What do we really know about PRN use in agitated children with mental health conditions: a clinical review

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ABSTRACT
What is the evidence that ‘pro re nata’ (PRN) medication is effective for ending agitated outbursts in children and adolescents in psychiatric emergency rooms or inpatient units? Literature search was performed for studies of PRN medication use in children and adolescents that included an outcome measure. One randomised controlled trial, three prospective studies and six retrospective studies that included some outcome measure were identified. Outcome measures were heterogeneous, and frequently did not use standardised metrics assessing agitation level to measure effectiveness. The single small Randomized Controlled Trial (RCT) does not find a difference between placebo and medication, and outcomes of other studies do not control for potential placebo effect of the intervention itself as opposed to the medication. There is insufficient evidence to support the common practice of PRN medications for the management of acute agitation, and no data with which to inform clinical practice, such as which medicines and doses are helpful for specific populations or situations. Psychiatrists have no evidence-based medication interventions for acutely managing agitated outbursts in children and adolescents.

BACKGROUND
Acute episodes of non-delirious, severe agitation (rages or outbursts) resulting in behaviour that poses danger to self or others is a common reason for children to be psychologically referred and are the chief complaint in up to half of outpatient referrals.1,2 Outbursts account for up to 70% of children admitted to inpatient units.3–5 Behaviour during episodes is characterised by screaming and verbal threats, throwing objects, property destruction and aggressive behaviour such as hitting, kicking and spitting.3

Verbal de-escalation is the first-line intervention for agitated outbursts in acute settings such as emergency rooms and inpatient units, although we found no data describing how often this intervention is successful in halting episodes or preventing harm to youth and those around them.6 Placing a child in a protected space against his/her will during episodes is proscribed by guidelines except ‘to prevent dangerous behaviour to self or others and to prevent disorganisation or serious disruption of the treatment programme including serious damage to property.’6 Behaviour modification, a long-standing treatment for children with behaviour problems,7,8 has become increasingly avoided as the emphasis has been on trauma-informed care.9,10 Clinicians use ‘as needed’ or ‘pro re nata’ (PRN) medication with the goal of terminating problematic behaviours during episodes of severe agitation that can be dangerous and upsetting, both to those witnessing and experiencing the episode.4,11 Guidelines about pharmacological management of agitation are based on common practice or consensus,12,13 and are often unclear on what data the recommendations are based.

OBJECTIVE
The goal of this paper is to critically review the existing data on the effectiveness of PRN medication use for non-delirious agitated outbursts in children and adolescents in inpatient and emergency psychiatry settings.

STUDY SELECTION AND ANALYSIS
A comprehensive literature search was conducted using MEDLINE and PubMed databases (update: May 2018) for articles containing studies of PRN medication use in children and adolescents in emergency or inpatient settings. Search terms included PRN, pro re nata, as needed, emergent or stat medications and psychiatry. Results were restricted to child and adolescent subjects, inpatient or emergency psychiatry settings and published in English. On review, case reports were excluded, as were articles that did not include a specific outcome measure of individual doses of medication. Citations of relevant articles were hand searched for additional pertinent references that previous searches had omitted. This is a similar review process as documented in a recent systematic review of this topic,14 and we located the seven articles identified in this existing review that met our search criteria, plus three additional studies.15–17

FINDINGS
Ten studies were identified that provided outcome data related to the use of PRN medications in youth. One study was a randomised, double-blinded placebo-controlled trial, three were prospective open studies and six were chart reviews. Diagnoses of the population in each study are summarised in table 1.

Older studies
Evans and Di Scipio18 performed a retrospective review of PRN medications given over the course of a year to 47 adolescents (mean IQ 70) in a long-term residence where length of stay (LOS) was 12–18 months. A total of 1469 doses of PRN medicine (90%) and chlorpromazine (10%) were administered, either orally (91%) or intramuscularly (9%). At the conclusion of data collection, eight nurses who worked during the study were asked retrospectively about the situations in which medications were used, patients’ attitudes and effectiveness (not defined). Based on nursing reports, violent behaviour and paranoid thinking accounted for intramuscular administration in 10% of cases, and patients requested medication to help them regain control in 20%. The remaining 70% were given to ‘agitated, resistant adolescents’, and in these cases, nursing surveys noted rapid onset (within a few minutes) of calming effects, which led the authors to suggest that medication ‘appeared to provide for both patient and nurse an acceptable way of terminating a stalemated power struggle’.

Vitiello et al19 reviewed charts of 49 adolescents (mean age 15±2; mean IQ 70) in a state hospital, who were given a total of 1263 PRNs over the course of a year. Fourteen per cent of patients received no PRNs; 18% received >50 PRNs. Medications administered were based on clinician choice, and included antihistamines (54%), neuroleptics (24%) and sedative-hypnotics (chlordiazepoxide 17%, diazepam 4%). Effects of the PRNs were obtained from nursing chart notes. The drug was considered ‘effective’ if the nursing chart noted it as such or if symptoms improved within 1.5 hours; it was ‘ineffective’ if it was called ineffective or if no
improvement was observed by 1.5 hours. If documentation was insufficient to determine this, effect was categorised as ‘dubious’. Most (54%) administrations resulted in ‘dubious’ effectiveness, with 32% noted as effective and 14% as ineffective. For neuroleptics and antihistamines, intramuscular administration was more effective (41% and 44%, respectively) than oral (25% and 29%, respectively). Similarly, across all medication types, dubious effectiveness was noted more frequently for oral (60%) compared with intramuscular administration (33%). PRNs were given for disruptive behaviour, and most often between 12:00 and 14:00 hours and 20:00 and 23:00 hours. Dystonic reactions (n=3) occurred only with haloperidol which was dosed on average at 7 kg orally and 8 mg intramuscularly. The authors concluded that effectiveness of PRNs was far from demonstrated and potentially influenced by a large placebo effect.

In the only randomised controlled trial of PRN medication use to date, Vitiello et al.19 studied 21 children aged 5–13 years (mean age 8.2 years, IQ range 68–119) randomly assigned to receive PRN diphenhydramine or placebo, with the route of administration (either oral or intramuscularly) determined by clinical appropriateness. Diphenhydramine was given five times orally and four times intramuscularly; placebo was given four times orally and eight times intramuscularly. The dose of diphenhydramine was determined by weight (≥25 kg received 50 mg, <25 kg received 25 mg). Medication was given for aggressive, disruptive or self-injurious behaviours that were unresponsive to standard non-pharmacological interventions. Nurses decided when a PRN was needed. Nurses completed Conner’s abbreviated 10-item teacher rating scale20 and Clinical Global Impression21 scale before administration, and at 0.5, 1 and 2 hours after PRN administration. There was a significant time effect with all interventions, no drug versus placebo effect and a marginal route effect. Outcome measures were not standardised and relied on existing documentation, such as time in restraint or seclusion and need for administration of emergency medications. ‘Effectiveness’ was reported to be dubious, effective and ineffective. There was no difference in the number or duration of restraint episodes. Somnolence was the most frequently observed side effect, occurring only with haloperidol which was dosed on average at 7 kg orally and 8 mg intramuscularly. The authors concluded that effectiveness of PRNs was far from demonstrated and potentially influenced by a large placebo effect.

In seven cases of ziprasidone administration only, the BARS was used to measure behaviour just prior to the injections, and BARS and CGI-Improvement were used at 20–30 min following the injection. Mean BARS score decreased from 6.5±0.7 (violent/continuously active) to 3.1±1.3 (quiet/drowsy) and in 81% of cases, CGI-Improvement was ≤2 (much or very much improved). The authors concluded that ziprasidone was helpful for agitation. Drowsiness or sleep was reported as a side effect in 60% of administrations.

In a chart review of adolescents needing restraint for agitation in a psychiatric emergency room, Jangro et al.25 directly compared the effectiveness and tolerability of intramuscular ziprasidone 10 or 20 mg (n=28) with intramuscular haloperidol 2.5–10 mg given with lorazepam 1–2 mg (n=24). In seven cases of ziprasidone administration only, the BARS was administered which found time to calming was 30–45 min. There was no difference between groups in restraint duration (ziprasidone 55±5 min; haloperidol/oral lorazepam 65±7 min) or need for a ‘rescue’ medication within 60 min. There were no reported instances of excessive sedation or extrapyramidal symptoms.

Khan and Mican16 compared the efficacy and safety of intramuscular ziprasidone 10 or 20 mg (n=50) with intramuscular olanzapine 10 mg (n=50) in treating aggression from 2003 to 2005 in an inpatient child and adolescent psychiatry unit with an average LOS of 30 days. More children (≤12 years) were in the olanzapine group (n=15; mean age for total group 13.7±2.4) compared with the ziprasidone group (n=5; mean age 14.6±2.1). Most were receiving oral antipsychotics on a standing basis. Outcome measures were not standardised and relied on existing documentation, such as time in restraint or seclusion and need for administration of emergency medications. ‘Effectiveness’ was reported to be 90.2% for olanzapine and 84.9% for ziprasidone (p=0.733), although ‘effective’ was not defined. There was no difference in the number or duration of restraint episodes. Somnolence was the most frequently observed side effect.

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**Table 1** Diagnoses in samples

<table>
<thead>
<tr>
<th>Vitiello et al.19</th>
<th>Vitiello et al.26</th>
<th>Evans and Di Scipio16</th>
<th>Kahn and Mican16</th>
<th>Petti et al.11,18</th>
<th>Barzman et al.23</th>
<th>Jangro et al.25</th>
<th>Carlson et al.24,26</th>
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n/a, not available. SUD, Substance Use Disorder; OBS, Organic brain syndromes

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Second-generation antipsychotics: intramuscular ziprasidone

Stalker27 reviewed charts from 49 youth aged 8–18 (80% adolescents) in an inpatient setting who received intramuscular ziprasidone (43 received 20 mg; 6 received 10 mg) on a PRN basis for agitation, anxiety, threats or, less frequently, psychosis (n=2). Most injections (65%) were administered after 18:00 hours. Nursing notes, which were minimally informative, indicated only two youth continued to exhibit agitation or aggression during the ensuing shift and of those one required rescue medication within 4 hours. No adverse reactions were identified.

Barzman et al.23 completed a chart review of 59 hospitalised youth aged 5–19 years (75% adolescents), who were administered a total of 77 doses of intramuscular ziprasidone 10 or 20 mg. The Behavioural Activity Rating Scale (BARS)25 and CGI-Severity22 were used retrospectively to measure behaviour just prior to the injections, and BARS and CGI-Improvement were used at 20–30 min following the injection. Mean BARS score decreased from 6.5±0.7 (violent/continuously active) to 3.1±1.3 (quiet/drowsy) and in 81% of cases, CGI-Improvement was ≤2 (much or very much improved). The authors concluded that ziprasidone was helpful for agitation. Drowsiness or sleep was reported as a side effect in 60% of administrations.

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recorded side effect and no clinically significant adverse events occurred in either group.

**Oral liquid risperidone**
Carlson et al.\(^{15,26}\) conducted a prospective, institutional review board-approved study of PRN liquid risperidone in consecutively admitted children between 2002 and 2004 who had rage outbursts in the hospital. Children were aged 5–12 (mean age 9.6 years; SD = 2.1), median LOS for all admissions was 27 days and mean LOS was 102 ± 19.5. Within this sample, children with rages were significantly younger and stayed significantly longer. Outbursts were usually what precipitated the admission. There were 117 outbursts in 49 admissions, the first of which was treated behaviourally to determine the natural outburst duration, with PRN medication offered only if the episode lasted >1 hour. The average duration of the first unmedicated outburst was 50 min (SD = 32.5, median 45 min), with 36% of episodes ending in 30 min. Starting with the second outburst episode, the child was given the choice of a PRN ‘shot’ or oral liquid risperidone (all children preferred the oral alternative), which was dosed at 0.015 mg/kg. There was a dose increase of 0.02 mg/kg for the next outburst if the previous outburst lasted >30 min. A behaviour modification/positive reinforcement system was in place simultaneously to address outbursts. Outcome measure was time to behavioural control, as observed by nurses recording specific behaviours on the Children’s Agitation Inventory at 15, 30, 45, 60 min and up to 2 hours, and whether the child needed a second intervention (either isolation or another PRN medication). Of the 16 youth who had more than three outbursts and thus received liquid risperidone on more than one occasion, duration decreased from 44.36 ± 20.15 min to 25.62 ± 12.5 min (p < 0.004), although there was variability within the child and across episodes.\(^{15}\) Duration of all of the outbursts revealed 7% were <15 min, 11% between 16 and 30 min, 63% between 30 and 60 min and 19% >60 min. Also relevant was the factor analysis done on types of behaviours during the outburst and relationship to subsequent duration. Outbursts with high and intermediate anger behaviours (aggression to persons and property) peaked early and declined more rapidly than distress behaviours (crying, anxious, taking off clothes), which were less intense but lasted longer.\(^{16}\)

**Assorted medications**
Swart et al.\(^{17}\) gathered information from 338 charts of children aged 6–18 (average 12.3 ± 2.68) admitted to a residential treatment programme (LOS 94 ± 66 days). Of the 170 youth who received any PRN, 74.1% received a PRN plus another type of restraint. Medication given was based on attending physician’s orders, and included chlorpromazine (39.8%); lorazepam (19.1%); olanzapine (19.1%); trazodone (4.2%) or less frequently (each 2.2% or less, grouped together for analysis) quetiapine, loxapine, diphenhydramine, methotrimeprazine, clonazepam or risperidone. Effectiveness was measured by nurses recording ‘time to settle’ of >30 or <30 min. About 58% of administrations were ‘effective’ in <30 min, with olanzapine being slightly more ‘effective’ (61.2% of administrations) than chlorpromazine (55.3%) or lorazepam (53.7%). The study did not specify route of medication administration or medication dose. Sedation was observed with chlorpromazine, lorazepam and olanzapine; and disinhibition with lorazepam.

Petti et al.\(^{20}\) conducted a survey of hospitalised youth aged 7–17 (mean age 12 years) receiving PRN medications, including first-genera-
tion antipsychotics, antihistamines or, less frequently, orally disintegrating olanzapine. Of 57 eligible youth, 42 participated and were given a questionnai-

**DISCUSSION**
Agitated outbursts are a frequent and serious problem encountered throughout the continuum of child and adolescent mental healthcare. Nevertheless, the quality of the evidence supporting the use of PRN medication to treat them is limited. First, the heterogeneity of the samples makes it difficult to draw conclusions about the effectiveness of this intervention. For instance, the ages, IQs and treatment setting of each study population differed considerably. Two studies included children (mean age 8–9 years), three had children with a mean age of 12 years and the rest addressed adolescents. Of the adolescent group, two samples were primarily intellectually disabled youth in long-term facilities. Reason for medication administration also varied, typically including agitation, verbal threats or physical aggression; in some studies, reasons included anxiety, paranoid thinking or at youth’s request for ‘impending loss of control’. Diagnoses were equally heterogeneous (table 1), both within and between studies.

Vital to understanding effectiveness is the outcome measured. In order to evaluate outcome, we need a better understanding of the behavioural composition of outbursts and their natural history (ie, what does the child do during the outburst; how long does it take the child to calm down without any intervention). There is evidence that anger as opposed to distress outbursts have different trajectories.\(^{25}\) Some tanntrums are shorter than others even in the absence of an intervention. Thus, outcomes should include standardised metrics assessing the type and severity of behaviours at the start and end of the episode, duration of time to achieve acceptable behaviour and the type, route and side effects of the drug used.

Prospective studies used inconsistent outcome measures which included the BARS,\(^{24}\) Children’s Agitation Scale,\(^{16}\) CGI Scale,\(^{22}\) Connor’s teacher scale\(^{27}\) and youth’s report of whether the medication ‘worked’.\(^{28}\) Retrospective studies made some attempt to measure episode duration, typically interpreting existing nursing notes about activity and agitation level, or reporting commonly recorded metrics such as restraint duration or need for another dose of a PRN. One study noted that in 54% of medication administrations, the effectiveness was unclear based on chart review.\(^{19}\)

Further complicating decisions about drug effectiveness is that there is no way to accurately assess the placebo effect of giving a pill or an injection, including expectations and impact for unit staff assessing the child or the young people themselves. Injections may have a particularly potent placebo effect, given the invasiveness and sensations associated with administration. Vitiello et al.\(^{19}\) in their chart review, indicated that improvement was more likely with intramuscular administration over oral, regardless of what medication was given. In the single randomised controlled trial,\(^{20}\) medication (diphenhydramine) did not differ from placebo, although there was a trend for intramuscular to be more effective than oral administration. Evans and Di Scipio\(^{18}\) suggested that the rapid response that occurred in 70% of cases was probably the termination of a staff/patient power struggle, not really a drug effect.

Finally, medication pharmacokinetics should play a role in drug effectiveness. How long should it take a given medication to ‘work’? The sedating side effects of drugs used for PRNs are why the drugs are being used; patients are typically agitated, not psychotic or having anaphylaxis. The pharmacokinetic/pharmacodynamic models needed to explain drug onset of action are beyond the scope of this paper.\(^{29}\) Suffice it to say, the pharmacokinetic measure Tmax (time to maximum plasma level) is a reasonable metric to understand the timeline of drug side effects, given that a drug’s presence in plasma is a necessary precursor to drug effect.

The Tmax for all of the drugs used as oral PRNs is at least an hour, usually much longer. For the antihistamine diphenhydramine specifically, the Tmax is 1.3 ± 0.5 hours at a dose of 1.25 mg/kg in the elixir form,\(^{16}\) although intramuscular administration may act faster. The Tmax for oral hydroxyzine, another antihistamine used as a PRN, is about 2 hours.\(^{31}\) For antipsychotics, Tmax for oral haloperidol and chlorpromazine is 1.5 hours.
olanzapine 6 hours and risperidone 1–1.5 hours depending on whether the oral solution, m-tab or tablet are used. Intramuscular medication works more quickly, although is not often studied pharmcokinetically in youth, and exact speed depends on the drug and dose. Intramuscular administration is more consistent with a clinically relevant timeline than oral administration, although this is complicated by placebo effect, which as mentioned above may be greater with injections. Moreover, standards of care dictate that intramuscular medications should be given only when oral medications are offered and refused.

The study of diphenhydramine by Vitiello et al suggested an unimpressive effect with minimal improvement at 30 min and little difference from placebo. Studies of intramuscular ziprasidone indicated that children improved in 20–40 min, although they sometimes ended up asleep. In the only study to suggest some shortening of the episode with oral liquid risperidone, the intervention was likely influenced by length of stay and concurrent behavioural treatment on the inpatient unit. That is, children had shorter episodes later in the study, when they had been in the hospital longer and had a chance to benefit from behavioural interventions which have been shown to be useful in reducing PRNs. Given the natural history of untreated outbursts is 30–60 min, it is difficult to conclude that the medicated durations reported above necessarily represent a clinically significant drug effect.

These conclusions are similar to those drawn in reviews of PRN medication use in inpatient adults. A 2015 Cochrane review of randomised controlled trials examining the short-term outcome of PRN medication administration in patients with psychotic illnesses found 14 trials, of which none compared PRN use with standard medication regimen alone, leading the authors to conclude there was no evidence for this practice. This is notable especially given that antipsychotic medications are indicated for treatment of the underlying condition (psychosis or schizophrenia) in this population, which is frequently not the case with children and adolescents. Two systematic reviews, one of which included child and adolescent data, identified similar issues as this review, including lack of randomised controlled trials (primarily epidemiological and retrospective chart review), diversity of medications used, heterogeneous characteristics of the patient population, lack of standardised outcome measures and increased risk of adverse events. Despite the comparatively larger number of studies using adult populations, reviews of PRN use as management for acute agitation have reached similar conclusions about the lack evidence supporting this practice.

Existing policies complicate clinical practice of managing agitation in children and adolescents. Aggressive dosing may result in somnolence, which is a commonly observed side effect and difficult to effectively prevent given limited understanding of the individualised effects of medications and doses. Insofar as outbursts were more commonly observed in the evening, somnolence might be clinically acceptable, although not acceptable to regulators who take exception to drugs used as chemical restraint. Policy requires that PRN medication should not be used unless it is a standard treatment for the patient’s medical or psychiatric condition. There are no Food and Drug Administration-approved medications for the treatment of agitation outside of diagnoses of schizophrenia, bipolar mania and irritability in autism, which comprised a minority of children in these few studies. This state of affairs has been addressed before. Thus, medications commonly used as PRNs have no indication related to the underlying psychiatric diagnoses in the populations getting them. Understandably, the use of restraint and seclusion to maintain safety for the duration of agitated outbursts is severely limited by current policy. Clinicians are then caring for children and adolescents with agitated outbursts with no good evidence-based interventions in their armamentarium. If clinicians are limited in effective short-term options, parents and school personnel are left to handle children discharged as troubled as they were admitted, or the child gets referred to a long-term treatment setting.

Clinical implications

In conclusion, based on this review, available data do not provide a satisfactory answer to the question of whether PRN medications are an effective treatment for severe outbursts. Furthermore, there is insufficient data with which to develop evidence-based treatment guidelines, and we did not find evidence of effectiveness for the use of the medications mentioned in published guidelines. Current guidelines are thus based on unsubstantiated expert consensus or extrapolation from treatment of aggression in general. Further details such as PRN medication effectiveness by age, existing diagnoses, behaviours during the outbursts or accounting for standing medications are also uninformied by the existing literature. We need treatments to both shorten the duration of outbursts as well as ways of keeping them from occurring and recurring.

Limitations

Although PubMed and MEDLINE were systematically searched, we may have missed references. The search was confined to English language.

What next in research:

1. We need a label for the behaviour we are calling agitated, explosive outbursts or rages. What complicates even doing a search on the subject is not having a term. ‘Irritability’ is the current term but that encompasses a long-term mood state for which outbursts may or may not be a component. The behaviour also needs to be distinguished from general aggression which, again, implies something long term even when the concept is divided into types of aggression. Not having a label for the phenomenon of severe outbursts is at the heart of the hope that ‘prepubertal bipolar disorder’ was responsible, and the further hope that mood stabilisers and neuroleptics would eliminate this significantly impairing behaviour.

2. We need to understand the phenomenology of outbursts and whether their treatment varies by diagnosis, triggering cause, age, cognitive ability or behaviours expressed in the actual outburst.

3. We need placebo-controlled trials that, in addition to addressing whether or not a particular PRN medication is effective, also provide information regarding onset of drug effect about which we care and any interactions with other medications the child might be taking.

4. We need treatment interventions for explosive, agitated outbursts, which may include the development of medications that target this behaviour.

5. Finally, we need developmentally and diagnostically informed policies that go beyond the ‘one-size-fits-all’ approach that, however well-intended, are not always in the best interest of the people intended to be helped.

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Patient consent Not required.

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Disorders in psychiatrically hospitalized children with possible bipolar disorder.


Intramuscular olanzapine for the management of acute agitation and aggression in children and adolescents.


