Insomnia Moderates Outcome of Serotonin-Selective Reuptake Inhibitor Treatment in Depressed Youth

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Abstract

Objective: Insomnia is evident in the majority of youth with depression, and is associated with poorer outcomes. There are limited data on the impact of insomnia in response to acute treatment, which is particularly relevant with serotonin-selective reuptake inhibitors, given their tendency to worsen sleep architecture.

Methods: Three hundred nine children and adolescents (ages 7–18 years) were randomized to fluoxetine ($n = 157$) or placebo ($n = 152$) for 8–9 weeks (Emslie et al. 1997, 2002). Substantial insomnia at baseline was defined as a child's depression rating scale-revised [CDRS-R] sleep item ≥ 4 . Outcome measures were CDRS-R, response, and remission.

Results: Insomnia was reported in 172/309 (55.7%) youth, and was associated with higher depression severity and greater fatigue, suicidal ideation, physical complaints, and decreased concentration. While response rates were similar in those with or without insomnia overall (51.7% vs. 55.7%), there is a significant difference by age group. Among adolescents, those with insomnia were less likely to respond to fluoxetine (39.2%; 20/51) than those without (65.9%; 27/41; $p = 0.013$), while in children on fluoxetine, those with insomnia were more likely to respond to fluoxetine (69.4%; 25/36) than those without insomnia (41.4%; 12/29; $p = 0.027$). Insomnia did not impact the response to placebo in either age group. Within adolescents, the overall least squares means for CDRS-R total score (across the 8 weeks of treatment) were significantly different between those who had insomnia versus those who did not within the fluoxetine group (43.65 [SE = 1.31] vs. 36.58 [SE = 1.45], $F = 12.69$, $df = 1, 169$, $p = 0.0005$; $d = 0.82$), but not within the placebo group (44.91 [SE = 1.34] vs. 43.75 [SE = 1.68], $F = 0.29$, $df = 1, 179$, $p = 0.591$; $d = 0.15$).

Conclusions: While adolescents reporting substantial insomnia were less likely to respond to antidepressant treatment than those without insomnia, children were more responsive to fluoxetine when they had insomnia. Additional intervention targeting sleep disturbance may be warranted in adolescents.

Introduction

PREVALENCE RATES of major depressive disorder (MDD) range between 5 and 6% in adolescents (Costello et al. 2006), with a lifetime prevalence rate of $\sim 20\%$ by late adolescence (Lewinsohn et al. 1994, 1998; Birmaher et al. 2007). Depression in youth is associated with adverse outcomes, including substance abuse, functional impairment, suicidal behavior, and adult depression (Gould et al. 1998; Lewinsohn et al. 1998; Measelle et al. 2006a; Measelle et al. 2006b; Birmaher et al. 2007). While we have made progress in developing effective acute treatments for adolescent depression (Birmaher et al. 2007), remission rates remain low, with less than 40% achieving remission after 12 weeks of intensive treatment with the combination of antidepressant medication and CBT (Kennard et al. 2009).

Faster rate of response in the acute phase of treatment is associated with more complete improvement, with those responding to treatment (defined as a 50% reduction of symptoms) within the first

4 weeks being more likely to achieve remission after 12 weeks of treatment (Tao et al. 2009). The rate of response was also shown to be critical in adolescents in the treatment of serotonin-selective reuptake inhibitor (SSRI)-resistant depression in adolescents study. Individuals who respond early (first 6 weeks of treatment) are more likely to achieve full remission (Emslie et al. 2010; Vitiello et al. 2011).

Even among responders, residual symptoms are common. In the treatment for adolescents with depression study (TADS), 50% responders continued to have residual symptoms, with sleep disturbance, mood, and fatigue being most common (Kennard et al. 2006). Similarly, in our 12 week open trial of fluoxetine, residual symptoms were common even among remitters, with poor school performance, sleep disturbance, and mood being the most common residual symptoms (Tao et al. 2010). Teens with more symptoms remaining at the end of 12 weeks of treatment are less likely to be remitted at 18 and 36 weeks (Kennard et al. 2009), and are more likely to relapse (Emslie et al. 2008). Thus, identifying factors that

are associated with slower response will allow us to potentially target those specific areas to speed response and ultimately lead to higher remission rates.

Among adolescents with depression, ~75% report insomnia (Ivanenko et al. 2004). Concurrent insomnia and depression compounds illness severity and psychosocial difficulties (Sunderajan et al. 2010; O'Brien et al. 2011). Patients with insomnia are also at increased risk for suicidal behavior (Fawcett et al. 1990; Agargun et al. 1997), and this is true for adolescents, as well (Goldstein et al. 2008). Studies in adults have also demonstrated that insomnia reduces treatment response (Buysse et al. 1997; Thase et al. 1997) and increases risk of relapse or recurrence (Fawcett et al. 1990; Ohayon and Roth 2003). In our previous trial examining sleep polysomnography (PSG) in 113 youth with depression, subjects who relapsed by 12 months were more likely to have delayed sleep onset and decreased sleep efficiency (Emslie et al. 2001). On a subset of these patients, those with more impaired temporal coherence on sleep electroencephalography rhythms were also less likely to remit during the 12 month follow-up period. Of those who did remit, subjects with more impaired temporal coherence had faster rates of recurrence of depression (Armitage et al. 2002). Thus, patients with depression and disturbance in circadian rhythm are a more impaired subgroup and are more difficult to treat.

We report here on data from two double-blind, 8–9 week, placebo-controlled trials of fluoxetine in youth with MDD (Emslie et al. 1997, 2002) that were combined to examine the role of insomnia on treatment outcome.

Method

Data from two previously conducted trials of the efficacy and safety of fluoxetine in children and adolescents (Emslie et al. 1997, 2002) were combined to evaluate the impact of baseline insomnia on treatment outcome. The two studies were similar in design and inclusion/exclusion criteria. One study was a single-site study funded by the National Institute of Mental Health (NIMH); the other study was a multi-site study (15 sites) funded by Eli Lilly. Each study, including informed consent/assent, was approved by the investigational review board (IRB) for each site, and the consents were signed by participants' parents or guardians before study procedures being conducted. Participants may have also provided consent or assent depending on the requirements of the IRB.

Participants

Both studies combined included a total of 309 children and adolescents with moderate to severe MDD as defined by *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition Revised (DSM-III-R) (American Psychiatric Association 1987) or *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) criteria. Age, gender, race, and depression severity were similar across the two studies. For inclusion in these analyses, participants should have attended at least one post-randomization visit. Inclusion and exclusion criteria have been previously reported (Emslie et al. 1997, 2002). In general, participants were children and adolescents with a primary diagnosis of non-psychotic (MDD; single or recurrent) as defined by DSM-III-R or IV criteria, and with at least moderate severity (based on a Children's Depression Rating Scale-Revised [CDRS-R] total score ≥ 40 and a Clinical Global Impression-Severity [CGI-S] ≥ 4). Youth were of good general medical health, and did not have a history of bipolar disorder, psychotic disorder, anorexia/bulimia, or substance abuse or dependence. Other psy-

chiatric disorders were allowed, although depression was required to be the primary diagnosis. No other treatments for psychiatric conditions were allowed, including stimulants for ADHD, hypnotics for insomnia, or psychosocial treatments for any disorder.

Procedures

All participants underwent a 2-week, three-visit evaluation phase, which included a semi-structured diagnostic interview administered to all enrolled participants and their parents at each interview, to establish the diagnosis of MDD. The interviews were conducted by three different interviewers, at least one of whom was a psychiatrist. After three evaluation visits, participants entered a 1-week single-blind placebo run-in period. Responders to placebo were withdrawn from the study, and non-responders were randomized to fluoxetine or placebo for 8 (Emslie et al. 1997) or 9 weeks (Emslie et al. 2002) of treatment.

After randomization, visits in the single-site trial were weekly for 8 weeks; visits for the multi-site trial were at weeks 1, 2, 3, 5, 7, and 9. Dosing for the single-site study was 20 mg for the duration of the trial; dosing for the multi-site trial was 10 mg for 1 week, and then increased to 20 mg for the remainder of the study. For the purpose of this study (post hoc analyses), weeks of treatment are based on the number of weeks on 20 mg of fluoxetine. Thus, week 8 refers to participants having been on 20 mg for 8 weeks. (NOTE: participants in the multi-site trial had one week of 10 mg before increasing to 20 mg; consequently, those participants will have actually had 9 weeks of total medication exposure). Additional information about participants, study design, and outcomes has been previously reported (Emslie et al. 1997, 2002).

Measures

The primary outcomes for these *post hoc* analyses were response and remission status and depression severity. The measure of insomnia status at baseline was a moderator variable. Depression symptoms and severity were assessed using the CDRS-R (Poznanski and Mokros, 1996) and the scale CGI-S (Guy 1976), which were rated by the treating clinician at each visit. The CGI-Improvement scale (CGI-I) was assessed at each visit except for the baseline visit.

Response status. Response was operationally defined *a priori* as CGI-I of 1 or 2 (very much or much improved) at week 8 (or exit for patients who discontinued earlier). Patients with a CGI-I > 2 were considered non-responders. Thus, for this study, response status was a binomial outcome variable operationally defined as "response" or "non-response" to treatment.

Remission status. Remission was operationally defined *a priori* as a CDRS-R total score of ≤ 28 and CGI-I of 1 or 2 either at week 8 or at acute exit for patients who discontinued earlier. Patients with a CDRS-R total score of > 28 and/or CGI-I > 2 were considered non-remitters. Thus, for this study, remission status was a binomial outcome variable operationally defined as "remission" or "non-remission" of depression severity.

Baseline insomnia status. Baseline insomnia status was a moderator variable measured by the sleep item on the CDRS-R (a clinician-rated measure), with a score of ≥ 4 (referring to moderate or greater difficulty with insomnia nearly every night) at baseline as evidence of substantial baseline insomnia. Patients with a CDRS-R sleep item score of < 4 at baseline were considered as having only

occasional or no baseline insomnia. Thus, for this study, baseline insomnia status was a binomial moderator variable operationally defined as “insomnia” or “no insomnia.”

Covariates. Gender, age, and baseline CDRS-R total score (minus sleep item) were included as covariates in the models to evaluate the moderator effect of insomnia status on treatment outcomes of depression severity. We examined whether a “study effect,” as a result of the pooling of data from two previously conducted (albeit similar) trials, influenced the interpretation of the moderator effect of insomnia status on treatment outcomes of depression severity. Controlling for study effect led to similar direction and approximate magnitude of the moderator effects of insomnia status as those without controlling for study effect, and, thus, was eliminated from the covariate variables used in the analyses of the current study for the sake of parsimony and model fit. To further evaluate the role of a study effect on the interpretation of the moderator effect of insomnia status, we examined (in separate models) the study $\times$ age interaction and study $\times$ treatment interaction effects, and neither tests of the interaction effect was statistically significant in our models. Thus, both sets of additional analyses here seem to suggest that a “study effect” does not influence the interpretation of the moderator effect of insomnia status on treatment outcomes in the overall sample and by age group.

Statistical analysis

Demographic and clinical characteristics. Demographic and baseline clinical characteristics for the total sample of patients and for those with insomnia and no insomnia were described using the sample mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. To address whether there were baseline differences between the insomnia and non-insomnia groups, we used the two-independent sample *t*-test with the Satterthwaite method for unequal variances (for continuous outcomes) and the likelihood-ratio chi-square test or, when appropriate, Fisher’s Exact test (for categorical variables). The Pearson point-biserial correlation coefficient (r_{pb}) was also used to examine the relationship between baseline insomnia status (insomnia vs. no insomnia) and each of the individual baseline CDRS-R items (except for the sleep item). We also used a one-sample binomial test of a proportion for the observed proportion (rate) of response and remission at outcome (week 8) by insomnia status (insomnia vs. no insomnia) within each treatment and age group.

Multiple logistic regression. Multiple logistic regression was used to estimate the odds of response and, in a separate model, the odds of remission, while controlling for gender and baseline CDRS-R total score (minus sleep item), with the main effects and the two- and three-way interaction effects (incorporating treatment group, insomnia status, and age group) included in the model. For the insomnia status variable that interacts with the classification variables of treatment and age, the odds ratios (ORs; for insomnia status) were estimated at each combined level of the interacting covariate of treatment group and age group. The 95% Wald confidence intervals (CIs) were calculated for the adjusted ORs and the Wald Chi-square statistic was used to test for a significant association between each effect and response and remission status.

Linear mixed model analysis of repeated measures. A linear mixed model analysis of repeated measures was used to assess the moderator effect of baseline sleep (insomnia) status on

depression severity (continuously measured CDRS-R total score) of SSRI treatment (fluoxetine vs. placebo) across the 8 weeks of treatment. Restricted maximum likelihood estimation and Type 3 tests of fixed effects were used, with the Kenward–Roger correction (Kenward and Roger 1997) applied to the spatial-power covariance structure for unequally spaced repeated measures. Gender, age, and baseline CDRS-R total score (minus sleep item) were included as covariates in the mixed model analysis for the total sample. The mixed model analysis—adjusting for the covariates in the model—evaluated the main effects and the two- and three-way interaction effects (incorporating treatment group, baseline insomnia status, and time). The intercept was included as a random effect. The Treatment Group $\times$ Insomnia Status interaction was interpreted to ascertain the omnibus (overall) moderator effect of insomnia status on treatment outcome. Simple Treatment Group effects $\times$ Insomnia Status interaction (and least squares means) in each time period (week) were also assessed. Cohen’s *d* was calculated and interpreted as the effect size estimator for the between-subjects insomnia status effect within each treatment group.

To examine the moderator effect of insomnia status on depression severity (CDRS-R total score) by age group (children, adolescents), over the 8 weeks of treatment, the linear mixed model analysis of repeated measures similar to that just described was also carried out separately for children (≤ 11 years old) and adolescents (≥ 12 years old). For this analysis, however, gender and baseline CDRS-R total score (minus sleep item) were included as covariates in the mixed model.

All analyses were intent-to-treat (ITT); however, since subjects who did not return for at least 1 post-randomization visit were excluded, this is not a “pure” ITT analysis. All outcomes are *post hoc*.

We conducted all the statistical analyses using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC). The level of significance for all tests was set at $\alpha=0.05$ (two-tailed) and, due to the exploratory nature of these analyses, *p*-values were not adjusted for multiple testing.

Results

Demographic and baseline clinical characteristics

Insomnia was reported in 172/309 (55.7%) youth, with similar proportions in both treatment groups. There were no significant demographic differences between those with and without insomnia (Table 1), and most clinical characteristics were similar between the two groups. However, youth with insomnia had more severe depression, as evidenced by both the CGI-S and CDRS-R total scores. Even when the sleep item was removed from the CDRS-R, youth with insomnia continued to have a significantly higher total score. Increased depression severity was evident in both children (≤ 11 years) and adolescents (≥ 12 years) with insomnia. Children with insomnia also had shorter duration of the current episode of depression than those with no insomnia (27.1 ± 25.6 weeks vs. 56.8 ± 83.0 weeks; $p=0.005$), and they tended toward having higher rates of behavior disorders (47.1% vs. 29.7%; $p=0.051$) and anxiety disorders (41.4% vs. 25.0%; $p=0.067$). Other demographic and clinical characteristics within the child and adolescent subgroups were similar between those with and without insomnia.

The point-biserial correlations revealed that the presence of baseline insomnia was also associated with higher scores on several other baseline depressive items including fatigue and depressed mood (r_{pb} of 0.275; $p<0.0001$), suicidal ideation (r_{pb} of 0.172; $p=0.003$), schoolwork (r_{pb} of 0.168; $p=0.003$), and physical

TABLE 1. DEMOGRAPHICS AND CLINICAL CHARACTERISTICS (ALL PATIENTS): INSOMNIA VERSUS NO INSOMNIA

	ALL PATIENTS		
	Insomnia n = 172	No Insomnia n = 137	p-value
Age (Years)	12.7 ± 2.7	12.4 ± 2.4	0.31
Age Group			
11 and younger	40.7% (70)	46.7% (64)	0.29
12 and older	59.3% (102)	53.3% (73)	
Gender			
Female	50.0% (86)	44.5% (61)	0.34
Male	50.0% (86)	55.5% (76)	
Ethnicity/Race			
Caucasian	79.1% (136)	83.2% (114)	0.33
African American	8.1% (14)	5.8% (8)	
Hispanic	9.3% (16)	5.1% (7)	
Other	3.5% (6)	5.8% (8)	
# of Previous Episodes			
0	65.7% (113)	73.0% (100)	0.14
1	22.7% (39)	13.9% (19)	
2+	11.6% (20)	13.1% (18)	
Duration of Current Episode (wks)	40.2 ± 48.5	55.4 ± 88.2	0.07
Length of Illness (months)	18.4 ± 18.6	22.5 ± 26.7	0.13
# Comorbid Diagnoses			
0	36.6% (63)	42.3% (58)	0.49
1	27.9% (48)	23.4% (32)	
2	17.4% (30)	20.4% (28)	
3+	18.1% (31)	13.9% (19)	
Comorbid Dysthymia	24.4% (42)	24.8% (34)	0.93
Comorbid Anxiety Disorder	33.1% (57)	25.6% (35)	0.15
Comorbid Behavior Disorder	33.1% (57)	29.2% (40)	0.46
Baseline CGI-S	4.8 ± 0.70	4.3 ± 0.59	<0.001
Baseline CDRS-R Total	60.3 ± 10.3	52.3 ± 9.6	<0.001
Baseline CDRS-R Minus Sleep Item	55.7 ± 10.3	50.3 ± 9.4	<0.001
Exit CGI Severity	3.4 ± 1.4	3.1 ± 1.2	0.052
Exit CDRS-R Total	41.4 ± 15.9	36.4 ± 12.6	0.003
Exit CDRS-R Minus Sleep Item	38.7 ± 15.0	34.6 ± 12.3	0.012

CDRS-R, Children's Depression Rating Scale-Revised; CSI=S, Clinical Global Impressions-Severity.

complaints (r_{pb} of 0.172; $p=0.002$). Other symptoms were not significantly different after Bonferroni correction.

Treatment outcomes

Response and remission. Table 2. shows the impact of marked insomnia on response/remission to fluoxetine and placebo. Overall, observed response/remission rates to fluoxetine were not significantly different for the full sample between those with and without insomnia (51.7% vs. 55.7%); however, children with insomnia had significantly higher observed rates of response to fluoxetine than those without insomnia (69.4% vs. 41.4%), while adolescents with insomnia had significantly lower observed rates of response (39.2% vs. 65.9%) and remission (19.6% vs. 48.8%) to fluoxetine than those without insomnia. Observed response/remission rates to placebo were not significantly impacted by the presence or absence of insomnia in either age group.

Controlling for gender and baseline CDRS-R total score (minus the sleep item), a multiple logistic regression was used to estimate

TABLE 2. RESPONSE AND REMISSION TO TREATMENT BY PRESENCE OR ABSENCE OF INSOMNIA

Treatment	Total	Insomnia	No insomnia
Fluoxetine			
Response			
Total (n = 157)	84/157 (53.5%)	45/87 (51.7%)	39/70 (55.7%)
Children (n = 65)	37/65 (56.9%)	25/36 (69.4%)	12/29 (41.4%)
Adolescents (n = 92)	47/92 (51.1%)	20/51 (39.2%)	27/41 (65.9%)
Remission			
Total (n = 157)	57/157 (36.3%)	26/87 (29.9%)	31/70 (44.3%)
Children (n = 65)	27/65 (41.5%)	16/36 (44.4%)	11/29 (37.9%)
Adolescents (n = 92)	30/92 (32.6%)	10/51 (19.6%)	20/41 (48.8%)
Placebo			
Response			
Total (n = 152)	55/152 (36.2%)	34/85 (40.0%)	21/67 (31.3%)
Children (n = 69)	23/69 (33.3%)	14/34 (41.2%)	9/35 (25.7%)
Adolescents (n = 83)	32/83 (38.6%)	20/51 (39.2%)	12/32 (37.5%)
Remission			
Total (n = 152)	29/152 (19.1%)	16/85 (18.8%)	13/67 (19.4%)
Children (n = 69)	11/69 (15.9%)	5/34 (14.7%)	6/35 (17.1%)
Adolescents (n = 83)	18/83 (21.7%)	11/51 (21.6%)	7/32 (21.9%)

the odds of response/remission. There was a significant main effect of treatment (fluoxetine vs. placebo; $\chi^2=7.36$, $df=1$, $p=0.007$), a significant Treatment $\times$ Insomnia Status interaction effect ($\chi^2=4.27$, $df=1$, $p=0.039$), and a significant 3-way Treatment $\times$ Insomnia Status $\times$ Age Group interaction effect ($\chi^2=3.94$, $df=1$, $p=0.047$) (Table 3). When we examined the pattern of adjusted ORs, to interpret a moderator effect of sleep, we found that the effect of insomnia status differed by age group. For children who took fluoxetine, the predicted odds of response for those who had insomnia were 3.552 times the odds for those who had no insomnia (OR=3.552, 95% CI=1.258 to 10.028; $p<0.05$; Table 4). For adolescents who took fluoxetine, however, the predicted odds of response for those who had insomnia were 0.345 times the odds for those who had no insomnia (OR=0.345, 95% CI=0.144 to 0.824; $p<0.05$; Table 4). In other words, among adolescents who took fluoxetine, the odds of response for those who had insomnia were 65.5% lower than the odds for those who had no insomnia. In addition, for adolescents who took fluoxetine, the predicted odds of remission for those who had insomnia were 0.276 times the odds for those who had no insomnia (OR=0.276, 95% CI=0.104 to 0.728; $p<0.05$; Table 4). That is, among adolescents who took fluoxetine, the odds of remission for those who had insomnia were 72.4% lower than the odds for those who had no insomnia.

Continuous CDRS-R across 8 weeks of treatment. The moderator effect of baseline insomnia was further examined utilizing the CDRS-R total score across the 8 weeks of treatment. Controlling for baseline CDRS-R total score (minus sleep item), age, and gender, for the total sample, we found significant main effects of treatment (fluoxetine vs. placebo; $F=23.85$, $df=1$, 300,

TABLE 3. MAIN EFFECTS AND INTERACTION EFFECTS ASSOCIATED WITH RESPONSE AND REMISSION STATUS FROM THE MULTIPLE LOGISTIC REGRESSION MODEL

Variables	Total sample		Total sample	
	Response		Remission	
	Statistic	P value	Statistic	P value
Baseline Characteristics				
CDRS-R Total Score minus sleep item	$\chi^2(df=1)=1.18$	0.2759	$\chi^2(df=1)=9.97$	0.0016
Age Group (Children vs. Adolescents)	$\chi^2(df=1)=1.08$	0.2972	$\chi^2(df=1)=0.21$	0.6405
Gender	$\chi^2(df=1)=1.17$	0.2782	$\chi^2(df=1)=11.24$	0.0008
Insomnia Status (Insomnia vs. No Insomnia)	$\chi^2(df=1)=0.11$	0.7444	$\chi^2(df=1)=0.21$	0.6453
Trial Interventions				
Treatment (Fluoxetine vs. Placebo)	$\chi^2(df=1)=6.10$	0.0135	$\chi^2(df=1)=7.36$	0.0066
Interaction Effects				
Treatment $\times$ Insomnia Status	$\chi^2(df=1)=3.61$	0.0574	$\chi^2(df=1)=4.27$	0.0387
Treatment $\times$ Age Group	$\chi^2(df=1)=0.51$	0.4751	$\chi^2(df=1)=0.29$	0.5878
Insomnia Status $\times$ Age Group	$\chi^2(df=1)=0.70$	0.4024	$\chi^2(df=1)=0.16$	0.6843
Insomnia Status $\times$ Treatment $\times$ Age Group	$\chi^2(df=1)=3.15$	0.0760	$\chi^2(df=1)=3.94$	0.0471

Note: χ^2 =Wald Chi Square Statistic for Type 3 analysis of effects.
CDRS-R, Children's Depression Rating Scale-Revised.

$p < 0.0001$), insomnia status ($F = 4.28$, $df = 1$, 301 , $p = 0.039$), and time (overall mean decrease in CDRS-R total scores across the 8-week trial; $F = 36.53$, $df = 4$, 779 , $p < 0.0001$). Within the fluoxetine group, we found that the overall least squares means for CDRS-R total score (across the 8 weeks of treatment) were significantly different between those who had insomnia and those who did not ($39.76[SE = 0.99]$ vs. $35.78[SE = 1.09]$, $F = 7.12$, $df = 1$, 294 , $p = 0.008$; $d = 0.48$); this was not evident in the placebo group ($43.27[SE = 1.03]$ vs. $42.69[SE = 1.16]$, $F = 0.14$, $df = 1$, 307 , $p = 0.709$; $d = 0.08$).

Among adolescents, we found significant main effects of treatment ($p = 0.004$), insomnia status ($p = 0.006$), and time ($p < 0.0001$), as well as a significant Treatment $\times$ Insomnia Status interaction effect ($F = 4.20$, $df = 1$, 174 , $p = 0.042$). Pattern of adjusted least squares means for CDRS-R total score for the Treatment $\times$ Insomnia Status interaction for adolescents revealed that the overall least squares means for CDRS-R total score (across the 8

weeks of treatment) were significantly different between those who had insomnia and those who did not within the fluoxetine group ($43.65[SE = 1.31]$ vs. $36.58[SE = 1.45]$, $F = 12.69$, $df = 1$, 169 , $p = 0.0005$; $d = 0.82$), but not within the placebo group ($44.91[SE = 1.34]$ vs. $43.75[SE = 1.68]$, $F = 0.29$, $df = 1$, 179 , $p = 0.591$; $d = 0.15$).

Among children, we found significant main effects of treatment ($p < 0.0001$) and time ($p < 0.0001$), but no significant main effect of insomnia status ($p = 0.907$) or interaction effect of Treatment $\times$ Insomnia Status ($F = 0.17$, $df = 1$, 122 , $p = 0.677$). The pattern of adjusted least squares means for CDRS-R total score for the Treatment $\times$ Insomnia Status interaction for children also showed that the overall least squares means for CDRS-R total score (across the 8 weeks of treatment) were not significantly different between those who had insomnia and those who did not within the fluoxetine group ($34.07[SE = 1.45]$ vs. $34.52[SE = 1.59]$, $F = 0.04$, $df = 1$, 120 , $p = 0.836$; $d = 0.05$) or the placebo group ($41.31[SE = 1.53]$ vs. $40.49[SE = 1.54]$, $F = 0.14$, $df = 1$, 125 , $p = 0.710$; $d = 0.11$). The main effects and interaction effects for the total sample and by age group from the mixed model analysis are reported in Table 5.

Discussion

In this sample derived from two randomized controlled trials, 57% of children and adolescents had insomnia (difficulty initiating or maintaining sleep) of moderate or greater intensity nearly every night, as assessed from clinical interviews. Interestingly, the insomnia was equally evident in children and adolescents and males and females. Insomnia was associated with overall greater severity of illness. As expected, insomnia was also associated with daytime fatigue, trouble concentrating (evidenced by poor school performance), and increased physical complaints. As previously noted, insomnia was also associated with higher scores on suicidal ideation. In fact, of those who had scored > 3 on the suicidal ideation item on the CDRS-R ($n = 32$), 75% had insomnia.

Insomnia, independent of overall severity, had a significant negative impact on response and remission in adolescents treated with fluoxetine, but not to placebo. In fact, response in adolescents with insomnia treated with fluoxetine was essentially the same as the placebo response rate (around 39%), whereas in adolescents without

TABLE 4. ODDS RATIOS WITH 95% CONFIDENCE INTERVALS FROM THE MULTIPLE LOGISTIC REGRESSION MODEL FOR INSOMNIA STATUS AT EACH COMBINED LEVEL OF TREATMENT AND AGE GROUP ON RESPONSE AND REMISSION STATUS

Insomnia status $\times$ Treatment $\times$ Age group	Odds ratio (95% CI for odds ratio) Odds of response	Odds ratio (95% CI for odds ratio) Odds of remission
Insomnia vs. No Insomnia @Fluoxetine and Adolescents	0.345 ^a (0.144 to 0.824)	0.276 ^a (0.104 to 0.728)
Insomnia vs. No Insomnia @Fluoxetine and Children	3.552 ^a (1.258 to 10.028)	1.892 (0.657 to 5.447)
Insomnia vs. No Insomnia @Placebo and Adolescents	1.166 (0.462 to 2.943)	1.302 (0.423 to 4.012)
Insomnia vs. No Insomnia @Placebo and Children	2.097 (0.749 to 5.873)	0.909 (0.240 to 3.447)

^a $p < 0.05$

CI=confidence interval.

TABLE 5. MAIN EFFECTS AND INTERACTION EFFECTS ASSOCIATED WITH CDRS-R TOTAL SCORE ACROSS WEEKS 1 TO 8 FOR THE TOTAL SAMPLE AND BY AGE GROUP FROM THE LINEAR MIXED MODEL ANALYSIS OF REPEATED MEASURES

Variables	Total sample		Adolescents		Children	
	CDRS-R total score		CDRS-R total score		CDRS-R total score	
	Statistic	P value	Statistic	P value	Statistic	P value
Baseline Characteristics						
CDRS-R Total Score minus sleep item	F(df = 1, 299) = 88.32	<0.0001	F(df = 1, 170) = 69.89	<0.0001	F(df = 1, 122) = 15.05	0.0002
Age	F(df = 1, 290) = 0.82	0.3671				
Gender	F(df = 1, 291) = 0.20	0.6524	F(df = 1, 167) = 0.06	0.8035	F(df = 1, 119) = 1.23	0.2705
Insomnia Status (Insom vs. No Insom)	F(df = 1, 301) = 4.28	0.0393	F(df = 1, 175) = 7.59	0.0065	F(df = 1, 123) = 0.01	0.9073
Trial Interventions						
Treatment (Fluoxetine vs. Placebo)	F(df = 1, 300) = 23.85	<0.0001	F(df = 1, 175) = 8.50	0.0040	F(df = 1, 122) = 19.20	<.0001
Time (wk)	F(df = 4, 779) = 36.53	<0.0001	F(df = 4, 448) = 19.42	<0.0001	F(df = 4, 325) = 18.94	<.0001
Interaction Effects						
Treatment × Insomnia Status	F(df = 1, 300) = 2.56	0.1105	F(df = 1, 174) = 4.20	0.0420	F(df = 1, 122) = 0.17	0.6770
Treatment × Time (wk)	F(df = 4, 779) = 0.04	0.9964	F(df = 4, 448) = 1.03	0.3915	F(df = 4, 325) = 1.21	0.3073
Insomnia Status × Time (wk)	F(df = 4, 779) = 0.94	0.4413	F(df = 4, 448) = 0.32	0.8614	F(df = 4, 325) = 1.19	0.3150
Insomnia Status × Treatment × Time (wk)	F(df = 4, 779) = 0.21	0.9325	F(df = 4, 448) = 0.16	0.9584	F(df = 4, 325) = 0.54	0.7068

CDRS-R = Children's Depression Rating Scale-Revised.

insomnia, about two-thirds responded to fluoxetine. Interestingly, in children, the impact of insomnia was reversed, with 69% of children with insomnia responding to fluoxetine compared with 41% with no insomnia. This suggests that "marked" insomnia in depressed children is an indicator of medication responsive depression.

It is not clear from these analyses why there is a difference between children and adolescents. Insomnia in children was associated with shorter duration of illness and some comorbid disorders. Whether this is a factor in improved response in children is unclear. Polysomnographic (PSG) studies of sleep architecture in depressed and healthy children have demonstrated fewer differences than adolescent studies comparing PSG in depressed and healthy populations. Only one study of depressed child inpatients showed REM latency and sleep latency differences compared with healthy controls (Emslie et al. 1990). Developmentally, there are substantial changes in sleep architecture, including decreases in slow wave sleep across the age group. Insomnia (difficulty initiating and maintaining sleep) as an indicator of circadian rhythm disturbance is likely to be more evident in adolescents. A previous study utilizing actigraphy in depressed children and adolescents found decreased circadian amplitude in depressed adolescents compared with healthy controls, but not in children (Armitage et al. 2004). Therefore, these developmental differences in sleep architecture could contribute to differences in response to medication in depressed children and adolescents with insomnia.

Another consideration is the dosing of medication. These studies were unique in that the effect size of antidepressant response compared with placebo was greater in the children compared with the adolescents (Mayes et al. 2007). Both studies used a fixed dose of 20 mg of fluoxetine, which may have contributed to the slightly lower response rate in adolescents. This compares with the TADS in adolescents only where the mean dose of fluoxetine was 30 mg (March et al. 2004).

A final issue that should be considered is the impact of fluoxetine on insomnia, independent of antidepressant response. Overall,

fluoxetine did not have a marked negative effect on sleep in either age group. Only a relatively small number of subjects (8.8%; 12/137) demonstrated a worsening of insomnia if not present at baseline, with similar rates in both fluoxetine (7.1%; 5/70) and placebo (10.4%; 7/67). All youth with a worsening of insomnia were also non-responders.

Similarly, insomnia improved across the duration of the study, and there was no difference between children and adolescents. In subjects with insomnia, independent of the treatment group (fluoxetine/placebo), fewer responders had residual insomnia at exit (19/79; 24.1%) compared with non-responders (65/93; 69.9%). Essentially, while fluoxetine had little negative impact on sleep, it did not have any positive effects independent of treatment response. This was equally true for children and adolescents.

Conclusions

In conclusion, marked insomnia in depressed children and adolescents identifies a subgroup of patients who are more severe, have associated daytime fatigue, school difficulties, and higher rates of suicidal behavior. The presence of insomnia moderates the outcome of antidepressant response negatively in adolescents and positively in children, independent of baseline severity.

Clinical Significance

The clinical implications involve recognizing that sleep-wake dysregulation is an important variable to be considered when treating children and adolescents with depression, and that while this study only examines one SSRI, it is likely that most SSRIs have a limited impact on insomnia. Insomnia improves with treatment of depression in the majority of patients, and given the higher response rate in children, it would appear that initial treatment with antidepressants would be appropriate. In adolescents, however, adjunctive treatment for insomnia could be considered, although there is currently no evidence-based treatment for insomnia in

depressed adolescents. While more sedating antidepressants (e.g., mirtazapine) are available, they have not demonstrated effectiveness for treatment of depression in adolescents. There are no studies in depressed adolescents of concomitant hypnotics, though studies in adults have demonstrated greater efficacy with SSRIs plus hypnotics compared with SSRI plus placebo (Fava et al. 2006; McCall et al. 2006; Pollack et al. 2008; Fava et al. 2009; Ancoli-Israel et al. 2010; Fava et al. 2011a; Fava et al. 2011b).

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