Receptor mechanisms of antipsychotic drug action in bipolar disorder – focus on asenapine

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Abstract:
The atypical antipsychotic drugs are considered a first-line treatment for mania in bipolar disorder with many having a proven superiority to the classical mood stabilisers. This review addresses the pharmacological mechanisms underlying this therapeutic efficacy, as well as those mechanisms considered responsible for the adverse effects of antipsychotic drugs, with a particular focus on the recently introduced asenapine.
The high efficacy in bipolar mania of haloperidol, a relatively selective dopamine D2-like receptor antagonist, indicates that the one common receptor mechanism underlying antipsychotic effects on mania is antagonism at the D2 receptor. Serotonin receptors are implicated in antidepressant response, and relief of depressed mood in mixed states is likely to involve drug effects at one, or more likely several interacting, serotonin receptors. Asenapine shows a unique breadth of action at these sites, with potential effects at clinical doses at 5HT1A, 1B, 2A, 2C, 6 and 7 receptors. Antagonism at alpha2 adrenoceptors may also be involved.
Adverse effects include those classically associated with dopamine D2 receptor blockade, the extrapyramidal side effects (EPS), and which are relatively diminished in the atypical (in comparison with the conventional) antipsychotics. A variety of protective mechanisms against EPS associated with different drugs include low D2 affinity, D2 partial agonism, high 5-HT2A and 2C antagonism. Similar effects at the D2 and 5-HT2C receptors may underlie the low propensity for hyperprolactinaemia of the atypicals, although the strong prolactin-elevating effect of risperidone reflects its relatively high blood/brain concentration ratio, a consequence of it being a substrate for the p-glycoprotein pump. Weight gain is a further concern of antipsychotic treatment of bipolar disorder which is particularly severe with olanzapine. Histamine H1, alpha1 adrenergic and particularly 5-HT2C receptors are implicated in this effect, although the lower propensity for weight gain shown by asenapine which, like olanzapine, binds to these receptors, indicates that other protective receptor mechanisms, or subtle differences in the 5-HT2C receptor-mediated effects, may be important. Of other peripheral and central effects, the pharmacological basis of sedation (H1 receptors) and postural hypotension (alpha1 adrenoceptors) are rather better understood.
The relative benefits of atypical antipsychotics like asenapine can be understood from their receptor pharmacology, and this understanding is key to the future development of improved treatment for bipolar disorder.

Keywords:

Introduction

The antipsychotic drugs are a widely used pharmacotherapy, estimated in year 2000 as prescribed to 1.2% of the adult non-institutionalized European population [Alonso *et al.* 2004], a figure that is very likely to have increased in the past decade. While the largest proportion of these prescriptions is likely to have been for schizophrenia

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and related disorders, some may be used in treating, often with little in the way of an evidence base, a variety of behavioural problems in childhood and in the elderly. Antipsychotics have also been made available in the past decade to people with bipolar disorder, and are now a first-line treatment for mania. The most recent meta-analysis concluded that antipsychotic medication is, overall, significantly more effective than mood stabilizers in the treatment of acute mania [Cipriani *et al*. 2011]. This important study, employing a multiple-treatments meta-analysis, showed haloperidol to be significantly more effective than most other drugs including lithium and the atypical antipsychotics, other than risperidone and olanzapine. Furthermore, all antipsychotics had higher acceptability than lithium and several other mood stabilizers.

The aim of this article is to review the clinical pharmacology of the antipsychotic drugs, relating receptor actions to their therapeutic and adverse effects. While the major emphasis will be on the consequences of the use of the newer atypical antipsychotics in the treatment of bipolar disorder, there will be a particular focus on the most recently available of these, asenapine. As a pharmacological review, this article does not make recommendations regarding the value of prescribing particular drugs in any clinical situation, for which the reader is referred to evidence-based guidelines such as those published by the BAP [Goodwin and Consensus Group of the British Association for Psychopharmacology, 2009].

Comparative receptor pharmacology of asenapine

Asenapine is the latest addition to the antipsychotic drugs available for the treatment of mania in bipolar disorder in Europe and which include aripiprazole, olanzapine, quetiapine, risperidone and, in some countries, ziprasidone. Hereinafter this group of drugs will be referred to as the atypicals, although there are other drugs not specifically licensed for the treatment of bipolar disorder, notably clozapine and amisulpride, which are considered atypical antipsychotics. Clozapine, licensed solely for treatment-resistant schizophrenia, will occasionally be referred to in this review as it is sometimes considered the archetypal atypical and has some pharmacology in common with asenapine.

Originally developed by Organon (as Org5222), asenapine is described as a tetracyclic antipsychotic, reflecting its core molecular structure. It is unique among the antipsychotic drugs in being administered as a sublingual preparation, which enhances its direct absorption avoiding much of the hepatic metabolism which restricts its availability when administered orally.

The affinities and functional activities of asenapine at neurotransmitter receptors have been systematically determined by Shahid *et al*. [2009]; the affinities from radioligand binding assays they reported will be discussed below. In common with all antipsychotic drugs asenapine has a high affinity for the dopamine D2 receptor, substantially higher, in fact, than the other atypical drugs other than the partial agonist aripiprazole. Given that, as discussed below, it is the affinity at the dopamine D2 receptor that most likely mediates the anti-manic mechanism and thereby determines dose, affinity at other receptors can be described relative to the D2 value.

Interestingly, asenapine has a higher affinity for the D3 subtype of the dopamine D2-like receptors than for D2 itself, a property shared with ziprasidone alone among the atypicals. It also has a substantial affinity for the D4 receptor along with several, but not all, of the other atypicals, although there is now little to indicate this site is of functional importance in antipsychotic action.

The high affinity of asenapine for the 5-HT2A receptor too is greater than that for the other atypicals, although all have effective antagonist activity at this site. It is the 5-HT2A activity that is the primary pharmacology considered to differentiate these atypical drugs from the conventional antipsychotics. What differentiates asenapine pharmacologically from the other atypical antipsychotics is the breadth of its activities at other 5-HT receptors. Thus antagonism at 5-HT2B, 5-HT2C, 5-HT5A, 5-HT6 and 5-HT7 receptors is apparent at affinities at or greater than that for the D2 receptor; activity at the 5-HT2C site is particularly high. Furthermore, activities at 5-HT1A and 5-HT1B receptors may be great enough to have some functional effect at clinical doses. Asenapine appears to be a partial agonist at the 5-HT1A site [Ghanbari *et al*. 2009] as are most other atypicals except for risperidone and olanzapine.

Alpha1A adrenoceptor antagonism is likely to occur at clinical doses, an effect true for most other atypicals except aripiprazole. Asenapine has high relative affinities for the alpha2

adrenoceptors, as does clozapine and quetiapine; risperidone too may have some activity, particularly at the alpha2C site. However, in functional assays, the activity of both risperidone and asenapine at these sites is relatively low [Shahid *et al.* 2009].

Three further receptor actions have been reported: asenapine is a relatively effective antagonist at histamine H1 receptors, as are quetiapine, olanzapine and clozapine, and is, uniquely, an antagonist at H2 receptors. It has no effect at the muscarinic receptors, in contrast to the relatively high affinities at these sites shown by clozapine and olanzapine.

It is of course impossible to describe how each and every receptor activity, and their multiplicity of interactions, might contribute to the clinical profile of asenapine and the other atypical antipsychotics used in the treatment of bipolar disorder. However, there are some clear indications how certain receptor actions might be involved in both the beneficial and adverse effects of these drugs, as well as some intriguing potential mechanisms as yet inadequately explored.

Effects on bipolar symptoms

The neuronal dysfunction that underlies mania and manic episodes remain obscure, even more so that the psychosis of schizophrenia. It is generally considered that the primary antipsychotic mechanism in schizophrenia involves antagonist action at the dopamine D2 receptor; occupancy of this receptor in the striatum correlates best with relief of positive symptoms of the disease [Agid *et al.* 2007]. Given the similar efficacy of the atypical antipsychotic drugs in treating mania, an efficacy extending to the conventional antipsychotic haloperidol, which is especially effective [Tohen and Vieta, 2009; Cipriani *et al.* 2011], it seems likely that this mechanism also underlies the anti-manic effect of all antipsychotic drugs. Mania is not inevitably psychosis, although it can develop psychotic features, and this suggests that the effects of the drugs are not solely 'antipsychotic' but are, using an outmoded description, 'major tranquillizers'. Current hypotheses of antipsychotic action address the role of dopamine hyperfunction in the aberrant attribution of salience model of psychosis [Kapur, 2003]. Whether this salience dysregulation syndrome can extend to include mania is unclear [van Os, 2009]. However, of the other subjective effects of antipsychotic-induced dopamine blockade, a reduction in motivational drive [Henry *et al.* 2006; Mavrikaki *et al.* 2010] is one consequence that could result in attenuation of manic behaviour. Whatever the neuropsychological mechanism, the efficacy of the relatively selective high activity D2 antagonist haloperidol indicates that dopamine D2 antagonism alone, or partial agonism/antagonism in the case of aripirazole, is a sufficient pharmacological mechanism for the relief of acute mania common to all antipsychotic drugs. The role, if any, of the D3 receptor in these processes is as yet unclear, and we still have no clear understanding of the influence of the relatively higher affinities for this dopamine D2-like receptor subtype shown by asenapine and ziprasidone.

What is likely to differentiate the antipsychotics in the treatment of bipolar disorder will therefore relate not solely to antimanic effects but also to other aspects of treatment relating to symptom relief and side effects. The other side of the bipolar disorder coin is depression. Of the atypicals, quetiapine is licensed for bipolar depression, while others including asenapine [Szegedi *et al.* 2011], have demonstrated the improvement of depressive symptoms in patients with manic episodes. Notably, augmentation of antidepressants with atypical antipsychotics has strong support for its efficacy in major depression [Nelson and Papakostas, 2009].

Current understanding of antidepressant action primarily revolves around pharmacological effects regulating the activity of serotonin neurotransmission, although a variety of other mechanisms, mostly not inconsistent with serotoninergic regulation, have been proposed. Certainly the antipsychotic drugs used in bipolar disorder have effects on serotonin receptors. As well as all having a high affinity at the 5-HT2A receptor, asenapine, olanzapine and clozapine have very high relative 5-HT2C receptor affinities. The 5-HT2C receptors have strong evidence supporting their potential as targets for antidepressant action [Jensen *et al.* 2010]. Most atypicals, namely asenapine, ziprasidone, quetiapine and aripiprazole, have a partial agonist activity at 5-HT1A receptors which may be functional at clinical doses. Further potentially valuable effects of asenapine, some of which are shared with other atypicals, include antagonism of the presynaptic 5-HT1B receptor that may lead to an increase in serotonin release, antagonism of inhibitory alpha2 adrenoceptors found on serotonin neurons resulting in their increased

activity, and actions at 5-HT6 and 5-HT7 receptors. The latter two receptors have attracted much recent research interest; both agonists and antagonists at the 5-HT6 receptor have been reported to have potential antidepressant and anxiolytic effects [Wesolowska, 2010]; this receptor is also a target for procognitive drugs. The 5-HT7 receptor too is considered a valuable target for antidepressant drugs [Hedlund, 2009]. Notably both these reviews highlight the particular potential of 5-HT6 or 5-HT7 antagonists in augmenting the effects of established antidepressant drugs, indicating the possibility of an enhanced antidepressant action associated with their antagonism in conjunction with other pharmacological mechanisms increasing synaptic serotonin by e.g. alpha2 adrenergic or 5-HT1B receptor antagonism as may occur with asenapine. However this synergism may also be true of other established antidepressant targets including the 5-HT2A [Blier and Szabo, 2005] and 5-HT2C receptors.

Adverse effects

Extrapyramidal side effects

A consequence of dopamine D2 receptor antagonism, the main anti-manic mechanism of the antipsychotic drugs, is an inhibition of dopaminergic function in the basal ganglia, regions of the brain controlling automatic motor function. This results in the acute extrapyramidal side effects (EPS), which include the relatively immediate effects of akathisia, dystonia and parkinsonism, as well as tardive dyskinesia (TD), a severe and occasionally irreversible problem associated with chronic antipsychotic drug treatment. The avoidance of these acute and chronic EPS has driven the development of the second generation of antipsychotic drugs. A common pharmacological feature of all atypical antipsychotic drugs used in bipolar disorder is 5-HT2A receptor antagonism; this receptor activity is considered to differentiate the atypical from conventional antipsychotics. It is proposed to contribute to the lower propensity for EPS shown by some of these drugs; however 5-HT2A receptor blockade cannot completely prevent EPS, which for most of these drugs is higher than placebo. Other protective mechanisms may be involved in diminishing the emergence of EPS due to D2 receptor antagonism. These include the lower affinity for the D2 receptor shown by quetiapine and clozapine (of which their high doses are a consequence), which may permit the rapid displacement of drug from the receptor by neuronally-released dopamine; other mechanisms may also be involved [Reynolds, 2004]. 5-HT2C receptors are also important in the pharmacology and physiology of dyskinesias and antagonism at this 5-HT2 receptor subtype appears to be a particularly important mechanism in ameliorating a model of TD [Creed-Carson *et al*. 2011].

Hyperprolactinaemia

A further consequence of dopamine D2 antagonism by antipsychotic drugs, acting at receptors in the pituitary gland, is a disinhibition of the release of prolactin. Much of the work on drug-induced hyperprolactinaemia has focused on risperidone, which among the atypical antipsychotics used in bipolar disorder has the greatest effect on prolactin. This can result in galactorrhoea and gynaecomastia, and may contribute to sexual dysfunction [Haddad and Wieck, 2004]. Effects of drug-induced hyperprolactinaemia on the hypothalamic-pituitary-gonadal axis can have further consequences, including amenorrhoea and osteoporosis. However it is important to emphasise that such side effects are not all inevitable consequences of hyperprolactinaemia; it is only when the raised prolactin results in a sustained functional hypogonadism with e.g. oestrogen deficits that effects such as osteoporosis are likely to emerge [Halbreich *et al*. 1995; Meaney and O'Keane, 2007].

Prolactin secretion is under inhibitory control by dopamine and will occur following inhibition of dopamine D2 receptors in the pituitary gland; these neuronal receptors are accessed directly by drugs from the blood supply without the restriction of an effective blood-brain barrier. Drugs such as risperidone that are poorly brain-penetrant or are substrates for the p-glycoprotein pump [Ejsing *et al*. 2005] are likely to affect receptors in the pituitary to a greater extent than in the brain. Thus *in vivo* measures of drug occupancy of human brain D2 receptors in striatal and extrastriatal regions correlate poorly with prolactin concentrations [Agid *et al*. 2007]. The lack of a prolactin-elevating effect by aripiprazole is a consequence of its partial agonism at the D2 receptor.

In addition to dopamine D2 antagonism, actions on other systems including serotonin receptors can influence prolactin secretion. 5-HT2A and 5-HT2C receptors are particularly implicated in the control of prolactin secretion; these receptors have opposing effects to those of D2 receptors

[Bagdy, 1996]. While risperidone shows us that 5-HT2A receptor antagonism cannot overcome the effects of D2 blockade on prolactin release, olanzapine can effectively block prolactin release due to a 5-HT2C agonist [Scheepers *et al*. 2001]. Thus antagonism at the 5-HT2C receptor may in theory contribute to the relatively limited effects on prolactin seen by several of the atypical antipsychotics, including asenapine, olanzapine and ziprasidone, that have high affinities for the dopamine D2 receptor but even stronger effects at the 5-HT2C site.

Metabolic effects

The prevalence of obesity and metabolic syndrome, with increased risk of eventual cardiovascular disease and type II diabetes, are substantially elevated in patients receiving antipsychotic drugs. Several drug-related mechanisms may contribute to these problems, including effects both influencing food intake and on glucose and lipid metabolism. The metabolic consequences of different antipsychotic drugs vary substantially; these variations reflect differences in receptor pharmacology and provide clues as to the underlying pharmacological mechanisms. These mechanisms relate primarily to those receptors that mediate drug effects on food intake and are reviewed in detail in a recent publication [Reynolds and Kirk, 2010]; notably but not exclusively they include the serotonin 5-HT2C, histamine H1 and alpha1 adrenergic receptors.

The two drugs with the greatest effects on body weight, olanzapine and clozapine, also have high affinity for the 5-HT2C and histamine H1 receptors, which has implicated these receptors in antipsychotic-induced weight gain and obesity. Attempts to identify receptor mechanisms of weight gain by correlation between receptor affinities of drugs and their weight gain liabilities have proposed effects at histamine H1 receptors to be important [Kroeze *et al*. 2003; Matsui-Sakata *et al*. 2005]. However these approaches are simplistic and arguably flawed [Reynolds and Kirk, 2010]. Limitations of such simple correlational clinical studies include their inability to account for any synergistic interactions between receptors, for antagonist/agonist differences or for possible protective mechanisms. An experimental study in animals suggests that actions at the 5-HT2C receptor in combination with D2 antagonism, rather than H1 antagonism, can account for olanzapine-induced weight gain [Kirk *et al*. 2009].

There are clinical reports of possible protective effects of aripiprazole against the metabolic consequences of clozapine and olanzapine [Chen *et al*. 2007; Masopust *et al*. 2008], supported by experimental studies in which both aripiprazole and ziprasidone can diminish olanzapine-induced hyperphagia in the rat [Kirk *et al*. 2004; Snigdha *et al*. 2008]. The inherent pharmacological mechanisms that this is likely to reflect have not been identified but are discussed by Reynolds and Kirk [2010]. For aripiprazole they might include dopamine D2 partial agonism, as well as (partial) agonism at some forms of the 5-HT2C receptor. For ziprasidone, 5HT1B antagonism or weak partial agonism may be a contributing factor [Audinot *et al*. 2001] in addition to the partial agonism at 5-HT1A receptors that both drugs exhibit [Kirk *et al*. 2004; Reynolds *et al*. 2006].

It is perhaps surprising that asenapine shares the high relative affinities at 5-HT2C and H1 receptors of clozapine and olanzapine yet avoids inducing the profound weight gain associated with these drugs; in bipolar patients asenapine showed a mean increase of 1.9kg *vs* 4.1kg with olanzapine over 12 weeks [McIntyre *et al*. 2009]. While effects on 5-HT1B and/or 5-HT1A receptors could conceivably contribute, asenapine administration demonstrates a notable lack of effect on 5-HT2C receptor density in rat brain [Tarazi *et al*. 2010]. This is similar to that of the weaker antagonists risperidone and quetiapine and is in contrast to the down-regulation seen with olanzapine [Tarazi *et al*. 2002]. The difference could conceivably relate to a 5-HT2C antagonism by asenapine in the absence of the inverse agonism exhibited by olanzapine and clozapine [Herrick-Davis *et al*. 2000] although this is untested; whatever the mechanism, it does indicate profoundly different pharmacological influences between asenapine and olanzapine on these important receptors involved in the control of body weight.

While an increase in type II diabetes may be a consequence of metabolic syndrome in patients receiving antipsychotic drugs, an acute and obesity-independent diabetes is occasionally reported. It may be no coincidence that the two antipsychotic drugs most associated with weight gain, clozapine and olanzapine, are also particularly associated with this rapid-onset diabetes [Newcomer, 2005]. The pharmacological basis for this iatrogenic effect is again unclear, although experimental and clinical observations suggest that peripheral M3 muscarinic receptor antagonism as well as central 5-HT2C

effects may contribute (reviewed by Reynolds and Kirk [2010]). In this respect it is notable that asenapine, unlike olanzapine and clozapine, has no effect at muscarinic receptors.

Further central and peripheral effects

Other problematic side effects include sedation, which is particularly great with clozapine and, of the atypicals used in bipolar disorder, highest in quetiapine and olanzapine and least in aripiprazole [Haddad and Sharma, 2007], reflecting relative antagonism at histamine H1 receptors which is considered to be the main mechanism. Asenapine has a significant relative effect at H1 receptors, albeit less so than quetiapine and olanzapine, and its sedative properties probably reflect this; somnolence is the most frequently reported side effect for asenapine although it is generally transient, occurring at the initiation of treatment [Citrome, 2009].

Postural hypotension, is a further concern which can occur particularly with risperidone and quetiapine [Haddad and Sharma, 2007]. Alpha1 adrenoceptor antagonism is the likely mechanism, and asenapine has a relative affinity for this receptor that is similar to that of risperidone and somewhat less than quetiapine. However it occurs more frequently early in treatment, and this amelioration may relate to the compensatory up-regulation of alpha1 adrenoceptors that is seen with asenapine [Choi *et al*. 2010].

QT interval prolongation, involving disturbance of potassium channel function, is induced by some antipsychotics occasionally, but not inevitably, resulting in the arrhythmia of *toursades de pointes* and, potentially, sudden cardiac death [Alvarez and Pahissa, 2010]. This has been a particular concern with several of the conventional antipsychotic drugs, as well as the atypical antipsychotic sertindole [Yap and Camm, 2003]. However all the atypicals studied in a major survey (including olanzapine, quetiapine and risperidone) are associated with an increased rate of sudden cardiac death [Ray *et al*. 2009], no less so than the conventional drugs, and drug-induced arrhythmia was considered to be the most plausible mechanism, although other factors may contribute. Ziprasidone can cause substantial QT prolongation but there is no consistent evidence of further cardiac pathology with this agent. Asenapine appears to have small effects on the QT interval, less than quetiapine, and below the threshold considered to be clinically significant [Chapel *et al*. 2009].

Mechanisms underlying iatrogenic QT-interval prolongation include inhibition of the repolarising cardiac potassium channel $K_v11.1$ coded by the hERG (*KCNH2*) gene. As there is much individual variability in the QT interval and susceptibility to arrhythmias, a variety of genetic risk factors may also contribute, as will other influences including electrolyte abnormalities and acquired cardiac dysfunction [Yap and Camm, 2003]. Nevertheless many of the atypicals appear to depress the function of the hERG channel in experimental models [Alvarez and Pahissa, 2010].

Concluding comments

The atypical antipsychotics are, as a class, effective agents for the treatment of bipolar mania, reflecting their activity as antagonists at dopamine D2 receptors. This review has attempted to demonstrate that they can be distinguished not so much in this effect but in other aspects of the clinical consequences of their pharmacology. These pharmacological mechanisms may lead to differences in their potential in ameliorating other affective symptoms and, most obviously, in certain common and limiting adverse effects. For asenapine, this may particularly reflect the uniquely complex breadth of actions at 5-HT receptors, several of which are implicated as antidepressant targets, as well as the relative freedom from weight gain through as yet undefined mechanisms. A better understanding of the pharmacological bases for the various therapeutic and adverse effects of these drugs will inevitably provide valuable indications for the design of improved agents for the treatment of bipolar illness, as will a better understanding of the underlying pathology of this disorder.

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