Research Review
SPEAKER SERIES

Bipolar Depression: new data and guidelines May 2010

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Professor Young's research interests focus on the cause and treatments for severe psychiatric illnesses, particularly mood disorders. His research has been supported by the UK Medical Research Council, the Wellcome Trust, the Stanley Medical Research Institute, the Canadian Institutes for Heath Research (CIHR), the National Institutes of Health (USA) and numerous other funding agencies. As a result, he has published over 300 peer-reviewed publications.

Professor Young trained in Medicine and Psychiatry at the University of Edinburgh. He has held academic appointments at the Universities of Edinburgh, Oxford and Newcastle upon Tyne, latterly holding the Chair of General Psychiatry at Newcastle.

Professor Young is the North American Editor of "Neuropsychiatric Disease and Treatment". He is also a member of numerous professional and scientific societies and is currently Treasurer of the International Society for Affective Disorders and a Fellow and Member of the executive council of the CINP.

This publication is a summary of a presentation by Professor Allan Young, Director of the Institute of Mental Health and holder of the Leading Edge Endowment Fund Chair in Research in the Department of Psychiatry at the University of British Columbia, Vancouver, Canada. Professor Young spoke about new data and guidelines to help further our understanding of bipolar depression in his address to mental health professionals at the recent RANZCP 2010 Congress in Auckland, New Zealand.

Mental health-related disorders are disabling and their burden is often underestimated. A recent study has shown that mental disorders and other neuropsychiatric conditions make up as much as 28% of all non-communicable diseases worldwide.[1] Mood disorders have been found to make up a significant proportion of that percentage, with bipolar disorder, and in particular its depressive phase, being a significant contributor.[1] Furthermore, bipolar depression is often misdiagnosed and frequently exhibits limited response to antidepressants. Not surprisingly then, bipolar depression is increasingly being recognised as one of the greatest challenges in modern psychiatry.[2] Despite this, the treatment of acute depressive episodes in bipolar disorder continues to be understudied and controversial.

A variety of drugs have been used to treat bipolar depression. For mild-to-moderate episodes of bipolar depression, most treatment guidelines advocate the use of first-line monotherapy with conventional 'mood stabilisers' especially lithium.[3-8] However, recent studies have shown that the response to lithium in such patients is modest and may take several weeks.[9-11] Recent studies have also shown that atypical antipsychotics may be effective in bipolar depression; olanzapine has been shown to have modest effects in bipolar depression, while quetiapine has been shown to have a robust effect in the treatment of this condition.[12-16] Recent guideline recommendations for acute bipolar depression reflect this clinical trial data, with quetiapine monotherapy now being included in the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines as a first-line therapy for bipolar depression.[17]

Bipolar disorder

Bipolar disorder is a complex disorder with multiple symptom domains including depression, mania, psychosis, anxiety, substance misuse, cognitive impairment, neuroendocrine abnormality and sleep disturbance. It is an illness that can occur at any age and the course of the illness is distinctively variable and multidimensional, presenting with symptomatically polar opposite phases (see Figure 1).[18] Subsyndromal states and co-morbidities are very common, especially the abuse of drugs and alcohol. Depression and cognitive impairment are increasingly being recognised as playing a big part in the clinical issues related to treatment of this disorder.

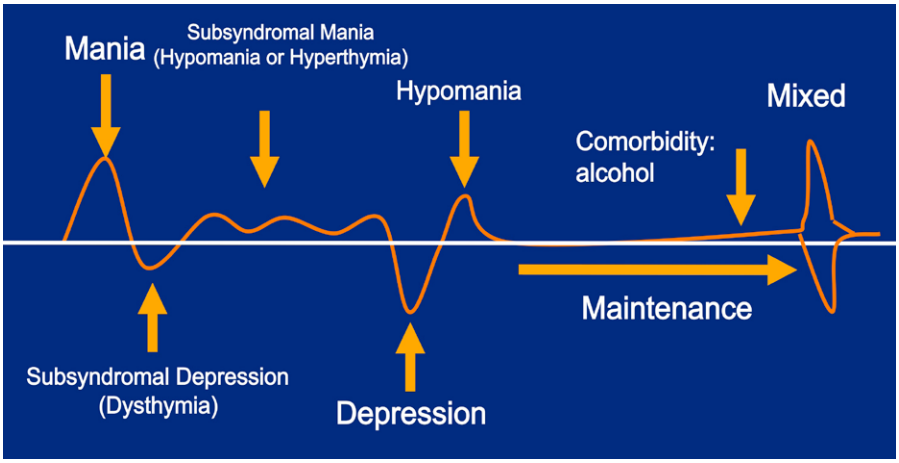

Figure 1: A schematic of the untreated disease course of a patient with bipolar I disorder. In a mixed manic state, patients meet the criteria for both a manic and a depressive episode.[18]

Limitations of conventional (typical) antipsychotics

Conventional antipsychotics such as haloperidol and chlorpromazine, have limitations including failure to correct primary disorders of thought, alleviate negative symptoms or associated depression, or to arrest disease progression. They have also been shown to have significant side effects including sedation, anticholinergic, antiadrenergic and hyperprolactinaemic effects, and extrapyramidal syndromes including tardive dyskinesia, dystonia and treatment-emergent Parkinsonism.[19-21] These

limitations appear to be at least as significant in bipolar disorder as they are in schizophrenia. In fact, a study investigating the use of haloperidol in patients with bipolar disorder or schizophrenia, showed that the incidence of treatment-emergent Parkinsonism was significantly ($p < 0.001$) higher in patients with bipolar disorder than in patients with schizophrenia.[22] It has also become clear that 50% of patients do not respond adequately to conventional antipsychotic drugs. Furthermore, compliance rates also tend to be low with these drugs and this non-compliance is partly attributable to side effects.

Atypical antipsychotics and the role of dopamine

Findings from pharmacological, structural and functional magnetic resonance imaging studies indicate that the dopaminergic system may play a central role in bipolar disorder just as it does in schizophrenia.[23] The blockade of dopamine D2 receptors appears to be necessary for the antipsychotic action of atypical antipsychotics. While the atypicals are not a particularly coherent pharmacological class, in that they do not have one single common mechanism of action, they do all tend to block dopamine D2 and serotonin 5-HT_{2A} receptors. There are, however, marked differences between the individual drugs in their affinity for these receptors.[24-26] While typical antipsychotics have been shown to have a narrow threshold of D2 receptor occupancy, studies have shown that atypical antipsychotics differ widely in their D2 receptor occupancy.[26-31] Given their pharmacological differences, the atypical antipsychotics should probably not be considered a `uniform' class of drugs.

Antipsychotics for bipolar mania

Antipsychotics have been used to treat mania since the mid 1950's and have been favoured over drugs such as lithium and valproate because they appear to have an early treatment effect. On the whole, treatment of mania is generally effective and we usually see considerable symptom resolution within the first 3-4 weeks of treatment.

More recently, the use of atypical antipsychotics in the treatment of bipolar mania has been investigated. A combined analysis, by Vieta and colleagues, of two placebo-controlled studies of quetiapine monotherapy up to 800 mg/day for the treatment of bipolar mania, showed a significant ($p < 0.05$) improvement in Young Mania Rating Scale (YMRS)[46] scores from Day 4 onward in the quetiapine group compared with placebo. The observed treatment advantage of quetiapine over placebo continued to increase to Day 21 and Day 84.[32]

Interestingly, all of the atypical antipsychotics investigated for treating bipolar mania appear to be roughly equivalent in their efficacy and are similar to the older drugs.[32-35] Additionally, extra antimanic efficacy can be seen when we use antipsychotic drugs together or if we combine them with lithium or divalproate.[36-38]

Bipolar Depression

We tend to think about bipolar disorder as an illness where patients have an episode and then return to full health. In actual fact, patients are symptomatic in the long-term and studies have shown that patients are only symptom free for approximately 50% of the time.[39,40] Furthermore, these studies revealed that the predominant symptom pole is depressive and this is evident even in bipolar I disorder.

Is it unipolar or bipolar?

Major depressive episodes are often not recognised as bipolar disorder. Hantouche and colleagues have shown that following an initial evaluation of 250 patients with mood disorders, 6% were diagnosed as bipolar I, 22% as bipolar II and 72% as unipolar. However, subsequent systematic evaluation revealed these rates were 6%, 40% and 54%, respectively.

In clinical practice, when we see an episode of depression, the first question should be `Is this bipolar or unipolar'? This diagnosis has significant implications for treatment.

So what should we be looking for?

Several clues indicate the likelihood of bipolar disorder in a patient who presents with depression.[41,42]

- Family history `loaded' with affective illness or substance abuse
- Early age of onset (< 25 years) with high episode rates
- Psychotic or atypical features
- Seasonal pattern
- Antidepressant `misadventures'
  - Treatment-emergent hypomania or agitation
  - Erratic or uneven antidepressant responses
  - Multiple antidepressant failures

Drugs for bipolar depression

Olanzapine

A study investigating the efficacy of olanzapine and olanzapine in combination with fluoxetine in the treatment of bipolar I depression was undertaken by Tohen and colleagues in 2003.[12] Their study randomized 833 adult patients with bipolar I depression and a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 20, to receive either placebo (n = 377), olanzapine 5-20 mg/day (n = 370) or olanzapine/fluoxetine 6/25 mg/day, 6/50 mg/day or 12/50 mg/day (n = 86). Their findings showed that olanzapine was significantly ($p < 0.001$) better at improving mean MADRS total scores than placebo and that olanzapine plus fluoxetine was significantly ($p < 0.001$) better at reducing MADRS scores than either olanzapine alone or placebo. This reduction in depressive symptoms was evident by week 1 of the trial and was maintained throughout the 8 weeks of the study. Interestingly, analysis of the individual MADRS items showed that olanzapine in combination with fluoxetine was significantly more effective in reducing the core mood symptoms of depression, including sadness, inability to feel, lassitude and pessimism, than olanzapine monotherapy or placebo. Furthermore, olanzapine monotherapy did not significantly differ from placebo on any of these core mood symptoms. These researchers did not investigate the effects of fluoxetine alone in this study because they believed that fluoxetine was highly likely to destabilize bipolar I depression. Based on these findings, it is questionable as to whether olanzapine monotherapy is a robust antidepressant in bipolar depression.

Lamotrigine

Studies by Calabrese and colleagues in the 1990's investigated the effects of the anticonvulsant lamotrigine on bipolar I depression and results indicated that the agent may have antidepressant efficacy.[43] These findings kicked off the use of lamotrigine for bipolar I depression. A recent meta-analysis undertaken by Geddes and colleagues of data from 1072 patients from five randomized controlled trials initiated by GlaxoSmithKline investigating the efficacy of lamotrigine in acute bipolar depression, showed an overall modest benefit for lamotrigine over placebo when the studies were pooled.[44] The effect of lamotrigine compared with placebo was not statistically significant in four of the individual studies and the pooled data show a difference that would be below clinical significance. Lamotrigine should still be considered a valuable antidepressant for bipolar depression, but the evidence for its benefit is weaker than we would have hoped.

Aripiprazole

The atypical antipsychotic aripiprazole, known for its antimanic effects, is a D2/D3 partial agonist. Attempts to show that it has antidepressant efficacy in bipolar disorder were undertaken by Thase and colleagues, who undertook two separate 8-week multicentre, randomized, double-blind, placebo-controlled studies investigating the efficacy of aripiprazole monotherapy in outpatients with bipolar I disorder who were experiencing a major depressive episode.[45] Studies 1 and 2 randomized 186 and 187 patients to aripiprazole, respectively, and both randomized 188 patients to placebo. In both studies, aripiprazole was initiated at 10 mg/day then flexibly dosed

at 5-30 mg/day. While statistically significant differences in the change in MADRS total score were observed during weeks 1-6, aripiprazole did not achieve statistical significance versus placebo at week 8 in either study. There may be other reasons for this observed effect, but nevertheless, based on this data we cannot say that aripiprazole monotherapy is anti-depressive in bipolar depression.

Ziprasidone

Preliminary unpublished studies have shown similar findings to those with aripiprazole, but these studies lacked robust methodology.

Quetiapine (Seroquel™)

Quetiapine is a blocker of the norepinephrine transporter and this may well be its foremost mechanism of action. It is also a D2, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptor antagonist.

Initial studies of quetiapine monotherapy, the well known BipOLar DEpRession (BOLDER) I and BOLDER II studies, indicated that quetiapine monotherapy was robustly antidepressant in the treatment of bipolar depression (see Figure 2).[13,14] In the BOLDER I study, 542 patients with bipolar I (n = 360) or II (n = 182) disorder experiencing a major depressive episode were randomly assigned to 8 weeks of quetiapine 600 mg/day (n = 180), quetiapine 300 mg/day (n = 181) or placebo (n = 181).[13] The findings showed that quetiapine at a dose of either 600 mg/day or 300 mg/day was associated with significantly ($p < 0.001$) greater mean improvements in MADRS total scores (the primary outcome measure) compared with placebo from week 1 to week 8 (see Figure 2). The same findings were found for Hamilton Depression Scale total scores. Furthermore, evaluation of the 10 individual MADRS items showed that 8 items were significantly ($p < 0.05$) improved from baseline compared with placebo in 300 mg/day quetiapine recipients, as were 9 items in the quetiapine 600 mg/day group; these items included apparent sadness, reported sadness, inability to feel, pessimistic thoughts and suicidal thoughts. The BOLDER II study involving 509 patients with bipolar I or II depression, randomized to either quetiapine 300 mg/day, quetiapine 600 mg/day or placebo, showed similar findings to the BOLDER I study.[14]

Following on from the BOLDER studies, the Efficacy of Monotherapy Seroquel in BipOLar DEpressioN (EMBOLDEN) I study by Young and colleagues was undertaken to compare the efficacy of quetiapine with that of lithium 600-1800 mg/day, and the EMBOLDEN II study by McElroy and colleagues was undertaken to compare the efficacy of quetiapine with that of the antidepressant SSRI paroxetine 20 mg/day in bipolar depression.[15,16] The EMBOLDEN studies followed the design of the BOLDER studies with both quetiapine 300 mg/day and 600 mg/day being used, and investigated the acute phase up to 8 weeks with change in MADRS total score as the primary outcome measure. Both studies also incorporated a continuation phase, where patients who had responded to quetiapine in the acute phase were randomized to receive quetiapine 300 mg/day or 600 mg/day for between 26 and 52 weeks. In both of the EMBOLDEN studies, quetiapine separated from placebo at week 1 and continued on to week 8 (see Figure 3). Lithium did not separate from placebo and it has been suggested that lithium's effects may be slow; if this study had gone on for longer, a response may have been observed with lithium. Therefore, while lithium appears to be ineffective in the acute phase of this illness, it should not be discarded as an augmenter or for longer term treatment. The EMBOLDEN II study again showed that quetiapine 300 and 600 mg/day separated from placebo for an antidepressant effect but paroxetine did not. However, paroxetine did have an anxiolytic effect. Findings from the continuation phase, which have been submitted for publication, revealed that quetiapine has a robust effect at 1 year for preventing relapse of a mood event or depression (see Figure 4).

Both of the EMBOLDEN studies used the YMRS[46] score to investigate treatment-emergent mania/hypomania. In both studies, quetiapine at either dosage, lithium or paroxetine did not significantly increase the incidence of this adverse effect compared with placebo.

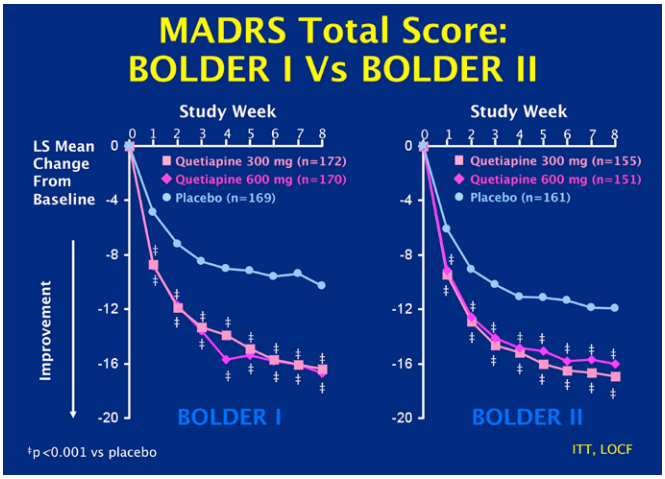

Figure 2: Quetiapine at both 300 mg/day and 600 mg/day doses significantly reduced MADRS total scores compared with placebo in patients with bipolar depression in both the BOLDER I and BOLDER II studies.[13,14] ITT = intent to treat, LOCF = last observation carried forward, LS = least squares

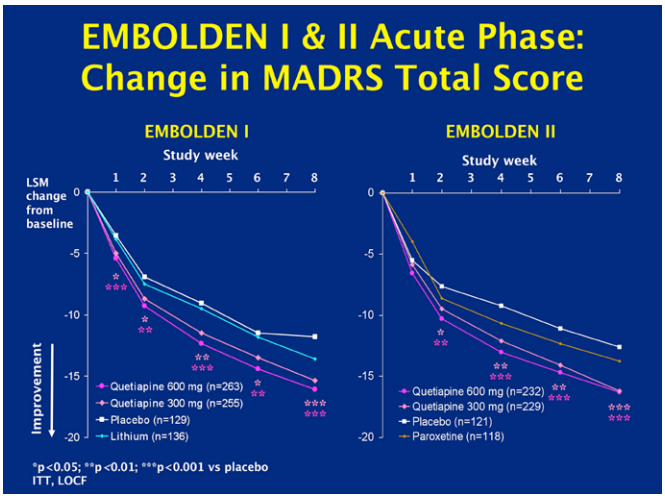

Figure 3: Quetiapine at both 300mg/day and 600 mg/day doses significantly reduced MADRS total scores compared with placebo in patients with bipolar depression in both the EMBOLDEN I and EMBOLDEN II studies. Lithium and paroxetine did not significantly differ from placebo.[15,16] ITT = intent to treat, LOCF = last observation carried forward, LSM = least squares means

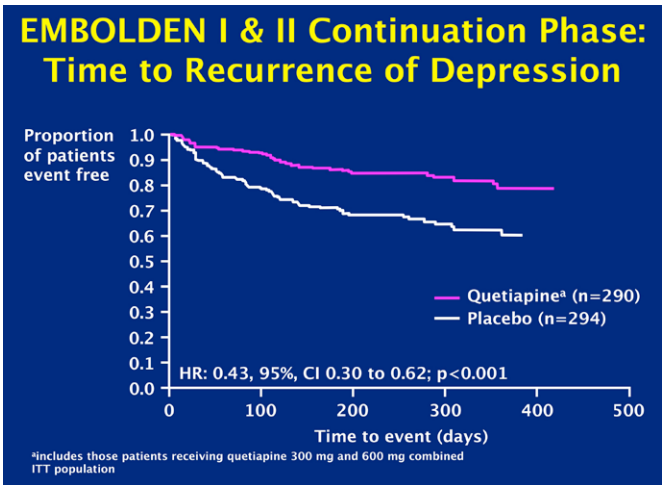

Figure 4: EMBOLDEN I and II continuation studies show a robust long-term effect for quetiapine compared with placebo in time to recurrence of depression. ITT = intent to treat

In summary:

- Atypical antipsychotics were introduced for schizophrenia
- Atypical antipsychotics are all antimanic
- Olanzapine monotherapy has modest efficacy in bipolar depression
- Aripiprazole and ziprasidone have failed to show antidepressant efficacy in bipolar depression
- Quetiapine has been shown to be antidepressant in bipolar depression
- Quetiapine has demonstrated pharmacological effects which may underlie these antidepressant effects
- Quetiapine is included as a first line option in CANMAT guidelines[47]

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