Clinical Case Reports

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CASE REPORT

Asenapine augmentation in bipolar disorders: a case series

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Funding Information
No sources of funding were declared for this study.

Received: 9 December 2015; Revised: 1 February 2016; Accepted: 6 February 2016

Clinical Case Reports **2016; 4(5): 499–504**

doi: 10.1002/ccr3.526

Key Clinical Message

Asenapine, a novel second-generation antipsychotic is effective in acute treatment of bipolar I disorder patients in combination with mood stabilizers even in resistant cases. Although there is no evidence for asenapine's efficacy to be superior to currently available agents, asenapine's favorable weight and metabolic profile are of clinical interest.

Keywords

Antipsychotics, asenapine, bipolar disorders, second-generation antipsychotics.

Introduction

Over the years, both first- (FGAs) and second-generation antipsychotics (SGAs) continue to gain increasing evidence of being effective in the treatment of psychotic symptoms. Currently, they represent the first-line treatment of schizophrenia and bipolar disorder (BD), although they are widely used in psychotic depression and other clinical conditions, such as agitation and/or behavioral disturbances. Despite representing an indispensable tool for the treatment of severe psychotic disorders, SGAs are widely known to provoke a number of unwanted side effects that the clinician must be aware of, and handle carefully to provide the patient the best available treatment in the short- and long-term regimen. However, even with respect to the long-term use of some of the most effective SGAs, it is imperative for clinicians not to overlook the risk linked to the onset of potentially severe metabolic side effects such as weight gain, dyslipidemia, insulin resistance, and type-II diabetes.

Asenapine is one of the latest SGAs introduced in the clinical practice with a peculiar receptor profile. Its chemical structure is somewhat related to that of mirtazapine, while sharing with this antidepressant some pharmacological properties, in particular serotonin (5-HT) receptors of type 2A (5-HT2A), 5-HT2C, H1, and α2 receptor antagonism. However, its mechanism of action is more complex especially with reference to dopamine receptors of type 2 (D2) antagonism, and interaction with several other 5-HT receptor subtypes (5-HT7, 5-HT6, 5-HT5, 5-HT2B, 5-HT1D, 5-HT1A, 5-HT1E, 5-HT1B, 5-HT3) [1, 2]. Furthermore, it shows antagonism at the levels α1, D3, D4, D1, and H2 receptor, and no appreciable antimuscarinic activity [3]. These unique properties may explain the increasing focus of research toward the use of this drug in other conditions, other than schizophrenia and acute mania for which it was initially licensed, in particular mixed states.

Asenapine is subjected to a high hepatic first-pass metabolism, so that its bioavailability after oral administration is equal to 2%. Therefore, asenapine must be administered sublingually, with an increase in bioavailability of 35% [4, 5]. The time of the peak serum concentration (Tmax) of asenapine is 0.75 h, with a half-life of approximately 24 h [6]. The hepatic metabolism of this drug involves the activation of cytocrome P450 through the CYP1A2 and, partially, CYP2D6 isoforms. The activation of the enzyme UGT1A4 b-glucuronidase enables its direct elimination in the urines.

In Europe, asenapine can be prescribed for the treatment of moderate or severe manic episodes associated with BD of type I (BDI) in adults [7]. In the USA,

asenapine is registered for the treatment of acute and long-term schizophrenia in adults and for the acute treatment of manic or mixed episodes associated with BDI [8]. This was based on the results of several randomized controlled studies supporting its efficacy and good tolerability in both short- and long-term use in schizophrenic and BD patients in monotherapy [6, 7, 9–26] and in BD-mixed episode [27–29]. The recommended dose of asenapine in monotherapy is 10 mg twice a day that can be reduced to 5 mg twice a day depending on the patient's response. If asenapine is used in combination with another drug to treat manic episodes, the dose should be 5 mg twice a day, which can be increased if necessary to 10 mg twice a day [17].

However, it is common in the clinical practice that BD patients with a manic or mixed episode, besides antipsychotics, require coadministration of different drugs, in particular mood stabilizers. It is, thus, of great importance then to assess efficacy and tolerability of an effective "anti-manic" SGA. Actually, during the registration phase, the efficacy and tolerability of asenapine was evaluated in both monotherapy and in association with another mood stabilizer, such as lithium or valproate, a rather common scenario in the clinical practice, in order to verify its safety in the long-term use [25]. In any case, the information on this topic is still limited to [18, 29–33] that, however, would indicate adjunctive asenapine in BD is effective and safe [30].

Therefore, given the paucity of available information, the aim of this study was to present some case reports of BD patients treated acutely with asenapine as add-on treatment, and followed up for 2 years.

Case report # 1

The patient was a 30-year-old philosopher, single, with hyperthymic temperament, positive family history for BD (mother), use of cannabinoids (THC), and alcohol since the adolescence for recreational purposes.

The first psychopathological symptoms date back to October 2003 when, after an intense period of THC use, he showed increased energy, ideative acceleration associated with persecution and control delusions, so that he decided to leave his house and go abroad. He was stopped at the railway station by his family and was admitted to a first aid unit where he was given olanzapine and lorazepam that provoked symptoms' disappearance. However, in 2006, with no apparent reason, the patient progressively began to develop mood elation, ideative acceleration, psychomotor restlessness and insomnia, so that he had to be admitted to a psychiatric ward where he was treated with a combination of antipsychotics (haloperidol and chlorpromazine) and mood stabilizers (lithium salts). 1 year later (June 2007), he relapsed again, with no insight, so that he had a mandatory hospitalization. At the discharge, his treatment consisted of lithium, haloperidol, olanzapine, alprazolam, and anticholinergic drugs. Afterward, he consulted regularly a local psychiatric service, but had two hospital admissions in the next 2 years. Subsequently, he maintained an overall euthymic level, but complained of different side effects, such as weight gain, mood lowering, and artistic vein blunting, so that he decided to stop abruptly the treatment. In a few days, he showed a relapse, with mood elation, alteration of the thought contents with grandiosity ideation, and partial insight, treated with chlorpromazine IV. As he refused to take oral FGAs, he decided to consult us. At the first visit, he was still agitated with a partial insight and moderate grandiosity thoughts. He accepted the proposed treatment with valproate starting from 500 mg/die up to 1500/die, and asenapine, starting from 10 mg/die up to 20 mg/die. After 2 weeks, the patient showed a significant improvement of symptom that disappeared in 1 month (CGI-S score at baseline: 6,: and CGI-I score-after 1 month: 1). In the next 2 years, the patient remained euthymic and could won a doctorate fellowship. In addition, he started a love relationship still ongoing and could engage regularly in different sport activities, so that he resumed the original body weight. No extrapyramidal symptom, no significant side effect, and no alteration of blood and urine tests or EEG were observed during the long follow-up.

Case report # 2

The patient # 1 was a 30-year-old lawyer, married with two children. She had a positive family history for psychiatric disorders, with her father suffering from OCD and alcohol abuse and her mother from BD2. She had no personality disorder, nor suffered from any medical disease. Her familial, social ad work adjustment was good until her marriage with an older colleague who, as she discovered after the nubs, was alcoholic. She became very unhappy when she noted her husband's problem, but nevertheless she decided that she had to save him. Therefore, they decided together to have children as soon as possible. The first child (a boy) was born 1 year after the marriage and the second (a girl) the next year and a half from the first delivery. The first symptoms (intense agitation sleeplessness and mood elation) started abruptly during the second postpartum period. She was convinced that their babies were extraordinary with the special mission to save the world. Moreover, she had become extremely upset and nervous when somebody entered the babies' rooms and interfered with her nursing rituals that she had to start over and over again since the beginning

according to severe and rigid rules. As the symptoms progressively worsened, her physician diagnosed a postpartum mood change and prescribed her benzodiazepines and haloperidol that were ineffective, so that, after 2 weeks, patient consulted us. On that occasion, she showed a moderate agitation and a meager insight, was still convinced that her babies were "genial", and complained of stiffness and sedation (CGI-S score at baseline: 6). Therefore, we prescribed her valproate (up to 1000 mg/die in a week) and sublingual asenapine (5 mg bid the first week and then 10 bid). After 3 days of this regimen, the patient showed a normal sleep pattern, without sedation and, 1 month later, the mood had returned to normal level and grandiosity ideation had totally disappeared (CGI-I score after 1 month: 1). After 6 months, asenapine was reduced to 5 mg bid, as the patients was in good psychopathological conditions, with no relevant mood shift, nor significant side effect.

Case report # 3

The patient # 3 was a 40-year-old single woman working as high-school teacher. She had a cyclothymic temperament and obsessive and anxiety-like personality traits. The family history was positive (mother suffering and institutionalized for BD I). The former psychopathological disorders seem to date back to about 15 years ago when, after the breakup of a relationship, she began to suffer from mood lowering, asthenia, decreased appetite, restlessness and anxiety, negative thoughts, and low self-esteem, so that she had to be admitted to a psychiatry unit, where she remained 1 month, with symptom remission. The treatment was continued for about 6 months. However, subsequently, she started to suffer from periodical seasonal mood lowering (especially late summer and fall). In 2009, after the worsening of her mother's psychopathological conditions, she had another depressive episode that required hospitalization. After being discharged, she showed a satisfactory balance until the summer 2013, when she showed mood elation, energy increase, thought acceleration, irritability, and involvement into useless activities, excessive shopping. This condition, that she neglected and considered normal, lasted about 4 months and was followed by a severe depressive episode associated with guilt feelings, worthlessness, apathy, social withdrawal. For this reason, the patient was visited by us and admitted to the psychiatric ward where she recovered in 2 weeks. She was diagnosed as suffering from BD1, a diagnosis that she refused as she refused to take the prescribed lithium salts. Therefore, after a few months, she showed another manic episode characterized by agitation, involvement in dangerous activities, sleeplessness, increased energy, excessive and useless shopping, driving irrespective of the rules, impairment of work, refusal of any limits and advices, hypersexuality. She had just a partial insight and refused to be hospitalized or to take drugs that could provoke severe side effects. Therefore, we convinced her to take at least a drug such as asenapine 5 mg bid that could target both the symptoms and act as a mood stabilizer (CGI-S score at baseline: 5). She accepted and started the treatment that she is still continuing, now associated with lithium salts, with no side effect. Such a treatment increased significantly her compliance to the point that she is still following the therapeutic regimen after 18 months, without showing any relapse (CGI-I score after 2 months: 2).

Case report # 4

The patient was a 45-year-old manager, single, with a cyclothymic temperament. His first psychopatological symptoms occurred at 17 years of age, when, after a significant weight gain, he was obsessed by the weight and began to implement daily purging behaviors that led to a 12 Kg weight loss in the next 2 months. Such symptoms seemed to resolve spontaneously within a year. By the age of 20, when he was attending the University, he began to progressively develop alcohol-abuse behavior for recreational and anxiolytic purposes. In 2012, after stressful life events (job loss and brother's death) the alcohol-abuse behavior worsened and became a real addiction. Furthermore, he showed grandiosity ideations that caused the admission to a psychiatric hospital, where he was treated with gabapentin, clonazepam, sodium oxibate, and hypnotics. He maintained good psychopathological conditions for about 1 year, when, after the end of a love relationship, he had a mixed episode, with persecutory delusions that led to a significant impairment of social and occupational functioning and, finally, to an overall decline. Moreover, during an alcohol-intoxication state, the patient attempted suicide while jumping from the first floor of his house. He reported just one mild fracture of the right foot and was hospitalized again in a psychiatric hospital where he was treated with valproic acid (1500 mg/day) and olanzapine (10 mg/day). However, during the following months, the patient showed a series of depressive episodes and weight gain so that he stopped the treatment. In May 2014, he suffered from another mixed episode, with a worsening of the alcohol abuse that led to a severe car accident. For these reasons, he was admitted again to a psychiatric hospital (CGI-S score at admittance: 7), and treated with valproate (1000 mg/day), disulfiram (200 mg/day), diazepam and asenapine (20 mg/die), with a rapid mild improvement of symptoms in the first days that became more evident in the next 3 week (CGI-I 2). After 3 months, the patient's

treatment was limited to valproate and asenapine that he is still continuing after 18 months. He had no significant side effect, except hypotension in the first month that disappeared subsequently.

Discussion

The case reports described herein support the efficacy and tolerability of asenapine given as add-on treatment in severe BD patients.

Our observations, although collected in a small sample size and with an open design, may be considered in agreement with the available literature on general clinical efficacy and tolerability of asenapine in patients with BD and schizophrenia. Furthermore, it represents an original contribution for its possible role as augmentation agent. Indeed, the information on this use of asenapine is quite limited. A first 12 weeks randomized controlled double-blind trial investigated its adjunctive administration, at flexible doses of 5 or 10 mg, to an ongoing open-label lithium or valproate treatment. Patients randomized to asenapine were 159 and 167 to placebo, 116 completed the study with similar proportion for asenapine (38%) and placebo (33%). Asenapine resulted to be significantly superior to placebo with respect of total reduction in YMRS score at week 3. Rates of response and remission for asenapine and placebo were, respectively, 47.7% versus 34.4% and 43.2% versus 30.1%. Those patients who completed the 12 weeks study were offered to enter into a 40-weeks extension aimed to evaluate the long-term safety and tolerability of asenapine (total duration of asenapine implementation: 52 weeks). Of the initial 77 patients enrolled, only 34 subjects completed the 52 weeks study. Given that only a small number of patients entered the extension, it was difficult to draw clear statistical conclusions, however, the tolerability seemed to be good. Overall, the authors note that adjunctive asenapine to lithium or valproate was more effective than mood stabilizer monotherapy in the core study and was well tolerated for up to 52 weeks [23]. A recent comprehensive review and case series on the rationale of implementing asenapine as an adjunctive treatment for BD also support the evidence that this might be a viable option [30]. In this study, the authors focus toward the use of this drug as adjunctive treatment in manic/mixed episodes including the case reports of four BD women treated with add-on asenapine. Despite the need of additional data on this topic, it is underlined that the available evidence supports the efficacy and safety of adjunctive asenapine in BD [30]. Two more case reports were recently published. The first paper described a treatment-resistant manic patient with comorbid cannabis addiction. After an initial treatment based on mood stabilizers associated to FGAs and SGAs (levomepromazine and olanzapine), asenapine was introduced as add-on treatment to valproic acid. About 6 weeks later, a symptomatic remission was observed with a significant improvement in psychomotor agitation and irritability with no relevant side effects [34]. The second paper reported the case of a catatonic manic episode, in which asenapine (10 mg/day) was introduced as augmentation of clozapine (800 mg/day) with a successful improvement in mood, sleep, impulsivity, psychomotor agitation, and speech during the following 10 days and without any significant side effects [34].

Conclusion

Our observations showed that asenapine is effective in BD patients who do not respond, do not tolerate, or do not want to take other antipsychotics. In addition, the sublingual route of administration of this compound, that is mandatory for achieving its sufficient bioavailability, with no doubt fastens the therapeutic response, while suggesting that asenapine could be used as a rapid oral acting "as needed" in those manic or agitated patients that sometimes refuse an injection. This finding is an agreement with those reported by a recent double-blind, placebo-controlled trial showing that sublingual asenapine provoked a significantly greater improvement of patients with acute agitation, that was comparable to that of intramuscular antipsychotics [35]. Although one possible side effect of sublingual administration is oral hypoesthesia, which may reduce the compliance, none of our patients reported this symptom. In addition, compared to other SGAs, asenapine resulted to be well tolerated, with negligible side effects. Only one patient complained of hypotension and one by mild sedation at the beginning of the treatment that disappeared after 1 month. However, we cannot rule out that some of the reported side effects might be due to concomitant medications.

Taken together, available data BD would support the use of asenapine as a first-line option for acute mania and mixed scenarios. Our case reports would add indications for the potential use asenapine as a second-line alternative for refractory cases. Given the stability of our patients after 2 years of follow-up, asenapine seems to be particularly useful also in relapse prevention. Although there is no evidence for asenapine's efficacy to be superior to currently available agents, asenapine's favorable weight and metabolic profile are of clinical interest. A caveat is that the data reviewed regarding asenapine are from its manufacturer. No independent studies of asenapine's efficacy or safety are available.

Therefore, further double-blind studies are needed to assess the possible usefulness of asenapine as

augmentation strategy in BD, as well as to investigate the tolerability and safety of the different associations.

Consent

Written information consent was obtained from the patients for publication of these case reports. A copy of the written consent is available for review by the Editor of this journal on request. Permission to publish these cases was also given by the Ethics Committee of Pisa University.

Acknowledgment

None.

Conflict of Interest

None declared.

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