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Effectiveness of Antidepressant Medications for Symptoms of Irritability and Disruptive Behaviors in Children and Adolescents

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Abstract

Objectives: Chronic irritability is a common presenting symptom in children and youth in both clinical settings (25%) and in the community (6%–8%). Treatment of irritability is relatively understudied. The purpose of this article is to synthesize evidence regarding the efficacy and safety of antidepressant medications for the treatment of irritability and related symptom dimensions in children and youth.

Methods: Systematic review of the literature was conducted to identify studies (including youth aged 6–18) that assessed the effectiveness of antidepressant medications for the treatment of irritability or related behavioral phenotypes, including aggression or symptoms of. Studies of youth with developmental disabilities or autism spectrum disorders were excluded.

Results: We identified 99 studies (three randomized trials) assessing the effect of antidepressants in improving irritability, aggression, or oppositional symptoms as secondary outcomes. Only two studies specifically measured the outcome of irritability. Eight of the 11 studies reported significant effects on aggression, oppositionality, or irritability with antidepressant exposure, although effect sizes in all, but two of these, studies were less than 0.25. These effects were significantly reduced, but remained significant in seven of these studies after controlling for changes in comorbid depression scores with treatment. The other three studies reported no change, an increase in frequency of self-harm or aggressive behaviors or benefit in only a subsample of youth who tolerated the antidepressants after 1 year of follow-up.

Conclusion: Antidepressant medication exposure appears to have a small effect on irritability and related symptoms in youth. Heterogeneity in the study sample and absence of irritability being measured as a primary outcome across studies restrict the validity of the conclusions. Irritability is a debilitating outcome that needs specific attention in medication treatment studies.

Keywords: irritability, depression, treatment, antidepressant, youth, children

Introduction

Irritability is defined as a tendency toward negative affective states, predominantly anger, with frequent temper outbursts. Chronic, as opposed to episodic, irritability is a common presenting symptom in children and youth in both clinical settings and in the community. The absence of a diagnostic profile to describe chronic irritability before disruptive mood dysregulation disorder (DMDD) in DSM-5 has curtailed specific estimates of its prevalence. Considering DMDD, three epidemiologic studies found 1-year prevalence rates of DMDD ranging from 3.3% to 8.2% in preschool children (Copeland et al. 2013; Dougherty et al. 2014) with similar findings in older youth (Copeland et al. 2013). However, rates are significantly higher in clinical samples (22% in Roy et al. 2014 and 26% in Axelson et al. 2012). When irritability is measured as the irritability dimension of oppositional defiant disorder (ODD), which includes the items, often loses temper, often touchy or easily annoyed, and often angry and resentful, it appears to be stable across childhood and clinically impairing in ∼11% of youth (Kuny et al. 2013).

However measured, the presence of irritability is a very poor prognostic factor for a child. Irritable youth are disproportionately affected by suicidality, substance use, and lower goal attainment (Holtmann et al. 2010) and require higher acuity mental health services, especially inpatient services (Carlson et al. 2009).

Pharmacologic treatment studies of irritability in children and youth

Chronic irritability has long been recognized to present in the context of many psychiatric conditions. The pharmacologic rationale for its treatment is not robust. As clinical studies document that irritability most commonly occurs in the context of disruptive behavior disorders (DBDs) (Axelson et al. 2012), most pharmacologic studies of treatment of irritability or related constructs such as oppositionality and aggression have been conducted in samples with high rates of attention-deficit/hyperactivity disorder (ADHD). Perhaps not surprisingly, these studies support the use of stimulants as well as psychosocial or behavioral training interventions for

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reducing irritability and oppositional behaviors (Nevels et al. 2010; Gorman et al. 2015). One study of youth with severe mood dysregulation (SMD) noted a significant reduction in irritability in response to add-on antipsychotic medication (risperidone) (Krieger et al. 2011), and a large randomized controlled trial (RCT) of youth with ADHD demonstrated a mild to moderate reduction of parent-rated oppositionality with risperidone as an adjunct to stimulant treatment and parent skills training (Gadow et al. 2014).

No studies, to date, have specifically examined the effect of antidepressant medications for the treatment of irritability in children and youth. There are several reasons why this is needed, both to identify the potential benefits and harms of doing so. The consistent association between ODD irritability and later life mood and anxiety disorders provides the strongest theoretical rationale for their role in use in treating irritability. Irritability is included as a core diagnostic symptom of unipolar depression in youth. A recent study suggests that while irritable mood, as opposed to sadness, as a primary feature of major depressive episodes is rare, irritability commonly occurs with depressed mood (Fava et al. 2009; Stringaris et al. 2013). Thus, clinically impairing irritability in youth may respond to antidepressant medications irrespective of whether a clinical diagnosis of depression is present. As children with DBDs often have comorbid internalizing disorders, antidepressants may also have a role for their irritability.

As a counterpoint, the use of antidepressants in youth with mood difficulties has been tempered in recent years given the physician vigilance regarding potential risk of increased suicidal ideation and irritability with antidepressant exposure. In an irritable sample, this concern may be of higher salience. Studies by Leibenluft and colleagues have shown that chronic irritability (SMD) is a problem distinct from bipolar disorder (for a review, see Dickstein and Leibenluft 2012). However, the specific effects of antidepressant exposure on chronically or episodically irritable youth have not been tested in other clinical trials, suggesting that clinicians should still be very cautious about antidepressant effects in these groups of patients.

The aim of this article is to synthesize evidence from pharmacological treatment studies regarding the efficacy of antidepressants for the treatment of irritability in children and youth. We will also report evidence of side effects or harm reported in these studies.

Recognizing that core features of chronic irritability may include temper outbursts, anger, and difficulty getting along with others, we included studies where the outcomes were measured as irritability or irritable mood, as well as proxy outcomes with overlapping symptoms such as aggression, or oppositional behaviors. We also included any studies which included youth whose treatment outcome would have included changes in status or severity of a diagnosis with core feature of irritability (i.e. SMD or disruptive mood dysregulation disorder). We sought to include more outcomes than irritability because few studies measure irritability specifically. However, we acknowledge *a priori* that these outcomes require comparative analysis.

Methods

Criteria for considering studies within this review

Any original study (open trial, randomized placebo-controlled trials (RCTs), case series, case reports, and reviews), reporting outcomes on behavioral dimensions of interest in children and adolescents following treatment with antidepressants, was eligible for inclusion. Study participants had to be children or adolescents under the age of 19 (inclusive). To be eligible, studies had to have at least one primary or secondary outcome measure related to the behavioral dimensions of irritability, oppositionality, or aggression. For example, studies that not only examined improvements in major depressive disorder (MDD) symptoms as the primary outcome measure but also reported improvements in oppositional behavior were selected for review.

Search method for identification of studies

Articles were obtained through scientific databases such as Web of Science, OvidSP, Google Scholar, and Pubmed, using the key words, oppositional defiant disorder, conduct disorder, disruptive behavior disorder, irritability, impulsivity, aggression, antidepressant, SSRI, SNRI, and tricyclic antidepressant. Searches were limited to articles published in English, and no gray literature was searched for available evidence. Filters regarding age group, study population, and type of evidence were utilized when available. A total of 12,544 studies were identified from Web of Science, Ovid, PubMed, and Google Scholar. In addition, reference lists from identified studies as well as from published reviews and books regarding pharmacological treatments of DBDs were used to identify additional relevant evidence. Abstracts of studies were examined using the eligibility criteria for studies. Articles examining populations with developmental disabilities, including autism spectrum disorders, were excluded to describe medication effects on a typically developing sample. Articles without a measure of irritability, oppositionality, or aggression were excluded. In total, we identified nine studies assessing the effect of antidepressants in improving irritability, aggression, or oppositional behavior symptoms as secondary outcomes. The included studies were published between 1982 and 2013.

Results

Studies reporting the effect of SSRI exposure on disruptive behavior symptom outcome

Randomized or placebo-controlled studies. Prince et al. (2000) conducted a 9-week placebo-controlled discontinuation trial to study the efficacy of nortriptyline on ADHD symptom response among 35 participants aged 6–17 who had a confirmed ADHD diagnosis (Table 1). The study sample was primarily male ($n = 28$, 80% males). Effects on disruptive behavior (ODD) symptom change using a DSM checklist were also reported. While 75% of these youth had been on previous medication trials, the authors did not specify whether there was a pretrial medication washout period. In the first 6 weeks of the trial, participants received a mean dose of 1.8 mg/(kg·d) of nortriptyline. All medication responders ($N = 25$) were randomized into a 3-week, double-blind, placebo-controlled discontinuation phase. During this phase, responders were randomized to either continue with the current dose of nortriptyline or taper off the medication to placebo over 1 week. During the open phase of the trial, there was progressive and significant reduction in ODD symptom checklist scores by week 6 compared with baseline (–48%, $t = 7.8$, $p < 0.001$). Using a 30% reduction in ODD symptom checklist scores as an indication of response, it was determined that by the end of the open trial phase, 78% of the participants responded positively to the medication. After the discontinuation phase, participants randomized to remain on nortriptyline had significantly lower scores on the ODD symptom checklist than placebo participants ($t = 2.5$, $p < 0.02$). Compared with baseline ratings, participants in the nortriptyline group sustained their response ($t = 4.9$, $p < 0.0003$). However, participants in the placebo group

experienced a significant increase in the ODD symptom checklist scores ($t = -2.8$, $p < 0.02$) compared with their week 6 scores. On the Clinical Global Impressions Scale for ODD, 62% of youth receiving medication were considered to be much improved, while only 11% of those getting placebo were considered to have improved ($x^2 = 5.6$, $p < 0.02$).

The Treating Adolescents with Depression Study (March et al. 2004) was a 12-week RCT aimed to evaluate differential effects of fluoxetine (FLX), cognitive behavioral therapy (CBT), combination therapy (COMB), or placebo (PBO) on depressive symptoms among adolescents aged 12–17 ($N = 439$). Dosing of fluoxetine started at 10 mg/d to a maximum of 40 mg/d based on clinical response. As a secondary analysis, Jacobs et al. (2010) examined the differential effects of the four treatment conditions on co-occurring oppositionality within the sample. Oppositionality was assessed immediately before treatment, at week 6, and at the end of treatment using the oppositional behavior subscale of the Conners Parent Rating Scale-Revised Long Form. At the end of the 12-week treatment period, all four treatment groups experienced a decrease in oppositionality. Examining the differential effects, COMB ($F_{(1,415} = 13.44$, $p < 0.01$) and FLX ($F_{(1,411} = 10.32$, $p < 0.01$) treatment groups were significantly more improved when compared with PBO at 12 weeks, whereas the CBT ($F_{(1,413} = 2.39$, $p > 0.05$) group was not different from PBO. Both COMB ($F_{(1,413)} = 27.00$, $p < 0.01$) and FLX ($F_{(1,405)} = 22.43$, $p < 0.01$) were superior in their effect on oppositionality in comparison with CBT, but did not differ from each other. These findings remained significant after controlling for change in depression scores in the model.

These results indicate that depressed adolescents receiving FLX either alone or in combination with CBT experienced greater reduction in oppositionality compared with those who did not receive the medication. The study did not have sufficient power to examine whether treatments led to differential rates of remission in DBD diagnoses.

The Treatment of Resistant Depression in Adolescents Trial (TORDIA) was a 12-week RCT aimed to assess the relative efficacy of several antidepressants alone or in combination with CBT on SSRI-resistant depression among adolescents ($N = 334$). In a secondary analysis, Hilton et al. (2013) evaluated the differential effects of the treatments on comorbid ODD and conduct disorder (CD) measured using the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 2001), as well as on changes in DBD symptoms measured using the K-SADS-PL (Hilton et al. 2013). The antidepressants of interest were fluoxetine, citalopram (SSRI), and venlafaxine (non-SSRI). Participants were randomized to one of four treatment arms: (1) switch to alternative SSRI, (2) switch to venlafaxine, (3) switch to alternative SSRI + CBT, and (4) switch to venlafaxine + CBT. Overall, there was a significant reduction in rates of DBD diagnoses at 24 months across all treatment groups (10%–2.8%; odds ratio [OR] = 0.95, 95% confidence interval [CI] 0.89–1.00, $z = -1.99$, $p = 0.046$). There were no differential effects of medication on DBD symptoms ($\beta = -0.01$, SE = 0.01, $z = -0.65$, $p = 0.51$), despite a trend of participants treated with SSRI showing a greater reduction in rates of DBDs over time compared with participants treated with venlafaxine (OR = 0.90, 95% CI 0.81–1.00, $z = -1.89$, $p = 0.06$). Between-group treatment differences were not significant, suggesting that there were no significant differences in outcome in the presence of additional CBT or between antidepressant types. The decline in the Children's Depression Rating Scale Revised score from 0 to 12 weeks and from 12 to 24 weeks modestly correlated with a decline in the symptoms of ODD ($r = 0.20$ and $r = 0.21$, $p < 0.001$).

Uncontrolled studies. Zubieta and Alessi (1992) conducted an open-label trial to study the effects of trazodone treatment on symptoms of ADHD, ODD, and CD among 20 children (aged 5–12) hospitalized for behavioral stabilization (Table 1). Sixteen of the 20 (80%) children participating in the study were male. The outcome measure used was a coding of count of all *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition. Revised. (DSM-III-R) (American Psychiatric Association, 1987) symptoms of ADHD and disruptive behavior as being present or improved using a symptom checklist. After the medication trial, the symptom domains were rated as being clinically improved or not improved. All participants were started on trazodone, and the medication trial length was on average 27 days for medication responders (Mean Dose: 4.8 ± 1.7 mg/kg) and 24 days for nonresponders (Mean Dose: 2.7 ± 2.0 mg/kg). At baseline assessment, the 20 youth endorsed 114 of 160 possible ODD (160 = 8 DSM-III-R symptoms endorsed by 20 youth) symptoms as being present. After the medication trial, 54% of these endorsed items were rated as improved. Specifically, the symptoms, often argues with adults and often loses temper, were noted as improved in 67% and 60% of cases, respectively. In total, after a minimum of 2 weeks at the maximal dose of trazodone, 13 participants were classified as medication responders and seven participants as nonresponders.

Studies reporting effect of SSRI treatment on aggression or irritability

Randomized or placebo-controlled studies. Carlson et al. (1995) conducted an inpatient, double-blind, placebo-controlled crossover trial to assess the differential efficacy of desipramine (DMI), methylphenidate (MPH), and combination (COMB) therapy in treating 16 male children (aged 7–12) who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994) criteria for ADHD and DBD, as well as a mood disorder (Table 2). The trial lasted 16–18 weeks, depending on the time it took to achieve therapeutic levels of DMI. DMI was titrated to achieve plasma levels between 125 and 225 ng/mL. Eleven of the 16 boys had a diagnosis of having MDD, and the rest had dysthymic disorder. The primary aim of the treatment was to improve boys' oppositional and aggressive symptoms. Diagnoses were made using the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version. Oppositional behaviors were rated at school on a weekly basis using the ADD-H Comprehensive Teacher Rating Scale (ACTeRS)-oppositional subscale, and in the inpatient unit using the Inpatient Global Rating Scale (IGRS). Measurements during the inpatient stay were taken in the morning and in the evening. ODD and CD items were tallied to create a behavior score. To allow for the comparison of scores, results were transformed to t scores (mean = 50, standard deviation = 10) based on data from all children admitted to the hospital unit. Each child was observed on MPH alone, DMI alone, and on COMB therapy of these two treatments. The outcomes measured during each treatment phase were then compared with placebo treatment and baseline ratings.

There were no significant differences across treatment groups on the ACTeRS-oppositional scale at school. In the hospital, aggression scores from the IGRS were significantly improved ($p < 0.05$) when DMI treatment ($t = 48.6$) was compared with placebo scores using the evening measurement ($t = 55.9$) and when COMB treatment ($t = 47.8$, $t = 48.9$) was compared with baseline ($t = 55.8$, $t = 53.3$) or placebo ($t = 55.7$, $t = 55.9$) for both morning and evening measurements, respectively. A separate analysis of the 11 children

Table 1. Studies Reporting Effect of SSRI Exposure on Disruptive Behavior Symptom Outcome

Reference	*Study duration*	*Subjects (no. at intake)*	*Age (years)*	*Study design*	*Drug and dosage*	*Measures of oppositionality outcomes*	*Clinical outcomes*
Randomized or placebo-controlled studies							
Prince et al. (2000)	Six-week open phase and 3-week discontinuation phase	Children and adolescents with a confirmed ADHD diagnosis (35)	6–17	Placebo-controlled discontinuation trial	Nortriptyline: mean dose of 80 mg (1.8 mg/(kg·d)	Oppositional Rating Scale	Significant reduction in ODD Symptom Checklist scores by week 6 of active medication trial in comparison with baseline (–48%, t = 7.8, $p < 0.001$). Significantly lower ODD scores for nortriptyline treatment group than placebo group (t = 2.5, $p < 0.02$) after randomized discontinuation phase.
Jacobs et al. (2010)	Twelve weeks	Clinically depressed adolescents (439)	12–17	Placebo-controlled randomized trial	Fluoxetine: starting dose of 10 mg/d to maximum of 40 mg/d	Conners Parent Rating Scale—Revised Long Form	Improvements in oppositionality in all four treatment groups. Significant improvements in COMB ($p < 0.01$) and FLX ($p < 0.01$) groups compared with PBO. Improvements in CBT nonsignificant compared with PBO ($p > 0.05$). COMB ($p < 0.01$) and FLX ($p < 0.05$) both superior to CBT, but COMB and FLX not significantly different ($p > 0.05$).

(*continued*)

Table 1. (Continued)

Reference	*Study duration*	*Subjects (no. at intake)*	*Age (years)*	*Study design*	*Drug and dosage*	*Measures of oppositionality outcomes*	*Clinical outcomes*
Hilton et al. (2013)	Twelve weeks (trial), 12 weeks (follow-up)	Adolescents with moderately severe MDD or dysthymia who did not respond to previous SSRI treatment (334)	12–18	Randomized controlled trial	Averages during week 6–12: fluoxetine (33.8 mg/d), citalopram (31.2 mg/d)	Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version	Significant reduction in rates of DBD diagnoses over time after treatment (10%–2.8%; OR = 0.95, 95% CI 0.89–1.00, z = −1.99, $p = 0.046$). No differential effects of medication on DBD symptoms ($p = 0.51$) and no effects of additional CBT compared with medication alone on DBD symptoms ($p = 0.75$). Observed trend of participants treated with SSRI showing greater reduction in DBD diagnosis rates compared with participants treated with venlafaxine (OR = 0.90, 95% CI 0.81–1.00, z = −1.89, $p = 0.06$).
Uncontrolled studies							
Zubieta and Alessi (1992)	Average trial length: 27 days (responders) and 24 days (nonresponders) +8.8 months of follow-up	Hospitalized children with a history of impulsive/aggressive behavior who were unresponsive to other previous treatments (20)	5–12	Open-label trial	Responders: trazodone (4.8 ± 1.7 mg/kg) nonresponders: trazodone (2.7 ± 2.0 mg/kg)	DSM-III-R Symptom Checklist	One hundred fourteen of 160 ODD symptom dimensions noted as being present at the beginning of trial, with 54% rated as improved after the trial.

ADHD, attention-deficit/hyperactivity disorder; CBD, cognitive behavioral therapy; CI, confidence interval; COMB, combination therapy; DBD, disruptive behavior disorder; FLX, fluoxetine; MDD, major depressive disorder; ODD, disruptive behavior; OR, odds ratio; PBO, placebo.

Table 2. Studies Reporting Effect of SSRI Treatment on Irritability or Aggression Symptoms

Reference	*Study duration*	*Subjects (no. at Intake)*	*Age years*	*Study design*	*Drug and dosage*	*Measures of oppositionality outcomes*	*Clinical outcomes*
Randomized or placebo-controlled studies							
Carlson et al. (1995)	Usually 16–18 weeks	Psychiatrically hospitalized male children with diagnoses of ADHD, MDD/ dysthymic disorder, or both—children also had either a diagnosis of CD or ODD (16)	7–12	Double-blind, placebo-controlled crossover trial	Desipramine: titrated to achieve plasma levels between 125 and 225 ng/mL	ADD-H Comprehensive Teacher Rating Scale, Inpatient Global Rating Scale	Significantly improved ($p<0.05$) Aggression scores for DMI treatment ($t=48.6$) compared with placebo treatment ($t=55.9$) during the evening shift, and for DMI + MPH combination treatment ($t=47.8$, $t=48.9$) compared with baseline ($t=55.8$, $t=53.3$) and placebo ($t=55.7$, $t=55.9$) for both morning and evening shifts on the Inpatient Global Rating Scale.
Uncontrolled studies							
Garland and Weiss (1996)	Follow-up of at least 1 year	Referred children with obsessive difficult temperament and complaints of inflexibility, irritability, emotional reactivity, and somatic symptoms (8)	8–11	Case series	Clomipramine, Imipramine, Paroxetine, Fluoxetine: Dependent on individual child-refer to study	Parental reports	Parental reports of dramatic improvements in obsessive irritability. Parental observations of a calmer less rigid child, improvements in perfectionism and somatic symptoms. Relapse occurred when medication was discontinued.
Constantino et al. (1997)	At least 5 weeks (trial)	Children hospitalized for a psychiatric issue, not specifically selected for increased aggressiveness (19)	13–17	Open label trial	Fluoxetine (10–40 mg/d), Paroxetine (20–40 mg/d), Sertraline (50–100 mg/d)	Modified version of the Overt Aggression Scale	No significant improvement in any dimension of aggression between the first 2 and last 2 weeks of treatment (all tests $p>0.05$). Likelihood of having a week with at least one aggressive incident (vs. a week with no incident) higher when subjects are on SSRI than off SSRI ($x^2=4.96$, $p<0.05$).

(*continued*)

Table 2. (Continued)

Reference	*Study duration*	*Subjects (no. at Intake)*	*Age years*	*Study design*	*Drug and dosage*	*Measures of oppositionality outcomes*	*Clinical outcomes*
Armenteros and Lewis (2002)	Six weeks	Children with long-standing history of impulsive aggression referred for psychiatric services to an outpatient clinic (11)	7–15	Open-label trial	Citalopram: initial dose of 10 mg/d—weekly adjustments of 10 mg in either direction	Modified Overt Aggression Scale, Child Behavior Checklist, Conners Continuous Performance Test	Significantly improved weekly mean total score for aggression from baseline (ES = 1.9, F7 = 4.98, $p < 0.001$) with scores on Aggression against Objects subscale significantly lower than baseline (F6 = 7.9, $p < 0.001$). Significantly lowered total irritability scores on weeks 1,2,5, and 6 compared with baseline (F7 = 2.95, $p = 0.02$).
Blader (2006)	Twelve months (after discharge)	Children admitted to psychiatric inpatient clinic with main complaint of aggression, with a primary diagnosis of a DBD, eventually discharged to reside in the community (83)	8–13	Prospective follow-up study	Not specified	Child Behavior Checklist, New York Parent Rating Scale for Disruptive Behavior	Significantly higher Physical Aggression (effect = 6.25 ± 4.5, $p < 0.01$) and Nonphysical Disruptive Behavior (effect = 34.79 ± 25.3, $p < 0.01$) at 6-month follow-up, but significantly improved Physical Aggression (effect = –4.44 ± 3.6, $p < 0.01$) and Nonphysical Disruptive Behavior (effect = –26.1 ± 20.4, $p < 0.01$) scores at 12-month follow-up for SSRI-treated children in comparison with non-SSRI-treated children.

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; DBD, disruptive behavior disorder; DMI, desipramine; MDD, major depressive disorder; ODD, disruptive behavior.

who met the criteria for MDD revealed that neither MPH (t = 48.5) nor DMI (t = 46.8) alone produced significant changes in behavior scores on the IGRS compared with placebo (t = 55.2) and baseline (t = 54.8). However, COMB therapy did show a trend toward improvement (t = 45.5, $p = 0.07$) compared with placebo, particularly in youth with ADHD combined type.

Uncontrolled studies. Garland and Weiss reported cases of 8 children (aged 8–11) with obsessive difficult temperament (ODT) and their response to serotonergic medication (Garland and Weiss 1996) (Table 2). The authors describe ODT as consisting of irritability—obsessive rigidity with extreme, negative emotional reactions in response to minor changes. In this study, irritability was measured through subjective parent report. The serotonergic medications used in the trial were clomipramine, imipramine, paroxetine, and fluoxetine in varying dosages. Parents reported a dramatic improvement in irritability at low to moderate doses of serotonergic medication, with typical responses noted within days of starting the medication. Parents observed improvements in irritability, perfectionism, and somatic symptoms over the next 2 weeks, further improving with dose increases. Improvements were not seen with imipramine treatment. These responses were sustained with medication over periods of a year or more, but relapse occurred when medication was discontinued.

Constantino et al. (1997) conducted an open-label trial to assess the effects of SSRI treatment on aggressive behavior in 19 hospitalized adolescents (aged 13–17) who had a wide range of psychiatric diagnoses. Although it was not the primary outcome, the frequency of aggressive behaviors was assessed weekly with a modified version of the Overt Aggression Scale. These patients received fluoxetine (10–40 mg/d), paroxetine (20–40 mg/d), or sertraline (50–100 mg/d) for at least 5 weeks to treat depressive symptoms, and the results from the three medications were combined to assess the treatment effect. When the number of aggressive events per week was compared between the first and last 2 weeks of the 5-week SSRI trial, no significant differences were observed, indicating that there was no overall improvement in any dimension of aggression. Thirteen of the 19 patients were assessed both on and off SSRIs. The number of aggressive episodes per week while on SSRI medication was compared with the number of aggressive episodes per week while off SSRI medication. The condition of being on SSRI was associated with an increased likelihood of physical harm toward self ($x^2 = 6.25$, $p < 0.01$), while the likelihood of physical harm toward others was no different between the two conditions of being on or off SSRI ($x^2 = 0.07$). The likelihood of having a week with at least one aggressive incident (vs. a week with no incident) was also higher while participants were on SSRI than off SSRI ($x^2 = 4.96$, $p < 0.05$).

A 6-week open-label trial conducted by Armenteros and Lewis assessed the short-term effects of citalopram on aggression and irritability in 11 participants aged 7–15 who had a history of aggressive behavior (Armenteros and Lewis 2002). Nine of the 11 patients in the 6-week medication trial had a DSM-IV diagnosis of ODD. After a full medication washout period, participants were given citalopram at an initial dose of 10 mg/d and weekly adjustments of 10 mg were made, according to treatment response. Aggression and irritability scores for each subject were evaluated weekly using the Modified Overt Aggression Scale (MOAS) (Kay et al. 1988). While the MOAS total aggression scores were significantly improved from baseline (effect size = 1.9), the significant change was in the Aggression against Objects subscale ($F_6 = 7.9$, $p < 0.001$), as change scores on the MOAS Verbal Aggression, Aggression against Self, and Aggression against Others subscales were not significantly different from baseline at any week. Total irritability scores were significantly reduced by the end of the trial (effect size = 1.9). In addition, parental reports on the Child Behavior Checklist (CBCL) decreased significantly for aggressive behaviors (effect size = 0.50) and externalizing problems (effect size = 0.55). Clinical Global Impressions-Severity ratings also declined significantly at the end of treatment ($F_7 = 5.78$, $p < 0.001$), and on the Clinical Global Impressions-Improvement scale, 9 of 11 participants were classified as either much improved or improved at the end of the trial. There was no significant effect of citalopram on CPT scores for impulsivity.

A prospective follow-up study was conducted by Blader (2006) to examine postinpatient discharge community outcomes of aggressive children treated with specific pharmacotherapy medication classes. Eighty-three children (aged 8–13) admitted to a psychiatric inpatient unit with a main complaint of aggression and a primary diagnosis of having DBD participated in the study. At 3, 6, and 12 months after discharge, parents completed the CBCL and the New York Parent Rating Scale for Disruptive Behavior (NYPRS) to assess aggressive and disruptive behaviors. Psychostimulant, antimanic, antipsychotic, alpha 2-agonist, and SSRI medication exposure intervals were determined at each follow-up interval. A measure of treatment effect was calculated by taking the mean difference between the scores of children treated with a specified medication and the scores of children not treated with the medication, adjusted for scores at admission and for concurrently administrated medications. We comment on SSRI findings only in this review.

Symptom scores did not significantly differ between groups who were or were not currently exposed to SSRIs at 3 months postdischarge. Exposure at 6 months postdischarge was associated with significantly higher NYPRS Physical Aggression (unit difference from unexposed group = 6.25 ± 4.5 [95% CI], $p < 0.01$) and Nonphysical Disruptive Behavior (unit difference from unexposed group = 34.79 ± 25.3 [95% CI], $p < 0.01$) scores at 6-month follow-up. However, at 12-month follow-up, children treated with SSRIs had significantly improved outcomes on the NYPRS Physical Aggression (Effect = –4.44 ± 3.6, $p < 0.01$) and Nonphysical Disruptive Behavior (Effect = –26.1 ± 20.4, $p < 0.01$) scores, relative to children not taking SSRIs at the time. The rate of treatment with SSRIs decreased significantly over the assessment times (z-trend = 2.55, $p < 0.02$), and data were not reported in such a way to estimate which youth were persistently versus intermittently exposed at each time point.

Adverse effects of antidepressant exposure across all studies

As oppositionality, irritability, and aggression were not the primary outcomes in any of these studies, none of these reports identify if adverse effects related to medication exposure differed in the presence of these outcomes. Specific measures of adverse events were reported in all studies except for Blader (2006) using a variety of measures of side effects or adverse events. The most significant adverse events were reported in the TADS trial, where suicide-related events occurred in 23 youth (Emslie et al. 2006). It was reported that participants in the FLX group had significantly more incidences of suicide-related events than PBO (OR = 3.7, 95% CI 1.00–13.7, $p = .0402$) (Emslie et al. 2006). Within the TORDIA trial, no significant difference across medication groups (all participants were taking medication) in frequency of self-harm, suicidal ideation, or suicide attempts was noted (Brent et al. 2008). In total, there were 6 (3.6%) suicide attempts within SSRI treatment groups and 11 (6.6%) suicide attempts within venlafaxine treatment

groups (Brent et al. 2008). There were 31 (18.5%) total self-harm adverse events (suicidal ideation, attempt, or self-injurious behavior) in the SSRI treatment groups and 37 (22.3%) total self-harm adverse events in the venlafaxine treatment groups (Brent et al. 2008).

Emslie et al. (2006) reported on psychiatric adverse events in their study. Psychiatric adverse events were clustered into different spectrums such as mania, irritability/depression, agitation, anxiety, and other. The mania spectrum included items of mania, hypomania, and elevated mood. Six subjects reported to have experienced an item within this spectrum. The irritability/depression spectrum included items of hypersensitivity, irritability, anger, worsening of depression, and crying. Seven subjects reported to have experienced an item within this spectrum. A total of five subjects exhibited symptoms in the agitation spectrum, which included items of agitation, akathisia, nervousness, and restlessness. Three subjects reported anxiety/panic symptoms. Patients treated with FLX (either alone or in COMB) reported more psychiatric adverse events than patients treated with CBT or PBO. All comparisons were underpowered in this study due to small sample size.

Other studies noted physical side effects at rates occurring higher in medication than placebo groups, cardiovascular events with venlafaxine (Brent et al. 2008), sedation, insomnia, and upper abdominal pain with fluoxetine (Emslie et al. 2006), and orthostatic hypotension and drowsiness with trazodone (Zubieta and Alessi 1992).

Although they did not have a placebo group, the study of 19 hospitalized youth with aggression and mixed diagnostic profiles by Constantino et al. (1997) identified a significant association between likelihood of physical harm to self while the youth was taking an SSRI compared with a drug naïve period ($X^2 = 6.25$, $p < 0.01$), but no difference in likelihood of harm toward others whether the youth was, or was not, on an SSRI (Constantino et al. 1997).

Discussion

This is the first study to examine the effect of antidepressant medication on measures of irritability, oppositionality, and aggression in children and adolescents. As the main aim of the study was to examine the impact of antidepressants on irritability, it was disappointing that we could review only two studies that included this outcome, both of which were uncontrolled studies (Garland and Weiss 1996; Armenteros and Lewis 2002). Garland and Weiss noted that exposure to various SSRIs resulted in clinically observed improvements in irritability and reduced rigidity and perfectionism in their case series of youth with obsessive difficult temperament. Armenteros and Lewis noted large treatment effects of citalopram on physical aggression and irritability-specific outcomes in 11 adolescents with disruptive behaviors and aggression (Armenteros and Lewis 2002). To confirm the specificity of these gains to antidepressant treatment, we recommend that future controlled studies of antidepressant treatment include a measure specifically for irritability.

Of the remaining studies, the majority suggested improvements in either rate of remission of ODD or overall reduction in symptoms of aggression after exposure to antidepressant medications. These outcomes are not the same as irritability, although the youth in these studies were also likely to be irritable. These effects are small or difficult to quantify with accuracy because of sample size limitations. The two most rigorously controlled studies noted at most a small effect size (<0.2) of antidepressants for outcomes of oppositionality (Jacobs et al. 2010) or oppositionality and CD symptoms combined (Hilton et al. 2013). Studies classifying youth as responders on the basis of clinician judgment noted significantly larger effects, although these studies were open label (Zubieta and Alessi 1992; Prince et al. 2000). There were no obvious differences in the methodological rigor (sample size, study design) between positive versus negative studies. Whether antidepressant medications reduce disruptive behaviors, particularly oppositional ones, through their impact on irritability is an important hypothesis to test. Respecting that not all youth with disruptive behavior symptoms are irritable or have comorbid internalizing symptoms is a key variable to factor in before declaring some utility of antidepressants in their treatment regime. It is of high clinical relevance given the potential clinical impact of treating irritability or internalizing comorbidity in this population of high-risk youth.

All of the studies reviewed included samples with mixed comorbidity. Improvements in irritability or oppositionality resulting from antidepressants therefore may be the result of the impact of antidepressants on other outcomes, most logically, depression or anxiety symptoms. There is some evidence supporting these assertions. For example, the two studies, which could classify participants as being in remission from a depressive episode, found stronger evidence of reduction in oppositionality or conduct symptoms in remitters, as opposed to nonremitters. In the TADS study, youth whose depressive episode remitted with any (CBT, antidepressant, or both) treatment modality had significant reductions in oppositionality scores compared with placebo. However, among nonremitters, only the two medication-exposed groups had significant reduction in oppositionality (Jacobs et al. 2010). The TORDIA study also found that remitters displayed a statistically significantly greater reduction in DBD symptoms from baseline to week 24 in comparison with nonremitters (Hilton et al. 2013). These studies suggest that treatment response and ODD symptoms may be linked in some youth with depression. Since the only randomized studies included youth with a diagnosis of MDD, it is important to examine this question in controlled studies on youth who do not have depression. The other studies in this review suggest that there is some effect of antidepressants on irritability and ODD symptoms that is likely independent of depression. Tests of which symptoms mediate irritability response are needed.

From a treatment perspective, the importance of measuring irritability in pharmacotherapy studies cannot be underscored. Currently, there is substantial clinical research interest in recognizing the presence of a subdimension of irritability within ODD and considering the validity of the diagnosis of DMDD. There is substantial comorbidity between ODD and DMDD in clinical samples (Axelson et al. 2012), attesting to the common feature of irritability and its relationship with oppositional disruptive behavior. Others have suggested that there is reasonable expectancy that the mood difficulties of DMDD and its predecessor, SMD Disorder, may respond to antidepressant medications (Krieger et al., 2013). This review highlights the dearth of studies in support of such an approach and the need for more studies particularly in youth whose comorbid ADHD is optimally managed using evidence-based treatments.

Limitations

There are several methodological limitations inherent to this review, which are related to study design, sample constitution, and measurement of irritability.

(1) No controlled studies measured irritability as a primary outcome. As such, the secondary comparisons on irritability or DBD symptoms reported in this review are *post hoc* evaluations likely to be underpowered and at heightened risk for error or incorrect interpretation.

(2) Only two studies used the same outcome scale (MOAS, CBCL), thus results could not be combined for greater confidence and generalizability.
(3) The studies reviewed consisted of heterogeneous samples where youth have multiple comorbid disorders, have failed previous medication trials, or were being treated in a hospital, attesting to their severity. The impact of any intervention on specific symptoms may be less marked in a complex highly impaired sample. The effect of antidepressant medications on irritability or disruptive behavior may be more substantial in a general clinical sample, even if the majority of these youth would be expected to be concurrently treated with stimulant medications. Despite this limitation, we can say that the results we observed are effects we might anticipate in a moderate to severely impaired sample with children and youth with comorbid psychiatric disorders.
(4) We only have child or youth report of irritability and DBD symptoms in one study (Zubieta and Alessi 1992). The report of irritability in youth may be more valid than from parents; however, this review is based on parent-reported irritability predominantly.
(5) Five of the 11 studies comprised male patients exclusively or in majority (Zubieta and Alessi 1992; Carlson et al. 1995; Prince et al. 2000; Armenteros and Lewis 2002; Blader 2006). No study examined sex differences in symptom response. Further research about the impact of antidepressants on girls' irritability, disruptive, or aggressive behavior is needed.
(6) We looked for treatment effects of antidepressants on a variety of potentially related outcomes (i.e., irritability, aggression, oppositionality), although these outcomes may be differentially responsive to antidepressant medications. Furthermore, this review included antidepressants of the SSRI and tricyclic classes and trazodone, which each have different mechanisms of action and may be differentially effective for youth with disruptive behaviors, as opposed to youth with internalizing disorders. For example, the two studies that examine the effect of tricyclic antidepressants (Carlson et al. 1995; Prince et al. 2000) reported significant results for aggressive behaviors, whereas the results across SSRI studies were mixed. There are insufficient data to comment regarding differential responsiveness, but additional research is needed to explore this rational possibility.

Conclusion

This review has identified evidence of small to moderate benefit of antidepressant medication for outcomes of irritability, oppositionality, and aggression in youth. The most robust evidence came from two high-quality clinical trials of antidepressant or CBT treatment for depression, which identified small effect sizes for antidepressant exposure on secondary disruptive behavior outcomes (Jacobs et al. 2010; Hilton et al. 2013). Major limitations are the small number of small studies, mixed samples with high impairment, preponderance of male subjects, predominance of parent report on behavior outcomes, and no controlled study exploring irritability as a primary outcome.

Irritability is a difficult symptom to place diagnostically and appears to be difficult to treat. Roy et al. (2014) reviewed treatments for DMDD, a diagnosis characterized by irritability. The authors suggest that it is likely that many irritable youth will benefit from stimulant treatment given the high comorbidity with behavior disorders. Studies are needed that randomize stimulant-optimized youth to antidepressant or placebo. Ideally, this would be in an outpatient population over several months' duration. As noted by Blader (2006), response to medication needs to be evaluated against the placebo condition and natural course of the behavior. Such studies are very difficult to do, but are critically important to irritable youth who by their nature will require sustained mental health treatment and for whom the burden of treatment is substantial.

We recommend that studies measure irritability as an outcome, using a scale validated for youth for this purpose (i.e., Stringaris et al. 2012), and aim to study the sex differences in responsiveness in less clinically impaired samples. Given the burgeoning literature regarding the place of irritability as a core feature of ODD, and the clinical utility of the diagnosis of DMDD, more treatment studies are gravely needed for these irritable youth with high impairment and service use.

Clinical Significance

Antidepressant medications are associated with small reductions in irritability, aggression, and behavioral symptoms in youth with depression as a primary diagnosis as well as for youth with primarily behavioral diagnoses. As no study in this review examined irritability as a primary outcome, and significantly more studies are needed before declaring an estimate of the likely treatment effect of antidepressants on irritability. Respecting that the majority of irritable youth may have comorbid behavioral or neurodevelopmental disorders, the impact of antidepressant treatments on irritability is likely best evaluated in studies where these comorbidities are first treated optimally with evidence-based treatments for disruptive behavior (i.e., stimulants and behavioral interventions).

Disclosures

No competing financial interests exist.

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