The role of atypical antipsychotics in treatment of bipolar disorder

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Abstract

In the 1990s, a new group of antipsychotics emerged, also known as second-generation and described as atypicals because of the low incidence of extrapyramidal side-effects (EPSE). These drugs were considered to be a great step forward in the treatment of schizophrenia; the low incidence of EPSE allowed patients to avoid the stigma of the well-recognised movement problems caused by the typical antipsychotics. Almost a decade later, these atypical drugs began to be used widely in bipolar disorder. In this paper we review their pharmacology, neurobiology and uses in various forms of bipolar disorder.

Key words: bipolar disorder, atypical antipsychotics

Introduction

Antipsychotic drugs, also known as 'neuroleptic' drugs, were originally used to treat schizophrenia, first being demonstrated to act against psychosis in 1953 (1). The first generation of antipsychotics largely exerted their action through antagonism of the dopamine D2 receptor and included drugs such as chlorpromazine and haloperidol. These first-generation drugs are sometimes described as 'typical' due to their extrapyramidal side effects (EPSE).
In the 1990s a new generation of antipsychotics emerged possessing a higher affinity for 5-HT2A receptors than for D2 receptors (2). Initially marketed for the treatment of schizophrenia, these were termed 'atypical' antipsychotics because of the lower rates of associated EPSE and their different pharmacology. These atypical drugs include, risperidone, olanzepine, sertindole, quetiapine, asenepine, zotepine, aripiprazole and amilsulpride, although the mechanisms of action of aripiprazole and amilsulpride are somewhat different from the rest, aripiprazole being a partial dopamine agonist and amilsulpride being a selective D2/D3 antagonist (2). Clozapine, which is reserved for the treatment of resistant schizophrenia in the UK, is also considered to be among the atypical antipsychotic drugs (3). Although in recent years some have claimed that the distinction between typical and atypical antipsychotics is artificial and misleading (4,5), nevertheless, there is convincing evidence that typical and atypical antipsychotics exert different effects on neurosurvival and neurogenesis, the former promoting apoptosis, and the latter enhancing neurogenesis (6).

Over the last decade, atypical antipsychotics have often become the treatment of choice for bipolar disorder. There has been a surge in their popularity for the treatment of bipolar disorder (7). However, it should be noted that research has largely centred on bipolar-I disorder and consequently any implications for bipolar II disorder, mixed state or cyclothymia should be considered with caution. In the UK, NICE now recommends atypical antipsychotics as first-line for treatment of mania and preventative therapy, as well as second-line for treatment of bipolar depression (8). To explore the role of atypical antipsychotics in bipolar disorder, we shall examine the putative neurobiology that underlies their action. The ideal would be to have a single drug to treat mania, depression and mixed states in addition to providing long-term maintenance. However, the reality is that these entities constitute different indications and consequently each will be discussed separately. Because there are significant contraindications to the treatment of bipolar disorder with alternative drugs, notably lithium and antiepileptic drugs, treatment with atypical antipsychotics in particular groups will be discussed. A treatment algorithm will then be proposed.

Neurobiology

Receptor Specificities

Since olanzapine, quetiapine and risperidone have similar pharmacology and are all commonly used as mood stabilisers, the discussion will be focused on their properties. Atypicals have a variety of receptor activities, possessing serotonergic (5-HT1A and 5-HT2A), dopaminergic (D1 and D2), histaminergic (H1), adrenergic (α1and α2) and cholinergic (M1) affinities (9). To discuss all of these would be beyond the scope of this paper. Some of the actions that have been less studied will be discussed.

Atypicals are partial agonists of the 5-HT1A receptor, which is a presynaptic receptor on serotonergic neurons. (9) That is, these drugs act to create a consistent level of inhibition of serotonin release. SSRIs similarly increase the stimulation of these autoreceptors by increasing the amount of 5-HT in the synapse. The partial agonist activity of atypicals could be perceived as mood-stabilising by avoiding extremes of serotonin discharge, according to the monoamine hypothesis. Since its conception, much of the research surrounding this monoamine hypothesis has focussed on serotonin and noradrenaline; increasingly, however, there is a growing awareness of the importance of dopaminergic signalling in bipolar disorder. Higher CSF levels of the dopamine metabolite homovanillic acid (HVA) are found in mania, while concentrations are reduced in depression. Moreover, DA levels in the mesocorticolimbic system, which are associated with motivation and reward, are found to be high in mania and low in depression. This finding has the helpful corollary of providing a putative explanation for the causal role of stress in the pathogenesis of depression, since glucocorticoids reduce DA levels in the prefrontal cortex, while long-term use of antidepressants is able to elevate it (3). Nonetheless, while the D2 antagonism of atypicals is considered an important aspect of their function, they have a much lower affinity than typical antipsychotics, so it is thought that this may underly their comparatively small dysphoric effect (9).

As well as directly antagonising dopaminergic function, atypicals also indirectly act on DA release by antagonising presynaptic 5-HT2A receptors on dopaminergic neurons. This has the result of enhancing DA release in the prefrontal cortex (9). Atypicals thus cause a rather paradoxical action on mesocorticolimbic dopamine, increasing levels but decreasing responsiveness; it is possible that the latter is counteracted by the former but it seems likely that the brief adherence of the drug molecule to the D2 receptor permits some response to the raised synaptic DA.

To summarise this evidence, it is not possible to delineate, with any great specificity, the exact mechanism of action of atypicals at the receptor level, but it does seem likely that mood stabilisation requires a balance beween 5-HT and DA that is particular to different brain regions (9). It is possible that atypicals might raise mood through serotonin but prevent the mediation of mania by dopaminergic reward.

Distant Actions

As well as the direct actions of atypicals, their function on downstream processes has also been explored, notably in relation to neurogenesis, neurosurvival and neuroplasticity. These mechanisms will be explored briefly, through some examples.

In simple terms, olanzapine has been shown to up-regulate Bcl-2 (which protects against apoptosis), CREB (a transcription factor mediating the long-term effects of activation of the cAMP pathway) and BDNF (which promotes neurogenesis and facilitate neuroplasticity). (10) In addition, quetiapine has been shown to prevent the down-regulation of BDNF caused by stress. (3)
Glycogen synthase kinase-3 (GSK-3) is known to alter neuronal function by several mechanisms, affecting gene expression and modifying survival and plasticity of neurons. Its activity is also found to be abnormal in affective disorders, so it seems a likely target for pharmacotherapy. It is inactivated by phosphorylation via the Akt (PKB) pathway, which can itself be modulated by the downstream targets of both dopamine and serotonin. Both antidepressants and quetiapine result in GSK-3 inhibition in mice, the effects potentiating each other in combination. (11)

Neuroplasticity is also thought to be defective in bipolar disorder and lithium is considered to have a role in enhancing neuroplastic processes. In a recent study on rats, olanzapine and lithium were shown to affect neuronal transmission in CA1 pyramidal cells of the hippocampus. However, while lithium acted to increase long-term potentiation without altering baseline synaptic transmission, olanzapine had no lasting effect on long-term potentiation but did create a steeper dose-response relationship than in controls. (10) Atypicals, thus appear to function differently to lithium, in this regard, at a fundamental level but with a potentially similar outcome.

Treatment of Mania

On conducting a systematic review, Bridle and colleagues found that quetiapine and olanzapine were both superior to placebo in treating acute mania (defined as lasting 10 weeks or less). These had a similar effectiveness to valproate but it is unclear, based on current research, whether there is a statistically significant difference from the effect of lithium (12). In practical clinical terms, in a medication-naïve patient, it is easier to treat acute mania with atypical antipsychotic medication, without the medical work-up and dose-loading that is necessary before reaching therapeutic lithium levels. In the light of the term 'antipsychotic', it is also worth pointing out that their use in mania is not merely confined to treating psychosis, as they have also been shown to be effective in non-psychotic mania (13); in fact, atypicals have been demonstrated to be particularly useful in treating the agitation and aggression that sometimes feature in manic episodes (14).
In terms of which particular atypical to use, olanzapine and quetiapine have been shown to have similar effectiveness (12); the best evidence exists for olanzapine (15), although this may merely be an artefact of its longevity. It should be noted that the evidence base for resperidone in the treatment of acute mania is weak, with trials either being small or only including those patients who had already responded to the drug (14). There is some evidence for the use of aripiprazole. Indeed, its better adverse-effect profile, particularly with regard to metabolic disturbance, (which is common with other atypicals) makes it an attractive option, but it has yet to be compared against other antipsychotics (16). More recently, a new atypical called asenapine has also been approved (28).

Clinicians should always be wary of polypharmacy, as adverse effects can be additive and sometimes even potentiate each other. However, where clinically indicated, there is sometimes a case for it in the treatment of bipolar disorder.
Although polypharmacy, also described as combination therapy, can lead to additive adverse effects, when used cautiously, with knowledge of the pharmacology of each of the drugs and their potential interaction, it has an important role in effective management of bipolar disorder. In acute mania, a combination of either lithium or valproate with an atypical has been shown to have a 20% better response rate than either lithium or valproate monotherapy (17). There is also evidence from a small trial for superiority of a combination of quetiapine with lorazepam over lorazepam monotherapy (13).

Treatment of Bipolar Depression

Research into depression in the context of bipolar disorder has been somewhat inadequate for two reasons. First, although most patients with bipolar disorder spend a much greater period of time in a depressed mood state rather than in an elevated one, the majority of studies have focused on mania rather than depression (18). Second, authors have often avoided comparison with antidepressant monotherapy due to the justifiable fear of pushing patients towards a mixed state, even though there is thought to be less risk of this with modern SSRIs than there was with monoamine oxidase inhibitors and tricyclic antidepressants.

Olanzapine monotherapy has been shown, in randomised controlled trials, to be superior to a placebo in the treatment of depression, as measured by the change in MADRS score (19). Quetiapine monotherapy has also been shown to be effective (18), with an 8-week trial recently confirming its advantage over placebo (20). On the other hand, no statistically significant difference from placebo was found with aripiprazole treatment for bipolar depression (19).
As for combination therapy, adding fluoxetine to olanzepine has been found to yield better outcomes than olanzapine monotherapy (18).

Treatment of Mixed States

Mixed states, so called because they exhibit features of both manic and depressive episodes, occur in 40% of bipolar patients, but research into them has been somewhat limited (22) and where it has been conducted, a variety of definitions for a mixed state have been used (23). NICE considers treatment of mixed states to be identical to manic episodes (9). In general terms, a systematic review found that the manic component of mixed states responds more rapidly and more substantially to atypicals than the depressive component. In particular, olanzapine and aripiprazole improve both manic and depressive features, while risperidone has only been shown to act on manic symptoms (21,22). Evidence is lacking for the roles of risperidone and quetiapine in the treatment of depressive symptoms (21).

Regarding combination therapy, olanzapine plus either valproate or lithium has been shown to be superior to valproate or lithium monotherapy but a similar trial with risperidone did not show any advantage (21). Adding fluoxetine to olanzapine is not superior to olanzapine monotherapy and may even be inferior (21).
Recently a new atypical asenapine has also been approved for mixed states (28).

Prevention

Beynon and colleagues conducted a comprehensive systematic review and meta-analysis on prevention in bipolar, examining 34 trials. They found evidence for three drugs in monotherapy for reduction in mania (lithium, olanzapine and aripiprazole) and three for reduction of depression (valproate, lamotrigine and imipramine), when compared to a placebo, although tricyclic antidepressants are now seldom used in practice, because of concerns about mixed states. One trial even showed that treatment with olanzapine resulted in fewer manic episodes and total mood episodes than lithium therapy but depressive episodes were more common (23). In addition to the effects on mania and depression, atypicals have also been shown to have a role in lowering rates of mixed states and prolonging the time period before they recur (21).

In terms of individual antipsychotics, the atypical with the best evidence base for prevention is olanzapine (15). Quetiapine is often claimed to be effective, but the evidence for its use relies on a trial where only those patients who had already responded to quetiapine were included; the study is, nevertheless, useful, as it has some implications for trying patients on the medication, but it is very weak evidence on which to base recommendations for a first-line therapy.

On the basis of the absence of good evidence for a single antipsychotic drug preventing both mania and depression, combinations with other drugs have been suggested. However, Beynon and

colleagues have commented that there is still no strong evidence for combination therapy (23). Nonetheless, aripiprazole may also have a role in combination with lithium or valproate in preventing manic episodes (16). Moreover, quetiapine as an adjunct to lithium or valproate has been shown to be superior to monotherapy in preventing all mood episodes, including mixed states (21), in a combination which has been shown to be cost-effective in the UK and US health models (24).

Some issues to consider when using atypicals in bipolar disorder

Adverse Effects

The adverse effect profile (side effect profile) is often a significant reason for choosing one drug over another. Indeed it is an important factor in adherence. The traditional dichotomy holds that while typical antipsychotics have more extrapyramidal adverse effects, atypicals cause metabolic adverse effects. Some argue that the total side effect burden from the atypicals is no less severe (16). Aripiprazole is known to have a better adverse effect profile, with lower rates of hyperprolactinaemia, elongation of QT interval and metabolic complications (17). In terms of the neurocognitive burden, atypicals seem to compare favourably. Dias and colleagues recently examined this aspect of drugs used for bipolar disorder and found that, while lithium is detrimental for psychomotor speed and verbal memory and antiepileptic drugs seem to exert a negative effect on cognition, atypicals are associated with a small improvement in cognition, although this finding requires validation with further investigation (25).

Age

Unfortunately, there have been no trials of the atypicals in children and adolescents and lithium is currently the only licensed treatment for bipolar disorder in those under the age of 18. However, NICE guidelines suggest the off-license use of adult treatments where appropriate, albeit starting at lower doses (8).

Regarding the elderly, there have, in recent years, been concerns about prescribing antipsychotics for behavioural disturbances in dementia; it is natural that there have been similar apprehensions using them in the treatment of bipolar disorder. Bhalerao and colleagues examined data from the US Department of Veterans Affairs on individuals with bipolar disorder; they found marked differences between drugs. Mortality for patients taking risperidone was highest at 11.8 deaths per 100 person-years. The figures for other drugs were: olanzapine 10.3, quetiapine 5.3 and valproate 4.6 (comorbid antiepileptic medication being excluded from the results). The same pattern emerged from the data after multivariate and propensity-weighed analyses, but the mechanism for the increased mortality remains unclear, as death from all causes increased proportionately. Nonetheless, this is a serious caution against the use of risperidone and olanzapine in the elderly (26).

Formulation

In those patients for whom taking multiple tablets in a day is considered unacceptable, an extended-release form of quetiapine is now available and has been found to be equally effective to the immediate-release form (28).

Pregnancy

Drug	Guidance
Lithium	Avoid in 1st trimester
Valproate	Highly teratogenic, causing major and minor abnormalities as well as developmental delay; avoid throughout pregnancy and in any pre-menopausal women without adequate contraception
Atypicals (olanzapine, quetiapine, risperidone, aripiprazole)	Can cause extra-pyramidal side effects and withdrawal symptoms in the neonate, so avoid in 3rd trimester

Table 1 suggests that atypicals could be used in the first half of pregnancy (of course, after having weighed up the gains and the possible negative effects on the foetus of the treatment in detailed discussion with the patient) and lithium for the second half, though this is by no means straightforward, as lithium dosing changes as pregnancy advances.

Hepatic and Renal Impairment

Drug	Hepatic Impairment	Renal Impairment
Lithium	No concerns	Avoid if possible
Valproate	Avoid if possible	Reduce dose
Olanzapine	Reduce starting dose	Reduce starting dose
Quetiapine	Reduce starting dose	No concerns
Risperidone	Reduce dose	Reduce dose
Aripiprazole	Use with caution in severe impairment	No concerns

Table 2 suggests that lithium might be the first choice in hepatic impairment, while quetiapine and aripiprazole can be used in renal impairment. It should be noted that reduced doses may not result in reduced effectiveness, as organ dysfunction may prolong the half-life of the drug.

Conclusion

Table 3: Quick reference guide to use of atypicals in bipolar

Indication	Treatment of Mania	Treatment of Depression	Treatment of Mixed States	Prevention
1st Choice	Olanzapine *or* valproate or asenapine	Olanzapine *or* quetiapine	Olanzapine *or* aripiprazole asenapine	*Mania:* lithium, olanzapine *or* aripiprazole *Depression:* valproate *or* lamotrigine
2nd Choice	Olanzapine + valproate	Olanzapine + fluoxetine	Olanzapine + valproate	Quetiapine *or* + aripiprazole Lithium *or* valproate

Table 3 shows an outline of recommendations for the use of atypical antipsychotics, though this would not be complete without reference to some other mood stabilisers, which have been included for the sake of clinical utility. It should also be used in combination with tables 1 and 2 to ascertain the relevant contraindications. The distinction between 1st and 2nd choice therapy represents a preference for monotherapy over the increased side effects and risks of combinations, although these combinations have better success rates than the 1st choice drugs alone, so might be used first-line if clinically indicated.

Having summarised the information, a few salient points emerge. First, olanzapine monotherapy may be used as first-line for treatment of any acute state as well as for prevention of relapse. Second,

in addition to being associated with the highest mortality in the elderly, risperidone has only been demonstrated to act against mixed states, and only partially at that, so it should usually be avoided. Quetiapine has a few indications but the evidence is generally weaker than for olanzapine. Aripiprazole has a favourable adverse effect profile but again its uses are limited. Selective polypharmacy/combination therapy still seems to be beneficial in certain cases.

In terms of how to apply this information to clinical practice, the obvious problem with dividing up pharmacotherapy into the different indications in Table 3 is that very often a clinician will be trying to achieve two or more aims simultaneously; for instance, it may be desirable to treat a current mixed state but also to avoid the recurrence of a depressive episode from which the patient has recently emerged. Hence, the doctor must identify the particular priorities of treatment for each individual patient and tailor treatment appropriately. Moreover, most patients with bipolar disorder will not be medication-naïve and their clinician must weigh the risks and benefits of switching from an already established treatment rather than just altering the dose.

Finally, as mentioned initially, the vast majority of research has been conducted in bipolar-I, so our conclusions are much more cautiously applied to bipolar-II and cyclothymia.

GP Comment

What have I learned from this paper?

This paper highlights the use of atypical antipsychotics in the management of bipolar disorder, explaining their modes of action and side effect profiles. Antipsychotics are recommended by NICE as first-line in the management of acute mania and hypomania, quetiapine as an additional treatment in moderate or severe bipolar depression, and olanzapine in long-term management to prevent relapse.

Dr Jenny Hopwood, GP Trainee.

References

1. Rang HP, Dale MM. Pharmacology [Internet]. Churchill Livingstone, Elsevier; 2007 [cited 2013 Feb 11]. p. 829. Available from: http://books.google.com/books?id=mtNy9DgYCIgC&pgis=1
7. Brugue E, Vieta E. Atypical antipsychotics in bipolar depression: neurobiological basis and clinical implications. Progress in neuro-psychopharmacology & biological psychiatry [Internet]. 2007 Jan 30 [cited 2013 Feb 2];31 (1):275–82. Available from: http://dx.doi.org/10.1016/j.pnpbp.2006.06.014
2. Meltzer H. Mechanism of action of atypical antipsychotic drugs. … . The Fifth Generation of Progress (KL Davis, D … [Internet]. 2002 [cited 2013 Jan 8]; (d). Available from: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:MECHANISM+OF+ACTION+OF+ATYPICAL+ANTIPSYCHOTIC+DRUGS#6
3. Rebec G V, Bashore TR, Zimmerman KS, Alloway KD. "Classical" and "atypical" antipsychotic drugs: differential antagonism of amphetamine- and apomorphine-induced alterations of spontaneous neuronal activity in the neostriatum and nucleus accumbens. Pharmacology, biochemistry, and behavior [Internet]. 1979 Nov [cited 2013 Feb 9];11 (5):529–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/43515
4. Tyrer P, Kendall T. The spurious advance of antipsychotic drug therapy. Lancet [Internet]. 2009 Jan 3 [cited 2013 Feb 11];373 (9657):4–5. Available from: http://dx.doi.org/10.1016/S0140-6736(08)61765-1
5. Owens DC. Antipsychotics: is it time to end the generation game? Prescriber2 [Internet]. 2011;22 (19):48–50. Available from: http://www.prescriber.co.uk/SpringboardWebApp/userfiles/espres/file/novemberEalert/antipsychotics.pdf
6. Nandra KS, Agius M. The differences between typical and atypical antipsychotics: the effects on neurogenesis. Psychiatria Danubina [Internet]. 2012 Sep [cited 2013 Feb 11];24 Suppl 1:S95–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22945197
8. NICE. Bipolar disorder [Internet]. London: NICE; 2006 [cited 2013 Feb 2]. Available from: http://www.nice.org.uk/cg038

9. Yatham LN, Goldstein J, Vieta E, Bowden C, Grunze H, Post R, et al. Atypical Antipsychotics in Bipolar Depression: Potential Mechanisms of Action [Internet]. J Clin Psychiatry. 2005 [cited 2013 Feb 2]. Available from: http://altcancerweb.com/bipolar/bipolar-depression/atypical-antipsychotics-bipolar-depression-mechanism-action-2005.pdf
10. Shim SS, Hammonds MD, Tatsuoka C, Feng IJ. Effects of 4-weeks of treatment with lithium and olanzapine on long-term potentiation in hippocampal area CA1. Neuroscience letters [Internet]. 2012 Aug 22 [cited 2012 Nov 26];524 (1):5–9. Available from: http://dx.doi.org/10.1016/j.neulet.2012.06.047
11. Li X, Rosborough KM, Friedman AB, Zhu W, Roth KA. Regulation of mouse brain glycogen synthase kinase-3 by atypical antipsychotics. The International Journal of Neuropsychopharmacology [Internet]. 2007 Feb 1 [cited 2013 Feb 2];10 (01):7–19. Available from: http://journals.cambridge.org/abstract_S1461145706006547
12. Bridle C, Palmer S, Bagnall A, Darba J, Duffy S, Sculpher M, et al. Newer drugs for treatment of mania associated with bipolar affective disorder. 2004;8 (19).
13. Jones RM, Thompson C, Bitter I. A systematic review of the efficacy and safety of second generation antipsychotics in the treatment of mania. European psychiatry : the journal of the Association of European Psychiatrists [Internet]. 2006 Jan [cited 2013 Jan 8];21 (1):1–9. Available from: http://dx.doi.org/10.1016/j.eurpsy.2005.02.002
14. Berk M, Dodd S. Efficacy of atypical antipsychotics in bipolar disorder. Drugs [Internet]. 2005 Jan [cited 2013 Jan 8];65 (2):257–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15631544
15. Gentile S. Atypical antipsychotics for the treatment of bipolar disorder: more shadows than lights. CNS drugs [Internet]. 2007 Jan [cited 2013 Jan 8];21 (5):367–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17447826
16. Dhillon S. Aripiprazole: a review of its use in the management of mania in adults with bipolar I disorder. Drugs [Internet]. 2012 Jan 1 [cited 2013 Jan 19];72 (1):133–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22191800
17. Lin D, Mok H, Yatham LN. Polytherapy in bipolar disorder. CNS drugs [Internet]. 2006 Jan [cited 2013 Jan 8];20 (1):29–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16396522
18. Möller H-J, Grunze H, Broich K. Do recent efficacy data on the drug treatment of acute bipolar depression support the position that drugs other than antidepressants are the treatment of choice? A conceptual review. European archives of psychiatry and clinical neuroscience [Internet]. 2006 Feb [cited 2013 Jan 8];256 (1):1–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16078087
19. Tohen M, McDonnell DP, Case M, Kanba S, Ha K, Fang YR, et al. Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. The British journal of psychiatry : the journal of mental science [Internet]. 2012 Nov [cited 2012 Nov 8];201 (5):376–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22918966
20. Sanford M, Keating GM. Quetiapine: a review of its use in the management of bipolar depression. CNS drugs [Internet]. 2012 May 1 [cited 2013 Jan 19];26 (5):435–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22519923
21. Fountoulakis KN, Kontis D, Gonda X, Siamouli M, Yatham LN. Treatment of mixed bipolar states. The International Journal of Neuropsychopharmacology [Internet]. 2012 Aug 1 [cited 2013 Jan 19];15 (07):1015–26. Available from: http://journals.cambridge.org/abstract_S1461145711001817
22. McIntyre RS, Yoon J. Efficacy of antimanic treatments in mixed states. Bipolar disorders [Internet]. 2012 May [cited 2012 Dec 4];14 Suppl 2:22–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22510034
23. Beynon S, Soares-Weiser K, Woolacott N, Duffy S, Geddes JR. Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials. Journal of psychopharmacology (Oxford, England) [Internet]. 2009 Jul [cited 2013 Jan 8];23 (5):574–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18635701
24. Plosker GL. Quetiapine: a pharmacoeconomic review of its use in bipolar disorder. PharmacoEconomics [Internet]. 2012 Jul 1 [cited 2013 Jan 19];30 (7):611–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22559293
25. Dias V V, Balanzá-Martinez V, Soeiro-de-Souza MG, Moreno RA, Figueira ML, Machado-Vieira R, et al. Pharmacological approaches in bipolar disorders and the impact on cognition: a critical overview. Acta psychiatrica Scandinavica [Internet]. 2012 Nov [cited 2012 Nov 8];126 (5):315–31.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/22881296
26. Bhalerao S, Seyfried LS, Kim HM, Chiang C, Kavanagh J, Kales HC. Mortality risk with the use of atypical antipsychotics in later-life bipolar disorder. Journal of geriatric psychiatry and neurology [Internet]. 2012 Mar [cited 2013 Jan 19];25 (1):29–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22467844
27. Joint Formulary Committee. British National Formulary (online) [Internet]. BMJ Group and Pharmaceutical Press. London: BMJ Group and Pharmaceutical Press; [cited 2013 Feb 11]. Available from: http://www.medicinescomplete.com
28. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. J Affect Disord. 2010, Nov; 126 (3) : 358-65