Alternative Approaches for Addressing Acute Agitation in Schizophrenia and Bipolar Disorder

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Abstract

Importance: The prompt effective treatment of acute agitation among patients with schizophrenia or bipolar disorder can alleviate distressing symptoms for the patient and decrease the risk of escalation to aggression and the potential for serious harm to the patient, health care providers, and others.

Observations: A commonly used approach for the management of acute agitation has been the intramuscular administration of antipsychotic medications and/or benzodiazepines. However, US Food and Drug Administration–approved treatments with alternative routes of delivery now include inhaled loxapine powder and, more recently, dexmedetomidine sublingual film. Two formulations of intranasal olanzapine for acute agitation are in development.

Conclusions and Relevance: Intranasal formulations offer the potential for favorable pharmacokinetics and onset of action combined with ease of delivery obviating the need for injections and are thus consistent with patient-centered factors such as preference and self-administration. In this review, alternative methods of medication delivery are discussed, with an emphasis on the potential for intranasal administration to treat acute agitation in adult patients with schizophrenia or bipolar disorder.

Acute agitation among patients with psychiatric conditions is seen in general emergency departments, psychiatric emergency departments, inpatient psychiatric units,1 long-term care,2 and community settings. In the glossary of technical terms contained in the original iteration of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, psychomotor agitation is defined as “excessive motor activity associated with a feeling of inner tension. The activity is usually non-productive and repetitious and consists of behaviors such as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still.”3 Self-reported symptoms from patients with schizophrenia and bipolar disorder living in community settings include reports of feeling uneasy, restless, or nervous.4

Acute agitation is a unique state separate from but may progress to aggression or violence.1,5 Not all patients who are agitated become aggressive or violent, and not all events of aggression or violence are preceded by agitation, but escalation of severity of agitation can lead to aggression or violence.1 In a study of patients admitted to a psychiatric hospital, more than 90% experienced moderate to severe levels of aggressivity during an episode of agitation, and while most psychiatric patients are not violent, schizophrenia and bipolar disorder increase the risk of violence.7 Prevalence of aggressive or violent behavior is higher among patients with schizophrenia or bipolar disorder, approximately 10%–12% varying by population, than in the general population, approximately 2%. Patients with schizophrenia, bipolar disorder, and other psychotic disorders are responsible for the majority of aggressions/assaults in psychiatric inpatient wards, and a study reported that aggression was the presenting condition in 26% of psychiatric emergency department visits.7,8 In emergency care settings, agitation may also be associated with general medical conditions, as well as substance use or withdrawal (eg, alcohol, cocaine, methamphetamine, and other street drugs).9 In a prospective study of agitation among patients treated in an urban emergency department, causes of agitation...
Injury to health care providers. Moreover, patients or individuals in the care setting, and caregivers, physical and psychological suffering for the patient, other behavior. Delayed or inadequate treatment can lead to escalation to aggressive or violent behavior requiring more invasive interventions. Whenever possible, noninvasive routes of administration are preferred over intramuscular (IM) injections. The use of physical restraint or seclusion may be indicated under certain conditions, though there is the potential for negative physical and psychological impacts for both agitated patients and health care providers.

The early identification and treatment of agitation in mild or moderate states may help to lower the risk of escalation to aggressive or violent behavior requiring more invasive interventions. Unfortunately, evidence suggests that coercive measures continue to be common in clinical practice. A study of the management of acute agitation at psychiatric emergency departments in European countries reported that a majority (59.5%) of episodes involved the use of restraint or seclusion, suggesting that opportunities may have been missed to treat lower-acuity episodes that may have been responsive to less coercive interventions.

Different strategies are used to manage acute agitation versus managing risk of future aggressive behavior. Hostility, as measured in the Positive and Negative Symptom Scale (PANSS), has been used as a marker for aggressive behavior and has been evaluated in analyses examining specific antihostility action of medications over a longer term. Long-term management of aggressive behavior is beyond the scope of this article, which will focus on acute agitation.

The current commonly used medical interventions for acute agitation have limitations. This review focuses on advances in formulations using alternative routes of administration that have the potential to offer effective and less invasive options with favorable safety profiles to treat acute agitation in patients with schizophrenia or bipolar disorder.

**UNMET MEDICAL NEED**

**Current Usual Care**

Current options for treatment of acute agitation include first-generation antipsychotics (eg, haloperidol, loxapine), second-generation antipsychotics (eg, aripiprazole, olanzapine, asenapine, ziprasidone, risperidone), and benzodiazepines (eg, lorazepam, midazolam), though not all treatments are approved by regulatory agencies for acute agitation (Table 1).

Ketamine, a noncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist, has been used for in-hospital and emergency department treatment of agitation, though its use is associated with elevated rates of sedation and need for intubation and potential for worsening of psychosis.

**Clinical Points**

- The treatment of acute agitation in patients with psychosis or bipolar disorder should prioritize noninvasive/noncoercive interventions and place shared decision making at the center of patient care. When verbal de-escalation techniques alone are insufficient, pharmacologic management using antipsychotics may be required.
- While oral and intramuscular formulations of pharmacologic agents continue to be commonly used to treat acute agitation, novel agents with alternative routes of delivery are becoming available, such as inhaled loxapine and dexmedetomidine sublingual film, or are in clinical development, including intranasal olanzapine.
- Intranasal formulations are designed specifically to address the unique nasal anatomy and physiology and can provide several benefits, including reliable, favorable pharmacokinetics, ease of delivery, and its noninvasive administration being consistent with patient-centered factors such as preference and self-administration.

were identified as alcohol related (83% of cases), drugs other than alcohol (12%), psychiatric (20%), and medical (11%). Finally, acute agitation can develop in other conditions, including Alzheimer’s disease or dementia, with studies reporting prevalence ranging from 22% to 68% in community and long-term care settings. The diverse etiologies and treatment options for the many causes of acute agitation are beyond the scope of this review, which will focus on acute agitation in the context of schizophrenia and bipolar disorder.

In addition to being an important clinical concern, agitation is uncomfortable for the individual. Hence, it is imperative to treat agitation in order to reduce distress and decrease the risk of escalation to aggressive or violent behavior. Delayed or inadequate treatment can lead to physical and psychological suffering for the patient, other patients or individuals in the care setting, and caregivers, including injury to health care providers. Moreover, inadequate treatment may result in other negative consequences for the patient, such as the intervention of police and the criminal justice system that could result in incarceration and potentially further delays in the effective treatment of any underlying psychiatric condition.

Several international guidelines support a broadly staged but flexible approach to the treatment of acute agitation. Initial steps include identification of the agitated patient, ongoing assessment of safety for the patient, staff, and others, along with initiation of an assessment of severity and cause of the agitation. Verbal de-escalation techniques in an appropriate environment are preferred over immediate pharmacologic intervention. However, when these strategies are not successful or feasible, medication may be an additional tool as part of the continued de-escalation efforts. The goal of medical therapy is to calm the patient without excessive sedation, using a fast-acting medication with minimal side effects. Patient consent and involvement in the selection of the type and route of administration as much as possible are critical principles for pharmacologic intervention.

Whenever possible, noninvasive routes of administration are preferred over intramuscular (IM) injections. The use of physical restraint or seclusion may be indicated under certain conditions, though there is the potential for negative physical and psychological impacts for both agitated patients and health care providers.

The early identification and treatment of agitation in mild or moderate states may help to lower the risk of escalation to aggressive or violent behavior requiring more invasive interventions. Unfortunately, evidence suggests that coercive measures continue to be common in clinical practice. A study of the management of acute agitation at psychiatric emergency departments in European countries reported that a majority (59.5%) of episodes involved the use of restraint or seclusion, suggesting that opportunities may have been missed to treat lower-acuity episodes that may have been responsive to less coercive interventions.

Different strategies are used to manage acute agitation versus managing risk of future aggressive behavior. Hostility, as measured in the Positive and Negative Symptom Scale (PANSS), has been used as a marker for aggressive behavior and has been evaluated in analyses examining specific antihostility action of medications over a longer term. Long-term management of aggressive behavior is beyond the scope of this article, which will focus on acute agitation.

The current commonly used medical interventions for acute agitation have limitations. This review focuses on advances in formulations using alternative routes of administration that have the potential to offer effective and less invasive options with favorable safety profiles to treat acute agitation in patients with schizophrenia or bipolar disorder.
### Table 1. Overview of Select Medications Used for the Management of Acute Agitation Among Inpatients With Acute Psychosis or Mania

<table>
<thead>
<tr>
<th>Agent</th>
<th>Formulation</th>
<th>Time to Peak Plasma Concentration (T&lt;sub&gt;max&lt;/sub&gt;)</th>
<th>Half-life (t&lt;sub&gt;1/2&lt;/sub&gt;)</th>
<th>Dose Ranges Used in Clinical Trials</th>
<th>Adverse Events</th>
<th>Potential Benefits</th>
<th>Potential Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-generation antipsychotics</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Haloperidol&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IM</td>
<td>20–60 min</td>
<td>10–37 h</td>
<td>5–10 mg</td>
<td>Dry mouth, constipation, EPS, salivary hypersecretion, somnolence</td>
<td>• Onset of efficacy ranges from 30 to 60 min</td>
<td>• Higher rates of acute EPS than observed with the second-generation antipsychotics</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>2–6 h</td>
<td></td>
<td>10–15 mg</td>
<td></td>
<td></td>
<td>• Potential for adverse cardiovascular events, such as QT interval prolongation</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Inhaled</td>
<td>2 min</td>
<td>6–8 h</td>
<td>10 mg</td>
<td>Cough, throat irritation, dysgeusia, sedation, EPS, bronchospasm</td>
<td>• Approved for agitation associated with schizophrenia or bipolar mania</td>
<td>• Although most adverse events were local (throat irritation and dysgeusia), acute EPS and bronchospasm have been reported</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Response occurs in as early as 10 min</td>
<td>• Product is contraindicated in patients with a current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm</td>
</tr>
<tr>
<td><strong>Second-generation antipsychotics</strong></td>
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<tr>
<td>Aripiprazole</td>
<td>IM</td>
<td>60–180 min</td>
<td>75 h</td>
<td>5.25–15 mg</td>
<td>Headache, dizziness, anxiety, akathisia, weight gain</td>
<td>• Approved for agitation associated with schizophrenia or bipolar mania, but no longer commercially available in the US</td>
<td>• More headache and dizziness when compared to placebo in clinical agitation studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Less sedation than lorazepam</td>
<td>• Onset may be later than other IM formulations (45–90 min)</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>• Less somnolence than olanzapine</td>
<td>• Some clinical trial data suggest that IM aripiprazole may be inferior to IM olanzapine</td>
</tr>
<tr>
<td>Asenapine</td>
<td>SL</td>
<td>30–90 min</td>
<td>24 h</td>
<td>10 mg</td>
<td>EPS, akathisia, dizziness, nausea, somnolence</td>
<td>• Onset of efficacy has been observed as early as 15 min after dose</td>
<td>• Single study requires replication; not FDA-approved for agitation</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>IM</td>
<td>15–45 min</td>
<td>Range of 33–40 h</td>
<td>2.5–10 mg</td>
<td>Dizziness, somnolence, hypotension, orthostatic hypotension, weight gain</td>
<td>• Approved for agitation associated with schizophrenia or bipolar mania, olanzapine is among the most well-studied medications for agitation treatment in patients with psychosis or mania</td>
<td>• Risk of hypotension (not be used simultaneously with benzodiazepines)</td>
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<td></td>
<td></td>
<td>• May be more sedating than other second-generation antipsychotics</td>
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<tr>
<td>Risperidone</td>
<td>PO</td>
<td>60 min</td>
<td>3 h</td>
<td>2–6 mg</td>
<td>Dizziness, nausea, acute EPS, somnolence, akathisia</td>
<td>• Available as a liquid formulation</td>
<td>• Higher rates of acute EPS when compared to other second-generation antipsychotics, but lower than haloperidol</td>
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<td></td>
<td>• Onset of efficacy has been observed as early as 30 min after dose</td>
<td>• Data comparing risperidone to other second-generation antipsychotics is of relatively low quality</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>IM</td>
<td>15–60 min</td>
<td>2–5 h</td>
<td>10–20 mg</td>
<td>Somnolence, EPS, dizziness, vomiting</td>
<td>• Approved for agitation associated with schizophrenia</td>
<td>• Among second-generation antipsychotics, there is a higher risk of QT interval prolongation</td>
</tr>
</tbody>
</table>

(continued)
### Table 1 (continued).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Formulation</th>
<th>Time to Peak Plasma Concentration (T&lt;sub&gt;max&lt;/sub&gt;)</th>
<th>Half-life (t&lt;sub&gt;1/2&lt;/sub&gt;)</th>
<th>Dose Ranges Used in Clinical Trials</th>
<th>Adverse Events</th>
<th>Potential Benefits</th>
<th>Potential Drawbacks</th>
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<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
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<tr>
<td>Lorazepam</td>
<td>IM</td>
<td>≤ 180 min</td>
<td>14 h</td>
<td>2–4 mg</td>
<td>Extreme sedation, ataxia, dry mouth, dizziness</td>
<td>• May benefit patients experiencing alcohol or sedative withdrawal</td>
<td>• Does not address underlying psychosis or mania</td>
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<tr>
<td></td>
<td>PO</td>
<td>120 min</td>
<td>12 h</td>
<td>0.5–2 mg</td>
<td></td>
<td></td>
<td>• Falls, especially in the elderly</td>
</tr>
<tr>
<td>Midazolam</td>
<td>IM</td>
<td>30 min</td>
<td>3 h</td>
<td>5–15 mg</td>
<td>Sedation, drop in oxygen saturation, respiratory failure</td>
<td>• May benefit patients experiencing alcohol or sedative withdrawal</td>
<td>• Does not address underlying psychosis or mania</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Shorter half-life, may require more frequent dosing</td>
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<td></td>
<td></td>
<td></td>
<td>• Higher rates of respiratory depression (when compared to lorazepam)</td>
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<td></td>
<td></td>
<td></td>
<td>• Falls, especially in the elderly</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>SL film</td>
<td>~120 min&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 h</td>
<td>120–180 µg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Excessive sedation, nausea and vomiting, hypotension, bradycardia</td>
<td>• Approved for agitation associated with schizophrenia or bipolar I or II disorder</td>
<td>• Does not address underlying psychosis or mania</td>
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<td></td>
<td></td>
<td>• Novel mechanism</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Noninvasive administration</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adapted with permission from Ward and Citrome.<sup>22</sup>

<sup>b</sup>Intravenous haloperidol is available, but not well studied and used less frequently due to increased risk of cardiovascular adverse events.

Abbreviations: COPD = chronic obstructive pulmonary disease, EPS = extrapyramidal symptoms, FDA = US Food and Drug Administration, IM = intramuscular, PO = oral, SL = sublingual.

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For patients with schizophrenia or bipolar disorder, antipsychotics are preferred over benzodiazepines, as they address the underlying psychiatric disorder.21,23 If the patient cannot cooperate with oral medications, short-acting IM second-generation antipsychotics, such as IM ziprasidone or IM olanzapine, are preferred for the acute control of agitation; IM aripiprazole appears slightly less efficacious than other second-generation antipsychotics.21,23,29 IM second-generation antipsychotics are superior to IM haloperidol in terms of tolerability and perhaps efficacy, but administration of IM haloperidol remains common.29 For individuals with dementia, antipsychotics have been used “off-label” as a treatment of agitation, as-needed use of IM olanzapine and aripiprazole has been studied in registrational studies, and on-going use (not “as needed”) of oral brexpiprazole has received US Food and Drug Administration (FDA) approval for the treatment of agitation associated with dementia due to Alzheimer’s disease.31–34 Benzodiazepines are commonly used when an initial dose of an antipsychotic does not adequately control the agitation or if acute withdrawal from alcohol or sedatives is suspected.7,21 Although the FDA has approved non-IM formulations of loxapine (inhaled) and dexmedetomidine (sublingual) for the treatment of agitation associated with schizophrenia or bipolar disorder, both must be administered under the supervision of a health care professional.35,36

While IM formulations predominate in the treatment of acute agitation, unmet medical needs remain. In particular, there is a need for treatment options that can be used quickly in the community setting to help avoid progression to aggression. Considerable interest and research have been invested in formulations with alternative routes of delivery. Three groupings of medication interventions based on formulation were identified by a panel of international experts on agitation: IM/intravenous, oral, and inhaled, and each formulation was evaluated and scored in terms of 9 attributes:

1. Rapid onset of action
2. Calmness without sedation
3. Easy to administer
4. Noninvasive route of administration
5. Noncoercive and nontraumatic delivery
6. Good safety profile
7. Favorable tolerability
8. Adequate patient preference
9. Promotion of long-term adherence to treatment of the underlying condition

IM and IV formulations scored high in rapidness of action but relatively low otherwise, primarily because of their coercive and invasive nature. Oral formulations scored high for their ease of administration and noninvasive and nontraumatic characteristics but
Addressing Acute Agitation

Currently Available Rapid-Acting Formulations for Noninvasive Administration

Currently available rapid-acting formulations using noninvasive routes of administration have focused on pulmonary administration, such as with inhaled loxapine powder, and sublingual administration, such as with sublingual asenapine tablets (not specifically approved for agitation) and sublingual dexmedetomidine film.

Inhaled loxapine has been approved by the FDA for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults since 2012.43 The formulation is delivered via a single-use handheld device that requires the patient to actively exhale and then inhale and hold their breath for up to 10 seconds to ensure dose delivery. Overall, inhaled loxapine is rapidly absorbed, with quick onset of action and comparable efficacy to IM lorazepam, olanzapine, haloperidol, aripiprazole, and lorazepam, but can cause pulmonary adverse effects.38

Clinical development of the formulation included a phase 2 trial and phase 3 trial in adult patients with schizophrenia and a phase 3 trial in adult patients with bipolar mania.36 The 2 phase 3 randomized, double-blind, multisite, placebo-controlled, parallel-group trials each enrolled >300 participants who received inhaled loxapine 5 mg, 10 mg, or placebo.44,45 In the trial including patients with bipolar mania, both doses of loxapine were superior to placebo in reducing agitation as measured by change in the PANSS Excited Component (PANSS-EC) score at 2 hours (P < .0001 for both doses).44 Comparable results were observed in the trial of patients with schizophrenia (5-mg group vs placebo group, P = .0004; 10-mg group vs placebo group, P < .0001).45 Relative to placebo, reductions in PANSS-EC scores were observed for both dosages at the first time point after administration, 10 minutes in both trials (P ≤ .0003). Treatment effect size, as measured by the number needed to treat (NNT) versus placebo for response (Clinical Global Impressions—Improvement scale score of 1 or 2 at 2 hours post administration), was 3 (95% confidence interval [CI] 3–4) for inhaled loxapine pooled across all dosages and studies; this compares favorably to NNT values for IM treatments (Figure 1).46 Only the 10-mg dose strength is commercially available in the United States.43

With regards to safety and tolerability of inhaled loxapine, common adverse events (incidence ≥ 2% and greater than placebo) are dysgeusia (14% for the 10-mg group, 5% with placebo), sedation (12%, 10%), and throat irritation (3%, 0%).43 However, inhaled loxapine is not widely used. In the United States, its use is limited to health care settings that have immediate access on site to supplies and health care professionals competent in the management of acute bronchospasm, can be administered only after an assessment of pulmonary status, and can be administered only once in a 24-hour period, as mandated by a Risk Evaluation and Mitigation Strategy.43,47 Acquisition cost is also higher compared with generic IM medications.35

The most recent addition to the group of noninvasive formulations for treatment of acute aggression is dexmedetomidine sublingual film, approved by the FDA in...
April 2022 for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults.24 It is the first FDA-approved treatment for acute agitation using a sublingual route of administration, though it has been available as an IV formulation since 1999 for use as an anesthetic agent.24,36,48 Dexmedetomidine is a $\alpha_2$-adrenergic receptor agonist and, unlike antipsychotics, does not have binding affinity to dopamine receptors.36,49

Results of 2 phase 3 clinical trials, 1 in patients with schizophrenia49 and 1 in patients with bipolar I/II disorder,50 showed significant improvements in PANSS-EC scores with 180-µg and 120-µg doses of dexmedetomidine compared to placebo at 2 hours, with significant differences in the least squares mean differences from placebo ($P < .001$ for both doses). Sublingual dexmedetomidine also demonstrated rapid onset of action, with statistically significant separation from placebo observed at 20 minutes in patients with bipolar disorder ($P \leq .009$) and 20–30 minutes in patients with schizophrenia.49,50 A post hoc analysis of combined study results reported the NNT for response versus placebo observed at 20 minutes in patients with schizophrenia was 3 (95% CI, 3–10).51 Across both studies, the most common adverse reactions (incidence ≥ 5% and at least twice that of placebo) associated with oral olanzapine monotherapy in adults with schizophrenia were postural hypotension, constipation, weight gain, dizziness, personality disorder, and akathisia and in adults with bipolar I disorder (manic or mixed episodes) are asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, and tremor.55

Long-term daily use of olanzapine has been associated with more adverse weight gain and metabolic events compared with other second-generation antipsychotics.22 A meta-analysis identified olanzapine as one of the most efficacious and safe treatments for agitation.54 The most commonly encountered adverse events (≥ 5% and at least twice that of placebo) associated with oral olanzapine monotherapy in adults with schizophrenia are postural hypotension, constipation, weight gain, dizziness, personality disorder, and akathisia and in adults with bipolar I disorder (manic or mixed episodes) are asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, and tremor.55

Intranasal delivery is a promising route of delivery that is being explored for acute agitation treatments, with 2 intranasal formulations of olanzapine in the initial stages of development. Olanzapine, in its rapidly acting IM formulation, is a well-studied antipsychotic used for the management of acute agitation in patients with psychosis or bipolar mania.7,22 A meta-analysis identified olanzapine as one of the most efficacious and safe treatments for agitation.54 The most commonly encountered adverse events (≥ 5% and at least twice that for placebo) associated with oral olanzapine monotherapy in adults with schizophrenia are postural hypotension, constipation, weight gain, dizziness, personality disorder, and akathisia and in adults with bipolar disorder (manic or mixed episodes) are asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, and tremor.55

Long-term daily use of olanzapine has been associated with more adverse weight gain and metabolic events compared with other second-generation antipsychotics.22

INP105 (Impel NeuroPharma, Seattle, WA) is being studied for the acute treatment of agitation in adolescents and young adults with autism spectrum disorder (NCT05163717)48 and has been evaluated in healthy volunteers with a plan to further develop the intervention for the treatment of acute agitation in schizophrenia and bipolar disorder.25,57 The formulation delivers a powdered form of olanzapine using a proprietary propellant-powered intranasal delivery device. The phase 1 pharmacokinetic study in healthy adults compared INP105 to IM and oral disintegrating tablet (ODT) olanzapine formulations, with similar
Addressing Acute Agitation

pharmacokinetic characteristics for the intranasal delivery as with IM administration. At equivalent doses, INP105 resulted in similar area under the curve (AUC) and $C_{\text{max}}$ as IM olanzapine and similar AUC but higher $C_{\text{max}}$ than olanzapine ODT. Median $t_{\text{max}}$ was less for INP105 (15, 10, and 9.5 minutes for 5 mg, 10 mg, and 15 mg, respectively) than for olanzapine IM (20 and 15 minutes for 5 mg and 10 mg, respectively) or olanzapine ODT (120 minutes). Treatment-emergent adverse events (TEAEs) occurred in 74% of participants receiving INP105, with postural dizziness/dizziness, orthostatic hypotension/hypotension, nasal congestion, fatigue, headache, and restlessness being most the common TEAEs (> 5%) reported across all INP105-treated groups combined.57

NRL-4 (Neurelis, Inc., San Diego, CA) is being developed for the treatment of acute agitation associated with schizophrenia and bipolar disorder.58 The proprietary formulation contains olanzapine and an alkylsaccharide absorption enhancer, dodecyl maltoside (DDM, Intravail).59 Alkylsaccharides are safe, nontoxic, odorless, tasteless, nonmutagenic, and nonsensitizing at concentrations up to 25%.60 DDM is generally recognized as safe for oral administration.60 It is thought to enhance drug uptake by promoting the temporary loosening of tight junctions between cells of the nasal epithelial mucosa and potentially via transcellular transport mechanisms in nasal epithelial cells.59 DDM is already in use in 2 FDA-approved intranasal formulations of treatments for acute neurologic conditions: sumatriptan nasal spray (Tosymra),61 indicated for the acute treatment of migraine, and diazepam nasal spray (Valtoco),62 indicated for the treatment of seizure clusters associated with epilepsy. The administration device used with these products is a simple single-use device that does not require coordination with breath or other complex patient maneuvers, and presence of a health care provider is not necessary for administration.60 The clinical development program of NRL-4, including phase 1 clinical trials, is underway.

**INTRANASAL ADMINISTRATION OF CNS DRUGS**

Intranasal administration offers several potential benefits while presenting specific challenges around formulation and pharmacokinetics based on the anatomy and physiology of the nasal cavity (Table 2). FDA-approved intranasal formulations are currently available for several central nervous system (CNS) drugs used as acute or ongoing treatments, including esketamine, nalmefene, naloxone, dihydroergotamine, sumatriptan, zavegepant, zolmitriptan, midazolam, and diazepam (Table 3).73

**Nasal Anatomy and Physiology**

The nose and nasal cavity play a role in heating and humidifying inspired air, removing particles and dust, and olfaction.64 The internal structures of the nose include

<table>
<thead>
<tr>
<th>Table 2. Potential Advantages and Challenges Associated With Intranasal Formulations of CNS Drugs Relative to 1 or More Other Routes of Administrationa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ease of delivery</strong></td>
</tr>
<tr>
<td>◾ Ease and speed of administration</td>
</tr>
<tr>
<td>◾ Noninvasive</td>
</tr>
<tr>
<td>◾ Minimal risk of injury</td>
</tr>
<tr>
<td><strong>Favorable pharmacokinetics</strong></td>
</tr>
<tr>
<td>◾ Potentially high bioavailability</td>
</tr>
<tr>
<td>◾ Absorption into the general circulation, avoiding first-pass metabolism</td>
</tr>
<tr>
<td>◾ Possibility of direct-to-brain delivery</td>
</tr>
</tbody>
</table>

**Patient experience**

| ◾ Patient acceptability/preference |
| ◾ Self-care or partner administration |
| ◾ Potential for at-home/community use |

2 large irregularly shaped nasal cavities (Figure 2). The nasal cavity is subdivided into 4 areas: the vestibule, respiratory region, olfactory region, and nasopharynx-associated lymphatic tissue (NALT). The nostrils open into the vestibule, a small area lined with squamous epithelial cells that are unsuited to extensive drug absorption. At the back of the cavity lies the NALT, a part of the mucosal immune system involved in protection from infection. The large, central portion of the cavity is divided into the respiratory and olfactory regions; these regions are relevant for intranasal drug delivery due to the presence of a rich vasculature, which provides access to the general circulation, and the presence of olfactory and trigeminal nerves, which allow for the possibility of direct-to-brain delivery of drugs.64

The nasal mucosa has several characteristics that are relevant to drug absorption. The epithelium is covered by a biphasic mucus layer with an outer layer of higher viscosity adhesive properties.64 Mucus is continuously moved biphase to some molecules. The membranes of the respiratory and olfactory regions are composed of ciliated pseudostratified epithelium of columnar and other cells connected by tight junctions, which become increasingly impermeable to molecules larger than 1,000 Da.64,74

**Intranasal Drug Delivery and Transport to the Brain**

Intranasal formulations are designed specifically to optimize absorption across the nasal mucosa and achieve
adequate bioavailability. Excipients may be added to increase solubility and ensure an adequate dose in a small volume or to increase absorption across the mucosal membrane and achieve adequate bioavailability. Some excipients, such as chitosan glutamate and DDM, have not been associated with nasal mucosal toxicity, while many others have been shown to have negative impacts on nasal mucosa. Novel carriers, such as nanoparticles, are being researched for intranasal delivery. For example, in vitro studies using cell culture have tested the cellular penetration capacity of chitosan-coated cubosomes of paliperidone palmitate with promising results.

Different drug delivery device combinations are also being developed, as seen in the propellant-powered delivery device for INP105 that is designed to target drug delivery to the upper nasal cavity and has been tested in preclinical and clinical trials. Current oral and IM formulations of antipsychotics in humans. Studies remain at the preclinical stage with various advanced deliveries, such as nanoparticles, dendrimers, and in situ gels, being explored with a number of antipsychotics, including haloperidol, asenapine, risperidone, and olanzapine.

The presence of sensory neurons in olfactory mucosa of the nasal cavity opens the possibility of direct-to-brain transport of some drugs, which may come with benefits in greater CNS therapeutic bioavailability and less systemic adverse effects. Studies of intraneuronal transport have reported transport times of 1.5 hours to 6 hours via the olfactory nerve, and thus this pathway is not likely a main mode of drug transport to the brain. Extracellular diffusion through perineural spaces has been reported to require 0.7 hours to 2.3 hours to reach the olfactory bulb. Other mechanisms, such as bulk flow through perivascular spaces around arteries supplying the olfactory bulb, may also be involved.

Morphine and carbamazepine have been shown to follow direct olfactory nerve pathways, while sumatriptan may be transported via both direct olfactory and indirect circulatory pathways to the brain. Current oral and IM formulations of antipsychotics reach the brain through systemic pathways, but little is known of the potential for direct-to-brain delivery of antipsychotics in humans. Studies remain at the preclinical stage with various advanced deliveries, such as nanoparticles, dendrimers, and in situ gels, being explored with a number of antipsychotics, including haloperidol, asenapine, risperidone, and olanzapine.
Intranasal Administration of Other CNS Drugs

Several CNS treatments are currently available in intranasal formulations that are used in community settings, and these may be self-administered or administered by a caregiver or care partner. These CNS treatments provide relevant guidance on the potential of intranasal formulations for favorable pharmacokinetics, as well as positive patient-related factors, in the treatment of other CNS conditions, including acute agitation.

Sumatriptan for migraine is available as a subcutaneous injection, an oral tablet, and intranasal formulations for use in the community. Early studies showed the subcutaneous injection was the fastest acting of these formulations but was also associated with more adverse events than oral sumatriptan. The intranasal formulation had similar efficacy as the oral tablet but with a shorter time to onset of action. The first commercially available early intranasal formulation was limited by low bioavailability and slow absorption. A formulation containing the permeation enhancer DDM provided a more rapid absorption profile in healthy volunteers, with a tmax of 0.25 hours after a 10-mg single dose compared with 2.0 hours after a 20-mg dose of the original intranasal formulation (P < .05, paired t test). The enhanced intranasal formulation resulted in systemic exposure similar to subcutaneous sumatriptan (4 mg), and a long-term safety study reported adverse events similar in pattern, frequency and severity as those seen in previous research on triptans and intranasal formulations. Moreover, patients were more satisfied with the intranasal treatment compared with their usual migraine medication. A sumatriptan nasal powder is also available; it is delivered via a breath-activated delivery system.

Benzodiazepines, specifically diazepam and midazolam, are the cornerstone of rescue therapy for seizure clusters in epilepsy. Until 2019, diazepam rectal gel was the only rescue therapy available for use in the community, and while effective, it had drawbacks, including low social acceptability, particularly among adults. A pharmacokinetic study of an intranasal formulation of diazepam in healthy volunteers reported a similar tmax between intranasal and rectal formulations, with less variability in bioavailability with the intranasal formulation. Absolute bioavailability of the intranasal formulations are 97% for diazepam and approximately 44% for midazolam, compared to their respective IV formulations. Among the benzodiazepine formulations available for use in the community, intranasal administration leads to the quickest onset of action from time of administration compared with rectal, IM, and sublingual routes. Additionally, intranasal delivery may lead to shorter total times from seizure onset to cessation, due in part to less time required to administer an intranasal formulation than an IV formulation.

Safety studies of benzodiazepine nasal spray rescue therapy confirm it to be well tolerated. Diazepam nasal spray was associated with minimal nasal irritation and no clinically relevant olfactory changes. Intranasal benzodiazepine rescue therapy is associated with high levels of patient satisfaction. Finally, in one clinical trial, a subset of patients have been reported to successfully self-administer diazepam nasal spray.

Naloxone has been used for decades to treat symptoms associated with opioid overdose, and an FDA-approved, over-the-counter intranasal formulation is now available. The pharmacokinetic profile of the approved intranasal naloxone formulation (2–8 mg) was compared with IM naloxone (0.4 mg) in healthy volunteers. Plasma concentrations and AUC with all doses of intranasal naloxone were equal to or exceeded

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**Anatomy of the Nasal Cavity (sagittal view)**

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The 2 nasal cavities are formed by the cribriform plate of the ethmoid, the palate, the central septum, and the outer walls with 3 turbinates. The nostrils open into vestibule, which is lined with squamous mucosa. The central area of the cavity comprises the large respiratory mucosa and a smaller olfactory mucosa above. The outer wall of each cavity is convoluted into 3 turbinates. The superior turbinate is smallest and is situated in the upper, posterior portion of the cavity. The middle and inferior turbinates are increasingly larger in size. The respiratory region is the largest (approximately 130 cm²) part of the nasal cavity, covering about 80%–90% of the total surface area. It is highly vascularized and thus a prime site for systemic drug absorption after nasal administration. It is also everted from the trigeminal and other nerves. The olfactory region is smaller, with a total surface area of 2–12.5 cm² or ≤ 10% of the cavity’s total surface area.

The region also contains olfactory sensory neurons, making it the only site where the central nervous system is in direct contact with the external surface of the body. This allows for the possibility of direct-to-brain delivery of drugs. At the cavity’s posterior lies the NALT connected to the nasopharynx. Abbreviations: CSF = cerebrospinal fluid, NALT = nasopharynx-associated lymphoid tissue.
those with intramuscular naloxone; t\textsubscript{\textendash} was similar between formulations. In a separate cohort, 90% or more of participants were able to correctly administer the intranasal formulation without prior training.\textsuperscript{101}


CONCLUSION

An unmet medical need remains for effective and acceptable alternative treatments for acute agitation associated with schizophrenia or bipolar disorder. Several novel routes of administration are possible, including inhaled loxapine, dexmedetomidine sublingual film, and 2 intranasal olanzapine formulations in clinical development. Intranasal administration is currently being used for other CNS conditions, and it offers the potential to provide effective treatment in both community and hospital settings. This intranasal mode of medication delivery may also be more acceptable to patients with acute agitation and the health care providers treating them than currently available interventions.


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Addressing Acute Agitation


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