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SPECIAL ARTICLE

Management of asenapine treatment in clinical practice: Recommendations from a panel of experts☆

Eduard Vieta[a,*], **José Manuel Montes**[b], **Pedro Iborra**[c], **Alfonso Mozos**[d], **Cristina Sáez**[e], **Antonio Benabarre**[a]

[a] *Hospital Clínic, Universidad de Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain*
[b] *Hospital Universitario Ramón y Cajal, Universidad de Alcalá, CIBERSAM, IRYCIS, Madrid, Spain*
[c] *Hospital Clínico Universitario de San Juan de Alicante, Sant Joan d'Alacant, Alicante, Spain*
[d] *Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, La Coruña, Spain*
[e] *Hospital Psiquiàtric Universitari Institut Pere Mata, Reus, Tarragona, Spain*

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Abstract
Introduction: The choice of an antipsychotic should be based on bipolar disorder (BD) symptoms and the particular needs of each patient, as well as the adverse events potentially associated with treatment. Asenapine is an atypical antipsychotic indicated for the management of type-I BD, with distinct pharmacokinetic and receptor affinity profiles.
Material and methods: Recommendations document developed by a panel of experts with extensive experience in the use of asenapine in psychiatric care, including emergency department, hospital, and outpatient care. Recommendations were discussed in a single meeting and were based on both the clinical experience of the panel of experts and the empirical evidence provided in the scientific literature.
Results: The present document describes the patient profile that best suits the pharmacodynamic characteristics of asenapine, as well as the advantages and limitations of the pharmacokinetics associated with the sublingual route. The document also addresses the main safety issues of asenapine and suggests interventions aimed at mitigating the most frequent adverse reactions associated with asenapine treatment. Finally, the article provides advice on dosing and overall management of asenapine treatment, including the combination with other treatments and the switch from other antipsychotics to asenapine.
Conclusions: In this recommendations document, we provide clinicians with guidance on the use of asenapine in real-life practice, including the identification of patients who best suit the characteristics of this antipsychotic.

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

PALABRAS CLAVE
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Uso de asenapina en la práctica clínica: recomendaciones de un panel de expertos

Resumen
Introducción: La selección del antipsicótico adecuado para el tratamiento de pacientes con trastorno bipolar (TB) debe basarse en los síntomas presentes, así como en las necesidades terapéuticas de cada paciente y en los posibles efectos adversos asociados al tratamiento. Asenapina es un antipsicótico de segunda generación indicado para el tratamiento de pacientes con TB de tipo I, cuyo perfil farmacocinético y farmacodinámico presenta características diferenciales con respecto al resto de antipsicóticos.
Material y métodos: Este documento de recomendaciones ha sido elaborado por un panel de expertos con experiencia en el uso de asenapina en los ámbitos de la atención psiquiátrica de urgencias, hospitalaria y ambulatoria. Las recomendaciones se debatieron en una única reunión y fueron elaboradas a partir de la práctica clínica de los expertos y la evidencia proporcionada por la literatura científica.
Resultados: Se describe el perfil de pacientes que mejor se ajusta a las características farmacodinámicas de asenapina, así como las ventajas y limitaciones del perfil farmacocinético asociado a la administración sublingual. Se abordan también las principales características de seguridad de asenapina, así como las posibles medidas a tomar para mitigar los efectos adversos más frecuentes. Finalmente, el documento proporciona una orientación acerca de la dosificación y el manejo general del fármaco, incluyendo las combinaciones con otros fármacos y el cambio de otros antipsicóticos a asenapina.
Conclusiones: Este artículo proporciona una orientación para el uso adecuado de asenapina, así como para la identificación de los pacientes en los que este antipsicótico puede resultar más adecuado.

Introduction

Bipolar disorder (BD) affects between 1% and 2% of the population, and is one of the most debilitating of diseases.[1,2] Although BD was once considered merely a cyclical alternation of depression, mania and euthymia, clinical experience and scientific evidence suggest it is a complex disorder that can present in diverse clinical forms, which go beyond this conception.[3,4]

In addition to mood stabilisers such as lithium and some anticonvulsants, atypical or second-generation antipsychotics have been used in recent years to broaden the range of options for the pharmacotherapeutic approach to treatment of the disorder.[5] However, the different pharmacodynamic profiles of atypical antipsychotics have very different efficacy and tolerability, therefore the particularities of each must be considered so that they can be used in the most appropriate way possible.[6,7]

Asenapine is a second-generation antipsychotic approved in Europe for the treatment of moderate to severe manic episodes associated with type I BD in adults.[8] In placebo- and olazapine-controlled clinical trials, asenapine showed superiority over placebo at 3 and at 12 weeks.[9–11] In comparisons with olanzapine, asenapine showed no lower efficacy, and less weight gain than that associated with treatment with olanzapine.[10] Moreover, asenapine's efficacy in the specific treatment of mania-associated depressive symptoms was assessed in various post hoc analyses of placebo-controlled clinical trials. According to these analyses, treatment with asenapine resulted in greater reduction in depressive symptoms compared to placebo than treatment with olanzapine.[12–15]

A naturalistic study has recently been published in which the outcome of treatment with asenapine was assessed with and without the comorbid use of substances, and an improvement was observed in global functionality as well as psychotic, manic, depressive and anxiety symptoms.[16] However, most of the available information on asenapine comes from placebo-controlled clinical trials.[17] The strict selection criteria of these studies often result in populations that are too homogeneous, which may not represent the scenario observed in actual clinical practice. In this regard, the diversity of clinical profiles of BD together with the pharmacodynamic and pharmacokinetic particularities of each antipsychotic require a period of experience using the drug in clinical practice in order to thus optimise its therapeutic use.[18]

Objectives and methodology

This recommendation paper summarises the potential advantages and disadvantages of the use of asenapine in clinical practice, and provides tools for practitioners to better identify the patients who could benefit from this antipsychotic drug, beyond the information gained from clinical registration trials.

A panel of expert psychiatrists with clinical experience in the use of asenapine was formed to prepare the recommendations. A total of six experts were included, practicing

in various areas of psychiatric care: emergency, hospital, in-patient/community.

The various aspects of the clinical use of asenapine were discussed at a single meeting held on 9 December, 2016, in Barcelona. The meeting was structured around three thematic blocks: (1) indication; (2) tolerability, and (3) dosage and management. At the start of each block a summary of the evidence available in the scientific literature was presented, and at the end of the block the key ideas were summarised and agreed, along with the most relevant aspects for drawing up a recommendations document. Both the individual contributions of each expert and the key ideas agreed were summarised in a synthesis paper that was reviewed individually by the members of the panel of experts. The final document presents a summary of the most relevant aspects of asenapine, and general recommendations for the appropriate clinical use of the antipsychotic.

Results

Indication

Asenapine is indicated in Europe for the treatment of moderate to severe manic episodes associated with type I BD.[8] In addition to BD, the Food and Drug Administration (FDA) includes schizophrenia as an indication for the drug in the United States.[19]

The multipotential nature of asenapine derives from its affinity for multiple dopaminergic (D_2, D_3 and D_4), serotonergic ($5HT_{2A}$, $5HT_{2B}$, $5HT_{2C}$, $5HT_6$ and $5HT_7$) and adrenergic (α_{1A}, α_{2A}, α_{2B} and α_{2C}) receptors.[20] The antimanic activity of this atypical antipsychotic is associated with high affinity for D2 dopamine receptors, superior to that observed in other antipsychotics.[21,22] In addition to clinical efficacy in monotherapy, assessed in clinical trials of up to 40 weeks of follow-up,[9,10,23] positive results from the use of asenapine as an adjuvant to treatment with lithium or sodium valproate have also been reported.[11]

Beyond the typical symptoms of a manic episode, the DSM-5 diagnostic criteria for BD cover the presence of additional characteristics, including anxiety, mixed symptoms, etc.[24] Of the different characteristics of BD, management of episodes with mixed symptoms is particularly complex due to the coexistence of manic and depressive symptoms, when exclusively acting on the D_2 receptors could be counterproductive.

The complementary affinity of atypical antipsychotics for serotonergic receptors could partially compensate for this effect, resulting in greater effectiveness in patients with mixed symptoms. In the case of asenapine, the particularly multi-receptor profile manifests itself in effective improvement of all Young Mania Rating Scale (YMRS) symptoms, including those relating to irritability, euphoria and sleep.[25] It also has high affinity for the $5HT_{2A}$ and $5HT_{2C}$ receptors, a similar pharmacodynamic profile to that of antidepressants such as mirtazapine, with which it shares similarities in chemical structure.[22,26] This pharmacodynamic profile is consistent with the effect on depressive symptoms associated with mania observed in post hoc analyses, according to which treatment with asenapine resulted in a significant reduction in MADRS scores at 7 and 21 days of treatment.[14,15] In clinical practice, the antidepressant activity of asenapine makes it a good candidate for treating patients with mixed symptoms.[27] In line with this indication, a naturalistic study conducted in Spain on asenapine prescribing habits revealed that physicians tend to prescribe asenapine for patients with less severe manic symptoms but with a more complex clinical profile.[28] In addition, the multi-receptor profile of asenapine might also explain the lower intensity of sedation observed in clinical practice, perceived more as a ''calming effect''. According to present consensus, this sedative effect, less pronounced than that of other antipsychotics such as quetiapine, has less impact on cognitive function.

In addition to the differential pharmacodynamic profile, asenapine has particular pharmacokinetic characteristics. After sublingual administration, the drug reaches maximum plasma levels between 0.5 and 1.5 h.[29] This administration route is a differential element of asenapine, even compared to the oral-dispersible formulations (termed ''flash'') of other antipsychotic drugs that must ultimately be ingested for the drug to be absorbed. In a recent study that compared the speed of action of different antipsychotics, treatment with asenapine was associated with a significantly higher rate of response and remission at 4 and 7 days.[30] From the perspective of clinical practice, rapid onset of action has relevant consequences in different areas of usage of the drug. In the psychiatric emergency setting, the use of asenapine can, in many cases, avoid the need to administer anxiolytics, so that benzodiazepines, which are often used to reduce agitation and situations of aggressiveness during the initial days of administration, are used less.[31,32] The benefits of this pharmacokinetic profile have been observed in a clinical trial on patients attended in emergency departments with agitation of diverse causes, where asenapine showed efficacy comparable to previous studies with intramuscular antipsychotics.[31] Based on the experience of the panel of experts in the management of outpatients under chronic treatment for BD, the speed of action of asenapine enables patients starting a process of decompensation process to be quickly stabilised. In fact, in some cases the patients themselves have reported using asenapine as an alternative rescue medication to benzodiazepines. Finally, in the experience of the panel of experts in the hospital setting, because it does not require an initial dosage period the onset of antimanic activity is accelerated, reducing the length of hospital stay.

In summary, although asenapine is effective in treating acute mania in general, it has a differential multi-receptor profile and is particularly suitable for the treatment of patients experiencing episodes with mixed symptoms. In this regard, asenapine is also appropriate for patients with manic episodes and a more complex symptomatic profile, where manic symptoms could coexist with manifestations of dysphoria, anxiety or depression. The sedative effect of asenapine, characterised by causing less somnolence, is also beneficial for these patients, who will show better acceptance of the drug. Finally, given asenapine's rapid onset of action, administering anxiolytics concomitant with the first doses of antipsychotics, often used to reduce agitation and situations of aggressiveness, in many cases might not be necessary. Its rapid onset of action also makes asenapine

a suitable drug for stable patients starting a process of decompensation.

Tolerability

In general, the atypical antipsychotics have frequently been associated with adverse effects, particularly somnolence and metabolic disorders such as dyslipidaemia, insulin resistance and weight gain. In placebo- and olanzapine-controlled clinical trials, asenapine showed a slightly lower incidence of somnolence to that observed with olanzapine, but it was also more transient in nature (it rarely manifested beyond the first 45 min) and manifested especially during the first week of treatment.[33,34] Based on the risk of somnolence calculated from the results of controlled clinical trials, asenapine has been classified in group of antipsychotics of low somnolence.[35] In clinical practice, the appropriateness of this sedation profile should be assessed in each patient. In some cases, a less sedating drug could increase the patient's acceptance of the treatment, while reducing its impact on their quality of life. However, there are cases where longer or more intense sedation than that observed with asenapine may be desirable to combat an insomnia disorder associated with BD.

The low incidence of metabolic disorders is one of the most remarkable features of asenapine's safety profile. Irrespective of treatment with antipsychotics, BD is associated with an increased risk of metabolic disorders compared to that of the general population.[36] Furthermore, most of the drugs indicated for the treatment of BD – including many antipsychotics and stabilisers – carry a risk of metabolic syndrome and weight gain.[37,38] In clinical trials performed with asenapine no significant changes in weight or in levels of triglycerides, LDL cholesterol or HDL cholesterol were observed.[9–11,39] In comparisons with other atypical antipsychotics, asenapine showed a notably lower incidence of metabolic effects, especially in the short term.[40] In actual clinical practice, the reduced impact of asenapine on weight gain can be seen through follow-up of patients according to the Spanish consensus on the physical health of the bipolar patient, which recommends annual monitoring of glucose, cholesterol and triglyceride levels, and weight monitoring at each visit.[41]

Other tolerability problems traditionally associated with treatment with antipsychotics are the anticholinergic effects from the affinity of these drugs for muscarinic receptors.[42] Anticholinergic activity, which can be associated to a greater of lesser extent with both the classic and the atypical antipsychotics results in an increase in the incidence of symptoms such as dry mouth, constipation, blurred vision and tachycardia, as well as urinary complications and cognitive impairments.[43–45] Unlike other antipsychotics, asenapine has no appreciable affinity for these receptors, resulting in a very low incidence of the effects related to anticholinergic activity.[21]

Hyperprolactinaemia is another adverse effect associated with certain antipsychotic treatments and which frequently results in sexual dysfunction, menstrual disturbances, and other risks which, although frequently underestimated, can potentially be serious (osteoporosis, possible increased risk of breast cancer, etc.). The recently published Spanish consensus highlights asenapine as one of the safest drugs in this regard, along with aripiprazol.[46]

The most common adverse effects associated with treatment with asenapine are dysgeusia (manifested as an unpleasant taste in the mouth) and orolingual hypoaesthesia or paraesthesia, both associated with its sublingual administration. In pharmacokinetic studies performed with a small number of participants, the frequency of oral paraesthesia varied between 76% and 87%.[29,47] In one of these studies, performed in healthy volunteers, other sites for the tablet were tested, such as supralingual (contact of the tablet with the palate) and oral (placing the tablet under the cheek). The oral site resulted in similar bioavailability to that of the sublingual site and an appreciably lower incidence of paraesthesia.[29] However, these sites have not been studied in patients with BD, and therefore the therapeutic equivalence of this form of administration is not known. In all cases, fluid intake immediately after administration of the drug was associated with a significant decrease in bioavailability, therefore it is important that the patient does not ingest fluids or food for 10 min following the administration of asenapine.[8,29] This requirement makes management of local adverse effects difficult which, although they do not usually compromise continuing with the treatment,[48] should be alleviated by preventive intervention. Firstly doctor-patient communication is essential in managing potential local effects, since they are often perceived as less intense if the patient has been informed beforehand of their possible onset, and that they are self-limiting. In addition, it is important to administer asenapine after meals and last in the case of polymedicated patients, whenever possible. Finally the used of intensely flavoured mouth washes is recommended before administration of asenapine to improve the patient's acceptance of the medication.

Other adverse reactions observed with the long-term use of asenapine in more than 10% of patients were insomnia, depression, headache, dizziness, nausea and akathisia.[23]

In conclusion, asenapine's tolerability profile stands out above all due to its low impact on weight gain and metabolic disturbances. This feature makes it particularly suitable for patients who experience metabolic syndrome or weight gain with other antipsychotics, but also for patients diagnosed at an early age, when metabolic disorders can have a considerable impact on their future health. In any case, it is highly recommended to carry out the follow-up proposed in the Spanish consensus on the physical health of the bipolar patient.[41] Another notable aspect of asenapine's tolerability is less intense somnolence, with less cognitive impairment and of a shorter duration than that observed with other antipsychotics. Possible local discomfort associated with the sublingual administration could be partially alleviated by simple measures.

Dosage and management

Starting treatment with asenapine has the advantage of not requiring dose escalation. The recommended dose for most patients is 10 mg a day divided into two doses of 5 mg, although for severe mania it may be advisable to start treatment with 20 mg a day.[8] In healthy volunteers, the maximum dose of 30 mg a day (outside the range established in

the datasheet), divided into two doses of 15 mg and established after gradual escalation, did not give rise to serious adverse events.[47] However, all clinical trials with asenapine have been conducted based on a maximum dose of 20 mg a day.[48,49] Asenapine's half life (approximately 24 h) suggests that the administration of a single daily dose could be feasible in theory.[49] Therefore, in milder cases or patients who want to avoid daytime sedation, administration could be initiated with a single night-time dose.

The efficacy of sublingual administration is determined by its being taken correctly, since the drug must not be swallowed or chewed, and patients must avoid the intake of food and fluids for 10 min following administration.[8,26,29] In addition, and as outlined in the section on safety, whenever possible it is preferable to administer asenapine last, after meals and after other medication.

Asenapine is often administered to patients who are already being treated with other antipsychotics and require a change for reasons of safety (weight gain, metabolic syndrome, etc.), tolerability or lack of efficacy. In these situations, the indications provided by the Spanish Society of Psychiatry for changing an antipsychotic might apply to a switch to asenapine.[42] Furthermore, it should be borne in mind that, due to the low affinity of asenapine for muscarinic receptors, switching from antipsychotics with a higher anticholinergic profile – such as quetiapine, olanzapine or clozapine – could increase the risk of anticholinergic withdrawal syndrome, characterised by anxiety, restlessness and agitation. The safety of switching from other antipsychotics to asenapine was evaluated in a post hoc analysis of clinical trials that included partially stable patients who had changed to asenapine.[50] The analysis showed that in general it was safe to switch, even in patients who had abruptly discontinued treatment with the previous antipsychotic. The main adverse events presumably associated with this switch were insomnia, somnolence and headache. Doctor–patient communication is crucial to a successful switch. In this regard, adequately preventing the possible onset of some adverse effects during the period that the patient is taking two antipsychotics, stressing the transient nature of these effects, could encourage a more receptive attitude to the treatment.

In general, the combination of asenapine with other drugs prescribed for the management of BD has shown no clinically relevant interactions. The two most significant interactions described to date are[8]: (1) with paroxetine (mediated by CYP2D6, and resulting in increased levels of paroxetine increasing its efficacy and/or favouring tolerance), and (2) with fluvoxamine (mediated by CYP1A2, which results in increased levels of asenapine that increase the risk of toxicity). In addition, the sublingual administration route, which escapes the hepatic first-pass effect, eliminates the risk of pharmacokinetic interactions associated with affinity for various cytochromes and increases safety in patients with liver disease. In clinical trials, asenapine has been combined successfully with lithium and mood stabilisers such as sodium valproate.[11] In addition to lithium and the anticonvulsives, combinations of asenapine with other antipsychotics, antidepressants and benzodiazepines have been reported in the area of clinical practice.[28]

In conclusion, the use of asenapine in manic episodes has the advantage of not requiring dose escalation. Switching from other antipsychotics to asenapine presents no significant drawbacks if it is carried out according to the recommendations of the Spanish Society of Psychiatry. However, it is important to maintain good communication with the patient, warning them of the possibility of transient side effects. Treatment with asenapine is globally safe as an adjuvant to lithium, anticonvulsants, anxiolytics and other antipsychotics.

Discussion

This article provides a summary of the most noteworthy characteristics of asenapine, and recommendations for its use in patients with type I BD in clinical practice after expert consensus. Given the heterogeneity of the clinical forms of BD, correctly identifying the set of symptoms that present is of vital importance in selecting the most suitable antipsychotic for each patient.

The rapid onset of action and the possibility of starting treatment without dose escalation make asenapine an appropriate drug for acute episodes in general. In addition, its pharmacokinetic profile is particularly suitable for patients with agitation, although in the occasional case of extreme agitation patients might find it difficult to keep the tablet under the tongue. Finally, its sublingual administration is useful in patients with swallowing difficulties.

Asenapine has a markedly different pharmacodynamic profile to that of most atypical antipsychotics. Less pronounced sedation – with less potential impact on cognitive function – and the drug's high affinity for certain serotoninergic receptors give it a very favourable pharmacological profile for patients with mixed symptoms. Asenapine, therefore, appears to be especially suitable for patients with complex clinical symptoms, with manic episodes with dysphoria or symptoms of depression. It is also important to highlight the low impact of asenapine on weight gain and incidence of metabolic syndrome compared to that observed with other antipsychotics. The low incidence of these adverse effects should be taken into account for young patients in particular, and patients who have gained weight after treatment with other antipsychotics.

The recommendations put together in this document are the result of the structured consensus of a group of experts, and therefore in some cases they have the limitation of not being explicitly supported by or a direct conclusion of clinical studies. As we detail in the methods section, the information published in the scientific literature has been carefully considered during the preparation of the recommendations. Nevertheless, given the scant information published on the use of asenapine in routine clinical practice, some of the recommendations are based solely on the personal experience of the members of the panel of experts in the management of patients with BD. In these cases, the subjective source of the recommendation has been indicated in the text.

In conclusion, the controlled clinical trials, the observational studies and the expert consensus set out in this paper confirm that asenapine is an effective and generally well-tolerated option in the treatment of mania, with or without the presence of associated depressive symptoms, due to its

rapidity of action as well as its low metabolic syndrome risk profile.

Conflict of interests

Dr. Vieta has received funding for research projects and/or fees as a consultant and speaker for the following companies and institutions: AB-Biotics, Allergan, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo, Elan, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Solvay, Sunovion, Takeda, Instituto de Salud Carlos III, Séptimo Programa Marco (ENBREC), the Brain and Behaviour Foundation (NARSAD) and the Stanley Medical Research Institute. Dr. Montes has been a consultant or has been part of the group of speakers for AstraZeneca, Janssen, Bristol Myers Squibb, Lundbeck, Ferrer, Otsuka Servier and Rovi; he has received grants from the Ministry of Science and Innovation, Instituto de Salud Carlos III and CIBERSAM. Dr. Iborra has been a speaker for the following companies: AstraZeneca, Bristol-Myers Squibb, EliLilly, Glaxo-Smith-Kline, Lundbeck, Pfizer. Dr Benabarre has been a speaker for the following companies and institutions: AstraZeneca, Eli Lilly, Ferrer, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer. Dr. Cristina Saez has no conflict of interests to declare.

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