a risk for agranulocytosis (Farmer, 1990; Girard, 1990; Launay et al., 2000). This is especially true in patients with an enhanced susceptibility for these side effects (see chapter 9.1.1.3.4) and in combination therapies (Imbarlina et al., 2004).

9.1.9 Serotonin modulating antidepressants

9.1.9.1 Efficacy

Nefazodone and its structural analog trazodone block 5-HT2 receptors, but only weakly inhibit the reuptake of serotonin and noradrenaline (Blier et al., 2006). One of the active metabolites of serotonin modulating antidepressants (SMAs) has 5-HT1 agonistic properties. The drugs are reported to work as well as the TCA imipramine and other older antidepressants (Cyr and Brown, 1996; Ellingrod and Perry, 1995). Nefazodone and trazodone are also as effective as the SSRIs fluoxetine, sertraline and paroxetine (Avila et al., 2003; Sussman et al., 2001). Trazodone is reported to be as effective as the SNRI venlafaxine in ameliorating depressive symptoms, and better at relieving sleep disturbances. It is less good, however, at improving cognitive disturbances and retardation (Cunningham et al., 1994). The NaSSA mirtazapine shows significant clinical advantages compared with trazodone in terms of overall efficacy (van Mofwaert et al., 1995). The sedating properties of nefazodone and trazodone make them particularly suitable for agitated patients and patients suffering from insomnia (Boerner and Möller, 1999; Thase, 1999a).

9.1.9.2 Safety and tolerability

SMAs have a safety margin similar to TCAs, but a more favorable tolerability profile (Lader, 1996), with lower anticholinergic and antihistaminic activity (Taylor et al., 1995). The specificity of action of SMAs
on neurotransmitter systems is believed to be the reason for the enhanced safety and tolerability of the drugs (Nemeroff, 1994). The side-effect profile of SMAs is also different from that of SSRIs; the most commonly reported side effects are sedation, dry mouth, nausea, somnolence and dizziness (Cunningham et al., 1994; Cyr and Brown, 1996). Trazodone may enhance the risk of priapism. Patients taking SMAs report fewer complaints of nervousness, insomnia and sexual dysfunction compared with SSRIs (Preskorn, 1995). Nevertheless, several case reports show that the potential of nefazodone to cause severe hepatotoxicity and even fulminant hepatic failure (Conway et al., 2004; Schirren and Baretton, 2000; Tzimas et al., 2003) makes reliable clinical monitoring crucial (Lucena et al., 2003). The original producer has withdrawn nefazodone from the market, but in some countries, including the US, generic versions of the drug are available. Trazodone is still available in eastern countries, such as China and Hong Kong, Indonesia, Japan, Korea and Thailand.

9.1.10 Dopamine and noradrenaline reuptake inhibitors

9.1.10.1 Efficacy

The mechanism of action of DNRIs is still not completely clear or understood. The FDA classifies DNRIs as B-category antidepressants. In a variety of countries bupropion is approved only for smoking cessation, but not as an antidepressant. Nevertheless, it is used off-label for combination therapies, especially in the case of treatment-resistant depression.

Bupropion shows significant antidepressant efficacy at least equal to the SSRIs sertraline (Coleman et al., 1999; Croft et al., 1999; Kavoussi et al., 1997), fluoxetine (Coleman et al., 2001; Feighner et al., 1991; Workman and Short, 1993) and paroxetine (Weisbs et al., 2000). The same is true of comparison with the TCA doxepin (Feighner et al., 1986), but the improvement in sleep parameters was more pronounced in the doxepin group. Likewise, no difference in efficacy is evident between bupropion and the TCAs amitriptyline (Remick et al., 1982) and imipramine (Workman and Short, 1993). The same comparative study revealed no differences in efficacy between bupropion and the SNRI venlafaxine and the SMA trazodone (Workman and Short, 1993). Despite a few contradictory results, its good efficacy combined with a lower switch risk than SNRIs argues for recommending bupropion especially in the treatment of bipolar depression (Post et al., 2006; Thase, 2005).

9.1.10.2 Safety and tolerability

Compared with patients treated with the SSRI sertraline, patients treated with bupropion show a lower rate of serotonergic side effects, such as sexual dysfunction, gastrointestinal complaints, insomnia and agitation (Coleman et al., 1999; Croft et al., 1999; Kavoussi et al., 1997). Particularly in male patients, sexual dysfunction may be prominent and can be reduced by using an ER formulation of bupropion. In addition, side effects are reportedly fewer with bupropion than with fluoxetine (Coleman et al., 2001). Patients given doxepin had predominantly more anticholinergic and antihistaminergic side effects than those given TCAs (Feighner et al., 1986). Bupropion has also been classified as a B-group antidepressant for use during pregnancy. Although the risk for generalized seizures is considered to be a rare consequence of bupropion treatment (Montgomery, 2005), it must be taken into account in treatment plans using bupropion (Ross and Williams, 2005). This risk may be further enhanced under conditions that increase the chance of seizures, such as alcohol withdrawal, anorexia and bulimia (Horne et al., 1988). Indeed, in cases of accidental or intentional overdose, generalized seizures seem to be a relatively frequent complication (Pesola and Avasarala, 2002; Shepherd et al., 2004).

9.1.11 Herbal preparations used in the treatment of depression

Although herbal treatments make up a reasonable share of antidepressant prescriptions in some countries, e.g. Germany, whether they should be classified as antidepressants is a matter of ongoing controversy (Bauer et al., 2002c). The main reason is that RCTs have not shown these medications to be useful in cases of severe depression. An additional reason is the uncertainty regarding their precise pharmacological mechanism of action. Nevertheless, a variety of herbal substances with possible antidepressant effects have been investigated in less-sophisticated studies and less severely depressed patients. For most of these substances, e.g. Kava-Kava extract, no antidepressant effects could be demonstrated. For others, RCTs have shown antidepressant effects (Akhondzadeh et al., 2005), but to date, no placebo-controlled replication studies have been published.

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57 The mechanism of action of bupropion is still unclear. It may be related to inhibition of presynaptic dopamine and noradrenaline (norepinephrine) reuptake transporters (Foley et al., 2006), but positron emission tomography (PET) studies in humans show no effects on dopamine or noradrenaline transporters at therapeutic doses (Kugaya et al., 2003; Learned-Coughlin et al., 2003; Meyer et al., 2002).
9.1.11.1 Efficacy

The most studied of the herbal substances is St. John’s wort (Hypericum perforatum). It is worth noting that many different preparations of St. John’s wort are available over-the-counter, and these differ in the number, concentration and balance of active and inactive, helpful and potentially harmful constituents. Both serotonergic mechanisms and MAO inhibition have been proposed as antidepressant modes of action (Delitto and Beyer, 1998). In addition, mechanisms similar to those of SSRIs, but to a lesser extent, have been reported (Kasper and Schulz, 1999). Despite some controversy in findings (Shelton et al., 2001a), studies conclude that Hypericum is suitable for treatment of mild to moderate depressive syndromes (Kalb et al., 2001; Kasper, 2001; Lecrubier et al., 2002; Uebelhack et al., 2004; Wong et al., 1998) if preparations provide sufficient concentrations of hypericin. In some countries, it has already been approved for that indication. In randomized controlled studies, Hypericum was therapeutically equivalent to the SSRIs fluoxetine (Behnke et al., 2002; Schrader, 2000), paroxetine (Szegedi et al., 2005) and sertraline (Brenner et al., 2000; Gastpar et al., 2005). Indirect comparisons with fluoxetine show no relevant differences in efficacy (Volz and Laux, 2000). Even advantages of Hypericum over fluoxetine have been demonstrated (Fava et al., 2005a), but neither active compound exhibited statistically significant superiority over placebo. Nevertheless, remission rates were higher in SSRI-treated patients (Bjerkenstedt et al., 2005). Therapeutic equivalence to imipramine and superiority over placebo have been shown in the treatment of mild to moderate depression (Philipp et al., 1999; Woelk, 2000). Recent meta-analyses show inconsistent results (Linde et al., 2005). Hypericum reportedly shows effectiveness similar to low-dose TCA (Kim et al., 1999) or SSRI therapy (Kasper and Dienel, 2002), but problems of design in some studies prohibit definite conclusions.

9.1.11.2 Safety and tolerability

Comparative studies show significantly better tolerability of Hypericum compared with SSRIs and TCAs (Bjerkenstedt et al., 2005; Szegedi et al., 2005; Woelk, 2000). In particular, Hypericum was devoid of anticholinergic side effects, sedation, gastrointestinal disturbances and sexual dysfunction (Trautmann-Sponsel and Dienel, 2004). The substance is considered to be safer than TCAs with regard to cardiac function (Czekalla et al., 1997). Nevertheless, risks to be aware of include photosensitization (Kasper, 2001; Kasper and Schulz, 1999). Because Hypericum involves serotonergic mechanisms and monoamine oxidase inhibition, concurrent use of SSRIs and MAOIs should be avoided (Delitto and Beyer, 1998). Treatment with Hypericum, which induces both CYP3A4 and the drug transporter protein P-glycoprotein, can result in pharmacokinetic interactions with serious clinical consequences, such as loss of activity of comedication (Henderson et al., 2002; Hennessy et al., 2002; Izzo and Ernst, 2001). This outcome has been demonstrated for digoxin (Johne et al., 1999) and cyclosporine (Ruschitzka et al., 2000) owing to induction of hepatic metabolizing enzymes, and for contraceptives, especially in case of low-dose oral contraception (Murphy et al., 2005). To date no results have been published concerning discontinuation symptoms following tapering of Hypericum.

9.1.11.3 Morinda officinalis, Jieyu and Banxia Houpu decoction (Chinese traditional herbal medicine)

Morinda officinalis (Cui et al., 1995) and a decoction/brew of Banxia Houpu (Luo et al., 2000) are herbal medicines that have been used since ancient times...
in traditional Chinese medicine to treat depression-associated symptoms. Jieyu pill and decoction have been investigated in patients suffering from depressive symptoms and showed antidepressant properties in randomized, but not placebo-controlled studies (Feng et al., 2004; Shen et al., 2004). To date, putative antidepressant effects and possible mechanisms of action of *Morinda officinalis* and Banxia Houpu have been investigated in animal models of depression (Li et al., 2001; Zhang et al., 2002). In addition, phase III clinical trials are ongoing. It is thus premature to draw final conclusions about the possible antidepressant efficacy and effectiveness of these compounds.

9.1.12 Strategies in the event of non-response to antidepressant treatments: combination and augmentation

9.1.12.1 The concept of non-response to antidepressant treatment

Patients who do not respond to at least two antidepressant monotherapies (in some wider definitions even one) are usually referred to as treatment resistant. However, reasons for this ‘treatment resistance’ or ‘non-response to antidepressant treatment’ (see also Box 7, definition of pharmacotherapy-resistant depression) may vary and often do not reflect true resistance to treatment. The definition by Ananth (Ananth, 1998) as a ‘failure to respond adequately to two successive courses of monotherapy with pharmacologically different antidepressants given in adequate dose for sufficient length of time’ includes a number of prerequisites: correct diagnosis, adequate treatment in terms of dosage, duration and compliance, and unsuccessful previous therapy.

Before switching antidepressants, sufficient length of treatment (see chapter 9.1) and the adequacy of dosage should be considered. If in doubt, TDM (see chapter 9.1.1.1.3) may be helpful to ensure adequate blood levels of medication (Corruble and Guelfi, 2000). Switching strategies after unsuccessful antidepressant trials often results in low remission rates (Fava et al., 2006). Adli et al. (Adli et al., 2005) conducted a systematic review of whether dose escalation leads to additional benefit following failure of a medium dose. They concluded that ‘available data suggest differential efficacy of various pharmacological classes at more than medium dosage. Direct evidence shows no increase of efficacy with high-dose selective serotonin reuptake inhibitor (SSRI) treatment; however, indirect evidence suggests enhanced therapeutic efficacy with high-dose tricyclic antidepressants. Few clinical data show ultra-high-dose treatment with the irreversible MAOI tranylcypromine to be effective for refractory depression. Data concerning other selective compounds are insufficient to allow any definitive conclusion on the benefit of high-dose treatment.’ Recently published reviews summarize the actual knowledge about switching strategies (Ruhe et al., 2006b) and dose escalating strategies (Ruhe et al., 2006a) which are especially recommended in case of partial response.

Factors in addition to pharmacological treatment resistance that may lead to less favorable outcomes include psychiatric comorbidity, e.g. alcohol and substance abuse, personality disorders and anxiety and panic disorder (Adli et al., 2005). Sharan and Saxena (Sharan and Saxena, 1998) have identified several other factors predictive for poor response, including a family history of affective disorders, severity of depression, suicide attempts, number of previous episodes, long duration of depression prior to treatment, negative life events and poor social support. Awareness of these factors and adequate action, e.g. addition of psychotherapy with negative life events, are an a priori requisite for making pharmacological changes. In addition it is essential to be aware of all factors influencing the patients’ compliance (Demyttenaere et al., 2001a; Demyttenaere et al., 2001b). Treatment-resistant depression may also influence vulnerability to other mental disorders. For example, the incidence of dementia is significantly increased in older patients with insufficiently treated depression (Shim and Yang, 2006). In support of these results, magnetic resonance imaging (MRI) findings showing decreased hippocampal volumes in treatment-refractory depressed patients, and enhanced neuronal plasticity and cellular resilience may indicate a new direction for developing novel, improved therapeutics for difficult-to-treat depression (Manji et al., 2003).

Figure 3 summarizes a stepwise approach for managing non-response to an initial antidepressant.

9.1.12.2 General introduction to combination and augmentation

When a previous monotherapy has not been efficacious at all, even after a trial with maximum dosage, switching medication is usually recommended (Kennedy et al., 2001). A recently published analysis of the National Institute of Mental Health Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial pointed out that approximately 25% of patients non-responsive to citalopram benefit from switching either to sertraline, bupropion or venlafaxine (Rush et al., 2006c).
However, when response is partial, it may be unwise to discontinue premedication and risk worsening of symptoms. Thus, combination with another antidepressant or augmentation should be considered. Sufficient evidence now exists that combining antidepressants or augmentation strategies could be more effective than monotherapy in some patients (Kennedy et al., 2001). Combination treatment is defined as addition of another medication without expecting potentiation of efficacy of the previous drug (see Box 10). Benefits as well as side effects are additive. Usually, a medication with an alternative and different pharmacology or a drug with a dual mechanism of action is chosen for combination treatment (see also chapter 9.1.12.2.1). In contrast, augmentation means adding another agent that by itself may be not specifically helpful as a primary treatment of depression but that may enhance responsiveness to a given antidepressant (see Box). Examples for these strategies, ordinarily used in antidepressant non- or only partially responsive patients, include lithium, thyroid hormones, pin dolol and buspirone, and more recently, also some atypical antipsychotics. Table 19 summarizes common augmentation strategies.

Figure 3. A stepwise approach to managing patients with inadequate response to antidepressant therapy (adopted from Hirschfeld et al., 2002). * TDM should be implemented in routine care (Mann et al., 2006b). It is especially recommended in case of treatment failures.

9.1.12.2.1 Combination treatment

9.1.12.2.1.1 Combination of different antidepressants

Although we lack scientific evidence to define specific and effective next-step treatment options for treatment-resistant depressive disorders (Rush et al., 2004), combination of antidepressants is a very common strategy in such cases (de la Gandara et al., 2005a; Schatzberg, 2004). Generally, antidepressants with different pharmacological profiles are combined. In a recent literature search, Dodd et al. (Dodd et al., 2005) identified only 8 randomized trials between 1978 and 2004 that studied combinations of antidepressants, 5 of them including fluoxetine. In addition, 16 open-label trials were identified, most of them using again at least one SSRI. Combining antidepressants with predominant serotonergic and noradrenergic properties, e.g. prescribing SSRIs and SNRIs, is also one of the most frequent clinical therapeutic options (de la Gandara et al., 2005a). SSRIs and NaSSAs are also frequently used in combination. A combination of the SSRI fluoxetine and the tetracyclic α2-blocker mianserin showed superior efficacy over placebo in several studies (Dam et al., 1998; Ferreri et al., 2001). Especially in the case of prior treatment resistance, combining two dual-action substances, such as mirtazapine and venlafaxine, can be of clinical use, but more controlled studies confirming the superior effectiveness of these combinations are required (de la Gandara et al., 2005b; Rojo et al., 2005). Further reasons for combining different antidepressants are specific side-effect profiles, e.g. using antihistaminergic properties of one antidepressant for early amelioration of sleep disturbances or improvement of appetite, especially in geriatric depression.

9.1.12.2.1.2 Safety and tolerability

Combining two or even more antidepressants can enhance tolerability (King et al., 1994), owing to clinical effectiveness of lower doses: sexual dysfunction due to SSRI treatment may be reduced using lower dosages within combination strategies. For example, bupropion showed a reduced rate of sexual dysfunction compared with some SSRIs (Coleman et al., 1999; Coleman et al., 2001; Croft et al., 1999). At the same time, a variety of possible pharmacokinetic interactions (Baumann, 1996) enhances risk for severe adverse events, e.g. increased TCA toxicity due to cytochrome P-450 inhibition by fluoxetine or fluvoxamine (for more details see chapter 9.1.1.1). The fact that TDM of these compounds is not widely practiced
Box 10. Definition of combination and augmentation treatment

- **Combination treatment**: combination of two or more treatments, each of which represents an antidepressant alone.
- **Augmentation treatment**: efficiency amplification of an antidepressant treatment with a substance that alone does not exert sufficient antidepressant activity to be used as a monotherapy.

makes this risk more likely. Further increased risk is associated with additional somatic diseases that require additional pharmacologic treatment.

9.1.12.2.1.2 Combination of ECT and antidepressants

9.1.12.2.1.2.1 Efficacy

A further option in enhancing the effectiveness of antidepressant treatments may be concomitant use of ECT in combination with antidepressants. Such a step may be necessary due to possible non-responsiveness to ECT in 15–25% of depressed patients (Husain et al., 2004). However, study results regarding a putative benefit of combining ECT with TCAs (Lauritzen et al., 1996; Nelson and Benjamin, 1989) and the lack of benefit of other concomitant medication, like SSRIs, are still controversial (Lauritzen et al., 1996). In particular, investigations of the efficacy of modern antidepressants in combination with ECT, e.g. the dual-action substances mirtazapine and venlafaxine, are rare (Baghai et al., 2006b; Farah, 1997).

Owing to the severity of depressive syndromes in patients following medication treatment failure, the clinical recommendation is to combine ECT with antidepressants at moderate doses over the entire course of treatment. When that is not possible, antidepressants should be used at least during the last 2 weeks of ECT treatment to prevent exacerbation of depression following ECT during the usual latency until antidepressant response is achieved following initiating pharmacotherapy or to use continuation ECT (see chapter 12.2.3).

9.1.12.2.1.2.2 Safety and tolerability

Combining ECT with TCAs and SSRIs has been described as a safe procedure (Lauritzen et al., 1996; Nelson and Benjamin, 1989). Moreover, safety data on such combinations are available: in a recent study venlafaxine at dosages lower than 300 mg/day was shown to be safe in combination with ECT. In high-dose treatments above 300 mg/day, side effects of a cardiovascular nature, such as transient asystolia and bradycardia, were more frequent when ECT was combined with propofol anesthesia (Gonzalez-Pinto et al., 2002). Combination of ECT and MAOIs should be treated with particular caution. In fact, it should be avoided, if possible, owing to enhanced risk for sometimes lethal complications, especially shortly after starting pharmacological treatment (Naguib and Koorn, 2002). At the very least a 2-week washout period should be observed. The combination of ECT with lithium increases the risks associated with anesthesia (Hill et al., 1976; Hill et al., 1977; Reimherr et al., 1977), the risk of prolonged seizures (Sartorius et al., 2005) and the risk of cognitive disturbances. But it represents only a relative contraindication due to reports of safe use of this combination and the specific risk of discontinuing lithium treatment.

9.1.12.2.2 Augmentation treatment

Augmentation strategies have some advantages over switching antidepressants. They eliminate the period of transmission from one antidepressant to another and build on the partial response. Consequently, if they work, they can be rapidly effective; they may, however, also raise tolerability and safety issues. As combination treatment has been dealt with extensively in the previous chapter (see chapter 9.1.12.2.1), we will now concentrate only on the different augmentation strategies tested in unipolar depression.

9.1.12.2.3 Lithium

Of all the strategies listed in Table 19, lithium augmentation is the best described (Bauer et al., 2003; Bschor and Bauer, 2006; Zullino and Baumann, 2001).

A multitude of open and 12 randomized placebo-controlled trials, including a meta-analysis (Bauer et al., 2003), support the efficacy of lithium augmentation in the acute treatment of treatment-resistant unipolar depression. Lithium has been found to augment the therapeutic effects of a broad spectrum of antidepressants, including TCAs (Bauer et al., 2003; Bauer and Döpfmer, 1999) and SSRIs (Joffe et al., 1993; Katona et al., 1995). The meta-analysis by Bauer and Döpfmer (Bauer and Döpfmer, 1999) also demonstrated that lithium augmentation is superior to placebo augmentation, with a response rate of about 40–50% at week 3 or 4 across studies, but only 20% of patients respond as early as week 1. To allow full assessment of patient response, lithium augmentation should be administered for at least 4 weeks, ensuring
serum levels of 0.6–0.8 mmol/l (Bauer et al., 2002c). Once stabilized on the combination, it is unwise to withdraw lithium for at least a year (Bauer et al., 2000). However, the utility of lithium augmentation may be limited by side effects, e.g. polyuria, muscular weakness and tremor. Especially in older patients lithium toxicity may occur even within therapeutic plasma levels and might present itself with a clinical picture that is not always easy to differentiate from an increase in severity of depression. Electroencephalogram (EEG) may be a helpful monitoring tool for differential diagnosis in this clinical situation (Gallinat et al., 2000). Whether the potential neurotoxicity of lithium plays a major role in clinical practice or even has a distinct neuroprotective effect cannot yet be concluded. Patients on lithium therapy should be closely monitored and regularly assessed for the presence of side effects from the central nervous system (CNS) even when their serum lithium levels are within therapeutic levels. Research may be needed to develop better ways to monitor lithium, possibly by substituting plasma levels with other, more reliable indices. A candidate index could be red blood cell lithium levels. This issue has been discussed in an extensive review recently (Fountoulakis et al., 2006). It is also unclear whether lithium augmentation has the same efficacy across age groups. Some publications point to a low response rate and a high rate of severe side effects in the elderly.

9.1.12.2.4 Thyroid hormones

At least 13 prospective trials (9 open and 4 controlled double-blind studies) support the usefulness of triiodothyronine (T<sub>3</sub>) with most studies employing 25–35.5 µg/day (Bauer et al., 2002c). Women especially seem to respond favorably to thyroid hormone

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**Table 19. Biological treatment strategies for partial and non-responding patients with major depressive disorders.**  
Modified from WFSBP Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1 (Bauer et al., 2002c)

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Mechanisms/drug classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological augmentation</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>Mood stabilizer</td>
</tr>
<tr>
<td>Lamotrigine, valproate, carbamazepine</td>
<td>Anticonvulsants/mood stabilizer</td>
</tr>
<tr>
<td>Amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone</td>
<td>Antipsychotic agents, 5-HT&lt;sub&gt;2&lt;/sub&gt; antagonism</td>
</tr>
<tr>
<td>Pindolol</td>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt; autoreceptor antagonist, β-receptor blocker 5-HT&lt;sub&gt;1A&lt;/sub&gt; and D&lt;sub&gt;2&lt;/sub&gt;-receptor agonist</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Dopamine and noradrenaline release and reuptake inhibition</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Dopamine (D&lt;sub&gt;1&lt;/sub&gt;/D&lt;sub&gt;2&lt;/sub&gt;) agonist</td>
</tr>
<tr>
<td>Pergolide</td>
<td>Dopamine (D&lt;sub&gt;2&lt;/sub&gt;) agonist</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Dopamine (D&lt;sub&gt;2&lt;/sub&gt;) agonist</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Reuptake inhibition of biogenic amines</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Reuptake inhibition of biogenic amines</td>
</tr>
<tr>
<td>Hormone augmentation</td>
<td>Thyroid hormone</td>
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<tr>
<td>Triiodothyronine (T&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>Thyroid hormone</td>
</tr>
<tr>
<td>L-Thyroxine (T&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>Thyroid hormone</td>
</tr>
<tr>
<td>Estrogen (only women)</td>
<td>Ovarian steroid hormone</td>
</tr>
<tr>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>Adrenal androgen hormone</td>
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<tr>
<td>Miscellaneous</td>
<td>Peripheral cortisol suppression</td>
</tr>
<tr>
<td>Ketokonazole, metyrapone</td>
<td>Essential amino acid, 5-H'T' precursor</td>
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<tr>
<td>L-Tryptophan, 5-hydroxytryptophan</td>
<td>Food supplement</td>
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<tr>
<td>Ω-3 fatty acids</td>
<td>Vitamin</td>
</tr>
<tr>
<td>Folic acid (only women)</td>
<td>Vitamin</td>
</tr>
<tr>
<td>Non-pharmacological</td>
<td>Electric stimulation to elicit an epileptiform seizure in brain</td>
</tr>
<tr>
<td>Electroconvulsive therapy</td>
<td>Non-invasive stimulation of the cerebral cortex</td>
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<tr>
<td>[Repetitive transcranial magnetic stimulation]</td>
<td>Autonomic signals to limbic and cortical function</td>
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<tr>
<td>[Vagus nerve stimulation]</td>
<td>Chronotherapeutics</td>
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<tr>
<td>Phototherapy (bright light therapy)</td>
<td>Chronotherapeutics</td>
</tr>
<tr>
<td>Wakefulness therapy (sleep deprivation)</td>
<td>Chronotherapeutics</td>
</tr>
<tr>
<td>Physical exercise</td>
<td>Supportive procedure</td>
</tr>
</tbody>
</table>

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by guest on October 7, 2016 http://ijnp.oxfordjournals.org/ Downloaded from
augmentation (Altshuler et al., 2001). A three-arm, double-blind controlled study showed equal efficacy of augmentation with T₃ and lithium, and superiority to placebo (Joffe et al., 1993). A recently published STAR*D report confirmed the similar efficacy of T₃ and lithium with lower rates of adverse events and slightly (but nonsignificant) higher remission rates in the T₃ group (Nierenberg et al., 2006a). However, as not all controlled double-blind studies showed significant results in favor of T₃, a subsequent meta-analysis found inconsistent results favoring T₃ augmentation (Aronson et al., 1996). Recently, augmentation with L-thyroxine (T₄) has been postulated as an alternative to T₃, and open studies and functional neuroimaging support the efficacy of this approach (Bauer et al., 2002a; Bauer et al., 2005). Double-blind controlled studies are still missing, however. When adding T₄ evidence so far suggests that supraphysiological dosages should be used; comparison of only 150μg/day of T₄ with 37.5μg/day of T₃ showed significantly lower response rates for T₄ (24 vs. 53%) (Joffe and Singer, 1990). In some studies, dosage up to 500μg/day of T₄ have been used with good efficacy and satisfactory tolerability (Bauer et al., 1998). However, the use of T₄ in treatment-resistant unipolar depression is still experimental, and for now evidence is on the side of T₃.

9.1.12.2.5 Anticonvulsants

Surprisingly little has been published regarding a potential augmentative effect of anticonvulsants in unipolar depression. Open studies of valproate (Davis et al., 1996; Svestka et al., 1990) and carbamazepine (Post et al., 1986) suggest antidepressant properties (Normann et al., 2002; Post et al., 1986). However, verification by double-blind studies is still missing, and in addition, studies of augmentation with carbamazepine show that it induces metabolism of venlafaxine and citalopram, and that it may be necessary to increase the dose of the antidepressant (Ciusani et al., 2004; Steinacher et al., 2002).

In a double-blind add-on study to paroxetine in non-treatment-resistant patients, lamotrigine showed a faster onset of response but no significant difference in the outcome after 10 weeks (Normann et al., 2002).

As far as treatment-resistant depression is concerned, however, there is some evidence from open studies for the augmentative efficacy of carbamazepine (Cullen et al., 1991; Rybakowski et al., 1999; Varney et al., 1993). The augmentative efficacy of lamotrigine has been reported both in open and retrospective studies (Barbee and Jamhour, 2002), as well as in one small double-blind study (Barbosa et al., 2003). Most of these studies (Barbosa et al., 2003; Blier and Ward, 2003), however, were conducted in mixed samples of unipolar and bipolar II patients. Absent a separate analysis, it is impossible to draw any clear conclusions as far as unipolar treatment-resistant depression is concerned. In summary, the evidence for the usefulness of augmentation with anticonvulsants remains weak.

9.1.12.2.6 Pindolol

A potential role of 5-HT₁A agonists in treating depression and anxiety has been a major focus of research in the past decade (Blier and Ward, 2003). Pindolol is a β-adrenoreceptor antagonist. It also blocks 5-HT₁A and 5-HT₁B/₁D receptors, and therefore should prevent the negative feedback effect of increased somatodendritic serotonin (Dawson and Nguyen, 2000). As a consequence, this action may accelerate the onset of antidepressant action (Artigas et al., 2001; Artigas et al., 2006).

A meta-analysis by Ballesteros and Callado (Ballesteros and Callado, 2004) of nine randomized controlled studies on the augmentative effects of pindolol for SSRIs showed increased response with pindolol after 2 weeks. After 6 weeks no difference in outcome was observed. Despite positive open studies, three out of four controlled trials have failed to show advantage over placebo in treatment-refractory patients (Moreno et al., 1997; Perez et al., 1999; Segrave and Nathan, 2005). Only one small study applying once-daily high-dose pindolol (7.5 mg) demonstrated a significant advantage (Sokolski et al., 2004). In their review on pindolol augmentation, Segrave and Nathan (Segrave and Nathan, 2005) speculate that the 2.5-mg twice daily (t.i.d.) dose of pindolol that has been used in all but one of these investigations may be suboptimal for achieving reliable and significant occupancy of 5-HT₁A autoreceptors, as shown by positron emission tomography (PET) data (Rabiner et al., 2001) and may explain the contradictory nature of the results of investigations of pindolol augmentation.

9.1.12.2.7 Buspirone

Buspirone is a partial 5-HT₁A agonist that is believed to activate postsynaptic 5-HT₁A receptors and thus may enhance the action of SSRIs. In addition, it has been reported that it exerts affinity to D₁ and to a lesser extent to D₂ and D₃ receptors with α₁- and α₂- antagonistic activity (Millan et al., 2000). A major metabolite of buspirone enhances norepinephrine
release. Therefore, buspirone may also exert a dual mechanism of action. However, in two double-blind placebo-controlled studies, buspirone augmentation both to fluoxetine and citalopram failed to demonstrate significant benefit over placebo (Appelberg et al., 2001; Landen et al., 1998) The study by Appelberg, however, suggests at least a potential benefit in more severe depression in a post hoc subanalysis (Appelberg et al., 2001). Recently, the STAR*D study investigated the efficacy of buspirone versus bupropion augmentation in SSRI non-responders. In most outcomes, the rate of improvement was similar for both strategies, but buspirone was associated with more tolerability problems (Trivedi et al., 2006a). Clearly, further controlled studies are required to clarify the role of 5-HT1A agonist in augmenting antidepressants.

9.1.12.2.8 Tandospirone

Similar to buspirone, tandospirone is a 5-HT1A receptor agonist used in treating anxiety disorders. In a Japanese study, the efficacy of augmentation of clomipramine by tandospirone in 36 untreated outpatients with major depressive disorder was evaluated and compared with clomipramine monotherapy and clomipramine plus diazepam. Outcome after 6 weeks, measured with the HAMD (17 items, HAMD-17) and the Hamilton Anxiety Rating Scale (14 items; HAMA-14) showed no statistically significant difference. However, at 2 weeks, the percentage improvement of the HAMD-17 score in the tandospirone plus clomipramine group tended to be higher, though not statistically significant, than in the other groups (Yamada et al., 2003a). More studies are required to ascertain whether augmentation of antidepressants by tandospirone for a few weeks might enhance the onset of antidepressant response.

9.1.12.2.9 Second-generation antipsychotics

First-generation medium-potency antipsychotics, such as sulpiride, have been shown to accelerate and improve antidepressant (SSRI) treatment (Uchida et al., 2005). More recently, the use of atypical antipsychotics (see Table 19) to augment antidepressants in non-psychotic depressive disorder has also been advocated. In addition, antidepressant effects of monotherapy with some of those substances have been published both for bipolar (Post and Calabrese, 2004) and unipolar depression (Amore and Jori, 2001). Zhang et al. demonstrated that in the rat prefrontal cortex the combination of olanzapine and fluoxetine produced robust, sustained increases in extracellular levels of dopamine and norepinephrine up to 361 ± 28% and 272 ± 16% of the baseline, respectively, which were significantly greater than either drug alone (Zhang et al., 2000). Thus, the combination of olanzapine and fluoxetine has been tested in several controlled studies both in unipolar and, more extensively, bipolar depression. A small placebo-controlled study of olanzapine added on to fluoxetine supports this strategy (Shelton et al., 2001b). In a second study the olanzapine/fluoxetine combination was superior to olanzapine alone in the treatment of depression with psychotic features (Rothschild et al., 2004). Moreover, a larger double-blind study that compared monotherapy with fluoxetine, nortriptyline and olanzapine against olanzapine/fluoxetine combination in patients with treatment-resistant depression also significantly favored the antidepressant/antipsychotic combination (Shelton et al., 2005).

A large open study showed acute responsiveness of previously SSRI (citalopram) treatment-resistant patients to augmentation with low doses (0.25–2 mg/day, depending on age) of risperidone (Nemeroff et al., 2004). After a 6-week augmentation phase, 68.1% of the patients with treatment-resistant depression receiving add-on risperidone were classified as responders. However, significant superiority against citalopram monotherapy was not maintained in the subsequent double-blind continuation phase. Recently, another placebo-controlled study on risperidone augmentation that included 97 patients who met criteria for unipolar non-psychotic major depression and failed to respond, or only partially responded, to at least a 5-week trial of an adequate dose of antidepressant monotherapy. Primary outcome (remission status) was determined by a Montgomery–Åsberg Depression Rating Scale (MADRS) rating ≤10 to denote remission. At the end of 4 weeks of treatment 51.6% of the risperidone augmentation group remitted compared with 24.2% of the placebo augmentation group (p = 0.011) (Nemeroff et al., 2004). Augmentation with risperidone has also been compared with addition of bupropion as a second antidepressant to SSRIs in a small, double-blind study. Although there was no significant difference in any outcome score at the end of the study (week 6), risperidone produced a more robust effect as early as week 1 (Papakostas et al., 2004).

A non-inferiority trial comparing amisulpride with paroxetine treatment of major depression found no statistically significant differences between the treatment groups (Cassano and Jori, 2002). Open and retrospective data also support the augmentative
efficacy of quetiapine, ziprasidone (Papakostas et al., 2004) and aripiprazole (Barbee et al., 2004; Papakostas et al., 2005; Papakostas, 2005; Simon and Nemeroff, 2005), although controlled studies have yet to be published.

In conclusion, although it is possible to describe the augmentative effects of several atypical antipsychotics, controlled evidence is still sparse, comparator studies to established strategies such as lithium augmentation are lacking and we still need more clinical experience of the utility of this approach in treatment-resistant depression.

9.1.12.2.10 Ω-3 polyunsaturated fatty acids

Following publication of a potential epidemiological link between low fish intake and depression (Hibbeln, 1998), low Ω-3 fatty acid levels in depression and in women during the perinatal period have been found (Rees et al., 2005). In four of seven double-blind randomized controlled trials, significant improvement of depressive symptoms was seen after regular ingestion of eicosapentaenoic acid, an Ω-3 fatty acid, as an adjunct to antidepressant treatment compared with placebo (Nemets et al., 2002; Peet and Horrobin, 2002) (for detailed information see the reviews of Sontrop and Campbell, 2006, and Parker et al., 2006). Relatively high doses between 0.5 and 2.8 g/day have been used to achieve antidepressant effects (Freeman et al., 2006; Peet and Horrobin, 2002).

Owing also to publication of negative results (Silvers et al., 2005), to date it remains unclear whether this therapeutic option has clear antidepressant effects. Furthermore, we do not know whether it could be effective independent of other antidepressant treatments or efficacious only in patients with abnormally low Ω-3 fatty acid levels.

To date the safety and tolerability profile of Ω-3 fatty acid therapies seems to be excellent. Good tolerability has been reported even in post-partum depression (Freeman et al., 2006). Diarrhea is a very common side effect without markedly enhanced danger; it can, however, influence blinding procedures in double-blind studies. A somatic benefit for depressed patients, who often are at enhanced cardiovascular risk, has been proposed and needs to be further investigated (Frasure-Smith et al., 2004).

9.1.12.2.11 Other augmentation strategies

L-Tryptophan and 5-hydroxytryptophan used as serotonin precursors have been studied in depressive disorders with equivocal results. Some smaller studies employing L-tryptophan showed potentiation of MAOIs and augmentation of serotonergic antidepressants in treatment-resistant depression (for an overview see Nelson, 2000) and in seasonal depression refractory to light treatment (Lam et al., 1997). However, unambiguous controlled studies are still lacking.

Since an open pilot trial by Wharton with methylphenidate in treatment-resistant depression (Wharton et al., 1971), the use of stimulants has been documented in case series and one larger retrospective chart review suggesting efficacy in treatment-refractory depression (Stotz et al., 1999). Yet the only randomized controlled study carried out so far of methylphenidate in treatment-resistant depression (Zhang et al., 2000) could not find a significant advantage over placebo.

More recently, modafinil has been tested in an open pilot study as an add-on to antidepressants and showed a 43% response rate (Rasmussen et al., 2005). In a placebo-controlled study, however, it showed significant improvement in SSRI partial responders for fatigue and sleepiness, but only a trend to better outcomes in depression rating scales (Fava et al., 2005b). Clearly, more randomized, confirmative studies are needed.

Dopamine agonists such as pramipexole also demonstrated antidepressant activity in clinical trials (Corrigan et al., 2000; Goldberg et al., 2004).

Besides countering agitation and sleep disturbances, benzodiazepines may also have other augmentative effects on antidepressant treatment (Furukawa et al., 2000; Furukawa et al., 2001b). But their long-term use is clearly discouraged due to their inherent risk of addiction.

In some instances, e.g. perimenopausal depression, augmentation with estrogen has been recommended based on small pilot studies (Morgan et al., 2005; Rason et al., 2002; Schneider et al., 1997; Schneider et al., 2001). By the same token, estrogen carries health risks such as increased risk of endometrial and breast cancer, and thrombosis. A recent randomized double-blind pilot study tested antidepressant augmentation with the selective estrogen receptor modulator raloxifene, showing good tolerability of raloxifene and a non-significant trend to higher remission rates after 8 weeks (Grigoriadis et al., 2005). By the same token, estrogen carries health risks such as increased risk of endometrial and breast cancer, and thrombosis. A recent randomized double-blind pilot study tested antidepressant augmentation with the selective estrogen receptor modulator raloxifene, showing good tolerability of raloxifene and a non-significant trend to higher remission rates after 8 weeks (Grigoriadis et al., 2005). Clearly, more controlled studies with adequate sample sizes are required. Also, in women only, the substitution of folic acid (folate) improved the antidepressant action of fluoxetine (Coppen and Bailey, 2000). In addition, augmentation strategies using testosterone or dehydroepiandrosterone (DHEA) have been reported (Fava, 2001).
Except for lithium and T₃, there is still a lack of good methodological studies supporting other pharmacological augmentation strategies. This area has begun to receive more scientific attention, and ongoing studies like STAR*D (Fava et al., 2003; Nierenberg et al., 2006a; Trivedi et al., 2004), the Texas Medication Algorithm Project (Rush et al., 2003a; Trivedi et al., 2004) and the Berliner Algorithmus Projekt (Adli et al., 2002; Adli et al., 2003) will supply further evidence for augmentation strategies and develop evidence-based algorithms for treatment-refractory patients. Other national medication algorithms for the treatment of depressive disorders have also recently come into existence, e.g. in Korea (Lee et al., 2006) and in Australia (Ellis, 2004). Using treatment algorithms predominantly progressing from simpler to more complex strategies may help to improve response rates up to 90% (Thase and Rush, 1997).

### New developments and novel pharmacological treatment approaches

The therapeutic latency, the non-response rate of approximately 30% and the side effects of all antidepressants available so far are important reasons to continue the search for further treatment options for depressive disorders. Priorities of interest include developing new drugs with fewer side effects and possibly faster response due to the possibility of using higher-dose regimes (Norman and Leonard, 1994). The following sections describe some pharmacological principles that are currently not being used clinically and that may disclose novel approaches in the treatment of depression (Baghai et al., 2006c; Rupprecht et al., 2004).

#### Influence on melatonergic neurotransmission

Melatonin secretion underpins precise circadian rhythms (Lesieur et al., 1998). It is regulated via the cyclic AMP (cAMP) signal transduction cascade (Foulkes et al., 2004). Using treatment algorithms predominantly progressing from simpler to more complex strategies may help to improve response rates up to 90% (Thase and Rush, 1997).

A promising strategy that was not developed further was gepirone, an azapirone similar to buspirone that acts as a partial agonist at 5-HT₁A receptors (Silva and Brandao, 2000; Van Reeth et al., 1999). In animal studies gepirone shows anxiolytic and antidepressant properties (Silva and Brandao, 2000; Van Reeth et al., 1999). Thus far, three placebo controlled double-blind studies in depressed patients have been published. In all trials gepirone proved superior to placebo in the treatment of depression; it also showed good tolerability (Feiger, 1996; Feiger et al., 2003; Wilcox et al., 1996).

Although these data support possible antidepressant properties of gepirone, the manufacturer has halted its development. Development of other serotonergic substances as antidepressants, such as ipsapirone, fleinoxan and tandospirone, has also been stopped. Only tandospirone has been marketed, in Japan, as an anxiolytic drug.

#### Tachykinin receptor antagonists

The peptide family of tachykinins (Stout et al., 2001), in particular substance P (SP), have drawn attention to new developments within antidepressant pharmacotherapy (Kramer et al., 1998; Stout et al., 2001). The tachykinin NK₁ receptor is the receptor for SP, which is co-localized with monoamines in several regions of the CNS (Stout et al., 2001). Furthermore, intracerebroventricular administration of SP causes increased concentrations of catecholamine, and it has been shown that NK₁-receptor knockout mice exhibit reduced anxiety and stress-related behavior (Stout et al., 2001). Stimulation of enhanced hippocampal neurogenesis, too, an effect also observed after application of established antidepressants, has been reported (Kramer et al., 1998; Stout et al., 2001). Despite the fact that several synthetic NK₁-receptor antagonists are available (Stout et al., 2001), only the results of clinical trials with two substances have been published. In a double-blind study, an NK₁ antagonist was compared with SSRI treatment and showed
superiority over placebo (Kramer et al., 1998). The scores of both Hamilton depression and anxiety rating scales were significantly reduced. A further study demonstrated no superiority of MK 869 over placebo. A subsequent substance was examined, and a significant, but relatively small superiority in reducing HAMD scores compared with placebo was found (Kramer, 2002). A recent study confirmed the antidepressant properties of yet another NK₁ antagonist (Kramer et al., 2004), but this first promising antidepressant approach was not confirmed by clinical data in further studies. These uncertainties necessitate replicating the findings. Nevertheless, NK₁ antagonism appears to be a promising new antidepressant treatment principle with an excellent tolerability profile. To date, the first NK₁ antagonist has been approved by the authorities not as an antidepressant, but as an antiemetic.

9.1.13.4 Treatment strategies influencing the hypothalamic pituitary adrenal system

9.1.13.4.1 Corticotropin-releasing hormone receptor antagonists

Up to now, one corticotropin-releasing hormone (CRH₁) receptor antagonist (R121919) has been investigated. In an open trial examining the safety and tolerability, not efficacy, of this compound in 20 depressed patients, a distinct reduction in HAMD and HAMA scores was evident within 4 weeks of treatment (Zobel et al., 2000). The activity of the hypothalamic pituitary adrenal (HPA) system was not altered following administration of the CRH₁ receptor antagonist. This indicates that the compound selectively blocked CRH₁ receptors, while the HPA system is also under control of CRH₂ receptors. Tapering off of the study medication resulted in a certain deterioration of the depressive syndrome. The compound was withdrawn from further development owing to the finding of increased liver enzymes in routine laboratory screening.

Due to the lack of placebo-controlled double-blind studies, further clinical trials using other CRH₁ receptor antagonists are required to clarify the possible antidepressant potential of these substances.

9.1.13.4.2 Steroid synthesis inhibitors

Inhibitors of steroid synthesis such as the fungicide ketoconazole and metyrapone have been reported to exert antidepressive effects. Case series and open trials reported antidepressant effects of ketoconazole (Anand et al., 1995; Ghadirian et al., 1995; Murphy, 1991; Sovner and Fogelman, 2002; Thakore and Dinan, 1995; Wolkowitz et al., 1993). In a placebo-controlled study, hints of the putative antidepressant efficacy of ketoconazole were found only in hypercortisolemic, but not in normocortisolemic, patients (Wolkowitz et al., 1999a). Another placebo-controlled double-blind study in treatment-resistant depression has shown insufficient antidepressant efficacy (Malison et al., 1999). Similar antidepressant effects have also been shown for metyrapone in case reports and open trials (Ghadirian et al., 1995; Murphy et al., 1991; Murphy, 1991; Raven et al., 1996), as well as in placebo-controlled double-blind studies. A study of eight patients found a reduction in the score of the MADRS of more than 50% within 2 weeks of treatment (O’Dwyer et al., 1995). A comparison of metyrapone with placebo in addition to serotonergic antidepressant therapy resulted in significant acceleration of antidepressant effects (Jahn et al., 2004). Definite proof of the antidepressant properties of ketoconazole and metyrapone, however, is still lacking.

A further limitation of therapy using steroid synthesis inhibitors is the risk of developing adrenal gland insufficiency, and substitution of hydrocortisone may be required during treatment (O’Dwyer et al., 1995). Nevertheless, at least in hypercortisolemic and severely depressed patients, this experimental therapeutical approach can be considered in the case of severe treatment resistance.

9.1.13.4.3 Neuroactive steroids

Neuroactive steroids modulate neurotransmitter receptors (Rupprecht and Holsboer, 1999) and show antidepressant and anxiolytic properties in animal studies (Bitran et al., 1991; Khisti et al., 2000). Antidepressants, in particular SSRIs, enhance the concentration of endogenous 3α-reduced neuroactive steroids within different areas of the brain (Rupprecht and Holsboer, 1999). These mechanisms may play a role in antidepressant treatment. However, synthetic analogs of 3α-reduced neuroactive steroids for the therapy of psychiatric disorders in humans are not yet available.

DHEA is a neuroactive steroid that displays both antagonistic properties at γ-aminobutyric acid (GABA_\text{A}) receptors and antiglucocorticoid effects (Rupprecht, 1997; Rupprecht and Holsboer, 1999; Wolkowitz et al., 1999b). One open study (Wolkowitz et al., 1997) suggested possible antidepressant effects of DHEA. An early placebo-controlled double-blind study performed using an add-on treatment of DHEA in depressed patients showed a significant reduction
in HAMD scores (Wolkowicz et al., 1999b). Yet DHEA concentrations were found to be enhanced in depressed patients compared with healthy volunteers (Heuser et al., 1998), which seems to contradict the indication of DHEA as treatment option in depressive disorders.

9.1.13.4.4 Glucocorticoid receptor antagonists

Synthetic glucocorticoid receptor antagonists block the effects of cortisol at glucocorticoid receptors. In initial casuistic studies the glucocorticoid-/progesterone-receptor antagonist mifepristone, used in some countries to terminate first-trimester pregnancy, improved depressive symptoms in antidepressant treatment-resistant depression (Murphy et al., 1993). An open-label study in patients with psychotic depression showed a reduction in the Brief Psychiatric Rating Scale (BPRS) scores in the majority of the patients (Belanoff et al., 2002), but reported no statistically significant differences. Symptom amelioration could be seen after 7 days in high-dose treatment groups. A placebo-controlled case series in five patients suffering from psychotic depression showed a reduction in HAMD score up to 26% (Belanoff et al., 2001), but again, only a non-significant trend to a difference between verum and placebo could be seen. A recent study demonstrated a statistically significant influence of mifepristone on psychotic symptoms measured using the BPRS, but no significant differences in other depression rating scales (DeBattista et al., 2006).

Because of the antagonistic effects of mifepristone at progesterone receptors, the use of this substance as an antidepressant seems to be limited. Further investigations using the selective glucocorticoid receptor antagonist Org 34517 have been carried out. Initial clinical experience supports the possible antidepressant efficacy of glucocorticoid receptor antagonists. Nevertheless, the results of placebo-controlled double-blind studies of sufficient power and over a sufficiently long treatment period are needed before the antidepressant potential of these substances can be reliably assessed.

9.2 Continuation and maintenance therapy with antidepressants, mood stabilizers and other medication

The need for continuation treatment has also been clearly demonstrated by placebo-controlled studies. Relapse rates ranged from 31 to 80% for remitted patients who were switched to placebo compared with 0–31% of those who received active tricyclic medication (Prien, 1990; Prien and Kupfer, 1986). Studies with SSRI continuation, amineptine, nefazodone and reboxetine have reported similar results. Tables 20 and 21, modified from Fakra et al (2006) depicts continuation and maintenance studies from 1988 to 2006, when most controlled maintenance studies with new antidepressants had been conducted.

As a rule of thumb, continuation of antidepressant treatment prevented roughly 50% of the recurrences that occurred under placebo, regardless of the duration of the study or the pharmacological nature of the antidepressant drug. Similarly, a systematic review by Hirschfeld (Hirschfeld, 2001) found that approximately one-third to one-half of patients successfully stabilized in acute-phase treatment will relapse if medication is not sustained throughout the continuation period, and only 10–15% will relapse if medication is continued. Therefore, it is recommended to continue the successful initial antidepressant or combination treatment at the same dose during the continuation phase (Thase, 1999b). For patients who remit on antidepressant together with lithium as augmentative treatment, combined treatment during continuation has been suggested to be more efficacious than antidepressants alone (Bauer et al., 2000; Bschor et al., 2002).

Although usually cited as compelling evidence for prophylactic treatment, the meta-analysis of Geddes et al. (2003) has a stronger focus on continuation treatment and prevention of early relapse. Of the 31 randomized trials included in this meta-analysis, most trials went on for 12 months and were conducted in acute responders to antidepressant treatment. Thus, they are truly continuation treatment studies. However, a few studies lasting up to 3 years also support the persistence of effectiveness.

Although not true for the majority of patients, some studies have suggested that continuous antidepressant treatment destabilizes patients (see Hirschfeld, 2000). However, at the end of his review Fava concluded that ‘at present we have no sound data that antidepressant drugs may worsen the course of depression and, if they do, whether the phenomena is generalized or very limited.’ Thus, unless the individual history of a patient shows evidence of negative effects from long-term antidepressant treatment, continuation therapy should be offered to every patient following recovery from a depressed episode. The situation may be different for other subtypes of depression, e.g. bipolar depression with a rapid-cycling course; these special conditions are, however, beyond the scope of this review.
The ultimate goal with any psychiatric disorder is to prevent recurrence of acute symptomatology and improve functionality and quality of life in patients. Clearly, this goal is no different with unipolar depression. The prophylactic effect of continuing antidepressant medication has been demonstrated in a multitude of studies (Geddes et al., 2003; Hirschfeld, 2000) (see Figure 4).

As already detailed in chapter 7 on the goals of treatment, long-term prophylactic treatment following continuation treatment is recommended in patients with a history of recurring episodes. Besides preventing relapses, antidepressants may add value by virtue of their neuroprotective properties (Sheline et al., 2003). Taken together, approximately 60% of patients at risk will experience a recurrent episode of

### Table 20. Maintenance treatment using one antidepressant in comparison to placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Length of treatment phase</th>
<th>Recurrence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute</td>
<td>Contin</td>
</tr>
<tr>
<td>Montogomery (1988)</td>
<td>456 initial 220 maint 182 complete</td>
<td>6 weeks</td>
<td>18 weeks</td>
</tr>
<tr>
<td>Frank (1990)</td>
<td>128 maint 106 complete</td>
<td>Until remission</td>
<td>17 weeks</td>
</tr>
<tr>
<td>Robinson (1991)</td>
<td>88 initial 47 maint 35 complete 20 maint</td>
<td>Until remission</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Kupfer (1992)</td>
<td>19 complete</td>
<td>(3–)5 years</td>
<td>1 year</td>
</tr>
<tr>
<td>Terra (1998)</td>
<td>128 maint 106 complete</td>
<td>Until remission</td>
<td>18 weeks</td>
</tr>
<tr>
<td>Robinson (1991)</td>
<td>88 initial 47 maint 35 complete 20 maint</td>
<td>Until remission</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Kupfer (1992)</td>
<td>19 complete</td>
<td>(3–)5 years</td>
<td>1 year</td>
</tr>
<tr>
<td>Terra (1998)</td>
<td>128 maint 106 complete</td>
<td>Until remission</td>
<td>18 weeks</td>
</tr>
</tbody>
</table>
Depression within 1 year if untreated, whereas those who continue treatment will have a recurrence rate of between 10 and 30% (Hirschfeld, 2001). If in doubt about the indication for maintenance treatment, an early decision in favor of long-term maintenance may improve long-term outcome: Solomon (Solomon et al., 2000) showed that the risk of a new episode increases by 16% with each successive recurrence. If a patient has had a history of at least two (Paykel and Priest, 1992) or three episodes (Prien et al., 1984), prophylactic treatment is recommended. Guidelines agree that maintenance dosages should be similar to acute and continuation treatment unless tolerability problems force reduction of the medication.

Of the 31 studies included in the meta-analysis by Geddes et al. (2003), 5 studies had a duration of 3 years and 6 a duration of 2 years. However, most of these studies included only a small number of patients and thus do not encourage firm conclusions by themselves. Among the randomized controlled trials, the study by Prien et al. (Prien et al., 1984) comparing imipramine and lithium alone or in combination against placebo supplied good evidence for the prophylactic efficacy of both the antidepressant and lithium. The efficacy of imipramine is also supported by a 36-month study of Frank et al. (Frank et al., 1990). Similar evidence for continuing prophylactic efficacy has been supplied for nortriptyline (Reynolds et al., 1999), sertraline (Keller et al., 1998) and citalopram (Klysner et al., 2002), as well as for the MAOI phenelzine (Robinson et al., 1991).

### Table 21. Maintenance treatment – studies comparing two antidepressants

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Length of treatment phase</th>
<th>Drug</th>
<th>Relapse/recurrence rate</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claghorn (1993)</td>
<td>717 initial</td>
<td>6 weeks</td>
<td>Paroxetine</td>
<td>15%</td>
<td>Parox. and Imip. &gt; placebo 50% more dropouts with Imip./Parox. due to side effect</td>
</tr>
<tr>
<td></td>
<td>219 conti</td>
<td>Double-blind phase</td>
<td>Imipramine placebo</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 year</td>
<td>placebo</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Franchini (1997)</td>
<td>77 initial</td>
<td>4 months</td>
<td>Fluvoxamine</td>
<td>18.7%</td>
<td>No significant difference between two treatments</td>
</tr>
<tr>
<td></td>
<td>64 conti</td>
<td>24 months</td>
<td>Sertraline</td>
<td>21.9%</td>
<td></td>
</tr>
<tr>
<td>Montgomery (1998)</td>
<td>580 initial</td>
<td>6 weeks</td>
<td>Mirtazapine</td>
<td>4.1%</td>
<td>Advantage of mirtazapine over amitriptyline and placebo for time to relapse in the survival analysis, and against placebo for the number of relapses</td>
</tr>
<tr>
<td></td>
<td>217 conti</td>
<td>Randomization during all treatment phases</td>
<td>Amitriptyline placebo</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Bump (2001)</td>
<td>116 initial</td>
<td>12 weeks</td>
<td>Nortriptyline</td>
<td>10%</td>
<td>Open study, comparable efficacy, but nortriptyline produced fewer residual depressive symptoms and side-effects</td>
</tr>
<tr>
<td></td>
<td>59 conti (elderly patients)</td>
<td>12 weeks</td>
<td>placebo</td>
<td>16%</td>
<td></td>
</tr>
</tbody>
</table>
addition to preventing new episodes, lithium normalizes the increased mortality rates for cerebrovascular and cardiovascular disorders in affectively ill patients (Angst et al., 2002a) and reduces the risk of suicide (Angst et al., 2002a; Goodwin et al., 2003; Souza and Goodwin, 1991). For a recent up-to-date review see also Müller-Oerlinghausen et al. (Müller-Oerlinghausen et al., 2006). In addition, potential neuroprotective effects, including preventive effects against Alzheimer’s dementia, can be of interest when prescribing long-term lithium prophylaxis. The usually recommended serum lithium levels for prophylaxis in unipolar recurrent depression are 0.5–0.8 mmol/l, but individual variations may occur. The use of extended-release forms of lithium has been strongly encouraged, as these enable once-daily dosing and are associated with fewer side effects, both favoring enhanced treatment adherence of patients.

9.2.1.1.2 Anticonvulsants in the prophylaxis of unipolar depression

Carbamazepine has been studied in two small double-blind comparator trials with lithium in recurrent major depression (Angst et al., 2002a; Rush, 1999). Both studies suggested equal efficacy for lithium and carbamazepine. However, for prophylactic treatment, the propensity of carbamazepine not only to induce its own hepatic metabolism but also to accelerate metabolism of drugs using CYP3A4 must be kept in mind. Some anticonvulsants, e.g. venlafaxine, mirtazapine, nefazodone, reboxetine and imipramine, are substrates of CYP3A4 and thus may not achieve sufficient plasma levels when used in combination with carbamazepine. CYP1A2 and CYP2C9, which contribute to carbamazepine metabolism, may also be inhibited by fluvoxamine. Given its potential interactions and lack of scientific evidence from placebo-controlled studies, carbamazepine can only be recommended as a subordinated choice when other strategies have failed.

For other anticonvulsants only anecdotal reports and small case series, no controlled studies, have been published for prophylaxis in unipolar depression.

9.2.1.2 General principles of long-term prophylactic treatment

As a general recommendation, prophylactic treatment of unipolar depression is not only restricted to pharmacotherapy. Maintaining a good doctor-patient relationship, monitoring adherence and psychoeducation are important as well. Whereas approximately 40–70% of patients adhere to their antidepressant drug regimen during the acute phase of therapy, only 15–50% still comply with therapy during the continuation phase (Melfi et al., 1998). Automated systems have been tested in primary care setting, alerting the
physician if a refill has been missed for a specified time. However, this approach did not improve compliance (Bambauer et al., 2006) and cannot substitute for a good doctor–patient relationship.

As preparation for long-term prophylactic treatment, patients and their relatives should be informed especially about topics such as expected course of illness, treatment options, medication efficacy and side effects, use of a daily self-reporting instrument for mood to detect early warning signs of relapse or recurrence, long-term perspectives and, if applicable, projected end of treatment. Patients should also be trained to distinguish between spontaneous, short-lasting mood fluctuations (bleeps) and true emergence of a new episode, which should be treated as soon as possible (Rush, 1999). In addition, psychotherapy, especially interpersonal therapy and cognitive behavioral therapy, should be included in the overall treatment portfolio (Baghai et al., 2006c). However, a detailed description of the proven efficacy of psychotherapy in addition to medication is beyond the scope of this review.

10 Specific age- and gender-related conditions

10.1 Gender-related differences

Gender differences in unipolar depression are a consistent finding in several longitudinal and cross-sectional studies (for review see Kahn and Halbreich, 2005; Kuehner, 2003). Lifetime prevalence shows an unadjusted mean female/male ratio of 2.1, whereas the point prevalence gender ratio is 1.7 (Kuehner, 2003). This estimate of differences in lifetime depression rates is calculated from large population-based studies comprising up to almost 45000 subjects and, for point and period prevalence rates, even up to 78000 subjects (DEPRES study (Depression Research in European Society) (Angst et al., 2002b)).

Several differences in comorbidity, symptomatology and coping style between genders have been described. Starting with comorbidities, frequent disorders comorbid with depression in females include anxiety (Breslau et al., 1995), somatoform disorders and eating disorders, especially bulimia (Marcus et al., 2005), whereas men are more likely to suffer from comorbid alcohol and drug abuse (Marcus et al., 2005). This gender difference may also be reflected in ways of coping with depression. For example, Angst et al. found that depressed men were more likely to increase consumption of alcohol, whereas women tried to cope through emotional release and religion (Angst et al., 2002b).

As far as other features of depression are concerned, recently published results of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study (Marcus et al., 2005) also show a significantly earlier onset of the first major depressive episode in women, and longer current major episodes for women compared with men. In addition, depression in women may also affect their offspring: children of mothers suffering from depression are at high risk for disruptive behavior and anxiety disorders as demonstrated in a large sample of the STAR*D trial (Pilowsky et al., 2006).

Some features of depression appear to be more prevalent among men than among women, e.g. a tendency to overreact and to attack in anger (Winkler et al., 2005a). Criterial major depressive episodes according to DSM-IV (American Psychiatric Association, 1994), however, are more prevalent in female than in male depressed patients (Angst et al., 2002b). In the large European DEPRES I and II study, women were significantly more likely to have five or more criterial symptoms of depression than men (female/male ratio 1.96).

Interestingly, differences in symptomatology are already apparent in adolescent depression. Bennett et al. (2005) interviewed 383 depressed adolescents with the Childhood Version of the Schedule for Affective Disorders and Schizophrenia (K-SADS-IV; Bennett et al., 2005) and the Beck Depression Inventory (BDI; Bennett et al., 2005). In this sample, with a mean age of 15.8 years, he found that depressed girls were more likely to exhibit guilt, body image dissatisfaction, self-blame, self-disappointment, feelings of failure, concentration problems, difficulty working, problems of sadness and depressed mood, fatigue and health worries than depressed boys. In contrast, depressed boys had higher clinician ratings for anhedonia, depressed morning mood and morning fatigue (Bennett et al., 2005).

Explanations for these gender differences are manifold, and several factors may contribute to them. According to Kuehner (2003), these factors include genetics, sex hormones, differing endocrine stress reactivity, a higher incidence of thyroid axis abnormalities, prior anxiety disorders, personality traits, neuropsychological factors, gender role and psychosocial factors, and life events, e.g. childhood...
sexual abuse. So far, there are no consistent findings for gender differences in heritability (Kendler, 1998). Only when broadening the criteria for depressive disorders does heritability of those disorders appear to be greater in women than in men (Kendler, 1998). In elderly patients, a higher heritability for depressive symptoms may be associated with female gender (Jansson et al., 2004). In addition, gender-specific effects of genetic polymorphisms, e.g. within the angiotensin I converting enzyme (ACE) gene, may play a role in varying responsiveness and speed of onset of antidepressant action. In women, D/D and I/D alleles have been associated with a faster onset of different antidepressant therapies (Baghai et al., 2003; Baghai et al., 2004). Overall, however, more research is needed to reach firmer conclusions concerning a gender-specific genetic preposition for depression and response to treatment.

Sex hormones may play an important modulatory role in the manifestation and course of depression, and also for treatment response. There exist specific vulnerabilities and complex interactions between brain mechanisms and gonadal hormones (Halbreich and Kahn, 2006). For instance, depressive symptomatology in vulnerable women seems to increase when their physiological estradiol levels decrease, e.g. perimenstrually, in the post-partum period or during perimenopause. Just as menopause seems to negatively affect SSRI treatment response of depressed women, antidepressant treatment seems to be influenced by estradiol levels (Pinto-Meza et al., 2006). At the same time, several studies have shown estrogen treatment to be effective in post-partum as well as perimenopausal depression (for review see Kahn and Halbreich, 2005; Riecher-Rossler et al., In Press). Estrogens may enhance serotonergic activity and, if combined, may induce a better responsiveness to SSRIs (Stahl, 2001) (for review see Kahn and Halbreich, 2005). Estradiol may be involved in desensitization at the 5-HT1A receptor (Bouali et al., 2003; Carrasco et al., 2004). Other neuroendocrine axes, such as the hypothalamic–pituitary–adrenal (HPA) (Kornstein et al., 2002) and thyroid axes (Kornstein et al., 2002), may also exhibit subtle differences between genders, thereby affecting vulnerability to depression.

In general, treatment should not differ between depressed men and women, but specific precautions must be taken into account (see also chapter 9.1.1.3.3). Clinically, gender differences in treatment response have been demonstrated in several studies (Frank et al., 1988; Kornstein et al., 2002; Yonkers and Brawman-Mintzer, 2002), but could not be confirmed by other studies (Scheibe et al., 2003; Thiels et al., 2005) or a combined analysis of several studies (Hildebrandt et al., 2003). When interpreting data, especially from randomized controlled studies, a major methodological pitfall is the underinclusion of women in the older studies (Yonkers and Brawman-Mintzer, 2002). This makes potential findings of gender-specific efficacy of tricyclics especially difficult to interpret. The situation is slightly different with SSRIs, where reported gender differences are based on more recent studies with equal gender distribution.

In a review of 30 randomized placebo-controlled trials of tricyclics conducted to obtain market authorization between 1979 and 1991, Wohlfarth et al. (2004) could not identify a gender difference in the efficacy of tricyclics. This finding contrasts with a meta-analysis of Hamilton et al. (1995) of all published trials with imipramine, which showed significantly different response rates of 62% for men and only 51% for women. On the other hand, several studies describe a significantly higher response rate for women to SSRI treatment compared with men, e.g. (Baca et al., 2004). A better efficacy of SSRIs was also demonstrated by an analysis of 15 randomized placebo-controlled studies conducted at the Northwest Clinical Research Center in Bellevue, Washington, between 1996 and 2003 (Khan et al., 2005). The researchers found that women had a significantly greater response than men to SSRIs, but not to SNRI antidepressants. The authors assume that this different responsiveness may be due to subtle differences in the serotonergic system between men and women (Bano et al., 2004; Bell et al., 2001; Nishizawa et al., 1997).

For other classes of medications, gender-specific differences are less clear. For example, better response rates to monoamine oxidase inhibitors (MAOIs) in women have been described in studies that include a substantial number of depressed patients with so-called atypical features (Davidson and Pelton, 1986) (see also chapter 5.2.1.3.3). However, atypical depression characterized by dysphoria and pronounced anxiety is a more likely finding in women than men, and MAOIs had previously demonstrated a good efficacy in this condition (Henkel et al., 2006). Thus, the finding of higher responsiveness to MAOIs for women may simply be due to the interaction of depression subtype and gender. This is a good example of the careful consideration of potential covariates that is essential in identifying true gender differences.

In summary, prevalence, symptomatology, treatment response and consequences of depression are not identical in men and women, and a gender-specific
psychiatric approach that takes into account gender-specific risk and influencing factors (see also chapter 9.1.1.3.3) – including gender roles – is warranted (Riecher-Rössler, 2000).

10.2 Age-related differences

10.2.1 Using antidepressant medications to treat depression in child and adolescent populations

10.2.1.1 Introduction

Identifying and treating depressive disorders in child and adolescent populations is often more complicated than in adult populations for two main reasons. First, the clinical features of depressive disorders in young patients may differ substantially from those of adult patients. Instead of manifesting neurovegetative or straightforward depressive symptoms, depressed children may exhibit behavioral problems that cause difficulties in psychosocial functioning at home or at school. Identifying these behaviors related to and underlying depression requires not only evaluating the patient but also talking to parents and teachers as informants. The second difficulty stems from the variety of treatment options based on relatively little evidence of efficacy and safety in children and adolescents. In addition, questions have been raised recently regarding the possibility of increased suicidal behavior in depressed youth treated with antidepressant medications (Leslie et al., 2005). All of these issues must be considered before deciding whether and how to treat young people with depression.

Comprehensive guidelines about identifying and treating this age group have been published elsewhere (Birmaher et al., 1998; Park and Goodyer, 2000). Likewise, because comprehensive reviews of evidence-based psychotherapies for depressed youth are available (Compton et al., 2004; Curry, 2001), this chapter instead will discuss the safety and efficacy of antidepressants. First, we will review randomized controlled trials (RCTs) of antidepressants in depressed children and adolescents. Next, we will discuss regulatory actions taken by drug safety agencies in the US and UK. Finally, we will offer recommendations regarding pharmacologic treatment of depressed children and adolescents.

While empirical studies of antidepressant medications have been conducted in depressed child and adolescent populations since the 1960s, the first well-designed, double-blind, placebo-controlled studies – most involving tricyclic antidepressants (TCAs) – did not take place until the mid- and late 1980s (Ambrosini, 2000). Since then, several RCTs, primarily of newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), have been conducted in child and adolescent populations. No RCTs of monoamine oxidase inhibitors have been conducted in depressed child or adolescent populations. The only RCT showing positive effects in childhood depression shows therapeutic benefits of ω-3 fatty acids in a 16-week-long clinical trial (Nemets et al., 2006).

In a recently published meta-analysis the effectiveness of antidepressants in comparison to placebo in the treatment of pediatric major depressive disorder has been confirmed (Bridge et al., 2007). It has been stated that the benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempts. Similar conclusions were drawn due to increasing suicide rates both in the US (14%) and the Netherlands (49%) after decreasing SSRI prescriptions (~22%) between the years 2003 and 2005 following warnings of U.S. and European regulatory agencies about a possible suicide risk with antidepressant use in pediatric patients (Gibbons et al., 2007).

A Cochrane meta-analysis of TCAs, as well as all known published RCTs of SSRIs and atypical antidepressants, will be described below. Whenever applicable, a distinction will be made between a given drug’s attributes in child (age 12 and under) and adolescent (age 13 and older) populations.

10.2.1.1.1 Tricyclic antidepressants

Given the ample evidence for efficacy in adult populations, multiple clinical trials of TCAs – including studies of amitriptyline, imipramine, nortriptyline and desipramine in the serotonergic system – have been conducted. A Cochrane review of 13 of these RCTs involving over 500 young people was completed by Hazell and colleagues (Hazell et al., 2002). Across child and adolescent populations, the effect size (ES) identified by this meta-analysis was statistically significant, but small (ES = 0.31, 95% CI 0.62 to 0.01; negative ES indicates a reduction in depressive symptoms). However, when subgroup analyses were conducted, no significant benefit was seen with children (ES 0.15, 95% CI –0.34 to 0.64), but a larger advantage was seen with adolescents (ES = 0.47, 95% CI: 0.92 to 0.02). This differential treatment response is consistent with the superior efficacy of TCAs in adult populations, and may be explained by

59 Age limits in the definitions of children and adolescents are varying between different countries (e.g. in Germany the legal age limit is 14 years). In the cited studies predominantly an age limit of 12 years has been used.
maturation of neurological pathways or other developmental differences between children, adolescents and adults (Bostic et al., 2005). Importantly, compared with placebo controls, in pediatric populations TCAs were associated with more vertigo, orthostatic hypotension and dry mouth (Hazell et al., 2002).

10.2.1.1.2 SSRIs and newer antidepressants

Given the lack of convincing evidence of effectiveness and the narrow therapeutic window of TCAs, more recent childhood depression trials have focused on SSRIs and other newer antidepressants. However, whereas 18 placebo-controlled RCTs of newer antidepressants have been conducted, only 12 have been published (Table 22). This section describes published SSRI trials with regard both to efficacy and to safety. In addition, data regarding unpublished trials were obtained from the report completed by the UK’s Committee on Safety of Medicine (CSM) of the Medicines and Healthcare products Regulatory Agency (Committee on Safety of Medicines, 2004), and a recent review of antidepressants in depression among youth (Cheung et al., 2005).

10.2.1.1.2.1 Fluoxetine

The first report about a case series of six patients, aged 10–17 years, showing self-injurious ideation or behavior during fluoxetine treatment of obsessive-compulsive disorder was published by (King et al., 1991).

Between 1990 and 2004, four trials of fluoxetine as a treatment for child and adolescent major depressive disorder were conducted, three of which were positive.

The negative study of fluoxetine, which was small and possibly underpowered, involved 40 adolescents from inpatient and outpatient settings. After 8 weeks on 20–60 mg of fluoxetine, authors did not identify significant differences for any of the outcome measures used; subjects responded equally well to fluoxetine or placebo. Other than weight loss, no drug-associated adverse events were reported (Simeon et al., 1990).

The first positive fluoxetine study, published in 1997 by Emslie et al., compared a 20 mg fixed dose of fluoxetine to placebo in a group of 96 children and adolescents aged 7–17 (Emslie et al., 1997). Subjects were treated for 8 weeks at a single site. At the trial’s end, compared with placebo, subjects assigned to fluoxetine scored significantly better on both prospectively identified primary outcome measures: the Clinical Global Impressions-Improvement Score (CGI-I) and the Children’s Depression Rating Scale-Revised (CDRS-R). Significantly more youth given fluoxetine ‘responded’ (i.e. received ratings of 1, ‘very much improved’, or 2, ‘much improved’, on the CGI-I). While endpoint mean CDRS-R scores were significantly better for fluoxetine-treated youth than for those who received placebo, the differences in terms of ‘remission’ (a dichotomous measure, prospectively defined as a score of <29 on the CDRS, and potentially less sensitive to change) did not reach significance. Response rates did not differ for children 12 and under compared with adolescents 13 and over. In comparisons with placebo, adverse events were not significantly increased in the fluoxetine-treated group.

In 2002, Emslie et al. published an 8-week multisite follow-up study of 219 subjects between the ages of 8 and 18 (Emslie et al., 2002). In this trial, the CDRS-R was again used as a primary outcome measure. While the mean 22-point drop in CDRS-R scores in the fluoxetine group was significantly different from the 14.9-point decrease noted in the placebo group, it did not achieve primary outcome ‘response’ criteria prospectively defined as a ≥30% decrease in scores. However, in post hoc analyses the authors demonstrated that primary outcome would have been achieved had response been defined at ≥20, 40, 60 or 70% decrease in CDRS scores, or if their calculation correctly reflected the fact that the CDRS-R scale has a minimum value of 17 instead of 0 (Cheung et al., 2005). While no information was provided regarding suicidality, patients receiving fluoxetine reported fewer adverse events than did those receiving placebo. Based on these results, fluoxetine received US Food and Drug Administration (FDA) approval to treat depressive disorders in children and adolescents.

In the double-blind relapse-prevention phase of the above-mentioned study, Emslie and colleagues continued to follow 40 subjects who remitted on fluoxetine; 20 of these fluoxetine responders were assigned to continue fixed-dose fluoxetine, whereas 20 others were switched directly from fluoxetine to placebo. Over the subsequent 32 weeks, when compared with those switched to placebo, fewer subjects who remained on fluoxetine relapsed (60 vs. 34%, respectively). Additionally, time to relapse was longer for those who remained on fluoxetine compared with those who were switched to placebo (181 days vs. 71 days, \( p = 0.046 \)). There were no statistically significant differences in adverse events (Emslie et al., 2004).

Fluoxetine, alone and in combination with cognitive-behavioral therapy (CBT), was compared with
<table>
<thead>
<tr>
<th>Agent</th>
<th>Author</th>
<th>N</th>
<th>Age</th>
<th>Dose (mg)</th>
<th>Length (weeks)</th>
<th>Sites (n)</th>
<th>Study characteristics</th>
<th>Results</th>
<th>Active treatment</th>
<th>Placebo</th>
<th>p value</th>
<th>Sig. ? (Y/N)</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Simeon et al., 1990</td>
<td>40</td>
<td>13–18</td>
<td>20–60</td>
<td>8</td>
<td>1</td>
<td>none assigned</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>N</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emslie et al., 1997</td>
<td>96</td>
<td>7–17</td>
<td>20</td>
<td>8</td>
<td>1</td>
<td>CGI-I (1 or 2)</td>
<td>56%</td>
<td>33%</td>
<td>0.02</td>
<td>Y</td>
<td></td>
<td>NIMH</td>
</tr>
<tr>
<td></td>
<td>Emslie et al., 2002</td>
<td>219</td>
<td>8–18</td>
<td>20</td>
<td>8</td>
<td>15</td>
<td>CDRS-R mean scores</td>
<td>38.4</td>
<td>47.1</td>
<td>&lt;0.008</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>March et al., 2004</td>
<td>439</td>
<td>12–17</td>
<td>10–40</td>
<td>12</td>
<td>13</td>
<td>CDRS-R (1 or 2)</td>
<td>41%</td>
<td>20%</td>
<td>0.09</td>
<td>N*</td>
<td>Lily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CDRS-R (cts)</td>
<td>FLX: 60.6%</td>
<td>34.8%</td>
<td>0.001</td>
<td>Y</td>
<td>NIH</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Keller et al., 2001</td>
<td>180*</td>
<td>12–18</td>
<td>20–40</td>
<td>8</td>
<td>10</td>
<td>HAMD (≤8 or ≥50%)</td>
<td>66.5%</td>
<td>55.2%</td>
<td>0.11</td>
<td>N</td>
<td>GSK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Berard et al., 2006</td>
<td>286</td>
<td>13–18</td>
<td>20–40</td>
<td>12</td>
<td>33</td>
<td>MADRS (≥50%)</td>
<td>18.98–8.24</td>
<td>19.79–9.88</td>
<td>0.13</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emile et al., 2006</td>
<td>206</td>
<td>7–17</td>
<td>10–50</td>
<td>8</td>
<td>40</td>
<td>K-SADS-L (cfb)</td>
<td>60.5%</td>
<td>58.2%</td>
<td>0.702</td>
<td>N</td>
<td>GSK</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Wagner et al., 2003</td>
<td>376</td>
<td>6–17</td>
<td>50–200</td>
<td>10</td>
<td>53</td>
<td>CDRS-R (mean reduction)</td>
<td>–22.84</td>
<td>–20.19</td>
<td>0.007</td>
<td>Y</td>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Wagner et al., 2004</td>
<td>174</td>
<td>7–17</td>
<td>20–40</td>
<td>8</td>
<td>21</td>
<td>CDRS-R (cfb)</td>
<td>36%</td>
<td>24%</td>
<td>&lt;0.5</td>
<td>Y</td>
<td>Forrest</td>
<td></td>
</tr>
<tr>
<td></td>
<td>von Knorring et al., 2006</td>
<td>244</td>
<td>13–18</td>
<td>12</td>
<td></td>
<td></td>
<td>Kiddie-SADS-P, MADRS</td>
<td>59%</td>
<td>61%</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Wagner et al., 2006</td>
<td>264</td>
<td>6–17</td>
<td>10–20</td>
<td>8</td>
<td>25</td>
<td>CDRS-R (cfb)</td>
<td>–21.9</td>
<td>–20.2</td>
<td>0.310</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Mandoki et al., 1997</td>
<td>40</td>
<td>8–17</td>
<td>37.5–75</td>
<td>6</td>
<td>1</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>N</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

* Authors note that results would have reached significance if response was defined as decrease in CDRS of ≥20, 40, 50 or 60%.
** Trial included 275 subjects, but 95 were randomized to imipramine and are not considered in the above analysis.
cfb = change from baseline; cts = change in total score (adjusted mean); n.a. = not available; GSK = GlaxoSmithKline.
placebo in the Treatment for Adolescents with Depression Study (TADS). The first phase of this National Institute of Mental Health (NIMH)-sponsored multisite RCT followed 439 adolescents (aged 12–17) with moderate to severe depression for 12 weeks. The fluoxetine plus CBT condition was superior to placebo on both primary outcome measures: CDRS-R total score and CGI-I score of 1 or 2. Fluoxetine alone was statistically superior to placebo on the CGI-I variable, but not the CDRS-R. Compared with placebo, there was a statistically significant increased risk of harm-related events—a category that included suicidal and non-suicidal behavior such as self-cutting—in the groups treated with fluoxetine (OR 2.19; 95% CI 1.03–4.62); however, there was no statistically significant increased risk of suicide-related events in the fluoxetine group. Whereas suicidal thinking decreased in all treatment groups, fluoxetine plus CBT was associated with the greatest reduction (March et al., 2004). Combination treatment with CBT and fluoxetine showed the greatest benefit-to-risk ratio for adolescents with moderate to severe depression, and was superior to monotherapy. Moreover, fluoxetine alone was more effective in treatment of depressed adolescents than CBT alone, whereas CBT alone did not differentiate from placebo (March et al., 2004; Pathak et al., 2005; TADS study group, 2003; TADS study group, 2005). Note that the placebo response rate was relatively low in the TADS study (35%) in comparison with other studies in children and adolescents, possibly due to specific inclusion criteria.

10.2.1.1.2.2 Paroxetine

Keller et al. treated 180 adolescents (aged 12–18) with either paroxetine or placebo in a multi-site, 8-week RCT. The HAMD-17 was the primary outcome measure; both response (end of trial score of ≤ 8 or a > 50% reduction) and change from baseline were assessed. Whereas youth treated with paroxetine improved on primary outcome measures relative to placebo, these improvements were not statistically significant in the case of imipramine (Keller et al., 2001). Adverse events were reported more often by patients receiving paroxetine (11 patients) versus placebo (2 patients). Additionally, paroxetine-treated patients had an increased risk of suicidal ideation compared with placebo-treated patients (5.4 vs. 0% respectively).

Two additional paroxetine studies, both conducted several years ago and previously unpublished, have recently been published (Berard et al., 2006; Emslie et al., 2006). Neither study demonstrated efficacy of paroxetine compared with placebo on primary outcome measures. In the first study (Berard et al., 2006), which focused on adolescents aged 13–18, more treatment-discontinuing adverse events and suicide-related behavior were reported in the paroxetine group compared with placebo (11.8 vs. 7.1% and 4.4 vs. 2.1% respectively; these differences were not statistically significant). In the second study (Emslie et al., 2006), which evaluated paroxetine in 206 children aged 7–17, serious adverse events were more commonly reported by children treated with paroxetine (6 subjects) versus placebo (1 subject). Additionally, treatment discontinuation due to an adverse event occurred more commonly with paroxetine (8.9%) compared with placebo (2%).

10.2.1.1.2.3 Sertraline

In 2003, Wagner et al. published the combined results of two separate 10-week trials involving 376 child and adolescent subjects (aged 6–17) with depressive disorders (Wagner et al., 2003). These studies were conducted at 53 sites in five countries, and the combined analysis was planned a priori. Although the individual trials did not reach statistical significance on the primary outcome measure (mean reduction in CDRS-R), when combined they demonstrated a small but statistically significant effect. Of note, at the study’s endpoint, the mean difference in CDRS-R score was significant for adolescents (sertraline: −28.95; placebo: −24.11; p = 0.01) but only borderline significant for children (sertraline: −31.44; placebo: −27.56; p = 0.5). Compared with placebo, three times as many sertraline-treated subjects discontinued treatment as a result of suffering adverse events.

10.2.1.1.2.4 Citalopram

Wagner et al. also published results from an 8-week trial of citalopram in 174 children and adolescents (aged 7–17) with depressive disorders (Wagner et al., 2004). Compared with placebo, response criteria (CDRS-R ≤ 28) were achieved by significantly more citalopram-treated depressed youth. Citalopram and placebo were discontinued due to adverse events at a similar rate (5.6 and 5.9%, respectively). No differences between children and adolescent populations were reported.

According to the CSM report, a large unpublished trial of citalopram in depressed teenagers (aged 13–18) did not demonstrate an antidepressant effect over placebo. Additionally, compared with placebo, greater percentages of citalopram-treated youth reported
self-harm or suicidal thoughts, made serious suicide attempts or required hospitalization.

In contrast, von Knorring et al. reported a response rate of about 60% for both citalopram and placebo in 244 adolescents (aged 13–18 years), but a better outcome in the citalopram group when the study results were controlled for the application of psychotherapy (von Knorring et al., 2006). In addition, a worsening of suicidal thoughts and a nonsignificant trend to a higher incidence of suicide-related events was seen more frequently in the placebo group.

10.2.1.1.2.5 Escitalopram

Wagner and colleagues conducted an 8-week RCT of escitalopram, the S-isomer of citalopram, involving 264 young subjects aged 6–17 (Wagner et al., 2006). Although the results across the entire sample did not reveal significant differences, subgroup analysis revealed a statistically significant drug versus placebo benefit for adolescents. Rates of discontinuation due to adverse events and rates of suicide-related behavior were similar for drug and placebo.

10.2.1.1.2.6 Venlafaxine

Venlafaxine, an antidepressant that inhibits reuptake of both serotonin and norepinephrine, has also been evaluated as a treatment for depressed youth. In 1997, Mandoki et al. published a trial involving 40 children and adolescents (aged 8–18), who received relatively low doses of venlafaxine (37.5 mg for children, 75 mg for adolescents) or placebo; all subjects also received weekly therapy with cognitive and behavioral elements. After 6 weeks, substantial improvement was noted in all subjects; however, there was no significant difference between the venlafaxine-treated subjects and those who received placebo. No serious adverse events were reported in the published paper; however, one subject was hospitalized after developing mania (Mandoki et al., 1997).

Emslie et al. conducted two RCTs of venlafaxine XR in a total of 334 subjects with depressive disorders aged 7–17; while unpublished, the results of these two trials were analyzed together and described in a recent review (Cheung et al., 2005). The combined analysis did not identify any significant differences between venlafaxine extended release (ER, XR) and placebo on the primary outcome variable of CDRS-R endpoint. Of note, when children (ages 7–11) and adolescent (ages 12–17) subgroup analyses were conducted, there was a suggestion of efficacy in the adolescent group (Cheung et al., 2005). According to the CSM report, more treatment-discontinuing adverse events, including hostility and suicidality, were identified in the group treated with venlafaxine.

10.2.1.1.2.7 Mirtazapine

Emslie et al. also conducted two RCTs of mirtazapine, a noradrenergic and specific serotonergic agent. These trials involved a total of 250 depressed youth (aged 7–17). While the results of these trials remain unpublished, a recent review indicates that no significant CDRS-R differences between mirtazapine and placebo conditions were noted at the end of either 8-week trial (Cheung et al., 2005). According to the CSM report, one mirtazapine-treated subject reported suicidal thoughts and one placebo-treated subject performed an act of self-mutilation.

10.2.1.1.2.8 Nefazodone

Two RCTs of nefazodone, a serotonin-modulating antidepressant, were conducted by Emslie and colleagues. While neither study has been published, one trial involving 195 depressed 12- to 17-year-olds was described in a recent review (Cheung et al., 2005). In this study, beneficial effects for nefazodone approached but did not achieve statistical significance on CDRS-R primary outcome variables. No nefazodone-related serious adverse events occurred. The CSM report included no data regarding this medication.

10.2.1.1.2.9 Bupropion

No RCTs have been conducted with this medication in child and adolescent populations.

10.2.1.1.2.10 Ω-3 fatty acids

Benefits of Ω-3 fatty acids have been shown in a 16-week-long RCT (Nemets et al., 2006).

10.2.1.2 Regulatory action by the UK and US

In June 2003, after evaluating unpublished manufacturer data revealing increased suicidality associated with paroxetine, the UK Committee on Safety of Medicine (CSM) advised that paroxetine should not be used to treat depressed youth. The FDA quickly followed suit. In August 2003, the manufacturer of venlafaxine sent letters to doctors explaining that, due to lack of efficacy and potential for increases in suicidality and hostility, the drug should not be used for young people. By December 2003, the Medicines and Healthcare products Regulatory Agency (MHRA)
warned against using all SSRIs, and the FDA urged extreme caution when using any newer antidepressant in pediatric populations (Leslie et al., 2005).

Given their concern regarding treatment-emergent suicidality, the FDA conducted a review of independently coded safety data from 24 studies of nine of these antidepressants (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, bupropion, venlafaxine, nefazodone and mirtazapine) in youth populations. Of note, these medications were prescribed in trials not only for depression but also for anxiety disorders and attention-deficit hyperactivity disorder. It is important to note that, among the 4400 patients treated with SSRIs or other newer antidepressants in these studies, there were no completed suicides. However, when evaluated together, the risk of ‘suicidality’ (defined as suicidal thinking and behavior) in the antidepressant trials was approximately twice that of placebo: 4 versus 2%, respectively (risk ratio 1.95, 95% CI 1.28–2.98), a finding that was supported by a recent re-analysis largely of the same studies (Wohlfarth et al., 2006). There was also a significant effect for treatment-emergent agitation and hostility (Hammad, 2006).

When the FDA restricted its analysis to trials of depressive disorders, statistically significant differences in suicidality and treatment-emergent agitation and hostility persisted (Hammad et al., 2006a; see Table 23). Depressed youth treated with paroxetine were most likely to experience treatment-emergent agitation and hostility (relative risk 7.69, 95% CI 1.80–32.99). Those treated with venlafaxine XR were most likely to experience suicidality (relative risk 8.84, 95% CI 1.12–69.51).

Based on the above analyses, the FDA concluded that a true risk may exist for some youth. As a result, in October 2004 the FDA issued a ‘black box’ warning alerting health-care providers and consumers about ‘an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents’ who are taking antidepressant medication (FDA Public Health Advisory, 2004) (FDA website). The FDA review panel included all antidepressants in its warning due to concern that limiting the black box to newer agents would encourage the use of older medications with narrower therapeutic windows and higher lethality in overdose (Gibbons et al., 2005); however, fluoxetine remains FDA-approved for the treatment of depression in youth. In December 2004, the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMEA) Scientific Committee similarly advised that newer antidepressants ‘are not authorized Europe-wide for the treatment of depression and anxiety disorders in children and adolescents. These compounds should generally not be used in this age group because clinical trials have shown an increased risk of suicidal behavior (European Medicines Agency, 2004). In June 2006, however, after further data reviews, the EMEA adopted a more favorable position towards fluoxetine; it recommended extending fluoxetine’s indication to include children, ‘8 years of age or older who suffer from moderate to severe depression and who do not respond to psychological therapy (European Medicines Agency, 2006’ (EMEA website: http://www.emea.eu.int/).

10.2.1.3 Investigations of other sources of evidence

Given the problems inherent in drawing conclusions about suicidality from studies not designed or powered for such a purpose (Emslie et al., 2005), several pharmaco-epidemiological and observational studies have been undertaken in order to further examine the link between newer antidepressants and suicide or suicidal behavior.

10.2.1.4 Antidepressants and completed suicides

One frequently utilized pharmaco-epidemiologic technique involves investigating whether regional changes in rates of prescription of newer antidepressants correlate with changes in suicide rates. Several of these large, retrospective studies have been carried out (Gibbons et al., 2005; Gibbons et al., 2006; Hall et al., 2003; Helgason et al., 2004; Ludwig and Marcotte, 2005; Olsson et al., 2003; Olsson et al., 2006; Søndergaard et al., 2006). An Australian study found substantially decreased rates of suicide in association with exposure to antidepressants, especially in older men and women, together with increased suicide rates in adolescents and young adults aged 15–24 (Hall et al., 2003). More recent studies by Olsson and colleagues (Olsson et al., 2006), as well as a large FDA meta-analysis found a similar age-dependent pattern of antidepressant-associated suicide risk (US Food and Drug Administration, 2007). Other American and international studies indicate an inverse relationship between rates of SSRI prescriptions and rates of suicide in child and adolescent populations (Gibbons et al., 2005; Ludwig and Marcotte, 2005; Olsson et al., 2003). According to an analysis of WHO data performed by the American College of Neuropsychopharmacology (ACNP) Task Force on SSRIs and Suicidal Behavior in Youth, over the past 14 years the suicide rate for adolescents and young adults (aged 15–24) has decreased by an average of 33% across 15
countries (Mann et al., 2006a). While such analyses are imperfect and subject to the ‘ecologic fallacy’ (Robinson, 1950), taken together, the reported studies show mixed evidence of increased suicidality or suicide rates among children and adolescents caused by SSRI use.

In addition to pharmaco-epidemiologic studies, other groups have used post-mortem toxicological analyses as a means of investigating a link between completed youth suicide and antidepressant medications. Evidence from a large-scale Swedish study (Isacsson et al., 2005) and two smaller American studies (Moskos et al., 2005; Tardiff et al., 2002) does not support an association between treating youth with antidepressants and subsequent completed suicide.

10.2.1.5 Antidepressants and suicidal behavior or non-fatal self-harm in depressed youth

In addition to completed suicides, information is also available regarding suicidal behavior and non-fatal self-harm. Several retrospective studies have investigated this potential link through queries of large databases of patient information. The results of these studies are mixed.

In 2004, Valuck et al. conducted a propensity-adjusted cohort study to examine links between antidepressant treatment and suicide attempts in over 24000 adolescents (aged 12–18) who were started on antidepressants after being newly diagnosed with depressive disorders. After adjusting for severity of symptoms, the researchers found that youth treated with SSRIs did not have statistically significant increases in rates of suicide attempts when compared with youth treated with other or multiple medications. Youth who continued treatment with any antidepressant for 6 months made significantly fewer suicide attempts than those who remained on medication for less than 8 weeks. (Valuck et al., 2004).

Martinez et al. conducted a nested case-control study comparing rates of fatal and non-fatal self-harm for over 146000 individuals in a large UK general practice database (Martinez et al., 2005). Identified cases were prescribed TCAs, SSRIs or other newer antidepressants for a depressive episode (unipolar or bipolar) or dysthymia. In the 6 months following index prescription, no suicides occurred in the 10- to 18-year-old cohort. However, compared with depressed youth treated with TCAs, depressed youth treated with SSRIs demonstrated ‘weak evidence’ for increased rates of non-fatal self-harm (adjusted odds ratio 1.59, 95% CI 1.01–2.50). Among the SSRIs evaluated, the greatest risk for non-fatal self-harm was associated with paroxetine. Jick and colleagues found a near-significant signal for increased rates of self-harm in paroxetine-treated youth (aged 10–19) in an earlier study of the same database (Jick et al., 2004). A potential criticism of these studies, but also of other naturalistic databases, is the mixed cohort of unipolar and bipolar patients. Antidepressants may induce switching into mania, which in adolescents is characteristically mixed in nature. Mixed episodes, however, are strongly associated with suicidal ideation (Dilsaver et al., 1994). In addition, the index episode in bipolar patients is characteristically depressive, and the age of onset of bipolar disorder is earlier than of unipolar disorder, leading to a potential overrepresentation of bipolar patients in such a cohort. Thus, the inclusion of bipolar adolescents may easily

| Table 23. Published placebo-controlled RCTs of SSRIs and newer antidepressants in children and adolescents |
|------------------|---------------------------------|-----------------|-----------------|-----------------|
| Drug             | Suicide-related events          | Treatment-emergent agitation or hostility |
|                  | Relative risk | 95% CI          | Relative risk | 95% CI          |
| Nefazodone       | No events     | n.a.             | 1.09           | 0.53–2.25       |
| Citalopram       | 1.37          | 0.53–3.50        | 1.87           | 0.34–10.13      |
| Fluoxetine       | 1.53          | 0.74–3.16        | 1.01*          | 0.40–2.55       |
| Mirtazapine      | 1.58          | 0.06–38.37       | 0.52           | 0.03–8.27       |
| Paroxetine       | 2.15          | 0.71–6.52        | 7.69           | 1.80–32.99      |
| Sertraline       | 2.16          | 0.48–9.62        | 2.92           | 0.31–27.83      |
| Venlafaxine XR   | 8.84          | 1.12–69.51       | 2.86           | 0.78–10.44      |
| Total            | 1.66          | 1.02–2.68        | 1.79           | 1.16–2.76       |

* FDA analysis of treatment-emergent hostility and agitation did not include data from the TADS study.

Boldface = statistically significant results.

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confound the results, making conclusions regarding the risk of suicidal ideation in unipolar depressed patients problematic (Berk and Dodd, 2005a; Berk and Dodd, 2005b).

In a recent meta-analysis by Dubicka et al. (Dubicka et al., 2006) the pooled risk of self-harm and suicidal behavior from randomized trials of newer antidepressants was determined. Self-harm or suicide-related events occurred in 71 of 1487 (4.8%) of depressed youths treated with antidepressants versus 38 of 1254 (3.0%) of those given placebo (fixed-effect odds ratio 1.70, 95% CI 1.13–2.54, p = 0.01). There was a trend for individual suicidal thoughts, attempts and self-harm to occur more often in youth taking antidepressants than in those given placebo, but none of these differences was statistically significant.

In a separate study, Simon and colleagues used a large American database to retrospectively analyze over 82000 index episodes of antidepressant treatment, 5107 of which involved youth aged 5–18 (Simon et al., 2006). Six months after the diagnosis of depressive disorders (coded as ICD-9 MDD, Dysthymia or Depressive Disorder NOS) and after initiating antidepressants, 3 youth and 28 adults completed suicide. Like Jick and colleagues, Simon and colleagues found a significantly higher rate of suicide attempts in the first week of treatment compared with subsequent weeks. However, when compared across the entire sample, there was no statistically significant increased risk of completing suicide the first month of treatment compared with subsequent months. Additionally, rates of serious suicide attempts, captured from 3 months before to 6 months after index antidepressant prescription, were highest in the month before antidepressants were initiated. When the newer antidepressants included in the FDA review were compared with older antidepressants not evaluated by the FDA, this decrease in suicide attempts in the month after treatment initiation was seen only with newer antidepressants. The authors state that these differences may reflect a more timely therapeutic effect of newer agents.

10.2.1.6 The use of antidepressants, and their risks and benefits

Several recent studies have used a meta-analysis to compare the risks and benefits of individual antidepressant agents that have been subject to randomized clinical trials in depressed youth (Bridge et al., 2005; Wallace et al., 2006; Whittington et al., 2004). The authors of each of these studies conclude that the risk-benefit profile is most favorable for fluoxetine. Two of the studies suggest that the risk-benefit profile of citalopram is also positive (Bridge et al., 2005; Wallace et al., 2006); one study suggests that the benefits of sertraline may also outweigh its risks when used in treating depressed youth.

In sum, the evidence about safety and efficacy of SSRIs is mixed. There is significant evidence for the efficacy of fluoxetine in treating depressed adolescents. Fluoxetine is the only agent approved by regulatory agencies in the US, UK and Europe for use in depressed youth. Importantly, in the well-designed TADS study, fluoxetine was helpful in a group of moderate to severely depressed youth that were not significantly helped by CBT (March et al, 2004). There is more limited evidence for the efficacy of sertraline, citalopram and escitalopram. Regarding safety, meta-analyses of RCTs suggest that SSRIs increase suicide ideation compared with placebo, but observational studies suggest that SSRIs do not increase suicide risk more than older antidepressants (Hall and Lucke, 2006). While there is no evidence of completed suicide from reported RCTs, compared with placebo, there is a higher incidence of self-harm and aggressive or impulsive actions, especially with paroxetine or venlafaxine treatment.

Based on all of the preceding data, the following recommendations might be considered regarding diagnosis and treatment of youth with depressive disorders (see also Box 11).

10.2.1.7 Conclusion

Although much is known about the effects of antidepressant medications in children and adolescents, research is needed to further improve our ability to treat depressed youth. In adolescents, high placebo response rates have been reported, but there is reasonable evidence for the effectiveness of fluoxetine. Apart from ω-3 fatty acids, there is no substantial evidence that antidepressant medication is useful in prepubertal children. The current evidence for prepubertal efficacy of antidepressants is not robust: the older postpubertal adolescents were in clinical trials, the more likely was the response to antidepressants. In addition, several questions regarding the safety of newer antidepressants remain.

Regarding efficacy, more information is needed to determine which children and adolescents respond to which treatments. Current treatment studies have been characterized by high placebo response rates and suboptimal response rates. Important questions
regarding the effects of early intervention and long-term treatment in both children and adolescents also remain.

The debate over the safety of these medications will also continue. If the risk is determined to be real, investigators must identify an etiology of self-harm and suicidal behavior, and conclude whether these behaviors can be predicted and neutralized. Given the known morbidity and mortality associated with untreated depression, all risks of treatment must be balanced against the risk of withholding treatment. Regardless of treatment status, all depressed children and adolescents will require psychoeducation and careful monitoring.

10.2.2 Antidepressant treatment in old age

10.2.2.1 General clinical considerations

The prevalence of depression appears to be independent of age (Patten et al., 2001; Steffens et al., 2000),

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The suggestions given are based more on clinical experience than on evidence-based medicine.

In countries where firearms are widely available, parents should be encouraged to remove firearms or other dangerous equipment from the house.
but a high rate of depressive symptoms requiring treatment (Chopra et al., 2005) in old age has been reported. In clinical work, prevalence rates may be artificially low owing to standardized diagnostic assessment procedures that are insufficiently adapted for use in the elderly (Wittchen et al., 1994). Under-detection of subthreshold depression, which shows a high prevalence in the old age (Horowitz et al., 2005), may be one explanation. The diagnosis of depression may thus be relatively rare in elderly patients, whereas subthreshold depression, which according to the Diagnostic and Statistical Manual of Mental Disorders, 4th revision (DSM-IV), and the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), also requires antidepressant treatment, may frequently be present. However, epidemiological data show that the prevalence of depression in old age is in fact high, is often underdiagnosed and undertreated, has a high rate of recurrence and is associated with significantly increased mortality (Katona, 1994). Because the prevalence of suicidal ideation is also relatively high in the old age, effective suicide prevention is especially needed for this age group (Pfaff and Almeida, 2005; Raue et al., 2007). In addition, older patients experience more and longer major depressive episodes together with increased general medical comorbidities (Husain et al., 2005). Considerable comorbidity exists with dementia, stroke and Parkinson’s disease, where patients often suffer from depressive symptoms. The response to antidepressant treatment in the elderly apparently does not differ from treatment response in younger patients. However, relapse rates are higher, and the longitudinal outcome is less favorable than for middle age (Mitchell and Subramaniam, 2005). Very few longitudinal studies follow the course of depressive illness in elderly people. The meta-analysis of data from 12 studies in primary care and in community secondary care showed that after 2 years, 21% of elderly depressed patients who were at least partially diagnosed and treated by primary care physicians had died. Among survivors, almost half remained depressed (Cole et al., 1999). Moreover, inadequate training in geriatrics may worsen this situation (Bartels et al., 2003), whereas elderly patients who receive adequate antidepressant treatment experience significantly better physical functioning (Callahan et al., 2005). The more adverse longitudinal course in old age may more plausibly be explained by medical comorbidity (see also chapter 5.2.4), immobility and psychosocial factors than by age itself (Mitchell and Subramaniam, 2005). It is also generally accepted that elderly depressed patients are particularly prone to the side effects of antidepressants, particularly cardiovascular side effects and treatment-related cognitive dysfunction (Moskowitz and Burns, 1986). Suboptimal regimes in 43.3% of elderly patients treated with antidepressants have been reported. These include both potentially hazardous (e.g. due to high-dose treatment with anticholinergic agents) as well as excessively low intensity and insufficient treatments (Wang et al., 2005). It may also be important to distinguish between young-old (aged <75 years) and old-old (aged ≥75 years). Both groups show marked differences in comorbidity (e.g. dementia), lifestyle and rates of institutional care. However, in most antidepressant trials this distinction has not been made, and patient samples in previous studies are usually heterogeneous and termed elderly, geriatric, senile or older adults, aged 55 or over (Mottram et al., 2006).

10.2.2.2 Efficacy of antidepressants in old age

Numerous randomized controlled trials of antidepressant treatment in late-life depression have been conducted, including all substance classes. The first question is whether antidepressant pharmacotherapy is effective at all in elderly patients, i.e. whether it shows therapeutic efficacy superior to placebo treatment. Roose and Schatzberg (2005) recently reviewed five placebo-controlled trials that were selected based on quality criteria in order to assess antidepressant efficacy and effectiveness. Useful data on TCAs are very limited because previous studies have often involved inadequate dosages of TCAs (e.g. imipramine and amitriptyline), which are not recommended for the use in elderly patients (Mamdani et al., 2000).

Thus, four of these randomized controlled trials (Rapaport et al., 2003; Roose et al., 2004; Schneider et al., 2003; Tollefson et al., 1995) compared different SSRIs (fluoxetine, sertraline, citalopram, paroxetine), and one trial compared fluoxetine and venlafaxine with placebo (Schatzberg et al., 2002). Three studies demonstrated a statistically significant difference in drug versus placebo response or remission rates (Rapaport et al., 2003; Schneider et al., 2003; Tollefson et al., 1995). The percentage of trials failing to show a significant difference between verum and placebo groups resembles results of non-geriatric trials, where medication is found to be more effective than placebo less than 50% of the time. In 1999, among other general medical principles, the World Psychiatric Association (WPA) recommended treating depressive symptoms in the elderly with the aim of complete remission. A more recent guideline of a
working group of the Royal College of Psychiatrists from the UK (Baldwin et al., 2003) also supported the efficacy of antidepressant drugs in elderly patients based on a previous Cochrane review (Wilson et al., 2001) and further meta-analyses (Gerson et al., 1999; McCusker et al., 1998; Mittmann et al., 1997). In contrast, little is known about augmentation strategies in elderly patients who have shown only modest improvement during previous treatment trials (Baldwin et al., 2003).

Another question is whether one class of antidepressants is more favorable in old age than others. Roose and Schatzberg (Roose and Schatzberg, 2005) selected six trials that compared at least two different antidepressants for further critical review. All randomized controlled trials in this review were comparison trials of two SSRIs or one SSRI compared with a TCA or mirtazapine (Bondareff et al., 2000; Navarro et al., 2001; Newhouse et al., 2000; Roose et al., 2004; Schatzberg et al., 2002). The response rates in these comparison trials were consistently higher than those seen with the same agents in placebo-controlled trials (50–73% vs. 35–72%) and may better reflect the effectiveness of medication in a clinical setting (Roose and Schatzberg, 2005). These trials did not demonstrate that one antidepressant is superior to another; nevertheless, some experts recommend the low-dose use of TCAs in the treatment of elderly patients. In a very recent Cochrane analysis (Mottram et al., 2006), 29 out of 163 identified trials were selected for further analysis, and 14 studies were selected for contributing efficacy data. Trials entering the meta-analysis of efficacy had to compare at least two active antidepressant drugs, because the meta-analysis aimed at comparing the efficacy of antidepressant classes, withdrawal rates and side-effect profiles in elderly patients. The trial duration varied between 4 and 8 weeks, and only 2 trials (comparison of moclobemide with imipramine and tianeptine) were conducted over 12 weeks or more (Dunningham et al., 1994). No significant differences in efficacy were found between classes of antidepressants (TCAs, TCA-related drugs, SSRIs, MAOIs and atypical antidepressants). However, the trials contained relatively small numbers of patients, possibly introducing a large type-2 error, which may explain the negative finding. Higher numbers of patients withdrawn irrespective of reason or due to side effects were observed during treatment with TCAs compared with SSRIs.

Electroconvulsive therapy (ECT) has also been shown to exert excellent effectiveness, which was better in younger than in older geriatric patients (Abrams, 2002; Greenberg and Fink, 1992; Oshima and Higuchi, 1999). Despite specific side effects, such as greater cognitive impairment, efficacy is greater in older than in younger patients, and reduced mortality in comparison with other treatments has been shown (Philibert et al., 1995). Further progress in understanding ECT and anesthesia has reduced the risks of the treatment. Some authors currently are therefore of the opinion that there are no absolute medical contraindications to the use of modified ECT which is encouraged now also in geriatric patients and in patients at particular medical risk (Abrams, 2002; Fink, 1999).

There is a broad clinical consensus that it is appropriate to include both antidepressant medication, specifically SSRIs, and nonpharmacological modalities in treatment plans for severe depression in the elderly (Alexopoulos et al., 2001).

10.2.2.3 Tolerability in elderly patients

The recent Cochrane analysis (Mottram et al., 2006) of side effects showed a small increased risk of gastrointestinal (including the experience of ‘dry mouth’) and neuropsychiatric side effects (drowsiness, dizziness, lethargy) associated with classical TCAs. However, further conclusions regarding the comparison of other classes of substances have not been possible due to the methodological limitation mentioned above. Thus, only the pharmacological profiles of specific drugs and their interactions with medical comorbidity and concomitant medication can determine the choice of antidepressants in elderly patients. In primary care, newer drugs that provide a superior safety profile, such as SSRIs, are gradually replacing TCAs as a first-line treatment (Gareri et al., 1998; Mamdani et al., 2000). Moreover, geriatric patients are more susceptible to side effects such as orthostatic hypotension and sedation. Cognitive disturbances, too, and even delirious states induced by the anticholinergic action of various antidepressants, e.g. TCAs, are more frequent. Elderly patients are at especially high risk for adverse drug reactions and drug-drug interactions (see also chapter 9.1.1.1.5) due to multimedication (Borchelt, 1995). Some side effects that raise particular concerns in younger patients, such as weight gain due to antihistaminergic effects, may be beneficial for elderly patients, who often suffer from anorexia and weight loss. In existing medical comorbidity, which may complicate the management of late-life depression, particular care should be paid in choosing an antidepressant. According to the guidelines from the UK (Baldwin et al., 2003), SSRIs should be preferred for depression that complicates vascular and
cerebrovascular disease, mainly because of safety and tolerability. In dementia, TCAs, SSRIs and moclobemide are effective; however, newer drugs are better tolerated and safer. For Parkinson’s disease no adequate trial data are available. SSRIs may aggravate parkinsonian symptoms, but this finding has not been established (Baldwin et al., 2003).

10.2.2.4 Dosage and duration of antidepressant treatment in old age

Comorbid medical conditions and concomitant medications require particular attention to pharmacodynamic and pharmacokinetic interactions. Even if no other medical disturbances are present, normal aging leads to differences in hepatic and renal function that require extraordinary awareness. Because of reduced hepatic metabolism and renal elimination rate in the elderly, appropriate dosages are lower than in younger patients (Chiu, 1997). In frail patients treatment should commence with a slow dosage and titrate gradually to the therapeutic dosage range (‘start low and go slow’). Moreover, the guidelines of the American Psychiatric Association (APA) emphasize that elderly patients typically require a lower dosage than younger patients to reach a particular blood level and tolerate a given blood level less well. However, the blood levels at which antidepressant medications are maximally effective appear to be the same as for younger patients (American Psychiatric Association, 2000; Wilson et al., 2001). Another critical issue is the duration of treatment in old age. Older patients apparently take longer to recover from depression and recovery goes on up to 12 weeks, provided that there has been some early improvement (Wilson et al., 2001). Currently at least 6 weeks of treatment is recommended to achieve optimal therapeutic effects (Wilson et al., 2001). However, little response (e.g. less than 25% recovery) during the first 4 weeks of the same treatment is associated with a low probability of remission (Mottram et al., 2006). Similar to younger patients, following remission, antidepressant medication should be continued at the same dose for at least 6 months in the case of initial episodes and longer in the case of recurrent illness, as described in Table 9 (Geddes et al., 2003).

11 Suicidality and antidepressants: depression and suicide

About two-thirds of people committing suicide suffer from depression. In 1970, Guze and Robins (Guze and Robins, 1970) published a meta-analysis of studies putting a lifetime suicide risk at 15%. This frequently quoted figure may overestimate the suicide risk, as it generalizes from high-risk hospitalized patients to all depressed patients (Boardman and Healy, 2001). Suicide rates in depressed patients in longer (> 10 years) follow-up studies range from 4% to 10.6% (Angst et al., 2005). A meta-analysis of 27 mortality studies by Inskip (Inskip et al., 1998) using contemporary data and modern analytic techniques led to an estimate of a lifetime suicide risk of 6% for affective disorders. Recently, Bostwick and Pankratz (Bostwick and Pankratz, 2000) found a hierarchy of lifetime suicide prevalences: 8.6% in people ever admitted for suicidality, 4% in patients admitted with affective disorder but not specifically for suicidality, and 2.2% in mixed inpatient and outpatient populations. Diagnostic uncertainties may also obscure accurate estimates of suicide rates for unipolar depression. A meta-analysis by Harris and Barraclough (1998) found a standard mortality ratio (SMR) of 21.24 for major depressive disorder that even exceeded the one calculated for bipolar patients. Ösby et al. identified all patients with a hospital diagnosis of bipolar ($n = 15386$) or unipolar ($n = 39182$) disorder in Sweden from 1973 to 1995 from the inpatient register and linked with the national cause-of-death register to determine the date and cause of death. The SMRs for suicide were 15.0 for males and 22.4 for females with bipolar disorder, and 20.9 and 27.0, respectively, for unipolar disorder (Ösby et al., 2001).

A more precise estimate of suicide mortality may be difficult due to methodological shortcomings, as outlined by Jules Angst and colleagues (Angst et al., 2005).

- The most severely ill, hospitalized patient samples are selected, and these are not representative.
- Lifelong follow-up studies are lacking.
- The diagnoses in representative suicide samples are retrospective.
- In order to compensate for the lack of decades-long follow-up studies, risk estimates are based on exposure years that assume an unproven time-related linear risk.
- Perhaps the most significant methodological problem: bipolar disorder and unipolar depression arising from an under-diagnosis of hypomania leading to an underestimate of bipolar II disorder.

The most definitive prospective, long-term, large cohort study on suicide risk in affective disorders may be that conducted by Angst et al. who followed up 406 patients with mood disorder from 1963 to...
2003 (Angst et al., 2005). By 2003, 11.1% of these patients had committed suicide, with the highest SMR being 26.4 for unipolar depressed patients. These data underscore the prominent role of early diagnosis and treatment of depression in suicide prevention.

Early diagnosis and public awareness have been proven to be effective tools in reducing suicide attempts and completed suicides in large, population-based studies. This finding was first demonstrated in a prospective, community-based trial in Gotland, Sweden (Rihmer et al., 1995; Rutz et al., 1989). The results were replicated recently (Henriksson and Isacsson, 2006) and seem also to hold true for larger, urban communities. For example, the Nürnberger Bündnis gegen Depression (Nuremberg Alliance against Depression) is a community-based, multifaceted, 2-year intervention that focuses on depression. The number of suicidal acts (fatal and non-fatal suicide attempts) showed a significant and clinically relevant reduction compared with both a 1-year baseline and a control region (minus 24%) (Althaus et al., 2006; Hegerl et al., 2006).

Patients with a history of suicidal behavior suffer from a greater burden of depressive illness (Claassen et al., 2006). As demonstrated by Balazs et al. (2006), the presence of such clinical features as irritability, distractibility and psychomotor agitation (‘mixed depression’ as quoted by the authors) are, besides hopelessness (Goldston et al., 2006; MacLeod et al., 2005), strong predictors of suicide attempts even in patients who do not otherwise fulfill diagnostic criteria for bipolar disorder. On the basis of these findings, Rihmer and Akiskal (2006) speculated that in these patients the use of antidepressants without concomitant mood stabilizers may exacerbate a pre-existing mixed state or generate de novo mixed syndromes, resulting in treatment resistance as well as a worsening of depression that ultimately may provoke suicidal behavior. In the context of this review, it may be appropriate to recommend that special caution be exercised in patients with the symptoms of hopelessness, irritability, distractibility and agitation who are prescribed an SSRI, since agitation occurs statistically significantly more frequently with SSRIs than with other antidepressants, e.g. TCAs. In the future, we may be even able to identify patients on risks for suicidal behaviour on a genetic basis; a recent report demonstrated that markers within GRIK2 and GRIA3 are associated with treatment-emergent suicidal ideation during citalopram therapy (Laje et al., 2007).

Different claims about the use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), and suicidality have been proposed. Antidepressants may decrease suicide rates on a population basis (Ludwig and Marcotte, 2005), but at the same time they may increase suicidality (or even suicide events) in some individuals early in treatment (Healy and Whitaker, 2003). Recent reviews by Hall and Lucke (2006) and Möller (2006a, b), show some supportive evidence for both views.

A study by Yerevanian et al. (2004) demonstrated that long-term treatment with antidepressants (SSRIs and tricyclic antidepressants (TCAs)), sometimes in combination with benzodiazepines, significantly reduces the risk of both completed and attempted suicide in more than 500 patients with major depression and dysthymic disorder. In addition, a multitude of epidemiological studies have demonstrated reduction of suicidality in regional populations in association with antidepressant prescription (Carlsten et al., 2001; Hall et al., 2003; Isacsson et al., 1997; Isacsson, 2000; Ohberg et al., 1998; Rihmer et al., 2000); for a short overview see (Hall and Lucke, 2006; Isacsson and Rich, 2005; Yerevanian et al., 2004). Investigating the suicide mortality of the 27 countries with data on annual sales of all SSRIs (and, of course, also other antidepressants) between 1980 and 2000, Ludwig and Marcotte (2005) found that after controlling for a variety of sociodemographic factors, an increase of one SSRI pill per capita in 2000 (a 13% increase over 1999 levels) was associated with a significant, 2.5% reduction in suicide rates in adults. As pointed out by Rihmer and Akiskal (2006), this effect is most prominent in countries with previous high suicide rates and low rates of treated depression, and can be separated from other covariables such as alcohol consumption or unemployment rates. In Iceland (population 286000) the relatively low suicide rate (around 30 suicides per year) was not decreased despite a huge increase in the use of antidepressants (Helgason et al., 2004).

When not properly conducted, however, open studies and population-based studies can easily be subject to several biases and errors in interpreting results (Möller, 2006a). It should also not be neglected that some of the recent epidemiological studies arose in response to the concerns of regulatory agencies of potential increased suicidality with antidepressants, and due to their largely uncontrolled nature, there is clearly room for an investigator bias. Randomized, control group studies, especially when placebo controlled, seem to be the best basis for statements about the suicide risk of certain antidepressants. But because suicide is, fortunately, a rare outcome in controlled studies, it cannot be reliably assessed. To improve the number of subjects and statistical power, pooled data
subjected to meta-analysis have been used (for the general methodological problems of using meta-analyses, please refer to chapter 4.4). To date, the largest database from randomized controlled trials (RCTs) is one assessed by Hammad et al. (Hammad et al., 2006b). They evaluated the rate of suicide in placebo- and active drug-treated groups of patients with major depression and various anxiety disorders participating in short-term RCTs. Data were available for 207 trials conducted in patients with major depressive disorder (MDD), including a total of 40028 patients, and 44 trials conducted in patients with various anxiety disorders, including a total of 10972 patients. The use of neither placebo nor antidepressants in short-term RCTs was associated with an increased risk of completed suicide among patients with MDD or various anxiety disorders. Nonetheless, as the authors conclude, because of the small numbers of suicides in these trials and the subsequent lack of statistical power, an increased risk of completed suicide in association with either drug or placebo treatment cannot be definitively excluded.

Thus, we can only assess other parameters that are more frequent and are linked to suicide with various degrees of certainty (and, of course, uncertainty; Klein, 2006). Even when softening the outcome criterion towards ‘suicidality’, not completed suicide, the results of such control group studies also have to be viewed critically and considering the methodological pitfalls inherent in the design of such studies. The low basal prevalence of suicidal behavior has the consequence that, for principal statistical reasons, it is almost impossible to perform a control group study with adequate statistical power to differentiate between the outcome results of two treatment groups, as the number of these events in a medium-sized or even a large control group study is small. This drawback could possibly be overcome by an enriched sample design; however, most of the respective control group studies on antidepressants do not deal with samples in which the symptom suicidality/suicidal thoughts is enriched. Indeed, the opposite is true: most studies exclude at least patients with serious suicidal thoughts. The principal ethical aim, i.e. to avoid harm to the patients, conflicts with the scientific objective of such studies. Thus the ideal control group design to answer the question whether antidepressants reduce suicidality cannot be realized for ethical reasons. The consequence of this dilemma might be that any indications of efficacy do not reach statistical significance and, in addition, are far removed from actual efficacy in real-life conditions (Möller, 2006a).

These limitations must be kept in mind when assessing suicidal behavior in controlled studies, both in those studies detecting a signal and those that do not. A secondary analysis by Möller of a 6-week double-blind controlled study comparing paroxetine and amitriptyline showed a marked reduction in suicidal thoughts for both medications (Möller et al., 1998). Similarly, Szanto (Szanto et al., 2003) demonstrated complete remission of suicidal ideation in elderly depressed patients after 12 weeks of either amitriptyline or paroxetine treatment. A review of data from several controlled studies by Möller (Möller, 2003) also demonstrated a greater benefit of SSRIs compared with placebo in reducing suicidal ideation.

But there is also conflicting evidence. Concerns started in 1990 with the observation of intense suicidal preoccupation during fluoxetine treatment in six patients, (Teicher et al., 1990), obviously contrasting neurobiological findings of decreased central serotonergic neurotransmission in suicide victims (Asberg, 1976). By the end of 1991, at least four other publications appeared, expressing concerns about the emergence of intense suicidality with fluoxetine. A reanalysis of the first survey on this topic, conducted by Fava and Rosenbaum (1991) suggested that the emergence of suicidality was about three times more frequent and are linked to suicide with various anxiety disorders, including a total of 10972 patients. In 4400 depressed children and adolescents, (Teicher et al., 1990), obviously contrasting neurobiological findings of decreased central serotonergic neurotransmission in suicide victims (Asberg, 1976). By the end of 1991, at least four other publications appeared, expressing concerns about the emergence of intense suicidality with fluoxetine. A reanalysis of the first survey on this topic, conducted by Fava and Rosenbaum (1991) suggested that the emergence of suicidality was about three times more likely with fluoxetine than with other antidepressants (ACNP, 1992). More recently Healey and Whitaker (2003) have argued that there is an increased risk of suicidal behavior in controlled trials, although the risk is relatively rare. In the Healey meta-analysis, this risk seemed to be especially increased in juveniles and adolescents as discussed previously in this review (see chapter 10.2.1). This report raised considerable public attention, especially in Great Britain and the US. To clarify this issue, the US Food and Drug Administration (FDA) commissioned an independent group of investigators at Columbia University to review all adverse events that suggested suicidal activity in controlled trials of SSRIs in children and adolescents. In 4400 depressed children and adolescents in a total of 24 studies, there were no completed suicides; however, the risk of suicidal ideation or activity was 4% on active medication and 2% on placebo (US Food and Drug Administration, 2005). The exact significance of this finding is not clear, and the FDA did not make any conclusions regarding causality. In addition, the methodological basis of the consecutive FDA black box warning (FDA Public Health Advisory, 2004) for marketed antidepressants about the use of these agents in younger patients raises questions, as outlined by Klein (2006).
A finding similar to the FDA warning was also reported by a recent meta-analysis of 702 randomized controlled trials including more than 87000 depressive and other psychiatric patients, primarily adult patients. In this analysis Fergusson et al. (2005) showed a significantly increased risk of suicide attempts (OR, 2.28), but not of completed suicides in patients taking SSRIs compared with placebo. In the pooled analysis of SSRIs versus TCAs, no difference was detected in the odds ratio of suicide attempts. This contrasts with another meta-analysis by Gunnell et al. (2005) of 277 randomized controlled trials of SSRIs compared with placebo in 40000 adult patients submitted by pharmaceutical companies to the safety review of the Medicines and Healthcare products Regulatory Agency (MHRA). The authors found no evidence that SSRIs increase the risk of suicide. As a consequence of the conflicting results in adults, the FDA recently asked manufacturers to review their adult databases on suicidal behavior in controlled antidepressant trials.

In response to the FDA request, the first meta-analyses of the specific suicide risk of newer antidepressants are now available. Acharya et al. (2006) evaluated all completed duloxetine trials in major depression until February 2004. The researchers compared the incidence of suicide-related events with duloxetine versus placebo in controlled trials, using the Mantel-Haenszel incidence difference (MHID) and exposure time-adjusted rate difference (MHRD) methods, and analyzed changes in HAMD Item-3 (suicidality) scores. The planned primary meta-analysis of differences in incidence (MHID) of suicidal behaviors during randomized treatment with duloxetine versus placebo did not indicate an association of risk with treatment. Analyses using MHRD methods and outcomes (completed suicide, non-fatal suicide attempt and suicidal ideation) also failed to show either increased or decreased risk of suicidal events in association with duloxetine treatment. Changes in HAMD Item-3 suicidality scores showed more improvement with duloxetine (MHID 9.56%, 95% CI 4.50–14.6, p < 0.001) and less worsening of suicidal ideation with duloxetine (MHID −4.25%, 95% CI −6.55 to −1.95, p < 0.001). Cheung et al. have argued that extrapolating data on antidepressants from adults to adolescents is questionable (Cheung et al., 2006), but the same is true in the opposite direction. Thus, modeling of potential excess suicides in adults from data generated in adolescents, as done, for example, by Gunnell and Ashby (2004), is highly questionable, especially with more data now available of studies in adult populations. Following up on FDA warnings, Simon et al. (2006) analyzed computerized health plan records from a total of 82285 episodes of antidepressant treatment between 1 January 1992 and 30 June 2003. Identifying death by suicide and serious suicide attempts, they found that the risk of suicide attempts was highest in the months before starting antidepressant treatment and declined progressively after starting medication. It was not significantly higher in the months after starting medication than in subsequent months. Comparing the 10 newer antidepressants included in the FDA black box warning with older antidepressants revealed that an increase in the risk of suicide was even more likely with the older drugs than with the newer antidepressants. In addition, a recent combined analysis of all placebo-controlled depression and anxiety studies with escitalopram found no signal for increased suicide risk with active medication treatment. On the contrary, suicidal ideation as measured with item 10 of the MADRS became significantly lower from week 1 onwards with active treatment (Pedersen, 2005).

Other important arguments against increased suicide rates with SSRIs are provided by epidemiological and toxicological studies. A controlled toxicological analysis of all suicide victims from 1992 to 1999 in Sweden showed that SSRIs were underrepresented compared with other antidepressants and that in suicide victims under the age of 15 (n = 52), different antidepressants (but no SSRIs) were detected in seven cases (Isacsson et al., 2005). In a study of the UK General Practice Research Database, Jick et al. found no suicides at all in 6976 depressed patients, 10–19 years old, who were prescribed antidepressants. Indeed, over this entire age group the database revealed 15 suicides, none of whom had been treated with antidepressants (Jick et al., 2004).

Grunebaum et al. (2004) presented the results of a methodologically very sound analysis of US-American data for the years 1985–1999 that also took into account unemployment and alcohol consumption as confounding factors in a multivariate approach. The relationships between the suicide, antidepressant prescription, unemployment and alcoholic beverage consumption rates were studied using generalized linear models. Suicide rates by antidepressant overdose were compared in SSRI s and TCAs. From 1985 to

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62 In a series of workshops on problematic papers, the Canadian Network for Mood and Anxiety Treatments (CANMAT) criticized the lack of heterogeneity analysis before including studies in patients whose diagnoses were unspecified. In addition, small differences in the numbers of rare events such as suicides may lead to misinterpretation of study results.
1999, the suicide rate fell 13.5%, with a greater decline among women, and antidepressant prescription rates increased over fourfold, with the increase mostly due to SSRIs. Prescription rates for SSRIs and other second-generation antidepressants were both inversely associated with suicide rates ($p = 0.03$ and $p = 0.02$, respectively). In a multivariable analysis adjusting for unemployment and alcoholic beverage consumption rates, SSRI antidepressant prescription rates remained inversely associated with the national suicide rate ($p = 0.03$).

A similar analysis of suicide data from the US performed by Gibbons et al. (2005) obtained somewhat more differentiated results. This study focused on the years 1996–1998 and categorized the national county-level suicide rates according to age, sex, income, race and antidepressant prescription rates (expressed as number of pills prescribed). The overall relationship between antidepressant medication prescription and suicide rate was not significant. Within individual classes of antidepressants, prescriptions for SSRIs and other new-generation non-SSRI antidepressants (e.g. nefazodone hydrochloride, mirtazapine, bupropion hydrochloride and venlafaxine hydrochloride) were associated with lower suicide rates (both within and between counties). A positive association between TCA prescription and suicide rates was observed, i.e. higher TCA prescription rates were associated with a higher suicide risk (which may be partially due to the higher toxicity of TCAs when taken with suicidal intent). Results were adjusted for age, sex, race, income and county-to-county variability in suicide rates. Higher suicide rates in rural areas were associated with fewer antidepressant prescriptions, lower income and relatively more prescriptions for TCAs. It should be noted that the authors also report similar results in favor of SSRI prescription in adolescents in a consecutive paper (Gibbons et al., 2006).

Thus, on the basis of the cited and additional studies and meta-analyses (Fergusson et al., 2005; Martinez et al., 2005) Cipriani et al. (2005a) concluded for depression in adults (not in children!) that ‘taking into account these limitations, we can get some useful insights for clinical practice. Firstly, current evidence that indicates no clear relation between SSRIs and suicide, together with available robust evidence of efficacy of treatment with antidepressant drugs in the pharmacological management of moderate to severe unipolar depression, should encourage doctors to prescribe effective doses of these drugs in such patients. Doctors should additionally be aware that SSRIs, similarly to tricyclics, may induce or worsen suicidal ideation and suicide attempts during the early phases of treatment, possibly because they cause agitation and activation particularly at that time. During these early phases, doctors should plan frequent follow-up visits and also consider a possible supporting role for family members and caregivers.’ In addition, doctors should give patients a realistic view about the time to onset of improvement; over-optimistic expectations of patients and doctors may result in disappointment and consequently hopelessness and suicidality.

Besides antidepressants, other medications, including lithium and antipsychotics, may also significantly reduce suicides in patients with mood disorder, as demonstrated by a meta-analysis of Baldessarini et al. (2003) and a recent study of Angst et al. (2005). In the analysis of data of the Zürich cohort study by Angst, long-term medication treatment with antidepressants alone or with a neuroleptic, or with lithium in combination with antidepressants and/or neuroleptics, significantly lowered suicide rates even though the subjects treated were more severely ill than those without medication.

Weighing risks against the benefits of antidepressants, it also has been argued that overdosing of antidepressants is potentially lethal, and thus it may be risky to supply a depressed patient with a potential means of suicide. Yet newer antidepressants especially show a large safety margin that makes lethal intoxication difficult, and several studies have shown that prescription medication is not commonly used as a means of suicide (Bradvik and Berglund, 2005; Henriksson et al., 2001; Isacsson et al., 1997). In addition, it has been demonstrated that, with the introduction of the newer antidepressants and the decreased use of older tricyclics, the rate of fatal toxicities of antidepressants has declined (Morgan et al., 2004).

In summary, data on increased suicidal behaviors from randomized controlled studies are conflicting, but the overwhelming evidence from epidemiological studies is in favor of reduced suicide rates with antidepressant treatment. Concerning the risk of using prescribed antidepressants as a suicide tool, the risk of lethal intoxication with antidepressants, although already rare, still declines with the replacement of the classical antidepressants by newer agents. It appears more evident that antidepressants are valuable tools in preventing suicides in depression (Goldney, 2006) instead of provoking it; and summarized on the basis of the available evidence, any increased risk of suicide that antidepressants may produce in a subset of (mostly adolescent) depressed patients appears to be
offset by the public health benefits of increased diagnosis and treatment of depression.

12 Other treatments for depression

12.1 Psychotherapy

Empirically supported psychotherapies are potent alternatives to and augmenters in combination with antidepressant medications. Efficacious psychotherapies may have particular benefits for depressed patients, such as pregnant women, who prefer to avoid medication. In non-industrialized countries, such psychotherapies may be the only feasible, affordable treatments for depression (Bolton et al., 2003).

Interpersonal psychotherapy (IPT) is a time-limited, diagnosis-focused treatment shown in repeated randomized controlled trials to have efficacy as both an acute and a maintenance treatment for major depressive disorder (Weissman et al., 2000). IPT defines depression as a treatable medical illness that is not the patient’s fault. It focuses on the connection between the patient’s mood and interpersonal life circumstances. It has been shown not only to relieve depressive symptoms but to build social skills. IPT has shown more modest benefit for dysthymic disorder (Browne et al., 2002; Markowitz et al., 2005). One large trial has indicated the efficacy of an adaptation of IPT (Interpersonal Social Rhythms Therapy) as an adjunctive treatment for bipolar disorder (Frank et al., 2005). Other studies have found that interpersonal counseling (IPC), a short, dilute version of IPT, relieves symptoms of subsyndromal depression (Weissman et al., 2000). Cognitive and behavioral therapies (CBTs) have also demonstrated efficacy in repeated randomized controlled trials for depression. Cognitive therapy focuses on the ‘automatic’ irrational thoughts that arise in the depressed state, in particular the ‘cognitive triad’ of negative outlooks. This consists of negative thoughts about oneself (‘I’m no good’), the environment (‘Things are overwhelming’), and the future (‘It’s never going to get any better’) (Beck et al., 1979). Patients learn to test the evidence for and against negative thinking, and to substitute more rational responses to the environment for overly negative depressive thinking. Cognitive techniques are frequently used in combination with behavioral interventions such as scheduling pleasurable activities. The two are used together in varying combinations, but CBT is generally more common than either pure cognitive or pure behavioral therapy. Cognitive therapy appears to have an ‘enduring effect’ that protects persistently against relapse even after acute treatment ends (Hollon et al., 2005a,b). Cognitive Behavioral Analysis System of Psychotherapy (CBASP; McCullough, 2000), an amalgam of behavioral, cognitive, interpersonal, and psychodynamic techniques developed specifically to treat chronic depression, equalled nefazodone in efficacy in one large trial, and the combination of CBASP plus nefazodone surpassed either treatment alone (Keller et al., 2000). As there was no placebo control condition in this study, however, the efficacy of CBASP requires further testing.

In addition to acute efficacy, cognitive therapies have been shown to enhance the efficacy of antidepressants, especially in combination treatment, possibly due to an influence on serotonin and noradrenaline levels (Gaszner, 2005). Due to a relative lack of research funding, there are far fewer trials of psychotherapy than of pharmacotherapy for the treatment of depression. Psychotherapy research is complicated by the need to manualize the therapies, to train therapists to follow these manuals, and to monitor therapist adherence in treating patients during the trial by taping and rating treatment sessions. Nonetheless, a series of randomized trials have generally shown equipotence of empirically-based psychotherapies with pharmacotherapy for non-delusional outpatients with major depression. An early, key study was the NIMH Treatment of Depression Collaborative Research Program (Elkin et al., 1989), which compared imipramine, pill placebo, IPT, and CBT in treating 250 outpatients with major depression. In that 16 week trial, all treatments showed equal overall benefits, but imipramine and IPT had greater efficacy for patients with more severe depression (HAMD > 20) relative to pill placebo with clinical management.

On the basis of their performance in controlled efficacy trials, interpersonal psychotherapy, and cognitive and behavioral therapies (CBTs) should be included in algorithms of standard treatment for depressive disorders. IPT and CBTs have already been included in numerous professional and national treatment guidelines (Karasu et al., 1993; Tylee, 2006; van den Broek, 2005). For patients with chronic or severe depression, the combination of pharmacotherapy and one of these empirically validated psychotherapies may be preferable to either monotherapy (Rush and Thase, 1999). Also in a recently published

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63 See chapter 19.8 for more detailed information in Annex 8: Additional information on psychotherapy.
meta-analysis the combined therapy outperformed psychotherapy, but this was only true in moderate chronic depression. No differences were found in non-chronic depression (de Maat et al., 2007).

12.2 Electroconvulsive therapy

Electroconvulsive therapy (ECT) is the safe induction of a series of generalized epileptic seizures for therapeutic purposes using brief-pulse stimulation techniques under anesthesia and muscle paralysis. Informed consent of the patient or the responsible legal guardian is mandatory (see also Box 12). Since the first publications, the excellent therapeutic effectiveness of this method in the treatment of depression has been described in a variety of reviews and meta-analyses (Abrams, 2002; Baghai et al., 2005; ECT review group, 2003).

12.2.1 ECT as first-line treatment

In the case of refusal of food and drink, and severe psychomotor retardation, ECT has been shown to be one of the safest therapeutic options with the fastest relief of symptoms (Gangadhar et al., 1982). Therefore, depressive stupor and inanition, as in melancholic, catatonic and/or psychotic depression, can be a first-line indication for ECT before other treatments are prescribed. If, due to other conditions, e.g., severe psychotic symptoms and/or high suicide risk, rapid improvement is crucial for the patient, ECT should be considered earlier than other therapeutic options (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). In psychotic depression, the remission rate for ECT approximates 90%, with relief experienced within 10–14 days (Petrides et al., 2001). The risks of suicide that mark severe psychiatric illnesses are quickly relieved by ECT, although attention to continuation treatment is essential to sustain the benefit (Kellner et al., 2005). Also, with other acute psychiatric syndromes, e.g., delirious mania and malignant catatonia, that mark systemic illnesses such as lupus erythematosus, neuroleptic malignant syndrome (NMS) and medication toxicity may require ECT as a first-line treatment (Abrams, 2002; Baghai et al., 2005), especially if it is not possible to differentiate between NMS and malignant catatonia. Intensive ECT, usually administered daily (en bloc), relieves the high rates of mortality associated with malignant catatonia and delirious mania (Fink, 1999; Fink and Taylor, 2003). In addition, when depression, mania and psychotic symptoms accompany systemic illnesses or are present during early pregnancy or the post-partum breastfeeding period, administration of medications is often precluded and ECT becomes a useful treatment option. In the case of severe and life-threatening adverse events of antidepressants, in psychotic depressed patients and also in the case of severe adverse events due to antipsychotics, ECT monotherapy can be a safe first-line treatment. This recommendation also holds for patients suffering from severe somatic diseases, including the risk of worsening due to antidepressant and antipsychotic pharmacotherapy (Beliles and Stoudemire, 1998; Franco-Bronson, 1996; Rothschild, 1996).

In addition, long duration and chronic course of the index episode are negative outcome predictors in depressive disorders that signal a higher risk for therapy resistance to medication and ECT (Beliles and Stoudemire, 1998; Prudic et al., 1990); more patients should be informed about these possible response rate modifiers as part of shared decision making concerning their antidepressant treatment. Nevertheless, the primary use of ECT is handicapped by

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Box 12. Administration of ECT according WHO recommendations (World Health Organization, 2005c)

- According WHO recommendations, just as with any other treatment, ECT should only be administered after obtaining informed consent.
- ECT should only be administered in the so-called modified form (which to date represents the standard procedure), i.e. with the use of anesthesia and muscle relaxation.
- The practice of using unmodified ECT should be stopped, but up to now this method is still used in some countries for traditional and financial reasons.

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44 See chapter 19.3 for more detailed information in Annex 3: Additional information on electroconvulsive therapy.

45 Exceptionally in the case of perilous disease, when there is no possibility of obtaining informed consent due to the character of the mental illness, ECT can also be administered after legal authorization and informed consent of the patient’s legal representative. Patients with stupor, manic excitement, catatonic mutism and in acute paranoid states may not be able to give written consent, and alternative consent processes, which vary with jurisdictions in different countries, must be applied. It is useful for physicians who are responsible for the more acute and severely ill psychiatric patients to consider ECT as a primary indication and to be acquainted with all the means for proper consent for treatment within their jurisdiction.
severe stigma and even legal restrictions against its use in some jurisdictions (Ottoson and Fink, 2004).

12.2.2 ECT as second-line treatment

The most common use of ECT is in patients for whom medications have failed to elicit remission or in whom medication toxicity has interrupted the course of therapy (Abrams, 2002; Baghai et al., 2005). Nevertheless, patients rarely receive ECT after the first two medication treatment failures, which are often used as a criterion for pharmacotherapy resistance (Möller, 1997; Prudic et al., 1996; Sackeim, 2001; Warneke, 1993). Use of ECT significantly enhances response rates (Davidson et al., 1978; Folkerts et al., 1997; Kroessler, 1985). This finding is especially true in patients suffering from psychotic depression, even if antipsychotic therapies have been applied adequately before (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001; Folkerts et al., 1997). Intolerable side effects of antidepressant medications, somatic comorbidities emerging during the pharmacological treatment (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001; Rasmussen et al., 2002) or worsening of depressive symptoms, including severe suicidality during antidepressant pharmacotherapy, can also be the reason for initiating an ECT treatment course (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001).

12.2.3 Maintenance and continuation ECT

As described in chapter 9.2 in addition to pharmacologic and psychotherapeutic continuation therapies, especially after pharmacotherapy treatment failures, ECT, too, can be an efficacious prophylactic tool (Kellner et al., 2005; Sartorius and Henn, 2005a,b), even given the absence of controlled studies. Continuation ECT should be considered when depressive symptoms recur, especially when adequate pharmacologic therapy fails. Even when the prior history of an individual patient shows an enhanced risk for recurrence of depression during continued pharmacotherapy, including both antidepressants and mood stabilizers, C-ECT should be a part of the treatment plan (Frey et al., 2001; McCall, 2001; Rabheru and Persad, 1997). The usual clinical procedure is to prolong the treatment intervals according to individual clinical requirements. During acute treatment, a patient usually receives two or three treatments per week. Afterwards, usually one treatment per week is applied for 4–8 weeks, then one treatment every 2 weeks and then one treatment every 4 weeks. This frequency should be maintained for at least 6 months. A frequently used alternative strategy (the so-called cafeteria style) is the individual decision whether to administer C-ECT treatment when the first signs of recurring depressive symptoms are reported (Abrams, 2002; Fink et al., 1996). Regular weekly evaluations help to judge the necessity to shorten treatment-free intervals on an individual basis. The same evaluation is necessary during the attempt to stop ECT treatment after 6 months. As soon as depressive symptoms recur, prolongation of C-ECT should go into effect.

12.2.4 Side effects

Varying with the anesthetic, the most frequent immediate unpleasant effects of ECT are headache, nausea and vomiting. On rare occasions, prolonged seizures that require anticonvulsant treatment may also occur (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). Due to predisposition of the patients or pharmacological interactions (lithium), the effect of muscle relaxants may be enhanced, requiring a longer period of assisted respiration (Hill et al., 1977; Reimherr et al., 1977). In bipolar depression ECT may induce hypomania or mania (‘switch’) (Angst et al., 1992).

All patients may be confused on awakening after a seizure. In addition, typical side effects that are more prominent in bilateral than in unilateral and in high-dose than in lower-dose ECT (ECT review group, 2003) are transient cognitive disturbances. These include short-term memory disturbances (van Waarde and Stek, 2001), a prolonged postictal reorientation period, memory disturbances that include anterograde or retrograde amnesia and rarely occurring effects on autobiographic long-term memory (Lisanby et al., 2000). Nearly all patients report amelioration of cognitive impairment after finishing the course of ECT treatment (Devanand et al., 1991).

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66 The terms ‘continuation treatment’ and ‘continuation ECT’ (C-ECT) are predominantly used to characterize maintenance treatment after successful treatment of the index phase. They are sometimes distinguished from ‘maintenance treatment’ and ‘maintenance ECT’ (M-ECT) (Sartorius and Henn, 2005a) based on theoretical considerations regarding switching to prophylactic treatment to prevent new episodes of depression. Because for individual patients this time point cannot be precisely defined, in the following text only the term ‘C-ECT’ is used.
Nevertheless, recent improvements in the use of ECT include methods to maintain good therapeutic efficacy together with better tolerability vis-à-vis cognitive disturbances. Using modified ECT techniques (Ghaziuddin et al., 2000), including unilateral or bifrontal pulse wave stimulation, anesthesia with muscle relaxation and sufficient oxygenation, these risks could be substantially reduced (Ghaziuddin et al., 2000; Sackeim et al., 1993; Sackeim et al., 2000).

A variety of case reports, case series and controlled studies confirm that ECT does not cause long-lasting functional (Krause et al., 1988) or any structural damage of the central nervous system (CNS) (Devanand et al., 1991; Krause et al., 1988; Lisanby et al., 2003b). But more research is needed to investigate the longer-term cognitive side effects of ECT (Greenhalgh et al., 2005).

### 12.2.5 Safety

In general, ECT is one of the best-tolerated antidepressant therapies, with low risk for severe complications, even lower than TCA. The mortality rate during ECT varies between 1:50000 and 1:25000 treatments (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). Severe complications that warrant special attention are seen in less than 1:10000 treatments (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001; Nuttall et al., 2004; Shiwach et al., 2001).

### 12.3 Other non-pharmacological treatments

#### 12.3.1 Introduction

Besides new pharmacological antidepressant treatment strategies, during the last decade several new biophysical approaches have been under investigation for the treatment of major depressive illness: repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), magnetococonvulsive therapy (MST) and, very recently, deep brain stimulation (DBS). These methods have in common that they directly or indirectly target brain regions that play a role in the pathophysiology of depressive disorders. All methods except MST differ from ECT in their presumed mechanisms of action, though they have often been discussed in comparison with ECT. rTMS was originally found to improve mood in patients suffering from Parkinson’s disease. This led to trials in the treatment of depression. rTMS, VNS, MST and DBS have been further developed in a hypothesis-driven manner based on the current view that depressive disorders affect integrated pathways that link select cortical, subcortical and limbic sites and their related neurotransmitter and molecular mediators (Padberg and Möller, 2003). However, these brain-stimulation methods use different ‘windows’ to access the anatomically defined pathways that show functional changes during the acute episode and attempt to modulate the system in the direction of a normal regulation of mood and emotions. rTMS is currently mainly targeted to cortical prefrontal sites (George et al., 2003; Padberg and Möller, 2003), whereas VNS enters the system by vagal afferents to the vagal nucleus and the nucleus tractus solitarius in the brain stem that are linked to regions of the brain involved in mood regulation, such as the amygdala, hippocampus and locus coeruleus (George et al., 2003).

MST employs the ECT approach of inducing generalized therapeutic convulsions in order to treat depression. However, the method induces a lower current in the CNS and attempts to be more focal compared with ECT to minimize side effects and particularly exerts its effect on frontal and prefrontal cortical and subcortical sites (Lisanby et al., 2003b). Very recently, interesting data have been presented using DBS to stimulate a subgenual cingulate region (Brodmann area 25) that is metabolically overactive in treatment-resistant depression and shows normalization in activity after recovery (Greenblatt et al., 1964; Lisanby et al., 2003b). However, other regions in the basal ganglia and their pathways to prefrontal limbic areas may also be putative targets in future studies.

Psychosurgical interventions, such as stereotactically applied bilateral orbitomedial lesions for resistant severe depression, possibly show similar therapeutic effects; however, at present they are of marginal clinical significance (Sachdev and Sachdev, 2005). Moxibustion must also be mentioned among physical treatment options for depression. But empirical data regarding this intervention are insufficient, and it mainly plays a role in traditional Chinese medicine (Cheng et al., 2005).

Due to the fact that placebo response rates can be high in the treatment of depression, it is sometimes difficult to approve new antidepressant treatments. Nevertheless, new non-pharmacological treatments have already been approved in some countries for the treatment of depression: TMS has been approved in Canada and Israel, and VNS is approved by the US Food and Drug Administration (FDA) as an add-on treatment for depression.
12.3.2 Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) was originally introduced in 1985 by Barker et al. as a non-invasive tool to electromagnetically stimulate the primary motor cortex in humans (Lisanby et al., 2000b). It has turned out to be a powerful research tool in neurophysiology and cognitive neuroscience. As an antidepressant intervention rTMS is usually targeted to the dorsolateral prefrontal cortex (DLPFC) based on well-replicated findings that show reversible functional changes in this region. The majority of studies focus on the left prefrontal cortex based on the observed asymmetry of prefrontal function associated with major depression (Lisanby et al., 2003b). A large number of different stimulation parameters, e.g. frequency and intensity of stimulation, have been applied in studies (Padberg and Möller, 2003), and the usual treatment duration has been 1–4 weeks of treatment.

About 25 randomized placebo-controlled clinical trials, including about 750 patients suffering from major depressive episodes, have been conducted to date investigating the safety and efficacy of rTMS as an antidepressant intervention (Berman et al., 2000b; Dolberg et al., 2002; Garcia-Toro et al., 2001a; Garcia-Toro et al., 2001b; Kaufmann et al., 2004; Loo et al., 2003; Miniussi et al., 2005; Mosimann et al., 2004; Nahas et al., 2003; Padberg et al., 1999; Padberg et al., 2002; Padberg and Möller, 2003; Pascual-Leone et al., 1996; Rossini et al., 2005). In the majority of these trials, significant placebo/verum differences have been observed, with antidepressant effects ranging from modest to substantial. Due to the methodological limitations of many of these trials stemming from rather small sample sizes, the difficulty of controlling sham rTMS and short observation periods, the current assessment of its efficacy in the wake of initial enthusiasm about its treatment potential is more sober. Several meta-analyses have been conducted (Berman et al., 2000b; Burt et al., 2002; Couturier, 2005; Dolberg et al., 2002; Ebmeier et al., 2006; Garcia-Toro et al., 2001a; Martin et al., 2003; Pascual-Leone et al., 1996; Schulze-Rauschenbach et al., 2005) that support the antidepressant efficacy of rTMS, but clinical effects are not very strong, and the clinical significance may be questionable. rTMS has also been directly compared with ECT in five parallel design trials (Grunhaus et al., 2000; Grunhaus et al., 2003; Pridmore et al., 2000; Schulze-Rauschenbach et al., 2005). In these trials, rTMS was found to be as effective as ECT in patients suffering from major depressive episodes without psychotic features, but to be inferior for psychotic depression (Grunhaus et al., 2000). Four trials have investigated combined treatment with active rTMS plus antidepressant compared with sham rTMS plus antidepressant to answer the question whether rTMS augments the effect of antidepressant medication (Lisanby et al., 2001b; Rumi et al., 2005). But only one study that combined rTMS with amitriptyline found a significant superiority of combined active treatment (Rumi et al., 2005). Apart from single studies and case reports, little is known regarding the stability of effects and potential maintenance treatment strategies (Pascual-Leone et al., 1996), and the largest body of evidence points to transient effects following completion of rTMS treatment (Pascual-Leone et al., 1996; Schüle et al., 2003). rTMS appears to be safe and well tolerated by patients within a range of parameters defined according to a consensus (Wassermann, 1998).

In conclusion, there is considerable evidence for the antidepressant efficacy of high-frequency rTMS over the left dorsolateral prefrontal cortex applied over 2–4 weeks, and rTMS may be applied successfully as adjuvant antidepressant intervention. However, the antidepressant efficacy of rTMS has still not been sufficiently proven owing to the methodological limitations of previous clinical trials. Up to now solely in Canada and in Israel it has been approved for the treatment of depression by the authorities.

12.3.3 Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is a stimulation technique with potential benefits in the treatment of depression which is currently used in investigational settings. A placebo controlled RCT in 40 depressed patients suggested beneficial effects of tDCS of the left dorsolateral prefrontal cortex which persisted one month after the end of the treatment (Boggio et al., 2007b). During the treatment there was no necessity for anesthesia but the overall tolerability was excellent. In addition an improvement of cognitive performance has been reported (Boggio et al., 2007a). In spite of the increasing interest in the new non-pharmacological treatment strategies (Rau et al., 2007) to date tDCS is at a very early stage of development in the treatment of depression and the reports about antidepressant effectiveness are awaiting their replication.

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67 See chapter 19.4 for more detailed information in for more detailed information in Annex 4: Additional information on transcranial magnetic stimulation.
12.3.4 Magnetic seizure therapy

MST is a variant of rTMS that uses stronger stimulation parameters (40% more intensity compared with standard rTMS stimulation, higher frequency and a prolonged impulse of about 0.4 ms) to intentionally induce an epileptic seizure for therapeutic purposes. It is hypothesized that MST might be a kind of convulsive therapy that retains the therapeutic efficacy of ECT with an improved side-effect profile. Indeed, MST should induce a secondary generalized seizure more focally in relevant brain regions (Lisanby et al., 2003b), as the magnetic field can penetrate scalp and skull without hindrance. Animal studies and safety data of clinical pilot studies in depression have been published supporting this notion (Lisanby et al., 2001c; Lisanby et al., 2003a; Moscrip et al., 2005). Its antidepressant efficacy is currently under investigation, and so far only case reports are available (Kosel et al., 2003; Lisanby et al., 2001a; Moscrip et al., 2005). MST is still at an early stage of development (Lisanby et al., 2003a) and is therefore restricted in most countries to use in experimental treatment designs.

12.3.5 Vagus nerve stimulation

In the 1980s and 1990s vagus nerve stimulation (VNS) was developed in animal models for its putative anti-convulsant action. It was introduced into the routine treatment of therapy-resistant focal epilepsies about a decade ago. It has been approved by the FDA. Theoretical considerations regarding the functional anatomy of the vagus nerve, which projects to areas of the brain relevant for generation and control of mood and emotions, as well as observations of mood changes in epilepsy patients undergoing VNS have triggered the application of VNS in depressive disorders (George et al., 2003). VNS has been investigated in a series of open and controlled clinical trials in depressed patients participating in an industrial development program, and recently the data of the complete trial set have been published (George et al., 2005; Nahas et al., 2005; Rush et al., 2000; Rush et al., 2005b; Rush et al., 2005a; Sackeim et al., 2001b).

The results of an open pilot study (Rush et al., 2000; Sackeim et al., 2001b) led to a double-blind randomized placebo-controlled multicenter trial that included 235 patients who received either active or placebo stimulation over a 10-week period (Rush et al., 2005a). Following the acute treatment period, all patients received continuous treatment, and long-term data have been published on 205 patients after 12 months of stimulation (Rush et al., 2005b). In the acute study, no difference in primary and secondary outcome measures between VNS and placebo treatment groups was observed (Rush et al., 2005a). To facilitate interpretation of the clinical meaning of the long-term data in terms of efficacy, a post hoc comparison study with the same inclusion criteria as the controlled VNS study was initiated, including 124 patients who received ‘treatment as usual’ (TAU) (George et al., 2005). After 12 months, a clinical response was found in 29.8% of the patients included in the VNS study, whereas only 12.5% responded in the TAU study; remission was achieved in 17.1% of the VNS study compared with 6.7% of the TAU study (George et al., 2005). Concerning the safety of VNS, the results of the studies in epilepsy were essentially confirmed. VNS carries significant health risks, including voice alteration, cough, dyspnea, neck pain, dysphagia, laryngismus, paraesthesia and pharyngitis (Rush et al., 2005a), which may improve gradually during treatment (Rush et al., 2005b).

Based on the efficacy and safety data, the VNS therapy system was recently approved by the FDA for the adjunctive long-term treatment of chronic and recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. Despite this approval, to date it is not known whether VNS exerts antidepressant effects superior to placebo or other treatments, and further controlled, parallel-design long-term trials are urgently needed. Because of its invasive nature, VNS should be strictly reserved for exceptional cases where the patient’s demand for this treatment is high, other interventions have failed and a clinical benefit is likely. In addition, although controversial (Annegers et al., 2000; Schachter, 2006), a connection has been suggested between VNS (used to treat treatment-refractory epilepsy) and sudden death.

12.3.6 Deep brain stimulation

Deep brain stimulation (DBS) is a well-established treatment for intractable Parkinson’s disease (PD) and other movement disorders, where usually the subthalamic nucleus, the globus pallidus internus or the thalamus is stimulated (Mayberg et al., 2005). An implantable stimulation system like the VNS system is used to stereotactically target relevant brain areas and generate a functional lesion in regions that are generators of symptoms of PD and other movement disorders.
disorders. For psychiatric disorders, published reports of treatment with DBS have been limited to cases of obsessive compulsive disorder and Gilles de la Tourette syndrome (Mayberg et al., 2005). Very recently, Mayberg and colleagues (2005) published six cases of patients treated with DBS of the subgenual cingulate cortex, hypothetically driven by previous studies showing the consistent involvement of this region in acute sadness in healthy volunteers and antidepressant treatment effects in depressed patients (Kopell et al., 2004; Mayberg et al., 1999; Mayberg et al., 2005). The authors found a striking and sustained remission of depressive symptoms in four of the six patients, associated with a marked reduction in local cerebral blood flow as well as changes in downstream limbic and cortical sites demonstrated by positron emission tomography (Mayberg et al., 2005).

DBS treatment is thus far only an experimental intervention in depression, and further extensive methodological research is needed to develop this approach towards a clinically applicable treatment (Schlaepfer and Lieb, 2005).

12.3.7 Total or partial sleep deprivation

Total sleep deprivation (TSD) is a non-pharmacological intervention that exerts rapid antidepressant effects in about 60–70% of depressed patients who stayed awake one complete night and the consecutive day (Benedetti et al., 2005; Wirz-Justice et al., 2005; Wu and Bunney, 1990) despite the fact that sometimes it is difficult to keep patients awake. During late-night sleep deprivation (partial sleep deprivation, PSD) patients are awakened between 1 and 2 a.m. and stay awake during the second half of the night and the complete consecutive day until at least 8 p.m. PSD is as effective and rapid as TSD and better accepted by depressed patients (Schilgen and Tolle, 1980). In contrast, early night sleep deprivation (SD) is ineffective in the treatment of depression (Wu and Bunney, 1990). To date, in addition to chronotherapeutic mechanisms, the induction of hippocampal neurogenesis has also been discussed as a possible mechanism of action (Grassi et al., 2006).

The clinical relevance of TSD is limited, since relapse after sleep deprivation is a frequent phenomenon observed in most patients with depression (Wu and Bunney, 1990). Different strategies for relapse prevention after SD are combination with lithium (Benedetti et al., 1999; Grube and Hartwich, 1990), pindolol (Smeraldi et al., 1999), bright light therapy (Colombo et al., 2000; Neumeister et al., 1996) or the serial administration of PSD up to twice (or thrice) a week (Kuhs et al., 1996; Kuhs et al., 1998). It was recently shown in several clinical trials that a ‘phase advance’ of the sleep period after SD can be used to prevent relapse in about 60% of responders (Kuhs et al., 1996; Lee and Chan, 1999). Nevertheless, due to the overall lower effectiveness in comparison with other antidepressant treatments and its transient effects, sleep deprivation is used in clinical routine predominantly as an augmentation strategy.

12.3.8 Bright light therapy (phototheraphy)

In seasonal affective disorders (SADs), bright white light therapy shows some usefulness in the treatment of depressive symptoms (Lee and Chan, 1999; Rosenthal et al., 1985). For other indications, such as non-seasonal depressive disorder, further research will be needed to determine the usefulness of phototherapy (Benedetti et al., 2001; Compton and Nemeroff, 2000; Prasko et al., 2002). Some studies report a good benefit in depressed patients receiving bright light therapy to augment antidepressant pharmacotherapy (Benedetti et al., 2003; Loving et al., 2002). In recent reports, phototherapy was also suggested as an efficacious adjunctive treatment in non-seasonal unipolar and bipolar depression (Martiny et al., 2005a; Martiny et al., 2005b; Terman and Terman, 2005). Nevertheless, due to the fact that some reports on the efficacy of light therapy are not based on rigorous study designs, more randomized controlled trials are necessary to adequately evaluate the therapeutic impact of phototherapy on non-seasonal depression (Golden et al., 2005). Because of these somewhat controversial results, due to the results of several RCTs (Lam et al., 2006; Ruhrmann et al., 1998) phototherapy could be considered in SAD as a first-line therapy, whereas in other forms of depression it can be tried as an augmentation strategy.

12.3.9 Exercise

A variety of publications have discussed the theoretical background of the beneficial effects of physical exercise in the treatment of depressive disorders. In addition, reviews report on and recommend exercise as a promising behavioral intervention, at least as an adjunct treatment of depression (Craft and Perna,
2004; North et al., 1990). Even long-term changes and antidepressant effectiveness of exercise during 20 weeks of treatment have been reported (Singh et al., 2001). Nevertheless, detailed reviews and a meta-analysis showed that the effectiveness of exercise in reducing symptoms of depression cannot yet be concluded owing to methodological weaknesses in studies published to date (Barbour and Blumenthal, 2005; Lawlor and Hopker, 2001). Preliminary evidence reported recently shows exercise to be an effective lower-cost augmentation strategy that reduces depressive symptoms in partial responders to antidepressant medication (Trivedi et al., 2006b; Trivedi et al., 2006c). For now, exercise can only be recommended as a supplemental therapeutic option during antidepressant therapies, with additional health benefits especially in the case of longer-term use. In addition, limited evidence supports the effectiveness of yoga breathing exercises as a complementary treatment of depression (Jorm et al., 2002), but at this time it is impossible to quantitatively assess its benefit.

12.3.10 Acupuncture

Because the use of complementary and alternative therapies is overrepresented in patients suffering from depressive syndromes (Kessler et al., 2001), the actual knowledge about the main therapeutic options in this field needs to be evaluated. Acupuncture has a long history in Eastern culture, and traditional Chinese medicine describes its influence on the body’s balance of health and energy. Traditional acupuncture involves inserting needles into specific trigger points at different parts of the body.

Despite a variety of published studies in this field, a recent review reports insufficient evidence for determining the efficacy of acupuncture in comparison with pharmacological antidepressant treatment (Smith and Hay, 2005). Also, adequate blinding of physicians and patients in clinical trials together with standardized outcome measures are necessary before clinical and scientific recommendations can be made (Smith and Hay, 2005).

An overall good safety and tolerability of acupuncture has been described. Especially in trials comparing TCA with acupuncture, the typical side effects were much less in the acupuncture groups (Luo et al., 1998). Studies comparing modern and better-tolerated antidepressants have not been published to date.

13 Antidepressant drugs in the treatment of anxiety disorders

The proven efficacy of antidepressant drugs in relieving anxiety symptoms in patients with depressive disorders led naturally to investigations of their potential to relieve symptoms and reduce associated disability in patients with anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, social phobia (also known as social anxiety disorder), post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). In clinical practice, the need for treatment should be determined by the severity and persistence of symptoms, and the level of disability and impact on social functioning; choice of treatment is influenced by patient characteristics (such as previous response, concomitant medication and contraindications), the evidence base supporting its use, patient and physician preference, and the local availability of the proposed intervention (Baldwin and Polkinghorn, 2005).

14 Health economics: the cost of illness

14.1 Background

The primary and central objectives of mental health services are the alleviation of symptoms and the promotion of quality of life. However, it is also widely recognized that economic considerations need to be taken into account. One reason is the widespread recognition that the costs of mental health problems can be substantial, and that they fall widely: on those who are ill, their families, the health-care system, other service systems and the wider national economy. Costs vary across countries for a number of reasons, including different means of calculating them, differences in health systems and differences in economies, including currencies. Thus, costs cannot be easily extrapolated from one country to another, particularly from developed to developing countries.

A second reason for paying more attention to economic issues is the apparently growing cost of treatment. Some of the newer modes of treatment for mental health problems – including the newer medications for depression – are marketed at higher prices than the older treatments they could potentially replace. This has raised questions about whether the newer treatments are cost-effective. Third, in many

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70 See chapter 19.6 for more detailed information in Annex 6: Additional information on acupuncture.

71 See chapter 19.9 for more detailed information in Annex 9: Additional information on antidepressant drugs in the treatment of anxiety disorders.
countries there is a better understanding of the interconnections between mental health problems, employment and social exclusion (and of the potential for effective treatments to have impacts across many areas of life), and hence growing interest in mental health among ministries responsible for employment and finance.

But the fundamental, pervasive, durable and most important reason for being interested in the economics of depression is that the professional, pharmaceutical and other resources required to provide treatment and support are not enough to meet the needs. Scarcity is a permanent feature of all health systems, indeed of all societies. In the face of such scarcity, choices have to be made among alternative uses of the same resource or service. Economics – and, in particular, economic evaluation — aims to provide decision makers with data that can inform and assist their decisions about how to allocate available resources.

14.2 The broad costs of depression

The cost of depression to a society is usually measured in a ‘cost-of-illness study’, which estimates the value of resources incurred as a result of an illness. The economic cost of an illness or condition is driven by a number of factors:

- prevalence
- treatment and service support rates
- effects of the illness on ability to work.

The costs measured in a cost-of-illness study are therefore usually separated into direct and indirect costs. Direct costs include the costs of treating the illness; in the case of depression these would include the cost of primary and secondary care contacts and the cost of antidepressant medication. Indirect costs include the economic impact of premature mortality (estimated in terms of lost productivity from lost life years) and the lost productivity from economic inactivity (non-availability for work – how many people with depression are unemployed or otherwise inactive because of their illness), absenteeism (days taken off work as a result of depression) and presenteeism (time at work but with reduced productivity because of depression-related symptoms). The output of a cost-of-illness study is expressed in monetary terms and is an estimate of the total burden of a particular disease to society. Such estimates are helpful, but they are not evaluative – they tell us nothing about whether treatment is needed or which treatment is most cost-effective.

There have been numerous cost-of-illness studies for depression. Here we summarize just a few to illustrate the main economic impacts of the illness.

- In England, unipolar depression was estimated to cost over £9000 million in 2000, of which only £370 million was direct treatment costs. The largest cost element was productivity losses: over 1 year, 109.7 million lost working days and 2615 deaths were attributed to depression (Thomas and Morris, 2003). Depression is a substantial financial burden compared with coronary heart disease, and is the leading single cause of death in the UK. In 1999, the estimated economic burden of depression was around £7000 million (Liu et al., 2002). Throughout Europe, 23% of the years of healthy life lost and 50% of years lived with disability (YLD) are caused by brain diseases. Thirty-five per cent of disability-adjusted life years (DALYs), a measure of lost health, are considered to be due to brain disease (Olesen and Leonardi, 2003). In addition, in Europe depression is undertreated, and antidepressant treatments are underused (Henriksson et al., 2006; Taleb et al., 2006).
- The cost of affective disorders (including both bipolar depression and unipolar depression) in the 25 countries of the European Union plus Iceland, Norway and Switzerland was modeled by Andlin-Sobocki and colleagues (Andlin-Sobocki et al., 2005) and estimated at €10,566 million in 2004. Nevertheless, the need for a pan-European epidemiological study to collect more complete data about the real costs of depression in Europe has been recommended (Andlin-Sobocki and Wittchen, 2005).
- The cost of depression in the Asia-Pacific region has also been examined. Hu et al. reviewed existing evidence and reported that the total cost of depression in Australia was US$1800 million in 1997, of which 22% was direct treatment costs, and US$1400 million in Taiwan in 1994, of which a quarter was direct treatment costs (Hu, 2004). Another study by Hu et al. that estimates the cost of depression in China is currently in press. In Pakistan, the high cost of depression prevents the majority of depressed patients from seeking treatment, which contributes to suffering from the illness and an associated loss of productivity (Gadit, 2004).
- The economic burden of depression in the US was relatively stable between 1990 and 2000, despite an increase in the proportion of sufferers receiving treatment. The total cost in 2000 was US$8310 million, of which almost a third was in direct
medical treatment costs (Greenberg et al., 2003). The burden of depression appears to be less than the economic cost of diabetes in the US, estimated at US$13,200 million in 2001 (American Diabetes Association, 2003).

There is a dearth of cost-of-illness studies from Africa, Asia, Eastern Europe, and Latin America (Hu, 2006). The cost-of-illness literature thus reminds us that depression places a financial burden not only on health and social services but also on the broader economy from days lost from work and productivity losses more generally (see 19.2 – Annex 2: Additional information on the types of economic evaluation). Moreover, the impact of depression on work – days absent and reduced productivity while at work – has income and career progression implications for individuals with the illness. Less readily measured – certainly not easily expressed in monetary terms – but of considerable importance are the effects of depression on performance of family and social role (Brown and Harris, 1978). In addition, the psychological distress of caregivers together with a higher intensity of depressive symptoms in patients may increase use of primary care services and, presumably, costs (Perlick et al., 2005).

It is therefore important that evaluations of costs and outcomes take a wide cost perspective that includes not only health service costs, and social and non-statutory service costs, but also losses to the economy and to the individual and family. For example, the direct cost of depression in England (Thomas and Morris, 2003) included the cost of hospital contacts, general practice consultations and drug consumption, while indirect costs included morbidity costs measured in terms of absenteeism and mortality costs in terms of the number of deaths due to suicide. Private costs to family and carers were excluded in this study. Thomas et al. found that a relatively small proportion of total costs were direct treatment costs and that total costs are driven by the ability of patients to return to work (morbidity costs). However, we will see that analyses that include morbidity and mortality costs are relatively rare. Instead, most economic evaluations tend to take a health systems approach, including only costs of primary and secondary care and medication.

The need for this wider perspective is illustrated by Simon et al. (Simon et al., 2000a), who reported secondary analyses of a randomized controlled trial (RCT) of an SSRI. They found that patients across both arms (SSRI and TCA) whose symptoms had improved 12 months after the start of the trial were more likely to continue in paid employment (if working at baseline) or to return to work (if not originally employed) compared with patients whose symptoms had not changed. Clinical improvement was also associated with fewer work days lost though illness, but not with the typical number of hours worked per week. For people whose symptoms improved, there was a marginally significant reduction in health-care costs, although not until the second year after initiating antidepressant treatment. The impact on employment was therefore both larger and more immediate than the impact on health service costs. Another study shows that the impact of symptom alleviation on workplace performance can be rapid (Berndt et al., 1998). Work performance in this US study improved for chronically depressed people as the severity of their symptoms reduced. Over two-thirds of the observed improvement in work performance was found to have occurred in the first 4 weeks after initiating treatment with an antidepressant. In Canada, Dewa et al. found that the use of recommended antidepressants at recommended doses improved symptoms and in turn improved employment outcomes for a large sample of workers (Dewa et al., 2003). Similarly, the large-sample, six-country Longitudinal Investigation of Depression Outcomes (LIDO) study found that patients with improved depression symptoms had less absenteeism (Simon et al., 2002). These employment changes are all the more significant in the face of ending stigma and discrimination by employers against people with mental health problems (McDaid et al., 2005).

14.3 Methodology: economic evaluation29

14.3.1 Core questions

Decision makers face two central questions when considering whether to use or recommend a particular treatment for depression. The first is the clinical question, which asks whether an antidepressant is effective in improving patient health, or – when considering two or more treatment options – which of them has the better or best outcomes. Once the decision maker knows that a particular treatment is effective, she or he wants an answer to the second question: Is it cost-effective? That is, does the treatment achieve the improved outcomes or quality of life at a cost that is worth paying?

These two questions (Is the treatment effective? Is it worth it?) sit at the heart of cost-effectiveness analysis.

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29 See chapter 19.2 for more detailed information in Annex 2: Additional information on the types of economic evaluation.
While it is always going to be necessary to reformulate these questions in ways that make them answerable with empirical research, their simplicity should never be forgotten. However, providing answers to these questions is obviously not that simple.

It must also be emphasized that cost-effectiveness analysis does what its name suggests: it looks at both costs and effectiveness (outcomes). So, comparing the costs of one treatment with another, without any evidence on outcomes, does not constitute an economic evaluation. Such an exercise might be a helpful description of service utilization patterns and associated costs, as we have just seen in looking at the cost-of-illness evidence, but it does not provide enough information to assist service professionals, managers or others facing the choice between two or more alternatives. Similarly, calculating the costs and outcomes of a single service could be interesting but cannot be classed as an economic evaluation unless those costs and outcomes are compared with equivalent data for another service, or even compared with the option of ‘doing nothing’, and so again the study cannot tell us whether the service is worth providing. Uncontrolled mirror design studies often run into this problem.

It is important to emphasize – as we will note again below – that an intervention’s cost-effectiveness is relative to the comparator in the evaluation, which makes the choice of comparator crucial.

14.3.2 Types of economic evaluation

There are a number of different modes of economic evaluation, each with their associated data needs, advantages, disadvantages and uses. Good accounts of health economic evaluation methods (although with very few mental health examples) are given by Drummond et al. (Drummond et al., 2005) and Drummond and McGuire (Drummond and McGuire, 2001). The methods used in health economic evaluations are developing quite rapidly, and consequently some of the techniques mentioned later in this report have been in use in empirical studies for only a short time.

A detailed account of the methods for economic evaluation is given in Annex 2: Additional information on the types of economic evaluation. In brief, cost-effectiveness analysis combines costs with a single disease-specific outcome measure such as a depression symptom scale. The incremental cost-effectiveness ratio (ICER) is computed as the difference in cost between the two treatments divided by the difference in outcomes. In a cost-utility analysis, effectiveness is reduced to a single outcome index of utility such as the quality-adjusted life year (QALY) or DALY. Incremental cost-utility ratios can thus be calculated and compared over different conditions and disease areas, allowing strategic decision makers in a health system to judge whether resources are most effectively deployed in, say, treating depression or treating breast cancer. Cost-benefit analysis generates monetary valuations of outcomes to compare costs and benefits directly, which in principle opens up a wider set of comparisons for decision makers, including non-health-care options. In cost-consequence analysis, costs are reported alongside a range of outcome measures in an attempt to capture the broader picture of the impact of the intervention. Finally, cost-minimization analysis involves assessment of costs only, given the already established equality of outcomes. A summary of methods for economic evaluation is given in Table 24.

14.3.3 Search strategy

We carried out a systematic review, searching on Medline, EMBASE and PsycINFO for the period January 1985 to November 2005. The search was restricted to articles with the key words ‘depression’ or ‘depressive disorder’ and ‘cost and cost analysis’, or ‘cost-effectiveness’ or ‘economic’. Following the search of the databases, a manual search of the references of included articles was undertaken to identify any relevant studies.

Information on the articles was recorded using a structured form included consideration of the following criteria:

- focused on adults with depression;
- included comparative analysis of alternative interventions;
- undertaken within a randomized controlled trial (RCT), non-random comparison or modeling study;
- considered the cost-effectiveness of antidepressants, or of care or case management when in combination with, or compared with antidepressants or of physical treatments;
- included the systematic assessment of both costs and outcomes, including cost-effectiveness, cost-utility, cost-benefit, cost-consequence and cost-minimization analysis.

14.4 Economic evidence for pharmacological treatment options

The literature search retrieved almost 3000 references, although only 50 are included in the final review.
Papers were excluded because they did not focus on depression, they did not include costs or they did not compare two or more alternative interventions.

The relative cost-effectiveness of antidepressants is determined by a number of factors, most importantly their relative efficacy. The SSRIs and other newer antidepressants have a considerably higher purchase price than the TCAs, and higher drug costs can lead to higher total costs. However, it is unclear how long this trend will continue, as many of the SSRIs and newer antidepressants are now coming off patent and in many countries (though not all) are then sold generically at a lower price: for example, in March 2000 a 30-day supply of fluoxetine (Prozac®) in the UK cost £19.34, but by March 2005 the equivalent generic fluoxetine price was £2.11. Cost-effectiveness is also influenced by patient adherence. Adherence is generally low and dropout rates high among individuals commencing antidepressant treatment, which has an impact on the effectiveness of the drug. One explanation for poor adherence is the unpleasant side effects associated with the drugs; these include as dry mouth, sedation, blurred vision and sexual dysfunction (see chapter 9.1.1.3). If the SSRIs and the other newer antidepressants have better side-effect profiles than the TCAs, the newer preparations may improve adherence and outcomes and thus also improve cost-effectiveness.

14.4.1 Selective serotonin reuptake inhibitors

We identified 32 papers that appraised the cost-effectiveness of selective serotonin reuptake inhibitors (SSRIs) for depression, though only 7 used data from prospective trials or naturalistic settings, with the remaining evidence coming from models.

Simon and colleagues (Simon et al., 1996; Simon et al., 1999a) carried out a prospective, naturalistic, randomized trial with economic evaluation comparing alternative antidepressant therapies. Patients attending primary care clinics in the US and initiating antidepressant treatment were randomized to fluoxetine (an SSRI) or desipramine or imipramine (TCAs). In the short term (6 months) treatment dropout was lower, there were fewer adverse effects and achievement of a therapeutic dose was more likely among patients randomized to receive fluoxetine. However, there were no significant differences in clinical outcomes or quality of life, nor were there any significant differences in cost, because the higher drug acquisition cost of fluoxetine was offset by lower outpatient and inpatient service use. A similar pattern of results was found at the 2-year follow-up. The authors concluded that restricting the first-line use of fluoxetine in primary care would probably not reduce overall treatment costs due to the lower hospital service utilization in that group.

Other RCTs have compared SSRIs with other antidepressants and psychological therapies. One compared the costs and outcomes of fluoxetine, citalopram and amitriptyline for major depression in central Europe and found no significant differences in cost or outcome between interventions (Hosak et al., 2000). The authors concluded that amitriptyline was no less expensive or more effective than citalopram or fluoxetine and advised that there was no advantage to

<table>
<thead>
<tr>
<th>Type of analysis</th>
<th>Outcome</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Cost-effectiveness</td>
<td>Disease-specific outcome such as depression scale</td>
<td>Meaningful and understandable analysis</td>
<td>Cannot compare across diseases</td>
</tr>
<tr>
<td>Cost-utility</td>
<td>Single outcome such as QALY or DALY</td>
<td>Can compare across diseases</td>
<td>Not suitable in all disease areas, particularly mental health, because of difficulties of utility measurement</td>
</tr>
<tr>
<td>Cost-benefit</td>
<td>Monetary</td>
<td>Understandable and simple analysis</td>
<td>Difficult to convert health outcomes into monetary terms</td>
</tr>
<tr>
<td>Cost-consequence</td>
<td>Specific range of disease and other relevant outcome dimensions</td>
<td>Includes range of outcomes in analysis</td>
<td>Difficult to draw firm conclusions if outcomes move in different directions</td>
</tr>
<tr>
<td>Cost-minimization</td>
<td>Outcomes must be identical to the treatment alternatives</td>
<td>Understandable and simple analysis</td>
<td>Can rarely be used because outcomes are rarely known with certainty to be equal</td>
</tr>
</tbody>
</table>
restricting patients from treatment with SSRIs. Another compared SSRIs, placebo and psychological treatment for common mental disorders, including depression, in Goa, India (Patel et al., 2003). Psychiatric outcomes were significantly better with antidepressant than placebo at 2 months, but no significant difference was detected at 12 months. Costs were lower in the SSRI group, suggesting that antidepressants are more cost-effective than placebo. Psychological treatment resulted in worse outcomes and higher total costs than placebo. The authors argued that affordable antidepressants such as fluoxetine should be the treatment of choice for common mental disorders in general health-care settings in India, since they are associated with improved clinical and economic outcomes, particularly in the long term.

Retrospective analysis of existing data was used to measure the cost-effectiveness of sertraline and TCAs for depression in primary care in the UK (Forder et al., 1996). The average cost of treatment was slightly greater for those receiving TCAs due to greater use of psychiatric services. In terms of cost-effectiveness, sertraline was found to dominate TCAs for all definitions of costs and outcomes.

In an attempt to clarify the relative cost-effectiveness of antidepressants as a first choice treatment for depression in primary care, Peveler and colleagues (2005) carried out a randomized controlled trial comparing TCAs, SSRIs and the TCA-related antidepressant lofepramine. The UK-based study found no significant difference in costs or outcomes between groups. However, for values placed on an additional QALY of over £5000 – the approach taken in examining net benefits or plotting a cost-effectiveness acceptability curve – treatment with SSRIs was likely to be the most cost-effective strategy.

The evidence from RCTs and retrospective analyses suggests that SSRIs may be more cost-effective treatments for depression than TCAs and are more cost-effective than placebo. Despite higher acquisition costs, SSRIs do not appear to increase overall treatment costs, as SSRIs result in reductions in subsequent health service utilization. In addition, SSRIs may generate better outcomes.

In comparison to the limited availability of economic evaluations from naturalistic settings and RCTs, there are a plethora of studies using modeling techniques to estimate the cost-effectiveness of SSRIs for depression. These models tend to use data from existing evidence for clinical effectiveness and outcomes, but expert opinion on costs and transition through the model, and are based in a variety of health systems and settings. The studies vary substantially in the quality of the data used, the robustness of assumptions employed, the techniques used to test them and generate findings, and consequently their usefulness for this review.

Assumptions need to be employed because there is inadequate data on some aspect of how the drugs will influence outcomes, service use and costs.

A decision-analytic model was used to analyze the cost-effectiveness and cost utility of SSRIs and TCAs in various combinations for depressive disorders in Canada and is a good example of how the evidence on the relative cost-effectiveness of the two types of antidepressants can be summarized (Canadian Coordinating Office for Health Technology Assessment, 1997). The meta-analysis of available clinical evidence showed that there were no statistically significant differences between the efficacy, completion rates and dropout rates of the antidepressants considered. The perspective of the economic evaluation was that of the health-care system, so only direct health-care costs (inpatient contacts, primary care contacts and drug costs) were included. The study suggested that from a Canadian perspective both TCAs and SSRIs should be part of an effective treatment strategy and that further research, preferably from RCTs, was needed to investigate the long-term cost-effectiveness of treatment for depressive disorders.

In an early model Jönsson and Bebbington (Jönsson and Bebbington, 1994) compared the cost-effectiveness of paroxetine and imipramine in people with depression in the UK. The 12-month cost per successfully treated patient was lower with paroxetine than imipramine, indicating that paroxetine was the more cost-effective. The results were sensitive to assumptions concerning the relative efficacy of the drugs, particularly treatment failure, and the authors concluded that although paroxetine had a high cost per day when patient adherence and the total cost of treatment are taken into account, it was the more cost-effective option. However, these findings were questioned a few years later when the model was reassessed with some key assumptions challenged and changed (Woods and Rizzo, 1997). With revised assumptions the model demonstrated that the TCA was at least equally if not more cost-effective than the SSRI. The authors advised that a policy of using TCAs as a first choice antidepressant, with SSRIs reserved for those patients not doing well, appears more cost-effective than the reverse sequence. The two studies use the same data but generate different results, confusing the issue of cost-effectiveness and highlighting the importance of the assumptions made in economic models.
Other modeling studies present evidence of the cost-effectiveness of SSRIs compared with TCAs (Le Pen et al., 1994; Nuijten et al., 1995) and compared with usual care (Nuijten et al., 1998), although no statistically significant differences in costs are reported. However, there is evidence suggesting that SSRIs are more costly and more effective than usual care (Kind and Sorensen, 1995). When maintenance treatment with SSRIs is compared with episodic treatment with a TCA, there are improved outcomes, but alongside higher costs (Hatzian drew et al., 1994).

Evidence of the cost-effectiveness of escitalopram compared with SSRIs and other newer antidepressants is accumulating. However, the majority of the evidence is from one economic model, applied to different health systems. In Austria, Belgium, Sweden, Norway and Finland, escitalopram was the dominant treatment strategy, achieving better outcomes with lower costs, both when health-care and broader societal costs are considered for patients with severe depression (Demyttenaere et al., 2005; Francois et al., 2002; Francois et al., 2003; Hemels et al., 2004a; Lothgren et al., 2004). It was also cost-effective in treating severe depression in Austria (Hemels et al., 2004b). When the model was applied in the UK, escitalopram was found to be a cost-effective option compared with generic citalopram (Wade et al., 2005a; Wade et al., 2005b) and had a cost-effectiveness profile comparable to the newer antidepressant venlafaxine. Only one prospective evaluation of escitalopram has been carried out as part of an RCT. Fernandez et al. (2005) demonstrated that escitalopram had similar efficacy to venlafaxine and patient costs were lower in the escitalopram group, though not significantly so. In both the models and the RCT, the reduction in costs was due to reduced hospitalization in the escitalopram group.

14.4.2 Selective serotonin and noradrenaline reuptake inhibitors

In common with evidence of the cost-effectiveness of SSRIs, decision and Markov models dominate economic evaluations for the newer antidepressants. The cost-effectiveness of venlafaxine for major depressive disorder has been estimated using models in a number of health-care systems: Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK, US and Venezuela (Casciano et al., 2001; Doyle et al., 2001). Using results from meta-analyses, venlafaxine had the highest expected success rate and the greatest number of symptom-free days in all countries. It yielded a lower expected cost in all countries except Poland in the inpatient setting, and Italy and Poland in the outpatient setting. The authors concluded that venlafaxine is a more cost-effective treatment than the alternatives and suggested that increased utilization of the compound in most settings across Europe and the Americas would have favorable impacts on health-care payer budgets. The model was re-analyzed when new data became available on the probability of relapse with different antidepressants (Casciano, 2003). The revised study disputed the treatment dominance of venlafaxine and concluded that venlafaxine was more effective than SSRIs but also more expensive.

The cost-effectiveness of venlafaxine for people in the acute phase of major depressive disorder was evaluated in a UK outpatient setting (Freeman et al., 2000). The model demonstrated that venlafaxine offered statistically significant improvements in depression-free days and that, from a health care perspective, the cost per depression-free day was lower for venlafaxine than for SSRIs or TCAs. Lenox-Smith and colleagues (2004) updated the Freeman model using revised data on costs and outcomes. They found that using venlafaxine as a first-line treatment strategy, and switching to an SSRI if necessary, was a dominant treatment strategy over first-line treatment with an SSRI, resulting in better outcomes with lower costs. A similar evaluation was undertaken in Italy (Casciano et al., 1999). The results suggested that venlafaxine was more cost-effective compared with SSRIs and TCAs for both inpatients and outpatients with respect to cost per successfully treated patient and cost per symptom-free day. Extended-release venlafaxine was found to be a cost-effective strategy among people with depression in Austria (Howard and Knight, 2004).

Finally, venlafaxine for people with major depressive disorder has been evaluated in both inpatient and outpatient settings in Canada and the US (Einarson et al., 1995; Einarson et al., 1997; Trivedi et al., 2004; van Baardewijk et al., 2005). Results from these studies suggested that venlafaxine was more effective, but costs were either more, less or the same as with treatment with other antidepressants. The results of all the models above are highly sensitive to the assumptions made and the unit costs used. At present, and on the basis of available evidence, it is difficult to draw firm conclusions regarding the cost-effectiveness of venlafaxine for depression. In the case of duloxetine, both acute and maintenance treatment seem to be cost-effective alternatives to SSRIs and TCAs (Dardennes et al., 1999; Lafuma et al., 1999).
14.4.3 Noradrenergic and specific serotonergic antidepressant

Only one study prospectively collected and analyzed data on cost-effectiveness, focusing on mirtazapine versus paroxetine in UK primary care attenders with depression (Romeo et al., 2004). Mirtazapine treatment resulted in significantly greater improvements in quality of life than paroxetine at 26 weeks. Although no significant cost differences were observed between the two groups, societal costs were lower with mirtazapine than with paroxetine. The results suggest that mirtazapine may be a cost-effective treatment choice for depression in a primary care setting.

Mirtazapine for people with moderate to severe depression has been investigated in modeling studies for the UK and Austria. In the UK study Borghi and Guest (Borghi and Guest, 2000) demonstrated that mirtazapine was both more effective and less costly compared with amitriptyline and fluoxetine. The higher acquisition costs of the preparation were offset by the lower costs of managing adverse events and lower health service utilization. In Austria, Brown and colleagues (Brown et al., 1999) established the cost-effectiveness of mirtazapine despite the differences in acquisition costs compared with other antidepressants such as amitriptyline and fluoxetine.

14.4.4 Serotonin-modulating antidepressants

Two models have evaluated the cost utility of nefazodone in depression, from the perspective of a US managed care organization (Revicky et al., 1997) and a Canadian health insurance organization (Anton and Revicky, 1995). In both models, cost-effectiveness was estimated for a 30-year-old woman with active depression, and in both studies the findings suggested that nefazodone is a cost-effective treatment compared with imipramine (a TCA) and fluoxetine (an SSRI). The results were highly sensitive to the assumptions made in the model, particularly those concerning efficacy and dropout.

14.5 Evidence on the cost-effectiveness of antidepressants and care management

Care management involves patient education, shared decision making and monitoring. The way in which individuals starting antidepressant treatment are managed clinically may influence their outcomes and thus the cost-effectiveness of the antidepressants. Three studies have investigated the cost-effectiveness of care management versus usual care in patients starting antidepressant treatment. In two trials clinical outcomes suggest there are no significant differences in depression-free days or in health-care costs (Simon et al., 2000b; Simon et al., 2002), whereas one describes superiority of care management (Wells et al., 2000). Although education alone of primary care physicians does not seem to improve patient outcomes (Gask et al., 2004; Thompson et al., 2000), care management or collaborative care involving doctor education, patient education and monitoring by an additional mental health worker can improve patient outcomes at modest costs (Simon et al., 2000b; Simon et al., 2002; Wells et al., 2000). In addition, identification and treatment of depression among patients with a history of high medical expenditures can decrease service use, improve depression outcomes and increase work productivity, though the cost of screening is high (Katzelnick et al., 1997; Von Korff et al., 1998). A decision-analytic model suggested that an increase in the appropriateness of care as seen in a care management program is likely to improve functioning outcomes and increase the value of health-care spending in terms of health benefits (Sturm and Wells, 1995).

14.6 Economic evidence for pharmacological treatment options

The economic evidence has some limitations. First, results from clinical trials are frequently inconclusive due to short follow-up periods and inadequate power to demonstrate differences in costs. Second, the results from economic models are strongly influenced by the assumptions made; in many cases conclusions change when new evidence becomes available, or when medication prices change or when a different view has been taken on the likelihood of an assumption (this is true particularly in modeling studies; a differentiation between analyses performed with an industrial sponsor and analyses independent of the pharmaceutical industry has been suggested). Third, the results of economic evaluations tend to be country-specific, as nations have different health systems and economic conditions. Notwithstanding these points, it is possible to identify some trends in the results, as well as some areas where further research is needed.

Evidence of the cost-effectiveness of SSRIs compared with TCAs is persuasive (Barbui et al., 2003). Many studies have demonstrated that SSRIs have higher acquisition costs, but lower subsequent health service costs, a pattern that may increase as SSRIs become available generically at much lower prices.
Evidence of the cost-effectiveness of the SSRI escitalopram is accumulating. Although it has a higher cost than the now generic citalopram, models have demonstrated that it achieves better outcomes and decreases the likelihood of an inpatient stay, resulting in lower costs.

Newer antidepressants have entered a crowded market, and except in one instance, real-life (RCT or observational) comparisons to existing antidepressants have yet to be undertaken (or at least published). In common with other evidence from economic models, it is difficult to summarize the cost-effectiveness of these interventions. In many cases, the models that have been constructed have relied entirely on expert views to project the costs, and the precise methods used by the expert panels to arrive at their resource use estimates are often not described fully or clearly in the literature. These inadequacies limit the generalizability and applicability of these studies and make it difficult to draw firm conclusions. On the basis of available evidence, however, the SNRIs venlafaxine (Freeman et al., 2000) and duloxetine or (Dardennes et al., 1999; Lafuma et al., 1999) the NaSSA mirtazapine (Borghi and Guest, 2000) appear to be cost-effective alternatives to SSRIs.

**14.7 Implications: economic evidence for pharmacological treatment options**

Growing awareness of the need to improve not only the effectiveness but also the cost-effectiveness of health-care interventions has produced various streams of demand for economic evidence. Two are relevant here. There are requests for measures of the overall resource or cost impact of a particular health problem, leading to cost-of-illness and ‘global burden’ studies. Much attention has recently focused on some of the non-health-care costs – which, as we have seen, can be very large for many people with depression. While cost-of-illness calculations can be helpful in raising awareness of the scale and breadth of impact of mental health problems, they are no substitute for evaluations that look at both costs and outcomes. There are also demands for economic evaluations of particular treatments or policies, generating cost-effectiveness and similar analyses, either carried out within clinical trials or using routinely collected, naturalistic data. Well-conducted economic evaluations can contribute pertinent evidence to the discussion and development of policy and practice. They can support decisions relating to the funding and provision of services and can help to improve the efficiency with which scarce health-care and related resources are allocated.

In this chapter we have reviewed the economic evaluation evidence on antidepressant medications, drawing on a new systematic search of the international literature. The quality of many studies is disappointing. Among the methodological weaknesses are (for summary see Box 13):

- small sample sizes, leaving studies underpowered to test economic hypotheses;
- narrow measurement of costs;
- the relative rarity of randomized controlled trials, and hence few studies with strong internal validity;

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**Box 13. Summary of economic evidence on antidepressant treatments**

**What we know:**
- Some, but not all analyses suggest that SSRI treatment is more cost-effective than treatment with TCAs.
- On the basis of available evidence, venlafaxine and mirtazapine appear to be cost-effective alternatives to SSRIs.
- A new way of care, called care management, has demonstrated its value in enhancing the effectiveness of antidepressants in one out of three studies.

**What we do not know:**
- Evidence of the cost-effectiveness of the new SSRI escitalopram compared with other SSRIs is accumulating.
- Large-scale real-life (RCT or observational) comparisons of newer antidepressants, such as NARIs, SNRIs or NaSSAs to SSRIs have yet to be undertaken.
- Modeled analyses have limited application because of the quality of the data on which they are based and the assumptions made.
- Most studies are based in developed countries, and given the fundamental differences in health systems across the world, it is difficult to know whether their findings can be generalized to other countries. Cultural factors may impact on patients’ adherence, prescription habits and finally on cost-effectiveness.

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Evidence of the cost-effectiveness of the SSRI escitalopram is accumulating. Although it has a higher cost than the now generic citalopram, models have demonstrated that it achieves better outcomes and decreases the likelihood of an inpatient stay, resulting in lower costs.

Newer antidepressants have entered a crowded market, and except in one instance, real-life (RCT or observational) comparisons to existing antidepressants have yet to be undertaken (or at least published). In common with other evidence from economic models, it is difficult to summarize the cost-effectiveness of these interventions. In many cases, the models that have been constructed have relied entirely on expert views to project the costs, and the precise methods used by the expert panels to arrive at their resource use estimates are often not described fully or clearly in the literature. These inadequacies limit the generalizability and applicability of these studies and make it difficult to draw firm conclusions. On the basis of available evidence, however, the SNRIs venlafaxine (Freeman et al., 2000) and duloxetine or (Dardennes et al., 1999; Lafuma et al., 1999) the NaSSA mirtazapine (Borghi and Guest, 2000) appear to be cost-effective alternatives to SSRIs.

**14.7 Implications: economic evidence for pharmacological treatment options**

Growing awareness of the need to improve not only the effectiveness but also the cost-effectiveness of health-care interventions has produced various streams of demand for economic evidence. Two are relevant here. There are requests for measures of the overall resource or cost impact of a particular health problem, leading to cost-of-illness and ‘global burden’ studies. Much attention has recently focused on some of the non-health-care costs – which, as we have seen, can be very large for many people with depression. While cost-of-illness calculations can be helpful in raising awareness of the scale and breadth of impact of mental health problems, they are no substitute for evaluations that look at both costs and outcomes. There are also demands for economic evaluations of particular treatments or policies, generating cost-effectiveness and similar analyses, either carried out within clinical trials or using routinely collected, naturalistic data. Well-conducted economic evaluations can contribute pertinent evidence to the discussion and development of policy and practice. They can support decisions relating to the funding and provision of services and can help to improve the efficiency with which scarce health-care and related resources are allocated.

In this chapter we have reviewed the economic evaluation evidence on antidepressant medications, drawing on a new systematic search of the international literature. The quality of many studies is disappointing. Among the methodological weaknesses are (for summary see Box 13):

- small sample sizes, leaving studies underpowered to test economic hypotheses;
- narrow measurement of costs;
- the relative rarity of randomized controlled trials, and hence few studies with strong internal validity;
• few large observational studies with appropriate standardization, and hence limitations on the external validity of some evidence;
• the scarcity of cost-utility analyses and cost-benefit analyses, making it impossible to use the existing evidence base to make comparisons of resource efficiency outside the mental health system;
• widespread use of economic models that may not accurately reflect the true clinical cost situation.

In many areas the economic evidence relied entirely on economic modeling. These models are based in many cases on expert views to project costs, and the precise methods used by the expert panels to arrive at their resource use estimates are not described fully and clearly in the literature. These inadequacies limit the generalizability and applicability of these studies and make it difficult to draw firm conclusions.

Economic evaluations of antidepressant treatment for depression are inherently context-bound. These evaluations describe the consequences of both the illness and its treatment for service systems and social relations, and these latter will vary from country to country, and often from locality to locality. Also, the economic value of work varies across different countries and cultures. Making generalizations across countries is therefore more difficult than with, say, clinical evaluations. The almost complete absence of economic evidence on depression treatments for all but a very few health systems of the world is therefore a further limitation.

14.8 Economic evidence for psychological treatment options
Depression is widely treated with psychological therapies, including cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), counseling and other forms of psychotherapy. Psychological therapies such as CBT and IPT have proven effectiveness in depression (see chapter 12.1), so economic evaluations essentially aim to investigate whether high initial treatment costs are offset by potentially lower drug costs and fewer visits to other health care professionals (the cost-offset question) or whether the additional costs are worth paying because of improved outcomes (the cost-effectiveness question). In standard care, psychological treatments generally tend to be delivered alongside treatment as usual, which may or may not include an antidepressant and this is reflected in the evaluative literature. In some instances, however, antidepressants have been directly compared with psychological therapies and we concentrate on this literature here.

In an early economic analysis, 120 patients initiating treatment for depression were randomized to one of four interventions: CBT by a clinical psychologist, counseling and case work by a social worker, amitriptyline prescribed by a psychiatrist and usual care from a general practitioner (Scott and Freeman, 1992). After 16 weeks, there were improvements in depressive symptoms in all treatment groups, but total treatment costs were twice as much in the specialist treatment groups compared with routine care. With such a short period of follow-up, it was difficult to draw conclusions, and the authors recommended a full economic evaluation with longer follow-up and one that included a wider definition of cost.

More recently, Miller and colleagues (2003) compared counseling and antidepressant therapy for the treatment of mild to moderate depression in primary care. At 12-month follow-up, there were no significant differences in outcomes and costs. Bootstrap analysis showed that the antidepressant intervention was the dominant cost-effective strategy for the majority of patients, indicating that the cost-effectiveness of counseling compared with treatment with an antidepressant for depression in primary care has not been proven.

The cost-effectiveness of psychotherapy and medication was investigated in trials in Canada, the US and the UK. In one study, patients with dysthymia were randomized to interpersonal psychotherapy (IPT) (Klerman and Weissmann, 1987), IPT with sertraline (an SSRI) or sertraline alone in an RCT in primary care (Browne et al., 2002). Clinical outcomes at 2-year follow-up demonstrated that there were no statistically significant differences between sertraline alone and sertraline plus IPT, but both were significantly more effective than IPT alone in reducing depressive symptoms. Societal costs were significantly lower in the IPT group, but there was no synthesis of costs and effects, so the incremental cost-effectiveness of the treatment is not known. The authors stressed the importance and potential economic value of combining psychotherapy and pharmacotherapy.

IPT, pharmacotherapy with nortriptyline (a TCA) or usual care were compared in a cost-effectiveness analysis in the US (Lave et al., 1998). Both IPT and the pharmacotherapy generated better outcomes than usual care at follow-up, although the pharmacotherapy group did slightly better than those assigned
to IPT. Costs were higher in the IPT and pharmacotherapy groups compared with usual care. The incremental cost per QALY gained was US$11,695 for nortriptyline and US$15,358 for IPT. Although the differences were not statistically significant, from a decision-making perspective there is a preference for the drug treatment.

A modeled cost-utility analysis compared IPT, imipramine (a TCA), a combination of the two, and placebo in patients with recurrent depression (Kamlet et al., 1995). Modeling and simulation methods were used to estimate the costs and benefits associated with each maintenance therapy, and the authors demonstrated that the drug maintenance treatment was cost-effective. Among patients with depression who had a partner with a criticizing attitude, significant improvements in outcomes were found in patients randomized to couples therapy compared with those randomized to antidepressants (Leff et al., 2000). There were higher treatment costs in the therapy group, but the higher costs were moderated by decreased use of other services, resulting in no significant differences in cost at follow-up. The authors warned that the results could not be generalized beyond individuals with depression who are living with a heterosexual partner and that conclusions were limited by large amounts of missing data in the economic evaluation. Cost-effectiveness studies concerning the role of family care are lacking, but there is a broad consensus about the importance and value of family care during the treatment of depressive disorders.

Psychotherapy is cost-effective in some patient groups (Table 25), but when compared directly with antidepressants, their cost-effectiveness needs further evaluation. The economic value of combining psychotherapy with pharmacotherapy also needs further examination.

Finally, new care arrangements have demonstrated their value in enhancing the effectiveness of antidepressants, but studies have only taken place in the US and – given the fundamental differences in health systems across the world – it is difficult to know whether their findings can be generalized to other countries.

The economic discussion to this point principally addresses acute treatment costs. In the very short run, psychotherapies are more labor-intensive and costly than pharmacotherapies. Over time, however, the fulcrum may shift: daily pharmacotherapy which might be continued indefinitely to maintain prophylaxis against depressive relapse and recurrence, whereas psychotherapy may either be discontinued, with ‘enduring effect’ (Hollon et al., 2005), or continued in less frequent (e.g. monthly) sessions. Empirically validated psychotherapies may also arguably help patients to neutralize psychosocial stressors (e.g., marital difficulties) that might provoke a future

<table>
<thead>
<tr>
<th>Psychotherapeutic method</th>
<th>Cost-effectiveness</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>IPT</td>
<td>Depends on the treatment setting; may be cost-effective (better outcomes no difference in cost) in secondary care but evidence from primary care less clear. When compared head-to-head with an SSRI, no evidence of cost-effectiveness</td>
<td>Browne et al., 2002; Guthrie et al., 1999; Kamlet et al., 1995</td>
</tr>
<tr>
<td>CBT</td>
<td>Not yet proven. Evidence from primary care of improved outcomes is always accompanied by substantially higher costs. Some evidence that self-help CBT and computerized CBT may be cost-effective</td>
<td>Bower et al., 2000; Kaltenthaler et al., 2002; Richards et al., 2003; Scott and Freeman, 1992; Scott et al., 2003</td>
</tr>
<tr>
<td>Counseling</td>
<td>No significant differences in costs or outcomes in clinical trials, though meta-analysis suggests counseling will produce significantly better outcomes for significantly higher costs</td>
<td>Bower et al., 2002; Bower and Rowland, 2006; Friedli et al., 2000; Harvey et al., 1998; Miller et al., 2003; Scott and Freeman, 1992; Simpson et al., 2003</td>
</tr>
<tr>
<td>Problem solving</td>
<td>Cost-effective from a societal perspective, but higher costs in intervention group from a health-care perspective. Additional costs of problem-solving treatment are offset by fewer days off work in the intervention group</td>
<td>Mynors-Wallis et al., 1997</td>
</tr>
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Table 25. Summary of cost-effectiveness of psychological treatments for depression
depressive episode. Thus over the longer duration of the treatment of this usually chronic illness, it is possible that antidepressant psychotherapy might have cost advantages relative to pharmacotherapy. Studies to assess this, however, are lacking.

15 Conclusions and implications

The Executive Committee and the Council of the Collegium Internationale Neuropsychopharmacologicum have considered the information contained in this report as well as other information available to its members and adopted a Consensus Statement about the use of antidepressants in the treatment of depressive disorders. The Consensus Statement is given here as a concluding summary of the review. In addition to providing a summary of the main findings of the review, the Consensus Statement also indicates future action that CINP will take in this area and makes a series of recommendations to governments, professional and non-professional organizations and the media.

Antidepressant Medications in the Treatment of Depressive Disorders: A Consensus Statement by the Collegium Internationale Neuropsychopharmacologicum

The International College of Neuropsychopharmacology,

Aware of the major public health importance of depressive disorders and of the suffering that these disorders cause to people who have them and their families;

Cognizant that even in highly industrialized countries only a small proportion of people with depression who could benefit from qualified help contact health-care services and receive adequate treatment;

Given that medical practitioners may fail to recognize depressive disorders in people who come to them seeking help and that their knowledge about the treatment of depression may be insufficient;

Concerned by the findings that the general population and health-care workers still attach stigma to depressive disorders;

Aware of the risks of suicide and physical illness that are elevated in people with depressive disorders;

Deeply concerned also by the tendency to consider depressive disorders to be minor ills of living and not illnesses that should be given appropriate care;

Considering that the potential benefits of these medications used in the treatment of depressive disorders outweigh the risks presented by the side effects of their application;

Stressing that the application of adequate treatment not only helps the persons who have the disease and their families, but also brings significant social and economic benefits to society;

Stressing also that the treatment of depressive disorders is a process in which the application of antidepressant medications, social support and psychological help and treatment must be used in a manner that will correspond to the needs of the individuals who are being treated, and of their relatives and other carers;

Recognizing that new information and knowledge about the treatment of depressive disorders is not reaching those engaged in health-care and that the general public is still insufficiently informed about the frequency of depressive disorders and possibilities of their effective treatment;

DECIDES

1. To publish the CINP Task Force report based on a review of Evidence about Antidepressant Medications and other Treatments of Depressive Disorders and employ it as a platform for the development of training programs and guidelines concerning the recognition and treatment of depressive disorders;

2. To develop specific guidelines concerning the use of antidepressant medications in the treatment of depressive disorders and to undertake all that is necessary to bring them to the attention of medical practitioners worldwide, engaging the World Health...
Organization and other institutions and organizations in this process;
3. To develop materials that will be suitable for the correct information of the general public about depressive disorders and the possibilities of their treatment.

AND RECOMMENDS

1. To governments to introduce educational programs concerning depressive disorders in all schools of health personnel and in in-service training of health staff to ensure that people with depressive disorders receive adequate help and treatment; these programs should include families as well.
2. To professional societies in the field of mental health to participate in the development of comprehensive treatment and rehabilitation programs for people with depressive disorders;
3. To non-governmental organizations of patients and their families to participate in the development of training materials and collaborate in other ways with professional organizations and institutions engaged in the programs designed to improve the treatment of people with mental disorders;
4. To the media to collaborate with professional organizations in the effort to bring well-balanced information about depressive disorders to the general public.

16 Acknowledgements

Work on this review has been supported by unrestricted grants made to the CINP by the following companies: Bristol-Myers Squibb Company, Eli Lilly and Company, Forest Laboratories, GlaxoSmithKline, H. Lundbeck A/S, Les Laboratoires Servier and Wyeth. The funds received served to organize and cover the expenses of travel and accommodation for meetings of the Task Force as well as national and regional meetings of experts. The funds were also used for administrative support in producing the review. None of the members of the Task Force nor any of the advisers received any fees nor honoraria for their work.

Prof. Xiao Zeping, President of the Shanghai Mental Health Center in Shanghai, China, Prof. Nikolaj Nesanov, Director of the Bekhterev Psychoneurological Institute in St. Petersburg, Russia, and Dr Edgar Belfort, Administrative Secretary of the Association of Psychiatrists of Latin America (APAL) in Caracas, Venezuela, organized and hosted regional meetings related to the project.

Prof. Möller, Chairman of the Psychiatric Department of the Ludwig-Maximilians-Universität München in Germany hosted one of the regional meetings and enabled two of the editors (Dr T. C. Baghai and Prof. H. Grunze) to carry out their work on the review.

Numerous individuals, institutions and the companies listed above provided the Task Force with publications and other relevant scientific materials. To all of them we express our most sincere and cordial gratitude.

17 Statement of Interest

Thomas C. Baghai accepted paid speaking engagements in satellite symposia and acted as a consultant for Janssen-Cilag, Organon, Pfizer and Servier.

David Baldwin acted as a consultant to and/or accepted paid speaking engagements in satellite symposia from a number of companies with an interest in anxiety and depressive disorders (Asahi, Cephalon, Eli Lilly, GlaxoSmithKline (GSK), Lundbeck, Pfizer, Organon, Pharmacia, Pierre Fabre, Roche, Servier, Sumitomo, Wyeth). He holds or has held research grants (on behalf of his employer) from a number of companies with an interest in anxiety and depressive disorders (Cephalon, Eli Lilly, GSK, Lundbeck, Organon, Pfizer, Pharmacia, Roche, Wyeth).

Barbara Barrett has acted as an independent consultant to Servier for the development of an economic model of agomelatine in the UK.

Pierre Baumann has served on the advisory boards of Pfizer and Lundbeck in Switzerland. He has been sponsored by almost all pharmaceutical companies involved in psychopharmacology in Switzerland to carry out studies, participate in symposia and organize congresses. He has stocks in Novartis and Roche.

Ursula Brand has no conflicting interests.

Max Fink has no commercial contracts or appointments and receives no funding from industry sources that may influence the conclusions of his contributions to the review.

Wolfgang Fleischhacker discloses that he received speaking/consultancy honoraria from Bristol-Myers Squibb (BMS)/Otsuka, AstraZeneca, Janssen-Cilag, Lundbeck, Pfizer, Servier and Wyeth. He also holds or has held research support from BMS/Otsuka, Janssen and Servier.

Konstantinos Fountoulakis has received support concerning travel and accommodation expenses from various pharmaceutical companies in order to participate in medical congresses. He has also received honoraria for lectures from AstraZeneca, Janssen-Cilag, Eli Lilly and a research grant from the Pfizer Foundation.
Toshiaki Furukawa has received research funds and speaking fees from Asahi Kasei, Astellas, Dai-Nippon, Eisai, Eli Lilly, GSK, Janssen, Kyowa Hakko, Meiji, Organon, Pfizer, Tsumura, Yoshitomi and Zelia. The Japanese Ministry of Education, Science and Technology, and the Japanese Ministry of Health, Labor and Welfare have also funded his research.

Karim Chalib has no conflicts of interest.

Guy M. Goodwin received grants from Sanofi-Aventis, Servier and honoraria from AstraZeneca, BMS, Eisai, Lilly, Lundbeck, Pfizer, Sanofi-Aventis, Servier and Wyeth. He serves on the advisory boards of Lilly, Lundbeck, PIVital, Sanofi-Aventis, Servier, and Wyeth. He has no shares in pharmaceutical companies. He holds or has held research grants from Sanofi-Aventis, Lilly, Stanley MRI, the Bailey-Thomas Trust and the MRC (UK).

Heinz Grunze receives research grants from Novartis, AstraZeneca, UCB Belgium and Pfizer. He occasionally supplies services as a consultant and/or paid speaker for AstraZeneca, Sanofi-Aventis, Desitin, Lilly, Janssen-Cilag, BMS and Pfizer.

Peter Jensen currently receives investigator-initiated grants from McNeil Pharmaceuticals and unrestricted educational grants from Pfizer, Lilly and McNeil, participates in speakers’ bureaus for CMED, the Union Chimique Belge Pharma, PsychCME, Continuing Medical Education Outfitters and the Neuroscience Education Institute, and consults to Best Practice, Inc., Janssen Pharma, Novartis and the Union Chimique Belge Pharma.


Martin Knapp discloses the following consulting services and research grants from the pharmaceutical industry pertinent to this review: Servier, Lilly, Organon, Sanofi-Aventis, Pfizer, Novartis.

Jeffrey Liebermann discloses that he holds or has held research grants from BMS/Otsuka, GSK, Janssen-Cilag, Neuroretics, Organon, Pfizer, Somaxon, Somerset and Wyeth. He holds or has held research grants from Somerset and Wyeth and holds equities from BrainCells, Corcept, Merck, Organon, Pfizer and Somaxon.

Jaromír Švestka acted as a consultant to and/or accepted paid speaking engagements in satellite symposia from AstraZeneca, Sanofi-Aventis, BMS, Desitin, Eli Lilly, Janssen-Cilag, Krka/Pfizer, Zenziva. He received support for participation in international congresses from BMS, Eli Lilly, Janssen-Cilag, Pfizer and Zentiva.

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Because David Healy has concerns about the review on principle, the CINP antidepressants Task Force decided to present his views without abridgment:

**HEALY:** ‘My principal concern with the report that I have read lies with the interpretation it puts on clinical trial data. The report adopts one of several possible interpretations, and ideally it might have considered how the evidence looks from a number of different points of view. I think the interpretation adopted is arguably the least supportable one, and this is of some consequence as the interpretation of these clinical trials feeds through to the views adopted as regards the possible economic benefits of antidepressants and their use in comorbid conditions etc.

The report adopts the position that a relatively modest superiority over placebo in a selected number of clinical trials means that antidepressants work. While most practicing clinicians have little doubt that antidepressants can be of benefit, the RCTs that are appealed to here do not demonstrate that antidepressants work. For the most part they have employed samples of convenience and it is not clear how generalizable the results from these studies might be – particularly to populations with comorbid physical disorders. Second, the studies are only a selection of those undertaken; a great number of studies demonstrating even less or no superiority of the antidepressant compared with placebo have not been published and accordingly have not been factored into the claims made here.

The response to this point – that these unpublished studies will often have involved failed assay systems – does not take care of the issue in this context. It may be reasonable to appeal to failed assay systems in a regulatory context, which requires

19 Annexes

19.1 Annex 1: Opinions and suggestions that could not be fully accommodated in the review

The Task Force and the editors have carefully considered the comments and suggestions made by the Advisory Group, participants in meetings and by experts consulted on specific issues. Most of the comments and suggestions could be accommodated by changes or additions to the text. There were, however, some views that could not be fully reflected in the review. They are listed below, in alphabetical order by author.

Max Fink suggested not publishing an annex containing information about psychotherapy within the CINP review because of insufficient scientific evidence about the effectiveness of several forms of psychotherapy in the treatment of depression. The CINP antidepressants task force agreed not to publish an extensive review about the use and usefulness of psychotherapy in depression because this would be beyond the scope of a technical review about antidepressants. Nevertheless, there was broad consensus in the task force and the advisory board that some psychotherapy forms, e.g. IPT (interpersonal therapy) and CBT (cognitive behavioral therapy), represent an important therapeutic option for many patients suffering from depression that should be taken into consideration in treatment plans together with antidepressant medication. A short chapter and an annex about the psychotherapy of depression therefore have been included.
demonstrations of a treatment signal, but these are not failed studies in a wider clinical context. Any wider assessment of what antidepressants might do or their utility needs to take these negative studies into account.

The greater problem, however, in the approach taken lies with the apparent willingness to adopt an interpretation which sees five patients out of ten responding to the antidepressant compared with four responding to the placebo, with the assessment of benefits dependent on rating scale data only, as evidence that the drugs work. One of several alternate interpretations of the 50% response to antidepressants versus 40% response to placebo in terms of the therapeutic response in the antidepressant group is that 80% of the response to the antidepressant comes from non-specific factors. We are unable to quantify the contribution of the various non-specific factors involved, while in contrast we can quantify the specific drug contribution. But this specific drug contribution is only 20% of the therapeutic response. One can make the argument that if the money and culture in psychiatry is to follow the evidence, it should follow the evidence of the 80% rather than the 20%.

This can be put another way. Of every ten people entered into clinical trials one specifically responds to an antidepressant and nine either don’t respond specifically to the antidepressant or fail to respond at all or respond adversely. Taking the approach that the authors in this report have taken privileges the response of one individual against the responses of nine and this is clearly problematic in terms of a report that may go to policy makers and others purporting to be a report that if implemented will lead to benefits.

I think it would be preferable to flag up the preliminary and provisional nature of the results. They point to the fact that antidepressants have benefits. They do not indicate that much science has been done in this area but rather that a great deal of science remains to be done. We should be attempting to establish for instance who responds to SSRIs versus who responds to antidepressants active on other systems. Selecting out responsive patients would be quite likely to lead to a much greater difference between the response to active treatment and response to a placebo. This would bring in areas like pharmacogenetics and questions about the effects of specific treatments on different constitutional or personality types rather than simply the effects of these agents on some disease process.

I think there is a signal failure in the field that we have permitted 800 odd trials or more to be done and published and perhaps an equal number to be done and left unpublished, since the first trials on Prozac, all of which essentially repeat the formula of trying to show a small difference between active treatment and placebo, without even in a small proportion of trials moving forward to determining who the treatment responsive groups of patients might be. This is an issue on which Tom Ban has written cogently. He has argued, and I would agree, that we have failed both in terms of the opportunity offered to advance the science of psycho-pathology and also in terms of the science of clinical thera-peutics.

The report bases almost everything on minimal rating scale changes. In terms of any hard outcomes that these clinical trials offer, one of the few hard outcomes is the data on suicidal act and completed suicide rates. When these are looked at, as the expert working group report from the MHRA in Britain, in 2004, reveals, there is a 2.6-fold increased rate of completed suicides in adults after treatment compared to placebo and a 2.4-fold increased rate of completed suicides or other suicidal acts on active treatment compared to placebo. These figures should raise questions for someone about the validity of constructing economic models that depend solely on rating scale results. Adverse responses such as completed suicides have not to the best of my knowledge been factored into the economic modes detailed in this report, but the adverse events from nausea to suicide offer the only hard outcomes we have. If even a proportion of the adverse responses were factored in it is doubtful that the economic benefits claimed could be substantiated.

There are a number of further points to note with this issue of suicides and suicidal acts that are at odds with the interpretation offered in the report on this specific point. The report covers the issue of pediatric suicidality primarily. It makes some mistakes. It claims that there were no suicides in the pediatric trials. In fact there were no known suicides in the set of pediatric trials submitted for registration purposes, but a very large number of patients dropped out because of adverse responses and were not followed up. It would be more correct to say there were no known suicides rather than there were no suicides. There were of course several pediatric suicides in controlled trials of recent antidepressants. But these occurred in trials other than the pediatric registration trials to which the report refers. These figures should raise questions for someone about the validity of constructing economic models that depend solely on rating scale results. Adverse responses such as completed suicides have not to the best of my knowledge been factored into the economic modes detailed in this report, but the adverse events from nausea to suicide offer the only hard outcomes we have. If even a proportion of the adverse responses were factored in it is doubtful that the economic benefits claimed could be substantiated.

In summary, if the object of this exercise or one likely outcome of the exercise is to put into the hands of planners results that will bear the weight of policy, then the report that I have seen is a dangerous structure that I would have thought is likely to collapse in the not too distant future with only a few pillars left standing such as the pillar on ECT. If the report is taken seriously by anyone within the pharmaceutical industry involved with drug development rather than just marketing, it will hamper innovative drug development.

CINP can stand back and say in the words of the Tom Lehrer song that it is not their department to consider what uses the report might be put to, but I can’t believe that CINP members with their particular backgrounds would be very happy for the organization to adopt such an ethical position.’
Some of David Healy’s critiques have been integrated in the review, e.g. additional chapters about suicidality and antidepressants in adult patients (see chapter 11) and dependence and withdrawal (see chapter 9.1.1.3.2). Some of his concerns have been discussed more extensively, e.g. the problem of unpublished studies (see chapter 4.4), the new trends in pharmacogenetic research to establish methods for an individualized antidepressant therapy (see chapter 8.3) and the problem of comorbid physical disorders in depressed patients (see chapter 5.2.4). Because other difficult issues such as the existing problem of misconduct in clinical science and subjective evaluation of study results concerning responder rates in clinical trials cannot be resolved completely, the CINP antidepressants task force decided to report David Healy’s view in full to empower readers to draw their own conclusions about these issues.

Ulrich Hegerl suggested changing the structure of the review and discussing antidepressant medications before the chapters about diagnosis and epidemiology because medications are already mentioned within the description of specific manifestations of depression. The CINP antidepressants task force decided not to change the structure of the document based on agreement that it is important to establish treatment plans after the correct diagnosis of depressive disorders and comorbid or comorbid diseases.

Florence Thibaut suggested including recommendations for clinicians with the level of evidence at the end of each chapter. The CINP antidepressants task force decided to leave out recommendations and to publish only a review about the usefulness of antidepressant medications that will constitute the basis for treatment recommendations formulated at a national level.

Wayne Katon suggested not including studies using modeling techniques in the economics chapter. He suggested adding other studies and references in the economics chapter, and he did not agree with the statement that the comparison of psychotherapy and medication reveals economic advantages for antidepressants. The economics experts within the CINP antidepressants task force agreed to present the results of modeling studies together with other kinds of economic studies, including a subchapter about differences in methodologies of economic evaluations. Because the use and usefulness of psychotherapy was not the main focus of this review, the CINP antidepressants task force agreed not to expand the chapter about psychotherapy.

Markus Kosel suggested adding references about DBS in the treatment of OCD. The CINP antidepressants task force agreed not to include such studies because predominantly the pharmacological and non-pharmacological treatment of depressive disorders has been evaluated in the present review.

Min-Soo Lee suggested including specific recommendations for pharmacotherapy. The CINP antidepressants task force agreed to include those recommendations because they represented un-referenced treatment schedules. Specific treatment recommendations will be integrated as mentioned at a later stage of the project, but not in the current review.

Shigenobu Kanba suggested not mentioning ECT three times in the review. The CINP antidepressants task force and the advisory board agreed to mention ECT in the chapter about combination therapies in treatment-resistant depression, in a short chapter about ECT, and in an additional and more extensive annex about this treatment method, because at present ECT still represents a very effective treatment method for severe and treatment-resistant depressive disorders.

### 19.2 Annex 2: Additional information on the types of economic evaluation

#### 19.2.1 Cost-offset studies

The simplest of economic studies are concerned only with costs, not (usually) because they see outcomes as irrelevant but because, in relation to the treatments or services under study, the health and quality of life outcomes have already been established from other research, or are (currently) not measurable because of conceptual difficulties or research funding limitations. One of these cost-only methods is the cost-offset study, which compares costs incurred with (other) costs saved. For instance, a new antidepressant may have a higher acquisition cost (higher price) compared with an older drug, but may reduce the need for inpatient admissions and thus lead to cost savings downstream.

While a cost-offset study is not an economic evaluation, and therefore cannot answer the ‘Is it worth it?’ question, it nevertheless addresses an issue that is often fundamental to health system decision making: Within a fixed or even shrinking budget (at least in the short run), are treatment changes affordable?

#### 19.2.2 Cost-effectiveness analysis

Probably the most intuitive and straightforward modes of economic evaluation are cost-effectiveness
and cost-consequences analyses. Both types of analysis measure outcomes using instruments and scales familiar to clinical researchers. Both are employed to help decision makers choose between alternative interventions available to or aimed at specific patient groups. A cost-effectiveness analysis (CEA) looks at a single outcome dimension – such as the number of life years saved, the number of depression-free days or the duration of time in remission – and then computes and compares the ratio of the difference in costs between the two treatments being evaluated with the difference in (primary) outcome (the incremental cost-effectiveness ratio or ICER).

A common finding is that a new treatment is both more effective (the outcome profiles are better than for the older or comparator treatment) and simultaneously more expensive. Decision makers therefore face the challenge of weighing up the outcomes against the higher expenditure necessary to secure them. The decision is far from straightforward in these cases. The widely used cost-effectiveness ‘plane’ (Figure 5) illustrates the range of possible CEA results and the difficult decision-making task in some circumstances.

The cost-effectiveness plane in Figure 5 shows the possible combinations of outcomes and costs when comparing two interventions or treatments. The point marked B indicates that the new treatment (say a new antidepressant drug) is both more effective (it has better outcomes) and less costly than the old treatment. The task for the decision maker looks quite straightforward in these circumstances: recommend wider use of the new treatment. However, many evaluations find that new treatment modes produce better outcomes than older interventions but at a higher cost (illustrated by point A). The choice facing the decision maker is now more complex: are the better outcomes worth the higher costs?

To aid such decision making, economists have developed cost-utility analysis (see below) and more recently the net benefit approach, linked to the construction of cost-effectiveness acceptability curves (CEACs). These show the probability that a new intervention will be reviewed by the decision maker as cost-effective for each prespecified or implicit valuation of an outcome improvement. Comparisons are then possible across quite disparate clinical areas (comparing, for example, depression treatment with dementia treatment; or psychiatry with oncology). This kind of decision context is exactly the one faced by decision makers one or two steps removed from the patient interface.

An obvious weakness with the strict cost-effectiveness methodology is the enforced focus on a single outcome dimension (in order to compute ratios) when we know that many people with depression have multiple needs for support and when most clinicians might expect to achieve improvements in meeting more than one need. Carrying multiple outcomes forward in an analysis is less tractable analytically, but three options are available, associated with three other modes of economic evaluation. One option – which is cost-consequences analysis – is to retain all or most outcome dimensions (measured using standard clinical scales). The other two options weight the outcomes, either in terms of money (cost-benefit) or in terms of utility (cost-utility).

A weakness noted earlier is that the comparator in a trial may not be appropriate, not giving decision makers the evidence base they need (in their local circumstances, or more generally).

19.2.3 Cost-utility analysis

An increasingly used evaluative mode that seeks to reduce outcomes to a single dimension is cost-utility analysis (CUA), which measures and then values the impact of an intervention in terms of improvements in preference-weighted, health-related quality of life. The value of the quality of life improvement is measured in units of ‘utility’, usually expressed by a combined index of the mortality and quality of life effects of an intervention. The best-known and most robust index is the quality-adjusted life year (QALY). CUA have a number of distinct advantages, including using a uni-dimensional measure of impact, a generic measure which allows comparisons to be made across diagnostic or clinical groups (e.g. comparing psychiatry with oncology or cardiology), and a fully explicit methodology for weighting preferences and valuing health states. But these same features are sometimes
seen as disadvantages: the utility measure may be too reductionist, the generic quality of life indicator may be insufficiently sensitive to the kinds of change expected in depression treatment, and a transparent approach to scale construction paradoxically opens the approach to criticism from those who question the values thereby obtained (Chisholm et al., 1997).

On the other hand, CUAs avoid the potential ambiguities with multidimensional outcomes in cost-consequences studies and are obviously more general than the single-outcome CEA. The transparency of approach is also to be welcomed. The result is an incremental cost-utility ratio for each intervention, relative to some comparator, which can be compared with similar ratios for other interventions (potentially from across the widest diagnostic range, i.e. not just from mental health). These cost-per-QALY ratios can then inform health-care resource allocation decisions or priority setting.

19.2.4 Cost-benefit analysis

Cost-benefit analysis (CBA) asks whether a treatment or policy is socially worthwhile in the broadest sense: Do the benefits exceed the costs? This kind of analysis would allow decision makers to consider the merits not only of allocating resources within health care, but also to consider whether it would be more appropriate to invest in other sectors such as housing, education or even the military. All costs and benefits are valued in the same (monetary) units. If benefits exceed costs, the evaluation would recommend providing the treatment, and vice versa. With two or more alternatives, the treatment with the greatest net benefit would be deemed the most efficient. CBAs are thus intrinsically attractive, but conducting them is especially problematic because of the difficulties associated with valuing outcomes in monetary terms.

Recent methodological advances in health economics offer ways to obtain direct valuations of health outcomes by patients, relatives or the general public. These techniques ask individuals to state the amount they would be prepared to pay (hypothetically) to achieve a given health state or health gain, or observe actual behavior and impute the implicit values. However, they are likely to be quite difficult to apply in mental health contexts. Another approach used to value health interventions is ‘conjoint analysis’. Individuals are asked to rank different real-world scenarios, which may consist of several dimensions (including, for instance, health outcomes, time inputs, discomfort, possible externalities and stigma), and by including cost as one of these dimensions, a monetary value can be elicited. While complex, this conjoint analysis approach has the advantage of not specifically asking individuals to put a monetary value on health states or health gain, which can make the technique easier to administer than traditional willingness-to-pay studies.

19.2.5 Cost-consequences analysis

A cost-consequences analysis has the ability to evaluate policies and practices in a way that arguably comes quite close to everyday reality, but it also has some limitations. For each treatment alternative a cost-consequences evaluation computes total (and component) costs and measures change along every one of the relevant outcome dimensions. The cost and outcome results are then reviewed by decision makers; the different outcomes are weighed up (informally and subjectively) and compared with costs. For example, the researcher could compute a series of ICERs (one for each measured outcome) for presentation to the decision maker. The decision calculus is therefore certainly much less tidy and more complicated than when using cost-effectiveness ratios or monetary or utility measures of impact (see below), but it could be argued that decision makers in health-care systems – from strategic policy-makers at the macro level to individual psychiatrists at the micro level – face these kinds of decisions daily.

On the other hand, the process of weighing up the various outcomes by the decision maker is subjective, hidden and ‘technocratic’, whereas the choice of the single outcome dimension in a CEA and the weighting algorithms in other evaluative modes (described below) are transparent, less likely to be influenced by the personal predilections or value positions of a few individuals, and (potentially) reflective of societal values.

19.2.6 Cost-minimization analysis

Another ‘cost-only’ approach is cost-minimization analysis, which seeks to find which of a number of treatment options has the lowest cost. A cost-minimization analysis is carried out in one of two ways. It often proceeds in the knowledge that previous research has shown outcomes to be identical in the treatment or policy alternatives being evaluated. In this sense the approach is really more accurately described as an ‘interrupted’ cost-effectiveness
The other way a cost-minimization analysis can proceed is to compare costs without any regard for outcomes. Such an approach is narrow and potentially misleading and should never be encouraged: it is not an economic evaluation.

Well-conducted cost-minimization analysis can therefore be thought of as a special type of cost-effectiveness analysis, where evidence on effectiveness demonstrates no difference between two or more interventions. In most instances, however, clinical and quality of life outcomes will not be equivalent, and more complex evaluations are required, which can make them far more informative, but correspondingly more complex to conduct.

19.3 Annex 3: Additional information on electroconvulsive therapy

Electroconvulsive therapy (ECT) is the safe induction of a series of generalized epileptic seizures for therapeutic purposes using brief-pulse stimulation techniques under anesthesia and muscle paralysis. Informed consent of the patient or the responsible legal guardian is mandatory. Since the first publication of a placebo controlled double-blind study indicating the efficacy of ECT in the treatment of depression (Greenblatt et al., 1964), the excellent therapeutic effectiveness of this method has been described in extensive studies (Abrams, 2002; Baghai et al., 2005). These studies are summarized in a variety of reviews and meta-analyses (Abrams, 2002; Baghai et al., 2005; ECT review group, 2003).

19.3.1 ECT as first-line treatment

In the case of refusal of food and drink, and severe psychomotor retardation, ECT has been shown to be one of the safest therapeutic options with fast relief of symptoms (Gangadhar et al., 1982). Therefore, depressive stupor and inanition, as in melancholic, catatonic and/or psychotic depression, can be a first-line indication for ECT. If, due to other conditions, e.g. severe psychotic symptoms and/or high suicide risk, rapid improvement is crucial for the patient, ECT should be considered earlier than other therapeutic options (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). In psychotic depression, the remission rate for ECT approximates 90%, with relief experienced within 10–14 days (Ottoson and Fink, 2004; Petrides et al., 2001). The risks of suicide that mark severe psychiatric illnesses are quickly relieved by ECT, although attention to continuation treatment is essential to sustain the benefit (Kellner et al., 2005). Also other acute psychiatric syndromes, e.g. malignant catatonia or a neuroleptic malignant syndrome (NMS) may show rapid benefit from ECT as a first-line treatment (Abrams, 2002; Baghai et al., 2005). Intensive ECT, usually administered daily (en bloc), relieves the high rates of mortality associated with malignant catatonia and delirious mania (Fink, 1999; Fink and Taylor, 2003). In the case of severe and life-threatening adverse events of antidepressants and in psychotic depressed patients ECT monotherapy can be a safe first-line treatment. This recommendation also holds for patients suffering from severe somatic diseases, including the risk of worsening due to antidepressant and antipsychotic pharmacotherapy (Beliles and Stoudemire, 1998; Franco-Bronson, 1996; Rothschild, 1996).

In addition, long duration and chronic course of the index episode are negative outcome predictors in depressive disorders that signal a higher risk for therapy resistance to medication and ECT (Beliles and Stoudemire, 1998; Prudic et al., 1990). Nevertheless, the primary use of ECT is handicapped by severe stigma and even legal restrictions against its use in some jurisdictions (Ottoson and Fink, 2004).

19.3.2 ECT as second-line treatment

Even if patients receive ECT only in rare cases immediately after reaching criteria for pharmacotherapy resistance, those treatment failures are the most frequent ECT indication (Möller, 1997; Prudic et al., 1996; Sackeim, 2001; Warneke, 1993). Use of ECT significantly enhances response rates (Davidson et al., 1978; Folkerts et al., 1997; Kroessler, 1985). This finding is especially true in patients suffering from psychotic depression, even if antipsychotic therapies have been applied adequately (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001; Folkerts et al., 1997). Intolerable side effects of antidepressant medications, somatic comorbidities emerging during the pharmacological treatment (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001; Rasmussen et al., 2002) or worsening of depressive symptoms, including severe suicidality during an antidepressant pharmacotherapy, can also be the reason for initiating an ECT treatment course (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001).

First- and second-line indications and rare last resort indications are summarized in Table 26.
19.3.3 Efficacy of ECT in depressive syndromes of differential etiology

19.3.3.1 Unipolar depression

The general efficacy and superiority of ECT compared with antidepressant pharmacotherapy has been described in controlled clinical trials and meta-analyses (ECT review group, 2003). Response rates between 80 and 90% (Prudic et al., 1990; Prudic et al., 1996) and even 100% (Sackeim et al., 2000) have been reported. Also, lower response rates of about 50–60% have been described in patients after several medication treatment failures receiving unilateral ECT (Sackeim et al., 2000). Nevertheless, in a recent study sustained response rates of 80%, superior to pharmacotherapy response rates (up to 70%), and remission rates of 75% (up to 87% for study completers suffering from psychotic depression) were found in major depressed patients treated with optimized ECT (Husain et al., 2004; Kellner et al., 2005; O’Connor et al., 2001; Petrides et al., 2001). A 20% better improvement compared with tricyclic antidepressants and a 45% better improvement compared with monamine-oxidase inhibitors (MAOIs) (Janicak et al., 1985) as well as a better improvement in comparison with the selective serotonin reuptake inhibitor (SSRI) paroxetine (Folkerts et al., 1997) have been described. In addition, a more rapid improvement in comparison with pharmacotherapeutic approaches has been reported (Abrams, 2002; Petrides et al., 2001; Sackeim et al., 1993). Most patients show a faster treatment response during ECT in comparison with pharmacotherapy (Sackeim et al., 1987). But also an advantage in speed of response in similarly efficacious pharmacotherapeutic approaches, such as lithium augmentation (Sackeim et al., 1993) after tricyclic antidepressant (TCA) treatment failure, has been described. Especially for patients who receive ECT after pharmacotherapy treatment has failed, longer treatment intervals until complete remission are to be expected.

Earlier reports showed lower-stimulation-energy bilateral ECT to be more effective than unilateral ECT (ECT review group, 2003; Sackeim et al., 1987;
Sackeim et al., 1993). But unilateral ECT may achieve efficacy rates equal to bilateral ECT if the dose regime is 6–8 times above the titrated seizure threshold (McCall et al., 2000; Sackeim et al., 2000).

19.3.3.2 Bipolar depression

ECT is an effective antidepressant therapy whether depressive episodes occur due to unipolar depression or bipolar disorder (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). As described in chapter 5.2.2.1 an enhanced switch risk, including the occurrence of hypomania or mania is associated with every highly effective antidepressant treatment. Infrequent switches from depression to mania may also occur during the course of ECT (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). But owing to a lack of randomized controlled trials and switch rates up to 30%, regardless of the antidepressant therapy, this clinical observation has also been discussed as an artifact (Taylor and Fink, 2006). In contrast to antidepressant pharmacotherapy, the electroconvulsive treatment has not to be stopped due to the anti-manic properties of ECT. Furthermore, ECT may be combined with lithium treatment to augment lithium effects and to prevent a switch into mania in high-risk patients. In this case, an enhanced risk for cognitive and medical side effects must be taken into account (Zarate et al., 1997). In the event of urgent indication for mood stabilizers, even combined use of ECT and anticonvulsants is possible and may yield clinical advantages in specific circumstances (Aarre and Bugge, 2002; Pearlman and Obedian, 1995; Zarate et al., 1997).

19.3.3.3 Dysthymia and double depression

Chronic depression in the case of dysthymia alone is not an indication for ECT treatment. Nevertheless, if the diagnostic criteria for MDD or double depression are present, dysthymia is not a predictor for a poor ECT response (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001).

19.3.3.4 Depressive syndromes in OCD

Patients suffering from OCD who do not respond to pharmacotherapy may respond following ECT predominantly if OCD is accompanied by depressive symptoms (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001), which often is the case. Also, the beneficial use of ECT during OCD continuation therapy has been reported (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001).

19.3.3.5 Comorbid personality disorder

Comorbid personality disorder is a predictor of poor response to ECT, and the recommendation for ECT should be made cautiously in such patients (Abrams, 2002; O’Connor et al., 2001). Nevertheless, in the case of resistance to pharmacotherapy, ECT should not be withheld from patients suffering from MDD with comorbid personality disorder (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). Rather, the information about lower response rates must be included in the patients’ information about the estimated treatment outcome.

19.3.3.6 Organic depression due to somatic disorders

Patients suffering from secondary depression associated with somatic diseases show lower response rates to biological therapies such as pharmacotherapy and ECT (Black et al., 1993; Coryell et al., 1985; Krystal and Coffey, 1997) in comparison with MDD. Nevertheless, ECT is clinically effective in patients suffering from depression after cerebral infarction (‘poststroke depression’) (Krystal and Coffey, 1997; Sackeim et al., 1987; Sackeim et al., 2000). Of course, for this patient group organic risk factors must be considered especially carefully during interdisciplinary neurological and psychiatric evaluations.

19.3.4 Combination of ECT and antidepressants

The majority of patients referred for ECT have had multiple trials of medication. Despite this experience, high remission rates to effective ECT – up to 90% in psychotic depression – can be expected (Abrams, 2002; Husain et al., 2004; Petrides et al., 2001). The use of bilateral or high-dose unilateral stimulation can enhance the effectiveness of ECT treatment (Husain et al., 2004; Sackeim et al., 2000). A further option for augmenting an ECT treatment course may be the concomitant prescription of antidepressants. However, findings from study of a putative benefit of combining ECT with TCAs (Lauritzen et al., 1996; Nelson and Benjamin, 1989) and the lack of advantages of other concomitant medications, like SSRIs, are still controversial (Lauritzen et al., 1996). In particular, the efficacy of modern antidepressants in combination with ECT, e.g. the dual-action substances mirtazapine, venlafaxine and duloxetine, has never been investigated in controlled studies. Nevertheless, some safety data are available, e.g. venlafaxine at doses...
lower than 300 mg/day has been shown to be safe in combination with ECT. In high-dose treatments above 300 mg/day, side effects of a cardiovascular nature, such as transient asystolia and bradycardia, were more frequent if venlafaxine treatment was combined with propofol anesthesia during ECT (Gonzales-Pinto et al., 2002).

19.3.5 Continuation ECT

As described in chapter 9.2, in addition to pharmacologic and psychotherapeutic continuation therapies, especially after pharmacotherapy treatment failure, ECT is an also effective continuation treatment (Fink et al., 1996; Kellner et al., 2005; Sartorius and Henn, 2005a; Sartorius and Henn, 2005b), even given the absence of controlled studies. Continuation ECT should be considered when depressive symptoms recur despite adequate pharmacological continuation therapy. Even when the prior history of an individual patient shows enhanced risk for recurrence of depression during continued pharmacotherapy, including both antidepressants and mood stabilizers, C-ECT should be part of the treatment plan (Frey et al., 2001; McCall, 2001; Rabheru and Persad, 1997). The usual clinical procedure is to prolong the treatment intervals according to individual clinical requirements. During acute treatment, a patient usually receives two or three treatments per week. Afterwards, usually one treatment per week is applied for 4–8 weeks, then one treatment every 2 weeks and then one treatment every 4 weeks. This frequency should be maintained for at least 6 months. A frequently used alternative strategy (the so-called cafeteria style) is the individual decision whether to administer C-ECT treatment when the first signs of recurring depressive symptoms are reported (Abrams, 2002; Fink et al., 1996). Regular weekly evaluations help to judge the necessity to shorten or prolong treatment-free intervals on an individual basis.

19.3.6 Safety

In general, ECT is one of the best-tolerated antidepressant therapies, with low risk for severe complications, even lower than TCAs (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). The reported mortality rate during ECT varies between 1:50000 and 1:25000 treatments (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). Severe complications that warrant special attention are seen in less than one in 10 000 treatments (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). ECT therefore is considered to be one of the safest medical procedures performed under anesthesia. Clinical conditions requiring special attention before and during ECT described in (Abrams, 2002; Baghai et al., 2005) are summarized in Table 27.

19.3.7 Side effects

19.3.7.1 Somatic side effects

The most frequent immediate unpleasant effects of ECT are headache, nausea and vomiting (varying with the anesthetic). Headache is reported in up to 45% of patients and can be treated symptomatically using analgesics such as acetylsalicylic acid or paracetamol or, if severe, by changing the induction medications. Patients suffering from regular migraine attacks are predisposed for postictal headache following ECT. In this case triptans, e.g. sumatriptan, can be applied orally or intranasally (Angst et al., 1992). Nausea occurs rarely following intravenous anesthesia and can be treated using metoclopramide. Other rare complications of ECT are cardiovascular events emerging from anesthesia. On rare occasions, the seizure is prolonged beyond the anticipated 30–180 seconds (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). This risk is considerably enhanced in patients receiving theophylline (Grogan et al., 1995; Rao et al., 1993). The treating anesthesiologist or psychiatrist will end the seizure by administering intravenous benzodiazepines (e.g. diazepam, lorazepam), anesthetics or other anticonvulsants. This event is best managed by ictal and postictal electroencephalogram monitoring (Grogan et al., 1995), which can also be of use in treating non-convulsive seizures, which rarely occur after ECT (Grogan et al., 1995; Rao et al., 1993).

In the case of prolonged effectiveness of muscle relaxants due to predisposition or lithium therapy (Hill et al., 1977; Reinherr et al., 1977), longer assisted respiration and subsequent measurement of oxygen saturation using finger or toe pulse oxymetry is necessary to prevent hypoxia. Aching muscles can be prevented by adequate muscle relaxation and are reported rarely.

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\(^{75}\) The terms ‘continuation treatment’ and ‘continuation ECT’ (C-ECT) are predominantly used to characterize maintenance treatment after successful treatment of the index phase. They are sometimes distinguished from ‘maintenance treatment’ and ‘maintenance ECT’ (M-ECT) (Sartorius and Henn, 2005a) based on theoretical considerations regarding switching to prophylactic treatment to prevent new episodes of depression. Because for individual patients this time point cannot be precisely defined, in the following text only the term ‘C-ECT’ is used.
In patients suffering from bipolar depression, ECT, like any other antidepressant agent (Angst et al., 1992), can induce hypomania or mania ('switch') (Angst et al., 1992). Concomitant lithium therapy (Zarate et al., 1997) can be used despite the higher risk of side effects such as prolonged muscle relaxation and confusional states. The use of mood stabilizers, such as valproate, lamotrigine or carbamazepine (if required, at lower doses than usual), is possible despite the anticonvulsant properties of these agents (Zarate et al., 1997). Both methods can significantly reduce the switch risk.

19.3.7.2 Cognitive side effects

All patients are confused on awakening after a seizure. The duration and severity of the post-seizure delirium vary with age (older patients have more severe and more prolonged periods of confusion), dosage and type of anesthetic, and the characteristics of the medications, both psychoactive and systemic, that have been prescribed. Special attention is paid to sedatives and anxiolytics, antipsychotics and lithium, which may enhance the confusional syndrome.

Transient cognitive disturbances are typical side effects that are more prominent in bilateral than in unilateral and in high-dose than in lower-dose ECT (ECT review group, 2003). These include short-term memory disturbances in up to 30% of patients treated (van Waarde and Stek, 2001). Postictal delirium, including a prolonged reorientation period and memory disturbances such as anterograde and retrograde amnesia, can be differentiated from rarely occurring effects on autobiographic long-term memory (Lisanby et al., 2000). In addition, cognitive deficits that are not a product of memory disturbances, such as concentration or attention deficits can occur. It can be difficult in an individual patient to differentiate cognitive side effects of an ECT treatment from cognitive disturbances caused by depression itself (Lisanby et al., 2003a). A variety of patients report amelioration of cognitive impairment after a course of ECT treatment (Devanand et al., 1991).

As described, the rate of cognitive disturbances depends on dose and application of electrical stimulation (Devanand et al., 1991; Krystal and Coffey, 1997). Sometimes patients experience profound and sustained memory loss, sufficient to interfere with their ability to return to work. Such instances are rare, but constitute the principal burden of complaints against the use of ECT (Abrams, 2002; Ottoson and Fink, 2004).

Nevertheless, recent improvements in the use of ECT include methods to maintain good therapeutic efficacy together with better tolerability concerning cognitive disturbances. Modified ECT techniques (Ghaziuddin et al., 2000), including unilateral and bifrontal pulse wave stimulation, anesthesia with muscle relaxation and sufficient oxygenation, could substantially reduce these risks (Ghaziuddin et al., 2000; Sackeim et al., 1993; Sackeim et al., 2000).

If cognitive disturbances occur despite these precautions, rapid improvement within 1 and up to

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**Table 27. Clinical conditions requiring special attention before and during ECT (adopted from Baghai et al., 2005)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced intracerebral pressure*</td>
<td>At present</td>
</tr>
<tr>
<td>Cerebral infarction*</td>
<td>Not older than 3 months</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>Not older than 3 months</td>
</tr>
<tr>
<td>Intracerebral tumor*</td>
<td>Including intracerebral edema</td>
</tr>
<tr>
<td>Any life-threatening anesthesia risk*</td>
<td>At present</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Cardiac arrhythmias, instable angina pectoris, myocardial infarction (older than 3 months), myocardial insufficiency, heart-valve abnormalities, not sufficiently treated hyper- or hypotonia, aortal aneurysm</td>
</tr>
<tr>
<td>Medical disorders</td>
<td>Disturbance of blood coagulation, severe liver diseases, severe pulmonary diseases, pheochromocytoma</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>Intracerebral neoplasias, intracranial bleeding, intracerebral vascular malformations, cerebral ischemia, cerebral inflammations, hydrocephalus, dementias, diseases of the basal ganglia, craniotomies, severe cerebral traumas</td>
</tr>
<tr>
<td>Orthopedic disorders</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Esophageal hernia</td>
<td>Increased aspiration risk; intubation recommended</td>
</tr>
<tr>
<td>Concomitant pharmacological treatment</td>
<td>If enhancing the ECT risks or reducing ECT efficacy</td>
</tr>
</tbody>
</table>

* In former times considered as absolute contraindications; today an individual risk/benefit-analysis is necessary.
4 weeks can be observed in most cases (Ghaziuddin et al., 2000). Follow-up investigations showed a complete reversibility of cognitive side effects following an ECT course (Ghaziuddin et al., 2000; Krause et al., 1988) and even improvement in comparison with the time interval before ECT treatment (Baghai et al., 2005; Krause et al., 1988). A variety of case reports, case series and controlled studies confirm that ECT does not cause long-lasting functional impairment (Krause et al., 1988) or any structural damage of the central nervous system (Devanand et al., 1991; Krause et al., 1988; Lisanby et al., 2003b).

19.3.8 Clinical precautions and special considerations

After many decades of research and clinical experience, clinicians have developed protocols for the safe treatment of patients who warrant ECT regardless of age, medical status or physical condition.

Conditions that carry higher somatic risks include recent myocardial or cerebral infarction, high intracranial pressure, normal pressure hydrocephalus with risk for herniation and every other untreated severe medical and life-threatening anesthesiological risk. If treated sufficiently, these conditions become relative contraindications, and a risk-benefit analysis must be performed for each patient on an individual and interdisciplinary basis. Other conditions associated with enhanced cardiovascular risk include coronary artery disease, arrhythmias, insufficiently treated hypertension and aneurysms. Other medical conditions, such as severe lung and liver diseases, disturbances of blood coagulation and untreated pheochromocytoma, also enhance the risk associated with ECT and anesthesia. Neurological diseases, including intracranial tumors and bleeding, vascular malformations, cerebral ischemia, acute infections and others enhance treatment risk. In general, each factor that enhances the risk of side effects for ECT and anesthesia should be taken into consideration. In the case of specific risks, interdisciplinary counseling may be necessary. Next, the higher somatic risk must be compared with the risk of insufficiently treated or prolonged psychiatric illness. Patients and relatives or responsible legal guardians need to be informed about risk-benefit ratios so they can share in the decision making.

19.4 Annex 4: Additional information on transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) was originally introduced in 1985 by Barker et al. as a non-invasive tool to electromagnetically stimulate the primary motor cortex in humans (Lisanby et al., 2003b). More recently, repetitive TMS (rTMS) has become a powerful research tool in neurophysiology and cognitive neuroscience. rTMS is usually targeted to the dorsolateral prefrontal cortex based on well-replicated findings that show reversible functional changes in this region using different neuroimaging techniques. The majority of studies focus on the left prefrontal cortex based on the observed asymmetry of prefrontal function associated with major depression (Lisanby et al., 2003b). A large number of different stimulation parameters, e.g. frequency and intensity of stimulation, have been applied in studies, and very few studies have compared different treatment modalities (Padberg and Möller, 2003). The usual treatment duration has been 1–4 weeks of treatment, and in most studies rTMS has been used as an add-on intervention with a stable antidepressant medication.

Some 25 randomized placebo-controlled clinical trials, including about 750 patients suffering from major depressive episodes, have been conducted to date investigating the safety and efficacy of rTMS as an antidepressant intervention (Berman et al., 2000b; Burt et al., 2002; Dolberg et al., 2002; Garcia-Toro et al., 2001a; Garcia-Toro et al., 2001b; Kaufmann et al., 2004; Loo et al., 2003; Minnissi et al., 2005; Mosimann et al., 2004; Nahas et al., 2003; Padberg et al., 1999; Padberg et al., 2002; Padberg and Möller, 2003; Pascual-Leone et al., 1996; Rossini et al., 2005). In the majority of these trials, significant placebo/verum differences have been observed, with antidepressant effects ranging from modest to substantial. Due to the methodological limitations of many of these trials stemming from rather small sample sizes, the difficulty of controlling sham rTMS used as placebo condition, modified double-blind designs with the person applying rTMS being aware of the condition and patient and rating psychiatrist being blinded, and the short observation periods, the level of evidence currently provided by the available data still needs improvement. Several meta-analyses have been conducted that differ largely in the studies selected and the methodology of analysis used (Burt et al., 2002; Couturier, 2005; Ebmeier et al., 2006; Martin et al., 2003; Pascual-Leone et al., 1996; Schulze-Rauschenbach et al., 2005). Most of these meta-analyses support the antidepressant efficacy of rTMS, but the clinical effects found are not very strong and the clinical significance may be questionable. rTMS has also been directly compared with ECT in five parallel design trials (Grunhaus et al., 2000; Grunhaus et al., 2003; Pridmore et al., 2000; Schulze-Rauschenbach et al., 2005). In these trials rTMS was found to be as effective as ECT in patients suffering
from major depressive episodes without psychotic features, but to be inferior for psychotic depression (Grunhaus et al., 2000). Surprisingly, only one study compared different rTMS modalities with antidepressant pharmacotherapy (clomipramine); however, no meaningful interpretation of the results in terms of efficacy was possible due to small sizes of treatment groups (Lisanby et al., 2001b). Four trials have investigated combined treatment with active rTMS plus antidepressant compared with sham rTMS plus antidepressant to answer the question whether rTMS augments the effect of antidepressant medication (Lisanby et al., 2001b; Rumi et al., 2005). Only one study that combined rTMS with amitriptyline reported significant superiority of combined active treatment (Rumi et al., 2005), whereas the other trials, which applied SSRIs and other substances, failed to show a significant difference between treatment groups. These results may support the idea of rTMS being particularly effective combined with distinct neuropharmacological actions, and this hypothesis should be systematically addressed by future studies. Apart from single studies and case reports, little is known regarding the stability of effects and potential maintenance treatment strategies (Pascual-Leone et al., 1996). The largest body evidence points to transient effects following completion of rTMS treatment (Pascual-Leone et al., 1996; Schüle et al., 2003).

rTMS appears to be safe and well tolerated by patients within a range of parameters defined according to a consensus (Wassermann, 1998). Side effects include the risk of seizure, which increases with higher intensity and higher frequency of stimulation as well as shorter intertrain intervals. Since safety criteria for limiting these stimulation parameters have been published, no additional seizures have been reported within these limits. Among the side effects that are frequently observed are slight local painful stimulation artifacts on the scalp, transient headaches following stimulation and single cases of autonomous arousal reactions, including dizziness and fainting (personal communications). Clinical contraindications include implanted devices (pacemakers), intracranial articles of ferromagnetic material, a history of epileptic seizures and brain injuries or surgery. Particular attention should also be paid to the psychiatric side effects of rTMS, including the risk for switching into hypomania and manic states, particularly in patients with bipolar disorder, and de novo induction of psychotic symptoms (Padberg and Möller, 2003; Rush et al., 2000).

In conclusion, considerable evidence argues for the antidepressant efficacy of high-frequency rTMS over the left dorsolateral prefrontal cortex applied over 2–4 weeks, and rTMS may also be successfully used as an adjuvant antidepressant intervention. Patients with psychotic symptoms appear to respond only poorly to rTMS. There is no evidence that rTMS-associated antidepressant effects are stable beyond the end of rTMS treatment. Thus, continuation therapy should be planned and initiated as recommended by current clinical guidelines. Since the antidepressant efficacy of rTMS has still not been sufficiently proven owing to the methodological limitations of previous clinical trials, the results of several ongoing placebo-controlled multicenter trials in the US and Germany are expected to clarify the role of rTMS within the range of antidepressant interventions.

19.5 Annex 5: Additional information on vagus nerve stimulation

In the 1980s and 1990s vagus nerve stimulation (VNS) was developed in animal models for its putative anticonvulsant action. It was approved by the FDA and introduced into the routine treatment of therapy-resistant focal epilepsies about a decade ago. Theoretical considerations regarding the functional anatomy of the vagus nerve also projecting to areas of the brain relevant for generation and control of mood and emotions, but also observations of mood changes in epilepsy patients undergoing VNS, have triggered the application of VNS in depressive disorders (George et al., 2003). A NeuroCybernetic Prosthesis (NCP) System is used for VNS that consists of a pulse generator implanted into the thoracic wall and subcutaneously implanted bipolar leads linked to the left vagal nerve. This system has been investigated in a series of open and controlled clinical trials as part of an industrial development program, and the data of the complete trial set have been published (George et al., 2005; Nahas et al., 2005; Rush et al., 2000; Rush et al., 2005b; Rush et al., 2005a; Sackeim et al., 2001b).

The first open study (D-01) showed clinically meaningful effects over a period of 2 years, with response rates between 42 and 45% (defined as at least 50% reduction of baseline HAMD scores) and remission rates between 21 and 22% (Rush et al., 2000; Sackeim et al., 2001b). However, all patients included in the first open study received additional antidepressant medication, which also was changed over time. The promising results of this open pilot study led to a double-blind randomized placebo-controlled multicenter trial (D-02 study) that included 235 patients who received either active or placebo stimulation during a 10-week period (Rush et al., 2005a).
After completion of the acute treatment period, all patients received continuous treatment, and long-term data on 205 patients following 12 months of stimulation were recently published (Rush et al., 2005b). Patients of the placebo group also received active treatment during the long-term period, and changes in the concomitant treatment (medication and psychotherapy) were allowed according to clinical requirements (‘treatment as usual’, TAU). The primary efficacy criteria of the acute study were the number of responders in the treatment groups. No difference between those groups was found in the acute study (15% response in the active vs. 10% response in the placebo group), nor were significant differences among the secondary efficacy criteria (self- and observer ratings) observed (Rush et al., 2005a). The negative finding in the acute study was discussed as being due to the low stimulation intensity applied in the active group (0.67 mA vs. 0.96 mA in the D-01 study). To make sense of the clinical meaning of the long-term data in terms of efficacy, a comparison study was initiated (D-04) that included 124 patients receiving only TAU (George et al., 2005). This study had the same inclusion criteria as the D-02 study: chronic depressive episode (duration longer than 2 years) or recurrent depression (more than four episodes, including the current episode), an HAMD baseline score > 20 and non-response after two to four appropriate antidepressant medication trials. After 12 months, a clinical response was found in 29.8% of the patients included in the D-02 study, whereas only 12.5% responded in the D-04 study; remission was achieved in 17.1% of the D-02 study compared with 6.7% of the D-04 study (George et al., 2005).

Concerning the safety of VNS, the results of the studies in epilepsy were essentially confirmed. Following the acute period, the D-02 study found voice alterations, increased cough, dyspnea, neck pain, dysphagia, laryngismus, paraesthesia and pharyngitis (Rush et al., 2005a). During long-term treatment over 1 year most of these adverse events showed a clear decline (Rush et al., 2005b).

Based on the efficacy and safety data, the VNS therapy system was recently approved by the FDA for the adjuvant, long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.

Despite the recent FDA approval, the body of evidence testifying that VNS exerts antidepressant effects superior to placebo is still limited and mainly based on long-term data compared with naturalistic treatment. A placebo-controlled trial is urgently needed to clarify the issues arising from the D-02 acute study, and to provide more data for the efficacy of VNS in depression. Because of its invasive nature, VNS should be reserved for special clinical cases where the patient’s demand for this treatment is high, several other interventions have failed and a clinical benefit is likely. VNS should only be used where thorough medical follow-up can be guaranteed.

19.6 Annex 6: Additional information on acupuncture

19.6.1 Efficacy

Due to the fact that the use of complementary and alternative therapies is overrepresented in patients suffering from depressive syndromes (Kessler et al., 2001), the actual knowledge about the main therapeuic options in this field need to be evaluated. The history of acupuncture in Eastern culture goes back more than 4000 years, and traditional Chinese medicine describes its influence on the balance of health and energy in the human body. The original practice involves inserting needles into specific trigger points at different parts of the body. Electro-acupuncture (EA) includes electrical stimulation of classical trigger points using sine wave and undulatory wave stimulation of different frequencies. An influence on β-receptor function (Fan, 1992) and central serotonergic (Fan, 1992) and noradrenergic (Meng et al., 1994) functions in depressed patients responding to EA has been suggested.

Despite a variety of published studies in this field, a recent review describes insufficient evidence to determine the efficacy of acupuncture in comparison with pharmacological antidepressant treatment (Smith and Hay, 2005). The cause for this uncertainty is the methodological quality of the investigations published up to now. Nevertheless, some of these controlled studies are presented below to describe the present state of information.

In a comparative randomized controlled trial 20 patients suffering from depression were treated with traditional acupuncture or the TCA amitriptyline. No significant differences between the treatment groups could be seen, but due to the relatively small number of patients, the study seems to be underpowered (Yang et al., 1994). Further studies investigated EA in comparison with amitriptyline and placebo in an analysis of two separate study parts. Again, therapeutic effects in the treatment groups showed no significant differences. A better therapeutic effect on anxiety and cognitive symptoms following acupuncture has been...
described (Allen and Schnyer, 1998). Similarly, a variety of Chinese RCTs found no significant differences between EA or computerized EA and amitriptyline treatment (Luo et al., 1985; Luo et al., 1988; Luo et al., 1990b; Luo et al., 1990a; Luo et al., 1998) (see (Luo et al., 1995; Meng et al., 2002) for review).

A further study compared acupuncture for depression with acupuncture for other complaints and a group of patients waiting for treatment (n = 35). Patients receiving depression-specific acupuncture showed significantly more improvement than the group receiving non-specific acupuncture, but no significant difference from the placebo condition in waiting-list patients could be seen (Allen and Schnyer, 1998). A single blind study also compared depression-specific and non-specific acupuncture with mianserin monotherapy in a total of 70 patients. Additionally, acupuncture improved depression more than treatment with mianserin. No differences between either forms of acupuncture could be seen (Roschke et al., 2000). Moreover, specific acupuncture showed a greater and lasting amelioration of symptoms in women suffering from depression during pregnancy (Manber et al., 2004). Other authors describe some evidence for the clinical effectiveness of acupuncture, but mention that further studies are needed before recommendations can be made (Gallagher et al., 2001; Manber et al., 2002). Note also that to be able to compare different investigations will require not only randomized controlled trials of adequate power but also a detailed description of standardized procedures in acupuncture. Finally, adequate blinding of physicians and patients together with standardized outcome measures are also needed before clinical and scientific recommendations can be made (Smith and Hay, 2005).

19.6.2 Safety and tolerability

An overall good safety and tolerability of acupuncture has been described. Especially in trials comparing TCA with acupuncture, typical side effects were much less in the acupuncture groups (American Psychiatric Association, 1994). Studies comparing modern and better-tolerated antidepressants have not been published up to now.

19.7 Annex 7: Additional information on chronotherapeutics: light and wake therapy

Chronotherapeutics refers to treatments that modulate the circadian and seasonal rhythms of mood and sleep regulation. These manipulations include wake therapy (sleep deprivation), sleep-phase advance therapy and light therapy (Wirz-Justice et al., 2005).

19.7.1 Wake therapy

Numerous studies have confirmed that the majority of patients with depression who abstain from a night’s sleep obtain immediate relief from depression (Kuhs and Tölle, 1991; Ostenfeld, 1973; Wu and Bunney, 1990), often with full, although temporary remission. This effect appears to be most pronounced in patients with bipolar illness and in those with diurnal or day-to-day mood variation (Kuhs and Tölle, 1991). The mechanism of action is unknown but may rest on the reduction of REM sleep, which is believed to be depressogenic (Riemann et al., 1994). Wake therapy has been – and remains in many countries – a standard method for treating depression, most often as an augmentation strategy with drug treatment. Wake therapy is used either in the form of a whole night’s waking (total sleep deprivation) or staying awake in the latter part of the night (partial sleep deprivation). A procedural elaboration, which sustains the first-day benefit, is to use sleep deprivation followed by a sleep phase advance in which the habitual sleep time is gradually approached over several nights (Berger et al., 2003; Voderholzer et al., 2003). Used on its own, a substantial number of patients will relapse into depression when resuming normal sleep (Wu and Bunney, 1990). However, new methods have been developed over the last decade that are designed to maintain the antidepressant response of wake therapy (Neumeister et al., 1996; Wirz-Justice et al., 2005). The simplest form simply repeats wake therapy for a number of nights, with recovery nights interspersed. A simple and well-tested protocol repeats wake therapy three times over a period of 5 days (Colombo et al., 2000). Other methods to sustain the antidepressant effect of sleep deprivation include combination with antidepressant drugs, pindolol, lithium and the use of bright light therapy, all of which have been shown to effectively reduce the relapse into depression after wake therapy (Benedetti et al., 1999; Colombo et al., 2000; Smeraldi et al., 1999; Szuba et al., 1994). Even though wake therapy is almost exclusively used in an inpatient setting for both inpatients and visiting outpatients, one study has been carried out using home wake treatment (Loving et al., 2002). The switch rate into mania for bipolar patients is no higher than with the use of antidepressant drugs (Colombo et al., 1999), and the suicide risk does not appear to be increased (Kuhs and Tölle, 1991; Vovin and Fakturovich, 1985). Caution is, however, warranted in
the course of wake therapy due to occasional steep mood swings experienced in the course of the protocol. There is some evidence to suggest that patients with high levels of anxiety and panic attacks improve less from wake therapy and that they may develop panic attacks on the day after sleep deprivation (Roy-Byrne et al., 1986). The research field needs larger trials with suitable control groups to assess the absolute magnitude of the wake therapy effect and trials of longer duration to assess the relapse pattern in different patient groups. A treatment manual (Benedetti et al., 2006) and guidelines are in preparation.

19.7.2 Light therapy

The modern and systematic use of light treatment in psychiatry stems from the observation by Rosenthal and colleagues in the early 1980s of recurrent winter depression and the subsequent evidence that light treatment alleviated the depressive symptoms (Rosenthal et al., 1984). Seasonal affective disorder (SAD) is now incorporated in the DSM-IV diagnostic system as a subtype of major depression (‘with seasonal pattern’) (American Psychiatric Association, 1994). Light therapy has seen an extensive research effort, and its antidepressant effect and chronobiological effects have now been established in several systematic reviews and in many clinical studies (Golden et al., 2005; Kripke, 1998; Terman and Terman, 2005; Tuunainen et al., 2004; Winkler et al., 2005b). Light treatment has been used in SAD as a monotherapy and in non-seasonal depression (chronic and recurrent) both as a monotherapy and as augmentation with drugs. Light treatment is performed by the use of a light box that produces 10000 lux, wide-screen, ultraviolet-filtered diffuse white fluorescent light. Narrow-band spectra with blue or green appearance have been investigated, but the data are insufficient to recommend their use. Additionally, there is a suspected retinal hazard of blue-light exposure, which may damage retinal structures and exacerbate age-related macular degeneration (Remé et al., 2001). Light boxes come in many designs, but larger screens that emit diffuse light are best tolerated and maximize desired stimulation of the peripheral retina.

Light treatment from ambulatory, battery-powered light visors is available, but controlled data have not shown a benefit relative to placebo dim light. Another variant is gradually incremental dawn simulation that mimics outdoor sunrise in the bedroom, where the signal is often absent or deficient. This method uses far lower light intensity than in post-awakening bright light therapy, yet has shown efficacy in several trials of SAD, where a simulated springtime sunrise is presented in winter (Avery and Norden, 1998). Finally, going outdoors into natural sunlight can be effective, assuming good weather conditions and seasonal availability of early morning sunlight (Wirz-Justice et al., 1996).

Treatment duration is in the range of 30 minutes to 1 hour, preferably in the morning upon awakening. A dose-response effect has been confirmed, thus enabling treatment regimens with shorter exposure duration at higher intensity (Søndergaard et al., 2006; Terman et al., 1990). For SAD, the duration of treatment extends throughout the dark season in order to forestall relapse (Lam et al., 1999). For non-seasonal depression, light therapy presumably works as an accelerating agent in combination with drugs, although recent evidence indicates only a short-lived positive effect when the lights are discontinued (Martiny, 2004; Martiny et al., 2006). Light treatment in non-seasonal depression should thus optimally be used until remission is reached and sustained for at least 8–12 weeks of daily treatment; it can easily be resumed if there is subsequent relapse. The use of light treatment thus far has not shown any long-term damage to the visual system (Remé et al., 2001). Acute side effects are limited to milder degrees of headache and blurring of vision, and nausea and irritability, which can be alleviated by decreasing light intensity or increasing the distance from the screen. Hypomania can occur but is often of milder degree and short-lived when light is discontinued. Patients with bipolar disorder should use light therapy only in conjunction with mood-stabilizing medication (Terman and Terman, 1999).

19.8 Annex 8: Additional information on psychotherapy

Empirically supported psychotherapies are potent alternatives to and augmenters in combination with antidepressant medications. Although psychotherapies have received less study than pharmacotherapies, randomized controlled studies have demonstrated the efficacy of some psychosocial interventions, acutely and as maintenance treatments, both as monotherapies and in combination with medication as antidepressant treatments. The empirically based psychotherapies, principally cognitive behavioral therapy (CBT) (Beck et al., 1979), interpersonal psychotherapy (IPT) (Weissman et al., 2000) and behavioral therapy (e.g. Martell et al., 2001), have advantages and disadvantages relative to pharmacotherapy, and differential benefits may exist among
these psychotherapies for depressed patients with particular moderating factors.

Most psychotherapy outcome research has involved individual psychotherapy, although group and family therapies have received some study. Empirically validated treatments are time-limited, diagnosis-focused and address current life problems rather than the past. Of the many forms of extant psychotherapy, only a few have received empirical assessment; the antidepressant benefits of the remainder remain unclear.

19.8.1 Psychotherapies as primary treatment for mood disorders

After decades of psychotherapists avoiding structured research, researchers in the 1970s began to conduct randomized controlled trials (RCTs) of psychotherapies for non-delusional outpatients with depressive disorders. In addition to incorporating research paradigms from pharmacotherapy trials (e.g. random assignment, blinded independent assessment), researchers wrote manuals to define particular treatment approaches, such as CBT and IPT. Treatment sessions were recorded to ensure therapist adherence to the treatment approach, which was reinforced by frequent supervision. Psychotherapies were initially compared with waiting lists or low-contact conditions, but increasingly also to active treatments, including antidepressant medication (e.g. Elkin et al., 1989).

These trials yielded repeated evidence of the efficacy of CBT and IPT as treatments for depressive disorders (Hollon et al., 2005), leading to their incorporation into national and professional treatment guidelines (American Psychiatric Association, 2000; Depression Guideline Panel, 1993; Karasu et al., 1993; Roth and Fonagy, 2004). Lacking funding from an industry, psychotherapy researchers have conducted fewer trials than pharmacotherapy researchers. In general, empirically supported psychotherapies have demonstrated similar response and remission rates to pharmacotherapy for outpatients with depressive disorders. They treat mood and demoralization more quickly than neurovegetative symptoms of depression, the reverse of the pattern seen for antidepressant medications. Beyond acute efficacy, IPT and CBT have been shown to provide prophylaxis against relapse and recurrence when prescribed as less frequently scheduled (e.g. monthly) maintenance treatments (Frank et al., 1990; Hollon et al., 2005). Studies of CBT suggest an enduring effect even for acute psychotherapy, a lasting protective benefit not seen when pharmacotherapy is discontinued (Hollon et al., 2005). This presumably indicates that psychotherapy provides patients with methods for handling new psychosocial problems, potential triggers of depressive episodes that arise in their lives after acute treatment ends.

The empirical evidence for psychotherapy as monotherapy for chronic depression is sparser and less strong. The Cognitive Behavioral Analysis System of Psychotherapy (CBASP) (McCullough, 2003) was as efficacious as nefazodone both acutely and as maintenance treatment in one large (n=681) study of chronic depressive disorders; the combination of nefazodone and CBASP was superior to either monotherapy (Keller et al., 2000). This impressive finding requires replication, as it is the only CBASP trial published to date. IPT and CBT have shown less benefit than pharmacotherapy for dysthymic patients (Markowitz et al., 2005; Ravindran et al., 1999), albeit combined IPT and sertraline was cost-effective relative to pharmacotherapy alone in one study (Browne et al., 2002).

19.8.2 Combination treatment with antidepressant medication and psychotherapy

Combined treatment studies often have been confounded by inadequate power, differential attrition and other methodological difficulties. Large sample sizes are required to find differences between active monotherapies and combined treatment. Nonetheless, no research trial has shown combined treatment to be less efficacious than antidepressant monotherapy (Manning et al., 1992). Given health economics considerations, combined treatment may best be reserved for patients with chronic, highly comorbid, severe depressions, or those at high suicide risk (Hollon et al., 2005; Rush, 1999). In an open trial in menopausal depressed women cognitive therapies have been shown to enhance the efficacy of the SSRI fluoxetine especially in combination treatments. As a possible mechanism of action a better normalization of serotonin and noradrenaline levels has been suggested (Gaszner, 2005).

19.8.3 Psychotherapy as adjunct to pharmacotherapy

Some depressed patients remit on antidepressant medication and require no additional treatment. Others, particularly chronically depressed patients, may improve symptomatically yet still function less than optimally, or feel unsure about social risks or career decisions. Such patients may benefit from adjunctive psychotherapy (Markowitz, 1993) to expand their social confidence or behavioral repertoire. In addition, so-called sequential therapy, the use of CBT...
after remission achieved with antidepressants for acute treatment, may be of use (see (Fava and Ruini, 2002) for review).

19.8.4 Differential therapeutics

Behavioral therapy helps patients to schedule pleasurable activities while avoiding painful ones. Cognitive therapy, usually combined with behavioral techniques, helps patients to identify cognitive distortions with depressive biases, thoughts that are unnecessarily painful, pessimistic and which inhibit potentially valuable activity. IPT defines depression as a medical disorder and focuses on the connection between mood and social situations or life circumstances; it has been shown to build social skills. Understandably, these therapies may have differing appeals and benefits for different depressed individuals.

A few RCTs have directly compared IPT and CBT (Elkin et al., 1989; Rossello and Bernal, 1999) or cognitive therapy and behavioral therapy (Jacobson et al., 1996). While showing non-significant differences in outcome, these trials allowed evaluation of moderators of treatment outcome. For example, patients with poor concentration may respond better to IPT than CBT, whereas those with a paucity of social skills may fare better in CBT than IPT (Sotsky et al., 1991). Far more research of differential therapeutics is needed.

19.8.5 Comparing medications and psychotherapies

Medications work faster than psychotherapies and are easier to administer to large populations, although the therapeutic alliance is equally important for both antidepressant modalities (Krupnick et al., 1996). Empirically validated psychotherapies lack medication interactions, and have low adverse effects and little risk of inducing mania in depressed bipolar patients. They may address social stressors, such as marital pressures, that could potentially trigger future episodes. Psychotherapies have potential advantages for depressed women during pregnancy and nursing; may be better accepted by adolescents, particularly given recent concerns about serotonin reuptake inhibitors in this population; and although not well tested for depressed children, may be indicated inasmuch as medication has not shown benefit. In non-industrialized countries, such psychotherapies may be the only feasible, affordable treatments for depression (Bolton et al., 2003). Psychotherapies adapted to different cultures must address the specific needs and sensitivities of individuals in those cultures.

Psychotherapies are not intended to treat depression with psychotic features, nor as monotherapy for bipolar I disorder (Frank et al., 2005; Miklowitz et al., 2003). Some severely depressed patients may be too depleted to engage in psychotherapy effectively. Patient preference is a predictor of treatment outcome and hence deserves consideration in treatment selection.

On the basis of their performance in controlled efficacy trials, IPT and CBT should be included in algorithms of standard treatment for depressive disorders.

19.8.6 The attitude to CBT and IPT in Korea

Evidence-based medicine has begun to influence the field of mental health in response to demands for accountability and to address the well-documented disparity between scientific evidence and actual practice (Chatterjee et al., 2006). Psychotherapy is widely practiced but has been less intensively studied than pharmacotherapy because it has no industry to fund it. Nevertheless, several prominent studies have demonstrated the effectiveness of psychological approaches in patients with depression.

Practice guidelines published by several countries, including the UK (National Institute for Health and Clinical Excellence, 2004), US (Beutler et al., 2000) and Canada (Segal et al., 2001b; Segal et al., 2001a) suggest that psychotherapies for depression such as CBT and IPT are equivalent to drugs in terms of efficacy (DeRubeis et al., 1999; DeRubeis et al., 2005; Hollon et al., 2002).

In Korea, pharmacotherapy for depression is widely used. CBT was introduced, but few RCTs of CBT in patients with depression have been published. Moreover, little is known about IPT among mental health professionals. Probably the most serious problems are the lack of IPT therapists (or supervisors) and a lack of systematic training programs. Our task is to resolve these problems.

Efficacious psychotherapies such as CBT and IPT are both primary treatments and alternatives to pharmacotherapy for depression. The issue of combined psychotherapy and pharmacotherapy deserves consideration. Many clinicians recommend combined treatment for patients with depression, based simply on the belief that combined treatment is more effective than either pharmacotherapy alone or psychotherapy alone. However, a meta-analysis showed that combined therapy is superior to psychotherapy alone for treatment of more severe, recurrent depression (Thase et al., 1997). Combined treatment and antidepressant...
alone, however, have similar efficacy and acceptability (de Mello et al., 2005; Markowitz et al., 2005). This absence of an adjunctive effect for psychotherapy seems counterintuitive.

Note that several characteristics of patients and disorders have been related to differential treatment response. Some studies show that psychotherapy helps to keep patients in pharmacotherapy (Pampallona et al., 2004) and to discontinue medication without increasing the risk for subsequent relapse or recurrence (Hollon et al., 2005). Combined treatment is likely to be recommended for patients with more complex or chronic disorders, or with a clinically unsatisfactory response to either monotherapy (Hollon et al., 2005). Yet whether combined treatment is more effective than either monotherapy is controversial. Further studies are required.

19.9 Annex 9: Additional information on antidepressant drugs in the treatment of anxiety disorders

The proven efficacy of antidepressant drugs in relieving anxiety symptoms in patients with depressive disorders naturally led to investigations of their potential to relieve symptoms and reduce associated disability in patients with anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, social phobia (also known as social anxiety disorder), post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). In clinical practice, the need for treatment should be determined by the severity and persistence of symptoms, and the level of disability and impact on social functioning; choice of treatment is influenced by patient characteristics (such as previous response, concomitant medication and contraindications), the evidence base supporting its use, patient and physician preference, and the local availability of the proposed intervention (Baldwin and Polkinghorn, 2005). In general, in comparison with mood disorders higher doses and longer time of treatment are required to achieve response in anxiety disorders.

19.9.1 Generalized anxiety disorder

In GAD, systematic reviews and placebo-controlled randomized controlled trials (RCTs) indicate that some SSRIs (escitalopram, paroxetine and sertraline), the SNRI venlafaxine, and the TCA imipramine are all efficacious in acute treatment (Baldwin and Polkinghorn, 2005; Mitte et al., 2005). The small number of comparator-controlled studies reveals no consistent differences in efficacy between active compounds (Mitte et al., 2005). Psychological symptoms of anxiety may respond better to antidepressant drugs than to benzodiazepines (Baldwin and Polkinghorn, 2005). Double-blind studies in patients who have undergone acute treatment indicate that continuing with an SSRI or SNRI is associated with a further increase in overall response rates. Relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication (escitalopram or paroxetine), compared with switching to placebo, for up to 6 months (Baldwin and Polkinghorn, 2005). When delivered singly, pharmacological and psychological treatments have broadly similar efficacy in acute treatment, but the comparative efficacy of drug and psychological approaches over the long term is not established. It is uncertain whether combining drug and psychological treatments is associated with greater efficacy than with either treatment given alone (Baldwin and Polkinghorn, 2005).

19.9.2 Panic disorder

Randomized double-blind placebo-controlled trials of antidepressants indicate that all TCAs (clomipramine, imipramine), and the SNRIs venlafaxine and the NARI reboxetine are efficacious in acute treatment. Comparator-controlled studies provide some evidence for the efficacy of mirtazapine and moclobemide. The side-effect burden associated with SSRI treatment in panic disorder is somewhat less than with other classes of psychotropic drugs (Baldwin and Birtwistle, 1998). Following acute treatment, continuing with SSRIs or clomipramine is associated with an increase in overall response rates, and placebo-controlled and other relapse-prevention studies in patients who have responded to acute treatment reveal a significant advantage for staying on active medication (fluoxetine, paroxetine, sertraline, imipramine) compared with switching to placebo, for up to 6 months (Baldwin and Polkinghorn, 2005). Pooled analyses and RCTs indicate that drug and psychological treatments, delivered singly, have similar efficacy in acute treatment, but suggest that CBT may be superior to TCAs in preventing symptomatic relapse (van Balkom et al., 1997). It has been mentioned that there is some uncertainty whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment given alone (Barlow et al., 2000; van Balkom et al., 1997), but a recently published meta-analysis showed that combined therapy was more effective.
than pharmacotherapy alone and was as effective as psychotherapy (Furukawa et al., 2006). Therefore, either combined therapy or psychotherapy alone has been recommended as a first-line treatment for panic disorder.

19.9.3 Social phobia

Systematic reviews and placebo-controlled RCTs indicate that a range of antidepressants are efficacious, including most SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), the SNRI venlafaxine, the MAOI phenelzine, and the RIMA moclobemide. Double-blind studies indicate that continuing SSRI or SNRI treatment from 12 weeks to 24 weeks is associated with an increase in overall treatment response rates. Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on antidepressant medication (escitalopram, paroxetine and sertraline), compared with switching to placebo for up to 6 months (Baldwin and Polkinghorn, 2005; Blanco et al., 2003). When delivered singly, pharmacological and psychological treatments have broadly similar efficacy in acute treatment, but acute treatment with cognitive therapy may be associated with reduced risk of symptomatic relapse at follow-up. It is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment given alone (Baldwin and Polkinghorn, 2005; Blanco et al., 2003).

19.9.4 Post-traumatic stress disorder

Randomized, placebo-controlled trials provide evidence for the efficacy of some SSRIs (fluoxetine, paroxetine and sertraline), the SNRI venlafaxine, the TCAs amitriptyline and imipramine, the MAOI phenelzine and mirtazapine on some outcome measures (Baldwin and Polkinghorn, 2005; Stein et al., 2000). Following response to acute treatment, continuing with venlafaxine or sertraline treatment over 6 months is associated with a gradual increase in overall treatment response. Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication (clomipramine, paroxetine, sertraline and fluoxetine, at higher dose), compared with switching to placebo (Fineberg and Gale, 2005). Combining treatment approaches may be superior to psychological approaches or serotonergic antidepressant treatment given alone. The evidence for enhanced efficacy of exposure therapy with clomipramine compared with exposure alone is inconsistent, but fluvoxamine has been shown to enhance the efficacy of exposure therapy and CBT. Relapse rates may be greater after initial treatment with a pharmacological rather than a psychological intervention (Simpson et al., 2004).

19.10 Annex 10: List of regional meetings and countries represented

<table>
<thead>
<tr>
<th>Regional meeting</th>
<th>Participating countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Petersburg, Russia</td>
<td>Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyz Republic, Russia, Ukraine, Uzbekistan</td>
</tr>
<tr>
<td>Munich, Germany</td>
<td>Austria, Denmark, Germany, Greece, Croatia, Czech Republic, Hungary, Poland, Serbia, Slovakia, Switzerland</td>
</tr>
<tr>
<td>Shanghai, China</td>
<td>Australia, China, Hong Kong, Indonesia, Japan, Korea, Pakistan, Philippines, Singapore, Taiwan, Thailand</td>
</tr>
<tr>
<td>Caracas, Venezuela</td>
<td>Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Honduras, Mexico, Nicaragua, Panama, Peru, Uruguay, Venezuela</td>
</tr>
<tr>
<td>Paris, France</td>
<td>France, Egypt, Luxembourg, Morocco, Spain, Sweden, Tunisia, Turkey</td>
</tr>
</tbody>
</table>
19.11 Annex 11: Suggestions concerning the organization of national review meetings

Aims of the meeting

The national meetings should help to bring together the experience and evidence about the use of antidepressant medications in the treatment of depressive disorders obtained in the countries where the meetings are taking place.

Participants

Participants in national meetings should be experts representing the fields of psychiatry, pharmacology, internal medicine and general practice, government officials dealing with mental health and with questions of medications, representatives of family or patient organizations, and persons representing insurance and the pharmaceutical industry. In all, it is expected that 12–15 participants will take part in the national meetings. Subsequently, it would be useful to bring the results of the review to the knowledge of larger audiences, both professional and non-professional, representing the stakeholders involved in the care for people with depressive disorders.

The agenda and method of work

All the participants should receive the CINP Technical Review in the language that they can easily use. The CINP Technical Review has been translated into Chinese, English, French, Russian and Spanish. It is also probable that an Arabic version will be prepared shortly. In some instances, a translation into the national language will be necessary. The meetings should take place after the participants have had a chance to examine the review and prepare their notes and proposals about additions, comments and changes that would reflect the national experience and evidence obtained locally and which has not been included in the review. The agenda should include a detailed examination of the CINP Technical Review and a discussion that will lead to the formulation of a national report to be added to and considered in conjunction with the review.

Administrative steps

The convener of the national meeting should prepare a list of participants, a detailed agenda and a timetable for the meeting indicating its location and proposed dates. The proposal should also list the members of the CINP Task Force or other experts that the convener would like to invite as resource persons to the meeting.

A budget for the meeting should be prepared, including expenditures for travel and accommodation of the participants, the cost of translation into the national language and the cost of hiring the meeting location if necessary. No honoraria should be requested. Proposals should be sent to Prof. N. Sartorius as soon as possible so that they can be included in the summary of work and proposals that will be submitted to the CINP.

Publication of findings

It is expected that each of the national meetings will produce a local publication in the national language or in English. The publication should assemble the points that will be relevant for the use of antidepressant medications in the country. Should the group decide to also publish the Technical Review in the national language the convener should inform the CINP accordingly. The national reports will be brought together, and their findings will be published in an international journal together with an update of the Technical Review (should an update prove to be necessary). The publications will be posted on the CINP website, together with the review.

19.12 Annex 12: Additional information on the European Federation of Associations of Families of People with Mental Illness (EUFAMI)

EUFAMI, the European Federation of Associations of Families of People with Mental Illness, is the representative body for voluntary organizations throughout Europe, promoting the interests and well-being of people with mental illness and their carers. Founded in 1992, EUFAMI is a democratic, member-led organization, registered in Brussels, under Belgian law. EUFAMI was formed by members of carer organizations who, overwhelmed by the trauma of severe mental illness in the family, and finding their ability to cope undermined, shared their experience of helplessness and frustration, and resolved to work together to help themselves and the people that they care for. Today, EUFAMI has 48 member organizations from 1 non-European and 26 European countries.

EUFAMI’s aims are to ensure the continuous improvement throughout Europe – and by association around the world – of the quality of care and welfare for people with mental illness and their families. To meet this need, EUFAMI lobbies governments to provide appropriate financial support for families and carers as an integral part of their budget. EUFAMI also works to establish a charter of rights of families
of carers and offers its services in teaching health professions and planning services for the mentally ill.

19.12.1 EUFAMI’s aims

- To achieve continuous improvement throughout Europe in mental health generally, in the quality of care and welfare for mentally ill people, and in the level of support for their caring relatives and friends.
- To enable member associations to combine their efforts and act jointly at the European level to achieve those aims.
- To strengthen and assist member associations in their effort to improve mental health conditions in their own territories, while fully respecting their national or regional autonomy.

19.12.2 EUFAMI’s principles

- Carers must be acknowledged as equal partners with professionals in the care team supporting the person with mental illness.
- Carers need support in their own right and have independent needs which must be recognized and respected.
- All people with mental illness should be cared for in an appropriate environment and provided with a comprehensive range of health-care and social care services.
- All people with mental illness should have the right to share in the opportunities, enjoyments, challenges and responsibilities of everyday life.

19.12.3 EUFAMI’s mission

- Contribute to removing the stigma surrounding mental illness by promoting positive images to counteract ignorance and misinformation.
- Highlight examples of good practice in the field of mental illness in order to promote good practice throughout Europe; identify examples of bad practice in the field of mental illness and campaign for positive change.
- Lobby for greater equality of legislation throughout Europe in order to bring about improvements in the health and social care of people with mental illness, and in the well-being of their carers.
- Promote and support further research into the causes and treatment of mental illness.
- Campaign for adequate resources for the health and social care of people with mental illness and their carers.

19.13 Annex 13: List of Advisors

AGUILAR Mario, Vice-President, Honduran Society of Psychiatry maguilarhn@yahoo.com

ALEMAN Luis Enrique, Secretary of the Nicaraguan Society of Psychiatry, Masaya lueman@ibw.com.ni; hijproye@ibw.com.ni

ALLAIN Hervé, Laboratoire de Pharmacologie, Université de Rennes I – Faculté de Médecine, 35043 Rennes Cedex, France Herve.Allain@univ-rennes1.fr

ALLILAIRE Jean-François, Chef du Service de Psychiatrie (Adultes), Consultation Chaslin, Hôpital de la Salpêtrière, 47, Bd de l’Hôpital, 75651 Paris Cedex 13, France jf.allilaire@psl.ap-hop-paris.fr

ALVAREZ M. Carmen, General Secretary, Venezuelan Society tatatiu@movistar.net.ve

ANSSEAU Marc, Chairman of the, Department of Psychiatry, University of Liège, B-4000 Liège, Belgium psychiatrie@ulg.ac.be

AVEDISOVA Alla, Head of New Drugs Division, Serbsky Centre for Social and Forensic Psychiatry, Moscow, 123367, Russia aavedisova@hotmail.com

AZORIN Jean-Michel, SHU Psychiatrie Adultes, Hôpital de Sainte-Marguerite, 13274 Marseille Cedex 09, France clancon@ap-hm.fr

BAUER Michael, Head of the Department of Psychiatry and Psychotherapy, Universitätsklinikum Carl Gustav Carus, D-01307 Dresden, Germany Michael.Bauer@uniklinikum-dresden.de

BAUMANN Pierre, University Department of Psychiatry, Site de Cery, CH-1008 Prilly-Lausanne, Switzerland pierre.baumann@chuv.ch

BECH Per, Psychiatric Research Unit, Frederiksberg General Hospital, 3400 Hillerød, Denmark pebe@fa.dk

BELFORT Edgard, WPA Zonal Representative, WFMH Board of Directors, Caracas 1010, Venezuela belfорт.ed@cantv.net; wpazone4@cantv.net

BELMAKER R.H., Beersheva Mental Health Center, Beersheva, Israel belmaker@bgumail.bgu.ac.il

BERK Michael, Barwon Health and Geelong Clinic, Swanston Centre, The University of Melbourne, Geelong, Victoria 3220, Australia mikebe@barwonhealth.org.au
FURUKAWA Toshiaki, Chair of the Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya 467-8601 Japan furukawa@med.nagoya-cu.ac.jp

GALLEGOS Rogelio, Mexican Health National Service Representative, Mexico rogeligallegos@hotmail.com

GASTELUMENDI Eduardo, Director, Neurosciences Institute; Past-President of the Peruvian Society of Psychiatry egastel@rcp.net.pe

GASZNER Peter, Országos Pszichiátriiai És Neurológiai Intézet, 1021 Budapest, Hungary h12890gas@ella.hu

GAVIRIA Silvia Sgaviria1@epm.net.co

GERARD Alain, Psychiatrist, Paris, France al.gerard@free.fr

GGINNARI ANTICH Guillermo, President, Venezuelan Society of Psychiatry, Caracas gginnari@cantv.net

GODARD Nathalie, Child Psychiatrist, Director of a private institution, Garches, France

GONZALEZ Celso, Psychiatrist Researcher, University General Hospital celsohuc@cantv.net

GOODWIN Frederick, 5712 Warwick Place, Chevy Chase, MD 20815, USA drgoodwin@aol.com

GORWOOD Philip, Paris, France philip.gorwood@lmr.ap-hop-paris.fr

GRIGORIEVA Elena A, Head of the Department of Psychiatry, Yaroslavl Medical Academy, Yaroslavl, 150000, Russia prof.gri-orieva@mail.ru

GU Niufan, Shanghai Mental Health Center, Shanghai, 200030 guniufc@hotmail.com

GUREJE Oye, Head of the Department of Psychiatry, University College Hospital, Ibadan, Nigeria gureje.o@skannet.com.ng

HAEN Ekkehard, Psychiatrische Universitätsklinik, Medizinische Einrichtungen des Bezirks Oberpfalz, 93053 Regensburg, Germany ekkehard.haen@medbo.de

HEALY David, North Wales Department of Psychological Medicine, Cardiff University, Hergest Unit, Ysbyty Gwynedd, Bangor, Wales LL57 2PW, UK David.Healy@nww-tr.wales.nhs.uk

HE Yanling, Shanghai Mental Health Center, Shanghai, 200030 heyl@sh163.net; heyl@public9.sta.net.cn

HEGERL Ulrich, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Universitätspoliklinikum Leipzig, Johannisallee 20, D-04317 Leipzig, Germany krausem@medizin.uni-leipzig.de

HINDMARCH Ian, HPRU Medical Research Centre, University of Surrey, Guildford, Surrey GU2 7XP, UK i.hindmarch@surrey.ac.uk

HÖSCHL Cyril, Director, Prague Psychiatric Center, 181 03 Praha 8, Czech Republic hoschl@ pcp.lf3.cuni.cz

HU Teh-Wei, Professor of Health Economics, University of California, School of Public Health, Berkeley, CA 94720, USA. thu@berkeley.edu

HWANG Tae-Yeon, Director, WHO Collaborating Center for Psychosocial Rehabilitation and Community Mental Health, Yongin Mental Hospital, Korea lilymh@dreamwiz.com; lilymh@empal.com

IRMANSYAH, Psychiatrist, Department of Psychiatry, Faculty of Medicine, University of Indonesia, Jakarta 10430, Indonesia irmans@indo.net.id

ISACSSON Goran, Karolinska Institute, Huddinge University Hospital, S-141 86 Stockholm, Sweden Goran.Isacsson@neurotec.ki.se

ISMAYILOV Nadir, Azerbaijan Medical University, Baku inadir@azdata.net

IVANOV Michail, Head of the Department of Psychopharmacotherapy of the Bekhterev Psychoneurological Institute, St-Petersburg 192019, Russia spbinsb@infopro.spb.su

IVONOVIC Fernando, Head of Bipolar Disorders Unit, Chile University ferlore@vtr.net

JAKOVLEVIC Miro, Department of Psychiatry, School of Medicine, University of Zagreb, Zagreb – Rebro, Croatia pro-mente@zag.hinet.hr

JIAQ Kaida, Shanghai Mental Health Center, Shanghai, 200030 jiangkaida@sh163.net

KANBA Shigenobu, Department of Neuropsychiatry, Kyushu University, Fukuoka, 812-8582, Japan skanba@npsych.med.kyushu-u.ac.jp

KASAKOVTSEV Boris, Deputy Head of the section of legislative regulation of specialized medical care,
RUSH John A., Jr., M.D., Vice-Chair, Department of Clinical Sciences, Department of Psychiatry, University of Texas SW Medical Center, Dallas, TX 75390-7208, USA
John.rush@utsouthwestern.edu

SALAZAR Gerardo Carmelo B, Department of Neurosciences, Lucena United Doctors Hospital, Manila, The Philippines
gbsneuro@mozcom.com

SALAZAR Ismael, Director of the Mental Health Hospital Social Security
apal2002@hotmail.com; isalazarg@hotmail.com

SALETU Bernd, Section of Sleep Research and Pharmacopsychiatry, Department of Psychiatry, Medical University of Vienna, 1090 Vienna, Austria
bernd.saletu@meduniwien.ac.at

SANCHEZ Carlos, Assistant, Latin American Psychiatric Association
csanchez@cantv.net

SCHLAEPFER Thomas E., Psychiatry & Mental Hygiene, Department of Psychiatry, University Hospital, Bonn 53105, Germany
schlaepf@jhu.edu

SECHTER Daniel, Besançon, France
daniel.sechter@ufc-chu.univ-fcomte.fr

SEMKE Valentin, Director of the Institute of Psychiatry of the Tomsk Scientific Centre, Siberian Division of the Russian Academy of Medical Science, Tomsk, Russia
redo@mail.tomsknet.ru

SIMON Gregory, Group Health Cooperative of Puget Sound, Centre for Health Studies. Seattle, WA 98101, USA
simon.g@ghc.org

STEFFEN Sigrid, Vice-President, European Federation of Associations of Families of Mentally Ill People (EUFAMI), 5020 Salzburg, Austria
kus.steffen@aon.at

STUPPÄCK Christoph, Universitätsklinik für Psychiatrie 1, Christian-Doppler-Klinik, Salzburg, 5020 Salzburg, Austria
c.stuppaeck@salk.at

SULTANOV Agabek A., Gashumbekoğlu, Manager of the chair of Psychiatry Medical University, Baku, Azerbaijan
gerai@hotbox.ru

SUN Xueli, 7# Xiao Xue Road, Chengdu, Sichuan 610041
sunxueli@tom.com; sunxueli58@163.com

TAN Chay-Hoon, Department of Psychological Medicine, National University Hospital, Singapore 119074
phctanch@nus.edu.sg

TANG Siu-Wa, Chair of the Department of Psychiatry University of Hong Kong
psychiat@hku.hk

TEN Vladimir, Head, Department of Clinical Psychology and Psychiatry Kyrgyz State Medical Academy, Bishkek 720023, Kyrgyz Republic
psycho@freenet.kg

THASE Michael E., University of Pittsburgh Medical Center, Pittsburgh PA 15213-2593, USA
thaseme@upmc.edu

THIBAUT Florence, University Hospital Ch.Nicole, INSERM, Rouen, France
Florence.Thibaut@chu-rouen.fr

UDOMRATN Pichet, President, The Psychiatric Association of Thailand (PAT), Department of Psychiatry, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand
upichet@medicine.psu.ac.th

VAHIP Simavi, Affective Disorders Unit, Ege University Department of Psychiatry Bornova-Izmir TR-35100, Turkey
simavi.vahip@ege.edu.tr

VAN PRAAG Herman M., Huize Berghorst, 7315 HD Apeldoorn, The Netherlands
h.m.van.praag@vanpraag.com

VIETA PASCUAL Eduard, Director of Research, Clinical Institute of Neuroscience, Director of Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS, 08036 Barcelona, Spain
evieta@clinic.ub.es

WANG Liwei, Shanghai Mental Health Center, Shanghai, 200030, P. R. China
lwwang163@163.com

WATANABE Yasuo, Department of Pharmacology/Pharmacotherapy, Nihon Pharmaceutical University, Saitama 362-0806, Japan
yasuwat@nichiyaku.ac.jp; yasuwatnb@aol.com

WIED Viktor D., Deputy Director of the Bekhterev Psychoneurological Institute, St. Petersburg 192019, Russia
wied@nm.ru

WOOLEY Stéphanie, Présidente, Association France Dépression, 4, rue Vigée Lebrun, 75 015 Paris, France

YAN Heqin, Director, Shanghai Mental Health Centre, Shanghai
yanhq@gmail.com; yanhqn@online.sh.cn

YI Chengdong, Director General, Shanghai Food and Drug Administration Bureau, Shanghai
gaolei@smda.gov.cn
YOUDIM Moussa B.H., Director of Eve Topf and National Parkinson Foundation (US), Centers of Excellence for Neurodegenerative Diseases, Technion-Faculty of Medicine, Haifa, Israel.
Youdim@tx.technion.ac.il

YOUNG Allan Hunter, LEEF Chair in Depression Research; Associate Director, Institute of Mental Health; Department of Psychiatry, University of British Columbia, Vancouver, BC Canada V6T 2A1, Canada
alyoung@interchange.ubc.ca

XIAO Zeping, Shanghai Mental Health Center, Shanghai, 200030, P. R. China
xiaozeping@gmail.com

XIE Bin, Shanghai Mental Health Center, Shanghai, 200030, P. R. China
myzhang@online.sh.cn

XU Yifeng, Shanghai Mental Health Center, Shanghai, 200030, P. R. China
hyyyyb@online.sh.cn

YU, Xin, Director of the Institute of Mental Health, Peking University 100083, Beijing, P. R. China
yuxin@bjmu.edu.cn

ZHANG Li, Director, CDC on Mental Health, Ministry of Health, Beijing, P. R. China
zhangli1410@sina.com

ZHANG Mingyuan, Shanghai Mental Health Center, Shanghai, 200030, P. R. China
myzhang@online.sh.cn

ZHOU Dongfeng, President, Chinese Psychiatry Association
zhoudf@public.fhnet.cn.net

ZVARTAU Edvin, Vice-rector, St.-Petersburg State Medical University, St. Petersburg, Russia
zvartau@spmu.rssi.ru

20 Abbreviations

+ 5-HT₁ = serotonin 1 receptor stimulation
5-HT₂ = serotonin 2 receptor antagonism
5-HT₃c = 5-HT₃c receptor antagonist
5-HT₃ = serotonin 3 receptor antagonist
α₁ = α₁ receptor antagonist
α₂ = α₂-receptor antagonism
all. 5HTT = binding to the allosteric site of the serotonin transporter

ACTH = adrenocorticotropic hormone, corticotropin
ACNP = American College of Neuropsychopharmacology
AD = Alzheimer’s disease
ADH = antidiuretic hormone
ADHD = attention-deficit hyperactivity disorder
AHCPK = Agency for Health Care Policy and Research
AIDS = acquired immune deficiency syndrome
APA = American Psychiatric Association
APD = amphetamine prodrug
APOE = apolipoprotein E
BAC = blood alcohol concentration
Bcl-2 = B-cell lymphoma 2 (anti-apoptotic protein)
BDI = Beck Depression Inventory
BDNF = brain-derived neurotrophic factor
BPRS = Brief Psychiatric Rating Scale
CANMAT = Canadian Network for Mood and Anxiety Treatments
CBA = Cost-benefit analysis
CBASP = Cognitive Behavioral Analysis System of Psychotherapy

CBT = cognitive behavioral psychotherapy
CD = combined depression (MDD and RBD)
CGI-I = Clinical Global Impressions-Improvement Score
CDRS-R = Children’s Depression Rating Scale-Revised
CEA = cost-effectiveness analysis
CEAC = cost-effectiveness acceptability curve
CIDI = Composite International Diagnostic Interview
CINP = Collegium Internationale Neuro-Psychopharmacologicum
CNS = central nervous system
COX = cyclo-oxygenase
CRF = corticotropin releasing factor (=CRH)
CRH = corticotropin releasing hormone (=CRF)
CSF = cerebrospinal fluid
CSM = Committee on Safety of Medicine (UK)
CUA = cost-utility analysis
DA = dopamine (D₂) receptor antagonist
DALY = disability-adjusted life years
DBS = deep brain stimulation
DCS = d-cycloserine
DEPRES = Depression Research in European Society
DGPPN = Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde
DHEA = dehydroepiandrosterone
DLPFC = dorsolateral prefrontal cortex
DNRI = dopamine and noradrenaline reuptake inhibitor
DRI = dopamine reuptake inhibition
DSM = diagnostic and statistical manual of mental disorders
EA = electro-acupuncture
ECT = electroconvulsive therapy
EMEA = European Medicines Agency
ENRICHED = Enhancing Recovery in Coronary Heart Disease Patients Randomized Trial
ER = extended release
ES = effect size
EUFAMI = European Federation of Association of Families of People with Mental Illness
ESEMeD = European Study of the Epidemiology of Mental Diseases
FDA = Food and Drug Administration
GABA = γ-aminobutyric acid
GAD = generalized anxiety disorder
GM = glutamatergic modulator
GP = general practitioner
H1 = blockade of histamine 1 receptors
HAM = Hamilton rating scale for anxiety
HAMD = Hamilton rating scale for depression
HIV = human immunodeficiency virus
HPA = hypothalamic pituitary adrenal
ICD = international classification of diseases
ICER = incremental cost-effectiveness ratio
ICPE = International Consortium of Psychiatric Epidemiology
IL = interleukin
IPC = interpersonal counseling
IPT = interpersonal psychotherapy
IR = immediate release
K-SADS = Childhood Version of the Schedule for Affective Disorders and Schizophrenia
LIDO = Longitudinal Investigation of Depression Outcomes
M1 = blockade of cholinergic muscarinic receptors
MAI = monoamine oxidase A inhibition
MADRS = Montgomery–Åsberg depression rating scale
MAOI = irreversible inhibitor of monoamine oxidase A and B
MAOBI = irreversible inhibitor of monoamine oxidase B
MAP = mitogen-activated protein
MBI = monoamine oxidase B inhibition
MCC = Medical Control Council of South Africa
MDD = major depressive disorder
MID = Mantel-Haenszel incidence difference
MHRA = Medicines and Healthcare products Regulatory Agency
MHRD = Mantel–Haenszel exposure time-adjusted rate difference
MINI = Mini International Neuropsychiatric Interview
MRI = magnetic resonance imaging
MST = magnetoconvulsive therapy
MT1/MT2 = melatonin 1 and melatonin 2 receptor agonist
MT = melatonergic antidepressant
M-TCA = modified tricyclic antidepressant
NA = noradrenaline (= norepinephrine)
NAR = noradrenaline-releasing properties
NARI = selective noradrenaline (norepinephrine) reuptake inhibitor
NaSSA = noradrenergic and selective serotonin antidepressant
NCP = NeuroCybernetic Prosthesis (System)
NGF = nerve growth factor
NIMH = National Institute of Mental Health
NK1 = neurokinin 1
NMDA = N-methyl-d-aspartate
NMS = neuroleptic malignant syndrome
NN = nomen nescio (unknown author)
NRI = noradrenaline (norepinephrine) reuptake inhibition/inhibitor
N-TCA = tricyclic antidepressant with primary noradrenergic effects
N-TetraCA = tetracyclic antidepressant with primary noradrenergic effects
OCDD = obsessive compulsive disorder
OR = odds ratio
PD = Parkinson’s disease
PET = positron emission tomography
PHQ = Patient Health Questionnaire
PKC = protein kinase C
PMDD = premenstrual dysphoric disorder
PSD = partial sleep deprivation
PTSD = post-traumatic stress disorder
QALY = quality-adjusted life year
RCT = randomized controlled trial
RBD = recurrent brief depression
RIMA = reversible inhibitor of monoamine oxidase A
rTMS = repetitive transcranial magnetic stimulation
SCID = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders
SMA = serotonin-modulating antidepressant
SMR = standard mortality ratio
SNRI = selective serotonin and noradrenaline reuptake inhibitor
S/N-TCA = tricyclic antidepressant with similar serotonergic and noradrenergic effects
SP = substance P
SRI = serotonin reuptake inhibition
SRS = serotonin reuptake stimulation
SSRI = selective serotonin reuptake inhibitor
TADS = Treatment for Adolescents with Depression Study
SAD = seasonal affective disorders
SD = sleep deprivation
SDLP = standard deviation of lateral position
STAR*D = Sequenced Treatment Alternatives to Relieve Depression
S-TCA = tricyclic antidepressant with primary serotonergic effects
S-TetraCA = tetracyclic antidepressant with primary serotonergic effects
TAU = treatment as usual
tDCS = transcranial direct current stimulation
TDM = therapeutic drug monitoring
TNF = tumor necrosis factor
TRD = treatment resistant depression
TSD = total sleep deprivation
UK = United Kingdom
US = United States of America
VNS = vagus nerve stimulation
WFSBP = World Federation of Societies of Biological Psychiatry
WHO = World Health Organization
WPA = World Psychiatric Association
XR = extended release
YLD = years lived with disability