Adjunctive Sleep Medications and Depression Outcome in the Treatment of Serotonin-Selective Reuptake Inhibitor Resistant Depression in Adolescents Study

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Abstract

Objective: In the Treatment of Resistant Depression in Adolescents, study participants who received medication for sleep had a lower response rate. This report sought to clarify this finding.

Method: Depressed adolescents who had not responded to a previous adequate serotonin-selective reuptake inhibitor (SSRI) trial were randomly assigned to another SSRI, venlafaxine, another SSRI + cognitive behavior therapy (CBT), or venlafaxine + CBT. Augmentation with sleep medication was permitted as clinically indicated.

Results: Youth who received trazodone were six times less likely to respond than those with no sleep medication (adjusted odds ratio [OR]=0.16, 95% confidence interval [CI]: 0.05–0.50, $p=0.001$) and were three times more likely to experience self-harm (OR = 3.0, 95% CI: 1.1–7.9, $p=0.03$), even after adjusting for baseline differences associated with trazodone use. None (0/13) of those cotreated with trazodone and either paroxetine or fluoxetine responded. In contrast, those treated with other sleep medications had similar rates of response (60.0% vs. 50.4%, $\chi^2=0.85$, $p=0.36$) and of self-harm events (OR = 0.5, 95% CI: 0.1–2.6, $p=0.53$) as those who received no sleep medication.

Conclusions: These findings should be interpreted cautiously because these sleep agents were not assigned randomly, but at clinician discretion. Nevertheless, they suggest that the use of trazodone for the management of sleep difficulties in adolescent depression should be re-evaluated and that future research on the management of sleep disturbance in adolescent depression is needed. The very low response rate of participants cotreated with trazodone and either fluoxetine or paroxetine could be due to inhibition of CYP 2D6 by these antidepressants.

Introduction

AMONG ADOLESCENTS WITH major depression, at least 40% do not show an adequate clinical response to first-line intervention, and only one-third show complete symptomatic remission to acute treatment (Brent et al. 1997; Emslie et al. 1997; March

et al. 2004; Kennard et al. 2006; Rush et al. 2006). Further, the persistence of residual symptoms puts patients at higher risk of relapse (Brent et al. 2001; Emslie et al. 2010).

Sleep disturbance is the most common residual symptom in adolescent depression in responders who failed to remit in the acute phase treatment (Kennard et al. 2006; Vitiello et al. 2011). In a

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sleep polysomnography study of depressed adolescents, those with delayed sleep onset were more than twice as likely as those without delayed sleep onset to have a recurrence of their depression (Emslie et al. 2001).

Adding an adjunctive medication targeting the depressed adult patient's residual symptoms has been recommended during the acute phase of treatment (Thase 2009). Initial studies among adults suggest that depression outcomes may be improved by concomitant treatment of depression and insomnia (Nierenberg et al. 1994; Buysse et al. 1997; Fava et al. 2006; Krystal et al. 2007; Manber et al. 2008). The American Academy of Child and Adolescent Psychiatry's practice parameters for the treatment of depression suggest the use of trazodone, diphenhydramine, and other agents as adjunctive and transient treatments for insomnia (Birmaher et al. 2007). In fact, trazodone is the most commonly prescribed agent for sleep difficulties in adolescents with mood and anxiety disorders (Owens et al. 2010). Given the recommendations for concomitant treatment of depression and sleep difficulties, it was surprising that this practice in Treatment of Resistant Depression in Adolescents (TORDIA) was associated with a much poorer response to treatment (Brent et al. 2008).

In the TORDIA trial, 334 depressed adolescents who had not responded to initial serotonin-selective reuptake inhibitor (SSRI) treatment were randomized to one of four treatments: Switch to another SSRI, switch to venlafaxine XR, switch to another SSRI plus cognitive behavior therapy (CBT), or switch to venlafaxine plus CBT. After 12 weeks of treatment, a higher proportion of youth treated with CBT plus medication were responders compared with those treated with medication alone (54.8% vs. 40.5%), but there was no differential response among the different antidepressant medications. However, youth who received nonstudy but protocol-permitted sleep medications when deemed to be clinically necessary showed a significantly lower response rate than those who did not (32.7% vs. 50.7%). In our initial report, we did not examine the impact of the various classes of sleep medications on depression outcomes, nor other confounding factors that may have explained these results, such as baseline depression severity (Brent et al. 2008). Therefore, we now try to further explore this surprising finding by asking the following questions: (1) was this association found across all classes of sleep medication and treatments?; (2) were there baseline characteristics associated with use of sleep medications that were also associated with nonresponse?; and (3) after controlling for these baseline differences, was there still an effect of sleep medication on outcome?

Methods

Participants

All participants had clinically significant depression despite adequate, pretrial treatment with an SSRI for at least 4 weeks (defined as a dosage of the equivalent of 20 mg of fluoxetine) and a final 4 weeks at a dosage equivalent to 40 mg of fluoxetine, unless this dose could not be tolerated. Significant depression was defined as a total score ≥ 40 on the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski and Mokros 1996), a score ≥ 4 on Clinical Global Impressions-Severity Subscale (CGI-S) (Guy 1976), and meeting *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) criteria for major depression. Exclusion criteria were as follows: Completing ≥ 2 prior adequate SSRI trials; history of nonresponse to an adequate trial of venlafaxine; prior trial of CBT, with ≥ 7 sessions; on medications with psychoactive properties,

excluding some study-allowed medications at stable doses (≥ 6 weeks duration); diagnoses of bipolar I or II, psychosis, autism, eating disorders, or substance abuse or dependence; hypertension (diastolic blood pressure ≥ 90); and women who were pregnant, breast-feeding, or sexually active and not reliably using contraception.

The study was approved by the local Institutional Review Board of each of the six sites; all participants gave informed assent (and consent after they turned age 18), and parents gave informed consent in accordance with local IRB regulations.

Randomization and treatment

Participants were randomly assigned to one of four treatments following the unsuccessful initial SSRI treatment: Switching to a second SSRI; switching to venlafaxine; switching to a second SSRI combined with CBT; or switching to venlafaxine combined with CBT. Randomization was balanced both within and across sites on: Incoming treatment medication, comorbid anxiety, chronic depression (duration ≥ 24 months), and suicidal ideation (Beck Depression Inventory item 9 ≥ 2). The SSRIs used for this study were fluoxetine and paroxetine before the FDA Black Box warning on antidepressants; after this warning, citalopram was used instead of paroxetine.

The dosage schedule for SSRI intake was 10 mg/day for the first week and 20 mg/day for weeks 2–6, with an option to increase to 40 mg/day if there was insufficient clinical improvement (Clinical Global Impressions-Improvement Subscale [CGI-I] ≥ 3). The venlafaxine dosages for weeks 1–4 were 37.5, 75, 112.5, and 150 mg, respectively, with an option to increase to 225 mg at week 6. If intolerable adverse effects developed after a medication increase, the participant's dosage was lowered to either 20 mg of an SSRI or to 150 mg of venlafaxine. By 12 weeks, the mean doses of SSRI were 33.8 mg (95% confidence interval [CI], 32.0–35.6), and for venlafaxine were 205.4 mg (95% CI, 199.0–211.7).

The protocol called for 12 sessions (60–90 minutes each) of CBT during the first 12 weeks, 3 to 6 of which were to be family sessions. The mean and median number of CBT sessions attended in the first 12 weeks was 8.3 (standard deviation [SD] = 3.6) and 9.0 respectively.

Sleep medications

All participants received sleep hygiene education. Of the enrolled 334 youth, 58 (17.4%) received at least one sleep medication based on the pharmacotherapist's clinical judgment. Of these, 48 (82.8%) received one sleep medication, 8 (13.8%) received two medications, and 2 (3.4%) were prescribed three different medications. The most frequently prescribed sleep medication was trazodone ($n = 33$, 57%), followed by antihistamines ($n = 20$, 34.5%), and GABA-acting non-benzodiazepines ($n = 11$, 19%; zolpidem [$n = 10$] or eszopiclone [$n = 1$]). Participants were classified into three sleep medication groups: No sleep medication ($n = 276$), trazodone (alone [$n = 26$] or in combination with other sleep medications [$n = 7$]; total $n = 33$), and any other, nontrazodone sleep medications ($n = 25$). All youth receiving trazodone were combined into one group, as the number of youth taking other sleep medications in addition to trazodone was too small for separate analysis.

Outcome and measures

The primary outcome, "adequate clinical response" at week 12, was defined as a 50% reduction in CDRS-R score and a CGI-I score

of 2 or less corresponding to “much” or “very much” improved. The 17-item CDRS-R is a measure of depression symptom severity based on separate interviews of the child and parent, resulting in total scores ranging from 17 to 113, with a total score of 40 or greater indicating significant depression (Poznanski and Mokros 1996). The CGI-I is a measure of clinical improvement, as rated by the independent evaluator on a scale of 1 (very much improved) to 7 (very much worse) (Guy 1976). Both the CDRS and CGI-I were completed by an independent evaluator blind to treatment status.

History of physical and sexual abuse was assessed among other traumatic events in the post-traumatic stress disorder section of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (Kaufman et al. 1997). The adolescents were also assessed for (1) hopelessness using the Beck Hopelessness Scale (Beck and Steer 1988); (2) severity of suicidal ideation by the Suicide Ideation Questionnaire—Jr. (SIQ-Jr) (Reynolds 1988); (3) substance use related impairment by Drug Use Screening Instrument (Kirisici et al. 1995); (4) parent and adolescent-reported family conflict using the Conflict Behavior Questionnaire (Robin and Foster 1989); (5) anxiety by the Screen for Child Anxiety Related Disorders—Child Version (Birmaher et al. 1999); and (6) other comorbidities using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (KSADS-PL) (Kaufman et al. 1997).

Baseline sleep symptoms were assessed using a composite measure consisting of four sleep disorder items from the KSADS-PL diagnostic interview, which assessed non-restorative sleep and early, middle, and terminal insomnia (each item scored 1–3). These items were summed into a total score with possible values ranging from 4 (no sleep disorder) to 12 (severe sleep disorder). Cronbach's alpha for this scale was 0.5.

Safety assessment

Safety assessments were completed during all pharmacotherapy visits and included a review of possible drug adverse effects, screening for symptoms of mania, and evaluation of suicidal thoughts and behavior as well as nonsuicidal self-injury (Posner et al. 2007; Brent et al. 2009). After concerns about the safety of antidepressants were raised by the FDA midway through this trial, safety assessments were increased to weekly assessments, either in person or via telephone. Side effects were assessed using the Side Effects Form for Children and Adolescents (SEFCA) (Klein et al. 1994) weekly for the first 6 weeks, and then bi-weekly. Treatment-emergent adverse events were defined as new-onset or worsening of symptoms and were reviewed during weekly conference calls. Serious adverse events were those that resulted in significant disability, threat to life, or emergency care.

Statistical analysis

One-way analysis of variance and Pearson chi square tests were conducted to examine the characteristics of the patients with different sleep medications for continuous and dichotomous variables, respectively. For baseline variables significantly associated with sleep medication, *post-hoc* pair-wise comparisons among the three sleep-medication conditions were conducted and alpha was set at 0.017 (0.05/3). Multivariate logistic regression was conducted to examine the association between sleep medication and response to depression treatment (CBT or pharmacotherapy). The regression controlled for age, gender, race, site, pharmacotherapy, and receipt of CBT, and the baseline variables that were found to be significantly associated with the patients' study condition.

Mixed regression models were used to examine whether change in insomnia scores was associated with sleep medication. The model included a fixed medication effect, a fixed time effect, and an interaction term, which, respectively, estimated the group effect (intercept), the rate of change over time, and the specific rate for each group (no sleep medication being the reference group).

STATA was used to conduct mixed regression models, and the Statistical Package for Social Sciences (SPSS 14.0) was used to conduct the remaining statistical analysis. Unless otherwise indicated, alpha was set at $p=0.05$.

Results

Depression response by sleep medication group

The use of trazodone was associated with a much lower rate of depression response compared with those who were treated with no sleep medication (15.2% vs. 50.4%, $\chi^2=14.7$, $df=1$, $p<0.01$). When participants were classified by CBT assignment, trazodone was associated with lower rates of response among those assigned to combination therapy (11.8% vs. 59.0%, $\chi^2=13.6$, $df=1$, $p<0.01$), with a non-significant trend in the same direction for those assigned to monotherapy (18.8% vs. 41.6%, $\chi^2=3.1$, $df=1$, $p=0.08$). Trazodone use was associated with lower rates of response in those assigned to either an SSRI (11.1% vs. 51.5%, $\chi^2=10.4$, $df=1$, $p=0.001$), or venlafaxine (20.0% vs. 49.3%, $\chi^2=4.7$, $df=1$, $p=0.03$). Within the SSRI group, none of those cotreated with trazodone and either fluoxetine (0% vs. 56.1%, Fisher's exact test [FET], $p=0.001$) or paroxetine (0% vs. 41.9%, FET, $p=0.27$) responded, whereas 40% of those cotreated with citalopram responded (vs. 56% of those who received citalopram but no sleep medication, FET, $p=0.64$).

In contrast, those treated with other, nontrazodone sleep medication had rates of response at least comparable to those who did not receive any sleep medication (60.0% vs. 50.4%, $\chi^2=0.85$, $df=1$, $p=0.36$). This finding was true in those who received combination therapy (70.0% vs. 59.0%, FET, $p=0.74$), monotherapy (53.3% vs. 41.6%, $\chi^2=0.76$, $df=1$, $p=0.38$), an SSRI (50.0% vs. 51.5%, $\chi^2=0.01$, $df=1$, $p=0.91$), or venlafaxine (77.8% vs. 49.3%, FET, $p=0.17$).

Characteristics of sleep medication groups

The three sleep medication groups showed an overall difference for the baseline insomnia measure ($F_{2,321}=3.9$, $p=0.02$, Table 1), but *post-hoc* pair-wise contrasts escaped statistical significance.

Compared with those receiving no sleep medications, patients who received trazodone were 4.8 times (95% CI: 1.4–16.0; $p=0.01$) more likely to be female (trazodone can contribute to priapism—painful, chronic erections—and therefore should not typically be prescribed to males), and 5.2 times as likely to be from 2 of the 6 study sites (95% CI: 2.3–11.5; $p=0.01$). They also were also more likely than patients with no sleep medication to have had a history of nonsuicidal self-injury (NSSI; 75.8% vs. 32.6%, $\chi^2=23.4$, $df=1$, $p<0.001$), higher mean SIQ-Jr scores, (52.4 ± 22.8 vs. 40.9 ± 22.2 , $t=-2.8$, $df=301$, $p=0.006$), and were more likely to have had history of physical or sexual abuse (42.4% vs. 23.0%, $\chi^2=5.9$, $df=1$, $p=0.015$). There was no significant association between initial treatment assignment in TORDIA and use of any specific sleep medication ($\chi^2=1.03$, $df=2$, $p=0.60$). There was no significant association between the 12-week treatment completion rate and the type of sleep medication (no medication, 68.8%; trazodone, 66.7%; other sleep medications; 76.0%; $\chi^2=0.66$, $df=2$, $p=0.72$).

TABLE 1. COMPARISON OF THE THREE SLEEP-MEDICATION GROUPS ON BASELINE MEASURES AND CHARACTERISTICS*

	None (n=276) N (%)	Trazodone (n=33) N (%)	Other sleep Rx, (n=25) N (%)	Overall p
Response to treatment	139 (50.4) ^a	5 (15.2) ^b	15 (60.0) ^a	<0.001
Sex (% female)	187 (67.8) ^a	30 (90.9) ^b	16 (64.0) ^a	0.02
Race/ethnicity (% white)	227 (82.2)	29 (87.9)	21 (84.0)	0.78
First episode of depression	71 (26.2)	11 (33.3)	3 (13.6)	0.26
Anxiety (including PTSD)	93 (34.4)	17 (51.5)	9 (37.5)	0.16
PTSD	21 (7.6)	3 (9.1)	0 (0.0)	0.33
ADHD	44 (16.1)	2 (6.1)	6 (24.0)	0.15
ODD/CD	29 (10.6)	1 (3.0)	3 (12.5)	0.33
Dysthymia	80 (29.2)	12 (36.4)	6 (25.0)	0.61
History of physical abuse	33 (12.2)	7 (21.2)	3 (12.0)	0.34
History of sexual abuse	43 (16.0)	10 (30.3)	2 (8.3)	0.08
History of physical or sexual abuse	62 (23.0) ^a	14 (42.4) ^b	5 (20.0) ^{ab}	0.04
History of suicide attempts	56 (20.4) ^a	12 (36.4) ^{ab}	11 (44.0) ^b	0.006
History of NSSI	88 (32.6) ^a	25 (75.8) ^b	12 (48.0) ^{ab}	<0.01
Switched to SSRI	134 (48.6)	18 (54.5)	16 (64.0)	0.29
Assigned to CBT	139 (50.4)	17 (51.5)	10 (40.0)	0.60
Being from sites 1 or 4	94 (34.1) ^a	24 (72.7) ^b	8 (32.0) ^a	<0.001
	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>	
Age	15.9 ± 1.6	15.8 ± 1.4	15.7 ± 1.8	0.85
Insomnia score**	7.8 ± 2.0	8.6 ± 1.9	8.6 ± 1.9	0.02
CDRS	58.7 ± 10.5	60.1 ± 9.2	58.1 ± 11.4	0.74
CGI-S	4.5 ± 0.6	4.3 ± 0.6	4.6 ± 0.8	0.19
CGAS	50.7 ± 8.0	50.4 ± 5.3	49.9 ± 7.5	0.89
Beck Depression Inventory	19.9 ± 12.1 ^a	27.2 ± 10.8 ^b	18.2 ± 11.0 ^a	0.003
SCARED	29.0 ± 15.4	32.2 ± 15.9	32.6 ± 18.9	0.34
Beck Hopelessness Scale	10.4 ± 5.6	12 ± 5.9	10.3 ± 5.2	0.28
DUSI	10.3 ± 17.8	16.0 ± 24.5	11.7 ± 20.7	0.26
CBQ-A	8.7 ± 6.3	10.4 ± 6.0	9.0 ± 5.5	0.36
CBQ-B	9.7 ± 5.8	7.3 ± 5.5	10.7 ± 6.5	0.054
SIQ-Jr	40.9 ± 22.2 ^a	52.4 ± 22.8 ^b	36.0 ± 19.1 ^a	0.009

*For any variable that is significant in the three-way comparison, groups with different superscripts (a, b) are significantly different from one another.

**A composite measure consisting of four sleep disorder items from the KSADS-PL diagnostic interview, which assessed non-restorative sleep and early, middle, and terminal insomnia (each item scored 1–3). These items were summed into a total score with possible values ranging from 4 (no sleep disorder) to 12 (severe sleep disorder).

ADHD = attention-deficit/hyperactivity disorder; CBQ-A, Conflict Behavior Questionnaire-Adolescent (Adolescent Version); CBQ-P, Conflict Behavior Questionnaire-Parent (Adolescent Version); CBT = cognitive behavior therapy; CDRS-R = Children's Depression Rating Scale; CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impressions-Severity; DUSI = Drug Use Screening Instrument; MDD = Major Depressive Disorder; NSSI = Non-Suicidal Self Injury; ODD/CD, oppositional defiant disorder/conduct disorder; PTSD = Post-traumatic Stress Disorder; SCARED = The Screen for Child Anxiety Related Emotional Disorders; SIQ-Jr = Suicide Ideation Questionnaire-Jr; SSRI = serotonin-selective reuptake inhibitor.

Participants receiving sleep medications other than trazodone were more likely to have a history of suicide attempt compared with youth receiving no sleep medication (44.0% vs. 20.4%, $\chi^2=7.4$, $df=1$, $p=0.007$). When compared with those on trazodone, patients on other sleep medications were more likely to be male (36.0% vs. 9.1%, $\chi^2=6.3$, $df=1$, $p=0.01$).

Family conflict, as reported by the parent, was significantly associated with receipt of sleep medications ($F_{2,315}=2.9$, $p=0.05$); however, none of the pair-wise comparisons was statistically significant.

Effect of sleep medication on outcome after controlling for baseline differences

Because there were baseline differences associated with the use of trazodone that might have influenced outcome, we conducted a logistic regression analysis of depression outcomes by each of the sleep medication groups controlling for baseline insomnia, self-

reported depression, suicidal ideation, history of suicide attempt and NSSI, history of physical or sexual abuse, and family conflict, in addition to age and gender, site, and medication and CBT treatment assignment. Even after adjustment, those who used trazodone were six times less likely to have responded (adjusted odds ratio [OR]=0.16, 95% CI: 0.05–0.50, $p=0.001$). Baseline sleep symptoms were not significantly associated with response (OR=1.09, 95% CI: 0.95–1.26, $p=0.22$). Moreover, there was no significant interaction between use of either category of sleep medication and baseline insomnia score ($p=0.62$), assignment to CBT ($p=0.57$), or type of antidepressant ($p=0.31$). Even after excluding the seven participants who received other sleep medications in addition to trazodone, trazodone was still significantly associated with a lower rate of adequate response compared with the no sleep medication group (adjusted OR=0.07, 95% CI: 0.01–0.33, $p=0.001$).

On average, trazodone was used for 5.1 weeks (SD=4.4, median=3.0, range: 1–12 weeks). The duration of trazodone treatment was not significantly associated with lower depression

response rates ($p=0.55$). In addition, the maximum trazodone dose used was not associated with lower depression response rates ($p=0.20$). Further, using logistic regression, the week during which trazodone was started was not significantly associated with weekly depression response ratings ($p=0.40$), failing to support the alternative explanation that trazodone was most often initiated as youth were deteriorating.

Side effects and adverse events by sleep medications

The type of sleep medications was significantly associated with gastrointestinal (GI) symptoms as measured by SEFCA ($p=0.002$). There were also differences by sleep medication group with respect to the frequency of NSSI ($p=0.05$), self-harm (defined as suicidal ideation, suicide attempt, or NSSI; $p=0.003$), irritability ($p=0.005$), and GI ($p=0.02$) treatment-emergent adverse events. *Post-hoc* comparisons showed that, compared with those receiving no sleep medications, patients who received trazodone had higher rates of GI (15.2% vs. 3.6%, FET, $p=0.01$), self-harm (42.4% vs. 18.5%, $\chi^2=10.1$, $df=1$, $p<0.001$), and irritability-related adverse effects (18.2% vs. 3.6%, FET, $p=0.003$). There were no differences by trazodone exposure with respect to other side effects or adverse events, and no association between other sleep medications and any side effects or adverse events. Controlling for baseline suicidal ideation, history of suicide attempt and NSSI, the above-noted baseline differences, demographics, and treatment assignment, trazodone was still associated with increased risk of self harm

(OR=3.0, 95% CI: 1.1–7.9, $p=0.03$), but other sleep medications were not (OR=0.5, 95% CI: 0.1–2.6, $p=0.53$).

Post-hoc, within the venlafaxine group, co-treatment with trazodone was positively associated with self-harm events (46.7% vs. 19.7%, $\chi^2=5.69$, $df=1$, $p=0.017$) and irritability (26.7% vs. 2.8%, FET, $p=0.003$). Similarly, within the fluoxetine group, those cotreated with trazodone, were more likely to experience adverse events, (90% vs. 47%, FET, $p=0.015$), including self-harm (50% vs. 18.2%, FET, $p=0.039$), and GI symptoms (30% vs. 1.5%, FET, $p=0.006$) (Table 2).

Use of sleep medication and change in sleep symptoms

The improvement in sleep symptoms was evaluated as a function of sleep medication group. Although sleep symptoms significantly improved over time ($p<0.001$), there was no sleep medication group by time interaction ($p=0.88$). That is, the rate of improvement among those receiving either trazodone or the other sleep medication was parallel to those on no sleep medication (Fig. 1).

Discussion

In the initial report of the TORDIA study (Brent et al. 2008) we found that depressed youth who also received a sleep medication were less likely to respond to treatment than those who did not receive a sleep medication. In this article, we attempted to dismantle this result. Among those who received sleep medications, it was only

TABLE 2. COMPARISON OF THE THREE SLEEP-MEDICATION GROUPS WITH RESPECT TO SIDE EFFECTS AND ADVERSE EVENTS*

	None (n = 276) N (%)	Trazodone (n = 33) N (%)	Other sleep Rx (n = 25) N (%)	p-Value
Side effects				
Appetite disturbance	111 (41.3)	16 (48.5)	9 (36.0)	0.61
Cardiovascular	118 (43.9)	14 (42.2)	9 (36.0)	0.75
Central nervous system	213 (79.2)	26 (78.8)	18 (72.0)	0.70
Headache	159 (59.1)	24 (72.7)	18 (72.0)	0.17
Dermatological	63 (23.4)	10 (30.3)	6 (24.0)	0.68
Dizziness standing up	95 (35.3)	14 (42.4)	8 (32.0)	0.66
Gastrointestinal	158 (58.7) ^a	29 (87.9) ^b	19 (76.0) ^{ab}	0.002
Genitourinary	28 (10.4)	3 (9.1)	3 (12.0)	0.94
Musculoskeletal	82 (30.5)	10 (30.3)	6 (24.0)	0.80
Irritability/anger	156 (58.0)	26 (78.8)	14 (56.0)	0.07
Lethargy/apathy	100 (37.2)	8 (24.2)	9 (36.0)	0.34
Mouth/nose	115 (42.8)	20 (60.6)	10 (40.0)	0.14
Ocular	31 (11.5)	5 (15.2)	1 (4.0)	0.45
≥1 adverse events	129 (46.7)	24 (72.7)	11 (44.0)	0.02
≥1 serious adverse events	31 (11.2)	4 (12.1)	3 (12.0)	0.95
Adverse events/serious adverse events				
Suicidal ideation/attempt	36 (13.0)	9 (27.3)	3 (12.0)	0.08
NSSI	15 (5.4) ^a	5 (15.2) ^a	0 (0.0) ^a	0.05
Self harm ¹	51 (18.5) ^a	14 (42.4) ^b	3 (12.0) ^a	0.003
Suicide attempt	12 (4.3)	2 (6.1)	3 (12.0)	0.16
Irritability	10 (3.6) ^a	6 (18.2) ^b	0 (0.0) ^{ab}	0.005
Flu-like symptoms	41 (14.9)	7 (21.2)	4 (16.0)	0.58
Aches	38 (13.8)	5 (15.2)	4 (16.0)	0.86
Accident/injury	15 (78.9)	2 (6.1)	2 (8.0)	0.72
Gastrointestinal	10 (3.6) ^a	5 (15.2) ^b	1 (4.0) ^{ab}	0.02
Musculoskeletal	13 (4.7)	1 (3.0)	2 (8.0)	0.60
Dermatology	12 (4.3)	3 (9.1)	1 (4.0)	0.39

¹Defined as suicidal ideation, suicide attempt, or self-injurious behavior.

*For any variable that is significant in the three-way comparisons, groups with different superscripts (a, b) are significantly different from one another.

FIG. 1. Insomnia scores at baseline and weeks 12 for the three insomnia medication groups (error bar represent ± 2 standard deviations). Shaded = baseline; white = 12 weeks.

those treated with trazodone that showed a poorer response to treatment, even after controlling for the greater baseline severity that was associated with the use of trazodone. This was most marked in those participants treated with either paroxetine or fluoxetine. Those treated with trazodone also had higher rates of irritability, GI upset, and self-harm adverse events. In contrast, use of other types of sleep medications was associated with similar rates of response and adverse events when compared with those who received no sleep medication.

We discuss these findings after placing them in the context of the limitations and strengths of this study. This study was not designed to test the impact of sleep medication on either sleep or depression response, as sleep medication was prescribed based on assessed clinical need, rather than random assignment. Further, as only a minority of all youth enrolled in the main study received sleep medications, our sample is underpowered to detect any but the largest effects. Further, we also did not employ a well-validated measure of sleep disturbance, and the Cronbach's alpha for the KSADS sleep items used was only 0.5, indicating limited reliability and which suggests that findings based on this measure should be interpreted cautiously. Only trazodone was prescribed to a sufficiently large sample that we were able to examine its individual relationship to depression outcomes. While we documented the number of weeks that sleep medications were prescribed, we did not monitor adherence and hence cannot comment on actual frequency of use and its temporal relationship to outcome. Too few youth received each of the remaining sleep medications, including antihistamines, benzodiazepines, and GABA-acting non-benzodiazepines, to examine their independent relationship with depression response. On the other hand, this is one of the very few studies that examine the relationship between medications for insomnia and treatment response in adolescent depression.

Because the youth who received trazodone in this study were more symptomatic in some ways than other participants, it is possible that the poor response in those treated with trazodone was simply a consequence of their poorer depression prognosis. However, the relationship between trazodone and poor response persisted even after controlling for those baseline variables associated with poor depression outcome. Nonetheless, it is possible that there were other, unassessed predictors of poor outcome that might have contributed to this association. It is also possible that trazodone was

ineffective in treating insomnia in adolescents and the continued sleep disturbance interfered with depression response.

Alternatively, the poorer response of participants cotreated with trazodone could be due to an interaction with the antidepressants used in this study. Trazodone, a sedating triazolo-pyridine antidepressant, has hypnotic action at low doses due to its blockade of 5-HT_{2A} receptors, as well as H₁ histamine receptors and α ₁ adrenergic receptors; at high doses, trazodone acts as antidepressant by blocking the serotonin transporter (Stahl 2009). Trazodone is metabolized to methyl-chloro-piperazine (mCPP), which is then metabolized by CYP 2D6. Both fluoxetine and paroxetine, which had the lowest response rates among those treated with trazodone in this study (0%), are potent CYP 2D6 inhibitors (Alfaro et al. 2000; Amchin et al. 2001). Cotreatment with trazodone and fluoxetine has been reported to result in increased levels of mCPP, the latter of which has been shown to be associated with anxiety, dysphoria, and agitation when administered intravenously (Murphy et al. 1989). Venlafaxine is a weaker inhibitor of 2D6 compared with fluoxetine and paroxetine, but may have been associated with a poor response based on the same mechanism (Amchin et al. 2001). Maes et al. (1997), documented an increase in the level of trazodone and mCPP when trazodone was combined with fluoxetine as compared with combining it with placebo. However, Maes et al. (1997) found that, in those depressed adults treated with combination of fluoxetine and trazodone, a more vigorous antidepressant response was correlated with higher mCPP plasma levels. Since we did not measure mCPP levels, we can only speculate about the possibility that cotreatment of trazodone with either paroxetine or fluoxetine, both potent 2D6 inhibitors, may have led to an increased accumulation of mCPP and a poorer response rate.

Participants treated with trazodone had more adverse events of self-harm, irritability, and GI side effects. Self-harm events were highly associated with nonresponse, as has been previously demonstrated in this and other samples (Asarnow et al. 2009; Brent et al. 2009; Vitiello et al. 2009). These adverse events could also be due to increased serotonergic activity resulting from the combination of two serotonergic agents. Moreover, higher rates of irritability and self-harm could be due to inhibition of CYP450 2D6 and higher levels of mCPP in participants who were cotreated with trazodone and an antidepressant that inhibited 2D6 as posited above. Other studies in adults have also shown an association between the use of sedative-hypnotics and suicidal thoughts, plans, and suicide attempts even after adjusting for demographic characteristics, chronic health conditions, past-year psychiatric illnesses, and sleep disturbances (Brower et al. 2011).

The association between use of trazodone and lower rate of depression response is concerning because trazodone is the most commonly prescribed insomnia medication for children with mood and anxiety disorders, despite unproven efficacy (Owens et al. 2010). While some studies suggest that the combination of hypnotics and antidepressants may be beneficial, this is based on only a few investigations that did not include adolescents (Nierenberg et al. 1994; Maes et al. 1997; Fava et al. 2006). Conclusions from adult depression research are not always generalizable to the treatment of depressed children and adolescents, as illustrated by the much greater effectiveness of tricyclic antidepressants in adults as compared with younger patients (Hazell et al. 2002). It may be that trazodone's mechanisms of action may interact with neurodevelopmental differences across the age span leading to adverse impacts in youth. Further studies are needed to extend this line of research.

With a nonexperimental design, and the lack of a validated sleep measures to assess outcome, it is difficult to evaluate the efficacy of

these sleep medications in improving sleep, but neither trazodone nor other sleep medication showed any evidence of differential improvement in sleep symptoms compared with the trajectory of those who received no sleep medication. These findings are consistent with one retrospective chart review, which reported that trazodone was only slightly better than fluoxetine in improving sleep in depressed adolescents, and that the combination of fluoxetine and trazodone, while not worse, was not superior to fluoxetine monotherapy, with regard to sleep (Kallepalli et al. 1997). At a minimum, this chart review, along with our findings, suggests the need for a critical re-evaluation of the efficacy of trazodone as a sleep aid in depressed adolescents and the need to explore alternative pharmacological and nonpharmacological approaches, such as CBT for insomnia, which in adult has been shown to accelerate SSRI response in a small randomized trial (Manber et al. 2008).

Conclusion

In this study of treatment-resistant depressed adolescents, we found an association between the use of trazodone as a hypnotic and poor clinical response and higher rates of self-harm and other adverse events. This association was particularly strong when trazodone was coadministered with either fluoxetine or paroxetine, which are potent inhibitors of CYP 2D6 activity and may have led to the accumulation of mCPP as a possible explanation for these findings. Further clinical research is required to inform of the management of sleep difficulties in adolescent depression.

Clinical Significance

Sleep difficulties are a prominent symptom in adolescent depression and have been associated with failure to remit and with recurrence. Clinicians should use trazodone with caution in depressed adolescents, particularly in combination with agents that inhibit CYP 2D6 and should consider nonpharmacological interventions and use of other medications first.

Disclosures

Dr. Emslie has received research support from Biobehavioral Diagnostics, Eli Lilly, Forest Laboratories, GlaxoSmithKline, and Somerset. He has served as a consultant for Biobehavioral Diagnostics, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Pfizer, INC Research Inc., and Lundbeck and Wyeth Pharmaceuticals; and has been on the Speakers Bureau for Forest Laboratories.

Dr. Birmaher is currently employed by the University of Pittsburgh and the University of Pittsburgh Medical Center/Western Psychiatric Institute and Clinic; has received research funding from the National Institute of Mental Health; is a consultant for Schering Plough; in the past 24 months has participated in forums sponsored by Dey Pharma, L.P.: Major Depressive Disorder Regional Advisory Board Meeting (06/2010) and Forest Laboratories, Inc.: Advisory Board Meeting (11/2008); has or will receive royalties for publications from Random House, Inc. (New Hope for Children and Teens with Bipolar Disorder) and Lippincott Williams & Wilkins (Treating Child and Adolescent Depression).

Dr. Wagner reports (01/2008 to 07/2010) she has received research support from National Institute of Mental Health and was on an advisory board for Forest Laboratories.

Dr. Asarnow has consulted on CBT, depression treatment quality improvement, and on an unrestricted grant from Pfizer; had unrestricted funding from Philip Morris; and a family member has funding from Bristol-Myers Squibb and has consulted for Roche, Novartis, Sanofi-Adventis, and Janssen.

Dr. Keller has, in the past 2 years, served as a consultant to or received honoraria from Abbott, CENEREX, Cephalon, Cypress Bioscience, Cyberonics, Forest Laboratories, Janssen, JDS, Medtronic, Organon, Novartis, Pfizer, Roche, Solvay, Wyeth, and Sierra Neuropharmaceuticals; has received grant or research support from Pfizer; and has served on advisory boards for Abbott Laboratories, Bristol-Myers Squibb, CENEREX, Cyberonics, Cypress Bioscience, Forest Laboratories, Janssen, Neuronetics, Novartis, Organon, and Pfizer.

Dr. Brent is currently employed by the University of Pittsburgh, School of Medicine, and the University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic; has received research support from the National Institute of Mental Health; and receives royalties from Guilford Press; and serves as UpToDate Psychiatry Editor.

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