EXPERT OPINION

Asenapine for the treatment of manic and mixed episodes associated with bipolar I disorder: from clinical research to clinical practice

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Introduction: Asenapine is a sublingually administered second-generation antipsychotic with proven efficacy for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. Its relatively favorable weight and metabolic profile, as well as the lack of appreciable activity at muscarinic cholinergic receptors and the sublingual administration are of clinical interest.

Areas covered: This paper comprises a review and commentary regarding the use of sublingual asenapine in the treatment of acute manic and mixed episodes of bipolar disorder. Basic principles in dosing, switching, management of side effects and co-administration with other medications are provided.

Expert opinion: Asenapine displays quick and reliable effects on manic symptoms, very low risk of depressive switches, efficacy on depressive symptoms during manic and mixed episodes, usually good tolerability and continued longer-term efficacy on residual and subthreshold symptoms. The fast-dissolving sublingual route of administration may favor those who have difficulties in swallowing medications. Also, the sublingual administration reduces the risk of overdose when more than the prescribed tablets are swallowed. The relatively low metabolic risk and the lack of anticholinergic side effects contribute to making this medication a useful tool for the treatment of patients with bipolar disorder.

Keywords: asenapine, bipolar disorder, mania, olanzapine

Expert Opin. Pharmacother. [Early Online]

1. Introduction

Acute manic, mixed and depressive episodes profoundly impact the lives of patients with bipolar disease and are often very lengthy, especially when the periods with residual symptoms are accounted for [1-4]. Also, acute bipolar episodes are burdened with psychiatric and medical comorbidities, yield frequent functional and vocational impairment and contribute substantially to social and health care costs [5-7].

Most second-generation antipsychotics (SGA) have proven effective for the treatment of acute manic and mixed episodes as well as for the longer-term management of bipolar disorder, e.g., for the continuation treatment in the subacute phase or for the maintenance prophylactic treatment.

Second-generation antipsychotics offer several benefits over first-generation antipsychotics (FGA), particularly in terms of improved tolerability. Compared to

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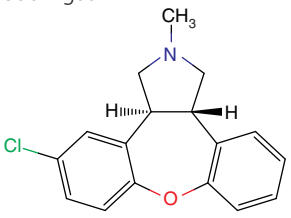
Box 1. Drug summary.

Drug name	Asenapine
Indication	Treatment of schizophrenia in the United States and other countries outside Europe (not discussed in the paper) Treatment of moderate to severe manic episodes associated with bipolar I disorder in adults, in Europe and United States
Route of administration	Sublingual
Chemical structure	
Pivotal trial(s)	Efficacy for bipolar disorder was established in two 3-week monotherapy trials and in one 3-week adjunctive trial in patients with manic or mixed episodes associated with bipolar I disorder in adults [25-27]

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their predecessors, most SGA are associated with a lower risk of extrapyramidal symptoms (EPS) and tardive dyskinesia, a lower risk of hyperprolactinemia and lower risk of contributing to a depressive switch. However, many SGA such as olanzapine, clozapine and even if to a lower extent quetiapine can still cause a high degree of other potentially harmful side effects, such as those related to metabolic dysfunction and those related to the anticholinergic properties [8,9].

The primary importance of the metabolic risks derives from the link to cardiovascular risk factors, and the attendant mortality risks [10]. In fact, patients with bipolar disorders, like those with schizophrenia and related psychoses, are at much greater risk than the general population for comorbid cardiovascular disease and premature mortality due to cardiovascular disease [11]; thus, effective agents with favorable metabolic profiles are most desired. Also, combining metabolically burdensome antipsychotics with mood stabilizers may exaggerate the metabolic impact of each [12] . This is likely because both lithium and valproate may be themselves associated with weight gain. Because atypical antipsychotic-mood stabilizer cotherapy will be a common and often necessary treatment, asenapine's favorable metabolic profile may be a particular advantage.

The primary importance of the anticholinergic side effects derives from the various physical and mental impairments associated with those adverse events [9].

Typical peripheral anticholinergic side effects include dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate, and decreased sweating. Typical anticholinergic central side effects include impairment in cognitive functions [9]. Because of asenapine lack of significant anticholinergic effects, the use of this medication may be advantageous, especially for those patients for whom anticholinergic effects may be particularly dangerous or burdensome.

Asenapine is approved in Europe for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults (**Box 1**). In the United States and other countries outside Europe, the medication is also approved for the acute treatment of schizophrenia, still in adults.

Although there is no evidence for asenapine's efficacy to be superior to currently available agents, its favorable weight and metabolic profile, as well as the lack of appreciable activity at muscarinic cholinergic receptors and the sublingual administration are of clinical interest [13].

This paper comprises a review and commentary regarding the use of sublingual asenapine in the treatment of acute manic and mixed episodes of bipolar disorder. Basic principles in dosing, switching, management of side effects and co-administration of asenapine with other medications are provided.

2. Pharmacology of asenapine

2.1 Metabolism

Commercially available in two strengths (5 and 10 mg), asenapine sublingual tablets dissolve in the saliva within seconds [13,14]. Rapidly absorbed in the sublingual, supralingual and buccal, mucosa, the medication has a bioavailability of approximately 35% (**Table 1**) and peak plasma concentrations occurring within 0.5 – 1.5 h. Sublingual bioavailability may vary depending on the amount of saliva, food and water intake. For instance, asenapine's AUC was reduced following the administration of water at 2 min (-19%) and 5 min (-10%) after dosing. Therefore, patients should avoid eating and drinking for 10 min after administration. The AUC of asenapine following administration of water 10 min after sublingual dosing was equivalent to the AUC when water was administered 30 min after dosing. Hence, drinking after 10 min is not a problem, in that it does not significantly change the AUC [13,14].

A high-fat meal immediately before sublingual administration can reduce asenapine exposure by 20% and exposure to

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Table 1. Asenapine pharmacokinetics.

Parameter	Asenapine
Metabolism	Hepatic via CYP1A2 oxidation (primarily) and UGT1A4 glucuronidation
Elimination	Urine (~ 50%), feces (~ 50%)
Half-life	~ 24 h
Protein binding	95% (albumin and α_1-acid glycoprotein)
Bioavailability	Sublingual: 35% Swallowed: < 2% (moderately decreased if administered with food/water)

asenapine can also be reduced by 13% when food is given 4 h after asenapine administration, possibly because of increased clearance of asenapine related to increased liver blood flow following food intake. However, these differences in exposure are smaller than the overall variability observed in studies, where overall exposure and maximum concentration varied 37 and 45%, respectively [13], and unlikely to have a significant clinical impact. When swallowed instead of absorbed sublingually, the bioavailability of asenapine is dramatically decreased to less than 2%; with the most likely pathways responsible for the first-pass effect being either 11-hydroxylation or N-oxidation [13,14].

After a single 5 mg dosing, asenapine reaches a mean peak plasma concentration of about 4 ng/mL within 60 min. It displays a mean half-lives of 24 h and achieves steady-state within 3 days. Asenapine is 95% protein bound with a large volume of distribution averaging 20 – 25 L/kg, suggestive of wide extravascular distribution.

Within the recommended dosages of 10 – 20 mg daily divided morning and evening, exposure increases 1.7-fold with a 2-fold increase in dose. Hence, asenapine exposure is not linear. Mean half-life in studies ranged from 13.4 to 39.2 h and steady-state concentrations of asenapine are reached within 3 days [13].

Asenapine is cleared through cytochrome P450 (CYP) oxidative metabolism and, to a lower degree, via direct glucuronidation by UGT1A4. CYP1A2 isoenzyme is the most important human cytochrome P450 enzyme involved in the metabolism of asenapine, followed by CYP3A4 and CYP2D6. CYP1A2 inhibitors such as fluvoxamine can increase asenapine exposure by approximately 30%. CYP1A2 inducers such as carbamazepine can decrease asenapine exposure by approximately 20%, as tested in healthy male subjects who received multiple doses of fluvoxamine or carbamazepine and one or two doses of sublingual asenapine 5 mg, respectively [13,14]. However, a population pharmacokinetic analysis indicated that smoking, which induces CYP1A2, had no effect on the clearance of asenapine. In a crossover study in which 24 healthy male smokers were administered a single 5-mg sublingual dose, concomitant smoking had no effect on the pharmacokinetics of asenapine [14].

Asenapine inhibits CYP2D6 and can result in 2-fold increases in paroxetine concentrations [13,14].

Co-prescription of asenapine with paroxetine or other medications metabolized for by CYP2D6 may require dosage adjustment [15]. No need of dosing adjustments is suggested related to renal impairment, mild to moderate liver impairment or based on age, gender and race. However, asenapine is not recommended in patients with severe hepatic impairment, which can increase up to 7-fold asenapine exposure [13,14].

2.2 Dosing

Asenapine monotherapy may be initiated at 10 mg twice daily and titrated down to 5 mg twice daily if tolerability issues occur or as deemed necessary by the treating clinician [14]. In fact, the majority of patients enrolled in the asenapine monotherapy bipolar disorder clinical trials initiated the medication at 10 mg twice daily and well tolerated this dose. A starting dosage of 5 mg twice daily is instead recommended when the antipsychotic is prescribed in combination with lithium or valproate. This dose can then be increased to 10 mg twice a day.

2.3 Pharmacodynamics

Asenapine has potent antagonism at serotonin, dopamine, norepinephrine and histamine, receptors, with no appreciable activity at muscarinic, cholinergic receptors. Asenapine appears to have relatively higher potency at serotonin receptors than at dopamine receptors. In addition to the antagonist activity at dopamine (D_2) receptors and serotonin (5-HT_{2A}) receptors, asenapine also has high antagonist activity for other dopamine (D_1, D_3, and D_4), serotonin (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6, and 5-HT_7), adrenergic (α_1 and α_2), and histamine (H_1) receptors. [14,16-18]..

Asenapine displays a moderate antagonistic affinity for the H_2 receptor and has no affinity for the muscarinic receptor. The low affinity for cholinergic receptors predicts a low risk for anticholinergic side effects such as dry mouth, urinary retention, constipation, blurred vision, confusion, and memory impairment.

Antagonism of histamine H1 receptors appears to be associated with the sedative effects of asenapine. Interestingly, blockade of H1 receptors would predict weight gain [19,20] but this effect was not strongly observed in the asenapine's clinical trial program [14].

Indeed, weight gain is a severe concern of antipsychotic treatment of bipolar disorder which is particularly severe with olanzapine. Histamine H1, alpha1 adrenergic and 5-HT2C receptors are implicated in this effect. However, the lower propensity for weight gain shown by asenapine which, like olanzapine, binds to these receptors, suggests that other protective receptor mechanisms, or subtle differences in the 5-HT2C receptor-mediated effects, may play an important role [21].

Asenapine displayed also low affinity for β1- and β2-adrenergic receptors, histamine H3 receptors and 5-HT3 receptors [16]. Moreover, chronic asenapine administration influences glutamate transmission in a region-specific and

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dose-dependent manner in rat brain and, unlike other antipsychotics, produces an upregulation of D1 receptors, which may be relevant to a lower liability for extrapyramidal effects [18,22].

In comparison with the other FGA and SGA, asenapine displays a higher affinity for all the receptors to which it binds except for 5HT1A and 5HT1B receptors (ziprasidone has higher affinity for the first, both ziprasidone and aripiprazole have higher affinity for the latter). In particular, Shahid *et al.* [16] demonstrated that asenapine binds to 5HT5A and 5HT6 with an affinity 15-fold superior to the other drugs examined, and to 5HT2C and α2B receptors with an affinity 30-fold higher. In highlighting the main differential pharmacodynamic properties of antipsychotic compounds, these authors also noted that asenapine differs from olanzapine that does not have any appreciable effect on 5HT1A and α2 receptors (besides having antimuscarinic action) and from risperidone that does not have remarkable affinity for 5HT6 receptors.

Studies of rat brain tissues, collected after asenapine administration, have shown that this drug increases 5HT1A receptor binding in medial prefrontal cortex (mPFC), dorsolateral frontal cortex (DFC), and hippocampal CA1 region, whereas decreases 5HT2A binding in mPFC and DFC [23]; in a similarly conducted research, Choi *et al.* [24] demonstrated also an increased α1 binding in mPFC and DFC, increased α2 binding in similar regions and surprisingly, given the lack of substantial affinity of asenapine for muscarinic receptors, increased cholinergic M1 – M5 binding in mPFC, DFC and hippocampal CA1 and CA3 areas.

3. Asenapine in the treatment of acute manic and mixed episodes (Table 2)

3.1 Short-term monotherapy studies

The efficacy of asenapine monotherapy in the treatment of bipolar disorder manic and mixed episodes in adults has been demonstrated in two similarly designed randomized placebo-controlled flexible-dose trials of 3 weeks' duration, using olanzapine as active reference [25,26]. Asenapine obtained also the indication as adjunctive therapy with either lithium or olanzapine, based on a placebo-controlled 12 weeks' acute and 40 weeks' extension trial [27].

After a single-blind brief run-in period, the first multicenter study randomized to treatment a total of 488 patients (placebo n = 104; asenapine n = 194; olanzapine n = 190), in a current manic (69.3%) or mixed episode (30.7%) (YMRS ≥ 20), excluding subjects with a rapid-cycling course and co-occurring recent substance misuse disorder [25]. Asenapine and olanzapine were started at 10 mg twice daily and 15 mg once daily, respectively, on day 1, allowing for a flexible dosage range (5 – 10 mg for asenapine, 5 – 20 mg for olanzapine) from day 2 onward. Almost all patients randomized to asenapine remained on their 10 mg twice daily initial dose (100% in week 1, 93% in week 2, 91% in week 3, mean daily dose = 18.2 mg) whereas almost half (48.1%) of olanzapine-treated subjects needed at least one dose escalation to 20 mg (mean daily dose = 15.8 mg). Significantly more patients receiving olanzapine completed the study (79.6 vs 62.9% on asenapine and 61.5% on placebo) but very low percentages of discontinuations were attributable to treatment-related tolerability issues (6.2% asenapine, 3.8% placebo, 4.2% olanzapine). The majority of discontinuations were due to withdrawal of consent (14.4, 12.5 and 8.4%, respectively). Both active medications fared significantly better than placebo in regard to mean change in YMRS total scores at day 21, the primary outcome measure of the study (-10.8 asenapine, -12.6 olanzapine, and -5.5 placebo), showing superiority over placebo since day 2. Asenapine and olanzapine yielded significantly better results as compared to placebo also in many secondary efficacy measures, with, respectively, greater percentages of response (42.3% and 50.0% vs 25.2%), remission (40.2% and 39.4% vs 22.3%) and greater improvement in CGI-BP mania severity scores.

The second companion study [26] randomized 488 patients (n = 98 placebo, n = 185 asenapine, n = 205 olanzapine) diagnosed with manic (68.9%) or mixed episodes (31.1%). Again completion rates were significantly higher with olanzapine (78.5 vs 67.0% asenapine and 58.2% placebo), and withdrawal of consent was the commonest reason to drop out the study (asenapine 13.5%, placebo 13.3%, olanzapine 7.3%). The large majority of individuals maintained the 10 mg BID (twice a day) asenapine dosage they were given the first day (100% in week 1, 93% in week 2, 88% in week 3, mean daily dose = 18.4 mg) differently from patients randomized to olanzapine (mean daily dose = 15.9 mg) who needed dose escalations to 20 mg (18% in week 1, 42% in week 2, 50% in week 3) or less frequently dose reductions to 5 or 10 mg daily (5% in week 2, 7% in week 3). Both active medications were significantly superior to placebo in reducing YMRS global score from baseline to the 21-day endpoint (-11.5 asenapine, -14.6 olanzapine and -7.8 placebo), with the advantage over placebo being apparent since day 2. Although asenapine yielded a nominally greater reduction in mean YMRS score as compared to the first trial, the difference from placebo in response (asenapine 42.6%, olanzapine 54.7%, placebo 34%) and remission (asenapine 35.5%, olanzapine 46.3%, placebo 30.9%) rates did not reach significance. Yet, these secondary efficacy outcomes were likely influenced by a slightly better performance of placebo. Significantly greater improvement in CGI-BP mania severity scores was detected both for asenapine and olanzapine.

3.2 Efficacy on depressive symptoms during mania

Szegedi *et al.* [28] reported the results of exploratory pooled *post hoc* analyses evaluating asenapine's effects on depressive symptoms in manic and mixed patients with significant baseline depressive symptoms, participating in the two randomized, placebo- and olanzapine-controlled trials mentioned above [25,26].

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Table 2. Randomized controlled trials of Asenapine for Bipolar Disorder in adults.

Design	Patients	Efficacy	Tolerability (ASE vs PLC vs OLZ)	Refs.
DBPC 3 wks monotherapy trial, ASE vs PLC vs OLZ. Pts with mania or mixed ep. (YMRS ≥ 20) whose onset was ≤ 3 months before screening. EC: rapid-cycling, current substance misuse. 7-day run-in washout period; 14 days minimum inpatient stay. ASE started at 10 mg BID (dose range 5 – 10 BID; mean dosage at endpoint: 18.2 mg). OLZ started at 15 mg QD (dose range 5 – 20 mg; mean dosage at endpoint: 15.8 mg) YMRS response defined as > 50% decrease from baseline in YMRS total score YMRS remission defined YMRS total score < 12	n = 488 BPI pts treated (n = 194 ASE, n = 104 PLC, n = 190 OLZ); 69.3% manic ep., 30.7% mixed ep. Completion rate: ASE 62.9%, PLC 61.5%, OLZ 79.6%	*(ASE vs PLC vs OLZ)* Mean change in YMRS score: -10.8 vs -5.5 vs -12.6 ($p < 0.0001$). The effect sizes (Cohen's d) for asenapine and olanzapine were 0.45 and 0.70, respectively. Response/remission rates %: 42.3/40.2 vs 25.2/22.3 vs 50.0/39.4 Mean change in CGI-BP mania score: -1.2 vs -0.7 vs -1.4 Mean change in MADRS score: -3.2 vs -1.8 vs -4.2	*(ASE vs PLC vs OLZ)* Discontinuations due to AEs %: 6.2 vs 3.8 vs 4.2 Treatment emergent/related AEs %: 73.7/60.8 vs 61.0/36.2 vs 71.4/52.9; SAEs %: 1.5 vs 3.8 vs 1.6 AEs in ≥ 5% of pts and at ≥ twice the frequency of PLC %: ASE sedation 18.6, dizziness 11.9, somnolence 8.8, fatigue 6.2, oral hypoaesthesia 5.2; OLZ sedation 18.5, dry mouth 14.3, dizziness 8.5, somnolence 7.4, increased weight 6.9 EPS-related AEs %: 7.2 vs 2.9 vs 7.9 No EPS in ≥ 5% pts on ASE; Akathisia %: 2.6 vs 1.9 vs 5.8%	[25]
DBPC 3-wks monotherapy trial, ASE vs PLC vs OLZ. Pts with mania or mixed ep. (YMRS ≥ 20) whose onset was ≤ 3 months before screening. EC: rapid-cycling, current substance misuse. 7-day run-in washout period; 14 days minimum inpatient stay. ASE started at 10 mg BID (dose range 5 – 10 BID; mean dosage at endpoint: 18.4 mg). OLZ started at 15 mg QD (dose range 5 – 20 mg; mean dosage at endpoint: 15.9 mg)	n = 488 BPI pts treated (n = 185 ASE, n = 98 PLC, n = 205 OLZ); 68.9% manic ep., 31.1% mixed ep. Completion rate %: ASE 67.0, PLC 58.2, OLZ 78.5	*(ASE vs PLC vs OLZ)* Mean change in YMRS score: -11.5 vs -7.8 vs -14.6 ($p < 0.007$, $p < 0.0001$) Response/remission rates %: 42.6/35.5 vs 34.0/30.9 vs 54.7/46.3 Mean change in CGI-BP mania score: -1.2 vs -0.8 vs -1.5 Mean change in MADRS score: -3.0 vs -1.9 vs -4.1	*(ASE vs PLC vs OLZ)* Discontinuations due to AEs %: 9.2 vs 4.1 vs 3.4 Treatment emergent/related AEs %: 75.7/55.1 vs 56.1/27.6 vs 66.3/46.8; SAEs %: 6.5 vs 7.1 vs 3.9 AEs in ≥ 5% of pts and at ≥ twice the frequency of PLC %: ASE sedation 8.6, dizziness 10.3, somnolence 11.9, increased weight 6.5 vomiting 5.4; OLZ sedation 14.1, dizziness 6.3, somnolence 11.2, increased weight 9.3, increased appetite 6.3 EPS-related AEs %: 10.3 vs 3.1 vs 6.8 EPS in ≥ 5% pts on ASE: Akathisia 5.4 vs 3.1 vs 4.9	[26] [27]

AE: Adverse event; ASE: Asenapine; CGI-BP: Clinical Global Impression-Bipolar Disorder; DBPC: Double-blind placebo controlled; EPS: Extrapyramidal symptoms; LI: Lithium salts; MADRS: Montgomery-Asberg Depression Rating Scale; OLZ: Olanzapine; PLC: Placebo; Pt: Patient; SAE: Serious adverse event; VALP: Valproic acid; YMRS: Young Mania Rating Scale; Wk: Week.

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Table 2. Randomized controlled trials of Asenapine for Bipolar Disorder in adults (continued).

Design	Patients	Efficacy	Tolerability (ASE vs PLC vs OLZ)	Refs.
DBPC 12-week core + 40-week extension study of ASE vs PLC plus open LI (0.6 – 1.2 mmol)/VALP (50 – 125 μg/mL) taken from 2 wks or longer. Pts with mania or mixed ep. (YMRS ≥ 20) whose onset was ≤ 3 months before screening. EC: rapid-cycling, current substance misuse, risk of harm to self or others, hospitalization for ≥ 3 wks for current ep. ASE started at 5 mg BID (dose range 5 – 10 BID; mean dosage at 12 wks endpoint: 11.8 mg, extension: 13.3 mg)	n = 326 randomized n = 204 treated for ≥ 3 wks (n = 158 ASE, n = 166 PLC); 61.1% manic ep., 39.9% mixed ep. n = 116 completed 12 wks; n = 34 completed 52 wks Completion rate %: ASE 67.0, PLC 58.2, OLZ 78.5	*(ASE vs PLC)* Mean change in YMRS score: wk 3: -10.3 vs -7.9; wk 12: -12.7 vs -9.3; wk 52 LI: -19.1 vs -20.9, VALP: -14.9 vs -18.3 Effect sizes for asenapine vs placebo were 0.24 at week 3 and 0.33 at week 12 Response/remission rates %: wk 3: 34.2/33.5 vs 27.0/21.5; wk 12: 47.7/43.2 vs 34.4/30.1; wk 52 68.4/65.8 vs 78.8/78.8 Effect sizes with asenapine vs placebo for YMRS response and remission, respectively, were 0.19 and 0.34 at week 3 and were 0.31 and 0.32 at week 12 Treatment difference (ASE-PLC) in mean change in MADRS score: wk 3: -0.62; wk 12: 0.04; wk 52: 0.53 Treatment difference (ASE-PLC) in mean change in CGI-BP: wk 3: -0.3; wk 12: -0.35; wk 52: 0.20	*(ASE vs PLC)* Treatment emergent AEs/SAEs/treatment related SAEs %: wk 12: 73.4/13.3/5.1 vs 68.7/14.5/3.0; wk 52: 78.0/22.0/12.2 vs 69.4/11.1/2.8 AEs in ≥ 5% of pts and at ≥ twice the frequency of PLC %: wk 12: sedation 13.3, somnolence 11.4, depression/depressive symptoms 6.3, oral hypoesthesia 5.7, increased weight 5.1; wk 52: sedation 14.6, depression/depressive symptoms 12.2, oral hypoesthesia 7.3, constipation 9.8, irritability 7.3 EPS-related AEs %: wk 12: 9.5 vs 12.0; wk 52: 22.0 vs 16.7 Akathisia wk 12: 3.2 vs 5.4; wk 52 4.9 vs 2.8	
9-week, double-blind extension of the 3-week acute trials (18, 19). Pts on ASE or OLZ continued their treatment. Pts on PLC were switched to ASE 10 mg BID on day 1, 5 – 10 mg BID thereafter and included only in safety analyses	n = 504 enrolled (74% of pts completing the acute trials). Completion rate %: ASE 62.0, PLC/ASE 53.0, OLZ 64.0	*(ASE vs OLZ)* Mean change in YMRS score: -24.4 vs -23.9 Response/remission rates %: 90.0/88.0 vs 92.0/91.0 Mean change in CGI-BP mania score: -2.9 vs -2.8 Mean change in MADRS score: -3.6 vs -2.4	*(ASE vs OLZ)* Discontinuations due to AEs %: 13.2 vs 9.6 Treatment emergent/related AEs %: 77.0/65.0 vs 78.0/64.0; SAEs/treatment related SAEs %: 12.0/3.0 vs 10.0/4.0 Most common AEs %: sedation (14.0 vs 18.0), dizziness (13.0 vs 7.0), somnolence (12.0 vs 14.0), insomnia (13.0 vs 10.0), headache (12.0 vs 15.0), weight gain (8.0 vs 14.0), dry mouth (4.0 vs 11.0) EPS-related AEs %: 15.0 vs13.0 (Akathisia: 7.0 vs 9.0)	[29]

AE: Adverse event; ASE: Asenapine; CGI-BP: Clinical Global Impression-Bipolar Disorder; DBPC: Double-blind placebo controlled; EPS: Extrapyramidal symptoms; LI: Lithium salts; MADRS: Montgomery-Asberg Depression Rating Scale; OLZ: Olanzapine; PLC: Placebo; Pt: Patient; SAE: Serious adverse event; VALP: Valproic acid; YMRS: Young Mania Rating Scale; Wk: Week.

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Table 2. Randomized controlled trials of Asenapine for Bipolar Disorder in adults (continued).

Design	Patients	Efficacy	Tolerability (ASE vs PLC vs OLZ)	Refs.
40-week, double-blind follow-up of the 3-week + 9-week extension trials (18, 19, 21). Pts on ASE or OLZ continued their treatment. Primary safety analyses	n = 218 enrolled (70.8% of pts completing the 9-week extension). Completion rate %: ASE 65.8, PLC/ASE 40.6, OLZ 63.6	*(ASE vs OLZ)* Mean change in YMRS score: -28.6 vs -28.2 Response/remission rates %: 97.8 vs 98.4 Mean change in CGI-BP mania score: -3.6 vs -3.5 Mean change in MADRS score: -4.8 vs -4.4	*(ASE vs OLZ)* Discontinuations due to AEs %: 8.9 vs 8.4 Treatment-emergent/related AEs %: 86.1.0/70.9 vs 79.4/61.7; SAEs/treatment-related SAEs %: 11.4/3.8 vs 10.3/2.8 Most common AEs %: sedation (16.5 vs 15.9), dizziness (12.7 vs 5.6), somnolence (13.9 vs 15.9), insomnia (20.3 vs 12.1), headache (13.9 vs 14.0), weight gain (13.9 vs 17.8), depression (15.2 vs 7.5) EPS-related AEs %: akathisia: 11.4 vs 10.3, parkinsonism 7.6 vs 3.7, bradykinesia 3.8 vs 1.9, dystonia 3.8 vs 0.9	[30]

AE: Adverse event; ASE: Asenapine; CGI-BP: Clinical Global Impression-Bipolar Disorder; DBPC: Double-blind placebo controlled; EPS: Extrapyramidal symptoms; LI: Lithium salts; MADRS: Montgomery-Asberg Depression Rating Scale; OLZ: Olanzapine; PLC: Placebo; Pt: Patient; SAE: Serious adverse event; VALP: Valproic acid; YMRS: Young Mania Rating Scale; Wk: Week.

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Using baseline depressive symptoms, the authors evaluated three groups: i) Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 20 (n = 132); ii) Clinical Global Impression for Bipolar Disorder–Depression (CGI-BP-D) scale severity score ≥ 4 (n = 170); iii) diagnosis of mixed episodes (n = 302) by investigative site screening. For each population, asenapine and olanzapine were independently compared with placebo using least squares mean change from baseline on depressive symptom measures.

Decreases in MADRS total score were statistically greater with asenapine vs placebo at days 7 and 21 in all populations; differences between olanzapine and placebo were not significant. Decreases in CGI-BP-D score were significantly greater with asenapine vs placebo at day 7 in all categories and day 21 in population 1; CGI-BP-D score reductions were significantly greater with olanzapine vs placebo at day 21 in population 1 and day 7 in populations 2 and 3.

These *post hoc* analyses show that asenapine reduced depressive symptoms in bipolar I disorder patients experiencing acute manic or mixed episodes with clinically relevant depressive symptoms at baseline. However, no multiplicity adjustment Bonferroni correction was applied and the analyses were carried using OC data (the original study methodology was based on LOCF data). Controlled studies of asenapine in patients with acute bipolar depression are necessary to confirm the generalizability of these findings.

3.3 Longer-term monotherapy studies

Based on a pooled sample constituted by the two described acute trials, a 9-week (total of 12 weeks including the 3-week trial) and a 40-week (total of 52 weeks) double-blind extension studies were conducted to compare, in a noninferiority design, asenapine to olanzapine on efficacy and tolerability measures. Patients (n = 504, 52.5% of those comprised in the acute trials intent-to-treat populations, 74% of those completing the acute trials) were enrolled in the first follow-up study [29] if they were willing to participate, and if clinical benefits were deemed likely by the treating clinicians. The subjects already receiving one of the two antipsychotics continued on the same regimen (asenapine n = 181, olanzapine n = 229), whereas those receiving placebo were switched to asenapine 10 mg twice daily on day 1 and 5 – 10 mg from day 2 onward (n = 94), but were included only in the safety analyses. Similar completion rates (62% asenapine vs 64% olanzapine) as well as similar percentages of concomitant medications (82% asenapine vs 77% olanzapine) were recorded for the two competing subgroups. No significant differences between groups on the main outcome measure (mean change in YMRS total score at day 84: asenapine -24.4 vs olanzapine -23.9) emerged. Asenapine and olanzapine were also associated with comparable percentages of response (90 vs 92%) and remission (77 vs 82%), and similar improvements in CGI-BP ratings.

A further extension study comprised n = 218 subjects (n = 79 asenapine, n = 107 olanzapine, n = 32 switched to asenapine from placebo after the 3-week acute phase), 61% of whom (13.8% of the initial randomized sample) completed a total of 52 weeks of follow-up (65.8% asenapine, 63.6% olanzapine, 40.6% placebo/asenapine). Mean daily doses taken of asenapine and olanzapine were 15.7 mg and 15.4 mg, respectively. Antiparkinsonian medications were prescribed to 13.9% and 8.4% of asenapine and olanzapine recipients, respectively, whereas lorazepam was prescribed to 34.2 and 37.4%. Notwithstanding it were not the primary objective of this long-term assessment, asenapine and olanzapine demonstrated sustained and comparable efficacy as marked by YMRS score decrease (-28.6 vs -28.2), response and remission rates (coinciding at 97.8 and 98.4%) and mean change in CGI-BP severity (-3.6 vs -3.5) [30].

3.4 Use in combination with mood stabilizers

Recently, Szegedi *et al.* [27] published the results of a third multicenter, randomized, double-blind, placebo-controlled 12-week trial followed by a 40-week double-blind placebo-controlled extension follow-up investigating the efficacy of asenapine as adjunctive treatment of ongoing (since at least 2 weeks) lithium or valproate. A total sample of 326 subjects fulfilling a diagnosis of manic (61.1%) or mixed (38.9%) episode were randomized to lithium (n = 64)/valproate (n = 90) plus asenapine or to lithium (n = 77)/valproate (n = 85) plus placebo; 204 of them (62.6%) completed at least the first three weeks of treatment. Serious risk of suicide or aggressive behaviors, current substance abuse/dependence, a rapid cycling course, and the need for long-lasting hospitalization (≥ 3 weeks) were all exclusion criteria.

Patients were given asenapine 5 mg BID (twice a day) on day 1 and could receive 10 mg BID from day 2 onward based on efficacy, safety and tolerability (mean daily dose = 11.8 mg during the first study phase; 13.3 mg during the extension period; 44.9% of patients increased their dosage from 5 to 10 mg at least one time); co-administered mood-stabilizer dosage could be changed to obtain target plasma levels of 0.6 mmol/l for lithium and 50 – 125 µg/ml for valproate. At the beginning of the extension study patients continued to get the same dosing of the first three weeks; further dose adjustments were allowed till the end of the study maintaining the cited ranges of 5 – 10 mg asenapine and targeted blood levels of lithium or valproate. An high discontinuation rate was apparent since the first phase of the study, with 116 individuals of the initial randomized population completing 12 weeks of trial (35.6%) and only 34 (10.43% of the initial sample, 44.16% of n = 77 people enrolled in the second study phase) going on till the end of the established 52 weeks' extension. Although overall completion rates were greater with placebo in the long term, early discontinuations within the first 2 weeks were lower with asenapine (8.9 vs 19.9%; n = 3 discontinuations, asenapine and n = 10 discontinuations, placebo due to lack of efficacy).

On intent-to-treat analysis, the primary outcome measure, change in YMRS score, was found to be significantly greater

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with asenapine vs placebo at the 3-week primary endpoint (-10.3 vs -7.9); results were already significant at week 2, and remained significant at the week 12 termination of the core study (-12.7 vs -9.3). The asenapine group showed significantly higher response rate at week 12 (47.7 vs 34.4%) and significantly higher remission rate at week 3 (33.5 vs 21.5%) and 12 (43.2 vs 30.1%). The active medication subpopulation did also significantly better in relation to CGI-BP scores reduction at both each of the two assessments. No significant differences between groups were recorded at week 52 endpoint in terms of mean YMRS total score changes, response and remission rates, but no firm conclusions can be drawn given the high dropout rates.

3.5 Tolerability in the short and longer term

In the acute monotherapy trials [25,26], treatment-emergent and treatment-related adverse events were recorded in 73.7 – 75.7% and 60.8 – 55.1% of asenapine recipients, 71.4 – 66.3% and 52.9 – 46.8% of olanzapine recipients and 61.0 – 56.1% and 36.2 – 27.6% of placebo recipients, respectively. The majority of observed side effects were of mild to moderate severity. The serious side effects were 1.5 – 6.5% for asenapine, 1.6 – 3.9% for olanzapine, and 3.8 – 7.1% for placebo. The most frequently reported side effects occurring in more than 5% of subjects receiving asenapine and at more than twice the frequency of placebo recipients were sedation (18.6 – 8.6%), dizziness (11.9 – 10.3%), somnolence (8.8 – 11.9%), fatigue (6.2%, in the first trial), oral hypoaesthesia (5.2%, in the first trial), increased weight (6.5%, in the second trial) and vomiting (5.4%, in the second trial). Olanzapine was associated with similar percentages of sedation (18.5 – 14.1%), somnolence (7.4 – 11.2%) and dizziness (8.5 – 6.3%) but caused more frequently dry mouth (14.3%, in the first trial), increased appetite (6.3%, in the second trial) and increased weight (6.9 – 9.3%).

Low rates of EPS emerged during treatment with asenapine (7.2 – 10.3%), comparable to those detected with olanzapine (7.9 – 6.8%). The most frequently reported symptoms in asenapine recipients were akathisia (2.6 – 5.4%, placebo 1.9 – 3.1%), dystonia (4.1%; placebo 1.9%, in the first trial) and bradykinesia (asenapine 2.2%, placebo 0.0%, in the second trial); 5.8 – 4.9% of individuals treated with olanzapine displayed akathisia. Similarly, the two antipsychotics brought about only minimal changes in the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) and Simpson-Angus Scale (SAS) scores at the study endpoint with respect to baseline evaluation.

Asenapine demonstrated a substantial advantage in comparison with olanzapine when considering the potential for weight gain (see **Table 3**). In fact, mean weight changes for asenapine, olanzapine and placebo in the two short term (3 weeks) trials were, respectively, 1.6 kg (asenapine), 1.9 kg (olanzapine) and 0.3 kg (placebo) in the first study [25] and 0.9 kg (asenapine), 0.1 kg (placebo) and 2.6 kg (olanzapine) in the second study [26]. Clinically significant weight gain (≥ 7% from the study outset) was 6.0% (asenapine), 0.0% (placebo), 12.9% (olanzapine) in the first study; and 7.2% (asenapine), 1.2% (placebo) and 19.0% (olanzapine) in the second study. Probably due to the short duration of the acute trials, no significant differences were apparent in general laboratory values and specific metabolic serum chemistries.

In the medium-term pooled 9-week (total observation, including 3-week trial = 12 weeks) extension trial [29], only 5% of patients on asenapine and 7% on olanzapine developed treatment-related severe adverse events. The most commonly reported side effects (above a 10% incidence) were sedation (14.4%), dizziness (13.3%) and somnolence (11.6%), insomnia (12.7%) and headache (11.6%) with asenapine, and sedation (17.5%), somnolence (14.4%), weight gain (14.4%), dry mouth (10.9%), insomnia (10.0) and headache (14.8) with olanzapine, respectively.

EPS were apparent in 14.9% of asenapine recipients and 13.1% of olanzapine recipients, respectively; akathisia was the most frequently encountered EPS in both groups (7.2% asenapine vs 8.7% olanzapine); minimal changes were recorded on BARS, AIMS, and SAS assessments at study endpoint.

The two antipsychotics differed more evidently with regard to anthropometric measures variations (see **Table 3**). In comparison with olanzapine, asenapine was associated with less worrisome weight gain (1.8 vs 3.8 kg), waist circumference change (1.8 vs 3.7 cm), less frequent clinically significant weight gain (18.8 vs 30.6%) and shifts to next higher BMI class (16.6 vs 29.3%); 6.6 vs 1.3% of the patients randomized to asenapine vs olanzapine, displayed a clinically significant weight loss. Minimal modifications and differences among groups were recorded in relation to blood chemistries, prolactin levels and electrocardiogram findings.

Both antipsychotics were well tolerated also in the long term (combined total 52 weeks), with low frequencies of treatment-related serious adverse events (3.8% asenapine, 2.8% olanzapine), and similar rates of tolerable side effects. In particular, asenapine was frequently (≥ 10%) associated in descending order with insomnia (20.3%), sedation (16.5%), depression (15.2%), headache (13.9%), somnolence (13.9%), weight gain (13.9%), dizziness (12.7%), nausea (12.7%) and akathisia (11.4%); olanzapine was associated with weight gain (17.8%), somnolence (15.9%), sedation (15.9%), headache (14.0%), insomnia (12.1%), and akathisia (10.3%) [29].

As observed in the acute and medium-term trials, in the extension (total of 52 weeks) study [30] olanzapine showed a greater tendency than asenapine to associate with weight gain (3.5 vs 6.0 kg), clinically significant weight gain (39.2 vs 55.1%), and waist circumference increase (2.6 vs 5.0 cm) [30].

In the combination trials [27], treatment-emergent side effects were shown by 73.4% of individuals on asenapine and 68.7% on placebo, at the end of the core study; percentages increased up to 78.0 and 69.4%, respectively, at the end of the extension phase. However, serious side effects

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Table 3. Anthropometric measures.

3-week monotherapy trials [25,26]	**OLZ**	**ASE**	**PLC**
Mean weight gain (kg)	1.9 – 2.6	0.9 – 1.6	0.1 – 0.3
Weight gain ≥ 7% (%)	12.9 – 19.0	6.0 – 7.2	0.0 – 1.2
Patients shifting to higher BMI (%)	15.5 – 15.9	8.3 – 10.2	3.5 – 6.0
Change from baseline waist circumference (cm)	1.9 – 2.0	1.0	0.1 – 0.9
9-week extension of monotherapy trials (12 weeks) [29]			**PLC/ASE**
Mean weight gain (kg)	4.1	1.9	0.5
Weight gain ≥ 7% (%)	30.6	18.8	9.6
% of patients shifting to higher BMI	29	17	13
Change from baseline waist circumference (cm)	3.7	1.8	1.2
40-week extension of monotherapy trials (52 weeks) [30]			**PLC/ASE**
Mean weight gain (kg)	6.0	3.5	1.7
Weight gain ≥ 7% (%)	55.1	39.2	21.9
Patients shifting to higher BMI (%)	Most patients remained in the same BMI category		
Change from baseline waist circumference (cm)	5.0	2.6	3.0
12-week core phase of the combination trial [27]		**ASE**	**PLC**
Mean weight gain (kg)	-	2.3	0.7
Weight gain ≥ 7%	-	19.5	5.2
Patients shifting to higher BMI (%)	-	18.8	7.5
Patients meeting criteria for metabolic syndrome (%)	-	14	16.3
40-week extension phase of the combination trial (52 weeks) [27]			
Mean weight gain (kg)	-	3.5	1.7
Weight gain ≥ 7%	-	36.6	19.4
Patients shifting to higher BMI (%)	-	22.0	11.1
Patients meeting criteria for metabolic syndrome (%)	-	17.1	22.2

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were noted in much lower and comparable frequencies of subjects (13.3%, asenapine vs 14.5%, placebo in core 12-week study; 22.0%, asenapine vs 11.1%, placebo in extension study (total of 52 weeks).

The most frequently reported side effects occurring in more than 5% of patients taking asenapine and at least twice as frequently than in the placebo subgroup were sedation (13.3 vs 6.0%; 14.6 vs 5.6%), somnolence (11.4 vs 4.2%), depression/depressive symptoms (6.3 vs 3.0%; 12.2 vs 5.6%), oral hypoesthesia (5.7 vs 0.6%; 7.3 vs 2.8%), and increased weight (5.1 vs 0.6%). EPS were detected less frequently in patients on asenapine than placebo during the 12-week core trial (9.5 vs 12.0%; 22 vs 16.7%, during the 40-week extension period). No significant differences emerged in AIMS, BARS and SAS total scores changes from the intake to the endpoints. Individuals randomized to asenapine gained a mean of 2.3 kg (placebo 0.7 kg) and 3.5 kg after 12 and 52 weeks, respectively; the other relevant recorded metabolic parameters differentiating asenapine from placebo were clinically significant weight gain (19.5 vs 5.2%; 36.6 vs 19.4% in the 40-week extension trial), shift to the next higher BMI class (18.8 vs 7.5%; 22.0 vs 11.1% in the 40-week extension trial). No differences between groups were apparent in frequencies of patients endorsing criteria for metabolic syndrome at short- and longer-term assessments.

3.5.1 QTc prolongation

Asenapine does not seem to cause clinically significant QTc interval prolongation, as evidenced both in schizophrenia and bipolar disorder trials.

An exposure-response (E-R) analysis was conducted on data from a thorough QTc trial for asenapine in 148 patients with schizophrenia. Following a parallel study design, study subjects received asenapine 5 mg twice daily (BID) for 10 days followed by 10 mg BID for 6 days, asenapine 15 mg BID for 10 days followed by 20 mg BID for 6 days, quetiapine 375 mg BID (for assay sensitivity; 16 days) or placebo for 16 days. At mean C_{max} for all asenapine doses, the E-R model predicted that the mean QTcF increase was less than 5 ms, i.e.. less than the International Conference on Harmonization-established threshold for clinical concern. The model predicted a mean increase of 7 – 8 ms for quetiapine. The corresponding upper bounds of the 95% confidence intervals were 11.2 ms and 7.5 ms and for quetiapine and asenapine, respectively [31].

4. Switching strategies

The asenapine package insert does not provide guidance to assist the physician in replacing an ongoing antipsychotic therapy with asenapine because of the absence of data from bipolar

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Table 4. Dose adjustments in special populations

Dose adjustment in patients with impaired kidney function
No dosage adjustment is necessary
Dose adjustment in hepatic impairment
Mild-to-moderate impairment (Child-Pugh Class A and B): No dosage adjustment if necessary
Severe hepatic impairment: Use is not recommended
Dose adjustment in the elderly
Available trial results did not include sufficient numbers of elderly subjects to make age-specific recommendations. However, an increase in asenapine exposure of about 40% has been reported in the elderly and, in the opinion of the authors of this paper, a reduced dosage may be warranted in patients older than 65 years
Dose adjustments are not necessary based on patient: Race, gender, or smoking status

clinical trials. We briefly report the results of a switching study [32] in patients with schizophrenia, which may be helpful for clinical practice with patients with bipolar disorder as well, even if switch tolerability and effectiveness is likely to be influenced by mood episode polarity and phase of treatment.

Current FGA and SGA were switched to asenapine 5 mg BID for the first week (with the possibility to increase the dosage at 10 mg BID at the discretion of the investigators after the first week) or to olanzapine 10 mg once daily (with a discretionary therapeutic range of 5 – 20 mg QD after the first week). The study focused on treatment-related side effects emerging during the 28 days switching period as compared with the remaining 26-week follow-up period. As confirmed also by our clinical experience, an abrupt switch to asenapine or olanzapine (within 3 days) was well tolerated in a substantial percentage (> 40%) of patients; similar discontinuation rates were detected in the asenapine abrupt switch subgroup in comparison with the slow tapering counterpart. The most frequently reported tolerability issues reported for asenapine during the 28 days switching period vs the following 26 weeks were: insomnia (11.1 vs 18.9%), somnolence (9.8 vs 13.9%) and headache (8.5 vs 14.5%) when substituting a SGA; somnolence (8.6 vs 13.2%), insomnia (4.6 vs 11.3%) and nausea (4.6 vs 5.3%) when substituting a FGA; somnolence (11.7 vs 15.0%), insomnia (10.0 vs 15%) and agitation (6.7 vs 10.0%) when substituting a depot medication. Interestingly, in corroboration of the information gained from bipolar trials, switching to olanzapine brought about higher incidences of weight gain irrespective of the antipsychotic that was tapered off.

Elevated and puzzling rates of insomnia were recorded when switching aripiprazole (> 20%) or ziprasidone (> 30%) into asenapine. Given that the pharmacodynamic of this latter is suggestive of a more sedative profile, the explanation of this result most likely lies in the substitution from a combined treatment regimen. In fact, the authors wisely tabled rates of main side effects stratified for number of previous antipsychotics, showing that as a whole insomnia occurred in 14.9% of subjects coming from a monotherapy and in 24.3% of subjects coming from two co-prescribed antipsychotics.

To sum up, a rapid switch into asenapine is frequently possible from both SGAs and FGAs. Whenever insomnia or agitation may be a problem, or when prescribing asenapine in substitution of sedative medications (e.g., olanzapine, quetiapine, chlorpromazine, etc.), a starting dosage of 10 mg BID is advisable. Slow-tapering/cross-tapering protocols may be recommended when the switch into asenapine is also an attempt to simplify a complex therapy regimen. We suggest particular caution when interrupting drugs with anticholinergic action such as clozapine and olanzapine because of the risk of triggering a discontinuation rebound syndrome characterized by symptoms of nausea, vomiting, abdominal cramping, sweating, headache, urinary urgency and muscle spasms. Tapering, rather than abruptly discontinuing antipsychotics with anticholinergic properties or temporarily associating an anticholinergic drug (e.g., trihexyphenidyl, biperiden, benztropine, etc.) may avoid or minimize withdrawal effects.

5. Prescription in pediatric and geriatric patients (Table 4)

Asenapine is not indicated in children and adolescent populations (see clinicaltrial.gov for ongoing pediatric studies) because efficacy and safety information in these populations is virtually absent. An increase in asenapine exposure of about 40% has been reported in the elderly [12] but there is paucity of data also on aging patients. Recently, Baruch *et al.* [33] reported on a small sample (n = 11) of severely manic subjects (mean YMRS = 33.5) aged ≥ 60 treated with asenapine (mean daily dose = 20 mg, starting dose for the first 3 days: 5 mg BID) and noted promisingly statistically significant results at day 28 (mean YMRS total score reduction: -21.4; response rate: 81.8%; remission rate: 63.6%). Apart from two male patients who discontinued the study medication due to an allergic reaction and to a severe peripheral edema (both adverse events completely resolved 3 days discontinuation), asenapine was well tolerated, causing only moderate sedation in three subjects.

The benign cardiovascular and safety profile of asenapine along with its low potential for pharmacologic interactions warrant larger randomized trials in geriatric patients suffering from bipolar disorder.

6. Discussion

Asenapine demonstrated to be an effective and well-tolerated treatment of manic and mixed episodes both in monotherapy and in combination with lithium of valproate, with an efficacy similar to equipotent dosages of olanzapine. Its placebo-corrected performance in reducing YMRS total score (5.3 – 5.7 points) falls within the previously recorded magnitude of SGAs efficacy in acute manic episodes (4.0 – 7.9 decrease) [34-39]. Asenapine also demonstrated sustained efficacy and a relatively favorable safety profile during the medium to long-term follow-up in patients who had initially

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responded and tolerated the drug. Similarly, the magnitude of YMRS score reductions in the medium (12 weeks) and longer term (40 weeks) was similar to results reported in comparable duration trials of haloperidol and other SGAs [37,40-42].

A recent meta-analysis of [43] evaluated the available evidences to explore efficacy and acceptability of mood-stabilizers and antipsychotics for acute mania based on reported YMRS mean reductions, dropout rates and relapse rates. The author concluded that olanzapine, risperidone and haloperidol should be considered first-line options. We would agree with this conclusion if clinicians had to manage only the acute manic phase and, in making its initial therapeutic choices, could disregard important issues such as the likelihood of precipitating depressive episodes, the risk of EPS, cardiovascular toxicity, the risks to incur in substantial weight gain and metabolic side effects. Indeed, morbidity of bipolar disorder extends well beyond the acute states and a good clinical care requires a careful appraisal of both psychiatric and medical outcomes [6,44-48].

In line with these observations, the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the treatment of acute mania [49] pointed to the need for a balance between the evidence for efficacy (CE) and several other important aspects such as safety, tolerability and interaction potential. To this end, the WFSBP guidelines suggested a recommendation grade (RG) 1 (full evidence from controlled clinical studies and good risk–benefit ratio) for aripiprazole, risperidone, valproate, and ziprasidone. Six other medications, including asenapine, were classified under RG 2 (full evidence from controlled clinical studies and moderate risk–benefit ratio). Five other drugs were classified as RG3 (limited positive evidence from controlled studies), whereas 11 other treatments were issued a RG4 (Evidence from uncontrolled studies or case reports/expert opinion) and 1 (verapamil) was classified as RG5 (inconsistent results from clinical trials).

Tolerability issues are particularly important for those medications that are approved for long-term maintenance and preventative treatment. However, even medications approved only for the acute treatment (such as asenapine) are often used for long periods. Among other reasons, it is important to note that evidence is accumulating to suggest that bipolar disorder is associated with significant chronicity and that residual, sub-syndromal symptoms very often persist between major syndromal episodes, which contributes to a prolonged need of antimanic agents. In asenapine acute registrational trials, olanzapine fared better than asenapine regarding percentages of retention in treatment, both in bipolar and in schizophrenia studies. Indeed, olanzapine has been associated with relatively good retention rates in several trials including the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study [50]. However, olanzapine is associated with severe metabolic consequences in the long term [51,52], whereas asenapine exhibited a lower risk of metabolic side effects. In the longer-term 40-week trial [30], clinically significant weight gain (≥ 7% increase from baseline) occurred in 21.9, 39.2, and 55.1% of patients in the placebo/asenapine, asenapine, and olanzapine groups, respectively. *Post hoc* analysis indicated that the NNH for clinically significant weight gain for olanzapine relative to asenapine was 7 (95% CI, 3 – 63). The mean ± SD increase in weight from baseline to study endpoint was 1.7 ± 6.0 kg (3.7 ± 13.1 lb), 3.5 ± 6.7 kg (7.7 ± 14.7 lb), and 6.0 ± 6.6 kg (13.2 ± 14.5 lb) in the placebo/asenapine, asenapine, and olanzapine groups. In this trial, the most frequent treatment-emergent adverse events were headache and somnolence with placebo/asenapine; insomnia, sedation, and depression with asenapine; and weight gain, somnolence, and sedation with olanzapine. Akathisia was the most frequently encountered EPS in asenapine patients. However, akathisia was reported in 2.6 – 5.4% of recipients, which remains a relatively low percentage.

Despite the relatively favorable long-term tolerability profile, the paucity of long-term and comparative effectiveness data on asenapine in bipolar populations remains a limitation. Also worth highlighting is the paucity of data in important subgroups including those with comorbid medical disorders (potential advantage for asenapine given metabolically favorable profile), rapid cycling, and concomitant psychiatric disorders (anxiety disorders in particular).

The pharmacodynamic of asenapine is suggestive of potential antidepressant properties based on its affinity and antagonistic activity on serotonin 5HT2A, 5HT2C, 5HT7 and adrenergic $\alpha 2$ receptors. The blockade of these receptors along with cortical increase in serotonin, dopamine and norepinephrine levels might contribute to an antidepressant effect, as suggested in animal models and preclinical studies [16,53-57]. Two *post-hoc* analyses focused on the efficacy and tolerability of asenapine in patients with mixed episodes and pointed to the efficacy on depressive symptoms. Mixed episodes are relatively frequent and often severe and are often complicated by high levels of agitation, anguish, hopelessness, anxiety symptoms, and a tendency to hazardous acting-outs such as suicide attempts or aggressive behaviors. Clinical management of mixed episodes often entails a complex balance of treatments with mood-stabilizers, antidepressants (to be avoided in most cases), antipsychotics and temporary use of tranquilizers, in the context of frequent mood switches/instability. The majority of FGA are efficacious anti-manic agents but they carry a substantial medium to long-term risk of precipitating post-manic depressive episodes [58], along with other bothersome adverse events, such as extrapyramidal side effects. Olanzapine alone and in conjunction with fluoxetine has proven effective for bipolar depression in a large 8-week trial [59]. Olanzapine also received FDA approval as a maintenance treatment in bipolar disorder, based on well-conducted long-term trials [60-62]. Therefore, so far, olanzapine together with lithium and quetiapine, is close to an ideal definition of "mood-stabilizer," owing to their antimanic, antidepressant and prophylactic actions. It seems that there is evidence to support use of asenapine for treating acute bipolar mixed states as well as some, albeit weak, evidence that asenapine

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may be effective for treating more subsyndromal mixed states with a predominance of manic signs and symptoms, but this will need to be more rigorously tested. To date, there is no credible evidence yet supporting the use of asenapine for bipolar depressive or depressive mixed states.

7. Expert opinion

We believe that the availability of several medications for the treatment of bipolar disorder is paramount for ensuring the best possible outcome for each patient. In fact, among patients with bipolar disorder, there clearly are differences between one patient and another in terms of likelihood to respond to one medication or to another. For instance, two medications may show an identical (i.e., 50%) response rate in clinical trials but clinicians are well aware of the fact that the 5 patients out of 10 respond to the first medication and not necessarily the same 5 of 10 that respond to the second. Such considerations are even more true when it comes to tolerability.

Our clinical practice has confirmed the favorable results of asenapine clinical trials and shown that this medication is an effective and relatively easy-to-use treatment. As suggested in *post hoc* analyses of asenapine studies [63], our observations confirm that early improvement predicts later outcome in manic or mixed episodes associated with bipolar I disorder.

The most frequent/significant side effects encountered in our clinical practice are sedation, somnolence, akathisia and dizziness, which however have been very rarely a reason for discontinuation. While somnolence and sedation may be advantageous during acute manic/mixed episode treatment, this will change during continuation and maintenance phase treatment. At these stages, somnolence, sedation and prolactin elevation (leading to sexual dysfunction and other potentially prolactin-related adverse effects) then become a liability [64,65]. However, in our experience somnolence and sedation most of the side effects above (e.g., somnolence, sedation, akathisia and dizziness) tend to be mild–moderate and often subside over time.

Asenapine carries a lower risk of weight gain, showing low to no antimuscarinic side effects and low risk for pharmacologic interactions. The lack of anticholinergic properties may contribute to the relatively low rate of cognitive dysfunction and confusion, as well as for the relatively low rate of peripheral side effects such as dry mouth, urinary retention, constipation, and blurred vision. However, the lack of anticholinergic properties may also contribute to the asenapine rate of akathisia that we usually find higher in asenapine patients than medications such as olanzapine. In our experience, mild akathisia is relatively frequent but usually respond to lowering the dose (when possible) or adding a low-dose beta blocker (e.g., propanolol 10 – 20 mg/three times a day, if there are not contraindications to these medications), a benzodiazepine or an anticholinergic medication. In most cases, akathisia subsides after a few days and the adjunctive medication can be discontinued. In cases when akathisia is present along with agitation, we have frequently observed that a dosage increase often ameliorates, rather than worsening, the clinical pictures.

The fast-dissolving sublingual route of administration often improves adherence to treatment, favoring those who have difficulties in swallowing medications. Also, the sublingual administration reduces the risk of overdose when more than the prescribed tablets are swallowed, given that – when the medication is swallowed instead of administered sublingually – the bioavailability falls to less than 2%.

Asenapine has also shown to be a useful adjunctive medication to ongoing therapy with lithium or valproate. Mood stabilizers monotherapy is likely effective in the milder episodes of mania but combination with an antipsychotic is the rule in moderate–severe and/or psychotic manic or mixed episodes, and requires a stronger and rapid therapeutic response [52,66]. Our clinical experience is consistent with the research trials and shows good efficacy and tolerability in the combination of asenapine with both lithium and divalproex.

Asenapine displays quick and reliable effects on manic symptoms, very low risk of depressive switches, efficacy on depressive symptoms during manic and mixed episodes, good tolerability and continued longer-term efficacy. Furthermore, it is conveniently administered via a sublingual route, does not need difficult or prolonged titration and shows a relatively low potential for pharmacologic interactions.

Declaration of interest

A Fagiolini is/has been a consultant and/or a speaker for Angelini, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Lundbeck, Jannssen, Otsuka, Pfizer, Sigma Tau and Takeida. RN Forgione is/has been a consultant for Angelini, Bristol-Myers Squibb and Lundbeck. The other authors declare no conflict of interest.

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