Editorial

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Next to schizophrenia, bipolar disorder is the most important condition for psychiatrists to recognise and treat. Indeed, the discovery by John Cade in 1949 of lithium as an effective treatment for mania,[1] and the finding in 1952 of chlorpromazine as an effective agent for acute psychotic states including mania, heralded the beginning of the modern era of psychopharmacology. Since this time, however, bipolar disorder has been relatively neglected by researchers, pharmaceutical companies and service planners. Lithium and antipsychotics have provided the mainstay of treatment for mania, whilst lithium has remained the 'gold standard' for the prophylactic treatment of bipolar disorder.

As a consequence of the relative neglect of the disorder, many important questions remained unanswered:

1. Is lithium a more specific and more effective treatment for mania than antipsychotics?
2. Do antipsychotics work in mania by sedation?
3. Is the effect of antipsychotics in mania related to the improvement in psychotic symptoms?
4. How do depressive symptoms respond when mania is treated with an antipsychotic, and what does this mean for the management of mixed manic states?
5. Do antipsychotics worsen depression in bipolar disorder, either when used acutely or in prophylaxis?
6. Is there a justification to continue antipsychotic drugs after the manic episode has resolved?
7. If the manic episode is treated with lithium or valproate, does combination with an antipsychotic confer any additional therapeutic advantage, either for mania, or for prophylaxis?

The situation began to change with the publication by Bowden and colleagues in 1994 of the first of the modern parallel-group, randomised, placebo-controlled trials of a new treatment (valproate) for mania.[2] The research conducted with olanzapine reported in detail in this issue of *Drugs in Context*, comprised a series of very well-designed studies, carefully planned to answer questions related not only to olanzapine treatment, but also to the broader problems of managing bipolar disorder. These multicentre trials are remarkable for the fact that clinicians were able to recruit sufficiently large numbers of suitable patients, for the trials to be completed successfully and for the questions to be answered meaningfully and unequivocally. These studies have also set the standard for trials of other drugs, including other atypical antipsychotics; such studies have appeared with other drugs with regard to mania, though we still await data for longer-term or prophylactic use in bipolar disorder.

On the basis of the trials in mania, we can now recognise that antipsychotic drugs are effective in managing mania, and this is not because of their sedative effects nor simply because they improve psychotic symptoms (i.e. delusions and hallucinations), but because they improve all aspects of the manic state. Olanzapine is comparably effective with the most commonly used drug for mania (haloperidol) and also has fewer acute side-effects.

Depressive symptoms are frequently experienced during mania. Unfortunately some of the recent clinical trials have excluded patients with mixed manic states. However, this was not the case in the studies of olanzapine. It was reported that depressive symptoms usually improve as the manic state improves upon treatment with both olanzapine and haloperidol. However, patients treated with olanzapine tend to have less risk of switching directly into depression, than those who are treated with haloperidol. One may regard depressive symptoms in a person with mania as being a 'characterological' response of the personality to the experience of mania; fuller mixed manic states occur in people in whom a depressive trait is a significant part of the normal personality.[3]

The presence of psychotic symptoms is not necessary to realise the antimanic effects of olanzapine or haloperidol. Psychotic mania is generally viewed as a more severe phase of the illness than non-psychotic mania, but some individuals seem to be more prone to develop psychotic symptoms than other individuals. In comparison with valproate, olanzapine appears

equally effective in improving psychotic mania, but more effective than valproate in relieving milder or non-psychotic mania. This important difference is in need of replication in further studies, as it has far-reaching implications for the future use of the two drugs in prophylaxis.

Monotherapy of mania with olanzapine, valproate or lithium is often insufficient to bring about remission. However, it has been shown that the addition of olanzapine to either lithium or valproate monotherapy confers additional efficacy.

After improvement in mania, patients admitted to hospital for the acute phase of treatment are usually discharged whilst still exhibiting at least mild symptoms of their bipolar state. Consequently, clinicians tend to continue them on antipsychotic medication for several months, even if they are also continuing on one of the so-called 'mood stabilisers' (i.e. lithium or valproate). Studies with olanzapine have shown that continuation of this antipsychotic, after mania has remitted during treatment with either olanzapine alone or in combination with a 'mood stabiliser', confers a distinct advantage. It reduces the risk of relapse into mania (and to a lesser extent prevents relapse into depression), even if the patient continues on lithium or valproate.

The role of olanzapine in prophylaxis is clarified further by the direct comparison between olanzapine and lithium for maintenance treatment, after remission of mania on a combination of both these drugs. Here, olanzapine was significantly more effective than lithium in preventing recurrence of mania, a property that was previously considered to be the one in which lithium excelled.

In conclusion, these key studies with olanzapine help us to answer many important questions about the nature and management of bipolar disorder. However, it remains to be seen to what extent these findings will translate into more generalised use in everyday practice, and ultimately whether they will influence the management of bipolar disorder in this setting.

References

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