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Treatment of Maladaptive Aggression in Youth: CERT Guidelines II. Treatments and Ongoing Management

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KEY WORDS

aggression, psychosocial intervention, psychotropic drugs, guidelines, behavior disorders problems

ABBREVIATIONS

CBT—cognitive behavioral therapy

NNH—number needed to harm

NNT—number needed to treat

PCIT—parent-child interaction therapy

RCT—randomized controlled trial

T-MAY—Treatment of Maladaptive Aggression in Youth

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abstract



OBJECTIVE: To develop guidelines for management and treatment of maladaptive aggression in youth in the areas of psychosocial interventions, medication treatments, and side-effect management.

METHODS: Evidence was assembled and evaluated in a multistep process, including systematic reviews of published literature; an expert survey of recommended practices; a consensus conference of researchers, policymakers, clinicians, and family advocates; and review by the steering committee of successive drafts of the recommendations. The Center for Education and Research on Mental Health Therapeutics Treatment of Maladaptive Aggression in Youth guidelines reflect a synthesis of the available evidence, based on this multistep process.

RESULTS: This article describes the content, rationale, and evidence for 11 recommendations. Key treatment principles include considering psychosocial interventions, such as evidence-based parent and child skills training as the first line of treatment; targeting the underlying disorder first following evidence-based guidelines; considering individual psychosocial and medical factors, including cardiovascular risk in the selection of agents if medication treatment (ideally with the best evidence base) is initiated; avoiding the use of multiple psychotropic medications simultaneously; and careful monitoring of treatment response, by using structured rating scales, as well as close medical monitoring for side effects, including metabolic changes.

CONCLUSIONS: Treatment of children with maladaptive aggression is a “moving target” requiring ongoing assimilation of new evidence as it emerges. Based on the existing evidence, the Treatment of Maladaptive Aggression in Youth guidelines provide a framework for management of maladaptive aggression in youth, appropriate for use by primary care clinicians and mental health providers. *Pediatrics* 2012;129:e1577–e1586

Maladaptive aggression is a nonspecific, serious symptom accompanying many childhood disorders, including oppositional defiant disorder, conduct disorder, attention-deficit/hyperactivity disorder, and bipolar disorder.¹ Aggressive problems affect 10% to 25% of youth,² and when severe, undermine academic and social functioning and lead to drug abuse, school dropout, depression, and incarceration.²⁻⁴

Given its prevalence and serious effects, maladaptive aggression is commonly a target of both psychosocial and medication interventions.¹ Psychotropic agents are increasingly prescribed to aggressive youth on an outpatient basis,⁵⁻⁷ despite limited efficacy and safety data.⁶ For example, sixfold increases in outpatient antipsychotic prescriptions were found between 1993 and 2002,⁸ followed by further increases between 2002 and 2006,⁹ largely with aggressive, nonpsychotic youth. These practices fall largely outside of indications approved by the Food and Drug Administration, raising concerns about efficacy, safety, role of alternative therapies, polypharmacy, and appropriate parent engagement and education.⁹ Furthermore, a significant portion of antipsychotic prescribing takes place by primary care physicians, including pediatricians. For example, an estimated 32.2% of antipsychotic prescriptions for children ages 2 to 18 during 1995–2002 were by non-mental health providers.¹⁰ Evidence-based guidance is necessary for implementing care that addresses patients' severity and source of symptoms, development, primary diagnosis, coexisting conditions, and family situations.¹¹

To address these needs, the Rutgers Center for Education and Research on Mental Health Therapeutics, in collaboration with Columbia University, the REACH Institute, and others, launched a consensus development initiative to address the outpatient management of

maladaptive, impulsive aggression in children and adolescents. Treatment of Maladaptive Aggression in Youth (T-MAY), the result of this collaboration, aims to provide a standardized approach for helping youth with maladaptive aggression seen in outpatient settings. T-MAY guidelines were developed through literature reviews, an expert consensus survey¹² a 2-day consensus conference, and workgroup discussions (for additional details see Knapp et al¹³ in the accompanying report).

The resulting treatment recommendations target the impulsive form of "maladaptive aggression," that is, a pattern of unplanned and poorly controlled aggression, as opposed to "predatory" aggression (see Knapp et al for details), and span 5 key areas: (1) Assessment and Diagnosis, (2) Initial Management and Treatment Planning, (3) Psychosocial Interventions, (4) Medication Treatments, and (5) Side Effects Assessment and Management. The first 2 areas are addressed in the accompanying report (Knapp et al); the remaining 3 are presented here.

METHODS

Literature Review

We identified relevant studies from 3 major sources: (1) Medline, PsycINFO, and CINAHL literature databases from 1980 to January 2012; (2) the Cochrane database for psychosocial interventions; and (3) bibliographies of other published reviews. Included were randomized controlled trials (RCTs) that (1) explicitly addressed overt aggression (ie, physical or verbal confrontation with others, oppositional or defiant behavior, explosive outbursts or irritability, or the destruction of property), (2) reported end-point means or change scores and SDs on valid rating scales of maladaptive aggression, (3) were published in peer-reviewed English-language journals, and (4) addressed youth <19 years. These inclusion criteria

were derived from our need to review RCTs that directly related to our treatment recommendations, as well as the lack of published systematic reviews that specifically targeted maladaptive aggression, defined as unplanned, poorly controlled, physical and verbal aggression toward others or property. Although we primarily sought RCTs conducted in outpatients, we also reviewed inpatient RCTs when outpatient RCTs were unavailable. All RCTs are summarized in Supplemental Table 1.

Searches related to psychosocial interventions used the following terms and closely related words: cognitive behavioral therapy (CBT), parent-child interaction therapy (PCIT), multisystemic therapy, psychoeducation, psychotherapy, psychosocial, problem solving, anger control, and family therapy. Searches related to medication treatments relied on an extensive list of medication terms and classes (see Supplemental Table 2). In light of a recent, comprehensive review on the pharmacotherapy of aggression by several T-MAY authors,¹⁴ we searched the additional medication literature only from 2005 to January 2012. For side-effect management and assessment, we used 40 terms and their related word forms (see Supplemental Table 2). We crossed each treatment category with terms for aggression (aggression, anger, angry, violent, conduct problems, conduct disorder, impulsive, oppositional, defiant, noncompliant, and delinquent).

As a clinical measure of study-defined response and of all-cause discontinuation, the number needed to treat (NNT) was calculated by subtracting the response (or discontinuation) rate for placebo/control from the response (or discontinuation) rate of the active drug/intervention and dividing 1 by that difference. For adverse outcomes for medication treatments, the number needed to harm (NNH) was calculated in

the same way. An NNT or NNH of 10 or less is generally considered clinically meaningful.¹⁵ We calculated NNTs and NNHs for categorical outcomes, as these translate statistical separation that can be clinically meaningless into a clinically palpable effect size, that is, the number of patients who a clinician needs to treat before he or she will see 1 additional good or bad outcome. Because of the use of different specific scales and the lack of 1 prevailing set of standardized criteria in the field, the definition of response differed between studies; however, all analyzed response rates were operationalized and used rater-based assessments. Moreover, the calculation of NNTs takes into account the difference between treatment and placebo in a given study in which the exact same criteria are applied to the treatment groups. For continuous variables, we calculated effect sizes by using the standard formula for Cohen's *d*.¹⁶ Effect sizes for individual aggression scales were pooled for each study. Study-based effect sizes and percent values were pooled and weighted by the study *N* across studies to derive weighted means for specific psychosocial interventions and medication classes. Articles were pooled in RefWorks, an online tool for research management.

Each recommendation was graded on the basis of the Oxford Centre for Evidence-Based Medicine grade of evidence (A–D) system (see www.cebm.net/levels_of_evidence.asp). In addition, the strength of each recommendation, in terms of the extent to which experts agreed that the recommendation is highly appropriate and a “first-line” practice, was reached for each recommendation. Recommendation strength was rated in 4 categories: very strong (>90% agreement), strong (>70% agreement), fair (>50% agreement), and weak (<50% agreement). The recommendations in the guidelines

were developed only in areas of management that had at least “strong agreement” among experts.

RESULTS

Literature Review

Psychosocial Interventions

The initial search for literature on psychosocial interventions for aggressive youth yielded 2030 hits. Applying the inclusion criteria described previously, we identified 24 studies meeting the inclusion criteria (Supplemental Table 1). In these studies, weighted mean age was 11.1 years; 80.7% of subjects were boys and 67.2% were white. In addition, we also reviewed recent systematic reviews on psychosocial interventions for aggression in youth.^{17–20} Because studies fell at 2 different ends of the age spectrum and used different treatments, we divided the major findings of our review by age.

Psychosocial Interventions for Younger Children

For younger children (ie, 8 years old or younger), the most-studied interventions were multicomponent treatment approaches and group parent training treatment programs. Two RCTs on group parent training, Helping Encourage Affect Regulation and Project TEAM, demonstrated the largest effect for aggression (ES [effect size] = 0.50 to 0.83),^{21,22} whereas multicomponent approaches (ie, Multimethod Psychoeducational Parent-Teacher Training program and Incredible Years and Dinosaur School program) showed low to moderate effects (mean ES = 0.23 to 0.38).^{23–25}

In other reviews in which the measure for aggression was defined more broadly,¹⁷ the Incredible Years program, which promotes positive parenting skills, interpersonal and social skills for children, and classroom management for teachers, demonstrated efficacy in managing persistent aggressive

behaviors, rated by both parent reports and independent observations of children with peers. It also demonstrated efficacy with foster care youth¹⁷ and Head Start families.^{21,26} When examining effects across the 3 program elements, however, parent training consistently had the largest treatment effect.

A recent meta-analysis found medium to large improvements (ES = 0.5 to 2.2) in child negative behaviors for both PCIT and Triple P,²⁰ which aims to improve positive parenting. PCIT has additionally been found to be effective for children (ages 3–6 years) with coexisting mental retardation and disruptive behaviors.²⁷ Our review found no RCTs on PCIT or Triple P that measured aggressive behavior according to our inclusion criteria, however, suggesting that the efficacy of these programs specifically on aggressive behaviors in young children requires further study.

Psychosocial Interventions for Older Children

Family interventions addressing parent-child relationships and communication have shown efficacy in reducing aggression in older youth. Brief Strategic Family Therapy, which aims to modify family interactions, has been efficacious in reducing anger and bullying behaviors among youth aged 8 to 18 years (mean ES = 0.66). Multisystemic therapy, an intensive program that seeks to increase family communication, parenting skills, academic performance, parental school involvement, and encourage positive peer activities, led to improved family and peer relations, and fewer problem behaviors and restrictive placements²⁸; however, the pooled effects of several RCTs that examined specific reductions in aggression were small (mean ES = 0.25) (Supplemental Table 1). Functional Family Therapy,^{29–31} a short-term family-based intervention for youths aged 10 to 18 years, also demonstrated improvement in family communication and parenting,

problem solving, recidivism, and offending among at-risk nonoffenders.³⁰ Evidence of Functional Family Therapy's success largely derives from matched group methodology, however, with the exception of 1 original study.³¹

Among individual psychotherapeutic approaches for aggression, CBT has substantial empirical support.³² Four RCTs examining CBT in youth ages 10 to 16 years demonstrated significantly reduced anger and aggression (mean ES = 0.58), 2 of which also showed a sustained reduction in anger episodes several months after intervention (Supplemental Table 1).

The Coping Power Program, entailing CBT with youth plus a parent intervention, also showed promise in reducing covert delinquency, although its impact on aggression has been more limited than on substance abuse. In addition, Coping Power reduced general delinquency, substance use, and teacher-rated aggressive behavior at a 1-year follow-up.^{33–36}

Group treatments in aggressive youth are generally not supported by evidence, although they are sometimes used when alternative psychosocial interventions are not available. We found only 1 RCT examining the efficacy of a group format on adolescent aggressive behavior, reporting minimal effects (Supplemental Table 1). These results are consistent with concerns that group modalities can exacerbate, rather than reduce, conduct problems.³⁷

Follow-up Effects of Psychosocial Interventions

Six of the 10 interventions had a follow-up component either within the same study or in a separate study. Of the 6, only a few of the studies had enough information to calculate ES for follow-up effects. The ES for these studies ranged from 0.23 to 1.50. The largest effect was seen with Brief Strategic Family Therapy (ES = 1.5), followed by

the Problem-Solving/Management Skills program that was applied in an inpatient setting (mean ES = 0.64) and CBT (mean ES = 0.63). With the exception of CBT, all of the studies conducted follow-up at 12 months after the initial intervention. All used the same aggression measure(s) at follow-up and all had at least 85% of the original sample. Because so few programs had a follow-up component, ascertaining which programs fared best after initial intervention was difficult. Further study of the sustainable effects of many of these programs is needed.

Medication Treatments

Study Characteristics

Characteristics and outcomes of studies investigating the efficacy and tolerability of psychotropic medications for the treatment of pediatric aggression are detailed in Supplemental Table 2. We identified 29 RCTs of pharmacotherapy for aggressive youth that included direct measures of aggression/anger. In these studies, weighted mean age was 9.5 years; 81.6% of subjects were boys, and 66.4% were white. Apart from 1 active-controlled study that compared 2 first-generation antipsychotics ($n = 31$), all trials were placebo-controlled. Except for 5 studies that focused on autism/pervasive developmental disorder (17%), most included youth with a primary diagnosis of disruptive behavior disorders, including oppositional defiant disorder, attention-deficit/hyperactivity disorder, or conduct disorder. All but 3 studies (focusing on maintenance) were acute intervention trials. Atypical antipsychotics were the most studied class (15 studies: 52%, $n = 1395$: 54%), followed by stimulants (6 studies: 21%, $n = 907$: 35%), mood stabilizers (6 studies, 21%, $n = 218$: 8%), and typical antipsychotics (2 studies: 3%, $n = 71$: 3%). Although most studies included predominantly or exclusively outpatients,

9 studies included only inpatients: 2 of 10 acute studies with risperidone, 2 of 2 studies with first-generation antipsychotics, 4 of 4 studies with lithium, and 1 of 1 study with carbamazepine. Although a prior systematic review of pharmacologic interventions for aggression in youth¹⁴ identified 6 studies with antidepressants, 4 with atomoxetine and 2 with α -agonists, these studies did not fulfill our stringent inclusion/exclusion criteria. We did not find any RCTs with β -blockers for aggression.

Efficacy

Compared with placebo, antipsychotics had the largest efficacy for aggression. Across 10 acute studies of risperidone versus placebo, the mean ES for aggression was 0.72 ($n = 698$, mean duration: 8.3 weeks). For maintenance treatment, mean ES was 0.40 ($n = 391$, mean duration: 13.3 weeks). For 2 trials of aripiprazole in autism, data were available only from reports at meetings, and no ES could be calculated. In the single, small study of haloperidol in inpatients ($n = 40$, duration: 4 weeks), the ES compared with placebo was 0.83. Stimulant studies demonstrated the next largest mean effect size, at 0.60 for 6 trials with 7 active arms ($n = 907$, mean duration: 6.2 weeks). For the 5 trials with methylphenidate, mean ES was 0.63 ($n = 579$, mean duration: 6.6 weeks). For the 2 trials for mixed amphetamine salts, mean ES was 0.42 ($n = 346$, mean duration: 3.5 weeks).

For mood stabilizers, outpatient studies were largely lacking. Across 6 trials, 5 of which were in inpatient settings, the mean ES was 0.47 ($n = 208$, mean duration: 5.3 weeks). Results were highly heterogeneous with respect to the specific medication used. The 1 outpatient study, an 8-week trial with valproate in a sample of 30 youth, found an ES of -0.13 , inferior to placebo. Among 4 inpatient studies, a moderate mean ES of 0.63 for 4 trials was observed with

lithium ($n = 164$, mean duration: 4.5 weeks). By contrast, the ES for carbamazepine (1 inpatient study, $n = 24$, duration: 6 weeks) was indistinguishable from placebo (ES = 0.06). Thus, evidence of efficacy among the mood stabilizers is limited to lithium, for which outpatient trials are lacking.

Across drug classes, the NNT was most beneficial for second-generation antipsychotics (NNT = 3), followed by an NNT = 4 for lithium and for stimulants (both for methylphenidate and amphetamines). (No analyzable data were available for first-generation antipsychotics.)

All-Cause Discontinuation

Regarding all-cause discontinuation rates, NNT was 5 for the maintenance studies with risperidone, 6 for stimulants, 7 for studies with other second-generation antipsychotics, and 14 for lithium. Conversely, all-cause discontinuation was more likely with carbamazepine (NNH = 7) and valproate (NNH = 10) compared with placebo.

Tolerability

Regarding tolerability, the mean difference in weight gain compared with placebo in short-term trials was 1.8 kg with risperidone, 1.2 kg with lithium, 0.9 kg with valproate, 0.8 kg with aripiprazole, 0.3 kg with carbamazepine, and -0.4 kg with stimulants. The corresponding NNHs for any weight gain were 3 for lithium, 5 for carbamazepine, 8 for valproate, and 10 for risperidone. Stimulant studies found less weight gain than with placebo. Regarding sedation, the NNH was 2 for haloperidol, 3 for risperidone, 10 for lithium, and 50 for valproate in the studies with available information. The NNH for hyperprolactinemia with risperidone was 12. Further details can be found in Supplemental Table 2. It should be noted that because the studies summarized previously are

limited to those that included measures of aggression, not all available information is included on metabolic and other harms that have been found to be associated with several of the drug classes, particularly with second-generation antipsychotics. For example, data for olanzapine, which has been linked to some of the most troublesome metabolic outcomes in studies for other indications, were not available for the target population of this review.

The previously cited psychosocial and pharmacologic treatment literature have important limitations. In particular, even among these studies addressing maladaptive aggression, few measured different types of aggression, such as the range from subtle, covert aggression to explosive, impulsive aggression, to planned, predatory aggression.³⁸ Nonetheless, findings are not insignificant, and along with the expert consensus survey results, were used to develop the treatment recommendations.

Follow-Up Effects of Pharmacologic Interventions

Only 2 studies reported data regarding the maintenance effect of medication after stabilization. In an 8-week study in children (aged 5–17 years, mean: 9 years) with autism who had received 6 months of risperidone, continued medication treatment was associated with significantly greater raw relapse rates compared with placebo-controlled risperidone discontinuation at 2 months (12.5% vs 62.5%).³⁹ Similarly, in a 6-month study in children with conduct disorder (aged 5–17 years, mean: 11 years) who had received 3 months of risperidone, continued medication treatment was associated with significantly greater raw relapse rates compared with placebo-controlled risperidone discontinuation at 6 months (27.3% vs 42.3%).⁴⁰ The fact that relapse rates off risperidone were considerably lower in youth with conduct disorder

(42.3%) compared with youth with autism (62.5%), despite a 3 times longer follow-up off risperidone in youth with conduct disorder, suggests the possibility that therapeutic gains that were made during medication treatment possibly can be carried over into a nonmedication phase in youth with sufficient capacity for interaction and social learning. Nevertheless, more studies are clearly needed to examine and address this further.

TREATMENT RECOMMENDATIONS

The following recommendations provide a guide to treating youth with maladaptive aggression, but should be implemented with consideration to other complex, comorbid conditions and environmental factors. Recommendations begin with the number 10, as these recommendations directly follow from the 9 recommendations presented in Knapp et al¹³ in this issue. Recommendations 10 and 11 pertain to psychosocial interventions, which should be the first line of treatment because of its lower risk, preceding the use of medication to address aggression except in emergency circumstances, as discussed further under Recommendation 12. Recommendations 12 to 20 address the initiation and management of medications, once it has been determined that a trial of medication is necessary. Further detail and justification for each recommendation can be seen in Supplemental Table 3.

Psychosocial Interventions

10. Provide or Assist the Family in Obtaining Evidence-Based Parent and Child Skills Training During All Phases of Care (Grade of Evidence: A; Strength of Recommendation: Very Strong)

Psychosocial interventions for aggressive youth are an effective, integral part of any treatment planning and should be age-specific, as developmental differences in cognitive, behavioral, affective,

and communicative abilities affect outcomes. Evidence-based psychosocial interventions must be available and accessible to the family. If clinicians are unable to locate appropriate programs, they should advocate for such interventions, obtain their own training, or seek colleagues who are willing and able to provide such treatments.

11. Engage the Child and Family in Taking an Active Role in Implementing Psychosocial Strategies and Help Them to Maintain Consistency (Grade of Evidence: B; Strength of Recommendation: Very Strong)

Family engagement in treatment significantly influences outcomes. More positive child-therapist and parent-therapist alliances also predict greater improvement, fewer perceived barriers to participation in treatment, and greater treatment acceptability.¹¹ Clinicians can promote treatment engagement by connecting the family with online resources or materials and community support. See the online Center for Education and Research on Mental Health Therapeutics Pocket Reference Guide for Primary Care Clinicians and Mental Health Specialists at www.TheReachInstitute.org/TMAY.html for further guidance.

Medication Treatments

12. Initial Medication Treatment Should Target the Underlying Disorder(s) (Grade of Evidence: A; Strength of Recommendation: Very Strong)

Youth with clinically significant maladaptive aggression often present with a range of symptoms that elude clear diagnosis and effective treatment. Accurate identification and effective treatment of the underlying condition may ameliorate impulsive aggressive behavior⁴¹ and minimize reactive approaches to prescribing that rely on multiple medications.⁴² If a primary disorder is identified (ie, a disorder that antedates the onset of the aggressive

symptoms and/or that also might be associated with aggressive symptoms), clinicians should focus on treating the primary disorder before using medication to address the aggression, except in emergency circumstances where the severity and frequency of aggressive symptoms may necessitate the simultaneous use of antiaggressive medications along with first-line treatments for the primary conditions.^{43,44}

13. When Available, Follow Evidence-Based Guidelines for the Primary Disorder (Grade of Evidence: A; Strength of Recommendation: Very Strong)

Based on recent advances in the pediatric psychopharmacology literature, specific classes of psychotropic medications have been identified as appropriate treatments for primary psychiatric disorders in children. Numerous studies indicate that the management of these primary disorders can reduce comorbid aggression.^{14,45,46} The American Academy of Child and Adolescent Psychiatry and other groups have published practice parameters on the diagnosis and treatment of various psychiatric conditions affecting children.^{44,47,48}

14. Consider Adding an Antipsychotic Medication, Taking Into Account the Latest Available Evidence on Efficacy and Safety of Individual Agents, If Severe Aggression Persists After an Adequate Trial of Treatments for the Underlying Disorder (Including Psychosocial Treatments) (Grade of Evidence: A; Strength of Recommendation: Strong)

A growing literature supports the efficacy of antipsychotics for the management of aggressive and disruptive behavior problems; however, this literature is insufficient to determine the comparative risks and benefits of antipsychotic use in pediatric populations, especially long-term. Although no data are available regarding the relative

superiority of 1 second-generation antipsychotic over another for aggressive behavior, recent findings from the adult literature help elaborate the potential distinctions between conventional and second-generation agents, and within the class of second-generation medications.^{49–53} These studies suggest that adverse metabolic outcomes are greatest among clozapine and olanzapine and intermediate with quetiapine and risperidone, but evidence on the comparative effectiveness and side effects of individual medication choices among youth with aggression is lacking except for results from the Second-generation Antipsychotic Treatment Indication Effectiveness and Tolerability in Youth study⁵⁴ and the forthcoming Metabolic Effects of Antipsychotics in Children study.

15. Use Recommended Titration Schedules and Deliver an Adequate Medication Trial Before Changing or Adding Medication (Grade of Evidence: A; Strength of Recommendation: Very Strong)

The definition of an adequate trial duration varies according to the targeted disorder and medication type. To evaluate treatment response, clinicians should refer to guidelines for treating specific disorders, clearly identify target symptoms, and monitor patients by using target symptom and side-effect rating scales. For guidance on specific medications, including titration and maximum doses, and potential drug interactions, see the T-MAY Prescribers' Toolkit and Pocket Guide at www.TheReachInstitute.org/TMAY.html.

16. If Insufficient Response, Try a Different Antipsychotic Medication (Grade of Evidence: D; Strength of Recommendation: Strong)

For some medications, several weeks may be needed to achieve a full therapeutic effect.⁵⁵ Clinicians should be cognizant that monitoring aggressive symptoms is difficult, as these behaviors tend to occur infrequently and in

different settings, making the evaluation of treatment effects challenging. Clear delineation of target symptoms, monitoring parameters (eg, rating scales), and goals of treatment should be used.

17. For a Partial Response to an Initial First-Line Antipsychotic, Consider Augmentation With a Mood Stabilizer (Grade of Evidence: B; Strength of Recommendation: Strong)

Even after psychosocial intervention, treatment of the underlying disorder, and a trial of antipsychotic therapy, symptoms may fail to respond or remit in some patients. In these circumstances, addition of a mood stabilizer may be an appropriate next step, despite the previously noted limitations of the evidence base for use of mood stabilizers in aggression, which are limited mainly to lithium in inpatient settings. According to our review of RCTs, there is evidence for the cotreatment with lithium with an antipsychotic, or even for monotherapy with lithium if an antipsychotic is deemed inappropriate.

18. Avoid Using More Than 2 Psychotropic Medications Simultaneously (Grade of Evidence: C; Strength of Recommendation: Very Strong)

Although the general rule that “less is more” is an important starting point, more than 1 medication is often required for patients with complex comorbid conditions or those with limited response to treatment⁵⁶; however, data regarding the long-term effects of combination medications in youth are scarce.

Side Effect Assessment and Management

19. Conduct Side Effect and Metabolic Assessments and Laboratory Tests That Are Clinically Relevant, Comprehensive, and Based on Established Guidelines (Grade of Evidence: A; Strength of Recommendation: Very Strong)

Medication adverse effects can cause subjective distress, impair physical

health, and compromise medication adherence. Thus, treatment selection should be guided by individual patient factors (eg, age, developmental stage, illness phase, type and severity of target symptoms, preferences, past response) and by medication factors. Choice of lower-risk agents is advisable to concurrently target sustained symptom benefits, treatment adherence, and physical health. Because alterations of alertness (sedation/somnolence or insomnia), weight gain, and metabolic abnormalities are frequent adverse effects, assessment of lifestyle behaviors (eg, bad eating habits, lack of exercise) that can affect risk for adverse effects is crucial.⁵²

20. Provide Accessible Information to Parents and Families About Identifying and Managing Side Effects (Grade of Evidence: B; Strength of Recommendation: Very Strong)

To optimize outcomes and maximize the benefit-to-risk-ratio of pharmacologic interventions, education of patients and families about psychotropic adverse effects in youth should be routine clinical practice (see the T-MAY pocket guide at www.TheReachInstitute.org/TMAY.html). Clinicians should promote healthy lifestyle changes that may reduce the risk of physical adverse events and medication consequences.

DISCUSSION

This paper reviewed the T-MAY recommendations regarding psychosocial interventions, medication treatments, and side effect assessment and management. Our comprehensive review yielded a strong evidence base for multiple psychosocial and several psychopharmacologic interventions. The different psychosocial therapy modalities had an overall effect size of 0.36 in the acute phase (range: 0.09–0.98, median: 0.37), with an NNT of 4 (range: 2–12, median: 4) for response and an

NNT of 16 (range: 9–77, median: 10) for treatment continuation. Although we report overall effect sizes, these programs varied significantly and any comparison even around a specific principle, such as the use of behavioral methods, is impossible because of differences regarding duration, target populations, age ranges of the children involved, measures used to measure aggressive behaviors, and even presence of comorbid conditions. For example, a number of studies focus on family functioning as the primary goal of treatment (eg, Brief Strategic Family Therapy, Integrative Family Therapy, Multisystemic Therapy, and Multidimensional Treatment/Multisystemic Family Preservation Program), but the approach varied even within the same type of treatment (ie, Brief Strategic Family Therapy), where 1 program used 100-minute sessions with families for 12 weeks⁵⁷ and another used 60-minute sessions anywhere from 4 to 20 weeks.⁵⁸ These same programs also used different aggression measures. Therefore, although we report overall effect sizes, the therapies vary enough that any comparative interpretation should be done cautiously, keeping in mind that outcomes are affected by how these programs are delivered, who is involved in the treatment, and how and by whom aggression is measured. These differences highlight the need for the field to agree on more tightly standardized design features and procedural characteristics of studies assessing psychosocial treatment effects on maladaptive aggression in youth, a common treatment target in clinical practice.

For pharmacologic treatments, the pooled effect size was 0.61 (range: –0.13 to 0.83, median: 0.63), with an NNT for treatment response of 4 (range: 3–12, median: 4) and an NNT for treatment continuation of 8 (range: NNT = 46 to NNT = 5, median: NNT = 9). Although the effect sizes for the acute treatment and

the NNT for treatment continuation were more favorable for pharmacologic interventions than for psychosocial treatments, a direct comparison of the effectiveness of the 2 treatment modalities is not possible because of the heterogeneity in study populations and design and the absence of head-to-head studies.

Notably, while psychosocial and psychopharmacological interventions were both found to be effective in reducing aggression among children and youth, the definition of aggression and of measured outcomes varied substantially. In addition, studies examining the long-term safety and efficacy of any of the psychopharmacologic agents are sparse, and evidence is lacking for combination medication approaches, although use of multiple medications is common in clinical practice. Studies that examined the effects of both psychosocial and medication treatment simultaneously on aggression are almost entirely absent. Only 1 randomized study, thus far, has examined the effects of parent training combined with risperidone versus risperidone treatment only on maladaptive and irritable behavior in 124 children (aged 4–13 years), with pervasive developmental disorders and frequent tantrums, self-injury, and aggression. In this 24-week study, antipsychotic treatment plus parent training resulted in a greater reduction of maladaptive behaviors than medication treatment alone, despite a lower risperidone dose requirement in the combination treatment group.⁵⁷ Nevertheless, although these results are encouraging, Clinical Global Impressions Scale scores did not differ and, clearly, further studies of direct comparisons and/or combination treatments focusing specifically on children with maladaptive aggression with or without comorbidities are sorely needed. Because of the limited evidence and need for further inquiry, clinicians must decide on the type and duration of

treatment within the scope of a child's clinical profile and developmental stage, cardiovascular risk, familial background, and environmental factors. Our treatment recommendations reflect these limitations. Although the evidence on the effect of psychosocial interventions on maladaptive aggression is limited, psychosocial treatments should be tried first because of their lower risk and for some of the treatments, the involvement of the entire family as opposed to just the child. If medication treatments are implemented, then treatments with fewer side effects should be considered first. Use of rating scales such as the Aberrant Behavior Checklist,⁶⁰ or Overt Aggression Rating Scale⁶¹ for target symptoms and careful side-effect monitoring are essential throughout this process and they should reflect the perspectives of parents, the patient, and other significant individuals in the patient's life (eg, teachers) if possible.

Although the development of T-MAY involved a comprehensive and systematic assessment of the available evidence as well as multidisciplinary expert opinion, these recommendations are subject to significant uncertainty, reflecting the many gaps in the RCT evidence base. In addition, even less is known about effectiveness under usual-care conditions for children treated in diverse specialty and nonspecialty practice settings; there is considerable need for research on outcomes in these "real-world" settings. Studies examining patterns of treatment and outcomes across settings and clinical disciplines (eg, pediatrics, psychiatry) may be warranted, including studies of how to coordinate efforts between primary care physicians and mental health providers to maximize aggression management and youth outcomes. Nevertheless, the T-MAY recommendations and tools provide a critical base for further research efforts, as well as clinical practice and guidelines.

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Treatment of Maladaptive Aggression in Youth: CERT Guidelines II. Treatments and Ongoing Management

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Aggressive in Youth Steering Committee

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