The Journal of Mind-Body Regulation

article

A Meta-Analysis of Randomized Placebo Controlled Trials of Antidepressant Medications in Depressed Children: Do the Benefits Justify the Risks?

Amanda A. Drews, PhD*; David O. Antonuccio, PhD†; Irving Kirsch, PhD‡

Depression affects a substantial portion of children and adolescents. Although most youngsters do not receive any intervention, the introduction of antidepressant medications has drastically affected the manner in which depressed children and adolescents are treated. Important questions have been raised about both the empirical support for and safety of using SSRIs in this population. Thus, the goal of the current study was to quantify the actual benefit of antidepressant medication to children and adolescents over and above the benefit of placebo. We searched three electronic databases (MEDLINE, PubMed, and PsycINFO) using the search terms "antidepressant" and "child[ren]" or "adolescents." Our search yielded 14 published antidepressant trials. Another 5 unpublished trials were found on the MHRA website. Within the 19 studies, we evaluated 11 SSRI-placebo comparisons and 9 tricyclic-placebo comparisons. A statistically significant difference in depressive symptoms favoring the medication condition was reported in 1 of the 9 tricyclic-placebo comparisons, 5 of the 6 published SSRI-placebo comparisons, and 1 of the 5 unpublished SSRI-placebo comparisons. It also was determined that 84% of the response to the medications examined in these studies was duplicated by placebo, leaving a maximum of 16% attributable to a true drug effect. Results suggestive of an overall benefit of SSRI medications compared to placebo for children and adolescents should be interpreted with caution given widely held concerns about publication biases toward positive medication results, high rates of placebo response, and lack of documented clinical (as opposed to statistical) advantage of such medications. Nevertheless, instead of telling parents of depressed youngsters what to do, providers may do well to consider thoughtfully and honestly educating parents (and their children) about benefits and risks associated with both medication and non-medication treatments and letting them decide for themselves how to proceed in the care of their children.

mbr.synergiesprairies.ca

Introduction

Clinical depression, defined to include major depressive disorder and dysthymic disorder, can be identified in children of all ages. Depression is estimated to affect 1–2% of school-age children (6–12 years) (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Fleming & Offord, 1990), with the prevalence rising sharply during adolescence, particularly among girls (e.g., Kessler, Avenevoli, & Merikangas, 2001; Petersen, Compas, Brooks-Gunn, Stemmler, Ey, & Grant, 1993). In fact, by age 18, lifetime prevalence rates of depression are estimated to be 20% with the preponderance of these cases being young adult females (Hankin, Abramson, Moffitt, Silva, McGee, & Angell, 1998; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993). Although fewer than half of children and adolescents with major depression receive treatment before the age of 18 years (Kessler & Walters, 1998), the introduction of the selective serotonin reuptake inhibitors (SSRI) and other newer antidepressants has led to rising prevalence of drug treatment among youths (Zito, Safer, dos-Reis et al., 2002). In 2002, approximately 6% of outpatient physician visits for U.S. children ages 5 to 17 involved the prescription, ordering, or provision of antidepressant medication (NCHS, 2004). One U.S. study concluded that as many as 59.5% of children treated for depression were prescribed antidepressant drugs (Olfson, Gameroff, Marcus, & Waslick, 2003). Roughly 11 million prescriptions for antidepressants were written for children in the United States during 2002 (Goode, 2004), and about 40,000 children in the UK were taking antidepressant medication in 2004 (Ramchandani, 2004). Despite the frequency with which these medications appear to have been dispensed, questions have been raised about the empirical support for using SSRIs in this population. Thus, the aim of the current study is to quantify the actual benefit to children and adolescents derived from the use of antidepressant medication compared with placebo.

** The Children's Mercy Hospital, Section of Developmental & Behavioral Sciences and Gastroenterology, Kansas City, Missouri, USA.*

† Fielding Graduate University & University of Nevada School of Medicine, Reno, Nevada, USA.

e-mail: oliver2@aol.com

‡ Harvard Medical School
Beth Israel Deaconess Medical Center, Brookline

Results of randomized controlled trials designed to test the efficacy of older, tricyclic antidepressant drugs have shown them to be no more effective than placebo for the treatment of major depression in children (Fisher & Fisher, 1996; Hazell, O'Connell, Heathcote, Robertson, & Henry, 1995). In contrast, relatively fewer published efficacy studies in children were initially available for the newer antidepressant drugs. As a result, pediatric practitioners were in a position to borrow heavily from the adult literature in making medication recommendations for their depressed pediatric patients. As detailed by Kirsch (2010), an analysis of 19 double-blind published clinical trials with depressed adults based on mean change and standard deviation in depression scores, rather than a response rate, showed that 75% of the drug effect was duplicated by placebo (Kirsch & Sapirstein, 1998). A subsequent pooled analysis of all 47 published and unpublished studies (also with depressed adults) submitted to the FDA for approval of six newer antidepressant drugs indicated that 82% of the drug effect was duplicated in the placebo group and the mean drug–placebo difference was less than 2 points on both the Hamilton Depression Rating Scales (Kirsch, Moore, Scoboria, & Nicholls, 2002), raising questions about the clinical significance of the drug effect (Antonuccio, Burns, & Danton, 2002). The most recent meta-analysis of adult studies conducted by Kirsch and colleagues (2008) showed antidepressants to have a clinically meaningful advantage over placebo only for the very severely depressed patients, a small minority of all depressed patients.

The lack of similar meta-analytic studies investigating the efficacy and safety of these medications in children was noted in the late 1990s, leading to the enactment of patent exclusivity incentives to increase antidepressant drug testing in pediatric populations. Soon thereafter, concerns about the association of suicidal behaviors and antidepressant drug use in children were raised (US Food and Drug Administration [US FDA], 2004). As a result, regulatory agencies both in the United States and in the UK, the FDA and the Medicines and Healthcare Products Regulatory Agency (MHRA), respectively, issued warnings and restrictions on the use of these medications (Committee on the Safety of Medicines, 2003; US FDA, 2004). In April 2003, the UK Committee on the Safety of Medicines banned paroxetine use for depression in children and adolescents and later, in December 2003, expanded the prohibition to all SSRIs except fluoxetine. Several months later in the United States, the FDA organized a joint meeting of the Neuro-Psychopharmacologic Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee and expertise consultants to evaluate the safety of selected antidepressants in children and adolescents. At this meeting it was decided that the data from extant pediatric trials would be reanalyzed (Leslie, Newman, Chesney, & Perrin, 2005). The joint commission met again in September 2004 to review the data and to advise the FDA on their finding that "there was a causal link between the newer antidepressants and pediatric suicidality" (Leslie et al., 2005). Though the risk was small (Hammad et al., 2006), roughly 4% suicidality in the medication condition vs. 2% in the placebo condition, the stakes were considered high. As a result, one month later, the FDA ordered pharmaceutical companies to add a "black box warning" to antidepressants advertisements, package inserts, and information sheets developed for patients and clinicians (Leslie et al., 2005). In May of 2007, the FDA ordered this warning to be expanded to young adults up to age 25 (Carey, 2007). Since being put in place, the warnings have been associated with an overall decrease in antidepressant use for mild, but not major, depression in children, while initiation of psychotherapy without medication has increased (Valluri et al., 2010).

Based on the antidepressant database, the National Institute for Clinical and Health Care Excellence (NICE) issued guidelines in 2005 indicating that antidepressants should not be used in children with minor depression. NICE advocated that all children should be given advice on diet and exercise. NICE also recommended that even with moderate to severe depression, antidepressants should not be used without first trying 12 weeks of psychotherapy and then, only with close monitoring, and in combination with continued psychotherapy should antidepressant medication be prescribed.

Concurrent with the warnings and restrictions placed on the use of SSRIs for depression in children and adolescents, data from both published and unpublished studies of newer antidepressant drugs in children and adolescents were publicly released (Committee on the Safety of Medicines, 2003). These newly available data, combined with those from already published studies, have permitted a more impartial assessment of the efficacy of new antidepressant drugs in the pediatric population. Several researchers have argued that this assessment has revealed exaggerated benefits of SSRIs in children and adolescents, a strong positive response to placebo in clinical trials, and a downplaying of potentially serious side effects (Garland, 2004; Jureidini et al., 2004; Whittington et al., 2004).

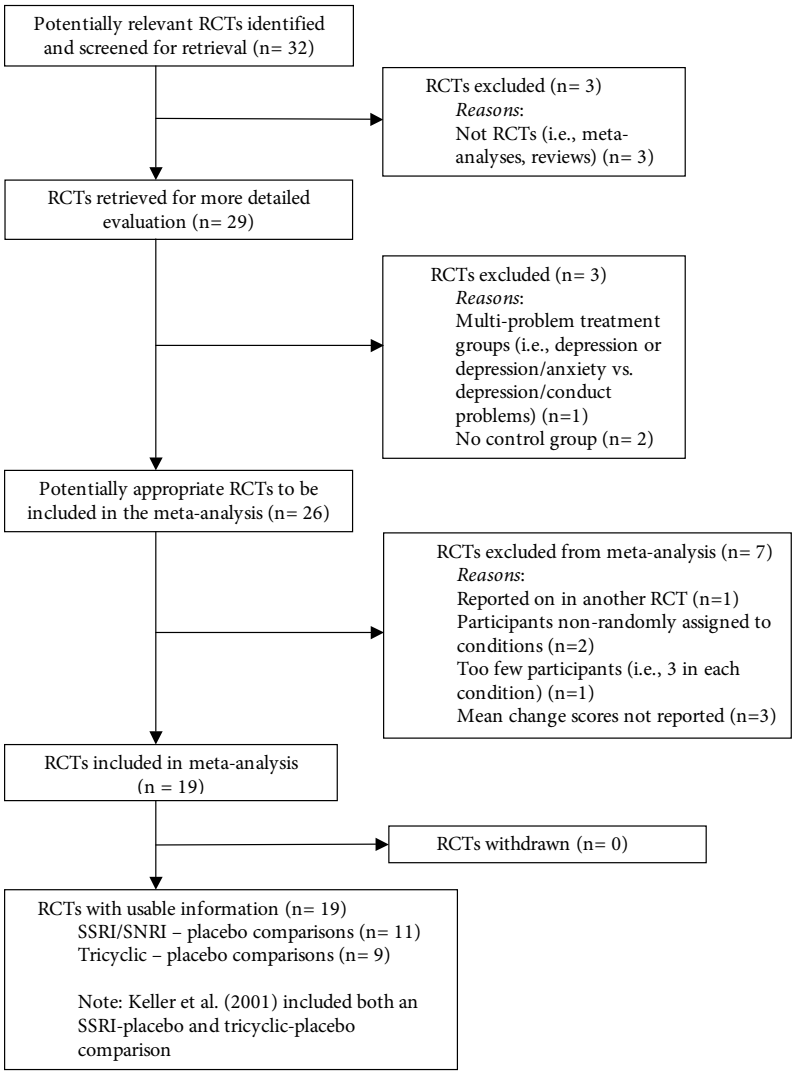

Figure 1. Study search and inclusion strategy

Consistent with Jureidini et al.'s urging for a "more critical approach to ensuring the validity of published data" and the widespread concern for the negative impact of unpublished data on the practice standards for the treatment of pediatric depression (Garland, 2004; Whittington et al., 2004), our meta-analysis differs from many previous reviews in a number of ways. First, we examined data from unpublished as well as published clinical trials. Second, we provided separate estimates of the benefits of SSRIs and tricyclic medication. And third, instead of merely comparing outcomes following medication to those following placebo, we assessed changes within the medication groups and changes within the placebo groups (cf. Kirsch et al., 2002; Kirsch & Sapirstein, 1998). It is important to know whether small differences between drug and placebo effects are due to lack of improvement following medication treatment or to substantial improvement following placebo treatment. This allows for a more clear determination of benefits relative to the risks associated with the use of antidepressant medication in children and adolescents.

Method

To identify studies appropriate for the meta-analysis, we searched three electronic databases (MEDLINE, PubMed, and PsycINFO) using the search terms "antidepressant" and "child[ren]" or "adolescents." Every database was searched from inception to August, 2004, and restricted to English language papers. The search produced 14 published randomized clinical trials; of these, 5 compared SSRIs to placebo; 8 compared tricyclics to placebo; and, 1 compared both an SSRI and a tricyclic medication to placebo. We also obtained data from 5 unpublished SSRI/SNRI trials from the MHRA website (www.mhra.gov.uk). In total, data from 19 published and unpublished studies were used in our analysis. Please see Figure 1 for a graphic summary of the study search and inclusion strategy.

Within-group effect sizes (d) were calculated as the mean post-treatment score minus the mean pretreatment score, divided by the pooled standard deviation (SD; Smith et al., 1980) for each group. Between-group ds were calculated by subtracting the within-group d for placebo from the within-group d for medication, a method that has virtue of adjusting for between-group differences in pre-treatment levels of depression (Kirsch & Sapirstein, 1998). For a complete description of the study methodology, please see Appendix A.

Results

A statistically significant difference in depressive symptoms favoring medication was reported in only 1 (i.e., Sallee, Vrindavanam, Deas-Nesmith, Carson, & Sethuraman, 1997) of the 9 tricyclic-placebo comparisons. Importantly, this difference was obtained on a clinician-rated, rather than a patient-rated, measure of depressive symptoms. Five of the 6 published SSRI-placebo comparisons reported significant between-group differences, compared to only 1 of 5 of the unpublished trials ($z = 2.10$, $p < .05$). Please see Table 1 for a summary of these findings.

Sample sizes and effect sizes for children receiving medication and placebo treatment are presented in Table 2. Mean effect sizes weighted for sample size, were 1.62 for the medication response and 1.36 for the placebo response. Subtracting mean placebo response rates from mean drug response rates revealed a mean medication effect of 0.26 standard deviations. This calculation (i.e., 1.36/1.62) indicates that 84%

Study	Clinical Criteria: MDD	Clinical Criteria: Duration (months)	Age: Range (mean) sex	N: Entered (%) drug/PBO	N: Completed (%) drug/PBO	Drug mg/d	Treatment duration (weeks)	Primary outcome measure	Treatment differences *Drug better on:*
Emslie et al. (1997)	K-SADS (MDD items) CDRS >40	None	7-18 (12.3) 50% ≥12 46%F	96 (91%) 48/48	60 (62%) 34/26	Fluoxetine Fixed 20	8	CGI CDRS Responder (CDRS <28) CDI BDI CGAS WSAS	CGI, fluoxetine 50% vs. PBO 33% (.03) CDRS (.004) None on rate of responders: Fluoxetine 31% vs. PBO 23% None on: CDI BDI CGAS WSAS
Emslie et al. (2002)	DICA CDRS-R >40 CGI-Severity ≥4	None	8-18 (12.7) 49%F	219 109/110	158 90/68	Fluoxetine fixed 20	9	CDRS-R MADRS HAM-A GAF CGI-Severity Responder (CDRS-R, 30% improvement)	CDRS-R (.001) MADRS (.023) CGI-Severity (.001) None on HAMA and GAF None on rate of responders: Fluoxetine 65.1% vs. PBO 53.5%
Geller et al. (1990)	K-SADS CDRS ≥30	2	12-17 (14.2) 48%F	35 (67%) NI	31 (91%) 12/19	NT Fixed 60-100 ng/ml	8	GAS CDRS	None on GAS and CDRS None on rate of responders: NT 8% vs. PBO 21%
Geller et al. (1992)	K-SADS-P CDRS ≥40	≥2	6-12 (9.7) 30%F	72 (67%) NI	50 (69%) 26/24	NT Fixed 60-100 ng/ml	10	Responder (CDRS ≤20) (K-SADS-P MDD items scores of 1 or 2)	None on rate of CDRS responders: NT 30.8% vs. PBO 16.7% None on rate of K-SADS-P MDD items responders: NT 46.2% vs. PBO 58.3%
Keller et al. (2001)	K-SADS-L HAM-D ≥12 CGAS <60	2	12-18 (14.85) 64%F	180 (65%) 93/87	133 (70%) 67/66	Paroxetine Max 40	8	Responder (HAM-D ≤8) *or* (≥50% reduction in baseline HAM-D) HAM-D total score	HAM-D ≤8, paroxetine 63.3% vs. PBO 46% (.02) None on rate of responders: Paroxetine 66.7% vs. PBO 55.2% None on HAM-D total score
*Keller et al. (2001)	K-SADS-L HAM-D ≥12 CGAS <60	2	12-18 (14.85) 62%F	182 (66%) 95/87	122 (65%) 56/66	IMP Max 300	8	Responder (HAM-D ≤8) *or* (≥50% reduction in baseline HAM-D) HAM-D total score	None
Klein et al. (1998)	K-SADS Diagnostic confirmation by a second clinician HDS ≥18	2	13-18 (15.1) 58%	45 (73%) 23/22	36 (80%) 18/18	DMI MAX 300 5mg/kg	6	HAM-D CGI SCL-90, depression scale	None on HAM-D, CGI SCL-90, depression scale (.05)
Kramer and Feiguine (1981)	PRS >7	≥6	13-17 (14.5) 65%F	20 10/10	20 (100%) 10/10	AMI Max 200	6	PRS MMPI-Form R Depression Adjective Checklist-Form A	None on the PRS or MMPI Depression Adjective Checklist (.001)
Kutcher et al. (1994)	K-SADS HAM-D ≥17 BDI ≥16	None	15-19 (17.7%) 64%F	60 (80%) 30/30	42 (70%) 17/25	DMI Fixed 200	6	HAM-D BDI SCL-58 Responder (50% reduction in HDS)	None on scales None on rate of responders: DMI 48% vs. PBO 35%
Kye et al. (1996)	K-SADS	None	12-18 (14.9) 40%F	31 (% NI) 18/13	22 (71%) 12/10	AMI Max 300	8	CGI HAM-D MDD symptoms	None on HAM-D, MDD symptoms CGI illness severity (<.07)
March et al. (TADS) (2004)	K-SADS-PL CDRS-R ≥45	1.5	12-17 (14.6)	221 109/112	180 91/89	Fluoxetine	12	CDRS-R Responder (CGI-Imp score of 1 or 2)	None on CDRS-R Responder: (CGI-Imp score of 1 or 2), fluoxetine 60.6% vs. PBO 34.8% (.001)

(Table continued on page 89.)

Study	Clinical Criteria: MDD	Clinical Criteria: Duration (months)	Age: Range (mean) sex	N: Entered (%) drug/PBO	N: Completed (%) drug/PBO	Drug mg/d	Treatment duration (weeks)	Primary outcome measure	Treatment differences: *Drug better on*
Puig-Antich et al. (1987)	K-SADS-P	None	6-12 (9.11)	42 20/22	38 16/22	IMP Max 5mg/kg/d	5	K-SADS depression scales K-GAS Responder (K-SADS-P depressed mood and anhedonia ≤2)	None on K-SADS depression scales or K-GAS None on rate of responders: IMP 56% vs. PBO 68%
Sallee et al. (1997)	SCID-P	None	14-18 (16.2) 31%F	NI	16 8/8	CMP Single IV dose of 200mg	1	HAM-D CGI-Severity BDI Responder (50% reduction in HDRS at day 6)	HAM-D (.04) CGI-Severity (.003) None on BDI None on rate of responders: CMP 88% vs. 38%
Wagner et al. (2003)	K-SADS-PL CDRS-R ≥45 CGI-Severity ≥4	1.5	6-17 53% ≥12 51%F	376 (62%) 189/187	299 (80%) 143/156	Sertraline Flexible dosing 50-200	10	Mean change in CDRS-R Responder (40% reduction in CDRS-R)	Mean change in CDRS-R (.007) Responder: Sertraline 69% vs. PBO 59% (.05)
Wagner et al. (2004)	K-SADS-PL CDRS-R ≥40	1	7-17 (12.1) 53%F	178 93/85	138 71/67	Citalopram Flexible dosing 20-40	8	Mean change in CDRS-R Responder (CDRS-R ≤28)	Mean change in CDRS-R (.05) Responder: Citalopram 36% vs. PBO 24% (.05)
Citalopram 2			13-18	244 124/120	153 74/79	Citalopram 10-40	12	Mean change from baseline in K-SADS-P total score	None
Paroxetine 2	DSM-IV C-GAS Total Score < 69 MADRS ≥16		13-18	275 182/93	192 126/66	Paroxetine Flexible dosing 20-40	12	Mean change from baseline in K-SADS-L depression subscale Responder (≥50% reduction in MADRS)	None
Paroxetine 3	DSM-IV		7-17	203 101/102		Paroxetine Flexible dosing 10-40	8	Mean change from baseline in CDRS-R	None
Venlafaxine 1	DSM-IV K-SADS-PL CDRS > 40 (w/ no greater than 30% decrease during screening) CGI- Severity ≥4	1	6-17		141 68/73	Venlafaxine Flexible dosing 37.5-225	8	Mean change from baseline in CDRS-R total score	None
Venlafaxine 2	DSM-IV K-SADS-PL CDRS > 40 (w/ no greater than 30% decrease during screening) CGI- Severity ≥4	1	6-17		193 101/92	Venlafaxine Flexible dosing 37.5-225	8	Mean change from baseline in CDRS-R total score	None

Table 1. Summary of quantitative data for included studies

* Keller et al. (2001) included both an SSRI-placebo and a tricyclic-placebo comparison

PBO: placebo; AMI: amitriptyline; DMI: desipramine; NT: nortriptyline; CMP: clomipramine; NI: not indicated (information not reported)

Measures: BDI, Beck Depression Inventory (Beck & Steer, 1984); CDI, Children's Depression Inventory (Kovacs, 1985); CDRS (-R), Children's Depression Rating Scale (Revised) (Poznanski & Mokros, 1995); CGAS, Children's Global Assessment Scale (Schaffer, Gould, Brasic, et al., 1983); CGI (-S) (-I), Clinical Global Impression (of Severity of Illness) (of Improvement of Illness) (Guy, 1976); DICA, Diagnostic Interview for Children and Adolescents (Herjanic & Reich, 1982); GAF, Global Assessment of Functioning Scale (Endicott, Spitzer, Fleiss, & Cohen, 1976); HAM-A, Hamilton Anxiety Rating Scale (Hamilton, 1959); HAM-D, Hamilton Rating Scale for Depression (Hamilton, 1960); K-SADS (-P) (-L), Kiddie Schizophrenia and Affective Disorders Schedule (Present State) (Lifetime) (Chambers, Puig-Antich, Hirsch, et al., 1985); MADRS, Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979); PRS, Psychiatric Rating Scale (Kramer & Feiguine, 1981); SCID-P, Structured Clinical Interview for DSM-III-R—Patient Version (Spitzer, Williams, Gibbon, First, 1990); WSAS, Weinberg Screening Affective Scale (Weinberg & Emslie, 1988)

Publication	Medication Type	Within Drug		Within Placebo		Between Group
		n	*d*	*n*	*d*	*d*
Emslie et al. (1997)	SSRI	48	1.04	48	0.60	0.44
Emslie et al. (2002)	SSRI	109	1.42	110	1.01	0.41
Geller et al. (1990)	TCA	12	2.25	19	1.58	0.68
Geller et al. (1992)	TCA	26	2.12	24	2.41	-0.29
Keller et al. (2001)	SSRI	93	1.85	87	1.44	0.41
Keller et al. (2001)	TCA	95	1.48	87	1.44	0.04
Klein et al. (1998)	TCA	18	0.95	18	0.57	0.38
Kramer & Feiguine (1981)	TCA	10	2.10	10	1.57	0.53
Kutcher et al. (1994)	TCA	30	0.84	30	1.31	-0.48
Kye et al. (1996)	TCA	18	1.37	13	1.27	0.11
March et al. (2004)	SSRI	109	2.59	112	2.29	0.3
Puig-Antich et al. (1987)	TCA	16	1.97	22	1.62	0.35
Sallee et al. (1997)	TCA	8	2.80	8	1.21	1.59
Wagner et al. (2003)	SSRI	189	1.27	187	1.07	0.20
Wagner et al. (2004)	SSRI	89	1.44	85	1.12	0.32
Citalopram study 2	SSRI	74	1.10	79	1.13	-0.03
Paroxetine study 2	SSRI	182	1.28	93	1.32	-0.04
Paroxetine study 3	SSRI	101	1.50	102	1.45	0.05
Venlafaxine 1	SNRI	68	1.33	73	1.19	0.15
Venlafaxine 2	SNRI	101	1.79	92	1.66	0.13
All trials		**1396**	**1.62**	**1299**	**1.36**	**0.26**

Table 2. Medication and placebo effect sizes as a function of publication and medication type

of the response to the medications examined in these studies was duplicated by the placebo response, leaving at most, 16% attributable to a true drug effect.

Conclusions

Based on the current meta-analysis, tricyclic medications demonstrated no significant pharmacological benefit for depressed children. On the other hand, results from the published investigations of SSRI efficacy revealed an overall benefit of medication over placebo, with 5 of the 6 SSRI–placebo comparisons demonstrating a statistically significant advantage for medication. With that said, we recommend consideration of five important caveats. First, the statistical benefit of SSRI medications was substantially more pronounced in published versus unpublished studies. That is, the proportion of published studies reporting significant differences between drug and placebo was significantly greater that the proportion of unpublished studies reporting significant results. This discrepancy makes it quite difficult for researchers, clinicians, and parents to accurately evaluate the effectiveness of these medications for children (Garland, 2004; Whittington et al., 2004). Second, while the SSRI medications may demonstrate a statistical advantage over placebo, they may not possess a clinically detectable advantage (Jacobsen, Roberts, Berns, & McClinchey, 1999). Jureidini et al. (2004) has noted that whereas almost half of the clinician-rated measures favored the SSRI, none of the patient-rated or parent-rated outcomes favored the antidepressants over placebo. Third, while children on antidepressant medications do sometimes improve, children on placebo medications likewise tend to improve. Indeed, in the current meta-analysis, we estimated that up to 84% of the response to the medications was duplicated by the placebo response. Fourth, the vast majority of these studies involve youths with major depression, making it difficult to generalize to the community where antidepressants may be used for more minor depression. And fifth, the included samples represent overlapping age ranges from age 6 to age 18, making it impossible to conduct a separate analysis of prepubertal children and post pubertal children, a difference that may matter.

Importantly, high placebo responder rates are not unique to pediatric depression. Significant response to placebos also has been documented in pediatric migraine trials (e.g., Fernandes, Ferriera, & Sampaio, 2008) as well as in tests of antiepileptic drugs (AEDs) in children with drug resistant partial epilepsy (e.g., Rheims, Cucherat, Arzimanoglou, & Ryvlin, 2008). Furthermore, in both cases, pediatric placebo responder rates were estimated to be significantly greater than those found in adult studies. This is in contrast to the current study which demonstrated placebo response rates among children to be similar to those in adult studies. Nonetheless, there is no currently agreed upon mechanism by which the placebo response may be enhanced among children relative to adults, although some have speculated that it may have to do with children's greater suggestibility (e.g., Takarangi & Loftus, 2010) and a reduced vulnerability to "unblinding" by medication side effects. In other words, adults may know more about medication side effects, allowing them to detect their actual treatment condition, and thereby reducing the placebo impact or enhancing the drug impact by altering expectations (Antonuccio et al., 1999; Hey & Weijer, 2010; Kirsch, 2010). What this means for the design of clinical trials of all new medications is that differences in outcomes between the active intervention and placebo could be statistically harder to detect in children, thus requiring that treatment groups be adequately powered (Fernandes et al., 2008).

The potential benefits of antidepressant medications in children must be considered within the context of the associated risks. To reiterate, consistent and clinically meaningful benefits of antidepressant medications, relative

to placebo, have not been demonstrated in depressed children. The cost, therefore, of exposing children to a documented increased risk of suicidal ideation and suicidal behavior (Bridge et al., 2007; Cheung et al., 2006; Garland et al, 2004; Hammad, Laughren, & Racoosin, 2006.; Jureidini et al, 2004; Roth, Boyle, Beer, Malik, & deBruyn, 2004; Whittington et al. 2004), though small, may be difficult to justify given these minimal relative benefits. It also can be argued that the possible risk of other commonly reported side effects such as agitation, insomnia, and gastrointestinal problems (Antonuccio, Danton, DeNelsky, Greenberg, & Gordon, 1999) are, likewise, not worth the clinically insignificant advantage of antidepressants over placebo for children.

A related question regarding the treatment of depression in children also has been posed—given how well placebos have done in clinical trials, i.e., should clinicians consider using them as a stand alone treatment for depression? For the ethical reasons highlighted by Foddy (2011), we do not support the deceptive use of placebos. However, we don't believe that deception is necessary to tap into the "nonspecific" factors involved in the use of placebos. A strong therapeutic alliance, the engendering of hope, an emphasis on problem solving skills, and the assurance of confidentiality, are likely among the nonspecific factors that make a placebo work. Such factors can and probably should be incorporated into any psychosocial or medication treatment ultimately offered to a depressed child.

Weighing risk and benefit

In possibly the best comparative study ever done in depressed adolescents (TADS, 2004), March and colleagues ranked the efficacy of the unitary and combined treatments (from best to worst) in this way: combination treatment (CBT + fluoxetine), followed by fluoxetine alone, followed by CBT alone, followed by placebo. Analyses (Kuehn, 2007; TADS, 2007) of the longer-term efficacy of these treatments indicated that CBT alone caught up with fluoxetine alone at the 18-week follow-up; CBT alone caught up with the combination treatment at the 36-week follow-up. When considering safety, the ranking of these treatments, again from best to worst, are entirely different: CBT alone, followed by placebo, followed by combination treatment (CBT + fluoxetine), followed by fluoxetine alone. In other words, despite the fact that suicidality decreased across all four arms of this study, the fluoxetine condition had a significantly higher rate of harm-related adverse events (e.g., suicidal ideation), physiological side effects (e.g., diarrhea, insomnia, and sedation), and psychiatric adverse events (e.g., irritability, mania, and fatigue) compared with placebo or CBT alone (TADS, 2004).

Therefore, based on these data, children and their families reasonably may be offered, as first line treatments, psychosocial alternatives such as exercise, interpersonal psychotherapy, and cognitive behavioral therapy that have been found to produce therapeutic effects in depressed children (e.g., Brown et al., 2006; Clarke, Rohde, Lewinsohn, Hops, & Seely, 1999; Harrington, Campbell, Shoebridge, & Whittaker, 1998; Harrington, Whittaker, & Shoebridge, 1998; Lewinsohn & Clarke, 1999) without the known medical side effects and associated risk of pharmacologic interventions. This is not to say that psychosocial and alternative interventions for childhood depression represent the inevitable cure for the condition. Weisz and colleagues (1996) reported that the effects of psychotherapeutic interventions with depressed children are positive but small (i.e., average effect size of .34) and of weak durability. Nonetheless, such psychosocial interventions appear to carry a lower risk of medical side effects and adverse events (TADS, 2004, 2007).

Using the TADS study as a guide, it is possible to tailor treatment to parent (as well as child and clinician) values and preferences. If parents' highest priority is safety, CBT alone (or another psychosocial intervention) would be a reasonable first choice. If parents' highest priority is efficacy, the combination of fluoxetine and CBT may offer the best short-term outcome. Alternatively, if a parent is willing to wait for improvement in his or her child's depressive symptoms, CBT alone may represent the best intervention in terms of both short-term safety as well as efficacy equivalent to combination treatment at longer term follow-up. It may be time to stop telling consumers what to do. Instead, arming them with an accurate summary of the available outcome and safety data may actually allow them to secure the promise of informed consent and, further, empower them to balance benefit and risk in accordance with their own values when making treatment choices for depressed children and adolescents. If medications are used, close monitoring is warranted given the identified risks, something that can be a challenge in today's primary care environment.

Appendix A: Following is a complete account of the current study's methodology:

To secure studies appropriate for the meta-analysis, we searched three electronic bibliographic databases (MEDLINE, PubMed, and PsycINFO) using the search terms "antidepressant" and "child[ren]" or "adolescents." Every database was searched from inception to August, 2004, and restricted to English language papers. We extracted additional clinical trial data from the references of retrieved articles, reviews and meta-analytic summaries on medication treatment of pediatric depression, as well as the FDA and MHRA websites.

This process yielded 21 published reports of controlled comparisons between antidepressant medication and placebo. Of these, seven studies were excluded from our analysis for reasons of methodological quality. Geller, Cooper, McCombs, Graham, and Wells (1989) was excluded because it was the same trial reported in Geller et al. (1992). Two additional trials (i.e., Kashani, Shekim, & Reid, 1984; Lucas, Lockett, & Grimm, 1965) were excluded because participants were not assigned to conditions randomly. Finally, Petti and Law (1982) was also excluded as it compared only three children on antidepressant medication to three children on placebo. This did not seem to us to constitute an adequately powered clinical trial and its conclusion would unjustly inflate the number of studies failing to find drug-placebo differences. Mean change scores were not reported for 3 (Boulos et al., 1991; Preskorn, Weller, Hughes, Weller, & Bolte, 1987; Simeon, Dinicola, Ferguson, & Copping, 1990) of the 21 published RCTs and, for that reason, data from them were subsequently eliminated from the meta-analysis. The sample sizes in these three trials were small (30, 22, and 32, respectively). Thus, it was determined that their omission would not substantially affect the outcome of our analysis. This resulted in 14 published randomized clinical trials available for inclusion in the meta-analysis; of these, 5 compared SSRIs to placebo; 8 compared tricyclics to placebo; and, 1 compared both an SSRI and a tricyclic medication to placebo.

In addition to the 14 randomized trials obtained through the published literature search, we procured data from 5 unpublished SSRI/SNRI trials from the MHRA website (www.mhra.gov.uk). Therefore, we included a total of 19 published and unpublished studies in our analysis. Among these, we evaluated 11 SSRI-placebo comparisons and 9 tricyclic-placebo comparisons. (One study, Keller et al. (2001), included both a tricyclic-placebo and SSRI-placebo comparison).

Within-group effect sizes (d) were calculated as the mean post-treatment score minus the mean pretreatment score, divided by the pooled standard deviation (SD; Smith et al., 1980) for each group. Between-group ds were calculated by subtracting the within-group d for placebo from the within-group d for medication, a method that has virtue of adjusting for between-group differences in pre-treatment levels of depression (Kirsch & Sapirstein, 1998). In studies reporting multiple measures of depression, an effect size was calculated for each measure and these were then averaged. In studies reporting the effects of two medications, a single mean effect size for both was calculated for the primary analysis. In a subsequent analysis, the effect for each drug was examined separately. Mean within-group and between-group effect sizes weighted for sample size (n) were also calculated (Hunter & Schmidt, 1990).

References

American Psychological Association Working Group on Psychoactive Medications for Children and Adolescents. (2006). *Report of the Working Group on Psychoactive Medications for Children and Adolescents. Psychopharmacological, psychosocial, and combined interventions for childhood disorders: Evidence base, contextual factors, and future directions*. Washington, DC: American Psychological Association.

Antonuccio, D. O., Danton, W. G., DeNelsky, G. Y., Greenberg, R. P., & Gordon, J. S. (1999). Raising questions about antidepressants. *Psychotherapy and Psychosomatics*, *68*, 3-14.

Antonuccio, D. O., Burns, D. D., & Danton, W. G. (2002). Antidepressants: A triumph of marketing over science? *Prevention & Treatment, 5,* Article 25. Retrieved from http://psycnet.apa.org/journals/pre/5/1/25c.pdf doi: 10.1037/1522-3736.5.1.525c

Beck, A. T., & Steer, R. A. (1984). Internal consistencies of the original and revised Beck Depression Inventory. *Journal of Clinical Psychology, 40*, 1365-1367.

Boulos, C., Kutcher, S., Marton, P., Simeon, J., Ferguson, B., & Roberts, N. (1991). Response to desipramine treatment in adolescent major depression. *Psychopharmacology Bulletin, 27*, 59-65.

Bridge, J. A., Iyengar, S., Salary, C. B., Barbe, R. P., Birmaher, B., . . . Brent, M. D. (2007). Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association, 297*, 1683-1696.

Carey, B. (2007, May 3). FDA expands suicide warnings on drugs. *The New York Times*. Retrieved from http://www.nytimes.com/2007/05/03/health/03depress.html

Chambers, W., Puig-Antich, J., Hirsch, M., Paez, P., Ambrosini, P. J., Tabrizi, M. A., & Davies, M. (1985). The assessment of affective disorders in children and adolescents by semi-structured interview. *Archives of General Psychiatry, 42*, 696-702.

Cheung, A. H., Emslie, G. J., & Mayes, T. L. (2006). The use of antidepressants to treat depression in children and adolescents. *Canadian Medical Association Journal, 174*, 193-200.

Clarke, G. N., Rohde, P., Lewinsohn, P. M., Hops, H., & Seely, J. R. (1999). Cognitive-behavioral treatment of adolescent depression: Efficacy of acute group treatment and booster sessions. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*, 272-279.

Committee on the Safety of Medicines. (2003). *Selective serotonin reuptake inhibitors (SSRIs): Overview of regulatory status and CSM advice related to major depressive disorder (MDD) in children and adolescents including a summary of available safety and efficacy data*. Retrieved from Medicines and Healthcare products Regulatory Agency Web site: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON019494

Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry, 60*, 837-844.

*Emslie, G. J., Rush, A. J., Weinberg, W. A., Kowatch, R. A., Hughes, C. W., Carmody, T., & Rintelmann, J. (1997). A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Archives of General Psychiatry, 54*, 1031-1037.

*Emslie, G. J., Heiligenstein, J. H., Wagner, K. D., Hoog, S. L., Ernest, D. E., Brown, . . . E., Jacobson, J. G. (2002). Fluoxetine for acute treatment of depression in children and adolescents: A placebo-controlled, randomized clinical trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*, 1205-1215.

Endicott, J., Spitzer, R. L., Fleiss, J. L., & Cohen, J. (1976). The global assessment of functioning scale: A procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry, 33*, 766-771.

Fernandes, R., Ferriera, J. J., & Sampaio, C. (2008). The placebo response in studies of acute migraine. *Journal of Pediatrics, 152*, 527-533.

Fisher, R. L., & Fisher, S. (1996). Antidepressants for children. Is scientific support necessary? *The Journal of Nervous and Mental Disease, 184*, 99-102.

Fleming, J. E., & Offord, D. R. (1990). Epidemiology of childhood depressive disorders: A critical review. *Journal of the American Academy of Child and Adolescent Psychiatry, 29*, 571-580.

Foddy, B. (2011). The ethical placebo. *The Journal of Mind Body Regulation, 1*(2). 53–62.

Garland, E. J. (2004). Facing the evidence: Antidepressant treatment in children and adolescents. *Canadian Medical Association Journal, 170*, 489-491.

Geller, B., Cooper, T. B., McCombs, H. G., Graham, D., & Wells, J. (1989). Double-blind, placebo-controlled study of nortriptyline in depressed children using a "fixed plasma level" design. *Psychopharmacology Bulletin, 25*, 101-108

*Geller, B., Cooper, T. B., Graham, D. L., Marsteller, F. A., & Bryant, M. B. (1990). Double-blind placebo controlled study of nortriptyline in depressed adolescents using a "fixed plasma level" design. *Psychopharmacology Bulletin, 26*, 85-90.

*Geller, B., Cooper, T. B., Graham, D. L., Fetner, H. H., Marsteller, F. A., & Wells, JM (1992). Pharmacokinetically designed double-blind placebo-controlled study of nortriptyline in 6- to 12-year-olds with major depressive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*, 34-44.

Goode, E. (2004, February 3). Stronger warning is urged on antidepressants for teenagers. *New York Times*. Retrieved from http://query.nytimes.com/gst/fullpage.html?sec=health&res=9C0DE5DC143BF930A35751C0A9629C8B63

Guy, W. (1976). *ECDEU Assessment Manual for Psychopharmacology.* Rockville MD: National Institute of Mental Health.

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology, 32,* 50-55.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry, 23*, 56-62.

Hammad, T. A., Laughren, T., & Racoosin, J. (2006). Suicidality in pediatric patients treated with antidepressant drugs. *Archives of General Psychiatry, 63*, 332-339.

Hankin, B. L., Abramson, L. Y., Moffitt, T. E., Silva, P. A., McGee, R., &Angell, K. E. (1998). Development of depression from preadolescence to young adulthood: Emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology, 107*, 128-140.

Harrington, R., Campbell, F., Shoebridge, P., & Whittaker, J. (1998). Meta-analysis of CBT for depression in adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*, 1005-1007.

Harrington, R., Whittaker, J., & Shoebridge, P. (1998). Psychological treatment of depression in children and adolescents: A review of treatment research. *British Journal of Psychiatry, 173*, 291-298.

Hazell, P., O'Connell, D., Heathcote, D., Robertson, J., & Henry, D. (1995). Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. *British Medical Journal, 310*, 897-901.

Herjanic, B., & Reich, W. (1982). Development of a structured psychiatric interview for children: Agreement between child and parent on individual symptoms. *Journal of Abnormal Child Psychology, 10*, 307-324.

Hey, S. P. & Weijer, C. (2010, July). *What questions can a placebo help anwer?* Paper presented at the workshop Using social science to elucidate placebos: Examining a powerful effect through a non-medical lens, Montréal, Canada.

Hunter, J. E., & Schmidt, F. L. (1990). *Methods of meta-analysis: Correcting error and bias in research findings*. Thousand Oaks, CA: Sage Publications.

Jacobson, N. S., Roberts, L. J., Berns, S. B., & McClinchey, J. B. (1999). Methods for defining and determining the clinical significance of treatment effects: Description, application, and alternatives. *Journal of Consulting and Clinical Psychology, 67*, 300-307.

Jureidini, J. N., Doecke, C. J., Mansfield, P. R., Haby, M. M., Menkes, D. B., & Tonkin, A. L. (2004). Efficacy and safety of antidepressants for children and adolescents. *British Medical Journal 328*, 879-883.

Kashani, J. H., Shekim, W. O., & Reid, J. C. (1984). Amitriptyline in children with major depressive disorder: A double-blind crossover pilot study. *Journal of the American Acadedmy of Child Psychiatry, 23*, 348-351.

*Keller, M. B., Ryan, N. D., Strober, M., Klein, R. G., Kutcher, S.P., Birmaher, B. . . . McCafferty, J. P. (2001). Efficacy of paroxetine in the treatment of adolescent major depression: A randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry,* 40, 762-772.

Kessler, R. C., Avenevoli, S., & Merikangas, K. R. (2001). Mood disorders in children and adolescents: An epidemiological perspective. *Biological Psychiatry, 49*, 1002-1014.

Kirsch, I. (2010, July). *Antidepressants and the placebo response.* Paper presented at the workshop Using social science to elucidate placebos: Examining a powerful effect through a non-medical lens, Montréal, Canada.

Kirsch, I., Moore, T. J., Scoboria, A., & Nichols, S. S. (2002). The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention & Treatment, 5,* Article 28. Retrieved from http://psycnet.apa.org/journals/pre/5/1/28c.pdf doi: 10.1037/1522-3736.5.1.523a

Kirsch, I., Deacon, B., Huedo-Medina, T., Scoboria, A., Moore, T., & Johnson, B. (2008). Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. *PLoS Medicine, 5*(2), 260-268.

Kirsch, I., & Sapirstein, G. (1998, June 26). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prevention & Treatment, 1,* Article 0002a. Retrieved from http://psycnet.apa.org/journals/pre/1/2/2a.pdf doi: 10.1037/1522-3736.1.1.12a

*Klein, R. G., Mannuzza, S., Koplewicz, H. S., Tancer, N. K., Shah, M., Liang, V., & Davies, M. (1998). Adolescent depression: Controlled desipramine treatment and atypical features. *Depression and Anxiety, 7*(1), 15-31.

Kovacs, M. (1985). The children's depression inventory (CDI). *Psychopharmacology Bulletin, 21*, 995-998.

*Kramer, A. D., & Feiguine, R. J. (1981). Clinical effects of amitriptyline in adolescent depression: A pilot study. *Journal of the American Academy of Child Psychiatry, 20*, 636-644.

Kuehn, B. M. (2007). Cognitive behavioral therapy shows promise for children with mental illness. *Journal of the American Medical Association, 297*, 453-455.

*Kutcher, S., Boulos, C., Ward, B., Marton, P., Simeon, J., Bruce, H., . . . Reed, K. (1994). Response to desipramine treatment in adolescent depression: A fixed-dose, placebo-controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 33*(5), 686-694.

*Kye, C. H., Waterman, G. S., Ryan, N. D., Birmaher, B., Williamson, D. E., Iyengar, S., & Dachille, S. (1996). A randomized, controlled trial of amitriptyline in the acute treatment of adolescent major depression. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*, 1139-1144.

Leslie, L. K., Newman, T. B., Chesney, P. J., & Perrin, J. M. (2005). The Food and Drug Administration's Deliberations on Antidepressant Use in Pediatric Patients. *Pediatrics, 116*, 195-204.

Lewinsohn, P. M., & Clarke, G. N. (1999). Psychosocial treatments for adolescent depression. *Clinical Psychology Review, 19*, 329-342.

Lewinsohn, P. M., Hops, H., Roberts, R. E., Seeley, J. R., & Andrews, J. A. (1993). Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *Journal of Abnormal Psychology, 103*, 133-144.

Lucas, A. R., Lockett, H. J., & Grimm, F. (1965). Amitriptyline in childhood depressions. *Diseases of the Nervous System, 26*, 105-110.

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry, 134*, 382-389.

Mulrow, C. D., Williams, J. W., Trivedi, M., Chiquette, E., Aguilar, C., Cornell, J. E., . . . Stamm, K. (1999). *Treatment of Depression: Newer Pharmacotherapies. Evidence Reports/Technology Assessments No. 7.* (Prepared by the San Antonio Evidence-Based Practice Center based at the University of Texas Health Science Center at San Antonio under Contract 290-97-0012). AHCPR Publication No. 99-E014. Rockville, MD: US Agency for Health Care Policy and Research.

National Center for Health Statistics. (2004). *Health, United States, 2004 With Chartbook on Trends in the Health of Americans* (Report No. 2004-1232). Hyattsville, MD: National Center for Health Statistics (US).

Olfson, M., Gameroff, M. J., Marcus, S. C., & Waslick, B. D. (2003). Outpatient treatment of child and adolescent depression in the United States. *Archives of General Psychiatry, 60*, 1236-1242.

Petersen, A. C., Compas, B. E., Brooks-Gunn, J., Stemmler, M., Ey, S., & Grant, K. E. (1993). Depression during adolescence. *American Psychology, 48*, 155-168.

Petti, T. A., & Law, W. (1982). Imipramine treatment of depressed children: A double-blind study. J*ournal of Clinical Psychopharmacology, 2*, 107-110.

Poznanski, E. O., & Mokros, H. B. (1995). *Children's Depression Rating Scale, Revised (CDRS-R) Manual*. Los Angeles, CA: Western Psychological Services.

Preskorn, S. H., Weller, E. B., Hughes, C. W., Weller, R. A., & Bolte, K. (1987). Depression in prepubertal children: Dexamethasone nonsuppression predicts differential response to imipramine vs. placebo. *Psychopharmacology Bulletin, 23*, 128-133.

*Puig-Antich, J., Perel, J. M., Lupatkin, W., Chambers, W. J., Tabrizi, M. A., King, J., . . . Stiller, R. L. (1987). Imipramine in prepubertal major depressive disorders. *Archives of General Psychiatry, 44*, 81-89.

Ramchandani, P. (2004). Treatment of major depressive disorder in children and adolescents. *British Medical Journal, 328*, 3-4.

Rheims, S., Cucherat, M., Arzimanoglou, A., & Ryvlin, P. (2008). Greater response to placebo in children than in adults: A systematic review and meta-analysis in drug-resistant partial epilepsy. *PLoS Medicine, 5*(8), 1223-1234.

Roth, D., Boyle, E., Beer, D., Malik, A., & deBruyn, J. (2004). Depressing research. *Lancet, 363*, 1335.

*Sallee, F. R., Vrindavanam, N. S., Deas-Nesmith, D., Carson, S. W., & Sethuraman, G. (1997). Pulse intravenous clomipramine for depressed adolescents: Double-blind, controlled trial. *American Journal of Psychiatry, 154*, 668-673.

Schaffer, D., Gould, M. S., Brasic, J., Ambrosini, P., Fischer, P., Bird, H., & Aluwahlia, S. (1983). A Children's Global Assessment Scale (CGAS). *Archives of General Psychiatry, 40,* 1228-1231.

Simeon, J. G., Dinicola, V. F., Ferguson, H. B., & Copping, W. (1990). Adolescent depression: A placebo-controlled fluoxetine treatment study. *Progress in Neuro-Psychopharmacol & Biological Psychiatry, 14*, 791-795.

Smith, M. L., Glass, G. V., Miller, T. I. (1980). *The benefits of psychotherapy.* Baltimore, MD: John Hopkins University Press.

Spitzer, R. L., Williams, J. B. W., Gibbon, M., First, M. B. (1990). *Structured clinical interview for DSM-III-R—Patient Version 1.0 (SCID-P)*. Washington DC: American Psychiatric Press.

Takarangi, M., Loftus, E. F. (2010, July). *Suggestion, placebos, and false memories.* Paper presented at the workshop Using social science to elucidate placebos: Examining a powerful effect through a non-medical lens, Montréal, Canada.

*Treatment for Adolescents with Depression Study (TADS) Team. (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression. *Journal of the American Medical Association, 292*, 807-820.

Treatment for Adolescents with Depression Study (TADS) Team. (2007). Treatment for Adolescents with Depression Study: Long term effectiveness and safety outcomes. *Archives of General Psychiatry, 64*, 1132-1144.

United States Food & Drug Administration (FDA). (2004). *Public health advisory: Suicidality in children and adolescents being treated with antidepressant medications.* Retrieved from United States Department of Health & Human Services Web site: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm

Valluri, S., Zito, J. M., Safer, D. J., Zuckerman, I. H. Mullins, C. D., Korelitz, J. J. (2010). Impact of the 2004 Food and Drug Administration pediatric suicidality warning on antidepressant and psychotherapy treatment for new-onset depression. *Medical Care, 48*, 947-954.

*Wagner, K. D., Ambrosini, P., Rynn, M., Wohlberg, C., Yang, R., Greenbaum, M. S., . . . Deas, D. (2003). Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: Two randomized controlled trials. *Journal of the American Medical Association, 290*, 1033-1041.

*Wagner, K. D., Robb, A. S., Findling, R. L., Jin, J., Gutierrez, M. M., & Heydorn, W. E. (2004). A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *American Journal of Psychiatry, 161,* 1079-1083.

Weinberg, W. A., & Emslie, G. J. (1988). Weinberg screening affective scale. *Journal of Child Neurology, 3*, 294-296.

Whittington, C. J., Kendall, T., Fonagy, P., Cottrell, D., Cotgrove, A., & Boddington, E. (2004). Selective serotonin reuptake inhibitors in childhood depression: Systematic review of published versus unpublished data. *Lancet, 363,* 1341-1345.

Zito, J. M., Safer, D. J., dosReis, S., Gardner, J. F., Soeken, K., Boles, M., & Lynch, F. (2002). Rising prevalence of antidepressants among U.S. youths. *Pediatrics, 109,* 721-727.

*References marked with an asterisk indicate studies included in the meta-analysis.