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Efficacy of Antidepressant Medication With Depressed Youth: What Psychologists Should Know

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Pharmacologic treatments for mental or emotional disorders are becoming increasingly popular, especially in managed care environments. Consequently, psychologists must remain cognizant of medication efficacy concerning specific mental disorders. This article reviews all double-blind, placebo-controlled efficacy trials of tricyclic antidepressants (TCAs) with depressed youth that were published in 1985–1994. Also, all group-treatment studies of depressed youth using fluoxetine, a serotonin-specific reuptake inhibitor (SSRI), are summarized. Results indicate that neither TCAs nor SSRIs have demonstrated greater efficacy than placebo in alleviating depressive symptoms in children and adolescents, despite the use of research strategies designed to give antidepressants an advantage over placebo. The implications of these findings for research and practice are discussed.

Given the current biological movement within psychiatry and within our culture at large, it is more professionally relevant than ever to remain abreast of psychopharmacologic developments (Kramer, 1993). Psychologists must become and remain informed about pharmacological efficacy in treating mental disorders regardless of professional or personal opinions about medication use. Because psychologists (a) may refer distressed individuals to physicians for medication treatment (Brandt, 1994; Eagen, 1994); (b) may be asked by physicians for input regarding diagnostic and medication issues; (c) may themselves pursue and obtain prescription privileges (Chamberlain, 1994; Sleek, 1994); and (d) may be pressured by managed care programs to refer clients for medication evaluations, they should continue to be knowledgable about medications and their effectiveness.

Recently, Greenberg and colleagues (Greenberg, Bornstein, Greenberg, & Fisher, 1992) published a review of tricyclic antidepressant (TCA) medication efficacy with depressed adults in the *Journal of Consulting and Clinical Psychology*. Similar to the work by Greenberg et al. (1992), this article reviews TCA efficacy, but the focus of our review is more specific—we examine scientific investigations of TCA efficacy with depressed children and adolescents. Additionally, we briefly summarize the limited data available on the efficacy of fluoxetine, a serotonin-specific reuptake inhibitor, in clinical treatment of depressed youth.

Primarily, two types of medications are prescribed to children and adolescents diagnosed with unipolar depression—TCAs (e.g., imipramine, desipramine, amitriptyline, and nortriptyline) and serotonin-specific reuptake inhibitors (SSRIs) (fluoxetine, sertraline, paroxetine, and fluvoxamine; Kaplan, Simms, & Busner, 1994). Although lithium and monamine oxidase inhibitors are sometimes used with youth, these medications have greater risks, and little research has been published pertaining to their use with depressed children and adolescents (Ryan, Meyer, Dachille, Mazzie, & Puig-Antich, 1988a; Ryan et al., 1988b; Strober, Freeman, Rigali, Schmidt, & Diamond, 1992). Despite what appears to be widespread general use of TCAs and SSRIs with children and adolescents, neither medication type has been approved by the Food and Drug Administration (FDA) for treating depression in youth. Additionally, limited research data are available pertaining to the efficacy of antidepressants in general with youth; in particular, to date, no published group treatment studies are available that evaluate the efficacy of sertraline, paroxetine, or fluvoxamine on depressive symptoms in youth.

Early studies on TCA efficacy with children were generally promising. For example, a 1973 study using imipramine (IMI) or amitriptyline (AMI; Weinberg, Rutman, Sullivan, Penick, & Dietz, 1973) reported "marked improvement" in 12 of 19 depressed children (as compared with 3 of 15 who did not receive antidepressant medication) after at least 1 month of treatment by their pediatricians. This study used an open-label protocol (i.e., there was no placebo control group, and physicians, participants, and parents were aware that the children were re-

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ceiving an active antidepressant medication). Similarly, Puig-Antich and colleagues reported that 6 of 8 children improved substantially after 6 to 8 weeks of IMI treatment (Puig-Antich, Blau, Marx, Greenhill, & Chambers, 1978). This study also was an open-label trial with a fixed-dose of IMI (4.5 mg/kg) with children diagnosed as having major depressive disorder.

Despite early positive response rates, several reviewers of open-label TCA efficacy studies with depressed youth concluded that serious methodological problems rendered the data inconclusive (Campbell & Spencer, 1988; Garfinkle, 1986; Moreau, 1990). For example, early studies, such as those cited earlier, were uncontrolled, open-label medication trials. The potentially powerful influence of placebo effects in medication trials may account for apparent positive outcomes in studies that do not include a double-blind, placebo-controlled comparison group (Fisher & Greenberg, 1989; Harrington, 1993; Leber, 1991).

The following review focuses primarily on TCA efficacy in treating children and adolescents in double-blind, placebo-controlled experimental trials published from 1985 through 1994. Although TCAs are sometimes used to treat a variety of disorders (e.g., attention-deficit hyperactivity disorder, enuresis, etc.) in children, this TCA review is limited to studies evaluating its efficacy in children and adolescents diagnosed as having unipolar depression. Additionally, the limited number of open-label and group studies of fluoxetine with depressed youth are summarized.

Method

Several literature-review strategies were used to obtain published studies on antidepressant efficacy with youth. First, computerized literature searches were conducted using *PsychLit* and *Medline*. Second, the 1994 issues of several relevant journals (i.e., *American Journal of Psychiatry, Journal of the American Academy of Child and Adolescent Psychiatry, Journal of Pediatrics, Pediatrics,* and *Psychopharmacology Bulletin*) were examined for treatment outcome studies on TCAs and SSRIs with depressed youth. Third, all 1994 articles on TCA and SSRI treatments with youth obtained were examined in detail to identify relevant citations.

A total of five double-blind, placebo-controlled TCA studies were identified in the literature review. Each of the five TCA studies is described here, and tables are presented to summarize overall findings. Three TCA studies involved adolescents, and two were conducted with prepubertal children.

One double-blind, placebo-controlled study of fluoxetine was identified in the literature review. Additionally, one open-label study has been published, and one "chart review" of fluoxetine efficacy with youth was located. Finally, one group study of fluoxetine side effects with youth was published prior to 1995. Due to the limited number of group studies and their uncontrolled nature, the results of the fluoxetine studies are summarized more generally than those of the TCA studies.

Results

Double-Blind, Placebo-Controlled TCA Studies With Children

TCA Study 1. Puig-Antich et al. (1987) published one of the first double-blind, placebo-controlled studies of TCA medication with depressed children. This study included 42 children (mean age = 9 years), who were administered either a placebo (n = 22) or IMI (n = 20; only 16 completed the trial). Before initiating either protocol, children were involved in a 2-week intensive diagnostic work-up period, free of drugs or placebos. Approximately 20% of the children who initially met the diagnostic criteria for major depression spontaneously recovered during the diagnostic work-up and were excluded from the study. Children were evaluated after 35 days (5 weeks) of placebo or IMI treatment. Outcome measures included the Schedule for Affective Disorders and Schizophrenia for School Age Children—Present Episode Version (K-SADS-P; Chambers et al., 1985) and the Kiddie Global Assessment Scale (K-GAS; Shaffer et al., 1983). Children were considered positive responders when they obtained K-SADS-P scores indicative of only slightly depressed mood and anhedonia (or no depressed mood and anhedonia). At the end of 5 weeks, clinical response rates were reported as 69% for the placebo group and 56% for the IMI group (see Table 1). The authors concluded that there was no clinical advantage of IMI over placebo, noting that the high placebo response made the possibility of IMI efficacy improbable.

In their conclusion, Puig-Antich and associates (1987) recommended a placebo washout period prior to initiating future drug trials. A placebo washout period usually consists of a 1- to 2-week period before the beginning of a study during which all participants are administered placebo treatment. Subsequently, participants who immediately respond to placebo administration are eliminated from the experimental protocol.

TCA Study 2. Geller, Cooper, McCombs, Graham, and Wells (1989) compared nortriptyline (NOR) efficacy with placebo in children (ages 5–12) with major depression. The design included a 2-week single-blind, placebo washout period. Twelve participants with a rapid placebo response were eliminated. Following the washout period, 60 participants were randomly assigned to the 8-week fixed-plasma-level NOR trial, which was double-blind and placebo-controlled. Ten participants dropped out of the study before completing the 8-week treatment protocol. Following treatment, 8 of 26 (31%) NOR participants had achieved a positive response, and 4 of 24 (17%) placebo partic-

Table 1
Reported Treatment and Placebo Response Rates in Double-Blind, Placebo-Controlled TCA Studies

Study	Medication used	Efficacy (%)	
		Medication	Placebo
Child studies			
Geller et al. (1989)	NOR	31	17
Puig-Antich et al. (1987)	IMI	56	69
Adolescent studies			
Boulos et al. (1991)	DMI	50	33
Kutcher et al. (1994)	DMI	48	35
Geller et al. (1990)	NOR	8	21

Note. TCA = tricyclic antidepressants; NOR = nortriptyline; IMI = imipramine; DMI = desipramine. Percentage differences between medication and placebo within studies are not statistically significant.

ipants had achieved a positive response (see Table 1). A positive treatment response was defined by a Children's Depression Rating Scale (CDRS; Poznanski, Krahenbuhl, & Zrull, 1976) score of 20 or less and item scores of 1 or 2 on criteria items for major depressive disorder on the K–SADS–P. Although the study was originally designed to include 60 participants, data analysis after completion of 50 participants showed no significant differences between NOR and placebo on treatment outcome measures. The authors stated, "We found that the probability of finding a statistical difference in response rate had we completed evaluation of 60 subjects was only 1 in 1,000. Therefore, the study was stopped at 50 subjects" (p. 104).

Double-Blind, Placebo-Controlled TCA Studies With Adolescents

TCA Study 3. Geller, Cooper, Graham, Marsteller, and Bryant (1990) conducted a random-assignment, double-blind, placebo-controlled study of NOR in participants ages 12 to 17 years. The protocol, similar to that of their previous study of NOR with children, included a 2-week placebo washout phase and an 8-week double-blind, placebo-controlled phase with weekly plasma-level monitoring. Of 52 participants initially enrolled in the study, 17 responded to the placebo washout, 4 dropped out, and 31 completed it (12 active and 19 placebo). Only 1 NOR participant (8%) responded to treatment (see Table 1). Therefore, the study, originally planned to have 30 NOR and 30 placebo-protocol completers, was terminated prematurely. A positive treatment outcome was defined as "a CDRS score of 25 or less and a score less than or equal to 2 on *DSM–III* criteria items on the K–SADS–P, except the concentration item, which could be less than or equal to 3" (p. 86). The authors reported that participants on medication exhibited worse depressive symptoms (as measured by the CDRS) at higher plasma NOR levels ($p = .002$). The authors concluded, "Preliminary findings indicate that NOR (200 mg daily) over a 6-week period is not significantly more effective than placebo in this population" (p. 62). Interestingly, the single NOR responder later developed bipolar disorder.

TCA Study 4. Boulos et al. (1991) reported a study of 30 adolescents, ages 15 to 20 years, given either placebo ($n = 18$) or 200 mg desipramine (DMI; $n = 12$). The participants were evaluated on the Hamilton Rating Scale for Depression (HAM–D; Hamilton, 1960) and Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) before the study, after 1 week of placebo washout, and after 6 weeks of treatment. The 1-week placebo washout procedure eliminated approximately 17% (9 participants) of the original research population ($n = 52$). An additional 13 participants dropped out of the study because of "personal" reasons ($n = 7$) or side effects ($n = 6$). Overall, the authors reported a 50% (6/12) response rate in the DMI group and a 33% (6/18) response rate to placebo (see Table 1). A positive response was defined as "a 50% or greater change in the HAM–D scores from pre-treatment to final values" (p. 60). The authors did not include an analysis of the patients' BDI scores posttreatment. Overall, the authors concluded that HAM–D score differences between the DMI and placebo groups were not statistically significant. Additionally, 33% ($n = 6$) of the initial DMI group dropped out of the study because of excessive adverse side effects, including allergic-type reactions, rashes, nausea, and vomiting.

TCA Study 5. Kutcher et al., (1994) conducted a study of 70 adolescents with major depression, ages 15 to 19 years, in a double-blind, placebo-controlled evaluation of a fixed dose (220 mg) of DMI. This 6-week trial was preceded by a 1-week placebo washout period during which 10 participants were eliminated from the treatment protocol. Eighteen participants dropped out during the study because of side effects. Overall, 42 adolescents completed the trial. A total of 15 were judged as improved at the end of the study, 48% of DMI-treated participants and 35% of placebo participants (see Table 1). The difference in response rate was not statistically significant. Treatment response was defined as "a decrease of 50% or greater" (p. 688) on the HAM–D. Participants also were administered the BDI and Symptom Checklist–58–R (Derogotis et al., 1974). The only between-group measure difference based on BDI and Symptom Checklist–58–R was "a trend that favored placebo over DMI ($p = .08$)" on the Anxiety subscale. Additionally, data were analyzed on an endogenous-depression subgroup and an atypical-depression subgroup, and in both cases no treatment effects were found. The authors reported that side effects were significantly worse for the DMI group: 13 of 30 DMI participants compared with 5 of 30 of the placebo group dropped out because of side effects. The authors concluded, "Given the findings of this study and our review of published reports, the routine use of DMI in adolescent depression is not, at this time, indicated" (p. 693).

Side Effects, Adverse Events, and Dropouts Associated With TCA Treatments

Within all five of the double-blind, placebo-controlled studies reviewed, participants treated with TCAs reported significantly more side effects than did those treated with placebo. Although this finding is not particularly surprising, the extent of side effects, adverse events, protocol dropouts, and the data analysis procedures used to address these issues are worth reviewing.

Side effects and adverse events. In most medication studies, distinctions are made between side effects and adverse events. Side effects are generally considered as "nuisance" symptoms (Puig-Antich et al., 1987; p. 83). For example, in the Puig-Antich et al. (1987) IMI study, side effects included "excitement, irritability, nightmares, insomnia, headache, muscle pains, increased appetite, abdominal cramps, constipation, vomiting, hiccups, dry mouth, bad taste, sweating, flushed face, drowsiness, dizziness, tiredness, and listlessness" (p. 83). In contrast, adverse events are usually identified as more serious symptoms that require lowering medication dosage or eliminating a particular patient from the research protocol. For example, in the Boulos et al. (1991) DMI study "6 patients dropped out because of severe adverse effects" (p. 62) that included allergic skin reactions and orthostatic hypotension.

The amount and significance of side effects and adverse events varied extensively across the five studies reviewed in this article. Specifically, in the NOR studies (Geller et al., 1989, 1990), with the exception of increased heart rate (approximately 20 beats

per minute), generally no differences were reported between side effects in the NOR and placebo groups. The authors stated, "The most common side effects . . . were those that are also symptoms of depression: tiredness, sleep disturbances, and headaches" (p. 89).

In contrast to the NOR studies, the IMI and DMI studies reported significant side effects, adverse events, or both during the research protocol. These negative medication effects included "pruritic maculopapular rash" and "nausea, vomiting, and laryngospasm" (Boulos et al., 1991, p. 61). Also, in the IMI study (Puig-Antich et al., 1987), the authors' discussion of various strategies for determining significance of side effects sheds light on problems associated with IMI treatment with children:

> One way to determine severity and clinical significance of side effects is to focus on those that made dosage adjustments downward necessary, or barred any further dosage increase. Such did not occur in the placebo group. In contrast, in 17 of 30 children receiving imipramine, the dosage could not be raised to 5 mg/kg/d. . . . In nine of these children, dosage could not be raised further because their PR interval had lengthened to the safety limit. . . . In the other seven children, clinical side effects were persistent and bothersome enough in the clinical monitor's judgment as to warrant no further dosage increases or a slight dosage adjustment downward. These were orthostatic hypotension (two subjects), marked irritability (two subjects), chest pain (one subject), and a behavioral syndrome of forgetfulness and perplexity (two subjects). (p. 84)

Dropout rates. Side effects and adverse events can significantly affect medication study outcomes by causing participants to discontinue medication treatment. For example, in the IMI study with children (Puig-Antich et al., 1987), 4 out of 20 (20%) of the medication group did not complete the study, whereas in the two DMI studies (Boulos et al., 1991; Kutcher et al., 1994), 6 out of 18 (33%) and 9 out of 30 (30%) medication participants dropped out because of side effects. For each of these studies, participants who dropped out of the treatment groups before completing the treatment protocol were eliminated from data analyses. The elimination of dropout participants from data analyses produced inappropriately inflated treatment-response rates. For example, although Puig-Antich et al. (1987) reported a treatment-response rate of 56% (9 of 16 participants), if all participants are included within the data analyses, the adjusted or intent-to-treat response rate is 45% (9/20). For the three studies that reported the number of medication-protocol participants who dropped out of the study, the average reduction in response rate was 16.5%. Overall, intent-to-treat response rates ranged from less than 8% to 45% (see Table 2 for intent-to-treat response rates for all reviewed TCA studies).

Table 2
Reported Treatment Response Versus Intent-to-Treat Response Rates

Study	Efficacy (%)	
	Medication	I-to-T
Child studies		
Geller et al. (1989)	31	NR
Puig-Antich et al. (1987)	56	45
Adolescent studies		
Boulos et al. (1991)	50	33
Kutcher et al. (1994)	48	26
Geller et al. (1990)	8	8[a]

Note. Statistical significance tests were not conducted. I-to-T = intent to treat; NR = not reported.
[a] At least 1 medication participant dropped out because of side effects.

Group Data on Fluoxetine With Children

Only a single study analyzing fluoxetine's effects on children was identified in this review (Jain, Birmaher, Garcia, Al-Shabbout, & Ryan, 1992). This was a chart review of 31 children and adolescents who were treated with 20 to 80 mg/day of fluoxetine on an inpatient unit. On the basis of Clinical Global Impression Scale (National Institute of Mental Health, 1976) scores, the authors reported that 54% (17/31) of patients exhibited "much to very much" improvement, whereas 43% (13/31) showed "minimal improvement or no change," and 3% (1/31) exhibited a "worsening" of symptoms (p. 261). The authors pointed out that "the response rate is consistent with other placebo response rates in other studies of depression in children and adolescents" (p. 263).

Group Data on Fluoxetine With Adolescents and Young Adults

Two studies have evaluated fluoxetine effectiveness with adolescents and young adults. In the only double-blind, placebo-controlled study of fluoxetine with youth that we found, Simeon, Dinicola, Ferguson, and Copping (1990) reported no statistically significant differences between the efficacy of 20 to 60 mg/day of fluoxetine and placebo with 40 adolescents ages 13 to 18 years. In a rather vaguely worded results section, the authors stated, "Approximately two-thirds of the patients showed marked or moderate clinical global improvement with both fluoxetine and placebo" (p. 791). However, the authors also noted that 5 participants from both the fluoxetine and placebo groups dropped out of the study, and consequently, intent-to-treat efficacy was "approximately" 50% (10/20) in each group.

The only other published group study of fluoxetine efficacy with youth was reported by Boulos and associates (Boulos, Kutcher, Gardner, & Young, 1992). This open-label study evaluated the efficacy of 5 to 40 mg/day of fluoxetine with 15 depressed adolescents and young adults (16–24 years old) who had been unresponsive to previous TCA treatment. Patients were evaluated after 6 to 7 weeks of treatment using the HAM-D and the Clinical Global Impressions scale. Overall, 53% (8/15) of the original patients were rated as having significantly improved Clinical Global Impressions scale scores at the conclusion of the study. Once again, however, the authors reported a higher improvement rate (73%; 8/11), because they omitted

4 participants who had dropped out of treatment because of side effects. The authors reported a 64% (7/11) improvement rate based on HAM-D scores (i.e., intent-to-treat response rate of 47%; 7/15). In this study, the authors noted that all patients were concomitantly receiving a range of psychosocial treatments. Treatment outcome summary data pertaining to the fluoxetine studies are included in Table 3.

Fluoxetine Side Effects in Depressed Youth

There has been one study specifically designed to investigate the side effects of fluoxetine in depressed youth. Riddle and associates (Riddle et al., 1990–1991) reported two or more fluoxetine-induced behavioral side effects in 50% (12/24) of treated children and adolescents (ages 8–16 years). Side effects included "motor restlessness = 11, sleep disturbance = 11, social disinhibition = 6, and subjective sensation of excitation = 3" (p. 196). Despite the breadth and extent of these side effects, the authors noted, "Lowering the dosage of fluoxetine was an effective intervention in most of the children and adolescents in whom fluoxetine was not discontinued" (p. 197). They also observed some children deriving a benefit from "doses as low as 5 or 10 mg/day" (p. 197). Finally, after acknowledging that fluoxetine is being administered to a growing number of youth, Riddle and associates concluded their report by stating, "A better understanding of the pathogenesis of these side effects awaits further advances in our understanding of the underlying mechanisms of action of fluoxetine in the developing brain" (1990–1991, p. 197). Interestingly, another publication from Riddle's research team reported the emergence of self-destructive phenomena in 14% (6/42) of children and adolescents (ages 10–17) who were being treated with fluoxetine for obsessive–compulsive disorder (King et al., 1991).

In some cases, the treatment outcome studies reviewed earlier on fluoxetine in child and adolescent groups also reported data on side effects associated with fluoxetine treatment for depression. As in the case with the Riddle et al. (1990–1991) study, the most prominent side effects produced by fluoxetine included hypomania or restlessness, insomnia or sleep disturbance, general irritability or social disinhibition, and gastrointestinal distress. Fluoxetine side effect rates are summarized in Table 4.

Table 3
SSRI-Treated Positive Responders

	If treatment dropouts are eliminated from analyses		If treatment dropouts are considered nonresponders	
Study	*n/N*	%	*n/N*	%
Jain et al. (1992)	17/31	54	17/31	54
Boulos et al. (1992)	8/11	73	8/15	53
Simeon et al. (1990)	10/15	67	10/20	50

Note. SSRI = serotonin-specific reuptake inhibitor.

Discussion

TCA Efficacy in Depressed Youth

The studies reviewed show that although TCA treatment with depressed children and adolescents initially seemed to hold promise, there have been no double-blind, placebo-controlled studies demonstrating their efficacy beyond placebo. "Controlled studies have failed to demonstrate that TCAs are superior to placebo in the treatment of childhood and adolescent depression" (Rosenberg, Holttum, & Gershon, 1994, p. 60). "Fewer than 250 adolescents have been studied to date in properly controlled studies [referring to TCAs]" (p. 588, Ambrosini, 1994). "There are as yet no controlled studies that demonstrate a superiority of active over placebo drug (including TCAs) for affective disorders in children or adolescents" (p. 589, Riddle, Geller, & Ryan, 1994).

Using the double-blind, placebo-controlled studies reviewed here, the estimated efficacy of TCAs for depressed youth ranges from approximately 8 to 45%. In comparison, it appears that placebo efficacy ranges from 17 to 68%. Of course, given the limited number of child and adolescent participants who have been evaluated in double-blind placebo-controlled studies, these estimated response rates are difficult to interpret.

TCA Side Effects and Adverse Events

The nature and extent of medication side effects associated with TCA treatment of depression is an important consideration when deciding whether to initiate medication treatment. From the current review, IMI and DMI use appears to be associated with a significant side-effect profile in over half of treated children. Further, approximately 20 to 33% of treated participants develop side effects that require discontinuing IMI or DMI treatment.

TCA side effects are particularly disturbing in prepubertal children. For example, there have been reports of TCA-induced hypomania, and recently DMI has been implicated in the sudden deaths of four prepubertal children (Kashani, Hodges, & Shekim, 1980; Popper & Elliot, 1990; Walsh, Giardina, Sloan, Greenhill, & Goldfein, 1994). Although DMI use has not been established as the causal factor in these children's deaths, potential cardiotoxic effects of DMI in youth have been noted (Walsh et al., 1994). DMI is the active metabolite of IMI, and IMI can produce potentially dangerous cardiac changes in youth. Withdrawal symptoms in children upon gradual cessation of IMI treatment have also been reported (Law, Petti, & Kazdin, 1981). Overall, dangers associated with using TCAs with depressed youth may sometimes outweigh potential benefits.

Placebo Effects

Perhaps the most important finding in this review is the consistently strong performance of placebos in alleviating depressed symptoms in youth. This finding is particularly impressive when the effects of using placebo washout procedures are considered. For example, in Geller's NOR studies, 12 of 72 and 17 of 52 participants were removed from the study because they

Table 4
Most Frequent SSRI-Associated Side Effects Reported

Side effect	Jain et al. (1992)		Riddle et al. (1990–1991)		Boulos et al. (1992)		Total	
	n/N	%	*n/N*	%	*n/N*	%	*n/N*	%
Mania/hypomania restlessness	7/31	23	11/24	46	5/15	33	23/70	33
Insomnia/sleep disturbance	4/31	13	11/24	46	4/15	27	19/70	27
Irritability or social disinhibition	6/31	19	6/24	25	NR	—	12/55	22
Gastrointestinal distress	4/31	13	NR	—	3/15	20	07/46	15

Note. SSRI = serotonin-specific reuptake inhibitor; NR = not reported.

exhibited a placebo response during the placebo washout period (Geller et al., 1989, 1990). Similarly, in the DMI studies by Boulos et al. (1991) and Kutcher et al. (1994), 11 of 52 and 10 of 70 participants were washed out before initiating the study. Although it is impossible to predict how treatment outcome results might have been affected by including placebo responders in the analysis, it is likely that their inclusion would have further enhanced placebo efficacy and possibly contributed to a finding that placebo treatment is more effective than TCAs for depressed youth.

SSRIs and Depression in Youth

It appears that TCA use with depressed youth is warranted only in cases of unusually unremittant depression (Mufson, Moreau, Weissman, & Klerman, 1993). Consequently, the efficacy of alternative medications should be evaluated (Ryan, 1990). Specifically, it has been speculated that specific serotonergic compounds may have greater efficacy in children and adolescents (Geller et al., 1990; Ryan, 1990). Ryan (1990) stated, "Other strategies that might be useful include . . . trying more serotonergic agents, fluoxetine, or fluvoxamine" (p. 78). Ryan (1990) based his suggestion to turn to SSRIs with youth on the disappointing performance of TCAs and on the fact that the noradrenergic system apparently does not fully develop either anatomically or functionally until early adulthood (Goldman-Rakic & Brown, 1982). Although Ryan's (1990) recommendations appear logical, thus far, as reviewed earlier, SSRI efficacy with depressed youth remains unsupported by existing research studies (Jain et al., 1992; Simeon, Dinicola, Ferguson, & Copping, 1990). Additionally, although initially SSRIs were thought to have less problematic side-effect profiles than TCAs, researchers focusing on fluoxetine's side effects in youth have recommended "vigilance" (King et al., 1991; Riddle et al., 1990–1991, p. 197). Consequently, to date, there is no support for the theoretical hypothesis that serotonergic compounds are more effective than TCAs in treating depressed youth. Nonetheless, frequent prescription of SSRIs to depressed children continues: "Despite its popularity, no systematic, matched, random-assignment controlled trials have been completed with fluoxetine in the treatment of depression children" (Bangs, Petti, & Janus, 1994, p. 1303). We recommend that additional research on SSRI efficacy with depressed youth be conducted to determine whether the current popularity of these medications has any scientific basis.

Issues Associated With Antidepressant Treatment Outcome Studies

In addition to the small number of depressed child and adolescent patients who have been properly evaluated in double-blind studies, there are a number of other problems and issues associated with the treatment outcome studies reviewed earlier.

Sample characteristics. Several sampling issues limit the generalizability of research findings on antidepressants with youth. First, most of the samples on whom antidepressant efficacy was evaluated were nonrandom convenience samples. Second, the samples tended to be quite variable. Although most samples were somewhat balanced with regard to gender, there were frequent examples of unequal sample sizes, and often patients with comorbid anxiety or conduct disorders were included in the samples.

Outcome measures. In the studies reviewed, various outcome measures and improvement criteria were used to determine antidepressant treatment efficacy. The outcome measures used were primarily physician- or clinician-based (although some self-report measures, such as the BDI, were occasionally used). However, despite the occasional inclusion of patient self-report outcome measures, patient improvement was virtually always defined by cutoff scores attained on clinician-based measures. Consequently, it is difficult to determine whether support for medication efficacy would be enhanced or reduced if results were based on patient ratings (or systematic behavioral observations) rather than clinician ratings. Notably, with regard to adult antidepressant treatment outcome research, Greenberg and associates (Greenberg et al., 1992; Greenberg, Bornstein, Zborowski, Fisher, & Greenberg, 1994) have reported that reliance on clinician ratings tends to produce more positive treatment efficacy outcomes than does reliance on patient ratings. This may be due to clinicians' ability to break the double-blind by observing medication side effects (Greenberg et al., 1992).

Diagnostic and placebo washouts. Using diagnostic and placebo washout periods in antidepressant treatment outcome studies has been both lauded and criticized (Breggin & Breggin, 1994; Leber, 1991). Generally, FDA-approved antidepressant medication trials with adults include placebo washout periods

similar to those used in the TCA treatment outcome studies reviewed earlier. Although an extensive review of adult studies was not undertaken, from this review it appears that rates of depressed youth excluded from studies on the basis of immediate response to placebo administration are slightly higher than rates of adult placebo responders. Perhaps the two best possible explanations for this difference include (a) the great suggestibility of some child and adolescent patients, (b) the inadequacy of adult depressive criteria for categorizing depression in youth, or (c) both (Harrington, 1993).

Differences in response to antidepressants. Concerning whether adults and youth respond differently to antidepressant medications, many hypotheses exist, but the data are generally insufficient. For example, although it is generally believed that antidepressant medications are effective in treating depressed adults, up to 40% of early double-blind, placebo-controlled outcome studies with depressed adults showed no significant differences between active medication treatment and placebo administration (Morris & Beck, 1974). Additionally, the effect size of antidepressant treatment with adults falls within the small-to-medium range (i.e., .22–.44; Cohen, 1977; Greenberg et al., 1992, 1994). Because of the limited data available on antidepressant medication treatment with youth, it is impossible to say whether, eventually, such treatments will be determined to be as effective as similar treatments with adults. The initial lack of evidence for antidepressant treatment efficacy with depressed youth has generated considerable speculation about possible neurobiological differences among adults, adolescents, and children (Ryan, 1990). At this point, the neurobiological basis for depression in youth is best characterized as speculative.

Implications for Psychologists

The research reviewed in this article may be surprising to some psychologists. When we began the process of reviewing antidepressant efficacy with depressed youth, we believed there would be at least some empirical evidence supporting antidepressant efficacy. We were taken aback to discover the extremely small number of double-blind, placebo-controlled studies on this important subject and the uniform lack of scientific evidence for antidepressant efficacy. As practitioners, we have worked closely with physicians when treating depressed children and adolescents, and we believe that at times we have observed significant beneficial effects shortly after administration of TCAs and SSRIs. After reviewing this literature we find ourselves consistently questioning previous and ongoing observations pertaining to antidepressant efficacy. Additionally, the recent work of Greenberg and colleagues has increased our faith in the power of placebo treatment (Fisher & Greenberg, 1989; Greenberg et al., 1992, 1994).

Overall, we believe increased skepticism about the efficacy of antidepressant medications with youth may have positive ramifications for psychologists and for child and adolescent mental health care. First, it may inspire research and development of more effective psychosocial treatments (which generally lack profiles of dangerous side effects; Mufson et al., 1993; J. Sommers-Flanagan & R. Sommers-Flanagan, 1995a, 1995b). Second, it may encourage practitioners to work longer and harder with families before referring them to a physician. Third, it may encourage more referrals from physicians to psychologists. Fourth, it may inspire additional research into differences between adult and child–adolescent depression, rather than the downward extension of adult diagnostic criteria to youth currently present in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994).

Currently, we use the following new guidelines before referring youth for medical consultation: (a) The youth is depressed despite the absence of clear environmental determinants (e.g., family conflict, divorce, etc.); (b) the depressive symptoms are severe and have strong physiological components (e.g., sleep disturbance, somatic complaints, appetite changes and associated weight loss or gain); (c) treatment response is lacking after 10 to 15 sessions of psychotherapy, family therapy, or cognitive–behavioral therapy; and (d) the patient expresses a clear preference for medication treatment over psychosocial interventions.

In conclusion, the basic finding of this review bears repeating: There has never been a double-blind, placebo-controlled study published indicating that antidepressant medications are more effective than placebo in treating child or adolescent depression. Of course, this finding is based on a limited number of studies, some of which have significant methodological problems. Certainly we should allow for the possibility that future research on antidepressants with depressed youth may provide more promising results. However, in the meantime, our review suggests that administering antidepressant medications to depressed children should be considered an experimental treatment procedure.

This review is not intended to provide comparisons of medical interventions to psychotherapy or psychosocial interventions. In fact, research on psychosocial treatments of depression in youth traditionally lags behind similar research with adults. Future medication and psychotherapy research with youth should focus on issues addressed in adult psychotherapy outcome research, namely, "What specific therapeutic interventions produce specific changes in specific patients under specific conditions"? (Strupp & Bergin, 1969, p. 20). This article underscores the need for more sophisticated and productive research on the efficacy of medication with youth and the need for psychologists to critically examine such research before lending support and credibility to pharmacologic treatments.

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