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Special Article

Canadian Guidelines on Pharmacotherapy for Disruptive and Aggressive Behaviour in Children and Adolescents With Attention-Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, or Conduct Disorder

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Objective: To develop evidence-based guidelines on pharmacotherapy for severe disruptive and aggressive behaviour in children and adolescents with attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), or conduct disorder (CD). The guidelines assume that psychosocial interventions have been pursued but did not achieve sufficient improvement.

Method: A multidisciplinary consensus group used the Grading of Recommendations Assessment, Development and Evaluation approach for rating evidence quality and for grading recommendations. We conducted a systematic review of medications studied in placebo-controlled trials for treating disruptive and aggressive behaviour in children and adolescents with ADHD, ODD, or CD. We followed consensus procedures to make 1 of 4 recommendations for each medication: strong, in favour (↑↑); conditional, in favour (↑?); conditional, against (↓?); and strong, against (↓↓).

Results: For children and adolescents with disruptive or aggressive behaviour associated with ADHD, psychostimulants received a strong recommendation in favour of use, while atomoxetine and alpha-2 agonists received a conditional recommendation in favour of use. If these patients do poorly with ADHD medications, the medication with the most evidence is risperidone. Risperidone also has the most evidence for treating disruptive or aggressive behaviour in the absence of ADHD. However, given risperidone's major adverse effects, it received only a conditional recommendation in favour of use. We recommended against using quetiapine, haloperidol, lithium, or carbamazepine because of the poor quality of evidence and their major adverse effects.

Conclusion: When severe disruptive or aggressive behaviour occurs with ADHD, medications for ADHD should be used first. Other medications have major adverse effects and, with the exception of risperidone, very limited evidence to support their use.

Lignes directrices de la pharmacothérapie du comportement perturbateur et agressif chez les enfants et adolescents souffrants du trouble de déficit de l'attention avec hyperactivité, du trouble oppositionnel avec provocation, ou du trouble des conduites

Objectif : Élaborer des lignes directrices fondées sur les données probantes de la pharmacothérapie du comportement perturbateur et agressif chez les enfants et adolescents souffrant du trouble de déficit de l'attention avec hyperactivité (TDAH), du trouble oppositionnel avec provocation (TOP), ou du trouble des conduites (TC). Les lignes directrices présupposent que des interventions psychosociales ont eu lieu mais n'ont pas entraîné suffisamment d'amélioration.

Méthode : Un groupe de consensus multidisciplinaire a utilisé l'approche de classement de l'analyse, de l'élaboration et de l'évaluation des recommandations pour coter la qualité des données probantes et pour classer les recommandations. Nous avons mené une revue systématique des médicaments étudiés dans des essais contrôlés contre placebo pour traiter le comportement perturbateur et agressif chez des enfants et des adolescents souffrant du TDAH, du TOP ou du TC. Nous avons suivi des procédures consensuelles pour faire de 1 à 4 recommandations pour chaque médicament : forte, en faveur (↑↑); conditionnelle, en faveur (↑?); conditionnelle, contre (↓?); et forte, contre (↓↓).

Résultats : Pour les enfants et les adolescents ayant un comportement perturbateur ou agressif associé au TDAH, les psychostimulants ont reçu une recommandation forte en faveur de l'utilisation, tandis que l'atomoxétine et les agonistes alpha-2 ont reçu une recommandation conditionnelle en faveur de l'utilisation. Si ces patients répondent mal aux médicaments du TDAH, le médicament qui compte le plus de données probantes est la rispéridone. La rispéridone compte aussi le plus de données probantes pour traiter le comportement perturbateur ou agressif en l'absence de TDAH. Cependant, étant donné les effets indésirables majeurs de la rispéridone, elle n'a reçu qu'une recommandation conditionnelle en faveur de l'utilisation. Nous n'avons pas recommandé l'utilisation de quétiapine, d'halopéridol, de lithium, ou de carbamazépine en raison de la mauvaise qualité des données probantes et de leurs effets indésirables majeurs.

Conclusion : Quand de graves comportements perturbateurs ou agressifs surviennent dans le TDAH, les médicaments du TDAH devraient être utilisés en premier. Les autres médicaments ont des effets indésirables majeurs et, à l'exception de la rispéridone, une évidence très limitée qui supporte leur utilisation.

Oppositional and aggressive behaviours are common in school-age children, while adolescents may also test limits, argue with adults, and break rules. Such behaviours are usually developmentally appropriate, but when they are severe and persistent, they may represent psychopathologies, such as ODD or CD, which are often comorbid with ADHD. Children and adolescents with severe disruptive and aggressive behaviour can pose safety risks, disturb family functioning, and experience considerable impairment in their emotional, social, and academic development.[1–3] Therefore, it is critical that they and their families receive comprehensive assessment, evidence-based treatment, and continued support and monitoring. Important steps toward this goal include the development of clinical practice guidelines, followed by measures to facilitate local implementation.[4,5] Until recently, however, limited synthesized information was available to guide assessment and treatment of disruptive and aggressive behaviour in children and adolescents.[6,7] Further, the use of second-generation antipsychotics to treat these problems has dramatically increased[8,9] despite limited evidence of efficacy[10] and serious adverse effects.[11] To address the above concerns, the T-MAY guidelines were developed by the Center for Education and Research on Mental Health Therapeutics.[6,7] These guidelines have many strengths, including their comprehensive scope, the contributors' expertise, and the rigorous methods for grading recommendations. A particularly important finding of the T-MAY literature review is that substantial evidence supports the use of psychosocial interventions, with

Abbreviations

ADHD	attention-deficit hyperactivity disorder
ASD	autism spectrum disorder
CD	conduct disorder
CGI-I	Clinical Global Impression—Improvement
CGI-S	Clinical Global Impression—Severity
EP	evidence profile
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ODD	oppositional defiant disorder
SoF	summary of findings
T-MAY	Treatment of Maladaptive Aggression in Youth

"an overall effect size of 0.36 in the acute phase (range: 0.09–0.98, median: 0.37)."[7, p e1583] Given this evidence for efficacy and the low risks, the authors make a very strong (meaning that more than 90% of the experts agreed with it) recommendation for providing evidence-based psychosocial interventions as the first-line treatment for children and adolescents with maladaptive aggression. They also recommend that psychosocial interventions should continue during all phases of care.[7] Indeed, even when it has been decided to pursue pharmacotherapy, continued or subsequent attempts to implement psychosocial interventions are likely to be useful.

Our group largely supports the T-MAY guidelines, especially the emphasis on family engagement, careful assessment and diagnosis, and the use of psychosocial interventions as first-line treatment and during all phases of care. However, we identified several limitations in the T-MAY literature review and recommendations regarding pharmacotherapy. First, the T-MAY guidelines focus specifically on aggression, and they do not make recommendations regarding pharmacotherapy for a broader range of disruptive behaviours, including oppositional defiant symptoms and conduct problems. Second, they do not consider studies of atomoxetine or alpha-2 agonists. Third, they make recommendations about the use of medication classes as a whole, specifically antipsychotics and mood stabilizers, without highlighting the different evidence for efficacy and adverse effects associated with different agents within each class. Fourth, their literature review considers together studies involving subjects with average intelligence, subaverage intelligence, and ASD, whereas our view is that these represent clinically distinct populations, and thus the evidence for each should be considered separately when formulating recommendations. Finally, we believe that for Canadian clinicians, it is useful to have guidelines developed by Canadian specialists who are sensitive to the Canadian context.

To address these limitations, we have developed these guidelines to be used in concert with the T-MAY guidelines. The scope of our guidelines is much narrower, as we assume that psychosocial interventions have already been implemented and have brought about insufficient improvement, leading to consideration of pharmacotherapy. We also focus on the management of disruptive and aggressive behaviours that occur in the context of ADHD, ODD, and CD. We provide specific recommendations for each medication, considering the populations and outcomes studied, the evidence for efficacy, the side effect burden, and our perception of the values and preferences of patients and families. Information regarding efficacy and adverse effects is concisely summarized, helping readers to weigh and compare the benefits and risks of each medication for themselves.

Objective

Our objective was to develop specific, evidence-based guidelines on pharmacotherapy for functionally disabling oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD, or CD. The starting point for these guidelines is that concerted efforts have already been made to provide evidence-based psychosocial treatment, and a collaborative decision has been reached with the family to consider pharmacotherapy as well. Using the GRADE approach,[12] we provide recommendations for all medications that have placebo-controlled evidence and are commercially available in Canada. The guidelines are intended mainly for clinicians who provide care for children and adolescents with behavioural problems, but we encourage clinicians to discuss them with families when pharmacotherapy is considered for this indication.

Clinical Implications

- When severe disruptive or aggressive behaviour occurs with ADHD, medications for ADHD should be used first.
- Risperidone is the only other medication supported by at least moderate-quality evidence for treating disruptive or aggressive behaviour.
- In the treatment of disruptive or aggressive behaviour, adverse effects of antipsychotics and mood stabilizers often outweigh the evidence for efficacy.

Limitations

- Research is limited regarding pharmacotherapy for disruptive behaviours in the absence of ADHD, although the most evidence exists for risperidone.
- In studies of ADHD medications, disruptive behaviours other than core ADHD symptoms were generally secondary outcomes.
- Studies of atomoxetine, guanfacine, and clonidine did not assess the effects on aggression specifically.

Methods

These guidelines were developed using the GRADE approach, a rigorous and widely adopted system for rating the quality of evidence and for grading recommendations.[13] The GRADE approach involves several steps: defining the question, specifying patient-important outcomes, conducting a systematic review of the relevant literature, rating the quality of the evidence, and deciding on the direction and strength of recommendations.[12] End points of the GRADE evidence summary are EP tables and the SoF table. EP tables are more detailed and provide an explicit judgment of each factor that determines the quality of evidence for each outcome. The SoF table is more concise and provides the overall assessment of the quality of evidence for each outcome.[12]

We considered the following question for each medication: What is the clinical efficacy and side effect burden, compared with placebo, in the treatment of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD, or CD? We assessed all medications with at least 1 randomized, placebo-controlled

Table 1 Explanation of Grading of Recommendations Assessment, Development and Evaluation recommendations[23]

Recommendation categories	Strong recommendation in favour of an intervention (↑↑) Conditional[a] recommendation in favour of an intervention (↑?) Conditional recommendation against an intervention (↓?) Strong recommendation against an intervention (↓↓)
Factors that influence the strength of a recommendation	Quality of the available supporting evidence Magnitude of the difference between the desirable and undesirable consequences Certainty about values and preferences of patients Resource expenditures entailed
Comparison of implications of a strong or a conditional recommendation	For patients: Strong recommendation: Most patients would want the recommended course of action, and only a small proportion would not Conditional recommendation: Most patients would want the recommended course of action, but a substantial proportion would not For clinicians: Strong recommendation: Most patients should receive the recommended course of action Conditional recommendation: Recognize that different choices will be appropriate for different patients, and make a greater effort to help patients arrive at a management decision consistent with their values and preferences

[a] We selected the term conditional rather than the often used weak, or the alternatives discretionary or qualified. Our rationale was that a weak recommendation may be misinterpreted to mean that the evidence is weak, when in fact factors other than the quality of evidence may contribute to a weak recommendation. The term conditional also appropriately suggests that clinicians should consider specific conditions when deciding whether to recommend an intervention.[56]

trial in a paediatric sample, where at least 1 of the 3 types of disruptive behaviour (oppositionality, conduct problems, or aggression) was included as a primary or secondary outcome. Subjects in the studies we considered were generally between the ages of 6 and 18 years.[14,15] For most medications, study outcomes did not capture all 3 types of disruptive behaviour, in which case we commented only on the disruptive behaviour that was measured. To ensure that we considered uncommon and rare adverse effects as well as common ones, we reviewed adverse effect data from numerous sources in addition to the Systematic Review associated with these guidelines.[14,15]

Methods pertaining to the two Systematic Reviews and the rating of evidence quality are described in separate reports.[14,15] The medications included in those papers are psychostimulants (short- and long-acting formulations of methylphenidate and amphetamines), atomoxetine, guanfacine (extended release), clonidine (immediate and extended release), risperidone, quetiapine (immediate release), haloperidol, thioridazine, lithium (immediate release), valproate (immediate and extended release), and carbamazepine (immediate release). We developed recommendations for each of these except thioridazine, which is no longer commercially available in Canada. Some risperidone studies involved subjects with subaverage intelligence (IQ = 36 to 84),[16–19] whereas others excluded potential subjects with at least mild intellectual disability (IQ $\geq$ 70 to 75).[20–22] In our opinion, these 2 groups represent clinically distinct populations; therefore, we conducted separate evidence reviews and provide separate recommendations for each. Studies of the other medications were generally in subjects with average intelligence. We excluded studies involving subjects with ASD, as this population was considered distinct from children and adolescents without ASD regarding the clinical presentation and likely pathophysiology of disruptive and aggressive behaviours.

In the GRADE approach, recommendations are partly based on the quality of evidence, but are conceptually distinct and determined separately by considering several other factors. These include the magnitude of the difference between the desirable and undesirable consequences of the intervention, certainty about the values and preferences of the patients, and the implications regarding resource use.[23] Thus, even if an intervention has high-quality evidence to support its efficacy, it may not receive a strong recommendation if the benefits are modest, if the risks are considerable, if it is uncertain how most patients would weigh the benefits and risks, or if it is not cost-effective when compared with acceptable alternatives.

To determine the quality of evidence, assess the side effect burden, and make a recommendation for each medication, we assembled a multidisciplinary consensus group comprising 12 members from across Canada with expertise in child and adolescent psychiatry, pediatrics, neurology, pharmacology, knowledge synthesis, and guideline development. All 12 consensus group members anonymously participated in online surveys through SurveyMonkey,[24] following an email invitation that included detailed instructions for applying the GRADE approach, as well as the evidence review for each medication. In the surveys, participants were asked to rate the quality of evidence and side effect burden for each

medication included in the systematic review, and to make a recommendation for each medication except thioridazine. In keeping with the GRADE approach, participants considered both the direction and the strength of a recommendation: they determined whether to recommend in favour or against each medication, and whether the recommendation is strong or conditional.[25] Thus 1 of 4 recommendations was made for each medication: strong, in favour (↑↑); conditional, in favour (↑?); conditional, against (↓?); strong, against (↓↓) (Table 1).

When making recommendations, participants used their clinical experience to consider perceived values and preferences of patients and families. These include placing value on psychosocial interventions, which help develop coping skills and foster self-efficacy; a preference to pursue pharmacotherapy only after psychosocial interventions have proved inadequate, or in emergency situations; a wish for improvement that is meaningful regarding daily functioning and quality of life; greater comfort with medications that are well studied and have been widely used for a significant duration; and concern regarding adverse effects, especially those that are serious or have long-term consequences.

The results of the surveys on psychostimulants, clonidine, guanfacine, risperidone, and quetiapine were summarized and then reviewed during an in-person meeting (March 5, 2014) attended by 7 of the 12 consensus group members. Differences in survey responses for these medications were discussed and resolved. For the remaining medications, results of the surveys were communicated and differences were resolved through emails and conference calls.

The guidelines were externally reviewed by members of the Canadian Paediatric Society, the Canadian Academy of Child and Adolescent Psychiatry, and the Centre for ADHD Awareness Canada. They were also reviewed by parents of children and adolescents with disruptive or aggressive behaviour in the context of ADHD, ODD, or CD. All feedback from the external reviews was considered by the consensus group and incorporated into the final document.

Results

Our SoF table, which provides the overall assessment of the quality of evidence for each medication, is presented as Table 2. The more detailed EP tables are presented in separate reports.[14,15] For most medications, placebo-controlled trials have been conducted both in children and in adolescents. However, as this was not the case for some medications, Table 2 indicates whether a given medication has been studied in children, adolescents, or both. In addition, the EP tables provide the age range of subjects in each trial included in the systematic review.[14,15]

A summary of our recommendations is presented as Table 3, along with ratings of the magnitude of benefit and side effect burden for each medication. More detailed information regarding our recommendations is provided in the sections that follow, and specific adverse effects of each medication are listed in online eTable 4.

Psychostimulants for Oppositional Behaviour, Conduct Problems, and Aggression in Children and Adolescents With ADHD, With or Without ODD or CD

- Quality of evidence: high
- Magnitude of benefit: moderate to large
- Side effect burden: minor
- Strength of recommendation: strong, in favour (↑↑)

When psychosocial therapy provides insufficient benefit, psychostimulants should be offered to most children and adolescents in most circumstances for the treatment of functionally disabling oppositional behaviour, conduct problems, and aggression in the context of ADHD. Efficacy has been demonstrated for aggression that is either overt (for example, physical assault and rage attacks) or covert (for example, stealing and fire-setting), but the evidence is stronger for overt aggression than for covert aggression.[26] Some evidence indicates that psychostimulants have a dose–response effect for disruptive and aggressive behaviour[14,26]; therefore, clinicians noting a suboptimal response should consider increasing the dose prior to recommending other medications, provided that the current dose is well tolerated. On average, methylphenidate and amphetamines provide similar benefit[26] and have similar adverse effects.[27] Nonetheless, because some patients respond better to one psychostimulant type than the other, a trial of each should usually be undertaken before using a medication from a different class.[27]

Atomoxetine for Oppositional Behaviour in Children and Adolescents With ADHD, With or Without ODD or CD

- Quality of evidence: high
- Magnitude of benefit: small
- Side effect burden: minor
- Strength of recommendation: conditional, in favour (↑?)

When psychosocial therapy provides insufficient benefit, clinicians may offer atomoxetine for the treatment of functionally disabling oppositional behaviour in children and adolescents with ADHD who have done poorly (regarding response or tolerability) with adequate psychostimulant trials. Despite widespread use of atomoxetine in combination with a psychostimulant, evidence to support this practice is very limited.[28] Adverse effects of atomoxetine are generally minor, but it may be associated with a small increase in risk (0.4% to 0.5%) of suicidal ideation or behaviour.[29–31]

Guanfacine (Monotherapy or in Combination With a Psychostimulant) for Oppositional Behaviour in Children and Adolescents With ADHD, With or Without ODD

- Quality of evidence: moderate

Table 2 Summary of findings: pharmacotherapy, compared with placebo, for oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD, or CD[14,15]

Medication	Population	Outcome	Placebo-controlled trials, *n*	Total number of participants, *n*	Effect size or OR (95% CI)	Quality of evidence
Psychostimulants	Children and adolescents with ADHD, with or without ODD or CD	Oppositional behaviour, conduct problems, and aggression	40	2364	Studies from 1970 to 2001[26]: Cohen *d*: Clinician: 0.77 (0.63 to 0.88) Parent: 0.71 (0.42 to 1.15) Teacher: 1.04 (0.79 to 1.32) Studies from 2002 to 2013: SMD: Parent: 0.55 (0.36 to 0.73) Teacher: 0.84 (0.59 to 1.10)	High
Atomoxetine	Children and adolescents with ADHD, with or without ODD or CD	Oppositional behaviour	15	1907	SMD 0.33, (0.24 to 0.43)	High
Guanfacine	Children and adolescents with ADHD, with or without ODD	Oppositional behaviour	2	678	SMD 0.43 (0.18 to 0.68)	Moderate
Clonidine	Children and adolescents with ADHD, with or without ODD or CD	Oppositional behaviour and conduct problems	6	545	SMD 0.27 (0.04 to 0.51)	Very low
Risperidone	Children and adolescents with average IQ and ODD or CD, with or without ADHD	Disruptive and aggressive behaviour	4[a]	429	SMD 0.60 (0.31 to 0.89)	High
Risperidone	Children and adolescents with low IQ and ODD or CD, with or without ADHD	Conduct problems and aggression	5[a]	398	SMD 0.72 (0.47 to 0.97)	Moderate
Quetiapine	Adolescents with CD, with or without ADHD	Conduct problems	1	19	SMD 1.6 (0.9 to 3.0)	Very low
Haloperidol	Children with CD	Aggression	1	61	Magnitude of effect was not reported, but a significant difference from placebo was found on some measures	Very low
Valproate	Children and adolescents with ODD or CD, with or without ADHD	Aggression	2	50	OR 14.60 (3.25 to 65.61) for response	Low
Lithium	Children and adolescents with CD	Aggression	4	184	OR 4.56 (1.97 to 10.56) for response or remission	Low
Carbamazepine	Children with CD	Aggression	1	24	No significant difference	Very low

ADHD = attention-deficit hyperactivity disorder; CD = conduct disorder; ODD = oppositional defiant disorder; SMD = standardized mean difference

[a] In 1 of these trials, 64% of subjects had an IQ of >84 and the remainder were in the 55-to-84 range[37]; thus this trial is included with the trials in subjects with average IQ, and with the trials in subjects with low IQ

- Magnitude of benefit: small to moderate
- Side effect burden: moderate
- Strength of recommendation: conditional, in favour (↑?)

When psychosocial therapy provides insufficient benefit, clinicians may offer guanfacine for the treatment of functionally disabling oppositional behaviour in children and adolescents with ADHD who have done poorly (regarding response or tolerability) with adequate psychostimulant trials. Guanfacine may be offered as monotherapy or in combination with a psychostimulant, depending on the clinical circumstances. More specifically, guanfacine monotherapy should be considered when psychostimulants have provided minimal benefit or have caused intolerable adverse effects. Conversely, combination treatment should be considered when psychostimulants have provided clinically meaningful benefit and are well tolerated, but significant behavioural challenges remain. Of note, in 2 studies that analyzed ADHD outcomes by age group, guanfacine was superior to placebo in children but not in adolescents[32,33]; it is unknown whether the same differential effect by age group would be found for oppositional behaviour. The side effect burden of guanfacine is moderate, and missed doses or abrupt discontinuation can cause rebound tachycardia and hypertension.[34] Thus the potential for medication nonadherence should be considered.

Clonidine (Monotherapy or in Combination with a Psychostimulant) for Oppositional Behaviour and Conduct Problems in Children and Adolescents With ADHD, With or Without ODD or CD

- Quality of evidence: very low
- Magnitude of benefit: small
- Side effect burden: moderate
- Strength of recommendation: conditional, in favour (↑?)

When psychosocial therapy provides insufficient benefit, clinicians may offer clonidine for the treatment of functionally disabling oppositional behaviour and conduct problems in children and adolescents with ADHD who have done poorly (regarding response or tolerability) with adequate psychostimulant trials. Clonidine may be offered as monotherapy or in combination with a psychostimulant, depending on the clinical circumstances. More specifically, clonidine monotherapy should be considered when psychostimulants have provided minimal benefit or have caused intolerable adverse effects. Conversely, combination treatment should be considered when psychostimulants have provided clinically meaningful benefit and are well tolerated, but significant behavioural challenges remain. However, it should be kept in mind that very-low-quality evidence supports the use of clonidine, and the magnitude of effect for oppositional behaviour and conduct problems is modest and uncertain, with the 95% confidence interval for the effect size ranging from almost 0 (no effect) to 0.51 (moderate effect). In addition, the side effect burden of clonidine is moderate, and missed doses or abrupt discontinuation can cause rebound tachycardia and hypertension.[35] Thus the potential for medication nonadherence should be considered, especially given that immediate-release clonidine (the only formulation currently available in Canada) is typically dosed multiple times per day.

Risperidone for Disruptive and Aggressive Behaviour in Children and Adolescents With Average IQ and ODD or CD, With or Without ADHD

- Quality of evidence: high
- Magnitude of benefit: moderate
- Side effect burden: major
- Strength of recommendation: conditional, in favour (↑?)

When psychosocial therapy provides insufficient benefit, clinicians may offer risperidone for the treatment of functionally disabling disruptive and aggressive behaviour in children and adolescents with average IQ and ODD or CD. In patients with comorbid ADHD, treatment with ADHD medication, starting with psychostimulants, should be pursued before considering risperidone. When risperidone is initiated in patients with comorbid ADHD, it may be added to a psychostimulant or used as monotherapy. Most of the placebo-controlled evidence supporting the use of risperidone for this indication is in children and adolescents with ODD or CD that is comorbid with ADHD. In 1 large ($n = 168$) study of children (6 to 12 years) with ADHD, ODD or CD, and serious physical aggression, the effect size for risperidone on the primary outcome measure of disruptive behaviour was 0.4 to 0.5 (moderate)[22] (95% confidence interval unreported). However, prior to the addition of risperidone or placebo, both groups showed considerable improvement with evidence-based parent training and open-label psychostimulant treatment. In addition, group differences were nonsignificant on most secondary outcome measures, including responder status, CGI-I, and CGI-S.[22,36] These considerations regarding the efficacy of risperidone, combined with its major side effect burden, are the reasons we gave it a conditional recommendation, despite high-quality evidence showing moderate benefit overall.

Comment is also warranted regarding a large ($n = 335$) maintenance study of risperidone in disruptive children and adolescents (5 to 17 years) with subaverage or average intelligence (IQ ≥ 55), 68% of whom had ADHD and 24% of whom received concomitant psychostimulant treatment. In this study, subjects who responded to 3 months of open-label risperidone were randomized to continue risperidone or switch to placebo for 6 more months.[37] Even though the rate of symptom recurrence was significantly lower in the group that continued risperidone, close to 60% of subjects who were switched to placebo did not experience

Table 3 Summary of recommendations: pharmacotherapy for oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD, or CD

Medication	Population	Outcome	Magnitude of benefit and side effect burden	Recommendation (strength, direction)	Dosing information
Psychostimulants	Children and adolescents with ADHD, with or without ODD or CD	Oppositional behaviour, conduct problems, and aggression	Benefit: moderate to large Adverse effects: minor Quality of evidence: high	Strong, in favour (↑↑)	Dosing varies by psychostimulant formulation; consult individual product monographs for dosing recommendations
Atomoxetine	Children and adolescents with ADHD, with or without ODD or CD	Oppositional behaviour	Benefit: small Adverse effects: minor Quality of evidence: high	Conditional, in favour (↑?)	Doses used in included studies: 0.5 to 2.0 mg/kg/day (up to a maximum of 90.0 mg/day) Canadian product monograph[57] recommended dosing for the treatment of ADHD: titrate in 3 steps up to a target dose of 1.2 mg/kg/day, not to exceed 80.0 mg/day; maximum dose is 1.4 mg/kg/day, not to exceed 100.0 mg/day
Guanfacine	Children and adolescents with ADHD, with or without ODD	Oppositional behaviour	Benefit: small to moderate Adverse effects: moderate Quality of evidence: moderate	Conditional, in favour (↑?)	Doses (extended-release formulation) used in included studies: 1.0 to 4.0 mg/day (monotherapy or adjunct to a psychostimulant) Canadian product monograph (extended-release formulation)[34] recommended dosing for the treatment of ADHD: in children 6 to 12 years and ≥25 kg, start 1 mg/day and increase in increments of no more than 1 mg/week up to a maximum of 4 mg/day (monotherapy or adjunctive therapy)
Clonidine	Children and adolescents with ADHD, with or without ODD or CD	Oppositional behaviour and conduct problems	Benefit: small Adverse effects: moderate Quality of evidence: very low	Conditional, in favour (↑?)	Doses (immediate- or extended-release formulation) used in included studies: 0.1 to 0.6 mg/day (monotherapy or adjunct to a psychostimulant) Canadian product monograph (immediate-release formulation)[58] recommended dosing: safety and efficacy in children not established
Risperidone	Children and adolescents with average IQ and ODD or CD, with or without ADHD	Disruptive and aggressive behaviour	Benefit: moderate Adverse effects: major Quality of evidence: high	Conditional, in favour (↑?)	Doses used in included studies: Monotherapy: 0.5 to 1.5 mg/day Adjunct to a psychostimulant: 1.0 to 2.5 mg/day Canadian product monograph[59] recommended dosing: safety and efficacy in children <18 years not established and use is not recommended
Risperidone	Children and adolescents with low IQ and ODD or CD, with or without ADHD	Conduct problems and aggression	Benefit: moderate to large Adverse effects: major Quality of evidence: moderate	Conditional, in favour (↑?)	Doses used in included studies: 0.5 to 4.0 mg/day Canadian product monograph[59] recommended dosing: safety and efficacy in children <18 years not established and use is not recommended
Quetiapine	Adolescents with CD, with or without ADHD	Conduct problems	Benefit: large Adverse effects: major Quality of evidence: very low	Conditional, against (↓?)	Doses (immediate-release formulation) used in included study: 200 to 600 mg/day Canadian product monograph[60] recommended dosing: not recommended for use in patients under 18 years

continued

Table 3 ***Continued***

Medication	Population	Outcome	Magnitude of benefit and side effect burden	Recommendation (strength, direction)	Dosing information
Haloperidol	Children with CD	Aggression	Benefit: some benefit, but magnitude uncertain Adverse effects: major Quality of evidence: very low	Strong, against (↓↓)	Not applicable, given the strong recommendation against its use
Valproate	Children and adolescents with ODD or CD, with or without ADHD	Aggression	Benefit: large Adverse effects: major Quality of evidence: low	Conditional, in favour (↑?)	Doses used in included studies: Monotherapy: 750 to 1500 mg/day (immediate release) Adjunct to a psychostimulant: 20 mg/kg/day (extended release) Canadian product monograph[61] recommended dosing for the treatment of epilepsy: start 15 mg/kg/day and titrate weekly by 5 to 10 mg/kg/day; maximum dose is 60 mg/kg/day
Lithium	Children and adolescents with CD	Aggression	Benefit: large Adverse effects: major Quality of evidence: low	Conditional, against (↓?)	Doses (immediate-release formulation) used in included studies: 900 to 1200 mg/day OR dosed to maintain a serum level of 0.6 to 1.0 mmol/L Canadian product monograph[62] recommended dosing for the treatment of bipolar disorder: dosing must be individualized for each patient according to blood levels and clinical response; use is not recommended in children <12 years
Carbamazepine	Children with CD	Aggression	Benefit: none Adverse effects: major Quality of evidence: very low	Strong, against (↓↓)	Not applicable, given the strong recommendation against its use

symptom recurrence. Given this result and risperidone's major side effect burden, tapering and discontinuing risperidone should be considered after 3 months of successful treatment.

Risperidone for Conduct Problems and Aggression in Children and Adolescents With Subaverage IQ and ODD or CD, With or Without ADHD

- Quality of evidence: moderate
- Magnitude of benefit: moderate to large
- Side effect burden: major
- Strength of recommendation: conditional, in favour (↑?)

When psychosocial therapy provides insufficient benefit, clinicians may offer risperidone for the treatment of functionally disabling conduct problems and aggression in children and adolescents with subaverage IQ and ODD or CD. In patients with comorbid ADHD, treatment with ADHD medication, starting with psychostimulants, should be pursued before considering risperidone. When risperidone is initiated in patients with comorbid ADHD, it may be added to a psychostimulant or used as monotherapy. In the placebo-controlled studies that support the use of risperidone for this indication, over one-half of subjects had comorbid ADHD and were often on a stable dose of psychostimulant.[16–19,37] Thus, even in children and adolescents with subaverage intelligence, efforts should be made to evaluate whether ADHD is present, in which case it should be the initial target of pharmacotherapy. The side effect burden of risperidone is major, leading to a conditional recommendation despite moderate-quality evidence showing a moderate-to-large effect size.

Quetiapine for Conduct Problems in Children and Adolescents With CD, With or Without ADHD

- Quality of evidence: very low
- Magnitude of benefit: large
- Side effect burden: major
- Strength of recommendation: conditional, against (↓?)

Based on currently available evidence, we suggest that clinicians refrain from offering quetiapine for the treatment of conduct

problems in children and adolescents with CD. Although quetiapine's effect size for this indication is estimated to be large, the estimate is uncertain and derives from 1 small (n = 19) study of poor quality in adolescents (12 to 17 years).[38] This very limited evidence for quetiapine's efficacy and its major side effect burden resulted in a conditional recommendation against its use, although the recommendation could change if more evidence to support its efficacy becomes available.

Haloperidol for Aggression in Children and Adolescents With CD

- Quality of evidence: very low
- Magnitude of benefit: some benefit, but magnitude uncertain
- Side effect burden: major
- Strength of recommendation: strong, against (↓↓)

We recommend that clinicians refrain from offering haloperidol for the treatment of aggression in children and adolescents with CD. Although the 1 placebo-controlled study of haloperidol for this indication in children (5 to 13 years) is positive on some outcomes, it is small (n = 61; 20 randomized to haloperidol) and of poor quality, and the magnitude of effect was not reported.[39] In addition, the side effect burden of haloperidol is major, outweighing the potential benefit for aggression in children and adolescents with CD.

Valproate for Aggression in Children and Adolescents With ODD or CD, With or Without ADHD

- Quality of evidence: low
- Magnitude of benefit: large
- Side effect burden: major
- Strength of recommendation: conditional, in favour (↑?)

When psychosocial therapy provides insufficient benefit, clinicians may offer valproate for the treatment of functionally disabling aggression in children and adolescents with ODD or CD. In patients with comorbid ADHD, treatment with ADHD medication, starting with psychostimulants, should be pursued before considering valproate. When valproate is initiated in patients with comorbid ADHD, it may be added to a psychostimulant or used as monotherapy. The 2 available placebo-controlled studies of valproate are both positive, but the samples are small (total n = 50).[40,41] One of these studies involved children (6 to 13 years) who all had comorbid ADHD and were treated with open-label psychostimulant prior to being randomized to valproate or placebo.[40] Even though the magnitude of effect of valproate is estimated to be large, it bears emphasis that the estimate is uncertain, the quality of evidence is low, and the side effect burden is major. Given these concerns, a clinical recommendation to use valproate in the treatment of aggression should generally come from a specialist with expertise in childhood behaviour disorders and experience with valproate. Further, the use of valproate for this indication is discouraged in female patients because of the risk of polycystic ovarian syndrome.[79]

Lithium for Aggression in Children and Adolescents With CD

- Quality of evidence: low
- Magnitude of benefit: large
- Side effect burden: major
- Strength of recommendation: conditional, against (↓?)

We suggest that clinicians refrain from offering lithium for the treatment of aggression in children and adolescents with CD. Four placebo-controlled studies of lithium for this indication have been reported,[39,42–44] and the magnitude of effect is estimated to be large; however, this estimate is uncertain, as results are inconsistent between studies and the overall quality of evidence is low. In addition, lithium's side effect burden is major, and given the need for regular blood work monitoring and the risk of dose-related toxicity, it is challenging to use lithium safely in children and adolescents with CD. These considerations led to a conditional recommendation against using lithium despite some evidence that it can be beneficial for aggression in the context of CD.

Carbamazepine for Aggression in Children and Adolescents With CD

- Quality of evidence: very low
- Magnitude of benefit: none
- Side effect burden: major
- Strength of recommendation: strong, against (↓↓)

We recommend that clinicians refrain from offering carbamazepine for the treatment of aggression in children and adolescents with CD. The only placebo-controlled study of carbamazepine for this indication in children (5 to 12 years) is small (n = 24), of poor quality, and negative.[38] In addition, the side effect burden of carbamazepine is major.

Discussion

Our recommendations reflect that much more evidence is available to support pharmacotherapy to treat disruptive and aggressive behaviour in children and adolescents with ADHD, compared with those without ADHD. For children and adolescents without ADHD, as well as those with ADHD who have done poorly with ADHD treatments, evidence-based medication options are limited and the medications that may be considered have major adverse effects. It should also be kept in mind that the benefits and tolerability of any medication for an individual patient may change over time, and little evidence is available regarding long-term benefits and safety. Thus, whenever medication is

used to treat disruptive and aggressive behaviour, its benefits and adverse effects should be clinically re-evaluated on an ongoing basis to determine whether continued treatment is warranted.

For children and adolescents with ADHD, only psychostimulants received a strong recommendation in favour of use. The clinical implication is that when medication is being considered to address disruptive and aggressive behaviour in the context of ADHD, a psychostimulant should usually be used first. Moreover, when a child or adolescent presents with disruptive or aggressive behaviour, it is critical to evaluate whether ADHD is also present, as targeting the ADHD with a psychostimulant is likely to improve the other behavioural problems as well. Given that some patients respond better to methylphenidate and others to amphetamines, both types of psychostimulant should generally be tried before using a medication from a different class.[27] Even if a psychostimulant has already been tried with little success in the past, the clinician should explore whether the trial was adequate regarding dose and duration. If not, a more rigorous trial of the same psychostimulant may be worthwhile.

Three nonpsychostimulant medications used for ADHD—atomoxetine, guanfacine, and clonidine—received a conditional recommendation for treating associated behavioural problems. However, the recommendation does not apply to the treatment of aggression specifically, as data for this outcome are lacking. While each of these medications was given the same grade of recommendation, the quality of evidence is high for atomoxetine, moderate for guanfacine, and very low for clonidine. The magnitude of benefit seems comparable for all 3 medications, with an effect size in the 0.3 to 0.4 range (atomoxetine 0.33, 95% CI 0.24 to 0.43[30]; guanfacine 0.43, 95% CI 0.18 to 0.68[14]; and clonidine 0.27, 95% CI 0.04 to 0.51[14]), but the estimate is highly uncertain for clonidine and head-to-head trials are not available. Other factors to consider when choosing among the 3 nonpsychostimulants include side effect burden, convenience of administration, risks associated with nonadherence, cost, and duration on the market (because newer medications may have risks that have not yet been identified). For example, we considered that the 2 available guanfacine studies involved the relatively new extended-release formulation, which is considerably more expensive than immediate-release clonidine (neither immediate-release guanfacine nor extended-release clonidine is currently available in Canada). Further, both guanfacine studies were funded by the pharmaceutical company, which may bias the results[45,46] (at least 3 of the 6 clonidine studies were not funded by industry[14]). These factors contributed to guanfacine and clonidine receiving the same grade of recommendation despite the quality of evidence being higher for guanfacine.

Our recommendations for using ADHD medications to treat disruptive and aggressive behaviour associated with ADHD are in keeping with guidelines for treating ADHD itself. Psychostimulants are consistently recommended as first-line medications for ADHD, whereas atomoxetine and alpha-2 agonists are generally considered subsequent treatment options, except in certain clinical situations (for example, comorbid substance abuse).[47] For both psychostimulants and nonpsychostimulants, benefits are usually somewhat greater for core ADHD symptoms than for associated behavioural problems. In the case of psychostimulants, the effect size is large for core ADHD symptoms,[48] but moderate to large for other disruptive behaviours.[14,26] In the case of atomoxetine, guanfacine, and clonidine, effect sizes are moderate for core ADHD symptoms,[30,49] but small (atomoxetine and clonidine) or small to moderate (guanfacine) for other disruptive behaviours.[14] These findings suggest that when children and adolescents with ADHD exhibit oppositional behaviour, conduct problems, and aggression, these symptoms may stem largely, but not entirely, from their ADHD.

If children and adolescents with ADHD and ODD or CD have suboptimal response or tolerability with ADHD medications, the next medication option with the most evidence for treating disruptive and aggressive behaviour is risperidone, which received a conditional recommendation in favour of use irrespective of patient IQ. Nonetheless, the evidence supporting risperidone's efficacy is less compelling in children and adolescents with average intelligence than in those with subaverage intelligence. Even though the quality of evidence in children and adolescents with average intelligence was rated as high according to the GRADE criteria, this rating is based on 4 placebo-controlled studies, of which 2 are small ($n \leq 25$),[20,21] 1 is negative,[21] and 1 is a maintenance study where less than two-thirds of subjects had average intelligence.[37] The remaining study is large, of good quality, and positive on the primary outcome measure; however, group differences on important secondary outcomes—responder status, CGI-I, and CGI-S—were nonsignificant.[22] These caveats notwithstanding, the overall benefit of risperidone for disruptive and aggressive behaviour was found to be moderate in children and adolescents with average intelligence, just slightly lower than the benefit in those with subaverage intelligence. This benefit must be weighed against adverse effects that are considered major, especially sedation, extrapyramidal symptoms, weight gain, metabolic abnormalities, and increased prolactin. Some of these adverse effects, such as extrapyramidal symptoms and increased prolactin, are dose-related. Other adverse effects, such as weight gain, may be similar in patients treated with the lower doses (0.5 to 2.5 mg) typically used to treat disruptive and aggressive behaviour, compared with higher doses (3 to 6 mg).[50,51]

For children and adolescents with behavioural problems associated with ADHD who have inadequate response or intolerable adverse effects with ADHD medications and risperidone, little evidence is available to guide subsequent pharmacotherapy. Similarly, aside from data on risperidone, little evidence is available to guide pharmacotherapy for children and adolescents with disruptive or aggressive

behaviour in the absence of ADHD. Based on 2 small placebo-controlled studies that are positive, we did give a conditional recommendation in favour of using valproate to treat aggression in children and adolescents with ODD or CD, with or without ADHD. However, the evidence for valproate is limited and of low quality, and clinicians and families must also consider its major side effect burden and potential challenges associated with obtaining regular blood work. We gave a conditional recommendation against using lithium to treat aggression in children and adolescents with CD, as the evidence regarding its efficacy is mixed and of low quality, its side effect burden is major, and, compared with valproate, we had even greater concerns regarding the challenges of blood work monitoring and the risk of dose-related toxicity. Carbamazepine received a strong recommendation against its use to treat aggression associated with CD, given the absence of any placebo-controlled evidence for efficacy combined with its major side effect burden and monitoring requirements.

The T-MAY guidelines recommend that if insufficient response is achieved with the first antipsychotic (no specific antipsychotic is indicated), a different antipsychotic should be tried.[7] This recommendation is rated as strong, meaning that 71% to 90% of the experts agreed with it, even though the grade of evidence based on the Oxford Centre system was D (lowest level). Indeed, the only placebo-controlled studies of antipsychotics other than risperidone are a small study of quetiapine[38] in adolescents with CD, a small study of haloperidol[39] in children with CD, and a small study of thioridazine[52] in children and adolescents with subaverage intelligence and ADHD or CD. Although the quetiapine study is positive, the haloperidol and thioridazine studies had mixed results, and all 3 studies are of very low quality. Given the very limited evidence for efficacy and the major side effect burden associated with quetiapine and haloperidol, we recommend against using them for conduct problems or aggression. We decided not to make a specific recommendation for any other antipsychotics, as no placebo-controlled evidence exists for them (or in the case of thioridazine, it is no longer commercially available in Canada). Therefore, clinicians and families considering other antipsychotics should be mindful that evidence is lacking, that antipsychotics generally have a major side effect burden, and that careful monitoring is required.[53–55] Indeed, it is the responsibility of the clinician to ensure that families are adequately informed regarding the evidence for efficacy and the adverse effects of any medication under consideration.

Limitations of these guidelines relate, in large part, to the limitations of the available evidence. The quality of evidence was rated as high or moderate for psychostimulants, atomoxetine, guanfacine, and risperidone, but low or very low for clonidine, quetiapine, haloperidol, valproate, lithium, and carbamazepine. Moreover, even evidence rated as high or moderate quality should be interpreted with caution. For example, in the studies of ADHD medications, disruptive behaviours other than core ADHD symptoms were generally secondary outcomes. Some of these studies assessed oppositional symptoms but not conduct problems or aggression, and thus their findings may not be generalizable to these more serious forms of disruptive behaviour. In addition, it was not possible to analyze whether the effect of medication on disruptive or aggressive behaviour in these studies was moderated by the presence of a comorbid diagnosis of ODD or CD.

Another important limitation is that many studies were funded by the pharmaceutical industry, and even though we tried to account for potential bias when rating the quality of evidence, pharmaceutical industry influences on research are well documented.[45,46] It is also unclear how well findings from highly controlled research settings translate into effectiveness in real-world settings. An attempt was made to consider patient values and preferences by reviewing our clinical experience and incorporating feedback from parents of children and adolescents with disruptive or aggressive behaviour. However, values and preferences vary among people, and our own biases may have influenced our perceptions. Finally, despite our best efforts to base these guidelines on rigorous procedures for conducting a systematic review, rating evidence quality and side effect burden, grading recommendations, and developing consensus, the guidelines ultimately depend on consensus group members' judgments, which were not always unanimous. Nonetheless, through discussion, we were able to reach agreement on all of our recommendations.

Conclusion

First-line treatment for children and adolescents with severe oppositional behaviour, conduct problems, and aggression should be psychosocial interventions, which are supported by substantial evidence and have low risks.[7] Further, advocacy efforts are essential to make evidence-based psychosocial interventions widely accessible and affordable. However, when psychosocial interventions are inadequate or unfeasible, consideration of pharmacotherapy is warranted. For children and adolescents with functionally disabling behavioural problems associated with ADHD, these guidelines recommend the use of ADHD medications, starting with psychostimulants (including trials of both methylphenidate and an amphetamine) and then considering nonpsychostimulants. For children and adolescents with ADHD who have inadequate response or intolerable adverse effects with ADHD medications, and for those with disruptive or aggressive behaviour in the absence of ADHD, research is limited but the most evidence exists for the use of risperidone. However, because of its serious adverse effects, even risperidone was given only a conditional recommendation in favour of use, implying that greater effort is required to help individual patients and families arrive at a decision that is consistent with their values and preferences.[23] In fact, most of our recommendations are conditional, which speaks to the limitations of the evidence as well as the considerable side effect burden associated with many of the medications considered. Under such

circumstances, a primary task for the clinician is to engage the patient and family in a collaborative process to choose among reasonable options, including the option to forego medication.

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These guidelines have been endorsed by the Canadian Paediatric Society and by the Canadian Academy of Child and Adolescent Psychiatry.

Notice for readers: Guidelines cannot always account for individual variation among patients. These guidelines are not intended to supplant clinician judgment about particular patients or clinical situations. The guideline consensus group considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the treating clinician in collaboration with the patient and family in light of individual clinical circumstances.

Editor's Note

The opinions expressed in this paper are those of the authors and do not necessarily reflect the opinions of either *The Canadian Journal of Psychiatry* (*The CJP*) or the Canadian Psychiatric Association (CPA). This paper is not related to work done by the CPA's Committee on Professional Standards and Practice or its Subcommittee on Clinical Practice Guidelines, and its publication in *The CJP* should not be construed as an endorsement of the content.

References 63 to 102 can be found in eTable 4.

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