Use of olanzapine in the treatment of acute mania: Comparison of monotherapy and combination therapy with sodium valproate

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Introduction: The aim of this article is to review the literature and outline the evidence, if any, for the effectiveness of olanzapine as a monotherapy for acute mania in comparison with the effectiveness of its use as a combined therapy with sodium valproate. **Case study:** GR, a 55 year old male with no previous psychiatric history was assessed by the Consultation and Liaison team and diagnosed with an acute manic episode. He was placed under an involuntary treatment order and was prescribed olanzapine 10mg once daily (OD). After failing to respond adequately to this treatment, sodium valproate 500mg twice daily (BD) was added to the regimen. **Methods:** A literature search was conducted using Medline Ovid and NCBI Pubmed databases. The search terms mania AND olanzapine AND valproate; acute mania AND pharmacotherapy and olanzapine AND mania were used. **Results:** Two studies were identified that addressed the efficacy and safety of olanzapine for the treatment of acute mania. Both studies confirmed the superior efficacy of olanzapine in the treatment of acute mania in comparison to placebo. There were no studies identified that directly addressed the question of whether use of combination therapy of olanzapine and sodium valproate was more efficacious than olanzapine monotherapy. **Conclusion:** There is no evidence currently available to support the use of combination olanzapine/sodium valproate as a more efficacious treatment than olanzapine alone.

Case report

GR is a 55 year old Vietnamese male with no previous psychiatric history who was seen by the Consultation and Liaison Psychiatry team at a Queensland hospital after referral from the Internal Medicine team. He was brought into the Emergency Department the previous day by his ex-wife after noticing increasing bizarre behaviour and aggressiveness. He had been discharged from hospital one week earlier after bilateral knee replacement surgery twenty days prior to his current admission. GR was assessed thoroughly for delirium caused by a general medical condition, with all investigations showing normal results.

GR was previously working as an electrician, but is currently unemployed and is on a disability benefit due to a prior back injury. He currently acts as a carer for his ex-wife who resides with him at the same address. He was reported to be irritable, excessively talkative with bizarre ideas, and sleeping for less than two hours each night for the past four nights. He has no other past medical history apart from hypertension which is currently well controlled with candesartan 10mg OD. He is allergic to meloxicam with an unspecified reaction.

On assessment, GR was dressed in his nightwear, sitting on the edge of his bed. He was restless and erratic in his behaviour with little eye contact. Speech was loud, rapid and slightly pressured. Mood was unable to be established as GR did not provide a response on direct questioning. Affect was expansive, elevated and irritable. Grandiose thought was displayed with flight of ideas. There was no evidence of perceptual disturbances, in particular any hallucinations or delusions. Insight and judgement was extremely poor. GR was assessed to have a moderate risk of violence. There was no risk of suicide or self harm or risk of vulnerability.

After a request and recommendation for assessment, GR was diagnosed with an acute manic episode in accordance with Diagnostic

and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria and placed under an involuntary treatment order. He was prescribed olanzapine 10mg OD. After failing to respond adequately to this treatment, sodium valproate 500mg BD was added to the regimen. Improvement with the addition of the new medication was seen within a number of days.

Introduction

A manic episode, as defined by the DSM–IV-TR, is characterised by a distinct period of abnormally and persistently elevated, expansive or irritable mood lasting at least one week (or any duration if hospitalisation is required) and is associated with a number of other persistent symptoms including grandiosity, decreased need for sleep, talkativeness, distractibility and psychomotor agitation, causing impaired functioning and not accounted for by another disorder. [1] Mania tends to have an acute onset and it is these episodes that define the presence of bipolar disorder. Bipolar I Disorder is characterised by mania and major depression, or mania alone, and Bipolar II Disorder is defined by hypomania and major depression. [1] The pharmacological management of acute mania involves primary treatment of the pathologically elevated mood. A number of medications are recommended including lithium, anti-epileptics either sodium valproate or carbamazepine and second generation antipsychotics such as olanzapine, quetiapine, risperidone, or ziprasidone. [2] Suggested approaches to patients with mania who fail to respond to a single medication include optimising the current drug; switching to a different drug or using drugs in combination. [2] GR was initially managed with olanzapine 10mg OD and then after failing to respond adequately, sodium valproate 500mg BD was added. This raises the following question: Is the use of combination therapy of olanzapine and sodium valproate more efficacious than olanzapine monotherapy?

Objective

The objective of this article was to review the literature and outline the evidence that is available, if any, for the effectiveness of olanzapine as a monotherapy for acute mania in comparison with the effectiveness of its use as a combined therapy with sodium valproate. The issue of long term outcome and efficacy of these two therapies is outside the scope of this particular report.

Data collection

In order to address the question identified in the objective, a literature

search was conducted using Medline Ovid and NCBI Pubmed databases with limits set to only include articles that were written in English and available as full text journals subscribed to by James Cook University. The search terms mania AND olanzapine AND valproate; acute mania AND pharmacotherapy AND olanzapine AND mania were used. A number of articles were also identified through the related articles link provided by the NCBI Pubmed Database. A number of articles including randomised controlled trials (Level II Evidence) and meta-analyses (Level I Evidence) were reviewed, however no study was found that compared the use of olanzapine as a monotherapy with the use of combined therapy of olanzapine and sodium valproate.

Discussion

Efficacy of olanzapine as a monotherapy

Two studies were identified that addressed the efficacy and safety of olanzapine for the treatment of acute mania. The first, by Tohen *et al.* in 1999 [3], was a random assignment, double blind, placebo controlled parallel group study involving a sample of 139 patients who met the DSM-IV-TR criteria for either a mixed or manic episode with 70 assigned to olanzapine 10mg OD and 69 to placebo. Both treatment groups were similar in their baseline characteristics and severity of illness with therapy lasting for three weeks. After the first day of treatment, the daily dosage could be increased or decreased by 5mg each day within the allowed range of 5-20mg/day. The use of lorazepam as a concurrent medication was allowed up to 4mg/day. [3] Patients were assessed at baseline and at the end of the study. The Young Mania Rating Scale was used as the primary efficacy measure with a change in total score from baseline to endpoint.

The study found those treated with olanzapine showed a greater mean improvement in total scores on the Young Mania Rating Scale with a difference of -5.38 points (95% CI -10.31-0.93). [3] Clinical response (decrease of 50% or more from baseline score) was also seen in 48.6% of patients receiving olanzapine compared to 24.2% of those assigned to placebo. [3] Improvement was also seen in other measures such as the severity of mania rating on the Clinical Global Impression – Bipolar version and total score on the Positive and Negative Symptom Scale. [3]

A second randomised, double blinded placebo controlled study was conducted by Tohen *et al.* in 2000. [4] This four week trial had a similar methodology with identical criteria for inclusion, primary efficacy measure and criteria for clinical response. It was, however, designed to also address some of limitations of the first trial, particularly the short treatment period, and to further determine the efficacy and safety of olanzapine in the treatment of acute mania. [4] The study design, method and assessment were clearly outlined. The study involved 115 patients and experienced a -6.65 point mean improvement in the Young Mania Rating Scale score and also showed a statistically significant greater clinical response in the olanzapine group compared to the placebo group. [4] Both studies confirmed the superior efficacy of olanzapine in the treatment of acute mania in comparison to placebo in a number of subgroups including mania versus mixed episode and psychotic-manic episode versus non-psychotic. [3,4]

The efficacy of olanzapine as monotherapy has also been compared to a number of other first line medications including lithium, haloperidol and sodium valproate. Two studies were identified that evaluated the efficacy of olanzapine and sodium valproate for the treatment of acute/mixed mania. Both demonstrated olanzapine to be an effective treatment. [5,6] Tohen *et al.* (2002) [5] showed olanzapine to have a superior improvement in mania rating scores and clinical improvement when compared to sodium valproate, however, this may have been affected by differences in dosage regimens between the study and mean model dosages. [7] Zajecka (2002) [6] described no significant differences between the two medications. In comparison to lithium, a small trial by Beck *et al.* in 1999 [8] described no statistically significant differences between the two medications. Similar rates of remission and response were shown in a twelve week double blinded study comparing olanzapine and haloperidol for the treatment of acute mania. [9]

The evidence presented from these studies suggests olanzapine at a dosage range of 5-20mg/day is an efficacious therapy in the treatment of acute manic episodes when compared to placebo and a number of other medications.

Efficacy of combination therapy of olanzapine and sodium valproate

As mentioned previously, there was no studies identified that directly addressed the question of whether use of combination therapy of olanzapine and sodium valproate were more efficacious than olanzapine monotherapy. One study by Tohen *et al.* in 2002 [10] was identified that investigated the efficacy of olanzapine in combination with sodium valproate for the treatment of mania, however this was in comparison to sodium valproate monotherapy rather than olanzapine.

This study was a six week double-blind, placebo controlled trial that evaluated patients with failure to respond to two weeks of monotherapy with sodium valproate or lithium. 344 patients were randomised to receive either combination therapy with olanzapine or continued monotherapy with placebo. [10] Efficacy was measured by use of the Young Mania Rating Scale with results showing combination therapy with olanzapine and sodium valproate showed greater improvement in total scores as well as clinically significant improved clinical response rates when compared to sodium valproate monotherapy. [10] This improvement was demonstrated by almost all measures used in the study. However, assignment to valproate or lithium therapy was not randomized with a larger number of patients receiving valproate monotherapy. This was noted as a limitation of the study. [10] The lack of an olanzapine monotherapy group within this study also prevents exploration of a postulated synergistic effect between olanzapine and the mood stabilisers such as sodium valproate. [10]

The study by Tohen *et al.* (2002) [10] does show that olanzapine when combined with the use of sodium valproate shows superior efficacy for the treatment of manic episodes than sodium valproate alone which may indicate that combination therapy may be more effective than monotherapy. Whilst suggestive that a patient not responding to initial therapy may benefit from the addition of a second medication, these study results cannot be generalised to compare olanzapine monotherapy and sodium valproate/olanzapine combination therapy.

Conclusion

When first line monotherapy for the treatment of acute manic episodes fails, the therapeutic guidelines recommend combination therapies as an option to improve response to therapy. [2] However there is no evidence currently available to support or disprove the use of combination olanzapine/sodium valproate as a more efficacious treatment than olanzapine alone. As no studies have been conducted addressing this specific question, the ability to comment about the appropriateness of the management of GR's acute manic episode is limited.

This review has revealed a need for further studies to be undertaken evaluating the effectiveness of combination therapy for the treatment of acute manic episodes. In order to answer the question raised, it is essential that a trial be conducted with a large sample size; placebo controlled involving monotherapy with olanzapine and combination therapy in order to ascertain what approach is most effective. Another potential area for future research is for further assessment of what approach is best for those patients who fail to respond to initial monotherapy (increase current dose, change drugs or addition of medications) and then to identify whether characteristics of the patient such as whether they are experiencing a manic or mixed episode has any influence on the effectiveness of particular pharmacotherapies. This information would provide more evidence on which to base future recommendations.

There is clear evidence that supports the efficacy of olanzapine

monotherapy in the treatment of acute mania as well as evidence suggesting combined therapy with sodium valproate is also an effective treatment; however a comparison between the two approaches to management was unable to be made. When evidence is lacking, it then becomes appropriate to consider the progress of the patient in order to assess the efficacy of the current management plan, as GR experienced considerable improvement, this may indicate that his current therapy is suitable for his condition.

Consent declaration

Informed consent was obtained from the patient for the original case report.

Conflicts of interest

None declared.

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