



## RESEARCH ARTICLE

# Clinical pathway development to standardize pharmacological medication management of agitation in pediatric inpatient settings

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### Abstract

**Objective:** Acute agitation in pediatrics is commonly encountered in hospital settings, can contribute to significant physical and psychological distress, and management is highly varied in practice. As such, the development of a standardized pharmacologic guideline is paramount. We aimed to develop a novel clinical pathway (CP) for management of acute agitation for all hospitalized pediatric patients in Canada. **Methods:** Healthcare professionals in Canada with expertise in treating and managing pediatric agitation formed a working group and developed a CP through conducting a literature review, engaging key partners, and obtaining interdisciplinary consensus (iterative real-time discussions with content experts). Once developed, the preliminary CP was presented to additional internal and external partners via multiple grand rounds and a webinar; feedback from participants guided final CP revisions. **Results:** The working group created a pediatric inpatient CP to guide pharmacologic management of agitation and serve as an easy-to-use clinical and educational resource with three complementary sections including: 1) a treatment algorithm, 2) a quick reference medication chart, and 3) two supporting documents, which provide a general overview of non-pharmacologic strategies prior to CP implementation and an illustrative scenario to accompany the medication chart to ensure effective utilization. **Conclusions:** This is the first CP to standardize pharmacological treatment and management of acute agitation in children in inpatient settings in Canada. Although further research is warranted to assess implementation and support process improvement, the CP can be adapted by individual institutions to assist in prompt pharmacological management of pediatric agitation to potentially improve outcomes for patients, families, and healthcare professionals.

**Key Words:** *agitation, chemical restraint, child, adolescent, youth, pediatrics, paediatrics, clinical pathway*

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## Résumé

**Objectif:** L'agitation aiguë en pédiatrie survient couramment en milieu hospitalier, elle peut contribuer à une détresse physique et psychologique significative, et la prise en charge en est très variée dans la pratique. Ainsi, l'élaboration de lignes directrices pharmacologiques standardisées est essentielle. Nous cherchions à développer un nouveau parcours clinique (PC) de la prise en charge de l'agitation aiguë pour tous les patients pédiatriques hospitalisés au Canada.

**Méthodes:** Les professionnels de la santé au Canada qui ont l'expertise du traitement et de la prise en charge de l'agitation pédiatrique ont formé un groupe de travail et développé un PC en menant une revue littéraire, en embauchant des partenaires cibles, et en obtenant un consensus interdisciplinaire (discussions itératives en temps réel avec des experts en contenu). Une fois développé, le PC préliminaire a été présenté à des partenaires internes et externes additionnels lors de multiples grandes rondes et à un webinaire; les commentaires des participants ont guidé les révisions finales du PC. **Résultats:** Le groupe de travail a créé un PC pour patient psychiatrique hospitalisé afin de guider la prise en charge pharmacologique de l'agitation et de servir de ressource clinique et éducative facile à utiliser munie de trois sections complémentaires notamment : 1) un algorithme de traitement, 2) un tableau des médicaments de référence, et 3) deux documents de soutien, qui offrent un aperçu général de stratégies non-pharmacologiques avant la mise en œuvre du PC et un scénario illustré pour accompagner le tableau des médicaments afin d'assurer une utilisation efficace.

**Conclusions:** C'est le premier PC qui normalise le traitement pharmacologique et la prise en charge de l'agitation aiguë chez les enfants en milieu hospitalier au Canada. Bien que plus de recherche soit justifiée afin d'évaluer la mise en œuvre et de soutenir l'amélioration du processus, le PC peut être adapté par les institutions individuelles afin d'aider à une gestion pharmacologique rapide de l'agitation pédiatrique et de potentiellement aider à la gestion pharmacologique de l'agitation pédiatrique pour les patients, les familles et les professionnels de la santé.

**Mots clés:** agitation, contention chimique, enfant, adolescent, jeune, pédiatrie, pédiatrie, parcours clinique

## Introduction

Pediatric agitation is a behavioural syndrome that can be characterized by physical and psychological distress (1) that manifests clinically as restlessness, aggressiveness, and rapid fluctuations in emotions (2). Agitation frequently escalates and results in verbal and/or physical violence (3) toward healthcare staff (4–14), or self-harm, and may lead to severe injuries, such as unplanned extubation, bleeding

from surgical site(s), and hemorrhage (15–17), as well as delayed hospital discharge (18,19). If all other de-escalation strategies relevant and feasible to a situation fail, physical restraint(s) may be warranted (20,21) but can increase patient aggression and risk of injury (9,10), as well as psychological trauma for patients and caregivers (20,22). As such, prompt management of agitation in the inpatient setting to avoid harm to patients, families, and healthcare staff is paramount.

When agitation is mild and safety is not immediately threatened, verbal de-escalation (e.g., empathetic tones, use of simple language, and validating the patient's emotions), psychiatric evaluation, subsequent treatment of associated medical conditions and/or their unique triggers (e.g., removing stimuli and undiagnosed sources of pain for children with autism spectrum disorder (ASD)) (21,23–29), and minimizing seclusion are recommended (21,23–29). Due to the rapid onset and necessity for prompt risk reduction, pharmacological interventions are often implemented to mitigate agitation (20,21). However, there are currently few standardized safe and effective guidelines for pharmacological management of pediatric agitation. Consequently, practice is highly variable and pharmacological management may: 1) be implemented prematurely (i.e., when agitation is mild or below clinical thresholds) (1,30,31), 2) exacerbate underlying medical conditions (21,23–29) and/or 3) result in oversedation. Importantly oversedation has been associated with increased mechanical ventilation duration, hospital length of stay, and healthcare expenditures (32),

## Abbreviations

ADHD = Attention-deficit/hyperactivity disorder  
 ASD = Autism Spectrum Disorder  
 BCCH = British Columbia Children's Hospital  
 CAPD = Cornell Assessment of Pediatric Delirium scale  
 CHBC = Child Health British Columbia  
 CP = Clinical pathway  
 EPS = extrapyramidal symptoms  
 FGA = first generation antipsychotic  
 IM = intramuscular  
 IV = intravenous  
 ODD = oppositional defiant disorder  
 ODT = orally disintegrating tablet  
 PO = oral  
 PTSD = post-traumatic stress disorder  
 SGA = second generation antipsychotic  
 SL = sublingual

as well as dystonia, akathisia, neuroleptic malignant syndrome, and in rare cases, increased mortality (31).

Despite the adverse outcomes associated with agitation, there is currently no existing clinical pathway (CP) to assist with the pharmacological management of pediatric agitation across inpatient settings (i.e., medical and psychiatric settings). As healthcare staff frequently report a lack of sufficient training for treating agitation (33), a CP may be beneficial to facilitate the connection between clinical information and prompt treatment administration by outlining and standardizing care (21,34–39) to reduce practice variability (40–43), which can lead to reductions in hospital costs, patient complications, and hospital length of stay (40,41), as well as guiding trauma-informed care (44). Taken together, there is a need and opportunity to develop an inpatient pediatric agitation CP.

## Objectives

A provincial group of child and adolescent healthcare professionals formed the British Columbia (BC) treatment of Agitation with Least MEdication Restraint (B CALMER) working group to improve the management of pediatric agitation. Herein, we describe the CP development process which included a literature review, partner engagement (including family partners), and expert consensus to streamline medication management for hospitalized pediatric patients with acute agitation, including guidance for co-occurring medical conditions. This paper details the first interdisciplinary and provincial effort to generate a CP for pediatric agitation in Canada.

## Methods

The B CALMER working group was composed of a diverse team of healthcare professionals at BC Children's Hospital (BCCH) with expertise in the treatment and management of pediatric agitation, as well as consultation with the Child Health British Columbia (CHBC) Provincial Least Restraint Working Group. We used an established model for determining a CP (45), in which each step is described below.

### **1. Identifying the need for a pediatric agitation clinical pathway:**

Clinical pathways are typically developed if a condition displays the following: (1) high prevalence, or low prevalence with substantial risks associated with onset (e.g., physical injury); (2) spans multiple clinical settings; and (3) has substantial variation in clinical practice (43,46–48). Pediatric agitation is common and occurs across multiple clinical settings (e.g., intensive care unit, emergency department,

medical/surgical wards, psychiatric wards), and may escalate to aggression and physical violence towards self or others, resulting in increased utilization of healthcare resources and psychological distress to patients, health care providers and caregivers. Additionally, health care staff identify a lack of knowledge and information to guide decisions about pharmacological management of agitation in the context of co-occurring medical conditions (e.g., brain injury, ASD, malnutrition, and overdose (1,30,33,49)), as well as across institutions and clinics (17,20). These factors indicate that the development of a CP for inpatient pediatric agitation management is essential to improving care processes.

### **2. Assembling a team of experts to guide clinical pathway development:**

The B CALMER working group consisted of two pediatric consultation-liaison psychiatrists, three pharmacists, and a nurse clinician in BC, Canada who have content and clinical expertise in the treatment and management of pediatric agitation. Initial CP development was conducted by individual members (AC, DE, SL) and then shared with the CHBC Provincial Least Restraint Working Group for critical feedback and consensus generation. In addition, a pediatric intensive care unit clinical nurse educator provided ongoing guidance.

### **3. Compiling and reviewing existing pediatric agitation literature:**

A literature review was conducted in consultation with a research librarian to evaluate the current treatment guidelines for agitation in pediatric populations on medical wards for children/youth with medical conditions and illnesses. The literature review focused on: guidelines and reviews on management of aggression and agitation in pediatrics on medical wards and in the ICU (patients admitted to the medical wards with medical issues rather than agitation/aggression management in psychiatric patients) including pharmacological management, use of physical restraints or other behavioural management (de-escalation strategies) from Medline and PsycInfo databases and were restricted to articles from the previous 10 years (up to December 2022). There were no pathways or guidelines identified which provide suggestions on medication management of aggression or agitation on medical wards, including the intensive care unit. Several review articles outlined pharmacological and non-pharmacological strategies in the emergency room (i.e. the BETA guideline (29)) however these primarily addressed patients with psychiatric illness and did not address treatment of patients with medical comorbidities. These data were reviewed and used to inform pathway and manuscript development. Working group members also reviewed

institutional practices and guidelines to further inform clinical pathway development. However, evidence was frequently limited in the pediatric agitation literature; as such, content expertise, clinical judgment, and consensus discussion contributed to pathway generation when evidence was insufficient.

#### **4. Developing the clinical pathway to standardize care and facilitate best practices:**

The B CALMER working group conducted monthly meetings via telephone calls or videoconferences using Zoom (Zoom Video Communications, San Jose, CA) over an 18-month period from January 2021 to June 2022. Below we describe the iterative CP development.

##### **4.1 Preliminary development of an agitation pathway:**

Independent of the reasons listed previously, our team was also contacted in January 2021 with the request to develop a pathway to manage agitation safely on medical and surgical wards due to aggressive incidents associated with pediatric agitation being reported at BCCH. Following review of the available literature and pre-existing local pathways for agitation management in the Emergency Department and on the inpatient Psychiatry Units, we generated a preliminary CP draft (AC, SL, DE).

##### **4.2 Additional partner feedback to guide clinical pathway development:**

We sought feedback from a broader working group to achieve interdisciplinary consensus on agitation management. To iteratively guide development, team members provided feedback on the information presented and overall design. Partner feedback was obtained from a diverse cohort of representatives from Provincial Health Services Authority, Regional Health Authorities (i.e., Fraser Health, Interior Health, Northern Health, Vancouver Coastal and Providence Health, and Vancouver Island Health), and First Nations Health, as well as the CHBC Provincial Least Restraint Working Group, who are involved in the management of emergency/urgent care and inpatient pediatric agitation across BC. This included providers from child psychiatry, pediatric critical care, pharmacy, clinical education, adolescent medicine, pediatric clinical teaching unit, and eating disorder specialists. The partners reviewed each draft and provided feedback, which was directly incorporated into subsequent versions, as per group consensus and available evidence.

##### **4.3 Finalization of a clinical pathway for treatment of inpatient agitation:**

The CP was presented to additional internal and external partners via five grand rounds presentations (i.e., Pediatric Intensive Care Unit Education Day, a Clinical Teaching Unit Rounds, Adolescent Medicine Rounds, Child Psychiatry Department Meeting, and Psychiatry Resident Rounds) and one provincial webinar (i.e., CHBC and COMPASS Mental Health webinar) to gain constructive feedback prior to implementation in clinical practice. Once reaching consensus amongst the working group, external representatives from CHBC provided guidance and feedback to finalize our pathway. The CP was approved and released for use via the organization's website in January 2022. Collaboration between a diverse and representative working group should allow agitation management across multiple hospital settings.

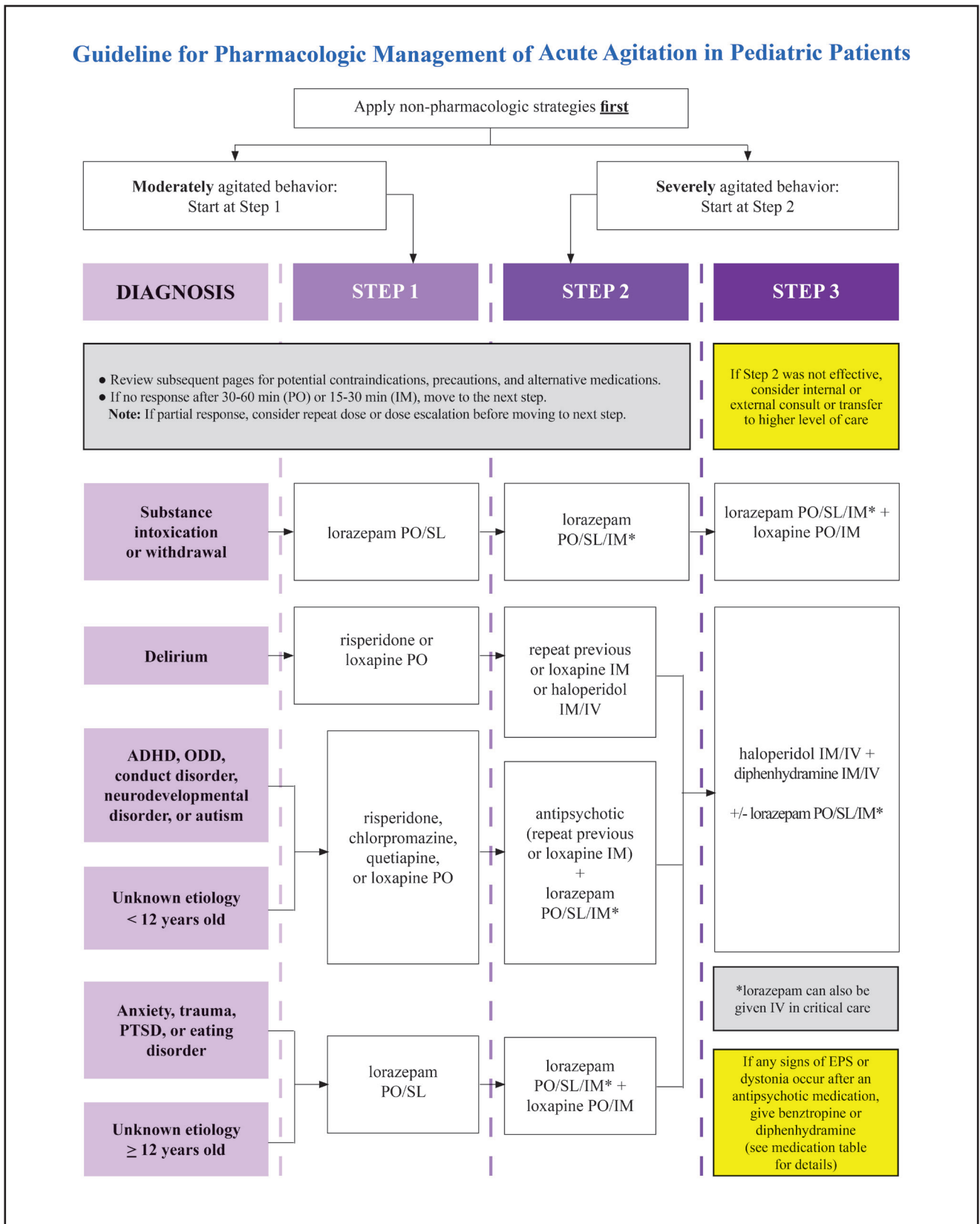
## **Results**

Following 18 months of iterative development, the B CALMER working group created a CP to guide pharmacologic management of pediatric agitation and serve as an easy-to-use clinical and educational resource with three complementary sections including: 1) a treatment algorithm, 2) a quick reference medication chart, and 3) two supporting documents. As pharmacokinetic and pharmacodynamic responses vary from individual to individual, staff must use their clinical judgment considering patient-specific factors and not solely rely on algorithm recommendations; these guidelines are meant to be flexible to adapt to local practice, which may vary according to preferences, available resources, and clinical settings.

### ***Pediatric agitation clinical pathway algorithm***

The CP treatment algorithm serves as an illustrative reference for healthcare professionals. In conjunction with the implementation of non-pharmacologic strategies (e.g., verbal de-escalation, identification of triggers, modification of environment) (see Supplemental Materials 1 for supporting document), the three steps to managing and treating children and adolescents with moderate-severe agitation for various underlying diagnoses are highlighted (Figure 1). For example, for a 14-year-old female diagnosed with ASD and anorexia nervosa complicated by bradycardia and electrolyte abnormalities who is experiencing severe agitation, the treatment algorithm suggests non-pharmacological strategies when possible, and if needed, risperidone, chlorpromazine, quetiapine or loxapine treatment administered orally. However, if this patient is refusing oral treatment and is felt to be at risk of QTc prolongation, a decision could be made

Figure 1 Clinical pathway treatment algorithm for managing inpatient pediatric agitation



Note. ADHD = Attention-deficit/hyperactivity disorder, IM = intramuscular; IV = intravenous; ODD = oppositional defiant disorder



**Figure 2. Medication consideration chart for treating and managing pediatric agitation in hospital**

		Antipsychotics (2nd generation)			Antipsychotics (1st generation)			Non-antipsychotic agents			
		quetiapine	risperidone	olanzapine	loxapine	haloperidol	methotrimeprazine	chlorpromazine	lorazepam	clonidine	diphenhydramine
P A T I E N T F A C T O R S	↑ QTc interval?	✗	⚠	✓	⚠	✗	⚠	⚠	✓	✓	⚠
	Hypotensive/ ↑ falls risk?	✗	⚠	⚠ (PO) ✗ (IM)	✓	✓	✗	✗	⚠	✗	⚠
	Anticholinergic delirium?	✗	✓	✗	⚠	✓	✗	✗	✓	⚠	✗
	Seizures/ ↑ seizure risk?	⚠	⚠	⚠	✓	✓	⚠	✗	✓	✓	⚠
	Eating Disorder?	⚠	⚠	⚠	✓	✗	⚠	⚠	✓	⚠	✓
	Developmental disorder/autism	✓	✓	✓	✓	✗	✓	✓	⚠ <sup>d</sup>	✓	⚠ <sup>d</sup>
D R U G F A C T O R S	Opioid use/ respiratory depression?	⚠	⚠	⚠	⚠	⚠	⚠	⚠	✗	✓	⚠
		quetiapine	risperidone	olanzapine	loxapine	haloperidol	methotrimeprazine	chlorpromazine	lorazepam	clonidine	diphenhydramine
	Routes/Dosage Forms	PO (TABLET)	PO (TABLET, LIQUID)	PO (TABLET, ODT) IM <sup>a,b</sup>	PO (TABLET, ODT) IM	PO (TABLET, ODT) IM/IV	PO (TABLET, ODT) IM/IV	PO (TABLET)	PO/SL (TABLET) IM	PO (TABLET, LIQUID)	PO (TABLET, LIQUID) IM
	EPS risk	+	++	+	++	++++	+	+	↓EPS	n/a	↓EPS
	Sedation properties	+++	++	++	+	+	+++	+++	++ <sup>d</sup>	++	++ <sup>d</sup>
	Useful as a PRN to treat acute agitation	✓	✓	✗ (PO/ODT) ✓ (IM)	✓	✓	✓	✓	✓	✗	✓
Time to onset of action	~30-60 min	~60-75 min	~15 min(IM) ~6 hr (PO/ODT)	~30 min (all forms)	~15 min (IM) ~3-20min (IV) ~2 hr (PO)	~30 min (IM) c ~15 min (IV) c ~1 hr (PO)	~30-45 min	~20-30 min (all forms)	~30-60 min	~30-45 min (PO) ~15-30 min (IM)	
Duration of action	~4-6 hr	~12-24 hr	~2 hr (IM) ~12-24 hr (PO)	~12 hr	~4-12 hr	~2-4 hr	~4-6 hr	~6-8 hr	~3-4 hr	~4-6 hr	

✓ optimal choice   
 ⚠ caution   
 ✗ less optimal choice

Note. EPS = extrapyramidal symptoms, IM = intramuscular; IV = intravenous; ODT = orally disintegrating tablet; PO = oral; SL = sublingual.  
<sup>a</sup> Peak serum level five times higher with IM form compared to PO  
<sup>b</sup> IM form CONTRAINDICATED within 1 hour of parenteral benzodiazepine  
<sup>c</sup> Peak serum level two times higher with IM/IV form compared to PO  
<sup>d</sup> Note: Increased risk of paradoxical agitation

based on patient specific factors to instead provide initial treatment with intramuscular olanzapine 2.5 mg.

**A medication comparison chart for multiple clinical settings**

As an adjunct to the treatment algorithm, a user-friendly quick reference medication chart was created to provide further education and support for interdisciplinary pediatric healthcare professionals and guide agitation management across hospital settings; this document will also assist with the standardization of pharmacologically managing

agitation and increase CP algorithm utilization. Furthermore, the chart outlines patient factors (e.g., common medical issues, neurodevelopmental factors) and drug factors (e.g., sedation properties, time to onset of action, duration of action) for consideration across first and second generation antipsychotic and non-antipsychotic medications (Figure 2).

For further consideration when pharmacologically managing agitation, we developed the “guide to implementing the medication comparison chart”, which provides a clinical scenario as an instructive example of how to use the

comparison chart in practice (see Supplemental File 2). For additional guidance when using the medication comparison chart, the authors also developed a quick reference guide to describe dosing, mechanism of action, adverse effects, and contraindications of commonly prescribed medications to treat pediatric agitation (see Table 1).

## Discussion

Despite agitation being a prevalent condition that is frequently associated with poor clinical outcomes among hospitalized children, staff often report inadequate training to manage agitation and thus practice remains highly variable. To promote a user-friendly and standardized approach to pharmacological management of pediatric agitation in hospital settings for patients with co-morbid medical conditions, we present a novel and consensus-driven CP developed by a diverse group of healthcare professionals (i.e., consultation-liaison psychiatrists, pharmacists, and a nurse clinician) who have content and clinical expertise in the treatment and management of agitation. The CP has three complementary sections (a treatment algorithm, medication chart, and two supporting documents) to ensure effective utilization. Although clinical evaluation is required, we envision that implementing the clinical pathway has the potential to improve the management of pediatric agitation in hospital and avoid undesirable effects of suboptimal pharmacologic administration.

Due to the multifactorial nature and multidisciplinary management of pediatric agitation (30), our CP and supporting documents were created to facilitate future education, implementation, and cross-departmental buy-in to ensure effective in hospital utilization. For example, the treatment algorithm, medication chart, and two supporting documents were reviewed and edited by multiple content experts and a clinical nurse educator to ensure that the documents were user-friendly and could be easily implemented as a reference tool at bedside. The treatment algorithm and medication chart are meant to be stand-alone documents in practice and have supporting text as an informative adjunct as required. The medication dosing suggestions and maximum doses were selected based on their use for treatment of a single episode of acute agitation. If these orders are continued beyond the acute episode, they should be aligned with suggested 24 hour maximum doses found in local institutional pediatric drug dosage guidelines.

Importantly, the CP provides recommendations guided by partner feedback and expert consensus due to a frequent lack of evidence-based literature; the CP was reviewed by multiple partners and content experts with an interest in improving and standardizing pediatric agitation pharmacologic

management in BC. However, our CP is not a prescriptive methodology and is meant to be implemented and modified as required by healthcare professionals across acute care settings; CPs are not created to replace the clinical judgment of individual healthcare professionals (50). Additionally, while CPs like ours are built to reduce variability in practice, they are not meant to homogenize patients in the eyes of healthcare professionals (46,50). Conversely, CPs help facilitate individual care by highlighting deviations from routine care and anticipated outcomes (50). Thus, this CP has the potential to improve outcomes for hospitalized children experiencing moderate-severe agitation, further integrate consult-liaison psychiatry and pharmacist teams across medical units in hospital, minimize the use of physical restraint and staff and patient injury, as well as provide education and guidance to healthcare professionals unable to obtain immediate psychiatric consultation to guide pediatric agitation management.

## Limitations

Although the CP was guided by expert consensus and partner feedback, there was consistent lack of published evidence for many recommendations. Consequently, a systematic review and/or meta-analysis was not conducted. Another limitation is the lack of a systematic approach to reach expert consensus (i.e., Delphi method), which authors tried to resolve by conducting multiple real-time discussions to arrive at pathway consensus, as ideas and critiques of the pathway were introduced, addressed, and reassessed to guide iterative development. Unfortunately, feedback statements from various partners were not systematically documented and thus qualitative analysis of prominent themes cannot be reported; however, feedback was directly incorporated into the pathway. Our sample comprised a relatively small cohort of clinicians at a single center, which may limit pathway generalizability. The B CALMER working group tried to address this limitation by consulting with the CHBC Provincial Least Restraint Working Group and including partners from multiple clinics/units within BCCH, which were comprised of a diverse cohort of healthcare professionals. This limitation could be further addressed by performing a large-scale environmental scan (e.g., nationally) and engaging individuals/families with lived experience to gain additional insight and generalizability. Lastly, although the current article describes development and content of a novel CP, future assessment of patient, family, and healthcare professional outcome improvement is warranted. Future revisions of this guideline could consider incorporation of 24 hour maximum doses to avoid additional adverse consequences such as suggested by other authors (51). Future

**Table 1. Description and clinical considerations of commonly prescribed medications for managing acute pediatric agitation**

Name	Usual Dose (For Acute Episode)	Mechanism of Action	Selected Potential Adverse Effects	Contraindications
Benztropine	EPS: 0.5-1 mg/dose PO/IM Max: 0.1 mg/kg/24h or 6 mg/24h Acute dystonia: 1-2 mg/dose IM/IV	Anticholinergic	Sedation, dry mouth, blurred vision, tachycardia, constipation, urinary retention.	Avoid: Age < 3 years (use diphenhydramine), anticholinergic delirium Caution: Ileus, narrow angle glaucoma
Chlorpromazine	0.5-1 mg/kg/dose PO (round to nearest 12.5 mg) Max: 50 mg/dose	FGA, low potency	Postural hypotension, tachycardia, QTc prolongation, lowered seizure threshold. Less risk of EPS vs. haloperidol, but more anticholinergic effects.	Avoid: Seizure disorders, anticholinergic delirium Caution: Cardiac conditions, other QTc prolonging medications
Clonidine	1 mcg/kg/dose PO Max: 50 mcg/dose	Alpha-2 agonist	Dizziness, hypotension, bradycardia.	Avoid: Hypotension, bradycardia Caution: Anticholinergic delirium
Diphenhydramine	1 mg/kg/dose PO/IM/IV (round to nearest 5 mg). Max: 50 mg/dose. Given with haloperidol to prevent dystonic reaction. Use IM/IV route for treating acute dystonia.	Anticholinergic, used to treat agitation or EPS/dystonia	Sedation, dry mouth, blurred vision, tachycardia, constipation, urinary retention. QTc prolongation in high doses. Paradoxical excitation can occur; more common in younger children and those with neurodevelopmental disorders.	Avoid: Anticholinergic delirium Caution: Ileus, narrow angle glaucoma
Haloperidol	0.025-0.075 mg/kg/dose PO/IM/IV Max: 5 mg/dose	FGA, high potency	High incidence of EPS and dystonic reactions in children and adolescents. IM route may have higher risk of dystonia, and IV route may have higher risk of QTc prolongation. Hypotension, lowered seizure threshold. Minimal anticholinergic effects.	Avoid: Cardiac conditions (particularly arrhythmias or prolonged QTc), other QTc prolonging medications Caution: Seizure disorders
Lorazepam	0.025-0.1 mg/kg/dose PO/SL/IM (round to nearest 0.25 mg) Max: 2 mg/dose (higher doses may be required for stimulant overdose or substance withdrawal; max single dose 4 mg)	Benzodiazepine	Confusion, mild cardiovascular suppression. Higher risk of respiratory depression when combined with opioids. Paradoxical excitation can occur; more common in younger children and neurodevelopmental disorders.	Avoid: Respiratory depression Caution: Patients taking opioids
Loxapine	0.1-0.2 mg/kg/dose PO/IM (round to nearest 2.5 mg) Max: 25 mg/dose	FGA, moderate potency	Moderate incidence of EPS and dystonic reactions, moderate anticholinergic effects.	Caution: Cardiac conditions, seizure disorders, other QT prolonging medications, anticholinergic delirium



Table 1. continued 1

Name	Usual Dose (For Acute Episode)	Mechanism of Action	Selected Potential Adverse Effects	Contraindications
Methotrimeprazine	Child: 0.125 mg/kg/dose PO Adolescent: 2.5-10 mg/dose PO Child & Adolescent: 0.06 mg/kg/ dose IM/IV (round to nearest 2.5 mg)	FGA, low potency	Sedation, anticholinergic effects, postural hypotension. Less risk of EPS vs. haloperidol, but more anticholinergic effects.	Avoid: Hypotension, anticholinergic delirium Caution: Seizure disorders, cardiac conditions, other QTc prolonging medications
Olanzapine	2.5-10 mg/dose 1M Max: 3 doses or 20 mg/24h, given 2-4 h apart (onset of PO route too slow for PRN use in acute agitation)	SGA	Postural hypotension (monitor before each IM dose), anticholinergic effects, lowered seizure threshold, akathisia. Minimal risk of QTc prolongation.	Do NOT combine IM route within 1 hour of parenteral benzodiazepine; reported cases of respiratory depression and death. Avoid: Hypotension, anticholinergic delirium Caution: Seizure disorders
Quetiapine	Child: 12.5-50 mg/dose PO Adolescent: 25-100 mg/dose PO	SGA	Sedation, dizziness, postural hypotension, tachycardia, QTc prolongation, anticholinergic effects, lowered seizure threshold. Lower risk of EPS than other agents.	Avoid: QTc prolongation, hypotension, anticholinergic delirium Caution: Cardiac conditions, other QTc prolonging medications, seizure disorders
Risperidone	Child: 0.125-0.5 mg/dose PO Adolescent: 0.25-1 mg/dose PO	SGA	Postural hypotension, EPS (in higher doses), lowered seizure threshold, akathisia. Minimal risk of anticholinergic effects.	Caution: Seizure disorders, cardiac conditions, CYP2D6 inhibitors (e.g., fluoxetine) — consider dose reduction with repeat/regular dosing of risperidone
Note. EPS = extrapyramidal symptoms; FGA = first generation antipsychotic; IM = intramuscular; IV = intravenous; PO = oral; SGA = second generation antipsychotic; SL = sublingual.				

revisions should consider the incorporation of standardized tools to measure agitation.

This is the first CP to standardize pharmacological treatment and management of pediatric agitation in hospital settings for patients with co-morbid medical conditions, which addresses a substantial gap in current Canadian guidelines of care. Although further research is warranted to assess implementation efficacy and process improvement, the current CP can be adapted by individual institutions to assist in prompt pharmacological management of pediatric agitation, which has the potential to collectively improve outcomes for patients, families, and healthcare professionals.

## Ethics Statement

As this working group aimed to establish a clinical pathway for clinical educational purposes and all members volunteered to participate in the pathway development initiative, ethics approval was not required for the current study.

## Authors' contributions

MDW and KG drafted the initial manuscript, and coordinated all manuscript edits and revisions; DE, KS, SL, JM, RC, and AC participated in the conceptualization and design of the study, developed and provided feedback on the clinical pathway, drafted sections of the initial manuscript, and

provided content expertise to guide manuscript editing. All authors approved the final manuscript as submitted.

## Data Access

Data sharing is not applicable to this article as no new primary data were created or analyzed in this study.

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## Conflict of Interest

DE is part of the Pharmacogenetic-Guided Antidepressant Prescribing (PGx-GAP) in Adolescents Data Safety Monitoring Board; KS is an unpaid BC representative of the Canadian Academy of Child and Adolescent Psychiatry (CACAP). All other authors declare no conflict of interest.

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## Supplemental file 1

### Steps in determining agitation management strategies

#### **Initial assessment**

Agitation signals distress and dysfunction, like an abnormal vital sign. There are many etiologies and contributing factors, and any child may become agitated in a stressful, anxiety-provoking, or painful setting. Importantly, children with neurodevelopmental disorders are more vulnerable to emotional and behavioural dysregulation. Common medical causes include delirium, brain injury, substance use or withdrawal, whereas common psychiatric causes include anxiety, psychosis, and catatonia; underlying factors, such as pain, procedural anxiety, and sleep deprivation, may also increase risk for agitation. Best practices for the evaluation and treatment of agitated children and adolescents in an emergency department setting recommends: *“There is consensus that management of agitation in the ED should be individualized, multidisciplinary, and collaborative. Medication should serve as one part of a comprehensive strategy to address the behavior. Clinicians should attempt to understand the etiologic factors leading to agitation, use non-pharmacologic de-escalations strategies, and choose medication based on the patient’s specific needs and history.”*[21, page 411]. These guidelines apply in any hospital setting.

#### **Engagement**

Engagement strategies aim to support the child’s safety by building rapport, supporting autonomy and sense of self-control, accessing the child’s regulation skills, and reducing triggers. Communication is key; use simple and direct language in a calm voice, describe roles, ask for child’s input, provide choices, and inform the child of each step. Attempt to problem solve together with the child and family and elicit typical coping skills.

#### **Environmental supports**

Environmental supports can help by reducing triggers, increasing a sense of calm, and building rapport. Place child/youth in a quiet area, decrease sensory stimulation, and offer distraction tools.

#### **Medication administration**

Medication may be offered or suggested for sedation, reduction of anxiety and dysregulation when engagement and environmental options are insufficient. Injectable medication may be used as a form of restraint when non-pharmacological strategies are not sufficient, and safety is a concern. If injectable medication is chosen, continue to offer oral medication as an alternative to the child/youth, prior to injecting a medication.

#### **Physical restraint**

Physical restraint may be necessary for patients whose agitation is severe enough that their or other’s safety is compromised. Seclusion and physical/mechanical restraint are options and should be determined based on the patient’s medical status, what has worked in the past for the patient, the availability of restraints, etc. Always return to engagement, environmental strategies and/or oral medication as soon as possible. Explain clearly that everyone wants the child/youth out of the seclusion room, or restraints to be removed as soon as it is safe to do so.



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## Supplemental file 2

### Guide to implementing the medication comparison chart

When choosing a medication to manage agitation, there are many factors to consider. Figure 2 details information specific to each individual patient (patient factors) and for each type of medication (drug factors). These include details related to a patient's underlying factors and medical status (e.g., risk of seizures, QTc prolongation, respiratory depression) and provides relevant medication related information to consider (e.g., time of onset of action, available routes and level of sedation).

For illustrative purposes, the authors have created the following clinical scenario. A 13-year-old boy admitted to ICU with severe burns is severely agitated and diagnosed with delirium (patient is disoriented, level of attention fluctuates, and Cornell Assessment of Pediatric Delirium (CAPD) scores are 18 to 20). He is at risk for arrhythmias due to hypermetabolic state and being on other QTc prolonging medication. Due to burns on his chest, an accurate ECG is not available. An overall plan to treat any underlying causes of delirium, such as reducing deliriogenic medication (benzodiazepines and morphine), is implemented. Non-pharmacological strategies for management of delirium and agitation are also in place. His agitation is sufficiently severe that there is concern for his safety. Figure 2 provides information that guides the clinician in determining safest and most optimal medication. Considering the risk of arrhythmias, the clinician will avoid QTc prolonging medication, if possible, thus olanzapine, clonidine and lorazepam are best choices. Lorazepam will likely contribute to his delirium; thus, clonidine and olanzapine are deemed the best options. The patient is already on an optimal dose of clonidine, so the clinician determines that olanzapine should be started. The patient's blood pressure is within the normal range, and there are no current concerns about respiration. Reviewing the chart, the clinician notes that olanzapine's duration of action is 12 to 24 hours, onset of action is 6 hours, and that olanzapine is sedating. A starting dose of 2.5 mg at hs is prescribed.