Treatment-resistant schizophrenia (TRS) is characterized by continuous psychotic symptoms for more than 2 yr, impacting on functioning despite appropriate pharmacological and psychosocial treatment (Brenner et al., 1990). Between 5% and 25% of patients with schizophrenia develop treatment resistance (Brenner et al., 1990).

Research indicates that patients with TRS may benefit from adjunctive treatment with anticonvulsants (Nasser and Thomas, 1990). The effect of anticonvulsants on TRS is hypothesized to act through the glutamatergic system. There is some controversy, however, regarding the action, specifically whether the glutamatergic system is in hyper- or hypofunction. The glutamate hyperfunction hypothesis (Deakin et al., 1989) is supported by findings indicating significantly greater numbers of glutamatergic synapses in the frontal cortex of patients with schizophrenia (Simpson et al., 1998). This theory contrasts with the longstanding glutamate hypofunction hypothesis, proposed following observations that N-methyl-D-aspartate (NMDA) receptor antagonists induced psychomimetic effects in humans (Luisada, 1978).

A randomized, placebo-controlled cross-over trial and several case studies report lamotrigine as an efficacious adjunctive therapy to clozapine in the management of TRS (Saba et al., 2002; Tiihonen et al., 2003). These results support the glutamate hyperfunction hypothesis where lamotrigine, as a glutamate release inhibitor augments the action of clozapine, a glutamate antagonist (Dursun et al., 1999). Investigations into the use of lamotrigine to augment other antipsychotics are limited. One small trial found significant symptom improvement over a 2-wk period when lamotrigine was added to clozapine but not risperidone, haloperidol, olanzapine or fluphenazine (Schwartz and Marsh, 2000). The specificity of results to clozapine was interpreted as suggesting antipsychotics with low dopamine receptor occupancy are glutamate antagonists, which augments their antipsychotic properties.

The generalizability of these results, however, is limited by the small sample sizes employed ($n = 1–7$ cases). Further investigation regarding the use of lamotrigine with medication other than clozapine in TRS is clearly indicated.

**Case reports**

We report five case studies, which suggest lamotrigine may be efficacious in patients receiving pharmacological treatment with clozapine and other antipsychotics.

K.W. is a 35-yr-old single unemployed female living in a schizophrenia fellowship hostel. She has experienced auditory and visual hallucinations and persecutory delusions for 20 yr. Treatment with typical and atypical antipsychotics and antidepressants has had limited effect. Lamotrigine, increased to 150 mg b.i.d., was added to risperidone 6 mg/d, paroxetine 20 mg/d and clonazepam 2 mg/d. K.W.’s symptoms improved considerably, including reduced self-inflicted injuries. After 6 months of adjunct lamotrigine treatment her Brief Psychiatric Rating Scale (BPRS) dropped from 63 to 33. K.W.’s Clinical Global Impression (CGI) improved 3 steps, from severely ill to mildly ill.

Z.L. is a 42-yr-old single unemployed female with a 17-yr history of schizophrenia. She experiences auditory hallucinations, loosening of associations, thought blocking, perseveration and inappropriate affect. Z.L. continued to have some positive symptoms, was however, stable on intramuscular (i.m.) haloperidol 150 mg 3-weekly and sodium valproate 400 mg b.i.d. Lamotrigine was introduced and gradually increased to 75 mg/d. Z.L. showed improvement in affect and concentration, with reduced thought blocking and perseveration. She demonstrated overall improvement in her level of functioning, although a BPRS score was not available. Her CGI improved 2 steps from severely ill to moderately ill over a period of 6 months.

R.L. is a 36-yr-old single unemployed male living in supported accommodation. His first episode of psychosis was at age 19 yr, following hallucinogenic drug abuse. R.L. has chronic persecutory and grandiose
delusions, disorganized thinking and behaviour and command auditory hallucinations, despite therapeutic trials on all groups of antipsychotic medication. Lamotrigine 100 mg/d was added to i.m. zuclopenthixol 300 mg 2-weekly and sodium valproate 1500 mg. R.L. showed improvement in all areas of his mental state. After 3 months of adjunct lamotrigine treatment his BPRS score dropped from 63 to 24 and his CGI improved 3 steps, from severely to mildly ill. R.L. continues to make progress.

W.B. is a 41-yr-old single female invalid pensioner with a 22-yr history of schizophrenia. She experiences auditory and visual hallucinations and persecutory delusions where people steal from her, sexually abuse her and try to kill her. W.B. becomes irritable easily and is labile in affect. She had been treated with oral and depot typical and atypical antipsychotics. W.B. was taking clozapine 450 mg/d and clonazepam 1 mg b.i.d. She commenced on lamotrigine 12.5 mg slowly increased to 50 mg/d. W.B. showed remarkable improvement with her BPRS score decreasing from 69 to 30 within 4 wk of adjunct lamotrigine treatment. Her CGI went from severely to mildly ill.

L.S. is a 54-yr-old single male invalid pensioner who developed schizophrenia at age 16 yr. He experiences both positive and negative symptoms, particularly auditory and visual hallucinations, poor executive functioning and blunted affect. L.S. had persistent symptoms for 38 yr with more than 40 hospital admissions. All groups of antipsychotics were trialled in addition to three courses of ECT. His medication consisted of i.m. zuclopenthixol 300 mg weekly, clonazepam 1 mg t.i.d. and benzotropine 0.5 mg b.i.d. Lamotrigine was added and slowly increased to 100 mg b.i.d. L.S. showed significant improvement on his BPRS score which dropped from 81 to 32 within 4 wk of adjunct lamotrigine treatment. His CGI improved 4 steps, from extremely to mildly ill. L.S. remained at this level for the next 12 months.

Discussion

We observed significant improvements in mental state in each case where lamotrigine was used as an adjunctive treatment to several antipsychotics including zuclopenthixol, risperidone, haloperidol and clozapine. Our observations contrast with the negative findings reported where no effect was found when lamotrigine was added to antipsychotics other than clozapine. This may reflect the limited generalizability of results from small samples, the lack of control groups and significant differences in pharmacological treatment methods. Our results suggest that for TRS patients, lamotrigine can be a beneficial adjunctive treatment in with a variety of antipsychotics, including conventional medications, a finding that has not been reported previously.

Although not explicitly tested, our observations lend support to the glutamate hyperfunction hypothesis of schizophrenia, consistent with the findings of a recent reported trial examining the effect of lamotrigine when combined with clozapine in TRS (Tiihonen et al., 2003). A further possible explanation for the observed efficacy of lamotrigine lies in the relationship between TRS and subclinical epileptic activity. An association between epilepsy and psychosis has long been recognized with the suggestion that epilepsy and psychiatric disorders have common pathological substrates (Schwartz and Marsh, 2000). Initial investigations, employing depth electrodes to detect abnormal discharges in patients with schizophrenia or epilepsy with psychosis support this hypothesis (Heath, 1962). The development of non-invasive protocols, such as magnetoencephalography will be important to investigate this hypothesis further. Although the processes of action are unclear, the clinical implications of adjunctive treatment with lamotrigine are considerable in patients with TRS.

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Statement of Interest

None.

References


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