

## ASENAPINE: PHARMACOLOGICAL ASPECTS AND ROLE IN PSYCHIATRIC DISORDERS

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### SUMMARY

Schizophrenia and bipolar disorders are serious psychiatric disorders with substantial health risks. Asenapine is a new second-generation antipsychotic, available as a sublingual tablet, approved in Europe for the treatment of moderate-to-severe manic episodes in adults, and in US for manic or mixed episodes of bipolar I disorder in adults and adolescents. In this review, we searched the available literature to appreciate the role of asenapine in the management of psychiatric conditions such as bipolar disorders and schizophrenia and describe its mechanism of action, efficacy and tolerability. Asenapine has demonstrated efficacy in the management of bipolar disorders and schizophrenia, while a possible role in the management of borderline personality disorder and agitation needs further research. Asenapine has favourable side effects profile and combining with other pharmacological treatment in post-traumatic stress disorder has shown promising results. Asenapine fulfils important requirements of efficacy and tolerability as an anti-psychotic. These findings should support psychiatrists and pharmacists in the care of their patients while on asenapine.

**Key words:** asenapine - schizophrenia - psychiatry - bipolar disorders - borderline personality disorders

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### INTRODUCTION

Schizophrenia and bipolar disorders (BD) are serious psychiatric disorders with a significant burden on the patients, their carers and the overall economy (Vieta & Montes 2018). BD mixed states represents a particular challenge; characterized by a complicated treatment course and a worse prognosis (Betzler et al. 2017), while schizophrenia as a chronic brain disorder is characterised by positive, negative and cognitive symptoms (Cortese et al. 2013). Asenapine is a new second-generation antipsychotic, available as a sublingual tablet, approved in Europe for the treatment of moderate-to-severe manic episodes associated with bipolar I disorder in adults, and in the US for the treatment of manic or mixed episodes of bipolar I disorder in adults and adolescents (Vieta & Montes 2018). In this review article, we searched the literature to assess asenapine efficacy and tolerability in the management of patients suffering from psychiatric disorders such as schizophrenia and BD.

In this article, a systematic search was conducted for the literature to review asenapine efficacy and safety in the management of schizophrenia and other psychiatric disorders, where the primary efficacy measures included Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression-Bipolar (CGI-BP-D), Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Negative Symptom Assessment (NSA-16) and Brief Psychiatric Rating Scale (BPRS).

### ASENAPINE PHARMACOLOGY AND PHARMACOKINETICS

Asenapine has D2 antagonistic activity (anti-manic) (Vieta & Montes 2018), strong antagonistic activity at 5-HT1A/7 receptors with anti-histaminergic, potent dopamine D1 antagonistic and negligible anti-cholinergic properties (De Boer et al. 1990). Asenapine influences transcription factors in catecholamine-synthesizing neurons of the substantia nigra, ventral tegmental area (VTA) leading to persistent/region-specific changes (Osacka et al. 2017, Majercikova et al. 2016) such as increased number of spontaneously active dopamine neurons (Oosterhof et al. 2015). Asenapine has higher relative affinity to D4 compared to D2 with a unique anti-aggression potency (Amon et al. 2017) as D4 has been implicated in aggression aetiology (El-Mallakh & McKenzie 2013). Asenapine enhanced cortical monoamine efflux (Franberg et al. 2009) and similar to clozapine, facilitated cortical NMDA-induced currents (Jardemark et al. 2010). Addition of asenapine to escitalopram markedly enhanced dopamine, noradrenaline and serotonin release (Bjorkholm et al. 2014) and reduced local cerebral glucose utilization, suggesting antipsychotic potential, without cognitive and extrapyramidal side-effects (SE) (Room et al. 1991). Asenapine also reduced reactive oxygen species production and apoptosis (Grossini et al. 2014).

Sublingual administration is essential as asenapine oral and sublingual bioavailability is <2% and 35% respectively, due to first pass metabolism and poor solubility. Following oral administration in rats, half-life

is ~33 hours with preferential distribution to highly perfused organs (Managuli et al. 2017). In humans, sublingual tablets have  $T_{max}$  (30-90 min) and elimination half-life (20-30 hours) (Dogterom et al. 2012). Asenapine is extensively metabolized (van de Wetering-Krebbbers et al. 2011), with inactive metabolites produced via glucuronidation (Lu et al. 2017), demethylation and oxidative metabolism. Valproate could reduce N-glucuronide and N-desmethyl-asenapine formation (Gerrits et al. 2012). Asenapine exposure was 20% lower after high-fat meal, whereas  $C_{max}$  decreased by only 10% (Dogterom et al. 2015). Caution is required when co-administering asenapine with substrates and inhibitors of CYP2D6, for example, asenapine as CYP2D6 inhibitor can raise paroxetine plasma levels (Citrome 2014).

## EFFICACY OF ASENAPINE IN BD MANAGEMENT

Clinical trials for asenapine as mono- and adjunct therapy in adult and paediatric patients (Vieta & Montes 2018) showed improved performance in learning, short-term and recognition tasks (Franza 2016) with changes in YMRS from day 2 (McIntyre et al. 2010) and longer time to recurrence of mood episode (Szegegi et al. 2017), with further decreases in YMRS and MADRS by week 3 (Azorin et al. 2013). In a large clinical trial, the mean change in YMRS was -24.4 for asenapine versus -23.9 for olanzapine, showing similar efficacy (McIntyre et al. 2009) and beneficial remission rates in patients suffering from co-morbid anxiety/irritability (Suppes et al. 2017). Asenapine response was faster compared to haloperidol or olanzapine (Buoli et al. 2017) and was effective in reducing clinically significant depressive symptoms (Vieta & Montes 2018) as highlighted by greater decreases in MADRS scores compared to olanzapine (Berk et al. 2015). Asenapine in paediatric and adolescent patients resulted in significant changes in YMRS (Findling et al. 2015, Findling et al. 2016) and in elderly, reduced YMRS score from 27.0 to 13.3 with 56% of patients achieving remission (Barak et al. 2016). Length of stay, relative risk of rehospitalisation and BPRS scores decreased including conceptual disorganization, grandiosity and unusual thought content (Ostinelli et al. 2015). For patients with mixed episodes, asenapine led to improvements in every domain of the 36-item Short-Form Health Survey compared to olanzapine (Michalak et al. 2014), while adding asenapine to lithium or valproate was effective and tolerated (Szegegi et al. 2012) with reduction in manic and psychotic symptoms (Grande et al. 2015).

## EFFICACY OF ASENAPINE IN SCHIZOPHRENIA MANAGEMENT

Asenapine was superior to placebo and with similar efficacy to other anti-psychotics in improving PANSS

total scores (Landbloom et al. 2017, Kane et al. 2010). In a study of inpatients with acute hallucinatory/delusional and mania/delusional states, positive effect ( $\geq 30\%$  reduction in PANSS scores) was achieved in 86.6% of the patients (Panteleeva et al. 2015) and times to relapse/impending relapse were significantly longer with asenapine with lower incidence of relapse (Kane et al. 2011). Changes in CDSS total score including hopelessness, self-depreciation, pathological guilt and observed depression were higher (Castle & Slott Jensen 2015). Asenapine and risperidone caused improvements on CGI-S and PANSS positive subscale scores (Potkin et al. 2007). Asenapine was superior to risperidone and olanzapine in decreasing negative symptoms in schizophrenia (Potkin et al. 2013); however, there is a need for large-scale, longer-term randomised trials (Hay et al. 2015).

## EFFICACY OF ASENAPINE IN OTHER PSYCHIATRIC CONDITIONS

Few studies highlighted asenapine role in borderline personality disorder management, where asenapine was superior to olanzapine in reducing affective instability score, while olanzapine was superior in reducing dissociation/paranoid ideation (Bozzatello et al. 2017). Asenapine caused significant improvement in CGI-BPD scales and general psychopathology domains (Martin-Blanco et al. 2014). Asenapine and clozapine with a high affinity to D4 receptor ( $D4/D2 > 1$ ), are considered more effective than other antipsychotic medications with a significant reduction in aggression particularly physical aggression (Amon et al. 2017). In agitated adults with a score of  $\geq 14$  on PANSS-Excited Component, asenapine showed greater improvements (NNT=3) (Pratts et al. 2014). Post-traumatic stress disorder patients who had not responded to selective serotonin reuptake inhibitors, venlafaxine or mirtazapine, showed a significant and clinically meaningful improvement (Pilkinton et al. 2016).

## TOLERABILITY AND SAFETY OF ASENAPINE

Treatment-emergent SE reported by  $>5\%$  of patients were sedation, somnolence, depressive symptoms, oral hypoesthesia and increased weight (Szegegi et al. 2012), with incidence for anxiety ( $\sim 10\%$ ) and insomnia ( $\sim 10\%$ ) (Kane et al. 2011).  $\geq 7\%$  weight increase was prevalent - NNH=17 (De Hert et al. 2012). Oral Hypoesthesia was a new adverse event compared with other antipsychotics (Bozzatello et al. 2017). Extrapyramidal symptoms occurred less with asenapine compared to haloperidol (Kane et al. 2010). In paediatric patients, somnolence/sedation/hypersomnia occurred frequently (42.4%) followed by oral hypoesthesia/dysgeusia (7.5%) with 34.8% patients experienced clinically significant weight gain (Findling et al. 2016). In older adults, the most

common SE included gastrointestinal discomfort (33%), restlessness (13%), tremors (13%), cognitive difficulties (13%) and sluggishness (13%) (Sajatovic et al. 2015). There are some reports of serious but rare SE such as allergic reactions and sudden death (Masters 2012), while overdose could lead to Neuroleptic Malignant Syndrome (Das et al. 2017). On the other hand, asenapine had a lower risk of developing type 2 diabetes compared to olanzapine (2.2 vs 3.5%, respectively) or dyslipidemia (2.8 vs 6.8%, respectively) (Maina & Ripellino 2014). Rise in prolactin was smaller compared to other antipsychotics (Samalin et al. 2013).

## DISCUSSION

Asenapine, a new second-generation antipsychotic, is used for acute schizophrenia, BD and as an adjunctive therapy with lithium or valproate (Tarazi & Stahl 2012). Asenapine advantages include sublingual formulation, early efficacy and good metabolic tolerability (Szegeedi et al. 2013). Obstacles for compliance include twice daily dosing, the need to avoid food and liquids for at least 10 minutes post-administration and the need for cooperation with sublingual administration (Henry & Fuller 2011). Asenapine preferentially increases dopamine, norepinephrine and acetylcholine levels in cortical and limbic brain areas and potentiates cortical glutamatergic neurotransmission (Tarazi & Neill 2013). Asenapine could control depressive symptoms and seemed superior to olanzapine or risperidone in schizophrenia negative symptoms. Asenapine had less incidence of extrapyramidal SE with little effects on cardiovascular system and QTc prolongation (Bishara & Taylor 2009). The fast-dissolving sublingual administration may support patients who have difficulties in swallowing and reduce the risk of overdose (Fagiolini et al. 2013). Asenapine has number to treat (NNT) 6 for response (minimum 20% decrease in PANSS total score) and NNH 13 for akathisia, 20 for oral hypoesthesia and 13 for somnolence (Citrome 2009). Economically, asenapine could reduce overall treatment costs as patients were less likely to be hospitalized with decrease in inpatient costs and a slight increase in pharmacy costs (Chitnis et al. 2015) with a better quality of life. Guidelines support asenapine as first-line monotherapy for BD, while in bipolar depression, asenapine alone or as adjunctive therapy is a third-line option (Yatham et al. 2013).

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Ayman Antoun Reyad: study design, literature review, first draft, approval of the final version.

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## References

1. Amon JS, Johnson SB & El-Mallakh RS: *Asenapine for the Control of Physical Aggression: A Prospective Naturalist Pilot Study*. *Psychopharmacology bulletin* 2017; 47:27-32
2. Azorin JM, Sapin C & Weiller E: *Effect of asenapine on manic and depressive symptoms in bipolar I patients with mixed episodes: results from post hoc analyses*. *Journal of affective disorders* 2013; 145:62-69
3. Barak Y, Finkelstein I & Pridan S: *The geriatric mania asenapine study (GeMS)*. *Archives of Gerontology and Geriatrics* 2016; 64:111-114
4. Berk M, Tiller JW, Zhao J, Yatham LN, Malhi GS & Weiller E: *Effects of asenapine in bipolar I patients meeting proxy criteria for moderate-to-severe mixed major depressive episodes: a post hoc analysis*. *The Journal of clinical psychiatry* 2015; 76:728-734
5. Betzler F, Stover LA, Sterzer P & Kohler S: *Mixed states in bipolar disorder - changes in DSM-5 and current treatment recommendations*. *International Journal of Psychiatry in Clinical Practice* 2017; 21:244-258
6. Bishara D & Taylor D: *Asenapine monotherapy in the acute treatment of both schizophrenia and bipolar I disorder*. *Neuropsychiatric disease and treatment* 2009; 5:483-490
7. Bjorkholm C, Franberg O, Malmerfelt A, Marcus MM, Konradsson-Geuken A, Schilström B, Jardemark K & Svensson TH: *Adjunctive treatment with asenapine augments the escitalopram-induced effects on monoaminergic outflow and glutamatergic neurotransmission in the medial prefrontal cortex of the rat*. *The international journal of neuropsychopharmacology* 2014; 18: 10.1093/ijnp/pyu068
8. Bozzatello P, Rocca P, Uscinska M & Bellino S: *Efficacy and Tolerability of Asenapine Compared with Olanzapine in Borderline Personality Disorder: An Open-Label Randomized Controlled Trial*. *CNS drugs* 2017; 31:809-819
9. Buoli M, Esposito CM, Godio M, Caldiroli A, Serati M & Altamura AC: *Have antipsychotics a different speed of action in the acute treatment of mania? A single-blind comparative study*. *Journal of psychopharmacology (Oxford, England)* 2017; 31:1537-1543
10. Castle DJ & Slott Jensen JK: *Management of depressive symptoms in schizophrenia*. *Clinical schizophrenia & related psychoses* 2015; 9:13-20
11. Chitnis A, Sun SX, Dixit S, Wang R, Tawah A & Boulanger L: *Changes in Patterns of Utilization and Cost of Health Care Services Associated With Initiation of Asenapine for the Treatment of Schizophrenia in Adults*. *Managed care (Langhorne, Pa.)* 2015; 24:58-64
12. Citrome L: *Asenapine review, part I: chemistry, receptor affinity profile, pharmacokinetics and metabolism*. *Expert opinion on drug metabolism & toxicology* 2014; 10:893-903
13. Citrome L: *Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic*. *International journal of clinical practice* 2009; 63:1762-1784
14. Cortese L, Bressan RA, Castle DJ & Mosolov SN: *Management of schizophrenia: clinical experience with asenapine*. *Journal of psychopharmacology (Oxford, England)* 2013; 27:14-22
15. Das S, Purushothaman ST, Bc M, Chatterjee SS, Kartha A & Rajan V: *Oral Asenapine overdose leading to Neuroleptic Malignant Syndrome (NMS)*. *Asian journal of psychiatry* 2017; 30:31-32

16. De Boer T, Tonnaer JA, De Vos CJ & Van Delft AM: Neurochemical studies with the potential antipsychotic compound trans-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrolidine maleate. *Arzneimittel-Forschung* 1990; 40:550-554
17. De Hert M, Yu W, Detraux J, Sweers K, van Winkel R & Correll CU: Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis. *CNS drugs* 2012; 26:733-759
18. Dogterom P, de Greef R & Peeters PA: The effect of food on the high clearance drug asenapine after sublingual administration to healthy male volunteers. *European journal of clinical pharmacology* 2015; 71:65-74
19. Dogterom P, Timmer C, de Greef R, Spaans E, de Vries D, van Vliet A & Peeters P: Asenapine Safety, Tolerability, and Pharmacokinetics After Single and Multiple Doses in Healthy Volunteers. *Clinical pharmacology in drug development* 2012; 1:131-143
20. El-Mallakh RS & McKenzie C: The dopamine D4/D2 receptor antagonist affinity ratio as a predictor of anti-aggression medication efficacy. *Medical hypotheses* 2013; 80:530-533
21. Fagiolini A, Forgione RN, Morana B, Maccari M, Goracci A, Bossini L, Pellegrini F, Cuomo A & Casamassima F: Asenapine for the treatment of manic and mixed episodes associated with bipolar I disorder: from clinical research to clinical practice. *Expert opinion on pharmacotherapy* 2013; 14:489-504
22. Findling RL, Landbloom RL, Mackle M, Wu X, Snow-Adami L, Chang K & Durgam S: Long-term Safety of Asenapine in Pediatric Patients Diagnosed With Bipolar I Disorder: A 50-Week Open-Label, Flexible-Dose Trial. *Paediatric drugs* 2016; 18:367-378
23. Findling RL, Landbloom RL, Szegedi A, Koppenhaver J, Braat S, Zhu Q, Mackle M, Chang K & Mathews M: Asenapine for the Acute Treatment of Pediatric Manic or Mixed Episode of Bipolar I Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015; 54:1032-1041
24. Franberg O, Marcus MM, Ivanov V, Schilstrom B, Shahid M & Svensson TH: Asenapine elevates cortical dopamine, noradrenaline and serotonin release. Evidence for activation of cortical and subcortical dopamine systems by different mechanisms. *Psychopharmacology* 2009; 204:251-264
25. Franza F: Risk and efficacy in cognitive functions in Bipolar Disorder II with atypical antipsychotic augmentation. *Psychiatr Danub* 2016; 28:13-17
26. Gerrits MG, de Greef R, Dogterom P & Peeters PA: Valproate reduces the glucuronidation of asenapine without affecting asenapine plasma concentrations. *Journal of clinical pharmacology* 2012; 52:757-765
27. Grande I, Hidalgo-Mazzei D, Nieto E, Mur M, Saez C, Forcada I & Vieta E: Asenapine prescribing patterns in the treatment of manic in- and outpatients: Results from the MANACOR study. *European psychiatry: the journal of the Association of European Psychiatrists* 2015; 30:528-534
28. Grossini E, Gramaglia C, Farruggio S, Bellofatto K, Anchisi C, Mary D, Vacca G & Zeppugno P: Asenapine increases nitric oxide release and protects porcine coronary artery endothelial cells against peroxidation. *Vascular pharmacology* 2014; 60:127-141
29. Hay A, Byers A, Sereno M, Basra MK & Dutta S: Asenapine versus placebo for schizophrenia. *The Cochrane database of systematic reviews* 2015; (11):CD011458. doi: CD011458
30. Henry J & Fuller M: Asenapine: a new antipsychotic option. *Journal of Pharmacy Practice* 2011; 24:447-451
31. Jardemark K, Marcus MM, Shahid M & Svensson TH: Effects of asenapine on prefrontal N-methyl-D-aspartate receptor-mediated transmission: involvement of dopamine D1 receptors. *Synapse (New York, NY)* 2010; 64:870-874
32. Kane JM, Cohen M, Zhao J, Alphs L & Panagides J: Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *Journal of clinical psychopharmacology* 2010; 30:106-115
33. Kane JM, Mackle M, Snow-Adami L, Zhao J, Szegedi A & Panagides J: A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *The Journal of clinical psychiatry* 2011; 72:349-355
34. Landbloom R, Mackle M, Wu X, Kelly L, Snow-Adami L, McIntyre RS, Mathews M & Hundt C: Asenapine for the treatment of adults with an acute exacerbation of schizophrenia: results from a randomized, double-blind, fixed-dose, placebo-controlled trial with olanzapine as an active control. *CNS spectrums* 2017; 22:333-341
35. Lu D, Xie Q & Wu B: N-glucuronidation catalyzed by UGT1A4 and UGT2B10 in human liver microsomes: Assay optimization and substrate identification. *Journal of pharmaceutical and biomedical analysis* 2017; 145:692-703
36. Maina G & Ripellino C: The risk of metabolic disorders in patients treated with asenapine or olanzapine: a study conducted on real-world data in Italy and Spain. *Expert opinion on drug safety* 2014; 13:1149-1154
37. Majercikova Z, Horvathova L, Osacka J, Pecenek J & Kiss A: Impact of repeated asenapine treatment on FosB/DeltaFosB expression in the forebrain structures under normal conditions and mild stress preconditioning in the rat. *Brain research bulletin* 2016; 127:29-37
38. Managuli RS, Gourishetti K, Shenoy RR, Koteswara KB, Reddy MS & Mutalik S: Preclinical pharmacokinetics and biodistribution studies of asenapine maleate using novel and sensitive RP-HPLC method. *Bioanalysis* 2017; 9: 1037-1047
39. Martin-Blanco A, Patrizi B, Villalta L, Gasol X, Soler J, Gasol M & Pascual JC: Asenapine in the treatment of borderline personality disorder: an atypical antipsychotic alternative. *International clinical psychopharmacology* 2014; 29:120-123
40. Masters KJ: Allergic reactions and sudden death with asenapine. *The Journal of clinical psychiatry* 2012; 73:720; author reply 720-1
41. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA & Panagides J: Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *Journal of affective disorders* 2010; 122:27-38
42. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA & Panagides J: Asenapine versus olanzapine in acute mania: a double-blind extension study. *Bipolar disorders* 2009; 11:815-826
43. Michalak EE, Guiraud-Diawara A & Sapin C: Asenapine treatment and health-related quality of life in patients experiencing bipolar I disorder with mixed episodes: post-hoc analyses of pivotal trials. *Current medical research and opinion* 2014; 30: 711-718

44. Oosterhof CA, El Mansari M & Blier P: Asenapine alters the activity of monoaminergic systems following its sub-acute and long-term administration: an in vivo electrophysiological characterization. *European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology* 2015; 25:531-543
45. Osacka J, Horvathova L, Majercikova Z & Kiss A: Effect of a single asenapine treatment on Fos expression in the brain catecholamine-synthesizing neurons: impact of a chronic mild stress preconditioning. *Endocrine regulations* 2017; 51:73-83
46. Ostinelli EG, Cavallotti S, Castelnovo A, Guanella E, Gambini O & D'Agostino A: Asenapine in the Treatment of Acute Mania: A Real-World Observational Study With 6 Months Follow-Up. *Journal of clinical psychopharmacology* 2015; 35:553-558
47. Panteleeva GP, Oleichik IV, Novozhenova TE & Sokolov AV: Clinical experience and perspectives of using asenapine in stopping acute endogenous psychosis. *Zhurnal nevrologii i psikiatrii imeni S.S.Korsakova* 2015; 115:21-29
48. Pilkinton P, Berry C, Norrholm S, Bartolucci A, Birur B & Davis LL: An Open Label Pilot Study of Adjunctive Asenapine for the Treatment of Posttraumatic Stress Disorder. *Psychopharmacology bulletin* 2016; 46:8-17
49. Potkin SG, Cohen M & Panagides J: Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *The Journal of clinical psychiatry* 2007; 68:1492-1500
50. Potkin SG, Phiri P, Szegedi A, Zhao J, Alphs L & Cazorla P: Long-term effects of asenapine or olanzapine in patients with persistent negative symptoms of schizophrenia: a pooled analysis. *Schizophrenia research* 2013; 150:442-449
51. Pratts M, Citrome L, Grant W, Leso L & Opler LA: A single-dose, randomized, double-blind, placebo-controlled trial of sublingual asenapine for acute agitation. *Acta Psychiatrica Scandinavica* 2014; 130:61-68
52. Room P, Tielemans AJ, De Boer T, Van Delft AM & Tonnaer JA: The effect of the potential antipsychotic ORG 5222 on local cerebral glucose utilization in freely moving rats. *European journal of pharmacology* 1991; 205:233-240
53. Sajatovic M, Dines P, Fuentes-Casiano E, Athey M, Cassidy KA, Sams J, Clegg K, Locala J, Stagno S & Tatsuoka C: Asenapine in the treatment of older adults with bipolar disorder. *International journal of geriatric psychiatry* 2015; 30:710-719
54. Samalin L, Charpeaud T & Llorca PM: Asenapine in bipolar I disorder: evidence and place in patient management. *Therapeutic advances in chronic disease* 2013; 4:5-14
55. Suppes T, Eberhard J, Lemming O, Young AH & McIntyre RS: Anxiety, irritability, and agitation as indicators of bipolar mania with depressive symptoms: a post hoc analysis of two clinical trials. *International journal of bipolar disorders* 2017; 5:36-017-0103-7
56. Szegedi A, Calabrese JR, Stet L, Mackle M, Zhao J, Panagides J & Apollo Study Group: Asenapine as adjunctive treatment for acute mania associated with bipolar disorder: results of a 12-week core study and 40-week extension. *Journal of clinical psychopharmacology* 2012; 32:46-55
57. Szegedi A, Durgam S, Mackle M, Yu SY, Wu X, Mathews M & Landbloom RP: Randomized, Double-Blind, Placebo-Controlled Trial of Asenapine Maintenance Therapy in Adults With an Acute Manic or Mixed Episode Associated With Bipolar I Disorder. *The American Journal of Psychiatry* 2017; appiajp201716040419
58. Szegedi A, Zhao J & McIntyre RS: Early improvement as a predictor of acute treatment outcome in manic or mixed episodes in bipolar-I disorder: a pooled, post hoc analysis from the asenapine development program. *Journal of affective disorders* 2013; 150:745-752
59. Tarazi FI & Neill JC: The preclinical profile of asenapine: clinical relevance for the treatment of schizophrenia and bipolar mania. *Expert opinion on drug discovery* 2013; 8:93-103
60. Tarazi FI & Stahl SM: Iloperidone, asenapine and lurasidone: a primer on their current status. *Expert opinion on pharmacotherapy* 2012; 13: 1911-1922
61. van de Wetering-Krebbbers SF, Jacobs PL, Kemperman GJ, Spaans E, Peeters PA, Delbressine LP & van Iersel ML: Metabolism and excretion of asenapine in healthy male subjects. *Drug metabolism and disposition: the biological fate of chemicals* 2011; 39:580-590
62. Vieta E & Montes JM: A Review of Asenapine in the Treatment of Bipolar Disorder. *Clinical drug investigation* 2018; 38:87-99
63. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, O'Donovan C, Macqueen G, McIntyre RS, Sharma V, Ravindran A, Young LT, Milev R, Bond DJ, Frey BN, Goldstein BI, Lafer B, Birmaher B, Ha K, Nolen WA & Berk M: Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar disorders* 2013; 15:1-44

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