Problems and solutions to filling the drying drug pipeline for psychiatric disorders: a report from the inaugural 2012 CINP Think Tank

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Abstract

The inaugural Collegium Internationale Neuro-Psychopharmacologicum (CINP) Think Tank, a small open meeting sponsored by the CINP, discussed impediments to developing new drugs for psychiatric disorders and approaches to overcome these impediments. Whilst neuropsychopharmacology has a rich pharmacopeia (current treatments benefitting many individuals), issues of treatment resistance, sub-optimal response and unwanted side effects remain problematic. Many scientific, economic and social issues are impeding the development of drugs (e.g. higher risk of failure, placebo effects, problematic regulatory environments, pressures imposed by patent protection, downward pressure on reimbursements and financial, legal and social risk aversion). A consensus of the meeting was that efforts to understanding the core pathophysiology of psychiatric disorders are fundamental to increasing the chance of developing new drugs. However, findings from disorders such as Huntington’s chorea, have shown that knowing the cause of a disorder may not reveal new drug targets. By contrast, clinically useful biomarkers that define target populations for new drugs and models that allow findings to be accurately translated from animals to humans will increase the likelihood of developing new drugs. In addition, a greater accent on experimental medicine, creative clinical investigations and improved communication between preclinical neuropsychopharmacologists, clinicians committed to neuropsychopharmacological research, industry and the regulators would also be a driver to the development of new treatments. Finally, it was agreed that the CINP must continue its role as a conduit facilitating vibrant interactions between industry and academia as such communications are a central component in identifying new drug targets, developing new drugs and transitioning new drugs into the clinic.

Received 2 July 2013; Reviewed 31 July 2013; Revised 13 August 2013; Accepted 19 August 2013; First published online 24 September 2013

Key words: CINP Think Tank, drug development, neuropsychopharmacology.
suggested for inclusion in more formal discussion at future Think Tanks.

In the strictest sense, the primary hypothesis that understanding the cause of a psychiatric disorder leads to new treatments was quickly challenged because of examples where discovering the cause of a disorder has not lead to new drugs being developed. For example, it is close to twenty years since the discovery of the mutations in the Huntington gene that causes Huntington’s chorea, (Gusella and MacDonald, 1995) but this has not lead to the development of effective therapies (Armstrong and Miyasaki, 2012). Contrariwise, an important insight into treating treatment resistant depression is derived from work with the N-methyl-D-aspartate receptor (NMDAR) channel blocker ketamine, but over-activity at NMDAR is not causal to depressive states (Aan Het et al., 2012). Hence, it was uniformly accepted that identifying the cause(s) of a disorder does not automatically lead to new therapeutics but that a better understanding of the aetiologies of psychiatric disorders will be a driver for on-going drug development. In addition, a greater understanding of underlying aetiologies will assist in matching populations of people with psychiatric disorders to specific mechanisms of drug action. This will be a critical advance given the heterogeneity of most psychiatric disorders and the complexity of their underlying causes.

These discussions were simply the forerunner to discussions on the multifaceted problems impeding drug development and that need to be confronted and overcome.

The emergence of neuropsychopharmacology

Taking a somewhat historical perspective, early debate focused on lessons learned from the development of existing drugs used to treat psychiatric disorders. Clearly, although these treatments are not optimal they represent significant progress that matches or exceeds that made in treating other disorders of the human central nervous system (CNS) such as the neurodegenerative disorders; Alzheimer’s disease, Huntington’s chorea and Parkinson’s disease (Armstrong and Miyasaki, 2012; Delrieu et al., 2012; Stocchi and Olanow, 2013). Notably, some of the advances in the neuropsychopharmacology of psychiatric disorders were based on misconceptions of the underlying pathophysiology. For example, the notion of lithium as a mood stabiliser initially grew from the idea that a build-up of uric acid was causing psychiatric symptoms and the discovery that lithium salts could help dissolve uric acid (Cade, 1949). However, the true drive to test the hypothesis in humans was mainly derived from the observation that lithium carbonate caused lethargy and unresponsiveness in guinea pigs, a behaviour thought to be analogous to alleviating psychotic symptoms. Behavioural observations in humans receiving drugs for other indications were central to recognising the antipsychotic and antidepressant potentials of chlorpromazine and imipramine (Lopez-Munoz et al., 2005; Lopez-Munoz and Alamo, 2009). These examples clearly show that astute clinical observations, such as the calming and relaxing effects of chlorpromazine during surgery being of potential benefit to psychiatric patients (Lopez-Munoz et al., 2005), are critical for understanding the potential of any new drug, and for acquiring insights into new treatments modes. This raises the question as to whether, in the current ‘real world’ clinical settings, sufficient clinicians still have the skills and the opportunity to observe patients in such a way that would allow them to identify treatment outcomes that would support the use of an established drug in treating another disorder, or orient a new drug towards its optimal therapeutic utilisation. The general view was that recently trained psychiatrists, and other younger clinicians in general, are no longer rewarded for undertaking an extensive characterisation of a patient’s symptoms and are under considerable pressure to formalise a diagnosis and a subsequent treatment regime (Tucker, 1998).

Further, as opposed to vast multi-centre double-blind trials, there are fewer opportunities for open and insightful examination of the potential of novel agents. This could result in clinicians failing to recognise unpredicted characteristics of drugs, when first used in humans, which may be of benefit in disorders other than those for which they are developed. The off-label prescription of drugs used in psychiatric disorders (Rowe, 2007) suggests that clinicians are still using their skills to explore the full therapeutic potential of new drugs but this is a long way from what could be a well-controlled, structured evidence-based medical approach to discerning the full therapeutic potential of new drugs.

Increasingly, new compounds are taken into double blind random control trials for a single intended indication based on predictions from animal and in vitro biochemical screening models. This is of concern because such approaches limit opportunities for clinical experts to use these new drugs in patients with various disorders where therapeutic benefits may be indicated and hence explore the full potential of a new compound.

One common factor related to most areas of neuropsychopharmacology is that current drugs are only effective in some individuals (Meltzer, 2013; Pfeiffer et al., 2013) but clinical trials are still rarely, if ever, designed to identify responders and non-responders with the objective of defining the differential clinical characteristics of these two groups. Being able to interrogate clinical trial data to obtain such outcomes would help clinicians to try and personalise treatment regimes based on specific drug and clinical characteristic matches.

Discussions acknowledged that the challenges in neuropsychopharmacology are to develop drugs that: (i) improve symptoms in people who are resistant to all current drugs; (ii) increase clinical benefits experienced by people who do not respond optimally to current
drugs; and (iii) improve drug side-effect profiles (Moller, 2005, 2008). Therefore, the field must continue to strive to understand: (i) the pathophysiology of psychiatric disorders; (ii) the basis of treatment responsiveness; and (iii) the mechanisms by which drugs generate side-effects.

**A growing understanding of the aetiology of psychiatric disorders: impact on treatment**

The growing arsenal of research technologies is increasing the probability that the underlying pathophysiology of psychiatric disorders can be elucidated. As an example, studies examining levels of gene expression in human CNS (Pongrac et al., 2002), neuroimaging (Buchsbaum and Wu, 1987) and peripheral metabolism (van Nimwegen et al., 2008) all suggest that people with schizophrenia have problems with energy and metabolism. Translating such findings into new treatments is dependent on accessible drugable sites that can be used to modulate perturbed pathways. In the area of psychiatry, this is no small challenge given there is likely to be a limited number of drugable sites in the human body (Drews, 1996; Hambly et al., 2006).

Whilst the notion that understanding the pathophysiology of psychiatric disorders will necessarily lead to new treatments is overly optimistic, a growing understanding of the aetiology of a disorder can aid decisions about which new drug may have therapeutic benefits. One example of such a relationship is the growing understanding that muscarinic receptors (CHRMs) have a role in the pathophysiology of schizophrenia and are complex drug targets. Thus, there is a significant body of evidence from neuroimaging and post-mortem studies to suggest that there are low levels of CHRMs in the CNS of people with schizophrenia (Raedler et al., 2007). There is also some data to support the hypothesis that CHRM1 is decreased in the cortex of people with that disorder (Dean et al., 2002; Scarr et al., 2006), whereas CHRM4 is changed in their hippocampus (Scarr et al., 2007). These data add to other research findings (Raedler et al., 2007) supporting the notion that treating people with schizophrenia with CHRM1 and CHRM4 agonists would have therapeutic benefits (Bymaster et al., 2002; Dean, 2004). This body of data assisted in facilitating a small placebo-controlled drug trial of xanomeline in people with schizophrenia (Shekhar et al., 2008). Xanomeline is a drug with a complex poly-pharmacy that includes being an agonist at CHRM1 and CHRM4 (Bymaster et al., 1997) and having potential antipsychotic properties according to preclinical testing (Andersen et al., 2003). The outcomes of the study in 20 people with schizophrenia were that those people who received xanomeline had lower total Brief Psychiatric Rating Scale scores from week one to the end of the study and lower total Positive and Negative Syndrome Scale (PANSS) scores resulting from lower PANSS Positive and Negative Symptom Sub-scales (Shekhar et al., 2008). In the cognitive domain the subjects that had received xanomeline had better verbal learning, short-term memory, list learning, story recall, delayed memory and digit span test. These data support the proposition that activating CHRM1 and CHRM4 would have a broad therapeutic benefit when treating schizophrenia but, unfortunately, the side-effect profile of xanomeline was not tolerable.

One problem in targeting specific CHRMs is that the orthosteric binding site of the five receptors in this family has been preserved through evolution (Adem and Karlsson, 1997) and it has been difficult to develop drugs that can differentiate between CHRMs at that site. By contrast, the discovery of allosteric binding sites on the CHRMs (Birdsall et al., 2001) was a precursor to showing these sites were not preserved across evolution and, therefore, it was possible to specifically target these sites on each of the five CHRMs (Conn et al., 2009a, b). Hence, there is now significant preclinical data to suggest that allosteric modulators targeting CHRM1 and CHRM4 could be useful in treating people with schizophrenia (Abi-Dargham et al., 2002; Bymaster et al., 2002; Chan et al., 2008; Marlo et al., 2009). Recently, it has been reported that some individuals with schizophrenia can be separated into a distinct population because of a marked loss of cortical CHRM1 (Scarr et al., 2009). Significantly, measuring orthosteric and allosteric agonist CHRM1 G-protein coupling, it has been shown that the cortical CHRM1 in people with schizophrenia, who have a marked loss in that receptor, respond normally to drugs that target the allosteric, but not orthosteric, CHRM1 site (Salah-Uddin et al., 2009). These data suggest that allosteric modulators may be beneficial in treating schizophrenia, whether or not the disorder is accompanied by a marked loss of cortical CHRM1 receptors.

The discovery of a sub-population of people with schizophrenia with extremely low levels of cortical muscarinic M1 receptors (Scarr et al., 2009) opens up the possibility that this group constitute a more biologically homogenous cohort that may have a discrete symptom profile and may be responsive to particular treatment regimes. The challenge will be to identify these individuals in the clinic, which should be feasible given that low levels of muscarinic receptors have already been reported in the CNS of people with schizophrenia using neuroimaging (Raedler et al., 2003). This in turn leads to the notion that all areas of drug discovery may be enhanced by the availability of viable biomarkers to aid diagnoses or response to treatment (Dean, 2011). Importantly, in the psychiatry arena, there are still no biomarkers to either aid in diagnoses or treatment selection that are being widely used in the clinical setting. Developing such biomarkers is now a major focus of many researchers and the success of these efforts will eventually be judged by whether or not clinicians use a well-characterised biomarker, or defined set of biomarkers, to help them in their clinical decision-making.
The impact of genetics on neuropsychopharmacology

Psychiatric disorders have a high degree of heritability (Cardno et al., 1999), an observation that has engendered considerable efforts to understand the genetics of these disorders and to determine whether pharmacogenetics and pharmacogenomics can aid in the delivery of personalised medicine (de Leon, 2009). However, genome-wide association studies on large cohorts of people with psychiatric disorders have led to only limited advances in understanding the pathophysiology of those disorders, have not really impacted treatment decision making and have not provided a plethora of potential new drug targets (Moskvina et al., 2009; Purcell et al., 2009; Sullivan et al., 2009). Moreover, it is naïve to assume that a gene that is associated with an altered risk for a disorder is necessarily causal and, whether or not it is causal, will be an accessible drug target. For example, there are variants of genes such as those disrupted in schizophrenia 1 (Millar et al., 2000) and neuregulin 1 (Stefansson et al., 2002) that carry an increased risk of specific psychiatric disorders including schizophrenia. By contrast, there is no clear evidence that their gene products themselves are accessible new drug targets. By contrast, understanding the biology of DISC1 (Wang et al., 2008) and NRG1 (Harrison and Law, 2006) may lead to the elucidation of new drug targets within their associated pathways. Alternatively, given the importance of these genes in early CNS development, to have eventual clinical benefit drugs targeting these pathways may have to be given long before the onset of frank psychiatric symptoms, which is not yet acceptable in people who finally develop disorders such as schizophrenia (Insel et al., 2013). Such early treatment could become possible with the availability of biomarkers for psychiatric disorders (Dean, 2011). In this regard, whilst it is encouraging that apolipoprotein E4 is now a well-established risk gene for Alzheimer’s disease (Bertram et al., 2007), there is no equivalent single risk gene for a discrete psychiatric disorder and therefore widespread genetics guidance on the best drug regime for a specific individual with a psychiatric disorder is not yet feasible, though polymorphisms of cytochrome P450 can be helpful to guide the choice of drug treatment based on a drug’s susceptibility to catabolism (de Leon, 2006).

With the development of deep sequencing technologies (Pop and Salzberg, 2008), it is feasible to explore sequence variations throughout the human genome. Such technologies suggest that large recurrent micro-deletions (Stefansson et al., 2008) and other copy number variants (Stefansson et al., 2009) may confer an increased risk of developing psychiatric disorders. Such on-going rigorous dissection of the human genome could eventually offer advances in pharmacogenetics (Rujescu et al., 2012) and result in progress towards more personalised treatments for people with psychiatric disorders (Evers, 2009). However, copy number variants encompass multiple protein-coding and other classes of gene so they are not targets per se for medication. Further, monogenic forms of schizophrenia, depression and sporadic forms of other psychiatric disorders do not appear to exist, rather we are dealing with hundreds of genes with small individual marked cumulative and interacting (‘epistatic’) effects, and a handful of very rare genes with large effects (Malhotra and Sebat, 2012). This may be why the dream of extracting new drug targets from the analyses of the human genome has not materialized and that genetics studies have yet to identify reliable biomarkers for psychiatric disorders. One problem in this regard is also the over-writing and scrambling of the genetic message by epigenetics in disorders such as autism, schizophrenia and other developmental disorders (Millan, 2013), which could be making sequencing data more difficult to interpret.

The use of animal models in drug discovery

Animal models are widely used both in the area of preclinical psychotropic drug discovery and in trying to understand the underlying pathophysiology of psychiatric disorders (Young et al., 2010). Whilst such models have not encapsulated the whole spectrum of complex disorders such schizophrenia, major depressive disorder or bipolar disorders, there are well-validated models that inform on specific dimensions of function (Segal and Geyer, 1985) or clusters of symptoms, such as cognitive deficits (Floresco et al., 2005).

Recently, the difficulty of using preclinical psychiatric models to make robust predictions about the outcomes of clinical trials has been lamented (Markou et al., 2009). This underpins a growing focus on whether there are behavioural homologies between animals and humans that can be used to develop behavioural models for drug discovery, which are more likely to identify lead compounds in pre-clinical testing. To improve such interconnectivity a more iterative approach would be required where tests focusing on homologous behaviours or responses in animals and humans are used. For example, this could involve monitoring drug-induced modifications of analogous behaviour in animals and healthy human volunteers. Such coordinated studies would then be followed by studies to identify specific functional changes in such drug-induced behaviours in patient populations with the view of identifying underlying pathophysiology or potential drug responsiveness.

In developing animal models that could be translated into models involving humans it is critical that these models are not reverse engineered from existing models in humans that involve human-specific processes such as language for the read-out. In addition, cumulative experience using animal models suggest future models should be directed towards elucidating the underlying biology of symptoms (Geyer, 2006), which are more likely to be based specifically on CNS system abnormalities,
rather than trying to model complex psychiatric syndromes with multiple aetiologies. However, this notion is controversial as it has been previously been rejected in favour of creating models based on a better understanding of disorders such as schizophrenia (Goodman et al., 2000; Spedding et al., 2005). Arguing for the development of symptom-based animal models are examples of the successful use of animal models to identify clinically efficacious drugs using non-verbal tests conducted in similar ways in both animals and humans. In one example, behavioural measures showed that beta-2 subunit containing nicotinic cholinergic receptors within the brain’s reward circuitry were essential to the behaviour of nicotine self-administration in rodents (Picciotto et al., 1998). Further work demonstrated that varenicline, a partial agonist at these receptors, decreased nicotine consumption in rodents (O’Connor et al., 2010). Parallel studies in humans self-administering nicotine confirmed that this drug could have similar effects, which led directly to a successful aid to smoking cessation (Rollema et al., 2010). Another example is the use of fear extinction, measured in both humans and animals using the startle response (Davis, 2006), where animal studies of the effects of drugs on the extinction of learned fear in a potentiated startle task (Walker and Davis, 2002) led to parallel studies in humans (Davis, 2006). Such studies contributed to the background knowledge that led to the demonstration of the clinical efficacy of the enhancement of extinction therapy by D-cycloserine in patients with acrophobia (Ressler et al., 2004). Similarly, the animal test most predictive of the clinical efficacy of antipsychotics relies on deficits in pre-pulse inhibition of startle first identified in patients with schizophrenia (Braff et al., 1978). In rats, gating deficits are reliably mimicked by administering the mixed dopamine agonist apomorphine, an effect robustly attenuated by all currently-employed antipsychotic drugs (Geyer et al., 2001). Taking this concept into the area of drug discovery, the lack of such effects in the apomorphine pre-pulse inhibition model in rats accurately predicted what was later shown to be a the lack of clinical antipsychotic efficacy of both mGluR2/3 agonists (Kinon et al., 2011) and PDE10 antagonists (see http://www.clinicaltrials.gov/ct2/show/NCT00463372?term=NCT00463372&rank=1) in humans.

Such approaches hold further promise in the development of cognitive enhancers for use in patients with schizophrenia (Young et al., 2009a, b). These examples highlight how it is possible to use an integrated animal–human approach to drug discovery. Finally, there is the potential to move classic animal tests to an environment that can accommodate humans. Hence, by using motion tracking in a specially prepared room it has been clearly shown that individuals in the manic phase of bipolar disorder are hyperactive (Henry et al., 2010). This simple test also reliably differentiates manic patients from acutely ill schizophrenia patients and has been used to validate parallel animal models using comparable measures of behavioural profiles (Perry et al., 2009). Thus, there is now convincing data to show that carefully constructed trans-species tests, which can be used in humans and animals, can help us to measure and characterize psychiatric symptoms. It is also logical that such tests, which can be used in both humans and animals, will give meaningful results about outcomes in humans when tested in animals using these carefully characterized models.

Nonetheless, limitations of experimental procedures must not be neglected. Notably, psychiatric disorders are characterized by the disruption of several higher cognitive domains, like abstract reasoning, verbal language and social cognition, which are not fully present in animals—at least not in rodents—and hence remain challenging to model both in regards to their causes and their potential control (Millan et al., 2012).

Future of drug development: the bigger picture

One major concern raised was the vicious circle of failure in bringing novel drugs to the market for the improved treatment of psychiatric disorders, which, in turn, decreases the appetite to take on further risks associated with developing new drugs for psychiatric disorders. This is the equivalent of a toxic gain of function and has seen a number of major companies close down or curtail CNS drug discovery programs (Abbott, 2011). Contributing to such unfortunate decisions are other problems that complicate the feasibility and increase the outlay for developing new drugs. These factors include long and costly development times along with a high risk of failure (Woodcock and Wooley, 2008), the impact of generic medication on long-term pricing structures, limited patent duration and the impact of government pricing (Tseng et al., 2003). More unexpectedly, companies have adopted a policy of risk avoidance, tending to avoid the development of drugs with even modest safety issues. There is also a somewhat naïve expectation that significant progress is being made toward personalised medicine for psychiatric disorders. This is fuelling high expectations that new drugs for psychiatric disorders must, as a very minimum, give excellent clinical outcomes in the declared targeted disorder or condition. The process of developing new psychotropic drugs is also complicated by the overall negative view of psychiatric...
drugs projected by some areas of the media, coupled with the reluctance of patients to accept a psychiatric diagnosis (Stuart, 2006). From a scientific viewpoint one disappointing brake on drug development is the reluctance to take on big challenges such as developing drugs for treatment-resistant patients with psychiatric disorders (Huskamp, 2003). Finally, the ever expanding psychiatric classifications has resulted in a cynicism about the discipline that now encompasses the field of neuropsychopharmacology, resulting in concerns as to whether effective drugs can be developed to treat diagnoses that themselves are a moving target (Whitaker, 2011). This issue interlinks with the notion that we should be more closely linking pathophysiology with symptoms even in a trans-ontological way and focusing on developing agents that correct specific anomalies, irrespective of their association with specific diagnostic entities. It is also important not to forget the substantial co-morbidity amongst psychiatric disorders with other CNS and somatic disorders (Millan, 2006).

The future of drug development: potential approaches

Drug development in neuropsychopharmacology has always struggled to balance therapeutic benefits vs. unwanted side-effects (Reynolds, 1992). Initially, it was thought that the best therapeutic benefit/side-effect profile would be achieved by developing drugs with specificity for a single site, a mind-set reinforced by naïve notions around outcomes from genomic drug discovery programs (Millan, 2006). However, the continued and effective use of drugs with complex pharmacology [e.g. clozapine (Kane, 1992) and tricyclic antidepressants (Lopez-Munoz and Alamo, 2009)] and the use of polypharmacy to treat psychiatric disorders (Ballon and Stroup, 2013) argues that highly selective drugs may not provide optimal treatment for such disorders. Indeed, drugs with multiple targets, and poly-pharmacy, may be efficacious because they target multiple pathways involved in the genesis of symptoms of multidimensional psychiatric disorders, though both strategies have their pros and cons (Millan, 2009). Additionally, it is now recognised that current diagnostic criteria define syndromes rather than a biologically homogenous disease (Tamminga et al., 2002). Thus, it could be that targeting multiple pathways will have therapeutic reach across different component disorders and sub-populations within the syndromes by better targeting their differing biologies.

The development of agomelatine, the first antidepressant with a non-monoaminergic (melatoninergic) component of activity (de Bodinat et al., 2010), argues for an informed approach to drug design. This is because the drug targets the melatonin system to counter disturbances in the sleep/wake and circadian cycle known to be associated with depression (de Bodinat et al., 2010) as well blocking the serotonin-2C receptor to reinforce catecholaminergic transmission (Englander et al., 2005) and combat depression (Gurevich et al., 2002). Another more recently described agent currently in clinical development, vortioxetine, interacts with serotonin transporters and a suite of 5-HT receptors, but its clinical efficacy remains under investigation (David et al., 2013). This multifaceted approach to drug design could well be applied to other psychiatric disorders where it is known that multiple neurotransmitters and CNS pathways contribute to overall pathophysiology (Dean, 2000, 2002). Studies from preclinical pharmacology support the notion that targeting multiple sites with poly-pharmacy may lead to more wide-ranging therapeutic options and outcomes in people with psychiatric disorders. As examples, the combination of Celecoxib and noradrenaline or serotonin uptake inhibitors increases rat cortical noradrenaline and serotonin output, respectively, (Johansson et al., 2012) whilst augmenting raclopride treatment with galantamine, but not donepezil, enhances antipsychotic-predictive behaviours in rats (Wiker et al., 2008).

Another major issue is the problem of increasing placebo effects in CNS drug trials (Kemp et al., 2010). In areas such as pain relief the modulation of endogenous opioids in the placebo group has been suggested as an explanation of placebo effects observed (Zubieta et al., 2005). No such clear biological explanation is available for the increasing impact of the placebo effects in psychotropic drug trials other than it corresponds to a mode of psychological-cognitive therapy of which the neural substrates likely remain nebulous. The placebo effect in drug trials in disorders such as schizophrenia is clearly increasing with time (Alphs et al., 2012), meaning it is becoming increasingly difficult to show efficacy of a new drug using a placebo control drug trial. Finally, it is significant that the placebo effect within a drug trial can vary with geographical regions of recruitment (Mentz et al., 2012), as this suggests variation in drug response due to differing genetic backgrounds or recruitment and ratings of patient response are not consistent across countries. To overcome the problem of the placebo effect, it was suggested that it could be worthwhile to use new drugs in adjunctive trials to show improved efficacy over an existing treatment. Whilst this remains a viable option, it was acknowledged that this strategy might result in these drugs not being approved as front-line treatments.

In was acknowledged that it will likely be necessary to change the regulatory environment as this is also impacting how drugs are developed. Safety issues have become a particular issue in view of the widespread use of simple, automated cellular screening tests, which may generate false-positives. An example of the impact of such approaches is that in today’s environment it is possible that dopamine and its precursors would be rejected as potential drugs because of their potential cardiac effects and for the same reason, plus the fact it is a cytochrome inhibitor, grapefruit juice would be viewed as a having safety issues (Joers et al., 2012). Another major challenge
facing neuropsychopharmacology is the development of drugs for people with psychiatric disorders that are resistant to current drugs. One difficulty hampering this endeavour is that such drugs may not attract sufficient levels of reimbursement to make their development economically viable, a problem not restricted to the area of neuropsychopharmacology (Kefford, 2012). Lastly, given the increasing complexity of getting drugs for psychiatric disorders into the clinic (Baldessarini, 2013) it may be necessary to consider extending the length of patent protection so that recouping costs over a longer period can allow a lower unit price for each treatment.

**Other issues**

Time constraints meant that not all significant developments, which could impact on future drug discovery were discussed. One of these was the potential for academic institutions to become more involved in developing drugs and taking them closer to market. An example of this approach is the Vanderbilt Centre for Neuroscience Drug Discovery (USA), which is currently beginning to partner with industry to get some of their compounds into clinical trials (Conn et al., 2009a, b). However, the most important advance along these lines is the European Union sponsored academia-industry pre-collaborative, ‘Innovative Medicines Initiative’, to enhance collaborative work for improving the discovery, characterisation and clinical development of new improved medication for CNS and other disorders. In addition, it is now seen as a key issue to get the European Medicines Agency, United States Food and Drug Administration and other regulators on board for discussions very early in the development of novel agents. It is also critical there are increased efforts to consult patients, their families and the representative associations for specific disorders to hear their point-of-view on the impact of new drugs as this is now recognised as ‘high value’ information (Walburn et al., 2001). Another important area not discussed was potential new drug delivery systems that may prove useful in either getting drugs that do not readily cross the blood-brain barrier into the CNS or in delivering drugs with beneficial therapeutic effects wholly or predominantly into the CNS, hence lessening unwanted peripheral side-effects (Valencia et al., 2012; Shah et al., 2013).

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<th>Pros</th>
<th>Cons</th>
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<td>An established record of drug development.</td>
<td>Possible decrease in clinicians having the time and/or inclination to undertake extensive clinical observations of drug trials, resulting in a decrease in the identification of alternate target populations based on behavioural responses.</td>
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<td>A growing understanding of the aetiology of psychiatric disorders.</td>
<td>Growing trend to move to double blind control trials on single indications based on animal or mechanistic hypotheses excluding experienced clinicians from using their clinical neuropsychopharmacological expertise.</td>
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<td>Increasing technological capabilities that can be used to investigate both aetiologies of psychiatric disorders and new potential drug targets.</td>
<td>Design of drug trials failing to capture important data such as responder/non-responder rates.</td>
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<td>Growing understanding of genetics and their usefulness in diagnosing psychiatric disorders and predicting treatment response.</td>
<td>Increasing problems with placebo effects in drug trials potentially masking a positive drug response.</td>
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<td>The development of models that can be applied to both humans and animals to increase the translation of preclinical findings to drugs, which reach the clinic.</td>
<td>Risk aversion, such as avoiding side-effects, affecting the development of potentially clinically valuable drugs.</td>
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<td>The on-going development of novel therapies targeting either multiple pathways or new sites such as allosteric sites on neurotransmitter receptors.</td>
<td>A problematic regulatory environment and, because of time needed to develop more complex drugs, the pressures imposed by the duration of patent protection.</td>
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<tr>
<td>Development of new drug delivery systems.</td>
<td>Downward pressure on reimbursements inhibiting willingness of industry to expend funds on drug development.</td>
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Table 1. The pros and cons facing drug development in neuropsychopharmacology
Summing up

The discussions at the inaugural CINP Think Tank recognised there were both drivers and inhibitors influencing the development of new drugs to treat psychiatric disorders (Table 1). At the end of the meeting some level of consensus had emerged which included the recognition that:

1. Understanding the core pathophysiology of psychiatric disorders may not necessarily lead to the development of new drugs, though it certainly is a fundamental step in the right direction.

2. Even when we know the cause of a disorder, it may not point toward new drug targets since there may be no pharmacologically accessible target or the primary event leading to the onset of illness may be decoupled in time having long ago triggered a cascade of downstream anomalies (e.g., triggering early neurodevelopmental changes).

3. Developing biomarkers for psychiatric disorders, similar to the use of APOE4 (genetic) and Abeta (biochemical: an approach enabling the effective monitoring of central amyloid) in Alzheimer’s disease (Nordberg, 2007), is critical in: (i) identifying subjects at risk of a disorder, (ii) improving diagnostic consensus, and (iii) providing early indications of pharmacoresponsiveness. However, as no validated biomarker is yet available, other surrogate markers of efficacy are needed for improving the development of new drugs for psychiatric disorders (see 4).

4. There is a need to accelerate the development of behavioural models that allow findings on drug indications and efficacy to be accurately translated from animals to humans.

5. Understanding the primary mechanism of action of any psychotropic drug may not pinpoint the cause of psychiatric disorders. For example, antipsychotics predominantly block dopamine D2 receptors (Seeman and Niznik, 1990) whereas dopamine release, not dopamine D2 receptor density, is abnormal in schizophrenia (Dean, 2013).

6. To successfully understand the full potential of new drugs there is a need to place a greater emphasis on experimental medicine, creative clinical investigations and improved communication between preclinical neuropsychopharmacologists, clinicians committed to neuropsychopharmacological research, industry and the regulators.

What is clear is that to develop drugs for psychiatric disorders that have improved efficacy, increased therapeutic reach and few side-effects there needs to be an on-going dialogue between all facets of the field of neuropsychopharmacology. This has been a key mission that has driven the CINP for more than fifty years and is perhaps more relevant than ever. Finally, it is worth noting the reflections of a member of the meeting who had experience of the first outflow of new medications to treat psychiatric disorders. These reflections highlighted that there was no clear forewarning of the explosion of new therapies for these disorders that began in the 1950s and, therefore, it is possible we are similarly unaware of the fact we are approaching imminent breakthroughs that could produce another new wave of much-needed medications.

Acknowledgments

The authors wish to acknowledge the commitment of the CINP to stimulating dialogue on important issues relating to the field of neuropsychopharmacology by acting as the sole sponsor of the inaugural CINP Think Tank. The authors would also like to thank Andrew Gibbons, Angelos Halaris, Amir, Kalali, Wolfgang Maier, Vincenzo Micale, Andrea Schimitt, Christian Schutz, Alexandra Sulcove and Chris Turk for being contributors to the discussions and debates at the Think Tank.

Statement of Interests

Brian Dean is an NHMRC Senior Research Fellow (APP1002240) and is supported by the Victorian Government’s Operational Infrastructure Support. Mark Geyer is supported by grants from the National Institute on Drug Abuse (DA02925) and the National Institute of Mental Health (MH61326, MH42228) and by the Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Centre. Elizabeth Scarr is an Australian Research Council Future Fellow (FT100100689).

Hans-Jurgen Moller has received grants, is a consultant for or is on the speakership bureaus of AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Schering-Plough, Schwabe, Sepracor, Servier and Wyeth.

Torgny H. Svensson has received grants from the Swedish Research Council, the Karolinska Institutet, The Brain Foundation (Sweden), Torsten Soderberg’s Foundation, Astra-Zenica, Organon, Schering-Plough, Merck Sharpe and Dome, Lundbeck and Astellas and is a consultant or on the advisory board of Astra-Zenica, Janssen, Otsuka, Pfizer, Organon, Schering-Plough, Merck Sharpe and Dome, Lundbeck, Carnegie Health Care Fund and the Nobel Foundation.

Mark Geyer has received consulting compensation from Abbott, Acadia, Addex, Cerka, Lundbeck/Otsuka, Merck, Neurocrine, Omeros, Takeda, and Teva as well as holding an equity interest in San Diego Instruments. Dr. Geyer also has research grant support from Intracelluar Therapeutics, Johnson & Johnson, NIDA, NIMH and the U.S. Veteran’s Administration VISN 22 Mental Illness Research, Education, and Clinical Centre.
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