DOI: 10.5455/bcp.20130409040324

Asenapine: A Novel Hope in the Treatment of Schizophrenia and Manic and Mixed Episodes of Bipolar I Disorder

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ÖZET:

Şizofreni ve bipolar I bozukluğun manik veya karma döneminin tedavisinde yeni bir ümit: Asenapin

Bu derlemede, şizofreni ve bipolar I bozukluğun manik veya karma döneminin tedavisinde Türkiye'de de ruhsat almış olan asenapin'in farmakolojik profili, etkinliği ve tolerabilitesi ve güvenliği ile ilişkili verileri irdelemeye çalıştık. Asenapin daha çok şizofreninin pozitif belirtilerine ve bipolar I bozukluğun manik veya karma dönemleri üzerine etkili olmasının yanısıra, yan etkileri (kilo artışı, glukoz metabolizması ve lipid profile üzerine etkileri) düşük olan bir antipsikotik ilaçtır. Farklı etki mekanizmaları olan yeni ilaçların tedavi seçenekleri arasında yer alması, psikofarmakoloji alanında ümitlerimizi tazelemektedir.

Anahtar sözcükler: Asenapin, antipsikotik ilaçlar, şizofreni, bipolar bozukluk, mani, karma dönem, farmakoterapi

Klinik Psikofarmakoloji Bülteni 2013;23(1):99-106

ABSTRACT:

Asenapine: A novel hope in the treatment of schizophrenia and manic and mixed episodes of bipolar I disorder

In this review, we aimed to study the pharmacological profile, efficacy, and tolerability and safety data of asenapine, a drug approved in Turkey, in the treatment of schizophrenia and manic and mixed episodes of bipolar I disorder. As an antipsychotic drug with a low side effect profile (weight gain and other effects on glucose metabolism and lipid panel), asenapine is effective in the treatment of the positive symptoms of schizophrenia as well as the manic or mixed episodes associated with bipolar I disorder. Different mechanisms of action of new drug entities hold out hopes for improved treatment in psychopharmacotherapy.

Key words: Asenapine, antipsychotic drugs, schizophrenia, bipolar disorder, mania, mixed episode, pharmacotherapy

Bulletin of Clinical Psychopharmacology 2013;23(1):99-106

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Gönderme tarihi / Date of submission: 8 Şubat 2013 / February 8, 2013

Kabul tarihi / Date of acceptance: 25 Şubat 2013 / February 25, 2013

Bağıntı beyanı:
M.C.: Yazar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemiştir.

Declaration of interest:
M.C.: The author reported no conflict of interest related to this article.

INTRODUCTION

Schizophrenia is a globally prevalent, severe, chronic psychiatric disorder; leading edge research on the treatment of schizophrenia is carried out intensively both in our country and in the rest of the world (1-33). While impairing social functioning and occupational capacity, schizophrenia is an illness with a frequent occurrence of premature death due to its adverse effects on physical health (metabolic syndrome, diabetes mellitus (DM) type II, cardiovascular illness, etc.) and suicide risk (5-7). Antipsychotics have been used in the treatment of schizophrenia since 1952, in which chlorpromazine was used for the first time in the treatment of psychosis. However, impaired insight as well as the low efficacy and serious side effects of these drugs have led to poor adherence among schizophrenic patients (5-8). Both typical and atypical antipsychotics, which have been in use to date, are effective in treating the positive symptoms of schizophrenia whereas the negative symptoms and especially metabolic side effects of the drugs have remained problematic (9-19).

Both typical and atypical antipsychotics display their effects on the positive symptoms of schizophrenia, basically by blocking dopaminergic D_2 receptors. Moreover, atypical antipsychotics have a common feature of 5-HT_{2A} blocking. That is why, some authors have named atypical

antipsychotics *"serotonin-dopamine antagonists (SDA)"* (5). The term "atypical" should not suggest those drugs that are effective only on those receptors. While almost all atypical antipsychotics are similar to typical antipsychotics in terms of their efficacy on the positive symptoms of schizophrenia, their anti-dopaminergic (extrapyramidal symptoms, elevation of prolactin, etc.), metabolic and cardiac side effects as well as drug-drug and food-drug interactions are rather different because of the remarkable dissimilarity of their pharmacodynamics and pharmacokinetics. Among atypical antipsychotics, the efficacy of clozapine, the first atypical antipsychotic of its class (namely the gold standard), on treatment-resistant patients is unique (14,15,19).

Currently, eight atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, amisulpride, ziprasidone, paliperidone and aripiprazole) with marketing authorization in Turkey are in use for the treatment of adult schizophrenia patients. In this review, we will discuss the ninth atypical antipsychotic asenapine which has been granted marketing authorization in Turkey, following US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval, for the treatment of schizophrenia and manic and mixed episodes associated with bipolar I disorder.

Asenapine is a new atypica antipsychotic, approved by the FDA in 2009 for the treatment of psychotic/nonpsychotic type, manic and mixed episodes associated with bipolar I disorder and schizophrenia. As asenapine is a tetracyclic member of the dibenzo-oxepino pyrroles, derived from a tetracyclic antidepressant mianserin, would be expected to have an antidepressant effect. Asenapine's mechanism of action is mediated by 5-HT_{2A} and D_2 receptor antagonisms. In addition, it has a potent antagonistic effect on serotonergic receptor subtypes 5-HT_{2B}, 5-HT_{2C}, 5-HT_6 and 5-HT_7, adrenergic receptor subtypes α_{1A}, α_{2A}, α_{2B}, α_{2C}, and dopaminergic receptor subtypes D_3 and D_4. Among those, asenapine is the most potent on serotonergic receptors with the order of 5-HT_{2C} > 5-HT_{2A} > 5-HT_7 > 5-HT_{2B} > 5-HT_6. Its serotonergic receptor profile (especially its affinity for the subtype 5-HT_7) may mediate a clinical efficacy on anxiety, as a mood stabilizer and on cognitive features. It has been suggested that asenapine might provide an additional aid for the remission of cognitive and negative symptoms due to its antagonistic effect on α_{2A} receptor subtype. Asenapine causes less anticholinergic side effects compared to other atypical antipsychotics due to its lack of significant effects on muscarinic receptors. Long term administration of asenapine leads to a dose-dependent increase of glutamate transmission in specific locations of rat brain and unlike other antipsychotics and causes up-regulation in D_2 receptor subtypes, which might explain its relatively low extrapyramidal effects. Pharmacological studies based on ligand chemistry have revealed that the target binding rate of 80% to D_2 receptor subtypes for optimal antipsychotic effect could be achieved by asenapine (5-10 mg/day, twice daily(BID)), administered sublingually (20-22). Partial agonist effect on 5-HT_{1A}, which has been seen only with two atypical antipsychotics, aripiprazole and ziprasidone, is another remarkable feature of asenapine (22). Despite asenapine's strong antagonist effect on 5-HT_{2B} and H_1 receptor subtypes, weight gain has not been recorded in short and long term clinical studies. Correspondingly, orthostatic hypotension and dizziness have been reported at very low rates despite asenapine's being a potent antagonist of the α1 receptor subtype (23,24).

Asenapine is available in 5-10 mg sublingual and fast dissolving tablets for transmucosal drug delivery. Its transmucosal bioavailability is approximately 35%. Asenapine is absorbed rapidly from oral mucosa and reaches to its peak plasma concentration (C_{max}) in 30-90 minutes. However, bioavailability decreases by about 2% in the case of oral intake of fluids within the first 10 minutes of sublingual administration or per oral intake of the sublingual tablet. Thus, avoiding oral intake of fluids and food within the first 10 minutes of sublingual administration as well as the compulsory compliance to BID regimen are crucial for the safety and efficacy of asenapine treatment (20). The steady state plasma concentration is reached in 3 days.

Asenapine binds to plasma proteins at high rates (95%). It is subject to direct glucuronidation (UGT1A4) and metabolized predominantly by CYP1A2 and at lesser rates by CYP3A4 and CYP2D6 isoenzymes (23). Asenapine is biologically transformed to a number of its metabolites in liver; however, none of its metabolites is considered to make a significant contribution to its overall pharmacological profile. The average elimination half-life of asenapine is 13-39 hours. Plasma concentration of asenapine increases excessively in the case of hepatic dysfunction (Child-Pugh scale, class C) whereas, no problem is encountered in case of renal dysfunction (23,24). Therefore, use of asenapine by patients suffering from severe hepatic dysfunction is not recommended (20).

The starting dose of asenapine is 5 mg; an effective dose range is reached by 5-10 mg BID and its maximum daily dose is 20 mg. As the concomitant use of asenapine with CYP1A2 inhibitors (such as fluvoxamine) leads to significant increase of its plasma concentration, it has to be used with caution when combined with such drugs (20). Because of asenapine's weak inhibitory effect on CYP2D6, concurrent use with CYP2D6 substrates, like paroxetine and fluoxetine may increase asenapine's plasma concentration. Asenapine, a potent antagonist of the α_1 adrenergic receptor subtype, may cause orthostatic hypotension; it is advised not to combine asenapine with an antihypertensive drugs with adrenergic mode of action (see Table 1) (20).

Clinical Efficacy Studies

Short Term Studies in Schizophrenia

The efficacy of asenapine in the acute phase of schizophrenia has been demonstrated by two phase III, randomized, multi-center, double-blind, placebo and active controlled clinical studies. A 6 week, randomized, fixed dose trial was conducted by Potkin et.al. (2007), comparing 10 mg asenapine BID, to 3-6 mg risperidone and placebo (25). Adulthood schizophrenia (n=182, randomized), CGI-S score over 4, PANSS total score over 60 and the existence of a minimum of two PANSS positive subscales (hallucinations, delusions, paranoid thinking, persecution, grandiosity, and disorganized behavior) were the inclusion criteria of the study. The risperidone group was given a sublingual placebo while the asenapine group was given a placebo in tablet form. Both sublingual and tablet forms were administered to the placebo group. Improvement from baseline in PANSS total scores with asenapine was equal that of the to risperidone group and significantly more than the placebo. In the asenapine group, remarkable decreases in PANSS total scores were detected by the beginning of 2nd week and recorded until the endpoint of the study. Both asenapine and risperidone achieved significantly more recovery when compared with placebo, in terms of PANSS positive subscale and CGI-S scores (42). Only asenapine demonstrated a significantly better recovery than placebo, in reference to PANSS negative and general psychopathology subscales.

Long Term Studies in Schizophrenia

A 52 week long term efficacy, safety and tolerability study carried out by Kane et.al. (2011) (26) and a recurrence prevention study (27) are the two randomized trials conducted in adult schizophrenic patients with asenapine. There are

Table 1: Asenapine pharmacokinetics

Parameter	
Metabolism	Hepatic via CYP1A2 oxidation (primarily) and UGT1A4 glucuronidation
Elimination	Urine (~ 50%), feces (~ 50%)
Half-life	~ 24 h
Bioavailability	Sublingual: 35% Swallowed: < 2% (moderately decreased if administered with food/water)

two studies comparing the efficacy of asenapine and olanzapine (28,29), one report observing the primary negative symptoms (29) and a recurrence prevention study (26) with 700 patients treated with 10 mg sublingual asenapine BID for 26 weeks (open label).

In another 52 week long term, double-blind, multi-center study, Shoemaker et.al. (2010) evaluated the tolerability of asenapine (5-10 mg, n=913) and olanzapine (10-20 mg, n=312) in adult patients with the diagnosis of schizophrenia or schizoaffective disorder. Patients whose baseline PANSS total score was greater than 60 (two or more PANSS positive subscale scores were over 4) were included (28). Patients who completed the study were given an option to continue the treatment for an additional period of 52 week. Blinding was removed during the extension period. Clinical symptoms (rated as PANSS total score and Marder factors), clinical global impression (CGI-S) and other efficacy criteria were evaluated as secondary endpoints. PANSS total scores at week 6 were similar for all treatment groups (asenapine - 17,9 and olanzapine - 19,0; not significant) (29).

Results of the extension period were reported separately (29). Asenapine (average 13,4±4,6 mg/day) patients (n=290) were followed up for an additional period of 311,0±146,1 days (range: 10-653 days). Olanzapine (average 13,4±4,1 mg/day) patients (n=150) were followed up for an additional period of 327±139,6 days (range: 15-631 days). Only small differences in PANSS total scores were recorded in both groups during the extension period (asenapine + 1,6 and olanzapine - 0,8; not significant). In both treatment groups a significant difference was observed in PANS subscales, PANSS Marder factors, and CGI).

Efficacy Studies for Bipolar I Manic and Mixed Periods

There are two publications about randomized, placebo controlled studies carried out by McIntyre et al. (2009 and 2010) in adults with bipolar manic or mixed episodes. In these studies, adult patients with nonpsychotic manic or mixed episodes were either randomized to a dose of 5-10 mg/day BID asenapine or to 5-20 mg olanzapine as an active control. The difference in the Young Mania Rating Scale (YMRS) total score at the endpoint was referred as the primary efficacy parameter. The average daily dose for asenapine in both studies was about 18 mg; there was a statistically significant remission at day 21 in terms of YMRS scores (30,31).

A post-hoc analysis conducted by McIntyre et.al. published in 2010 revealed that asenapine treatment was able to reduce major depressive symptoms, based on the Montgomery-Åsberg Depression Rating Scale (MADRS) total score as well as the assessed remission rates (total MADRS score ≤ 12) (5). This post-hoc analysis describes 3 sub-populations in two acute mania studies: 1) MADRS total score ≥ 20 (n=132); 2) Clinical Global Impression - Bipolar Disorder Depression Rating Subscale (CGI-BP-D) scale severity score ≥ 4 (n=170); 3) mixed phase (n=302). The reduction in MADRS total score was statistically significant higher in the asenapine group, when compared with the placebo group. The statistically significant changes in the MADRS scores were recorded on the 7th and 21st days in the first sub-population whilst on 7th day in the second and third sub-populations (32). The differences in remission rates were statistically significant in the second and the third sub-populations on the 7th and 21st days. In a 40 week extension study of acute monotherapy in mania with an unblinding at week 12 (33), the patients who were given placebo in the acute phase were switched to asenapine during the extension period. In this study, the average change from baseline in the YMRS total score was found to be – 23,9 (±7,9) for olanzapine and – 24,4 (±8,7) for asenapine. The difference between the asenapine and olanzapine groups, in the overall change of YMRS scores was not statistically significant.

Safety and Tolerability

Short Term

In the literature, there are three fixed dose and one flexible dose, 6 weeks studies carried out in adult schizophrenic patients, where 5-10 mg

asenapine was administered sublingually (n=572). The safety data demonstrate that the most frequently seen side effects were somnolence (13% for placebo and 13% for asenapine; n=378), sleeplessness (15% for asenapine), extrapyramidal side effects except akathisia (7% for placebo and 10% for asenapine) and akathisia (3% for placebo and 6% for asenapine). There was a dose dependent increase in akathisia occurrence (4% for 5 mg and 11% for 10 mg) in the asenapine group (20). In 5% of patients using asenapine, a temporary hypoesthesia lasting for approximately 1 after from intake was observed (20). Other metabolic parameters were recorded as follows: minimal change in fasting glucose (+3,2 mg/dl for asenapine and – 1,6 mg/dl for placebo); total cholesterol (+0,4 mg/dl for asenapine and – 3,6 mg/dl for placebo); triglycerides (+3,8 mg/dl for asenapine and – 13,5 mg/dl for placebo) and prolactin (–6,5 ng/dl for asenapine and – 10,7 ng/dl for placebo). The QTc interval was slightly prolonged only with 20 mg asenapine, whereas there was no statistically significant difference in QTc interval prolongation between placebo and 5 mg or 10 mg asenapine (20).

Long Term

The most frequently observed side effects reported for asenapine in a long term recurrence prevention study by Kane et.al. (26) were anxiety (8,2%), weight gain (6,7%) and somnolence (6,2%) (56). The difference in the frequency of EPS related adverse effects (3,1% and 4,7%; not significant), Abnormal Involuntary Movement Scale (AIMS) and Simpson-Angus Scale (SAS) scores was not statistically significant between asenapine and placebo groups. The ratio of patients with a weight change more than 7% was 3,7% for asenapine and 3,2% for placebo; the difference between groups was not statistically significant. During the double blind period the change from baseline for some metabolic parameters were calculated as follows: minimal change in fasting glucose (+2,09 mg/dl for asenapine and +0,02 mg/dl for placebo); total cholesterol (+0,9 mg/dl for asenapine and – 5,6 mg/dl for placebo) and triglycerides (+0,9 mg/dl for asenapine and – 11,2 mg/dl for placebo).

Weight gain (12% for asenapine and 29% for olanzapine) was the most frequently reported side effect with asenapine in a 52 weeks double-blind study by Shoemaker et al. (27). Other side effects reported were sedation (8% for asenapine and 10% for olanzapine), somnolence (9% for asenapine and 10% for olanzapine) and gastrointestinal side effects (9% for asenapine and 7% for olanzapine) (57). The rate of weight gain over 7% from baseline was remarkably higher with olanzapine (57,1%) than asenapine (22,0%). The differences from baseline or between groups, in total cholesterol and glucose levels were not statistically significant. However, change from baseline in the fasting triglyceride levels was found to be upwards for olanzapine (30,4±202,6 mg/dl) and downwards for asenapine (-9,8±92,2 mg/dl). The rate of mild EPS related symptoms was 18% (akathisia 14%) for asenapine and 8% (akathisia 4%) for olanzapine. There were minimal changes in both groups during the follow up period in the AIMS, Barnes Akathisia Rating Scale (BARS) and SAS scores. In both groups, prolactin levels decreased within the first two weeks of the study and remained almost unchanged for the course of the study. ECG anomalies were limited to general QTc prolongation for asenapine (2,4%) and olanzapine (1,3%). Prolongation in QTc was less than 500 ms for both groups. Only slight changes in body weight, EPS related adverse events, cholesterol and prolactin levels were recorded during the extension period of the study in both groups (28,29).

In reference to the data collected in the studies by McIntyre et al. conducted in patients suffering manic and mixed episodes associated with bipolar I disorder, the incidence of EPS of any type was 15% for asenapine, 13% for olanzapine, and 10% for placebo; clinically evident weight gain was seen profoundly more in olanzapine group (%31) than asenapine group (19%). Within the coverage of 40 weeks extension period, the AIMS, BARS, and SAS were used and the most frequently reported EPS related adverse event was akathisia (11,4% for asenapine and 10,3% for olanzapine); a noteworthy change was seen with asenapine during the acute

phase. Elevation of fasting glucose was observed in 10% of the placebo, 26% of the olanzapine and 22,2% of the asenapine groups. Changes in hepatic enzymes and prolactin level were not significant. The most frequently reported adverse events with asenapine were somnolence, dizziness, non-akathisia extrapyramidal side effects, and weight gain (30-33).

DISCUSSION

Schizophrenia and bipolar disorders are severe and chronic mental disorders. Despite important developments in relation to the pharmacotherapy of these illnesses, there still exist numerous unmet needs. Throughout the history of psychopharmacology, the most significant clinical response has been the alleviation of the positive of schizophrenia. Unfortunately, progress in the treatment of negative symptoms, depression and cognitive impairment has remained meager (5). Moreover, the compliance (adherence to treatment) is relatively low in the treatment of schizophrenia and bipolar disorder compared with other psychiatric disorders. Although various psychosocial approaches help improve compliance to a certain extent, this remains a problem.

Resistance to treatment is another major issue. Clozapine is still the only treatment option in resistant cases. Due to its serious side effects, clozapine can only be used in a limited way in specific patients, when risk/benefit balance is taken into account. In addition, response to treatment with antipsychotics demonstrates interpersonal variance. The clinician, the patient, and the family or caregivers should mutually agree on individualization of the treatment after consideration of personal traits of the patient as well as the benefits, side effects, and interactions of medications (1,14).

Asenapine is a new atypical antipsychotic agent with a broad therapeutic spectrum in the treatment of manic and mixed episodes associated with bipolar disorder and schizophrenia. Asenapine's antagonistic activity on 5-HT_{2A} receptor subtypes is more potent than its effect on D_2 receptors. We believe that asenapine represents a new atypical antipsychotic treatment option because of its clinically profound efficacy and, like ziprasidone and aripiprazole, its low risk of weight gain, glycemic dysregulation and dyslipidemia. Additionally, asenapine causes only a slight elevation in prolactin levels, it could be a preferable option for those patients with the history of galactorrhea, menstrual irregularities, gynecomastia and sexual dysfunction. Asenapine is subject to direct glucuronidation and its metabolization to a certain extent, is dependent upon CYP450 system, leading to a decreased potential of clinically significant drug-drug interactions. For example, combination of asenapine with carbamazepine, a drug known to decrease the plasma concentration of other drugs that are used concomitantly by inducing the activity of liver enzymes, could be a sound option.

Asenapine is the only antipsychotic drug that is commercially available in a sublingual form owing to its ability to dissolve readily and be absorbed across the buccal tissue. This could result in a treatment advantage for asenapine. Its high dissolution could help in monitoring adherence to medication, especially in patients with history or high risk of non-compliance with treatment. Fast absorption of asenapine, on the other hand, might be suitable for the management of acute agitation in manic episodes and schizophrenia.

One should be very careful about some issues while administering asenapine. Tablets should be contacted only with dry hands. Tablets should not be chewed and/or swallowed; oral intake of fluids and food should be prohibited during the first 10 minutes after sublingual administration and the patient/caregiver should be trained about those precautions (candies and chewing gums can be used for training). Patient should absolutely be informed that a temporary oral hypoesthesia could happen. Otherwise the patient might quit taking the medication because of this side effect; switching to its sour cherry flavored formulation could be beneficial (20).

Asenapine is a brand new antipsychotic that is effective in the treatment of manic and mixed episodes associated with bipolar I disorder and

schizophrenia. While almost all atypical antipsychotics are effective in the treatment of manic and mixed episodes associated with bipolar I disorder and schizophrenia, the majority of them (except aripiprazole and ziprasidone) are responsible for metabolic side effects; therefore, olanzapine, clozapine and quetiapine are not recommended as first line treatment options in most of the treatment guidelines. Asenapine, ziprasidone and aripiprazole could be advantageous, unlike other antipsychotics, as far as the common metabolic side effects are concerned. Comparative studies conducted with typical antipsychotics (except haloperidol) as controls are still lacking. Long term and naturalistic studies are crucial for the evaluation of efficacy under natural circumstances for new drug entities like asenapine. As a result, novel mechanisms of action of new drug entities appear to provide us with new hopes in psychopharmacotherapy.

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