

ATYPICAL ANTI-PSYCHOTICS IN ADULT BIPOLAR DISORDER: CURRENT EVIDENCE AND UPDATES IN THE NICE GUIDELINES

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SUMMARY

Background: The introduction of atypical antipsychotics in the management of adult bipolar disorder has been increasingly adopted in clinical setting. While new studies continue to emerge, NICE has recently updated the guidelines on the assessment and management of bipolar disorder.

Aim: To review the efficacy and tolerability profiles of atypical antipsychotics used to treat adult bipolar disorder in clinical practice, in relation to the latest NICE guidelines.

Methods: The recent NICE guidelines (CG185), published in September 2014 was analysed to identify second generation antipsychotics (SGA) for the various presentations of bipolar disorder in adults. A qualitative literature search was conducted to review the evidence to support these changes, and identify randomized controlled trials on off-label and newer SGAs.

Results and conclusions: With respect to atypical antipsychotics, NICE guidelines introduced olanzapine and fluoxetine combination therapy as first line treatment for moderate to severe bipolar depression; and improved clarity on the treatment of mania, hypomania and rapid cycling bipolar disorder. Evidence from our literature search favour these changes; and recognized other atypical antipsychotics such as aripiprazole, asenapine, lurasidone, ziprasidone and clozapine which could be of potential clinical benefit.

Key words: atypical antipsychotics - bipolar disorder - quetiapine - olanzapine - fluoxetine - risperidone - aripiprazole - asenapine - lurasidone - ziprasidone - clozapine - adult - NICE guidelines

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INTRODUCTION

Bipolar disorder is a chronic relapsing and remitting affective disorder, characterized by extreme mood fluctuations, ranging from mania to severe depressive episodes (Anderson et al. 2012, WHO ICD-10 F31, 1992). Mania is described as having “elated” mood, often associated with reduced need for sleep, amplified self-esteem, delusions of grandeur, pressured speech, and higher incidences of impulsive risk-taking behaviour. Conversely, depressive episodes present with similar symptoms as clinical depression – low mood, anhedonia, fatigue, guilt, worthlessness, lack of motivation, suicidality and associated biological disturbances including weight changes and concentration difficulties (Kendal et al. 2014).

Management of bipolar disorder depends on the onset and mode of presentation (mania, depressive, mixed picture); and follows a comprehensive physical and psychological assessment of patients, and involves a multidisciplinary team approach. The fluctuations in mood, complex presentations and symptom burden of bipolar disorder pose difficulties in identifying and maintaining curative treatment among patients. Traditionally, mood stabilisers such as lithium and valproate have been used as first line pharmacological treatments; antipsychotic medications, particular atypical or second

generation antipsychotics (SGAs) have been increasingly used in clinical practice with good efficacy (Grohol 2008). We aim to review the value of atypical anti-psychotics in the management of adult bipolar disorder, in conjunction with the recently updated NICE guidelines.

METHODS

Both the old and new National Institute for Health and Care Excellence (NICE) guidelines, and the British National Formulary (BNF) were reviewed, with a particular emphasis on second-generation or atypical antipsychotics in adult bipolar disorder. Subsequently, a literature search was conducted over PubMed, Cochrane Library (www.thecochranelibrary.com), MEDLINE, EMBASE and PsychInfo databases, for high-quality, independent, and highly sensitive randomized controlled trials (RCT) with search terms ‘atypical antipsychotic* (MESH)’, and ‘bipolar*’ in the article title, abstract or keywords. The search terms were narrowed to only include full text publications that were conducted in adult human populations, restricted by age between 18 to 64 years and in English Language. Articles were selected based on relevance to the clinical question i.e. evaluating the effectiveness of atypical antipsychotics in bipolar disorder for this subset of patients. Efficacy and

safety data from these trials were evaluated, and primary outcome measures which included mean changes in Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS) and/or Clinical Global Impressions Scale (CGIS) scores were sought (Montgomery and Ashberg 1979, Young et al. 1978, Guy 1976).

CURRENT GUIDELINES (SEPTEMBER 2014)

NICE guidelines

As recent as September 2014, NICE guidelines (CG185) have replaced NICE (CG38), published in July 2006 on the assessment and management of bipolar disorder. Care of bipolar patients across all ages, with a heavy focus on psychological therapy especially for younger patients and the maintenance of good physical health were highlighted in the latest issue. Key changes with respect to pharmacological management of adult bipolar disorder are summarized in Table 1.

British National Formulary (BNF) Guidance: Atypical Antipsychotics

Table 2 summarises the BNF recommendations for atypical anti-psychotics in the management of adult

bipolar disorder in terms of indications, dosage, and main side effects profile.

RESULTS: EVIDENCE FROM LITERATURE SEARCH

Quetiapine

Quetiapine 300-600mg/day is a well-established SGA used to treat bipolar disorder. A disproportionately high number of RCTs, particularly BOLDER I and II, and EMBOLDEN I and II have been conducted, proving its efficacy (Calabrese et al. 2005, Thase et al. 2006, Young et al. 2010, McElroy et al. 2010, Young et al. 2013).

BOLDER studies (Calabrese et al. 2005, Thase et al. 2006) evaluated the impact of quetiapine monotherapy on bipolar depression, and concluded significant improvements in MADRS scores in both rapid cycling and non-rapid cycling subgroups ($P \leq 0.01$). Response and remission rates (53% versus 28.4% placebo) were also significant; and cumulatively, these results were illustrated as early as the first week and maintained throughout study. They also reported that the most common side effects were dry mouth, constipation, somnolence, sedation and dizziness; of which, the latter three side effects were resolved by once-daily administrations of quetiapine in the evenings, and in addition, tackled insomnia issues and improved the quality of sleep in a subset of patients.

Table 1. Comparing the old and new NICE guidelines on the Assessment and Pharmacological Management of Adult Bipolar Disorder

Changes	NICE CG38 (July 2006)	NICE CG185 (September 2014)
Management of mania	<i>Acute mania:</i> Lithium, olanzapine, quetiapine, risperidone, valproate semisodium <i>Rapid Cycling Bipolar Disorder:</i> Lithium and valproate as first line, Lithium monotherapy as 2 nd line. If patients are already on Lithium, consider increasing the dose. Consider combinations of Lithium/Valproate with lamotrigine in bipolar II disorder with rapid cycling.	<i>Mania, Hypomania, Rapid Cycling Bipolar Disorder:</i> Lithium, haloperidol, olanzapine, quetiapine, risperidone Do not offer lamotrigine to treat mania
Moderate/Severe depressive episodes	SSRI (paroxetine should not be given to pregnant women), quetiapine if already on anti-manic medications that is not an antipsychotic. Consider increasing the dose of anti-manic agent or addition of second anti-manic agent including lamotrigine in patients with rapid cycling bipolar disorder, recent hypomanic episode, recent functionally impairing rapid mood fluctuations	Offer fluoxetine and olanzapine, or quetiapine on its own (if not already on other drugs) Consider lamotrigine if there is no response to fluoxetine and olanzapine, or quetiapine alone If already on Lithium, consider increasing Lithium dose to maximum, then add fluoxetine and olanzapine, or quetiapine alone
Long term Management	Lithium, olanzapine, valproate; combinations are possible where there are frequent relapses Carbamazepine can be used for prophylactic treatment, with specialist advice.	1 st line: Lithium If Lithium is ineffective, consider valproate. If Lithium is poorly tolerated/unsuitable, consider valproate or olanzapine. Consider quetiapine if Lithium has been effective during a previous manic/depressive episode

Table 2. Summary of the BNF guidelines of Atypical Antipsychotics used in Bipolar Disorder

Atypical Antipsychotic	Indications	Dose	Side Effects/Contraindications
Quetiapine	Mania	50mg BD on day 1, 100mg BD on day 2, 150mg BD on day 3, 200mg BD on day 4; max. 200mg/day	Dyspnoea, elevated triglyceride-cholesterol concentrations, peripheral oedema, increased appetite, sleep disorders. Avoid in breastfeeding
	Bipolar depression	50mg OD (night) on day 1, 100mg OD on day 2, 200mg OD on day 3, 300mg OD on day 4; max. 600mg/day	
Olanzapine	Monotherapy for mania	By mouth: 15mg daily adjusted to usual range of 5-20mg/day. Max. 20mg/day.	Side effects: increased appetite, hypertriglyceridaemia, hypercholesterolaemia, bradycardia, arthralgia, oedema, malaise
	Control of agitation/disturbed behaviour in schizophrenia/mania	IM injection: 5-10mg followed by 2.5-5mg after 2 hours if necessary; max. 3 injections/day for 3 days. Max. daily combined oral and parenteral dose 20mg.	Contraindications (injection): acute myocardial infarction, unstable angina, severe hypotension or bradycardia, sick sinus syndrome, recent heart surgery Pregnancy: only use if benefit outweighs risk; neonatal lethargy, tremor, hypertonia when used in 3 rd trimester Avoid in breastfeeding
Aripiprazole	Treatment and recurrence prevention of mania	15mg OD, max. 30mg	Hypersalivation, anxiety, drowsiness, malaise; less commonly depression Avoid in breastfeeding

EMBOLDEN studies replicated the anti-depressant findings and side-effect profile of BOLDER trials; but also imply that quetiapine 600mg/day was more effective than lithium since lithium did not generate statistical significance compared to placebo in these trials (Young et al. 2010, McElroy et al. 2010). Other discrepancies include the reduction in the emergence of treatment-related mania in EMBOLDEN trials compared to BOLDER studies. Suppes et al. 2010 also support the use of quetiapine 300mg/day monotherapy in extended release formulation in the treatment of acute bipolar depression (Suppes et al. 2010).

It is interesting to note that EMBOLDEN studies represent the only group indirectly comparing lithium with quetiapine for the treatment of acute depression; there are no RCTs to-date on the combination treatments of quetiapine and lithium in the management of bipolar depression. Pooled analyses by Vieta et al. 2012 however demonstrated the sustained benefit of quetiapine in combination with lithium or divalproex on mixed symptoms in bipolar I disorder over 12 to 36 weeks (Vieta et al. 2012). Mood events, symptom severity and risk of recurrences were significantly reduced in the treatment group, and quetiapine was shown to prolong time to manic, depressive or mixed event compared to placebo.

Quetiapine monotherapy or in combination with lithium or divalproex was also significantly effective in managing acute bipolar mania across a broad range of measured parameters, independent of baseline mania severity, presence of psychosis and development of somnolence or sedation (McIntyre et al. 2007). As with

its anti-depressant effects, its clinical effects were exerted early, within 4 days of initiation of treatment of quetiapine monotherapy and 7 days of combination therapy.

NICE recommends that quetiapine should be prescribed in mania, hypomania, and rapid cycling bipolar disorder; and considered as long term management only if lithium has been effective during a previous manic or depressive episode. In addition, either a combination therapy of olanzapine and fluoxetine or quetiapine monotherapy should be prescribed for moderate to severe depressive episodes. Available high-quality evidence, described above support the implementation of these recommendations.

Olanzapine and Fluoxetine

Olanzapine 5-20mg monotherapy in the treatment of mania was shown to be superior to placebo groups, with significant improvements in YMRS scores from baseline to end-point across selected RCTs (Baker et al. 2002, Baker et al. 2003, Tohen et al. 1999). Similarly, reports by Tohen et al. 2012 and De Fruyt et al. 2012 confirm its usefulness in bipolar depression in terms of MADRS scores, response and remission rates (Tohen et al. 2012, De Fruyt et al. 2012).

Olanzapine and fluoxetine as combination therapy (OFC) is a newly licensed recommendation to treat moderate to severe depressive episodes in bipolar disorder. Indeed these findings were established by Amsterdam and Shults 2005, Corya et al. 2006 and Tohen et al. 2003; importantly, the latter group

demonstrated that OFC was superior in all efficacy measures to olanzapine and placebo, with higher completion rates, lower discontinuation rates due to adverse events, higher rates of response and remission and quicker times to response and remission (Amsterdam and Shults 2005, Corya et al. 2006 and Tohen et al. 2003).

Concerns have been raised in the past that prescription of anti-depressants could cause the exacerbation of mania in bipolar patients (Ghaemi et al. 2003). Results from Tohen et al. 2003 reveal no significant differences in the incidences of treatment-emergent mania between groups; but instead exhibit small significant improvements in manic symptom ratings (Tohen et al. 2003). This group also reports no significant differences in adverse effects using OFC versus olanzapine, with the exception of higher incidences of nausea and diarrhea in the OFC group.

Both olanzapine and OFC have also shown to be efficacious against active mood stabilizers such as divalproex and lithium in the treatment of acute mania (Tohen et al. 2002, Tohen et al. 2003, Niufan et al. 2007, Cipriani et al. 2011). Symptom improvements and response rates with olanzapine were significant compared to lithium carbonate (Niufan et al. 2007), although there were significantly higher incidences of adverse events such as weight gain compared to the lithium group. Other adverse effects associated with olanzapine in this study include constipation, nausea, somnolence, nasopharyngitis, vomiting, diarrhea, dizziness and restlessness; and this is comparable across other trials. The statistically significant superiority of OFC versus lamotrigine in terms of changes in CGI-S, MADRS, and YMRS scores from baseline in bipolar depression was highlighted by Brown et al. 2009 (Brown et al. 2009). Similarly, the OFC group had significantly more treatment-emergent adverse effects than the lamotrigine group, where the OFC group reported higher rates of somnolence, sedation, weight gain and hypercholesterolaemia.

Risperidone

The most recent NICE guidelines⁵ recommend risperidone among other drugs in the treatment of mania, hypomania, and rapid cycling bipolar disorder. Apart from olanzapine, Cipriani et al. 2011 concluded the superiority of risperidone compared to mood stabilisers and haloperidol, in the treatment of acute mania (Cipriani et al. 2011). Both risperidone monotherapy (Hirschfeld et al. 2004, Vieta et al. 2012) and in combination with a mood stabilizer (Sachs et al. 2002) resulted in significant and rapid improvements in the mean YMRS from baseline to endpoint, in addition to other secondary outcome measures compared to the placebo group. There were no convincing trials demonstrating its usefulness against depressive episodes of bipolar disorder.

Aripiprazole

Aripiprazole has previously been described crudely as a “cleaner drug” compared to olanzapine, i.e. effective but less metabolic associated side effects. RCTs evaluating the treatment outcomes of aripiprazole alone versus placebo for bipolar disorder were limited; there were however marginally more studies involving aripiprazole in combination with other drugs such as lamotrigine (Carlson et al. 2012) or as adjunctive therapy (Marcus et al. 2011, Yatham et al. 2012).

Of those that did, the AMAZE study by Kanba et al. 2012 concluded the efficacy and safety of aripiprazole in the treatment of acute manic or mixed episodes (Kanba et al. 2012). The benefits of aripiprazole were observed as early as day 2 and maintained throughout the length of study by Young et al. 2009 (Young et al. 2009). However, only early efficacy was replicated by the change in MADRS and CGI-BP Severity Illness-Depression score in bipolar depression, but this was not sustained at the end-point of two randomized controlled trials (Thase et al. 2008). Aripiprazole as adjuncts to mood stabilizers have been proposed, but have yielded mixed results (Vieta et al. 2010, Carlson et al. 2012, Quante et al. 2010). These results suggest aripiprazole is only of value in the management of acute manic or mixed episodes, but not depressive episodes; and this was reiterated by reviews conducted by Brown et al. 2013, De Fruyt et al. 2012 and Cipriani et al. 2011 (Brown et al. 2013, De Fruyt et al. 2012, Cipriani et al. 2011).

In terms of side-effects, results from Brown et al. 2013 suggest that aripiprazole was not significantly different from placebo in terms of weight gain, defined as $\geq 7\%$ increase in body weight, which was one of the commonly reported side effects of olanzapine (Brown et al. 2013, De Fruyt et al. 2012). However, there was a significant increase in EPS-related adverse events and movement disorders in the aripiprazole group, compared to placebo and lithium, but not against haloperidol.

Asenapine

Early and sustained benefit of asenapine in acute manic states was described by McIntyre et al. 2009 and McIntyre et al. 2009; whilst Szegedi et al. 2011 reports its efficacy in reducing depressive symptoms in patients with bipolar I disorder presenting with manic or mixed episodes (McIntyre et al. 2009, McIntyre et al. 2009, Szegedi et al. 2011).

Asenapine also showed no significant difference in efficacy when compared against olanzapine in acute mania (McIntyre et al. 2009). Interestingly, in mixed states defined by DSM V (American Psychiatric Association, 2013), asenapine demonstrated superiority in the change of YMRS scores over olanzapine in reaching statistical significance regardless of depressive symptom severity, whilst olanzapine was superior to

placebo only at lower baseline scores (McIntyre et al. 2013). Superiority over olanzapine in bipolar depression was also confirmed by Szegedi et al. 2011 at certain points during the trial (Szegedi et al. 2011).

Commonly associated side effects include somnolence, sedation, and nausea, with weight gain, metabolic and EPS-related adverse events being comparable to other second generation anti-psychotics, but not aripiprazole and ziprasidone (McIntyre et al. 2009, McIntyre et al. 2010). Importantly, discontinuation rates of asenapine due to adverse events were low, favouring its long term use.

Pooled analyses of these results (Azorin et al. 2013) imply that asenapine is therefore beneficial as acute and maintenance treatment of mania, depressive episodes and mixed states, thus should be considered in clinical practice. However, its efficacy was disputed by Cipriani et al. 2011, warranting the increased need for prospective trials to assess the value of asenapine as monotherapy or adjuncts to mood stabilizers in the different subtypes of bipolar disorder (Cipriani et al. 2011).

Ziprasidone, Lurasidone and Clozapine

Due to the overlap between bipolar disorder and schizophrenia, atypical antipsychotics used to treat schizophrenia such as ziprasidone have been trialed with bipolar patients. Limited number of RCTs by Vieta et al. 2010 and Mech 2008 illustrated the benefits of ziprasidone monotherapy in bipolar I disorder patients presenting with mania, depressive or mixed episodes (Vieta et al. 2010, Mech 2008). Anti-depressant effects were also confirmed in a study by Bartolommei et al. 2014 with ziprasidone-clozapine combination therapy (Bartolommei et al. 2014). Ziprasidone seems to be an attractive option since it does not seem to be related to metabolic adverse effects associated with SGAs (Sacher et al. 2007). Nonetheless, there have been a few case reports (Baldassano et al. 2003) associating ziprasidone with the induction of hypomania and mania. Further comparative and longitudinal assessments are necessary, before firm conclusions can be made.

Lurasidone 20-120mg/day is a relatively new atypical antipsychotic, which could potentially be beneficial in patients with bipolar disorder. Woo et al. 2013 neatly reviews its efficacy as mono- and adjunctive treatment with lithium or valproate in bipolar depression from two RCTs (PREVAIL-1 by Calabrese et al. 2012 and PREVAIL-2 by Loebel et al. 2013) (Woo et al. 2013). Anxiety and depression scores were reduced, achieving similar NNT values for quetiapine and olanzapine-fluoxetine combination (Citrome et al. 2013), however not without adverse effects. Preliminary findings from PREVAIL-1 and PREVAIL-2 show that the commonest adverse events were nausea, headache, somnolence and akathisia. However, metabolic and weight changes were minimal, which suggest that lurasidone could potentially be better tolerated than SGAs.

Although clozapine's antipsychotic efficacy have been well-documented in the management of treatment-resistant schizophrenia (Wahlbeck et al. 1999), interestingly there have been limited RCTs conducted on its use in bipolar disorder. Suppes et al. 1999 represents one of the few groups who demonstrated significant clinical improvements and independent mood-stabilizing properties of clozapine in bipolar patients with mania compared to treatment as usual (Suppes et al. 1999).

CONCLUSION

We appraised the recent changes to the NICE guidelines with respect to the value of atypical antipsychotics for the treatment of adult bipolar disorder; and reviewed the evidence surrounding the efficacy and safety of current SGAs utilized in clinical practice. We not only support the changes undertaken in NICE CG185; but also provide evidence for and against the use of other SGAs which are not yet recommended by NICE, and pose interesting questions on the management of adult bipolar disorder in clinical practice.

We conclude that olanzapine monotherapy and in combination with fluoxetine, quetiapine, risperidone, aripiprazole and asenapine are useful in the management of adult bipolar disorder in the subsets of mania, depression or mixed episodes. All of these drugs have anti-manic effects; however only olanzapine, OFC, quetiapine and asenapine demonstrate anti-depressant features. NICE-recommended atypical antipsychotics, namely olanzapine, OFC, quetiapine, and risperidone were all shown to be rapidly acting, with their effects maintained throughout the course of RCTs. However, RCTs involving aripiprazole, a commonly prescribed drug for bipolar depression were less convincing. Despite having marginally fewer weight-related side effects compared to olanzapine and significant early improvements in some trials, aripiprazole was not efficacious at later stages. Asenapine, on the other hand, was shown to be effective in both the acute and long term management of all modalities of bipolar disorder, and could potentially be of benefit to some patients. Given the scarcity of trials on other atypical antipsychotics, such as lurasidone, clozapine and ziprasidone, firm conclusions cannot be made at this stage, however early trials seem promising.

In conjunction with the latest NICE CG185 recommendations, the choice of atypical antipsychotic(s) should therefore be based on a careful balance between efficacy, tolerability and adverse effects, patient preference, previous trials and tailored to specific physical needs; whilst considering other interventions including but not limited to mood stabilisers, psychological management and patient education. Newer antipsychotics offer attractive alternatives to existing medications; however their clinical use is presently limited due to the lack of controlled trials.

Limitations of our study include a qualitative and retrospective analysis of the literature, with restrictions to general adult patients and age. The focus of our study was mainly towards drug versus placebo trials, with limited inclusion of RCTs considering combination or adjunctive therapies. Further research would benefit from more prospective randomized controlled trials evaluating the efficacy of existing and newer atypical antipsychotics such as lurasidone, and different combinations of drug regimens in order to maximize clinical benefit whilst minimizing adverse events. The assessment of established atypical antipsychotics could also be trialed on different subgroups of patients.

Acknowledgements: None.

Conflict of interest: None to declare.

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