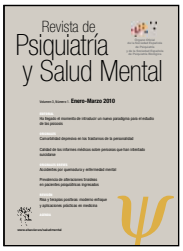
Rev Psiquiatr Salud Ment (Barc.) 2011;**4(2)**:101-108

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental



REVIEW

Asenapine: A new focus on the treatment of mania

Núria Cruz, Eduard Vieta*

Programa de Trastornos Bipolares, Hospital Clínic, Universitat de Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain

Received July 27, 2010; accepted October 8, 2010

KEYWORDS
Asenapine;
Antipsychotic;
Mania;
Bipolar disorder

Abstract

Development: Asenapine, recently marketed in United States and ready to be so in Europe, is a multimodal action second-generation antipsychotic, with high affinity for multiple dopaminergic (D_2, D_3 y D_4), serotonergic ($5HT_{2A}$, $5HT_{2B}$, $5HT_{2C}$, $5HT_6$ y $5HT_7$) and adrenergic (α_{1A}, α_{2A}, α_{2B} y α_{2C}) receptors. Asenapine has to be administered sublingually. After going through succesfully the preliminary phases of development, several clinical trials have been completed in two main indications: schizophrenia and mania. This article summarizes the available evidence on its safety and efficacy in acute mania and provides some prospect on its clinical immediate and future applications.
Conclusions: Asenapine is effective and generally well tolerated in the treatment of moderate-to-severe acute mania associated to bipolar I disorder. The sublingual administration may be a challenge (coadministration with food or other drugs needs to be avoided) but also an opportunity (improved treatment adherence). Due to its multimodal receptor profile, it may cause several side-effects, but most of those are relatively mild, with none being particularly outstanding. In Europe, asenapine is indicated for the treatment of acute mania only, but several trials are being conducted in schizophrenia and bipolar depression.

PALABRAS CLAVE
Asenapina;
Antipsicótico;
Manía;
Trastorno bipolar

Asenapina: un nuevo enfoque para el tratamiento de la manía

Resumen

Desarrollo: La asenapina, recientemente comercializada en Estados Unidos y presta a serlo en Europa, es un antipsicótico de segunda generación con acción multimodal, derivada de su afinidad por múltiples receptores dopaminérgicos (D_2, D_3 y D_4), serotonérgicos ($5HT_{2A}$, $5HT_{2B}$, $5HT_{2C}$, $5HT_6$ y $5HT_7$) y adrenérgicos (αa_{1A}, α_{2A}, α_{2B} y α_{2C}). Su administración se realiza por vía sublingual. Tras culminar las fases iniciales de desarrollo, se han conducido diversos ensayos clínicos en dos indicaciones principalmente: esquizofrenia y manía. Este artículo sintetiza la evidencia científica de su eficacia y seguridad en manía aguda y adelanta algunas de sus posibilidades clínicas inmediatas y futuras.

* Corresponding author.
E-mail: evieta@clinic.ub.es (E. Vieta).

1888-9891/$ - see front matter

Conclusiones: La asenapina es eficaz y generalmente bien tolerada en el tratamiento de la manía aguda moderada o grave asociada al trastorno bipolar tipo I. Su administración sublingual plantea el reto de evitar su coadministración con comida u otros fármacos, pero puede suponer una ventaja para la adherencia terapéutica. Por su perfil multimodal, puede asociarse a diversos efectos adversos, pero destaca por la baja intensidad de todos ellos, sin ninguno que sobresalga por encima de los demás. En Europa está indicada solamente para la manía aguda, pero se están realizando también numerosos ensayos en esquizofrenia y en depresión bipolar.

Introduction

Background on development of the molecule

Asenapine, a second-generation, atypical antipsychotic, was approved by the United States Food and Drug Administration (FDA) in August of 2009 for acute treatment of schizophrenia and the pure or mixed mania of bipolar disorder type I.[1,2] On 24 June 2010, the Committee for Medicinal Products for Human Use (CHMP) issued a favourable opinion for its authorization in Europe under the indication, "treatment of moderate to severe episodes of acute mania associated with bipolar disorder type I (EMA/CHMP/397789/2010)." This indication is based primarily on 3 positive clinical trials that support its efficacy and safety for this indication.[3]

The development of sublingual asenapine in humans began in 1996 for treatment of schizophrenia, and it was not until 2004 that it was studied for acute mania in bipolar disorder.[4,5]

Following its first preclinical study in 1990,[6] ORG 5222 (the original name of the asenapine molecule) was researched initially in Europe and Japan using an oral and intravenous formulation; however, due to the low oral bioavailability and the high first-pass hepatogastrointestinal metabolism associated with the oral formulation, development shifted to the sublingual formulation.[7]

Method

The bibliography and primary clinical trial sources from August of 2009 to the present were reviewed, searching on the term "asenapine" or "ORG 5222" at the following websites: http://www.pubmed.gov; http://www.fda.gov; and www.clinicaltrials.gov. Our systematic review focused on obtaining data from clinical trials conducted for the purpose of registering the molecule. Using the data obtained, we have attempted to create a composite of the pharmacokinetic and pharmacodynamic characteristics of asenapine, as well as its efficacy and safety and its practical application in the treatment of acute mania.

Pharmacodynamics

Asenapine is an innovative pharmacological agent in the clinical advancement of treatment for mania. Figure 1 shows asenapine's chemical structure. This new antipsychotic shows a high affinity for various receptors, including $5HT_{2A}$, $5HT_{2B}$, $5HT_{2C}$, $5HT_6$, and $5HT_7$ serotonergic antagonism; α_{1A}, α_{2A}, α_{2B}, and α_{2C} adrenergic antagonism; and D_3 and D_4 dopaminergic antagonism. A graphic representation of its pharmacodynamic profile is shown in figure 2. Just as in the case of the atypical antipsychotics, asenapine exhibits an affinity for D_2 receptors, with a striking serotonergic affinity in the $5HT_{2A}/D_2$ ratio. Although it is similar to clozapine in its high affinity for a variety of different receptors, it has no appreciable affinity for muscarinic receptors, the highest proportion being in the affinity ratio between the D_2 and the M_1, M_2, M_3, and M_4 receptors.[8]

Figure 1 Chemical structure of asenapine.

The multi-potential nature of this new, atypical antipsychotic has given rise to certain expectations based on both its efficacy and its tolerability. Asenapine's higher affinity for $5HT_{2A}$ receptors in comparison to D_2 receptors is what gives it its "atypicalness"—the mechanism responsible for the atypical antipsychotics' higher selectivity, which means a lower potential for EPS.[9,10] Antagonism of the $5HT_{2A}$ receptors results in increased dopamine activity in the brain's prefrontal cortex, which has also been indicated as a possible mechanism for the improved cognition.[11] The results of preclinical studies reflect an increase dependent on the dose of cortical dopamine[12] and on the hippocampus,[12] as well as an increase in norepinephrine and acetylcholine[13] comparable to the effects previously described for clozapine and quetiapine. These effects could also be associated with a certain antidepressant action.[14,15] The evidence emerging suggests that the $5HT_6$ receptor antagonism may offer benefits for cognition[16] and that the $5HT_7$ antagonism may confer

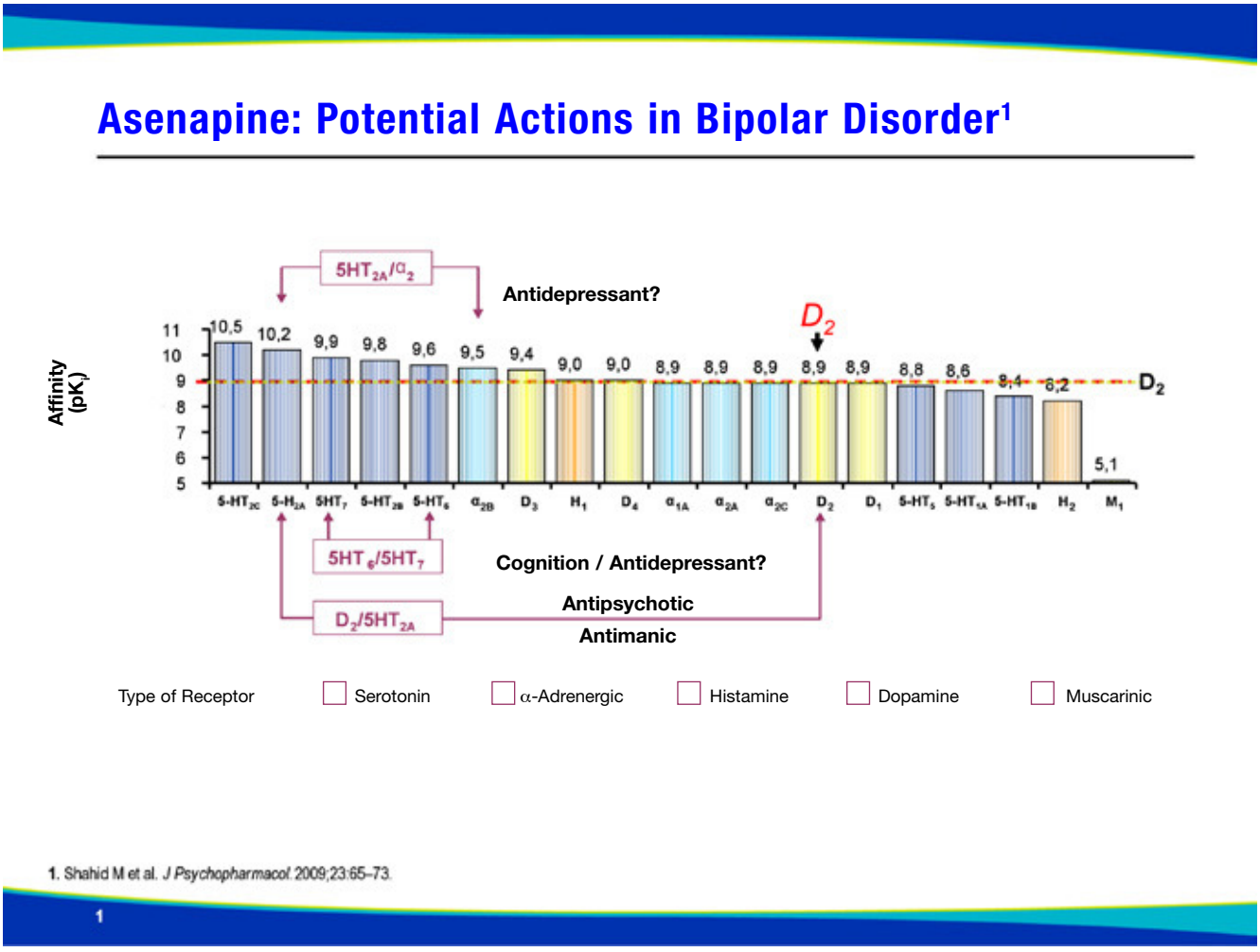


Figure 2 Pharmacodynamic profile for asenapine.

benefits for the control of anxiety and mood as well as for cognition,[17] though more exhaustive confirmation studies are required.[8] It has also been suggested that asenapine's α-adrenergic receptor antagonism improves the negative and cognitive symptoms via α_2 receptor antagonism, while improvement in the positive symptoms is via the α_1 receptors.[18] Data from preclinical studies also suggests that D_3 receptor antagonism may help to improve negative and cognitive symptoms[19]; again, however, the clinical evidence on these variables with asenapine requires more studies. In fact, in animal models, at doses higher than those required for antipsychotic activity, asenapine reduced cognitive performance due to disturbances in motor function.[20] However, this effect has also been observed with olanzapine and risperidone. On the contrary, in preclinical studies with monkeys, asenapine produced a substantial improvement in executive functions that was maintained following a long-term dosing period.[21] Other studies in rats have shown that long-term asenapine therapy, regardless of the dose, has ionotropic glutamate-type effects on the brain.[22]

Asenapine's scant binding affinity due to M_3 antagonism reduces the potential for the anticholinergic side effects and metabolic syndrome associated with olanzapine and clozapine.[23] Another of asenapine's effects, shared with the rest of the atypical antipsychotics, is that it induces the increase of dopamine in the nucleus accumbens, in comparison with the central region. Asenapine's pharmacological profile could translate to specific clinical benefits in the treatment of mania and in other indications, but pragmatic studies must still be conducted to confirm it—studies that continue those conducted to date and have a more exploratory and regulatory profile.

Pharmacokinetics

Asenapine has been studied in humans in the sublingual formulation and shows an ideal bioavailability of 35%, provided that during its absorption there is no interaction with liquids or foods, mainly fats, over a variable period of time (from 10 minutes to 4 hours) after it is administered. Asenapine shows a non-linear type of pharmacokinetics in relation to the dose. Administering the recommended range of 5-10 mg in two doses daily, exposure to the drug increases 1.7 times in the event the dose is doubled.[24,25]

Its half-life fluctuates between 13.4 and 39.2 hours.[24] Basically, asenapine undergoes hepatic metabolism via cytochromes CYP1A2, primarily, and CYP3A4 and CYP2D6 to a lesser degree, although this last one may take on clinical significance if asenapine is combined with other CYP2D6-dependent atypical antipsychotics—mainly chlorpromazine, olanzapine, clozapine, perphenazine, quetiapine, risperidone, sertindole, and thioridazine. No significant correlations were found between creatinine clearance and asenapine exposure in renal insufficiency. Then again, even though mild to moderate hepatic insufficiency did not affect asenapine exposure, severe hepatic insufficiency caused a 7-fold increase in exposure. Tobacco use has not been associated with changes in asenapine exposure.[26]

Efficacy of asenapine with acute mania in clinical trials

in figure 3 there is a summary of the studies with sublingual asenapine in acute or mixed mania, short- and long-term, and the study designs. Described below is the efficacy and safety data published to date that has prompted the authorization of asenapine in the United States and Europe. There are basically 3 trials—2 as monotherapy and 1 as therapy added to lithium or valproate—with their respective extension phases.[27-30]

Short-term efficacy as monotherapy

A total of 2 Phase III, randomised, three-branch, placebo-controlled, and active-control studies have been conducted with asenapine in acute phase, in a total of 977 bipolar type I patients with acute mania or mixed episodes (Ares 7501004 and Ares 7501005) over a period of 3 weeks. These were identically designed and placebo-controlled, with olanzapine as flexible-dose monotherapy.

A 5-10 mg dose of sublingual asenapine was administered, in two doses daily, in type I bipolar patients with acute manic or mixed episodes;

approximately 30% of the participants had a mixed episode and 70%had a pure mania episode. The individuals in both studies were randomly assigned to receive asenapine, olanzapine, or a placebo in a randomised treatment (2 : 2 : 1). The initial dose of asenapine was 10 mg, and the dose of olanzapine was 15 mg/day. After the first day, the dose was flexible, based on efficacy, safety, and tolerability, within a range of 5-10 mg in two doses daily for asenapine

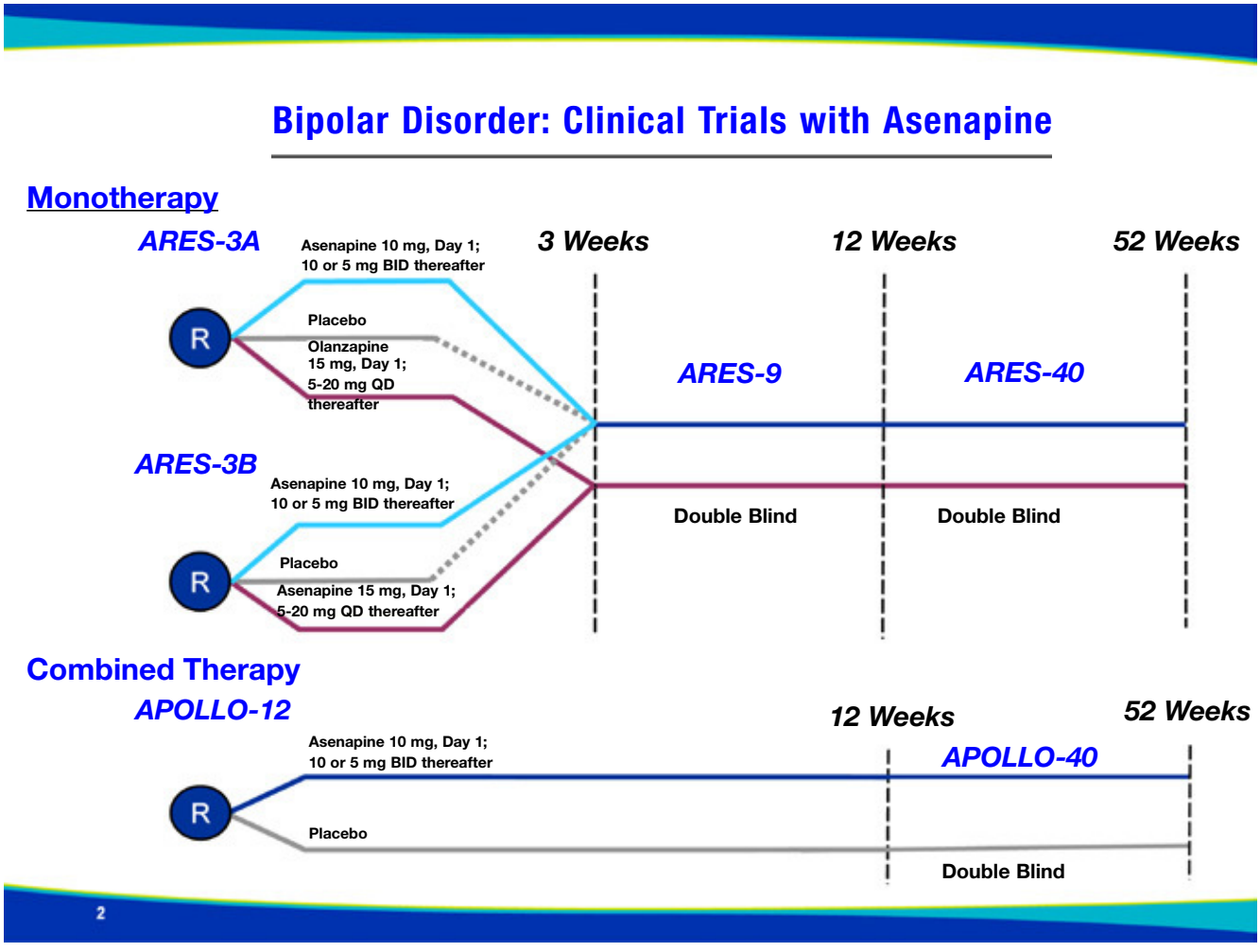


Figure 3 Clinical trials with sublingual asenapine in acute or mixed mania.

and 5-20 mg/day for olanzapine. Generally speaking, patients remained on their initial dose of asenapine, and less than 10% of subjects required the dose to be reduced. All participants had to be hospitalised for at least the first 7 days and then continued on an outpatient basis.

Benzodiazepines (lorazepam up to 4 mg/day) were permitted as concomitant medication in case of agitation from the day of screening until day 7 of the study, always with at least a 4-hour margin for any efficacy assessment, aspirin or non-steroidal anti-inflammatories for pain, and antiparkinsonian medication for extrapyramidal symptoms. In the event of insomnia, hypnotics were permitted (zolpidem 10 mg/day, zaleplon 20 mg/day, or temazepam up to 30 mg/day), up to a maximum of 3 nights per week. The primary variable for efficacy was the drop in score on the Young scale (Young Mania Rating Scale [YMRS]) compared to the baseline. The results of these first 2 studies are summarized below.

Ares 7501004 Study (registration number NCT00159744)
The average age of the participating patients was approximately 40 years, and the mean baseline score on the YMRS had a range of 28-30. The rates of abandonment were 33% for asenapine, 20% for olanzapine, and 42% for placebo. From the start of the study until day 21, the improvement in total score on the YMRS was statistically significant for both asenapine ($P<.007$) and olanzapine ($P<.0001$) in comparison with the placebo. At the end of the study, the mean change in YMRS score was 11.5±0.8 points for asenapine, 14.6±0.8 for olanzapine, and 7.8±1.1 for the placebo branch. The statistically significant improvement with asenapine and olanzapine, compared to placebo, was observed from day 2 onward. As secondary study variables, the percentage of responders, as determined by the YMRS (50% reduction compared to the baseline value), and the percentage in remission (total score of 12 or less) was higher for asenapine (42.6% and 35.5%, respectively) than for the placebo branch (34% and 30.9%, respectively), although it did not reach statistical significance. The number necessary to treat (NNT) so that one of the patients would benefit from the efficacy of asenapine versus placebo was 12, while the NNT for olanzapine versus placebo was 5.

Ares 7501005 Study (registration number NCT00159796)
This study also supports the efficacy of asenapine. The average age of the patients was approximately 40 years, and the mean baseline score on the YMRS varied from 28 to 29. The rates of abandonment were 37% for asenapine, 20% for olanzapine, and 38% for the placebo branch. From day 2 until day 21 of the study, the improvement in total score on the YMRS was statistically significant for both asenapine and olanzapine in comparison with the placebo branch. At the end of the study, the mean change in the YMRS baseline score was 10.8±0.8 for asenapine, 12.6±0.8 for olanzapine, and 5.5±1.1 for placebo. The statistically significant improvement in the YMRS with asenapine and olanzapine, compared to placebo, began to be observed from day 2 onward. The percentage of responders, as determined by the YMRS (50% reduction compared to the baseline value), and the percentage of patients in remission (total score of 12 or less on the YMRS), days 14 and 21, was higher for asenapine (42.3% and 40.2%, respectively) than for the placebo (25.2% and 22.3%, respectively). The NNT for asenapine versus placebo was 6, while for olanzapine versus placebo it was 5.

Medium- and long-term efficacy with monotherapy in acute mania: extension studies

Two extension studies have been conducted with patients who participated in the 3-week studies: a 9-week study (Ares 7501006, registration number NCT00143182) to evaluate non-inferiority versus olanzapine,[29,31] covering efficacy data for 12 treatment weeks, followed by another 40-week study (Ares 7501007, number NCT00159783) focused on long-term safety data.[30,31]

A total of 504 individuals received at least one dose of double-blind study medication during the 9-week extension study, representing a total of 181 patients who were treated with asenapine and 229 patients who were treated with olanzapine in the 3-week, acute-phase clinical trials A7501004 and A7501005 mentioned above (and continued on the same treatment in the extension study). In addition, 94 patients who were treated with placebo in the acute-phase clinical trials were reassigned to receive asenapine 5-10 mg twice a day in the extension study. The design and pharmacological branches for the extension studies are also represented graphically in figure 3.

Ares 7501006, number NCT00143182
The rates of abandonment were 47% for the asenapine group that had received the placebo in the acute-phase clinical trials; 38% for patients who continued taking asenapine; and 36% for patients who continued taking olanzapine.[31]

The primary efficacy analysis showed that asenapine was statistically non-inferior to olanzapine ($P>.05$), as measured by total YMRS score from the start until day 84 in patients who had 3 weeks of previous exposure to asenapine, with a mean of −20.1 (±10.7) and −21.3 (±9.6) for asenapine and olanzapine, respectively. The percentage of participants who were responders and remitters according to the YMRS was similar in the asenapine branch and the olanzapine branch ($P>.05$).

Ares 7501007, number NCT00159783
The primary study variable was safety and tolerability based on data for adverse episodes (AE) and extrapyramidal symptoms, laboratory values, and anthropometric measurements. Efficacy constituted a secondary variable and was measured as the change in YMRS calculated from reference week 3 until week 52 to compare asenapine and olanzapine. The placebo/asenapine branch was evaluated for safety only. The incidence of AE was 71.9%, 86.1%, and 79.4% for placebo/asenapine, asenapine, and olanzapine, respectively, where the most common AE were headache and somnolence with placebo/asenapine; insomnia, sedation, and depression with asenapine; and weight gain, somnolence, and sedation with olanzapine. Among the cases observed, the mean ± standard deviation for the change in total YMRS score at week 52 was −28.6±8.1 and −28.2±6.8 for asenapine and olanzapine, respectively. The lack of a long-term placebo comparator represents the

Table 1 Adverse effects of asenapine in comparison with other antipsychotics

Atypical antipsychotics: Report of adverse effects[1]							
Drug	QTc	Sedation	Weight gain	Glucose increase	EPS	Anticholinergic effects	Prolactin increase
Amisulpride	+	–	+	+	+	–	+++
Aripiprazole	–	–	+	–	++	–	–
Asenapine	+	+	+	+	+	–	+
Chlorpromazine	++	+++	++	++	++	++	++
Clozapine	+	+++	+++	+++	–	+++	–
Haloperidol	+	+	+	+	+++	–	++
Olanzapine	+	++	+++	+++	+/–	+	+
Quetiapine	++	++	++	++	–	+	–
Risperidone	+	+	++	++	++	+/–	+++
Sulpiride	+	–	+	+	+	–	+++
Ziprasidone	++	+	+/–	+	+/–		

EPS = extrapyramidal symptoms
[a] Adapted from Bishara D et al. *Neuropsychiatr Dis Treat*. 2009;5:483-490.

limitation of this study. In conclusion, the data obtained confirm that asenapine maintained its efficacy subsequent to the acute phase—from week 12 to week 52—and that it has good tolerability.

Efficacy in combination with lithium or valproate

A third, placebo-controlled study evaluated the efficacy of asenapine at doses of 5-10 mg/day in two doses daily in acute mania or mixed episodes in combination with lithium or valproate (these last ones without blinding) over 12 weeks (Apollo 12; 7501008); then, an extension study on safety was conducted up to 40 weeks (Apollo 12; 7501009) for patients who completed the first 12-week study. The results have not yet been published, but the results for the 12-week efficacy study are available, showing asenapine's superiority in combination, in comparison to the mood stabilizers as monotherapy, in terms of the improvement in acute mania symptoms in type I bipolar patients, which prompted the CHMP's positive opinion on its authorization in Europe.

Safety of asenapine in clinical trials

Asenapine has been well tolerated, overall, and has minimal effect on prolactin and metabolic parameters. Cardiovascular evaluations have found no reason for concern, and the effects of asenapine in terms of prolongation of the QTc interval were comparable to those of quetiapine, at the highest dosage range for asenapine, although the incidence of extrapyramidal symptoms (EPS) was higher with asenapine than with olanzapine in one of the studies.

The side effects most commonly associated with asenapine (observed in more than 1 out of 10 patients) are anxiety and somnolence. Other common AE (observed in 1-10 out of 100 patients) are weight gain, increased appetite, dystonia (slow or sustained muscle contractions), akathisia (restlessness), dyskinesia (involuntary muscle contractions), parkinsonism (slow movements and tremor), sedation, dizziness, dysgeusia (changes in taste), oral hypaesthesia (feeling of numbness in tongue or mouth), increased alanine aminotransferase (increase in liver protein levels), muscular rigidity, and fatigue.

In terms of safety, the incidence of AE associated with treatment were 65.7% for asenapine and 61.7% for olanzapine. Although the elevated prolactin, weight gain, and metabolic syndrome were more common in the olanzapine group, EPS were more common with asenapine.[32]

Table 1 summarizes the AE with asenapine in comparison with other antipsychotics.

A pharmacovigilance plan for asenapine will be implemented in the context of its authorization for marketing in Europe.[33]

Conclusions and therapeutic applicability

Despite the wide variety of antipsychotics available on the market, there remains a need to optimise treatment for bipolar disorder—in particular, to address the cognition and functional impairment issues associated with the chronicity of the disease. Any improvement in the tolerability profile of the atypical antipsychotics—especially in metabolic syndrome—could not only improve the patients' risk-benefit and quality of life but also increase the likelihood of therapeutic compliance. Asenapine dosing and titration in treatment of mania, based on evidence from the Phase III clinical trials that have been conducted, consists of administering a 10-20 mg/day dose, divided into two doses daily, that may be increased or decreased at a rate of 5 mg/day on a weekly basis, depending on tolerability. Its twice-daily sublingual dosage form and the recommendation that no food or liquids should be consumed for 10 minutes

following administration represents a drawback that may be an obstacle to its acceptance and necessitates a psychoeducational program for patients. It is possible that patients will complain about the bitter or unpleasant taste; however, the sublingual dosage form may make it easier to ensure that the medication has been taken and may represent an advantage in that it obviates passage through the gastrointestinal tract. Aripiprazole and ziprasidone share some of asenapine's tolerability advantages, but more alternatives are needed. Asenapine has affinity for a great number of receptors, being an antagonist for serotonergic, dopaminergic, and adrenergic receptors; unlike clozapine, however, it has no affinity for muscarinic receptors, which gives it better tolerability. Its mechanism of action could endow it with antidepressant properties.[34] In summary, asenapine's metabolic profile compares favourably with olanzapine, and it shows a low propensity for extrapyramidal symptoms in comparison with haloperidol. Compared to placebo, it is associated with a higher incidence of somnolence, dizziness, akathisia, EPS, and weight gain. In bipolar disorder, asenapine has been shown to be comparable to olanzapine in terms of its efficacy at 12 weeks, with efficacy maintained over 40 weeks and good long-term safety data.

In comparison with other antipsychotics, asenapine could have advantages in terms of tolerability and cognitive function, based on its pharmacodynamics; however, more studies are required to demonstrate its clinical value and ability to improve functional capacity over the long term. In the near future, conclusive data could be available on schizophrenia and bipolar depression that, if favourable—if study results are similarly positive—could mean an indication complementary to acute mania.

Conflict of interest

Dr Vieta has received research grants and served as consultant, advisor or speaker for the following companies: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Lundbeck, Novartis, Organon, Otsuka, Pfizer Inc, Sanofi-Aventis, Servier, Solvay, Schering-Plough, Takeda and United Biosource Corporation and Wyeth, research funding from the Spanish Ministry of Innovation, the Spanish Ministry of Science and Education, the Stanley Medical Research Institute and the 7th Framework Program of the European Union.
Dra. Cruz has no conflicto of interest.

Acknowledgments

The authors wish to express their gratitude to the *Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III, CIBERSAM* [*Centro de Investigación Biomédica en Red de Salud Mental* / Mental Health Network Biomedical Research Centre], and the *Generalitat de Catalunya* [Government of Catalonia] (2009 SGR 1022) for their assistance in the *Programa de Investigación del Trastorno Bipolar* [Bipolar Disorder Research Program] of Barcelona.

References

1. United States Food and Drug Administration. FDA Approves Saphris to Treat Schizophrenia and Bipolar Disorder. Press release, 14 August 2007. [Accessed August 2009] Available in: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm177401.htm
2. Schering-Plough Corporation. Saphris (Asenapine) Sublingual Tablets US Prescribing Information. Revised August 2009. [Accessed August 2009] Available in: http://www.spfiles.com/pisaphrisv1.pdf
3. Vieta E, Sanchez-Moreno J. Acute and long-term treatment of mania. Dialogues Clin Neurosci. 2008;10:165-79.
4. Stevenson R, Wolde HT. Update 4 – Akzo, Pfizer Scrap Asenapine Joint Development. 28 November 2006. [Accessed August 2009] Available in: http://www.reuters.com/article/companyNewsAndPR/idUSL286087420061128
5. United States Food and Drug Administration. Saphris (Asenapine) Sublingual Tablets. Briefing Book. 30 July 2009. [Accessed August 2009] Available in: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM173877.pdf
6. Costall B, Domeney AM, Kelly ME, Naylor RJ, Tomkins DM. Actions of ORG 5222 as a novel psychotropic agent. Pharmacol Biochem Behav. 1990;35:607-15.
7. Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. J Clin Psychiatry. 2007;68:1492-500.
8. Shahid M, Walker GB, Zorn SH, Wong EH. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. J Psychopharmacol. 2009;23:65-73.
9. Meltzer HY. Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. Psychopharmacology (Berl). 1989;99 Suppl:S18-S27.
10. Meltzer HY. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology. 1999;21(2 Suppl):106S-115S.
11. Roth BL, Hanizavareh SM, Blum AE. Serotonin receptors represent highly favorable molecular targets for cognitive enhancement in schizophrenia and other disorders. Psychopharmacology (Berl). 2004;174:17-24.
12. Tarazi FI, Moran-Gates T, Wong EH, Henry B, Shahid M. Differential regional and dose-related effects of asenapine on dopamine receptor subtypes. Psychopharmacology (Berl). 2008;198:103-11.
13. Huang M, Li Z, Dai J, Shahid M, Wong EH, Meltzer HY. Asenapine increases dopamine, norepinephrine, and acetylcholine efflux in the rat medial prefrontal cortex and hippocampus. Neuropsychopharmacology. 2008;33:2934-45.
14. Yatham LN, Goldstein JM, Vieta E, Bowden CL, Grunze H, Post RM, et al. Atypical antipsychotics in bipolar depression: potential mechanisms of action. J Clin Psychiatry. 2005;66 Suppl 5:40-8.
15. Brugue E, Vieta E. Atypical antipsychotics in bipolar depression: neurobiological basis and clinical implications. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:275-82.
16. Neale AC, Jenkins H, Amend D, Lesen M. A 14 day dose escalation, double-blind, randomized, placebo-controlled study of SB518 in adult patients with schizophrenia [abstract]. Neuropsychopharmacology. 2005;30 Suppl 1:S54.
17. Hedlund PB, Sutcliffe JG. Functional, molecular and pharmacological advances in 5-HT7 receptor research. Trends Pharmacol Sci. 2004;25:481-6.
18. Svensson TH. Alpha-adrenoceptor modulation hypothesis of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27:1145-58.

19. Joyce JN, Millan MJ. Dopamine D3 receptor antagonists as therapeutic agents. Drug Discov Today. 2005;10:917-25.
20. Marston HM, Young JW, Martin FD, Serpa KA, Moore CL, Wong EH, et al. Asenapine effects in animal models of psychosis and cognitive function. Psychopharmacology (Berl). 2009;206:699-714.
21. Jentsch JD, Shahid M, Wong E, Roth RH. Asenapine improves cognitive function in monkeys repeatedly exposed to the psychotomimetic drug phencyclidine. Schizophr Res. 2006; 81:85.
22. Tarazi FI, Choi YK, Gardner M, Wong EH, Henry B, Shahid M. Asenapine exerts distinctive regional effects on ionotropic glutamate receptor subtypes in rat brain. Synapse. 2009;63:413-20.
23. Johnson DE, Yamazaki H, Ward KM, Schmidt AW, Lebel WS, Treadway JL, et al. Inhibitory effects of antipsychotics on carbachol-enhanced insulin secretion from perifused rat islets. Diabetes. 2005;54:1552-8.
24. Gervin M, Barnes TRE. Assessment of drug-related movement disorders in Schizophrenia. Adv Psychiatr Treat. 2000;6:332-41.
25. Weiss EM, Bilder RM, Fleischhacker WW. The effects of second-generation antipsychotics on cognitive functioning and psychosocial outcome in Schizophrenia. Psychopharmacology (Berl). 2002;162:11-7.
26. Peeters P, De Greef R, Hulskotte E, et al. Asenapine: an overview of phase I pharmacokinetic studies. 2009. Paris, France, Poster presented at 9th World Congress of Biological Psychiatry, 28 June-2 July 2009.
27. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. J Affect Disord. 2010;122:27-38
28. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. Bipolar Disord. 2009;11:673-86.
29. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine versus olanzapine in acute mania: a double-blind extension study. Bipolar Disord. 2009;11:815-26.
30. 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; 126:358-65.
31. Schering-Plough Research Institute. Saphris (Asenapine) Sublingual Tablets. Briefing Document (Background Package). 30 July 2009. [Accessed August 2009] Available in: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM173876.pdf
32. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines, 10th Edn. London, UK: Informa Healthcare; 2009.
33. Summary of opinion 1 (initial authorisation) Committee for medicinal products for human use (CHMP); 24 June 2010 EMA/CHMP/397789/2010.
34. Vieta E, Franco C, Cruz N. Antipsychotics in bipolar depression: in reply. Int J Neuropsychopharmacol. 2010;13: 969.