Clinical Challenges in the Pharmacologic Management of Agitation

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ABSTRACT

Agitation, characterized by motor restlessness and accompanying mental tension that may escalate into violence, is a serious behavioral emergency encountered often in the emergency setting. Behavioral intervention (eg, verbal de-escalation, seclusion) should be the initial approach for management of agitated patients, but when these techniques are ineffective, pharmacologic treatment becomes necessary. This article reviews the clinical challenges in managing agitation in the emergency setting. An ideal agent for the acute treatment of agitated patients should be easy to administer and not traumatic; provide tranquilization without excessive sedation that may interfere with patient interaction, diagnosis, and selection of additional therapy; have a rapid onset of action and a sufficient duration of action to allow for transport of patients to appropriate services; and have low risk for significant adverse reactions and drug interactions. Currently available pharmacologic treatments for agitation do not fulfill all of these criteria, and there are significant unmet needs for novel antiagitation treatments that are rapid in onset, accepted by patients and staff, less invasive (as compared with intramuscular or intravenous formulations), and easy and safe to administer.

FOCUS POINTS

• Agitation demands rapid treatment that frequently precludes a thorough evaluation of etiology, therefore requiring rapidly acting treatments that are effective and safe.
• While nonpharmacologic intervention should be attempted whenever possible, medication may be administered voluntarily or under duress, with the aim of safely and swiftly making the patient less agitated and hostile.
• There are significant unmet needs for novel antiagitation treatments that are rapid in onset, accepted by patients and staff, less invasive (as compared with intramuscular or intravenous formulations), and easy and safe to administer.

INTRODUCTION

Agitation in adults is a psychiatric/medical emergency that requires rapid and effective intervention to avoid harm to patients, their families, other individuals receiving care in the emergency setting, and healthcare professionals. Ineffectively managed agitation can also greatly increase the overall cost of patient treatment and create additional expenses that may result from injury and time lost from work.

Agitation is characterized by excessive motor or verbal activity, which may include irritability, uncooperativeness, threatening gestures, and assault. It is a common clinical challenge in the emergency setting that may lead to violent, destructive behavior and cause extreme personal distress, while posing a physical risk to the patient, caregivers, nursing staff, and others. As many as 1.7 million medical emergency room visits per year may involve agitated patients, and 20% to 50% of emergency psychiatry visits in the United States may involve patients who are at risk for agitation. Approximately 10% of patients encountered in emergency psychiatry settings may become agitated or violent during assessment.

Schizophrenia and bipolar disorder are very common causes of agitation for individuals who present in the
emergency department.5,7,8 Patients with psychoses result in ~900,000 emergency department visits annually.5 Schizophrenia is disproportionately common among homeless people, with an incidence of 27%, which contributes to their high frequency of presentation with agitation in the emergency department.7 It is important to note that agitation among patients with schizophrenia or bipolar disorder may be precipitated or exacerbated by both patient-related factors (eg, male, younger age, history of substance abuse, poor adherence to antipsychotics, history of physically aggressive behavior),9,12 and the characteristics of the environment in which they are managed (eg, an overcrowded emergency department).13 Unpremeditated violence in patients with agitation is often preceded by a prodromal period of 30–60 minutes, during which they may exhibit increased pacing or loud speech.14 Recognizing these prodromal symptoms provides an opportunity for early de-escalation and/or offering pharmacologic treatment.

Several tools have been developed to assist in the identification of patients who are likely to become violent in different treatment settings. The Brøset Violence Checklist (BVC) measures confusion, irritability, boisterousness, physical threats, verbal threats, and attacks on objects with each scored for its presence (1) or absence (0). The sum of scores is then totaled with a total score of 0, suggesting that the risk of violence is small; scores 1 and 2 suggest that the risk of violence is moderate, and preventive measures should be taken; and scores ≥3 indicate that the risk of violence is very high and that action should be taken.15 The Historical, Clinical, and Risk Management Violence Risk Assessment Scheme is a 20-item scale that gathers information about past history of violence, current clinical status, and environmental/support factors that may increase risk for violence.16 It has been shown to be useful for the clinical psychiatric, forensic, and correctional settings.16 A third tool that may be useful for prediction of violence in the emergency department is the McNeil-Binder Checklist, which evaluates history of physical attacks or fear-inducing behavior within 2 weeks, absence of suicidal behavior, schizophrenic or manic diagnosis, male gender, and currently married or living together status, to predict violent behavior. It has been shown to have a sensitivity of 57.2% and a specificity of 70.0% for prediction of violence in psychiatric inpatients.17 None of these prediction tools have been evaluated in the emergency department and all but the BVC require at least some information about the patient’s history.

The occurrence of agitation and violence significantly impacts the agitated individual, other patients around him or her, and healthcare personnel.18 Results from one survey of psychiatric emergency services in the US indicated that agitation resulted in an average of 8 patient-to-staff assaults per facility each year.19 Most of these episodes caused injuries to personnel that were sufficiently severe to result in absences from work.19 Results from one study20 of violence in the emergency department indicated that 80% of respondents reported that at least one staff member had been injured by a violent patient in the preceding 5 years, and 43% reported physical attacks on staff at least once per month. Results from another survey21 of 106 emergency department personnel indicated that 57% were physically assaulted, 48% reported impaired job performance for the rest of the shift or the rest of the week after an incident of violence, 73% were afraid of patients as a result of violence, and 25% took days off because of violence.

The symptoms of agitation may be very similar across a wide range of diagnoses, including medical conditions, toxicity, and psychiatric illness (Table 1).22-27 The terms used to define agitation typically include increased psychomotor activity; aggression; disinhibition/impulsivity; and irritable, anxious, or labile mood.28 Numerous different definitions for agitation have been put forward in the medical literature, and they vary based on the condition (eg, dementia, traumatic brain injury, schizophrenia, bipolar disorder) believed to underlie patients’ symptoms.28 It has been suggested that the lack of a uniform and precise definition of agitation may contribute to misrecognition (both over- and underrecognition) of this condition and misdetermination of its causes in the acute care setting.28

The etiology of agitation is not completely understood, but

<table>
<thead>
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<th>TABLE 1 CONDITIONS ASSOCIATED WITH AGITATION22-27</th>
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<tr>
<td><strong>Medical causes:</strong></td>
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<tr>
<td>• Thyrotoxicosis</td>
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<td>• Encephalitis</td>
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<td>• Meningitis</td>
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<td>• Sepsis</td>
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<td>• Brain trauma</td>
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<td>• Dementia</td>
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<td>• Delirium</td>
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<td>• Seizure disorders</td>
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<td><strong>Toxicity:</strong></td>
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<td>• Intoxication (alcohol, cocaine, methamphetamine)</td>
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<td>• Alcohol withdrawal</td>
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<td><strong>Psychiatric disease:</strong></td>
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<td>• Schizophrenia</td>
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<td>• Schizoaffective disorder</td>
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<td>• Brief psychotic disorder</td>
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<td>• Bipolar disorder</td>
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<td>• Borderline personality disorder</td>
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<td>• Obsessive-compulsive disorder</td>
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<td>• Panic disorder</td>
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<td>• Posttraumatic stress disorder</td>
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it is believed that abnormalities in the biogenic amines—serotonin, dopamine, and norepinephrine—as well as the inhibitory neurotransmitter γ-aminobutyric acid (GABA) are all involved.29-31 It has been suggested that agitation associated with psychosis, mania, and substance abuse may be correlated with elevated dopaminergic neurotransmission, and that decreased GABAergic transmission is characteristic of agitation associated with dementia, depression, and anxiety.32

Agitation demands rapid treatment that frequently precludes a thorough evaluation of etiology. Clinicians therefore require rapidly acting treatments that are effective and safe, regardless of the genesis of agitation. It is important to note that treatment requirements and unmet needs for the management of patients with agitation vary from one setting to another and that those in the emergency department are very different from those for a patient presenting to a psychiatric clinic.33-36 The etiology of agitation for the patient in the emergency department may be unknown, while some patient history is likely to be available to personnel in the psychiatric clinic. Treatment selection may be more difficult in the emergency department versus the psychiatric clinic because healthcare professionals in the psychiatric clinic may have more information about efficacy of prior treatments in a given patient.

**ACUTE MANAGEMENT OF THE AGITATED PATIENT**

Diagnosis and establishment of the acute treatment plan for the agitated patient is difficult because of the immediate need for intervention, which may increase diagnostic difficulty.

Establishment of a provisional diagnosis is a crucial step in the management of the agitated patient, and medical causes of agitation and substance abuse should be ruled out, if possible, before assuming a psychiatric etiology. Patient characteristics that increase the probability of a non-psychiatric cause of agitation include lack of prior psychiatric history, older age, and new or pre-existing medical complaints.37,38 It has been suggested that a brief medical work-up be carried out in patients without a psychiatric history, with features not consistent with a psychiatric diagnosis (eg, lethargy, confusion), with abnormal vital signs, with sudden onset of agitation, and who are known to have recently started any new medications (eg, anticholinergics, steroids).39

Ideally, initial intervention in the agitated patient should be as nonrestrictive as possible. Techniques such as verbal de-escalation (“talking the patient down”) or destimulation (placing the patient in a quiet room) are effective in some agitated individuals and should be attempted prior to more forceful interventions.14,40

While nonpharmacologic intervention should be attempted whenever possible as a first step in the acute management of agitated patients, it is often ineffective in some individuals who present in the emergency setting.18 Rapid and safe tranquilization of aggressive/violent patients is often necessary; medication may be given voluntarily or under duress, with the aim of safely and swiftly making the patient less agitated and hostile. It should be noted that offering the agitated patient medication can go hand-in-hand with non-restrictive interventions such as verbal de-escalation and providing the patient with an opportunity for time in a quiet environment.41 Involuntary administration of medication should be considered coercive in the same sense as forced seclusion or restraint.

The goal of acute pharmacologic treatment for agitation is to calm the patient while avoiding excessive sedation that can interfere with the ability to continue the psychiatric evaluation and intervention.42,43 Excessive sedation that results in a requirement for continuous observation and/or assistance with toileting also increases the burden on emergency department staff.44 Prompt administration of effective medications to the agitated patient has the potential to reduce the probability of harm to self or others, permit accomplishment of needed diagnostic tests, attenuate psychosis, and reduce the requirement for restraint.45

The choice of medication for a patient with agitation should be guided by the etiology underlying the episode if it is known. For example, agitation resulting from organic causes (eg, hypoglycemia, hypoxia, thyroid storm) should not be treated with an antipsychotic, while administration of an antipsychotic and/or benzodiazepine is appropriate for agitation that has a psychiatric etiology.39 The remainder of this article focuses on treatment of agitated patients using antipsychotics and benzodiazepines.

Current drugs used for the acute treatment of agitation may be administered orally, intravenously (IV), or by injections into the muscle (intramuscular [IM]).44 Each of these routes of delivery may have important limitations. Administration of an oral agent may not be possible in a very agitated patient and this route of administration often results in a slow onset of action.44 Intravenous administration of medications may result in a very rapid onset of action, but establishing an IV line may be very difficult and potentially dangerous in the agitated patient. In addition, IV administration of some medications used to treat agitation may result in cardiac and/or respiratory complications.45 Results from one study45 have shown further that IM administration of haloperidol did not result in more rapid resolution of agitation than delivery of an oral concentrate. Similarly, comparison of the combination of oral risperidone and oral lorazepam versus IM haloperidol plus IM lorazepam in patients with agitation indicated no significant between-treatment differences in onset of action.46 Nevertheless, IM drug
administration generally achieves therapeutic concentrations more rapidly than oral delivery. A recent systematic review of clinical trials focused on the acute treatment of agitation indicated generally more rapid onset of action for IM versus oral administration of the same agents.

Intramuscular injections are easier to administer than IV infusions, and some patients will agree to this route of delivery for medications to more rapidly control their agitation. However, the onset of action with IM injection of a given medication may be slower and the pharmacologic effects more variable than those observed after IV administration of the same drug. For example, the onset of action with midazolam for calming agitated patients is 1–5 minutes for IV delivery versus 18 minutes for IM administration. Additionally, the pain associated with IM injection may be poorly tolerated by some patients. Any intervention that is aversive to the patient, particularly if it is administered involuntarily, may be viewed as punishment and has the potential to impair the physician-patient relationship and effective longer-term management after resolution of the episode of agitation.

Further, approaching the patient with a needle may increase stress for both patients and their families and escalate agitation. Both IV and IM administration of medications to the agitated patient are also associated with the risk for needle-stick injuries to emergency department staff. Despite these limitations, the relatively rapid onset of action for IM and IV administration of antipsychotics and/or benzodiazepines is an important advantage when the behavior of an agitated patient poses an imminent risk to himself and others, and parenteral drug administration is the only feasible treatment alternative.

The characteristics of an ideal medication for the acute management of agitated patients have been set forth by several investigators (Table 2). They include easy preparation by staff and nontraumatic administration (no needles) with no associated pain or requirement for restraint; rapid onset of action with little interpatient variability in pharmacokinetics and pharmacodynamics; sufficient duration of effect for transport of patients to appropriate services; tranquilization without excessive sedation that may interfere with patient interaction, diagnosis, and selection of additional therapy; and low risk for significant adverse reactions and drug interactions.

**GUIDELINES FOR ACUTE MANAGEMENT OF AGITATION IN THE EMERGENCY SETTING**

Several guidelines for the acute management of agitated patients have been published; those from the Joint Commission on Accreditation of Healthcare Organizations as well as the Centers for Medicare and Medicaid Services indicate that nonphysical forms of behavior management (eg, verbal intervention or show of force) are the appropriate first-line strategy. If medication is required, the use of oral drugs rather than IM preparations is recommended. The Expert Consensus Panel for Behavioral Emergencies consensus regarding the acute management of agitated patients in the emergency department setting differs somewhat from these guidelines. This consensus, based on responses to a survey completed by 48 experts in the acute management of agitated patients, indicated that first-line oral options for the acute treatment of agitation associated with schizophrenia are olanzapine alone, risperidone alone or combined with a benzodiazepine, and haloperidol plus a benzodiazepine. Parenteral agents supported by experts included IM olanzapine and IM ziprasidone. The experts recommended initial use of benzodiazepines when no information was available about the patient’s condition, when there was no specific treatment available for the patient’s condition, or when the patient was intoxicated. Haloperidol was viewed as being as effective as any currently available antipsychotic, and it was recommended that it should be administered alone or with a benzodiazepine unless the patient is medically compromised. While these expert recommendations provide guidance for optimal use of existing medications for the acute treatment of agitated patient, none of the currently recommended approaches meets all of the criteria for an ideal treatment set forth above (Table 2). LIMITATIONS OF CURRENT PHARMACOLOGIC TREATMENT OPTIONS

Oral Drug Administration

Oral agents, particularly atypical or second-generation antipsychotics, have been used extensively for the acute treat-

**TABLE 2**

**CHARACTERISTICS OF AN IDEAL MEDICATION FOR ACUTE MANAGEMENT OF THE AGITATED PATIENT**

- Easy preparation by staff and nontraumatic administration (no needles) with no associated pain or requirement for restraint; possibility for self administration.
- Rapid onset of action with little interpatient variability in pharmacokinetics and pharmacodynamics.
- Offset sufficiently slow for transport of patient to appropriate services.
- Provides tranquilization without excessive sedation that may interfere with patient interaction, diagnosis, and selection of additional therapy.
- Low risk for significant adverse reactions (acute movement disorders, especially dystonia, hypotension, cardiovascular events, dysphoria, neurologic events [eg, seizures]) and drug interactions.

Primary Ps
dose-related sedative potential while oral risperidone (not
for treatment of agitation) and IM olanzapine have higher
cated that oral ziprasidone and quetiapine (not approved
from them.

Another potential limitation of oral medications is patients
“cheeking” (taking, but not swallowing) oral tablets.

While not specifically approved for the treatment of agita-
tion, orally disintegrating formulations of several anti-
psychotics (eg, risperidone, olanzapine, aripiprazole) have
been developed. This formulation may facilitate anti-
psychotic delivery to agitated patients, particular those who
might not comply with treatment, but their pharmacokinetic
profiles, including time to maximum plasma concentration,
are equivalent to those for conventional tablets.

Intramuscular Injection

Intramuscular administration of conventional or atypical
antipsychotics provides more rapid onset of action than
oral delivery, but may be associated with higher risk for
adverse events and patient objections. Intramuscular zipra-
sidone has been shown to have an onset of action of ~30
minutes in agitated patients in one study. Intramuscular
olanzapine is also rapidly absorbed and produces signifi-
cant reductions in agitation within 30 minutes, but has
been associated with significant reductions in systolic and
diastolic blood pressure and pulse rate.

Objection to IM injection may create a barrier to this
approach to acute treatment of agitation in many patients.
Results from one survey indicated that patients most pre-
ferred pills or capsules, followed by liquid medication,
and then “an injection I agree to.” Physicians are also
concerned that injected medication will compromise the
physician-patient relationship.

Excessive Sedation

While tranquilizing or calming the agitated patient is
the central aim of pharmacotherapy, avoiding excessive
sedation that may interfere with further evaluation and
treatment is now also recognized as an important aspect
of intervention. Heavy sedation of patients may help to
ensure the safety of both patients and staff, but it also
makes it difficult or impossible to elicit useful information
from them. Review of randomized clinical trial data indi-
cated that oral ziprasidone and quetiapine (not approved
for treatment of agitation) and IM olanzapine have higher
dose-related sedative potential while oral risperidone (not
approved for treatment of agitation) and IM aripiprazole
have lower sedative potential. However, other studies
have suggested that IM olanzapine may have low risk for
sedation in the acute treatment setting.

While the risk with IM administration of antipsychotics
for excessive sedation that may interfere with further
patient evaluation and intervention appears to be lower
than that after oral delivery, results from several stud-
ies have indicated that IM formulations of some atypical
antipsychotics do have at least some liability for excessive
sedation. In contrast to the conclusions from Cañas,
results from a study comparing IM aripiprazole and
IM lorazepam indicated excessive sedation (Agitation-
Calmness Evaluation Scale score of 8 or 9) during the
initial 2 hours after first injection in 17.3% and 19.1% of
aripiprazole- and lorazepam-treated patients, respectively.
Parenterally administered benzodiazepines have also been
associated with excessive sedation. The combination of
these drugs with a conventional or atypical antipsychotic
may further increase the risk for excessive sedation versus
treatment with single agents.

Other Adverse Events Associated with Current
Acute Treatments for Agitation

All agents currently used for the acute treatment of agita-
tion have the potential for clinically important adverse events.
Conventional antipsychotics (eg, haloperidol) may produce
dysphoria, dystonia, and akathisia (in up to 33% of patients),
as well as postural hypotension leading to syncope, and pos-
sible cardiac events. In addition to being aversive to patients,
the symptoms of akathisia may be confused with the underly-
ing agitation. This has the potential to lead to inappropriate
increases in drug dosing. Conventional neuroleptics (eg, halo-
peridol) often require the use of concomitant anticholinergics
to prevent or treat extrapyramidal symptoms, and admin-
istration of these drugs can lead to cognitive disturbances.
Treatment with conventional neuroleptics may also lead to
neuroleptic malignant syndrome, particularly when admin-
istered in high doses to agitated patients. Acute dystonic
reactions, which may be life threatening, have been reported
to occur in 9% of agitated patients treated with haloperidol.
Due in large part to these limitations, the use of conventional
antipsychotics is no longer considered “best practice” for any
of the major conditions contributing to agitation.

Administration of atypical antipsychotics may also result
in significant adverse events when used in the acute care
setting. Treatment with olanzapine may lead to bradycar-
dia, orthostatic hypotension, and increased somnolence
when administered with lorazepam. Risperidone may be
associated with the development of extrapyramidal symp-
toms. Ziprasidone may produce nausea, headache, dizzi-
ness, and possible risk for QTc prolongation. Quetiapine
may result in orthostatic hypotension. Aripiprazole may
produce nausea and vomiting.
Medications used for the acute treatment of agitation also have the potential for clinically significant drug-drug interactions; this is especially important in patients with comorbid medical conditions. Lorazepam has a substantial potential for interactions with prescription drugs, drugs of abuse, and alcohol.\textsuperscript{77} Haloperidol, ziprasidone, aripiprazole, and quetiapine are all metabolized, at least partially, by cytochrome P450 (CYP) 3A4 and may interact with agents that induce or inhibit this enzyme, including carbamazepine, valproate, phenytoin, phenobarbital, rifampicin, quinidine, glucocorticoids, and macrolide antibiotics.\textsuperscript{79-81} Olanzapine is metabolized by CYP 2D6 and 1A2, and it may interact with fluoroxamine, fluoxetine, sertraline, and grapefruit juice.\textsuperscript{79,80} Risperidone is partially metabolized by CYP 2D6, but has little risk for clinically significant drug interactions.\textsuperscript{79,80}

**NEW ALTERNATIVES FOR ACUTE TREATMENT OF THE AGITATED PATIENT**

While conventional or atypical antipsychotics, used alone or in combination with a benzodiazepine, have been shown to be effective for the acute treatment of agitation, the results summarized in the preceding sections indicate that there is a clear need for new options for the initial pharmacologic management of the agitated patient who presents in the emergency setting. The magnitude of this need is clearly reflected by survey results indicating that 8.5% of patients who present with agitation require restraint during psychiatric emergency visits,\textsuperscript{56} suggesting that current approaches to treatment are far from optimal for rapidly calming these individuals. Asenapine sublingual tablets are a new option for the treatment of acute episodes of schizophrenia and for treatment of acute manic or mixed episodes of bipolar I disorder. Bioavailability is 35% when taken sublingually, but <2% if ingested.\textsuperscript{81} This formulation might be expected to have a rapid onset of action and be suitable for treatment of patients with agitation. An inhaled formulation of loxapine (AZ-004; inhaled loxapine), which penetrates deeply into the lungs, which has also been shown to be effective for reducing agitation, as measured by Positive and Negative Syndrome Scale—Excited Component scores in patients with schizophrenia and bipolar disorder with an onset of action <10 minutes.\textsuperscript{82}

**CONCLUSION**

Agitated individuals present often in the emergency care setting, and prompt and effective management of these patients is an important priority. A wide range of options has been employed in the acute treatment of agitation, but many have important limitations, including slow onset of action, excessive sedation, requirement of parenteral administration, and risk for potentially serious side effects and drug interactions. No currently available single agent or combination matches the characteristics of an ideal acute intervention for agitation, which include being easy to administer and not traumatic; rapid onset of action and a sufficient duration of action to allow for transport of patients to appropriate services; provision of tranquilization without excessive sedation that may interfere with patient interaction, diagnosis, and selection of additional therapy; and low risk for significant adverse reactions and drug interactions. Further study of alternative therapies for acute agitation that address some or all of these limitations is required.\textsuperscript{PP}

**REFERENCES**