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ASENAPINE: PHARMACOLOGICAL ASPECTS AND ROLE IN PSYCHIATRIC DISORDERS

Ayman Antoun Reyad[1] & Raafat Mishriky[2]

[1]*School of Pharmacy, University of Wolverhampton, Wolverhampton, UK*

[2]*Old Age Psychiatry, Birmingham and Solihull Mental Health NHS Foundation Trust, Birmingham, UK*

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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-Krebbers 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 Cmax 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 (Szegedi 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 (Szegedi 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/delusive and mania/delusive states, positive effect (≥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 ≥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 (Szegedi et al. 2012), with incidence for anxiety (~10%) and insomnia (~10%) (Kane et al. 2011). ≥7% weight increase was prevalent - NNH=17 (De Hert et al. 2012). Oral Hypothesia 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 (Szegedi 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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Contribution of individual authors:

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

Raafat Mishriky: study design, first draft, approval of the final version.

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Correspondence:

Ayman Antoun Reyad, MD
School of Pharmacy, University of Wolverhampton
WV1 1LY, Wolverhampton, UK
E-mail: a.antounreyad@wlv.ac.uk