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Case Series

Sublingual asenapine for agitation in malabsorptive states: three patient cases

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***Abstract*:** Gastric malabsorptive conditions may prevent patients from deriving benefit from orally administered medications intended for enteric absorption. While malabsorption is an increasingly common issue, current data on alternative oral options for agitation in these patients are very sparse. Sublingual (SL) asenapine is absorbed transmucosally, bypassing gut absorption, making it a viable consideration. We report on three patients, one with short bowel syndrome, one with viral gastritis, and one with aortic dissection who were trialed on SL asenapine for agitation after failing alternative antipsychotics. Two of these patients had an extensive history of psychiatric admissions for bipolar disorder and substance-induced psychosis. All three patients had significant reductions in agitation within 1–5 days, with no reported adverse effects. However, benefit of SL asenapine was hindered in two of these patients as they began inappropriately swallowing the medication, reducing bioavailability to nil. Clinicians should consider the use of SL asenapine for medically complex agitated patients where gastric absorption is questionable. There is an urgent need for guidelines on this matter, as well as more, alternative dosage forms for various medications that may help with agitation in this population.

Keywords: asenapine, agitation, case report, gastric bypass, malabsorption

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Introduction

Oral medications intended for systemic action in the body must first be enterally absorbed, typically by the small intestine. In patients with congenital or acquired gut malformations, absorption of both nutrients and medications may be limited, depending on the site of typical absorption and the extent of impairment. Congenital impaired states may include Crohn's disease or celiac disease while acquired malabsorptive states may include bariatric surgery, necrotizing enterocolitis (NEC), or trauma-related incidents and shock which may shunt blood away from intestines.[1] Furthermore, intestinal atrophy, dysmotility, and gastric pH alterations can affect medication absorption in critically ill patients.[2] In either congenital or acquired states, the patient may suffer from short bowel syndrome (SBS), sometimes known as 'short gut', which is the most common cause of gastrointestinal dysfunction worldwide in both adults and children.[3] Additional causes of impaired absorption of medications include excessive vomiting, anorexia nervosa, laxative abuse, or gastroparesis. Thus, the use of alternative administration routes such as intravenous (IV) are necessary for adequate efficacy in patients with absorption compromise.

Sublingually (SL) administered medications are placed under the tongue, wherein the drug is absorbed into systemic circulation through the mucosal membrane lining. SL medications rapidly disintegrate and are rapidly absorbed into systemic circulation transmucosally, bypassing the gut as well as first-pass metabolism. This property makes SL formulations ideal for situations in which fast onset is desired, or when intestinal absorption is questionable. It is worth noting that some medications must be formulated as SL, secondary to poor enteral bioavailability.[4] In addition, clinicians should be aware of the inherent differences in orally disintegrating tablets

(ODT) and SL, which are significant. While some studies have shown absorption of specific ODTs given sublingually, in general, the dissolution contents from ODT formulations must still be swallowed for adequate absorption, and SL tablets or films should not be swallowed.[5,6]

Asenapine is a second-generation antipsychotic displaying efficacy from its' potent antagonism of many serotonin and dopamine receptors. It is labeled for use in schizophrenia and bipolar disorder for treatment of acute mania in adult patients. Off-label, asenapine is used for acute agitation secondary to psychiatric and organic etiologies. Asenapine has two separate formulations, SL tablets (US brand name Saphris®) and a 24-h transdermal patch (US brand name Secuado®). SL asenapine has very poor bioavailability when swallowed (<2%), but 35% bioavailability when administered sublingually.[6] SL asenapine has a fast peak, occurring within 30 min–1.5 h, with noted efficacy for acute agitation within 15 min.[6] As expected, secondary to potent histamine-1 receptor antagonism, asenapine has a high rate of somnolence which is on-par with olanzapine, but less than quetiapine.[6,7] In comparison to other oral antipsychotics, both first and second generation, a 2019 meta-analysis by Huhn *et al.* found asenapine has a moderate risk of weight gain, akathisia, QTc prolongation, and prolactin elevation, but lower risk of Parkinsonian and anticholinergic side effects.[7]

In this article, we report on three patients seen by our consult-liaison psychiatry team, one with SBS, one with viral gastritis, and one with aortic dissection, who, after failing alternative antipsychotics, responded well to SL asenapine for acute agitation. The aim of this article is to showcase asenapine as a viable option for acute agitation, especially in these niche malabsorptive states where only minimal data exist.

Case presentation 1

Patient A is a 32-year-old African American male admitted to inpatient medicine due to abdominal pain and distension and electrolyte abnormalities. He reported watery stools five times per day with a weight loss of approximately 7% over the past month. He has a medical history of heart failure with reduced ejection fraction and SBS from a bowel resection due to NEC, and a psychiatric history of substance use disorder. His inpatient stay was complicated by Ogilvie's syndrome and nutritional deficiencies with recurrent psychosis possibly secondary to these insufficiencies. He reported using marijuana and methamphetamine and felt that he was not in need of a psychiatric consultation. His psychosis was thought to be secondary to substance abuse, but metabolic deficiencies like hyponatremia, severe hypomagnesemia, and hypovitaminosis D, and possible Wernicke-Korsakoff from low thiamine levels may have been contributing.[8,9] An 8-year history of antipsychotic use was noted, including risperidone, ziprasidone, divalproex, carbamazepine, paliperidone, chlorpromazine, olanzapine, and haloperidol, though the patient remarked having not taken any of these prior to admission. The patient's lack of insight into his medical and psychiatric conditions made adherence difficult, previously necessitating the use of the long-acting injectable antipsychotics fluphenazine decanoate and paliperidone palmitate. Cognitive examinations on the patient demonstrated significant impairment. Aggressive IV nutritional replacement of magnesium, potassium, zinc, thiamine, and B12 was necessary over several weeks due to his malabsorptive state. Repletion of electrolytes and nutritional needs were difficult due to his delusions of health and oppositional agitation.

Initially, patient A was given a trial of olanzapine 5 mg ODT thrice daily, but he frequently was nonadherent, necessitating treatment with olanzapine 5 mg intramuscular (IM) injection when his behaviors interfered with life-saving care. Due to ongoing symptoms of psychosis and agitation, he was switched to risperidone ODT at steadily increasing doses for around 2 weeks, until he was eventually taking a total daily dose of 8 mg, along with as needed doses of IM olanzapine for intermittent refusal. Given persistent agitation, there was concern for inadequate absorption of orally administered medications. The patient was switched to SL asenapine 5 mg nightly, and risperidone was stopped. Within a day the patient began requiring fewer as-needed medications for agitation, and became more cooperative with care. Increasing the dose of asenapine to 5 mg twice daily further benefited the patient with noted calmness, politeness, and organization. Unfortunately, as the patient was transferred to inpatient psychiatry, his alliance with the treatment team withered, and he began swallowing asenapine rather than keeping it under his tongue. An order-to-treat was ultimately obtained from the probate court allowing short-acting fluphenazine IM to be administered if the patient refused

oral fluphenazine 10 mg twice daily, which was of some benefit, though the patient required periodic as-needed medications for agitation. The patient continued to receive vitamin and electrolyte repletion and was subsequently discharged from the hospital on fluphenazine decanoate 25 mg intramuscularly administered every 3 weeks. He has continued to do well on this medication 1 year post-discharge.

Case presentation 2

Patient B is a 39-year-old Caucasian female with long-standing history of bipolar I disorder complicated by substance use disorder who presented to the emergency department for acute psychosis. She has a medical history of chronic bilateral osteomyelitis of her feet, pulmonary embolisms, HIV, and had recently eloped from the hospital following a lengthy stay for inpatient management of sepsis and *Clostridium difficile* infection. On readmission to the inpatient medicine service, she was restarted on her previously stabilized psychotropic medications, including lithium 1200 mg nightly and olanzapine 30 mg total per day.

However, the patient continued to display marked agitation, nonsensical and rapid speech, bizarre behaviors, and internal stimuli response concerning for mania with psychotic features. While oral chlorpromazine 50 mg twice daily was added to assist with agitated behaviors, the patient continued to require additional, as-needed medications for agitation. During this time, she began having self-reported diarrhea, as well as vomiting. Although nursing staff thought her vomiting was volitional, it appears that she had a viral gastroenteritis, supported by slight elevation in white blood cell count. To ensure her vomiting was not secondary to lithium toxicity, a serum level was obtained which was grossly subtherapeutic at 0.36 mMol/L, down from 0.86 mMol/L 5 days prior. In efforts to mitigate 'cheeking' and self-induced vomiting after medication use, the patient's chlorpromazine was discontinued and SL asenapine 10 mg nightly was initiated. Within a period of 3 days, the patient self-reported she was 'more sound of mind and body', and within 5 days was noted to have appropriate conversations, and did not require anymore as-needed medications for agitation. Within 2 weeks, the patient appeared to be at baseline. While an attempt was made to taper off of olanzapine completely, and maximize SL asenapine dosing, the patient appeared to revert back to a state of disorganization and mania. It was discovered that the nursing staff were erroneously allowing her to swallow the asenapine rather than insisting on sublingual administration. Due to continued inconsistencies in the asenapine dosing strategy and a resolution of vomiting, the decision was made to transition back to chlorpromazine and discontinue olanzapine. This patient has remained hospitalized for more than a year due to complex psychosocial factors, but is stable on chlorpromazine and lithium.

Case presentation 3

Patient C is a 33-year-old African American male with no history of psychiatric afflictions who was playing his favorite video game when he was abruptly interrupted by severe massive chest and back pain; he was brought by ambulance to the acute bay of the emergency room where an aortic dissection type A was discovered. He was immediately taken to the operating room for repair, but there was significant injury to the blood supply to lower extremities, gut, and kidneys. After several days of supportive care, his lower extremities had to be amputated due to insufficient arterial supply, and he was placed on continuous renal replacement therapy due to renal failure. The patient became malnourished as indicated by a downward trending prealbumin (nadir level 3.9 mg/dL) necessitating Dobhoff tube placement with tube-feeding. Any attempts to wean patient from IV sedation became impossible due to agitation and noncompliance with all support lines and systems. He was extremely delirious, unable to appreciate any aspect of his surroundings or caregivers. Agitation management with olanzapine injection and midazolam was unsuccessful, and the patient continued persistently hallucinating and confabulating. Oral administration of any medications was not possible due to his medical conditions resulting in malabsorption, and hepatic impairment was a relative contraindication for the use of valproic acid. He was then started on SL asenapine 5 mg daily, and titrated after 3 days to 5 mg twice daily, with resolution of his agitation, allowing for more stable care and transfer out of the intensive care unit setting. As he began to recover, asenapine was weaned back to 5 mg once daily, resulting in some recurrence of his irritability and agitation. The patient required extensive repeat surgeries and ultimately succumbed to his advancing ischemic disease.

Table 1. Summary of sublingual asenapine use for depicted patients.

Patient	Reason for gastric malabsorption	History of psychiatric illness	Oral medications trialed for agitation (prior to SL asenapine)	Effective dose of SL asenapine used	Time to noted benefit of SL asenapine
Mr. A	SBS secondary to NEC	Yes	Olanzapine ODT Risperidone ODT	5 mg twice daily	1 day
Ms. B	Viral gastritis/ vomiting	Yes	Olanzapine tablet Chlorpromazine tablet	5 mg every morning plus 10 mg every evening	3 days
Mr. C	Aortic dissection with end-organ failure	No	Olanzapine tablet	5 mg twice daily	3–5 days

IM, intramuscular; IV, intravenous; mg, milligrams; NEC, necrotizing enterocolitis; ODT, orally disintegrating tablet; SBS, short bowel syndrome; SL, sublingual.

Discussion

All three patients had significant response to SL asenapine, which was uniquely selected out of a concern for gut absorption or difficulty with route of delivery (summarized in Table 1). Response was rapid and was seen not only through a reduction of subjective agitation, but also objectively seen through a reduction in as-needed medication use. However, for patients A and B, it should be noted that the use of SL asenapine was limited by inconsistencies in actual sublingual administration. It is quite possible that the necessity to switch from SL asenapine to an alternative agent was secondary to the patient swallowing the tablet, reducing the bioavailability to nil.

Overall, asenapine has fair data to support use in agitation, with a 2017 study of three randomized, double-blind, placebo-controlled, phase III trials finding superior efficacy of SL asenapine over placebo for reducing hostility and agitation in bipolar I disorder.[10] A more recent study using the transdermal asenapine patch also found benefit *versus* placebo, when using the positive and negative syndrome scale hostility item and excited component (PANSS-EC).[11] The World Federation of Societies of Biological Psychiatry (WFSBP) 2009 guidelines for treatment of acute mania show SL asenapine as a category A/grade 2 recommendation, while the 2018 Canadian Network for Mood and Anxiety Treatment (CANMAT) guidelines recommend SL asenapine as second-line agent for agitation, behind intramuscular (IM) aripiprazole, IM lorazepam, inhaled loxapine, and IM olanzapine, but ahead of oral haloperidol, oral quetiapine, and oral risperidone.[12] Furthermore, asenapine has level 1 evidence to support efficacy in acute mania in CANMAT guidelines.[12] Similar benefits can be seen with asenapine compared to haloperidol and risperidone for schizophrenia.[13,14]

In keeping with SBS, nearly 200,000 bariatric surgeries were performed in the United States in 2020, with Roux-en-Y gastric bypass (RYGB) encompassing about 21% of those cases.[15] With obesity prevalence on the rise, clinicians may expect an increase in the rates of gastric bypass surgeries.[16] Careful consideration for medication selection in this population will be key. Overall, data on alternative options for patients with malabsorptive states are very limited, and a comprehensive review of current data is urgently needed. Clinicians should be cognizant that absorption of extended release products, such as duloxetine delayed release capsules or paliperidone which is formulated as an osmotic-controlled release oral delivery system, and even nonextended release products, may be diminished after gastric bypass.[17–19] One case report showcases schizoaffective disorder exacerbations in a patient 1 month after RYGB, despite stability on clozapine for the previous 3 years.[20] Minimal published data exist using asenapine in such niche cases. We found one other case report which investigated the use of sublingual asenapine in a 53-year-old female with history of anxiety, depression, unspecified personality disorder, and a RYGB who presented with a gastric bezoar secondary to pica.[21] This patient was started on ziprasidone 80 mg twice daily, but was switched to asenapine with a seemingly significant reduction in pica symptoms. While not

performed in any of the patients presented in this case series, the use of therapeutic drug monitoring may be beneficial to ascertain whether subtherapeutic concentrations is a rationale for treatment failure.[18,22] Furthermore, no formal diagnosis of malabsorption was made using methods such as the sugar absorption test or stool fat quantification. Patients A and C were seen by dietitians, who remarked on the severity of the protein-calorie malnutrition as evidenced by weight loss of greater than 5% within 1 month, depletion of body fat, and depletion of muscle mass.

To date, there are no guidelines which assist clinicians in choosing the most appropriate medication for patients with agitation or delirium when gut absorption cannot be relied on. While agitation etiology must always be determined, antipsychotics remain a staple of management in many instances. When intubated, the use of the alpha-2 agonist dexmedetomidine or benzodiazepines are commonly used for agitation management. However, patients may still require further management, with antipsychotics being trialed commonly.[23] Here, while some antipsychotics are formulated as short-acting injections, it may be preferable to use the oral route when possible. Although the advent of sublingual dexmedetomidine has provided a new option for agitation, unfortunately the majority of antipsychotics and other psychotropics available in the United States are not formulated in alternative dosage forms which best suit the needs of those with gastric malabsorption.[24] Thus, there is also a dire need for more sublingual, inhaled, or patch formulations of antipsychotics.

It is the opinion of these authors that SL asenapine may be a viable option for medically complex patients with agitation, such as those often seen by the consult-liaison psychiatry teams. In addition to these cases described, patients who are critically ill with end-organ failure, currently intubated, those with abdominal wounds necessitating an absence of enterally-absorbed medication administration, and those with difficulty swallowing may uniquely benefit from SL asenapine.[2] While some patients may find the taste of SL asenapine intolerable, and dysgeusia or oral hypoesthesia may be bothersome, none of our patients had any reported adverse events related to asenapine, and it appeared to be very well tolerated in the setting of agitated, confused, and psychotic patients.[25] Because of the moderate risk of QTc prolongation associated with asenapine, clinicians should periodically check an ECG especially in patients with electrolyte abnormalities, as are commonly seen in malabsorptive states. Worth noting, although SL asenapine is generic as of 2020, clinicians should be aware of the larger expense of this medication as compared to some other antipsychotics commonly used for agitation.

Conclusion

Three individual patients with varying psychiatric and medical illnesses had significant reductions in agitation from sublingual asenapine after having failed alternative oral antipsychotics, possibly secondary to malabsorption. There is an urgent need for review of alternative agents for agitation management and overall psychiatric care in patients with acquired or congenital gut malformations. Consult-liaison clinicians may consider sublingual asenapine a viable option for medically complex patients where rapid onset is needed and intestinal absorption is known to be compromised or is questionable.

Declarations

Ethics approval and consent to participate

An internal Institutional Review Board approval was waived due to the inclusion of less than four patients and de-identified data. This study did not constitute formal research and no consent for participation was required.

Consent for publication

All patients presented in this article provided written consent for publication. Next of kin provided written consent where applicable.

Author contributions

Bradley G. Burk: Conceptualization; Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

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Bentley Adams: Data curation; Formal analysis; Investigation; Writing – review & editing.

Badari Birur: Funding acquisition; Methodology; Project administration; Supervision; Writing – review & editing.

Pamela E. Parker: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – review & editing.

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