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Antidepressant Medication: Is It a Viable and Valuable Adjunct to Cognitive-Behavioral Therapy for School Refusal?

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Cognitive-behavioral therapy (CBT) is an evidence-based treatment for school refusal. However, some youth do not respond to CBT. The serious risks associated with school nonattendance call for novel approaches to help those who do not respond to CBT. Because school refusal is commonly associated with anxiety disorders, and the combination of CBT and antidepressant medication enhances outcomes in the treatment of anxiety disorders, combined treatment may be effective for school refusal. This narrative review evaluates the current evidence base for adding antidepressant treatment to CBT for school refusal. Six randomized controlled trials (RCTs), two open trials, six case studies/series, and one observational study were identified and reviewed. There is support for combined CBT and imipramine, but this medication is not typically used due to the risk of concerning side effects. Two recent RCTs failed to provide evidence for the superiority of combined CBT and fluoxetine. Further research in this area is required because the extant studies have a number of methodological limitations. Recommendations are provided for clinicians who consider prescribing antidepressant medication or referring for adjunctive antidepressant treatment for school refusal.

School refusal is a serious problem that is relatively common among clinic-referred youth. Berg's (1997) definition of school refusal includes five components: (a) reluctance or refusal to attend school by a child or teen, who (b) prefers to remain close to parental figures, and (c) is emotionally distressed at the prospect of going to school, (d) lacks antisocial behavior apart from resistance to attend school, and (e) does not hide the nonattendance from his or her parents. From a behavioral perspective, the youth's avoidance of school reduces his or her emotional distress (e.g., anxiety, depression) and the reduction in distress negatively reinforces the school refusal, yielding further nonattendance. Emotional distress often manifests as an internalizing disorder. For example, in a clinical sample of school-refusing youth, 54% were diagnosed with an anxiety disorder and 52% were diagnosed with depressive disorders (McShane, Walter, & Rey, 2001).

Typically classified as a semi-emergency, school refusal warrants treatment given the short- and long-term impact on the child's academic progress and employment opportunities (Buitelaar, van Andel, Duyx, & van Strien, 1994; McShane, Walter, & Rey, 2004). Moreover, school refusal is strongly associated with psychiatric diagnoses (Egger, Costello, & Angold, 2003), poor social relationships (Havik, Bru, & Ertesvåg, 2015), and family distress (Carless, Melvin, Tonge, & Newman, 2015). School refusal presents a significant challenge for clinicians because it manifests in a variety of ways and there are various comorbid diagnoses that may underlie the condition (Melvin & Tonge, 2012). Moreover, it usually becomes more difficult to treat the longer it continues. Treatment is often provided in an outpatient or community setting but inpatient psychiatric settings may be used for complex or chronic cases (McShane et al., 2001).

A recent meta-analysis (Maynard et al., 2018) evaluated the efficacy of psychosocial treatments for school refusal using data from six rigorous randomized controlled trials (RCTs) or studies with a quasi-experimental design. The studies primarily used cognitive-behavioral therapy (CBT) approaches (Blagg & Yule, 1984; Heyne et al., 2002; King et al., 1998; Last, Hansen, & Franco, 1998; Richardson, 1992) with one study using a group Rogerian approach (Sahel, 1989). Psychosocial treatments were found to be superior to a comparison group for attendance (Hedges's $g = 0.54$) but not for anxiety (Hedges's $g = 0.06$; Maynard et al., 2018). While the treatments collectively demonstrated a significant effect on school attendance, between 8% (King et al., 1998) and 40% (Richardson, 1992) of youth

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treated in these trials did not achieve optimal levels of attendance and were at risk of further academic and social impairment as well as emotional and family distress. These findings on nonresponse justify efforts to boost the effectiveness of existing treatments and to develop and evaluate novel approaches.

Adjunctive antidepressant medication offers the possibility of improving outcomes for youth with school refusal. Newer antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors, have been shown to be superior to placebo in the treatment of anxiety disorders in youth (Bridge et al., 2007; Strawn, Welge, Wehry, Keeshin, & Rynn, 2015). Because anxiety disorders commonly underlie school refusal (Heyne, Sauter, & Maynard, 2015; McShane et al., 2001), combining CBT with antidepressant medication may enhance response to treatment. Indeed, the combination of CBT with the SSRI sertraline yielded an even greater treatment response for children and adolescents with an anxiety disorder, relative to either of the treatments alone (Walkup et al., 2008). Based on the Clinical Global Impressions–Improvement Scale ratings, Walkup and colleagues found that 81% of youth treated with CBT plus sertraline were "much" or "very much" improved after treatment, which was significantly greater than the percentage of youth treated with CBT alone (60%) and fluoxetine alone (55%).

Together, these findings suggest the value of using antidepressants in the treatment of school refusal, to target the anxious symptoms commonly associated with school refusal. Two caveats warrant consideration. First, not all youth who refuse school experience anxiety disorders; some experience depressive disorders. A recent meta-analysis by Cipriani et al. (2016) found that antidepressants offered no clear advantage over placebo for children and adolescents with major depressive disorder. Thus, it is possible that antidepressants are less efficacious for school-refusing youth who experience depressive disorders. Second, in Strawn and colleagues' (2015) meta-analysis of antidepressant treatment for youth anxiety disorders, none of the included studies measured school refusal or school attendance as an outcome variable. Thus, while a body of research suggests that antidepressants may be worth considering in the treatment of school refusal, direct conclusions about the efficacy of newer antidepressants for school refusal cannot be drawn from these studies.

This paper provides a narrative review of the evidence base for combined CBT and antidepressants in the treatment of school refusal. It is intended to assist nonprescribing clinicians as well as medical practitioners in their decision making about the role of antidepressant treatment for school refusal. Efficacy, side effects, and safety are considered.

Method

Studies of antidepressant medication for school refusal were searched on MEDLINE and PsychINFO (OVID interface) on December 22, 2016, using the following search terms: (school refus* or school phobi*), AND (antidepressant, anti-depressant, psychopharm*, fluoxetine, sertraline, citalopram, escitalopram, venlafaxine, desvenlafaxine, duloxetine, amitriptyline, clomipramine, desipramine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, vilazodone, vortioxetine, selective serotonin reuptake inhibitor, serotonin noradrenaline reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, tricyclic antidepressant, SSRI, SNRI, or TCA). There were two reasons for focusing on studies of antidepressants rather than combined antidepressant and psychosocial treatment. First, studies of the treatment of school refusal using antidepressant monotherapy could provide indirect support for the potential value of combined treatment. Second, some studies that purport to evaluate antidepressant treatment of school refusal actually investigate combined treatment. Publications between 1967 and December 2016 were searched. Given the modest number of papers expected and the known variation in outcome measures (e.g., different cutoffs for judging the presence of successful outcome based on school attendance), studies were not excluded on the basis of their outcome measure(s).

This search yielded 72 papers that were reviewed by GAM. Review papers, commentaries, letters, and studies not containing any relevant data on antidepressant treatment for school refusal (n = 43) were removed, as were duplicates (n = 15), leaving 12 papers for review. One paper (Bernstein, Garfinkel, & Borchardt, 1990) described both an open trial and a controlled trial, making a total of 13 trials available for review. Supplementary findings from one of the 13 trials (Bernstein, Borchardt, et al., 2000) are described in three additional papers: one focused on adherence (Bernstein, Anderson, Hektner, & Realmuto, 2000), one focused on predictors of outcome (Layne, Bernstein, Egan, & Kushner, 2003), and one was a 1-year follow-up study (Bernstein, Hektner, Borchardt, & McMillan, 2001). The reference list of a recent meta-analysis of treatment for school refusal (Maynard et al., 2018) was also searched, yielding two additional trials (Walter et al., 2010; Wu et al., 2013). In total, 15 studies were available for the current review.

Results

Of the 15 studies of interest, 6 were case studies or series, 2 reported on open trials, 6 were controlled trials, and 1 was an observational study evaluating either monotherapy for school refusal or combined treatment for school refusal. A summary of the design and findings of each study can be found in Table 1. The following is a narrative review of these studies.

Case Studies/Series

Case studies or small case series have demonstrated the benefits of imipramine (Deltito & Hahn, 1993); the antiepileptic, mood-stabilizing medication gabapentin (Durkin, 2002); and citalopram (N = 3; Lepola, Leinonen, & Koponen, 1996). There were no benefits of escitalopram (Ding, Gadit, & Peer, 2014). Oner, Yurtbasi, Er, and Basoglu (2014) described the successful treatment of two adolescents in an inpatient setting. One adolescent received fluoxetine, family therapy, relaxation training, and social skills training; the other received a combination of fluoxetine, risperidone, and alprazolam together with cognitive-behavioral treatment that included exposure.

Obondo and Dhadphale (1990) reported on a case series of 10 Kenyan children with attendance problems (9 with school phobia and 1 with truancy), their ages ranging from 9 to 16 years (mean age = 12.5 years). All of the children received a psychosocial therapy (e.g., counseling or family therapy) and in 9 cases medication was also prescribed. Medications were described as being "mainly anti depressants" (p. 107). Eight of 10 youth returned to school within 3 months suggesting that medication and psychotherapeutic approaches may be beneficial.

These case studies and series suggest that medication, often combined with psychosocial approaches, might have utility in the management of school refusal. However, few studies clearly specified the criteria for school refusal or for successful school return.

Open Trials

There have been two open trials of medication for school refusal (Bernstein et al., 1990; Rabiner & Klein, 1969). Both trials evaluated imipramine combined with psychosocial treatment, such as parent counseling, psychotherapy, or family therapy. In the earlier trial, imipramine was combined with "parent counseling techniques" that included firm attitudes toward school attendance, accompanying the child to school, and waiting until anticipatory anxiety declined to the point that the child was able to attend school alone (Rabiner & Klein, 1969). At the end of 6 weeks of treatment (weekly sessions with the psychiatrist and case worker), 28 youth (age range = 7–14 years) had completed treatment and 24 of these (86%) returned to school. The Bernstein et al. (1990) paper included two studies: an open trial and an RCT. In the open trial, 8 weeks of imipramine or alprazolam were used alongside a "school reentry program" and "psychotherapy" in a sample of 17 youth (mean age = 14.17 years, age range = 9.5–17 years). Fifty-five percent of those treated with alprazolam returned to school and 50% of those treated with imipramine returned to school.

In sum, the two open trials evaluated short-term interventions that had moderate to high success in returning youth to school. In these trials, the criteria for school refusal were specified, reflecting greater methodological rigor relative to the case studies and series. The interventions were only described briefly, and neither study measured longer-term outcomes.

Randomized Controlled Trials

Of the six RCTs evaluating combined treatments for school refusal, four evaluated tricyclic antidepressants (TCAs; n = 3 imipramine, n = 1 clomipramine) and two investigated fluoxetine.

In the first controlled trial, conducted with 35 school-refusing children (mean age = 10.8 years), Gittelman-Klein and Klein (1971) compared a combined multidisciplinary treatment plus either imipramine or placebo. The children had "varying degrees of anxiety from mild discomfort to outright panic when away from their mothers or home" (p. 204). The multidisciplinary treatment included weekly counseling sessions for 6 weeks, with elements of psychoeducation and parenting skills aimed at improving attendance. After 6 weeks of treatment, the imipramine group was found to have superior attendance based on mothers' reports (over an unknown time period), with 81% of this group attending regularly, versus 47% of the placebo group. The authors found that significantly more of those receiving imipramine (79%) reported side effects on a standard form relative to those treated with placebo (47%). Age, dichotomized into younger or older than 11 years, was not found to influence treatment outcome. It was also observed that global improvement occurred for 21% of participants in the placebo group, even though 47% of this group returned to school, supporting the notion that school attendance and global functioning are not necessarily linked.

Berney et al. (1981) compared clomipramine to placebo in a group of 51 youth (age range 9–14 years) who had school refusal and a "neurotic disorder." Based on the limited details provided, these youth also received concurrent individualized psychotherapy and their parents received casework. Completer analyses were undertaken and both groups demonstrated significant improvement in school attendance but clomipramine was not superior to placebo.

Bernstein et al. (1990) conducted a placebo-controlled trial of the benzodiazepine alprazolam or imipramine for 24 children and adolescents (mean age = 14.1 years, age range 7–17 years) with a history of poor attendance and an anxiety and/or depressive disorder. Intervention included a school return plan that consisted of a graded return to school with a focus on areas the youth found to be difficult. Descriptive data on attendance outcomes suggest that treatment was highly successful. Among treatment completers there were high rates of school return (five of six participants in each medication arm).

In Bernstein, Borchardt and colleagues' (2000) second study of imipramine, 63 pubertal adolescents (mean age =

Table 1
Summary of Case Studies and Series, Open Trials, and Controlled Trials Evaluating Antidepressant Medication for School Refusal

	Study	*N*; mean age/ age range	School refusal details/ diagnostic profile	Medication, mean daily dose	Psychological treatment	Control group	Outcome measure	School attendance findings
Case study or case series								
1	Obondo & Dhadphale (1990)	School refusal *n* = 9; 12.5 yrs, 9–16 yrs Truancy *n* = 1; 13 yrs	Not specified/ emotional disorder—anxious, depressive, and/or aggressive behavior	"Mainly antidepressants"	Family therapy and/or individual counseling	–	Not specified	8/10 returned to school
2	Deltito & Hahn (1993)	*N* = 2; 7.3 yrs, 7–8 yrs	Not specified/both had separation anxiety, somatic symptoms.	Imipramine, 20 mg	No	–	Not specified	School refusal resolved
3	Lepola, Leinonen, & Koponen (1996)	*N* = 3; 12.3 yrs, 9–16 yrs	Not specified/all had panic disorder with agoraphobia	Citalopram, 20 mg	No	–	Not specified	School return achieved
4	Durkin (2002)	*N* = 2; 16.5 yrs, 16–17 yrs	Multiple years of nonattendance	Gabapentin, 600 mg; hydroxyzine, 100 mg	No	–	Not specified	Full-time work; return to school achieved
5	Ding, Gadit, & Peer (2014)	*N* = 1; 17 yrs	Not specified/likely amotivational syndrome, depression symptoms,	Escitalopram, 10 mg; risperidone, 2 mg	No	–	Not specified	School return was not achieved
6	Oner, Yurtbasi, Er, & Basoglu (2014)	*N* = 2; 11.5 yrs, 8 yrs, 15 yrs	Not specified/case 1. Separation anxiety disorder 2. Social phobia, ADHD	1. Fluoxetine, 20 mg 2. Fluoxetine, 40 mg; risperidone, 1 mg; alprazolam, 1 mg	Inpatient treatment plus 1. Family therapy CB techniques including exposure. Treatment length unclear 2. Cognitive-behavioral techniques including exposure, 5 weeks	–	Not specified	1. School return achieved 2. Symptom-free 6 months after discharge
Open trials								
7	Rabiner & Klein (1969)	*N* = 34; 7–14 yrs	Separation anxiety with panic as part of school refusal, 2 weeks refusal, absence of hallucinations or delusions	Imipramine, 25–200 mg	6 weeks parent counseling techniques	–	Return to school	86% returned to school

Table 1 (*continued*)

8	Bernstein, Garfinkel, & Borchardt (1990), Study 1	*N* = 17; 14.2 yrs, 9.5–17.0 yrs	Not specified/anxiety or mood disorder, mood disorder, or no disorder and anxiety/ depressive symptoms	Alprazolam, 1.43 mg (*n* = 10) or imipramine, 135 mg (*n* = 7)	8 weeks school reentry program, psychotherapy	–	Return to school	55% alprazolam 50% imipramine
Randomized controlled trials								
9	Gittelman-Klein & Klein (1971)	*N* = 35; 10.8 yrs	Distress at prospect of attending school and unable to attend for 2 weeks or distress while attending	Imipramine, 152 mg	6 weeks psychoeducation and parent skills training	Placebo and psychological treatment	Dichotomous maternal rating of "not back to school" and "back to school"	Return to school, 81% imipramine, 47% placebo
10	Berney et al. (1981)	*N* = 51; 9–14 yrs	Neurotic disorder with marked reluctance to attend school, 4-weeks duration	Clomipramine, 40 mg (9–10 yrs), 50 mg (11–12 yrs), 75 mg (13–14 yrs)	12 weeks individualized psychotherapy and casework for parents	Placebo	4-point scale ranging from 4 (*completely unable to attend*) to 1 (*able to attend school unescorted*) 4–5 days per week, though often under considerable pressure	Clomipramine = placebo
11	Bernstein et al. (1990), Study 2	*N* = 24; 14.1 yrs, 7–17 yrs	History of poor school attendance, anxiety and/or depressive disorder	Alprazolam, 1.8 mg vs. imipramine, 164 mg	8 weeks weekly psychotherapy with graded school return	Placebo	Chart review of school attendance. Return to school; improved attendance 1 (*complete refusal*) to 5 (*daily attendance*)	Return to school, 100% alprazolam, 100% imipramine, 75% placebo Improved attendance, 100% alprazolam, 100% imipramine, 80% placebo
12	Bernstein, Borchardt, et al. (2000)	*N* = 63; 13.9 yrs	20% absence over 4 weeks, anxiety and depressive disorder	Imipramine, 185 mg	8 sessions CBT	CBT and placebo	School records over past week	CBT + imipramine > CBT + placebo
13	Wu et al. (2013)	*N* = 75; 13.4 yrs, 6–18 yrs	>50% attendance for 4 weeks, mood disorder and psychological symptoms, parental awareness of absence	Fluoxetine, no mean dose reported	12 sessions CBT	CBT and placebo	School attendance over past month	CBT + fluoxetine = CBT + placebo
14	Melvin et al. (2017)	*N* = 62; 13.6 yrs, 12–18 yrs	>50% attendance for 4 weeks, anxiety disorder, at home with parent's knowledge, effort by parent to enforce attendance	Fluoxetine, 23.5 mg	12 sessions CBT plus 3 × monthly booster sessions	CBT alone, CBT and placebo	School attendance over past month	CBT + fluoxetine = CBT + placebo = CBT

(continued on next page)

Table 1 (*continued*)

	Study	*N*; mean age/ age range	School refusal details/ diagnostic profile	Medication, mean daily dose	Psychological treatment	Control group	Outcome measure	School attendance findings
Observational study								
15	Walter et al. (2010)	*n* = 18 (12%) received medication of *N* = 147; 15.1 yrs, 12–18 yrs	14 days without school attendance or 50 skipped classes in last school report; diagnosis of one or more of anxiety disorder, depressive episode, mixed disorder of conduct and emotions	Fluoxetine, methylphenidate, no mean dose reported	2–3 individual sessions + 1 parent/ family session per week	Inpatient CBT including parent sessions (average length = 7.8 weeks) plus optional follow-up outpatient treatment	School attendance over past 2 weeks—parent report	7 patients discharged on fluoxetine, 4 patients discharged on methylphenidate, 7 patients ceased medication due to lack of effect; significant improvement on absenteeism from pre- to 2-month follow-up. [a]

Note. ADHD = attention deficit/hyperactivity disorder; CBT = cognitive-behavioral therapy. Bernstein et al. (1990) included two separate trials, an open trial (labeled as Study 1) and a controlled trial (labeled as Study 2).

[a] Separate analyses for those receiving medication were not completed.

13.9 years) with school refusal were randomly allocated to either CBT plus imipramine or CBT plus placebo. Participants were required to have comorbid anxiety and major depressive disorders and to have missed at least 20% of school days in the past month, suggesting that a sample with a high level of symptoms was recruited. Mean absence from school at baseline was high (69.3%). The eight-session CBT program included psychoeducation, graded reentry to school that was structured through the use of a plan, cognitive therapy techniques, and homework. Mean imipramine dose was relatively high at 184 mg. The dropout rate was high (imipramine $n = 7$ [23%], placebo $n = 9$ [28%]) primarily due to participants declining to participate further ($n = 12$). Nonadherence, as measured by missed doses, did not differ between groups (Bernstein, Anderson, et al., 2000). Following treatment, improvement in school attendance was observed for the CBT plus imipramine group only (mean attendance in eighth week: 70.1% vs. 27.6% for CBT plus placebo). The difference between the groups was large and statistically significant. Both groups showed improvement on clinician- and self-reported anxiety and depression. For clinician-reported depression, there was a significant difference between treatments, favoring CBT plus imipramine. Participants and prescribing psychiatrists were able to guess treatment allocation at better than chance (Bernstein, Anderson, et al., 2000). As a result, participants in the active imipramine group may have given more favorable responses at posttreatment because they knew they had received the active treatment. This limitation aside, the study provides evidence of the superiority of a combined treatment approach.

Bernstein and colleagues (2001) conducted a 1-year follow-up of this sample. The follow-up sample was overrepresented with participants who had received imipramine and who were attending significantly more school at the end of treatment (Bernstein et al., 2001). School attendance data were not collected as part of the follow-up study. At 1-year follow-up substantial psychopathology was observed among participants, but there were no differences between the CBT plus imipramine group and the CBT plus placebo group with respect to rates of depressive or anxiety disorders (72%). Outpatient therapy was received by 78% of participants during the follow-up period (Bernstein et al., 2001), reflecting the high level of ongoing symptomatology observed among this group.

In China, Wu et al. (2013) compared the relative efficacy of 12 sessions of CBT with and without fluoxetine (20–60 mg). The sample comprised 82 youth (age range = 8–18 years, mean age = 13.4 years) with school refusal. For inclusion in the study, participants were required to have less than 50% attendance over the past 4 weeks and the "average time of not going to school" was 19.0 ± 24.9 weeks. Most participants experienced a psychiatric diagnosis[1] (including 34 cases of major depression/dysthymia, 17 of specific phobia, 15 of separation anxiety, and 13 of social phobia) and 9 experienced no disorder. The CBT treatment was drawn from the Heyne and Rollings (2002) manual. It is unclear whether cultural modification was made as has been recommended when using CBT with Chinese people (Lin, 2002). Treatment fidelity was not measured. No significant difference was found between the groups regarding the percentage of participants achieving more than 80% school attendance (CBT = 72.2%, CBT plus fluoxetine = 82.1%). This led the authors to conclude that adding fluoxetine did not provide a significant benefit. Both treatments were well tolerated. Wu et al. (2013) used an active approach to assess side effects and reported that between 13 and 21% of participants who received fluoxetine reported nausea, attention problems, dizziness, and dry mouth. The authors offered no explanation for why fluoxetine may not have had any additional benefit. One of the methodological limitations of the study offers a possible explanation—that is, no details were provided on the mean dose of fluoxetine, which is a reporting oversight. A subthreshold dose may explain a lack of additive or synergistic effect of fluoxetine and CBT.

The most recent RCT, conducted in Australia by Melvin et al. (2017), has the methodological strength of having two control groups. Sixty-two school-refusing adolescents (age range = 11–16.5 years, mean age = 13.6 years) were randomly allocated to CBT alone, CBT plus fluoxetine, or CBT plus placebo. The CBT alone control group allowed for determination of the potential additive or synergistic effect that might be observed with CBT plus fluoxetine. The CBT plus placebo group controlled for the nonspecific effect of taking a tablet. Average baseline attendance over the past 4 weeks was 15%, the lowest of all reported RCTs and well below the inclusion criterion of less than 50% attendance. Participants were required to present with one or more anxiety disorders. The most common anxiety disorders were social phobia (50%) and generalized anxiety disorder (24%). Over three quarters (77.4%) of the sample experienced comorbid disorders in addition to an anxiety disorder; 58.1% also experienced a depressive disorder, 32.2% experienced another anxiety disorder, and 24% experienced either oppositional defiant disorder or attention-deficit/hyperactivity disorder (ADHD). CBT was modified from the Heyne and Rollings (2002) manual with enhanced content addressing issues relevant to adolescence—namely, depressive symptoms and social anxiety. Acute treatment comprised 12 sessions provided twice weekly for the first two weeks. After this, three booster sessions were offered, one per month. Participants treated with fluoxetine received, on average, 22.5 mg and the study protocol allowed for dosing

[1] The authors did not refer to the instrument or procedure used to establish diagnosis.

between 10 and 60 mg. Following treatment, all groups improved significantly on attendance. Mean posttreatment attendance (measured over a month) was 55% (CBT), 44% (CBT plus placebo), and 56% (CBT plus fluoxetine). School attendance did not differ among groups, suggesting that the addition of fluoxetine did not provide an additional benefit to CBT alone. On average, attendance remained relatively stable over the 12-month follow-up period. Global functioning, measured by the Global Assessment of Functioning (GAF) Scale, improved over time but did not differ significantly among treatment groups. On average, pretreatment GAF scores were between 50.6 and 51.3 points across the three groups, and posttreatment scores were between 58.5 and 59.7 points. Adolescents reported greater satisfaction with CBT plus fluoxetine but it is worth noting that they were able to guess their random allocation to fluoxetine or placebo at a rate better than chance.

Observational Study

Psychiatric inpatient settings have been used to treat school refusal given the serious consequences of the condition (e.g., McShane et al., 2001). Inpatient units typically treat cases with a high level of complexity or severity, so it is likely that psychopharmacological treatments including antidepressants are more likely to be considered in this setting. Walter et al. (2010) conducted an observational study of a single intervention: CBT for anxious-depressed school absenteeism among 147 adolescents (age range = 12.1–18.1 years, mean age = 15.1 years) in an inpatient setting. The sample included youth with conduct problems so some youth in the sample may not have met commonly used criteria for school refusal. CBT was intensive with multiple individual sessions and a parent or family session each week. Treatment lasted between 3 and 18 weeks. Due to "poor response" to the intensive CBT approach, 18 participants (12%) had their treatment augmented with fluoxetine (for severe depression) or methylphenidate (for ADHD)[2]. The number of adolescents treated with each medication was not reported. Fluoxetine was continued postdischarge for seven youth and four continued methylphenidate, while the other seven adolescents stopped medication due to a lack of clinical benefit. It appears that responses were mixed because treatment cessation suggests an inadequate response or side effects. It is noteworthy that a relatively small percentage of participants were offered psychopharmacological intervention, which might suggest that combined treatment was a second-line treatment that was not often utilized in that context.

[2] No criteria were specified for poor response.

Discussion

School refusal remains a challenging clinical problem with only a small body of contemporary research available to advise on the best treatment approaches. The aim of this paper was to summarize the evidence for adding antidepressant medication to CBT in the treatment of school refusal and provide guidance to clinicians considering the role of antidepressant treatment.

The open trials reported here, and to some extent the case studies, provide foundational evidence for the viability of combined CBT and antidepressant treatment for school refusal. However, these studies often lacked rigor around the definition of school refusal and they did not assess longer-term outcomes. To date, six RCTs have been conducted, three of which demonstrated the benefits of combined treatment (Bernstein, Borchardt, et al., 2000; Bernstein et al., 1990; Gittelman-Klein & Klein, 1971). The other three trials did not demonstrate such benefits (Berney et al., 1981; Melvin et al., 2017 ; Wu et al., 2013). The controlled trials of imipramine plus CBT showed that it was superior to placebo plus CBT in improving school attendance (Bernstein, Borchardt, et al., 2000; Gittelman-Klein & Klein, 1971). However, the Bernstein et al. (2001) 1-year follow-up showed that many participants had anxiety and depressive disorders, suggesting that the sample experienced ongoing impairment and the need for more intensive treatments. Moreover, the trials of imipramine plus CBT did not use rigorous assessment of school attendance—they relied on mothers' reports of attendance over an unspecified time period (Gittelman-Klein & Klein, 1971) or school records related to just 1 week of school (Bernstein, Borchardt, et al., 2000). More recent studies (e.g., Melvin et al., 2017) have made use of school-based attendance data across a whole month. In contrast to the positive findings observed in the imipramine studies, Berney et al. (1981) found no significant difference between psychotherapy combined with clomipramine versus psychotherapy combined with placebo.

Contemporary studies of combined CBT and fluoxetine treatment (Melvin et al., 2017; Wu et al., 2013) have not demonstrated a superior response compared with CBT alone. These two studies utilized more rigorous criteria for school refusal. They also recruited samples with lower levels of baseline attendance (e.g., 15%; Melvin et al., 2017) compared with earlier studies (e.g., 31%; Bernstein, Borchardt, et al., 2000), suggesting greater impairment. However, the two studies are limited by modest sample size, which reduces the capacity to determine a difference between groups, if present. Further, it appears that there are no data on the long-term outcomes associated with combined treatment using fluoxetine. As there is only a small number of studies evaluating combined treatment using newer, more acceptable SSRI antidepressants, further evaluation in larger samples is

warranted in order to reach a firm conclusion about efficacy.

Beyond these limitations, there are three possible explanations for the apparent lack of increased benefit when using fluoxetine and CBT combined. First, school refusal is characterized by a diverse array of underlying mental health problems for the child or adolescent (e.g., social phobia, separation anxiety disorder, major depressive disorder, oppositional defiant disorder) together with mental health problems for their parents (Egger et al., 2003). Combined treatment may be superior to psychosocial treatment alone for some of these diagnostic subgroups but less so for others. This argument has been suggested in relation to the lack of efficacy of combined interventions for anxiety disorders in adults (Foa, Franklin, & Moser, 2002).

Second, studies vary with respect to the definition of what constitutes school refusal, selection criteria, and the definition of what constitutes a response to treatment. The differing definitions as well as variable study selection criteria may lead to some samples being more impaired than others, potentially rendering them less responsive to treatment.

Third, findings from a meta-analysis (Maynard et al., 2018) and two RCTs previously described (Gittelman-Klein & Klein, 1971; Melvin et al., 2017) demonstrate improvement in school attendance despite limited improvement in anxiety. One possible interpretation is that treatment may heighten anxiety through exposure to the feared stimulus of school. Measurement error may also contribute to the weak association between school attendance and anxiety outcomes, with a greater degree of error being present in anxiety measurement compared with the measurement of the more objective and binary variable of school attendance. Measurement differences including variable timing of assessment and informant (e.g., school vs. parent) will also create error variance. Furthermore, factors other than anxiety reduction may contribute to improvement among youth with school refusal (e.g., improvements in parenting practices, family functioning, or school support). If this is the case, the addition of an antidepressant—a treatment focused on anxiety reduction—may provide limited added benefit.

For most adolescents, SSRIs are safe and the side effects that are often present are minor and tolerable (Gordon & Melvin, 2013). This is perhaps reflected in the low rate of treatment discontinuation due to medication side effects as observed in the reviewed studies. More specifically, of the cases receiving fluoxetine and CBT, just 1 of 20 discontinued (Melvin et al., 2017) and 2 of 39 discontinued (Wu et al., 2013). This is consistent with trials investigating pharmacological treatments for anxiety disorder (Walkup et al., 2008).

At the same time, there are three uncommon but potentially serious side effects of newer antidepressants that may be observed by the clinician—namely, manic switching, serotonin syndrome, and increased suicidal thinking and behavior (Gordon & Melvin, 2013). Adolescents with a family history of bipolar disorder may be at risk of a manic switch during treatment. This may present as symptoms including grandiosity, decreased need for sleep, and euphoric mood. Serotonin syndrome occurs when an excess of serotonin is present in the body, usually seen in overdoses of antidepressants or when two agents (such as two antidepressants) are co-prescribed. Patients with the syndrome are suddenly confused, have muscle twitches or lack of coordination, vomiting with diarrhea, rapid heart rate, and high blood pressure (Gordon & Melvin, 2013). Serotonin syndrome needs urgent medical treatment. Last, increased risk of suicidal thoughts and behaviors has been detected in adolescents receiving treatment in antidepressant clinical trials. Hammad, Laughren, and Racoosin (2006) reported that approximately 4% of children and adolescents treated with antidepressants within clinical trials experienced treatment-emergent suicidal behaviors and thinking, compared with 2% who received placebo.

Regarding TCAs, concerns exist about anticholinergic side effects, along with their potential cardiotoxicity, and lack of efficacy in the treatment of child and adolescent depressive disorders (Hazell, O'Connell, Heathcote, & Henry, 2002). SSRIs are preferred over the older TCAs owing to the more favorable side-effect profile of the SSRIs and their wider therapeutic index relative to TCAs (Qin et al., 2012). These concerns likely explain the low levels of international prescription of TCAs for the treatment of child and adolescent mental illness between 2005 and 2012 (Bachmann et al., 2016).

Clinical Implications

Among psychosocial treatments, CBT is currently the treatment of first choice for school refusal given findings from a meta-analysis (Maynard et al., 2018). The extant research on combined treatment for school refusal is limited and does not provide a robust clinical guide about the role of adjunctive antidepressant. While newer antidepressant medications appear to be safe and well tolerated, further research is required for a clearer answer about the efficacy of combined antidepressant and CBT treatment in the management of school refusal. In this context, prescription of adjunctive antidepressant medication is seen as a second or third treatment option. There is no compelling evidence for the use of antidepressant monotherapy in the treatment of school refusal.

Until further research is conducted on the prescription of adjunctive antidepressants, clinicians will be faced with the issue of whether or not to consider a role for antidepressants in the management of school refusal. To help guide thinking on this issue, Table 2 provides a list of

Table 2
Factors That May Suggest a Role for Adjunctive Antidepressant Medication for School Refusal

- Limited response to CBT treatment for school refusal
- Presence of an anxiety or depressive disorder
- Severe case of school refusal
- Older age
- Family and young person have treatment preference for antidepressants
- Supportive family that will monitor antidepressant use

Note: CBT = cognitive-behavioral therapy.

factors that may increase the likelihood that an antidepressant is helpful in the management of school refusal. Each factor is expanded upon below.

Clinically, the decision to start antidepressant treatment will be influenced by the response to CBT treatment. In some cases, CBT may have a limited response. In other cases, children or adolescents will not readily engage in CBT and may even refuse to attend therapy appointments.

School refusal is not a psychiatric diagnosis recognized in the major nosologies (e.g., DSM-5 or ICD-10), but it is associated with anxiety or depressive disorder in around 50% of referred youth (Heyne et al., 2015). The presence of an anxiety or depressive disorder or other psychiatric disorder known to be responsive to antidepressant treatment justifies the consideration of antidepressant treatment. There is very little evidence to support the use of antidepressants in youth with school refusal who do not have a psychiatric disorder. In the study by Wu et al. (2013), fluoxetine was used to treat nine school-refusing youth without a psychiatric diagnosis, but there was no subanalysis of outcomes for this group. More broadly speaking, very little is known about the impact of antidepressants on children and adolescents without a psychiatric diagnosis. Adult findings are mixed, whereby the administration of SSRIs to healthy adults was found to improve positive affect (Simmons & Allen, 2011) or to have no effect on mood or anxiety or depressive symptoms (Gelfin, Gorfine, & Lerer, 1998).

The severity of school refusal may influence considerations about the role of antidepressant treatment. A review of the role of antidepressants may be prompted by school refusal that lasts for many months or the presence of severe anxiety or depressive disorders.

Age is another factor that can influence considerations about medical treatment. There is greater evidence for the efficacy of antidepressants among adolescents relative to children (Bridge et al., 2007). In addition, older age is associated with greater acceptability of antidepressant treatment, as reported by the parents of anxious children and teens (Brown, Deacon, Abramowitz, Dammann, & Whiteside, 2007).

Consistent with the principles of patient-centered care, the treatment preferences of the child or adolescent and his or her parents are highly relevant for shared decision making about school refusal treatment options. Little is known about school-refusing youths' and parents' treatment preferences, but research on anxiety and depressive disorders may be relevant. Brown et al. (2007) reported that parents consider CBT for child anxiety disorders to be more acceptable, believable, and effective in the short and long term, relative to pharmacotherapy. By the same token, ratings for pharmacotherapy were, on average, moderately acceptable. Dudley, Melvin, Williams, Tonge, and King (2005) similarly reported that CBT was the most popular first treatment preference of a sample of adolescents (66%) with a depressive disorder, as well as their parents (74%). Antidepressants were the second most popular (adolescents 29%, parents 17%). It should be noted, however, that severity of impairment is associated with more positive perceptions of the acceptability and believability of medication (Brown et al., 2007).

Parental capacity to supervise and monitor medication adherence is important and may influence a parent's decision to refer for antidepressant treatment, or a practitioner's decision to prescribe such treatment. This is because youth who refuse school may also refuse their medication. There is little information about adherence in studies of antidepressant medication for school refusal. Bernstein, Anderson, and colleagues' (2000) study of imipramine is the only study reviewed here that reported on adherence using pill counts. Nonadherence was similar between treatment groups and modest in size (10.7% imipramine, 11.8% placebo). Of interest, oppositional defiant disorder and poor family functioning were related to nonadherence in the whole sample, which suggests that these two clinical presentations signal the need for more support with adherence.

Conclusion

Developing improved treatments for school refusal is a worthy goal in view of the limitations of current treatments and the poor psychosocial outcomes associated with school nonattendance. There is a small number of controlled studies focusing on combined treatment—CBT and medication—for school refusal. Early studies using imipramine offered hope of improved outcomes, and recent studies using the more tolerable fluoxetine have not been able to demonstrate the superiority of a combined approach over CBT alone. This suggests that further investigation is warranted to provide a more substantive conclusion about the efficacy of combined treatments. While empirical studies do not currently provide definitive guidance on the role of antidepressants

in the management of school refusal, there are factors that guide clinicians' decision making regarding whether medication may be of benefit. These markers include a limited response to CBT, severe school refusal, the presence of an anxiety or depressive disorder, older age, family and child preference for antidepressants, and a supportive family that will monitor antidepressant use.

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