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Trazodone Is Only Slightly Faster Than Fluoxetine in Relieving Insomnia in Adolescents with Depressive Disorders

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ABSTRACT

This retrospective chart review examined the relative effectiveness of fluoxetine and trazodone in relieving insomnia associated with depressive disorders in adolescents (aged 13–17 years). We reviewed the hospital charts of consecutively admitted adolescents with a depressive disorder and insomnia, who received one of three treatments: fluoxetine (20 ± 2.2 mg), trazodone (71 ± 32 mg), or a fluoxetine-trazodone combination (fluoxetine 29 ± 2.2 mg, trazodone 68 ± 29 mg). Each treatment was examined in 20 patients. Insomnia was defined as a change in sleep patterns characterized by decreased total sleep time that was sufficient to cause clinical concern, and insomnia resolution was defined as sleep starting by midnight and lasting 6 hours. Mean time to resolution of insomnia was significantly faster in adolescents treated with trazodone rather than fluoxetine (2.5 vs. 5.1 days, $p < 0.05$). Trazodone seemed to save only about 3 days and insomnia resolved in all subjects by the 11th day of antidepressant treatment. Median time to insomnia resolution was 2 days (range 1–5 days) in the trazodone group and 4 days (range 1–11 days) in the fluoxetine group. This difference between trazodone and fluoxetine, although statistically significant, was generally not clinically significant in the management of insomnia associated with depressive disorders in adolescents. The resolution of insomnia was not faster for treatment with a combination of fluoxetine and trazodone in comparison to fluoxetine monotherapy. Insomnia resolution was slightly later in older children. These clinical findings await confirmation by a controlled study. Both drugs seemed effective in ameliorating sleep symptoms in this sample, although it is likely that they produced these changes by different mechanisms.

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SLEEP SYMPTOMS are a core feature of depressive disorders, and up to 75% of depressed adolescents may report insomnia (Ryan et al. 1987). The National Institute of Mental Health Epidemiological Catchment Area Study (Ford et al. 1989) found that the persistence of insomnia in adults was associated with an increased risk of recurrence of a major depressive episode, suggesting the possibility of preventing a return of depression if insomnia is adequately treated. However, the relative effectiveness of antidepressants in relieving the sleep symptoms associated with adolescent depression remains poorly studied. Our study was undertaken to evaluate the relative effectiveness and speed of response of fluoxetine and trazodone on insomnia associated with depressive disorders in adolescents.

The medical literature on adults appears to be divided about whether a sedating antidepressant (such as trazodone) or a nonsedating antidepressant (such as fluoxetine) should be used as a first-line treatment for depressive disorders associated with insomnia. Sedating antidepressants have been advocated because they can directly target insomnia through their sedative actions and perhaps provide more rapid relief from insomnia; this might improve compliance with an antidepressant regimen, especially in the face of the seeming lack of clinical effect for several weeks (Wheatley 1984). However, fluoxetine and other nonsedating antidepressants have also been demonstrated to improve sleep and other depressive symptoms in adults with depression and baseline sleep disturbance (Satterlee and Faries 1995). Trazodone, an antidepressant with prominent sedating properties, was found to produce a significantly greater improvement in adults than fluoxetine on the Hamilton Rating Scale for Depression/Sleep Disturbance Factor at the end of 1 week of treatment, but the difference disappeared after the first week (Beasley et al. 1991). An alternative approach to the pharmacological treatment of insomnia in depressed adults is targeting the depression, assuming that insomnia will resolve once the depression improves (Buysse and Perlis 1996). According to this view, a patient with depression and insomnia can be treated with any effective antidepressant, without regard to its sedating properties.

For our comparison of the effects of a sedating and a nonsedating antidepressant on sleep symptoms in adolescents, fluoxetine and trazodone were selected for two reasons. First, a review of our hospital database found trazodone and fluoxetine were the two most frequently prescribed antidepressants during the early 1990s. Second, although trazodone is a heterocyclic and fluoxetine is a selective serotonin reuptake inhibitor (SSRI), both are highly serotonergic, and sleep is highly serotonergically influenced. A comparison of these two drugs is of particular interest in view of their different effects on sleep (Marek et al. 1992, Beasley et al. 1991).

Trazodone has never been evaluated for its antidepressant effects in children and adolescents, and other heterocyclic antidepressants have not been shown to be effective in this population (Jensen et al. 1992, Popper 1992, Kye and Ryan 1995). However, Carrey and Baath (1996) published a review (and two case studies) on the potential effectiveness and tolerability of trazodone in treating insomnia associated with nonaffective conditions of youth. They also reported that low doses of trazodone (25–100 mg nightly) appeared effective in relieving chronic insomnia in 15 children and adolescents diagnosed with either anxiety, Tourette's disorder, attention-deficit/hyperactivity disorder, or stimulant-induced insomnia.

By contrast, several studies on fluoxetine in adolescent depression have been published. Fluoxetine appeared beneficial for some depressed adolescents in uncontrolled studies (Jain et al. 1992, Boulos et al. 1992), but conflicting results emerged from the available two double-blind placebo-controlled studies (Emslie et al. 1995a, 1997; Simeon et al. 1990). Whereas Emslie et al. (1995a, 1997) reported fluoxetine to be efficacious in depressed children and adolescents, Simeon and associates (1990) did not find evidence of clinical efficacy of the antidepressant in adolescents.

On the basis of our clinical experience in adolescents and the report of Beasley et al. (1991) in adults, we hypothesized that trazodone would produce a resolution of insomnia more quickly than fluoxetine in adolescents with depressive disorders. A retrospective chart review was undertaken to compare the time to insomnia resolution in adolescents treated with trazodone or fluoxetine for a depressive disorder.

METHODS

Subjects

Subjects were selected from an existing database of patients admitted to a university affiliated hospital. The database was searched for adolescents who had been discharged (during the 1990 to 1995 period) with

the diagnosis of any depressive disorder and had been treated with trazodone, fluoxetine, or a fluoxetine-trazodone combination. More than 350 charts were consecutively reviewed to accumulate a total of 60 charts, with 20 in each of group, of patients who had received trazodone alone, fluoxetine alone, or combined trazodone-fluoxetine treatment.

The selection of subjects for the study was based on the following inclusion criteria: (1) discharge diagnosis of a depressive disorder (major depression, dysthymic disorder, or depression not otherwise specified) made clinically by the attending psychiatrist and also by the adolescent team, using criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R,* American Psychiatric Association 1987); (2) formal psychological assessment concurring with the psychiatric evaluation; (3) presence of persistent insomnia at the time of admission; (4) treatment with fluoxetine alone, trazodone alone, or trazodone-fluoxetine combination during the hospitalization; and (5) length of hospital stay of at least 2 weeks after the start of the antidepressant. Excluded were (1) patients who had received a mood stabilizer (lithium, carbamazepine, or valproate) or a sedative (e.g., benzodiazepine) at any time during the hospitalization; (2) adolescents with comorbid active substance abuse; (3) patients with nightmares, sleep walking, or night terrors; and (4) patients whose medical records did not have clear diagnostic and sleep data.

Assessment of insomnia

Insomnia was defined as an alteration in sleep patterns, characterized by decreased total sleep time that was sufficient to cause concern to the adolescents or their parents. Most of the adolescents had difficulty in falling asleep (initial insomnia), but many patients were observed to have terminal insomnia (early morning awakenings with an inability to return to sleep) and middle insomnia (middle-of-night awakenings followed by return to sleep with difficulty). Based on clinical observations by the inpatient staff or patient self-reports, insomnia was judged to be resolved when a patient was noted to be asleep by midnight and to sleep continuously for at least 6 hours for at least three nights in a row.

Baseline sleep data were derived from multiple sources including parents' and adolescents' reports, admission psychiatric evaluations, patients' responses to the "sleep problems" item of the Beck Depression Inventory (BDI, Beck and Steer 1987), nursing notes, and physicians' admission and progress notes. To evaluate the effects of the antidepressant on insomnia, data from physician progress notes, discharge summaries, and nursing notes were used. Of these sources, nursing notes were particularly helpful in estimating the duration and continuity of sleep. According to hospital protocol, the nursing staff must observe each patient every 30 minutes after 11:00 PM and record whether each patient is sleeping or not. Thus, it was possible to assess the duration and continuity of sleep and thereby to describe the presence or absence of insomnia.

Procedures

Each chart was reviewed by one of the authors for demographic characteristics, psychiatric and psychological diagnostic evaluations, pretreatment scores on BDI (Beck and Steer 1987) scores, Beck Hopelessness Scale (BHS, Beck and Beamesdorfer 1974) scores, description of insomnia, and the response of insomnia to the antidepressant. The number of days between the time that an antidepressant was started and the time of clear resolution of insomnia were recorded as "days to insomnia resolution." Another author examined each chart to ensure that the selected cases conformed to the inclusion criteria and independently verified the number of days to insomnia resolution in each case. The range of antidepressant doses on the day of insomnia resolution were trazodone 25–150 mg and fluoxetine 10–20 mg. (The range of doses on the day of discharge were trazodone 75–200 mg and fluoxetine 10–20 mg.)

Both BDI and BHS data were missing in two cases, one in the trazodone group and the other in the fluoxetine group. One patient in the trazodone group completed the BDI only, but not the BHS. With the exception of their BDI and BHS, the data obtained from these patients were included in the analyses.

Data analysis

Using commercially available software (SPSS 6.1 for Power Macintosh, SPSS, Inc., Chicago, IL), we carried out multiple steps in the data analysis. First, in a preliminary analysis, we assessed the potential

TABLE 1. BASELINE CHARACTERISTICS OF 60 DEPRESSED ADOLESCENTS IN 3 ANTIDEPRESSANT-TREATMENT GROUPS

	Trazodone group	*Trazodone + fluoxetine group*	*Fluoxetine group*
Number of patients			
Total	20	20	20
Male	5	5	5
Female	15	15	15
Race			
Caucasian	100%	100%	100%
Others	0%	0%	0%
Age of subjects (years)			
Mean ± SD	15.4 ± 1.3	15.4 ± 1.3	15.0 ± 1.3
Range	13–17	13–17	13–17
Principal diagnoses			
Major depression	45%	70%	65%
Dysthymic disorder	35%	15%	5%
Depression NOS	25%	15%	15%
Axis 1 comorbid diagnoses			
Oppositional-defiant disorder	40%	15%	25%
Post-traumatic stress disorder	20%	5%	5%
Overanxious disorder	10%	15%	0%
Eating disorder NOS	5%	15%	5%
Anorexia nervosa	5%	0%	0%
Conduct disorder	5%	5%	0%
Attention-deficit/hyperactivity disorder	0%	0%	10%
Bulimia	0%	5%	5%
Psychoses	0%	0%	0%
Beck Depression Inventory scores			
Mean ± SD	22.1 ± 9.8	19.8 ± 8.1	22.8 ± 7.7
Beck Hopelessness scores			
Mean ± SD	8.72 ± 5.83	9.85 ± 5.1	8.89 ± 5.4
Dosage (mg)			
Mean ± SD		Trazodone	
Range	71.3 ± 31.7	67.5 ± 29.4	19.5 ± 2.24
	50–150	25–150	10–20
		Fluoxetine	
		19.5 ± 2.24	
		10–20	

sources of the relationships between the dependent and the independent variables (covariates). Pearson correlation coefficients (r) between the days to insomnia resolution and the three potential covariates (age, BDI scores, and BHS scores) were computed (two-tailed). We also assessed the relation of the dependent variable (days to insomnia resolution) with two other potential covariates (diagnosis and gender) by a two-way analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was then used to examine the relation of the treatment drug and the dependent measure (days to insomnia resolution), statistically controlling for the relation between age and days to insomnia resolution. Next, we conducted post-hoc multiple compar-

isons using Tukey's Honestly Significant Difference Test to analyze differences in the mean days to insomnia resolution between the three antidepressant groups. Finally, we assessed the response to antidepressants (days to insomnia resolution) by a survival analysis.

RESULTS

Subject characteristics

The trazodone only, fluoxetine only, and trazodone-fluoxetine combination groups were similar in age (mean 15 years old), sex distribution (67% female), BDI scores (means 20–23), and BHS scores (means 9–10), as shown in Table 1. The correlation between the number of days to insomnia resolution and age was significant ($r = 0.28$, $p < 0.03$, two-tailed). The number of days until insomnia resolution was longer in older children in all groups. The number of days to resolution of insomnia did not correlate significantly with BDI scores or BHS scores (BDI $r = 0.02$, $p = 0.86$; BHS $r = -0.05$, $p = 0.70$).

ANOVA did not reveal any group differences between boys and girls in the number of days to insomnia resolution ($F = 0.94$, $p = 0.33$). ANOVA also indicated that the three diagnostic groups of adolescents (dysthymia, major depression, depression NOS) did not differ in days to insomnia resolution ($F = 0.29$, $p = 0.75$).

Comparison of fluoxetine and trazodone: days to insomnia resolution

ANCOVA showed that type of antidepressant treatment had a significant main effect on days to insomnia resolution ($F = 8.78$, $p < 0.001$). ANCOVA also revealed a significant covariation of days to insomnia resolution with age ($F = 9.38$, $p = 0.003$, Table 2). Insomnia resolution was slightly later in 16 to 17 year olds than in 13 to 15 year olds (mean days to resolution of insomnia: 4.7 vs. 3.2 days). Post-hoc multiple comparisons of mean days to insomnia resolution between the antidepressant groups (Table 2), using Tukey's Honestly Significant Difference Test, indicated that trazodone produced a significantly faster resolution of insomnia than fluoxetine (2.5 ± 1.2 vs. 5.1 ± 2.9 days, $p < 0.05$). The trazodone-fluoxetine combination group was intermediate (4.1 ± 2.6) and did not differ in the number of days to insomnia resolution from either the trazodone group or the fluoxetine group. The survival analysis also suggested that trazodone was faster than fluoxetine in relieving insomnia ($x^2 = 3.5$, $p = 0.06$); although the group differences were not statistically significant, a strong trend favoring trazodone was found.

By the 11th day of antidepressant treatment, each of the adolescents in all three treatment groups no longer had insomnia (Figure 1). In all of these patients, once insomnia resolved, the patients continued to sleep well without a return of insomnia during the time period of the study. We did not focus on global response of depressive symptoms to treatment. However, our review of progress notes and discharge sum-

TABLE 2. ANALYSIS OF COVARIANCE (ANCOVA) FOR DAYS TO RESOLUTION OF INSOMNIA WITH AGE AND ANTIDEPRESSANT TREATMENT GROUP AS FACTORS

Source	*df*	*Mean square*	*F*	*p*
Age	1	44.44	9.38	<0.003
Drug treatment	2	41.59	8.78	<0.001

Post-Hoc Analysis of ANCOVA for Days to Insomnia Resolution

Days to insomnia resolution*	Trazodone	Trazodone + Fluoxetine	Fluoxetine
Mean ± SD	2.50 ± 1.19	4.05 ± 2.58	5.10 ± 2.86

*Difference between fluoxetine and trazodone was statistically significant ($p < 0.05$) using Tukey's Honestly Significant Different post-hoc comparison.

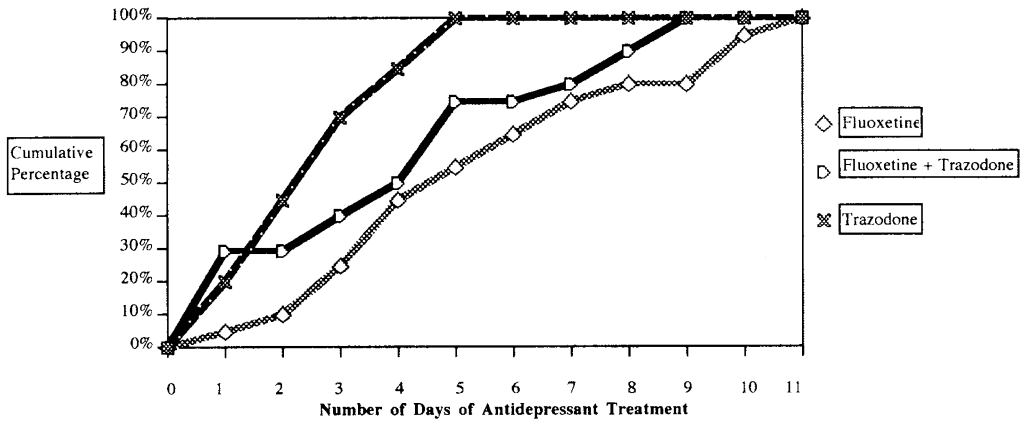

FIG. 1. While resolution of insomnia occurred in all patients by day 11, it was achieved faster in trazodone group.

maries revealed that, in general, depressive symptoms were viewed as improved to a clinically significant extent in the majority of cases in all antidepressant groups. In particular, the risk of suicide was judged to be mild to none.

DISCUSSION

These results are consistent with the hypothesis that sleep may improve earlier with trazodone monotherapy than with fluoxetine monotherapy, but this advantage is short-lived. We found that, after 11 days of antidepressant treatment, all depressed adolescents appeared to achieve insomnia resolution. Similar results have been reported in adults with depression and a baseline sleep disturbance: Beasley et al. (1991), in a randomized double-blind study, found that trazodone was superior to fluoxetine in improving insomnia, but only during the first week of antidepressant treatment.

Limitations

There were several methodological limitations to this retrospective chart review that require that findings to be interpreted cautiously. The main limitations are the retrospective nature of the study, the absence of a control or placebo group, and the lack of quantitative measures for baseline and outcome assessment. In the absence of a placebo group, it cannot be determined whether the findings represent true drug effects. However, it is neither ethical nor feasible, especially in the current managed care environment, to treat depressed hospitalized patients with a placebo. The lack of standardized diagnostic interviews and quantitative outcome data further limit the strength of our conclusions, especially concerning the possible influence of comorbidity. In addition, the generalizability of this information to general adolescent psychiatry practice is limited by our exclusion of a number of patient populations from our sample, including youths who had concurrently administered drugs (and possible drug interactions) and comorbid substance-related disorders.

Our study could also be strengthened by using polysomnographic measures and standardized sleep rating instruments (Buysse et al. 1989). It would have been very desirable to obtain standardized baseline measurements, such as diagnostic assessment, comorbidity data (especially pertaining to the assessment of anxiety, disruptive, or aggressive behaviors and disorders), and a measure of the severity and chronicity of sleep problems. It would also be preferable to use standardized outcome instruments, such as standardized assessment of individual sleep symptoms, quantification of sleep disturbance (severity, number, or duration of sleep symptoms), adverse effects of the antidepressants, and measures of depression, anxiety symptoms, and disruptive or aggressive behaviors.

Longitudinal follow-up data would have been valuable to determine whether there is a differential effect of the antidepressants on depressive symptoms and whether the change in sleep symptoms predicted change

in the depressive symptoms. Follow-up data would also be useful to compare the risk of inducing mania or some sleep-related condition that might correspond to fluoxetine-induced adverse behavioral activation (Riddle et al. 1990).

Given the methodological limitations of our study, it is not possible to draw any firm conclusions. However, our findings may justify a prospective controlled study incorporating the features just described.

Mechanism of insomnia resolution

If trazodone has a faster onset of anti-insomnia action than fluoxetine, there are several possible mechanisms by which trazodone might have produced insomnia resolution in this sample. The direct sedative actions might have been at least partially responsible for a slightly faster insomnia resolution in the trazodone group than in the fluoxetine group. That is, the apparent sedative/hypnotic properties of trazodone may be responsible for the small difference in the speed of insomnia resolution.

An alternative possibility is that the sleep-promoting effects of trazodone might be attributed to its putative effects on a psychiatric disorder, such as depression, or a comorbid condition, such as anxiety disorder or disruptive behavior disorder. In a similar manner, it is possible that the apparent clinical difference may be due to effects on a particular behavior. For example, a rapid reduction in aggressive behavior, irritability, or interpersonal conflicts might have facilitated sleep in adolescents who were receiving trazodone. In an open trial of trazodone in 22 children hospitalized for treatment-resistant impulsive or aggressive behaviors, Zubieta and Alessi (1992) found that behavioral improvement occurred in nearly 67% of the youths and persisted at 3- and 14-month follow-up. Their results supported observations described in a case series that trazodone may have an antiaggressive effect in children (Ghaziuddin and Alessi 1992).

Speculatively, trazodone could also have produced sleep improvement by acting on nonbehavioral symptoms, such as headache. Trazodone was reported to be efficacious in the treatment of pediatric migraine in a double-blind placebo-controlled study (Battistella et al. 1993). However, in the absence of reliable data on comorbidity, the mechanism by which trazodone produced sleep improvement in our sample remains unknown.

Fluoxetine is commonly regarded as nonsedating in comparison to trazodone, but sedation has been reported by some patients receiving fluoxetine. Examining the adverse behavioral symptoms of activation (e.g., anxiety, insomnia, and agitation) and sedation (e.g., somnolence and asthenia), Beasley et al. (1991) compared the incidence of activation/sedation of fluoxetine (median 20 mg daily) and trazodone (median 250 mg daily) in adults with depressive disorders. Activation was found significantly more often with fluoxetine than trazodone (15% vs. 3%), and sedation was reported significantly more often with trazodone than fluoxetine (43% vs. 22%). Interestingly, sedation was reported more often than activation in the fluoxetine group. These differences in activation and sedation did not seem to be clinically significant; the two treatments did not differ in discontinuation rates, side effects, or effectiveness.

The mechanism by which fluoxetine improves sleep in adolescent depression is not known. Although fluoxetine might facilitate sleep in some depressed adolescents through its sedative action, it is conceivable that sleep improvement in most cases is related to its beneficial effects on the depressive disorder or a comorbid condition. SSRIs have been used in children and adolescents for the treatment of 13 indications (DeVane and Sallee 1996), including depression, aggressiveness, obsessive-compulsive symptoms, and anxiety (Birmaher et al. 1994). Theoretically, fluoxetine can improve sleep by acting on a variety of disorders or symptoms.

Although fluoxetine has been shown to be effective in adults in alleviating insomnia associated with depression in at least one controlled study (Saterlee and Faries 1995), fluoxetine itself can be a cause of insomnia in all age groups. Fluoxetine can also exacerbate or induce insomnia (Riddle et al. 1990) and impair sleep architecture (Emslie et al. 1995b) in some adolescents with depressive disorders. In a sample of 24 youth (8–16 years old) receiving fluoxetine, Riddle and colleagues found that 11 (45%) of 24 showed insomnia and 50% showed other adverse "activating" effects, such as motor restlessness, social disinhibition, and subjective excitation. Discontinuation of fluoxetine or halving the dose led to complete resolution of these symptoms, suggesting that the symptoms were drug-related and dose-related. Unlike Riddle and colleagues, we did not find any cases of fluoxetine-induced insomnia, perhaps because we used smaller

starting doses, slower dosage increases, and lower final doses (10–20 mg daily in our sample vs. 20–40 mg daily in the study by Riddle et al.).

Because behavioral activation and sedation appear to be dose-dependent, the findings of our study might have been different if a lower trazodone dose or higher fluoxetine dose were used. If it is confirmed that fluoxetine is more activating in a higher dosage (>30 mg daily) in youth, then treatment at higher doses (for treatment-resistant depressive or obsessive-compulsive disorders) could be limited by this side effect in some cases. However, this study focused on depression-related insomnia, so our findings do not directly apply to fluoxetine-induced insomnia.

Although it is likely that fluoxetine and trazodone exert some effects on sleep through their serotonergic properties, it is not surprising that they produce different clinical effects in view of their pharmacological differences. Fluoxetine acts primarily by blocking the reuptake of the serotonin carrier into the presynaptic neuron, and trazodone is characterized by antagonism at the 5-hydroxytrytamine$_2$ (5-HT$_2$) postsynaptic receptor site, resulting in stimulation of other receptor responses to 5-HT, especially 5-HT$_{1A}$ (Marek et al. 1992, Charney et al. 1986, Barry and Schatzberg 1995). Whatever the mechanisms of trazodone and fluoxetine may be in resolving insomnia, there is no guarantee that they operate through the same physiological or even pharmacological effects.

Clinical implications

Is the apparently faster onset of insomnia resolution by trazodone a clinically significant advantage over fluoxetine? This question is particularly relevant in the current managed care environment with its emphasis with short hospital stays. Although trazodone may be superior to fluoxetine in speed of onset of antiinsomnia effect, the proper selection of an antidepressant is based on an understanding of numerous differences in properties among antidepressants, including overall safety, tolerability, efficacy, cost effectiveness, and simplicity (Leber 1995, Laska and Siegel 1995, Preskorn 1994). Because insomnia resolved with fluoxetine alone over an 11-day period, the use of trazodone (alone or in combination with fluoxetine) to accelerate treatment of insomnia may not be necessary in most cases. In fact, we found no significant difference in sleep symptoms between fluoxetine and fluoxetine-trazodone combination during the initial phase of antidepressant treatment.

Although the use of trazodone appears to produce a statistically significant advantage, it does not generally produce a clinically significant advantage in the management of insomnia in adolescents with depressive disorders. Trazodone cannot be recommended as a first-line treatment in adolescent depression because it has no demonstrated antidepressant effect in adolescents (Rosenberg et al. 1990). Moreover, it can cause priapism in all age groups (Thompson et al. 1990). Priapism (continuous penile erection) is a urologic emergency, and delayed treatment can potentially lead to irreversible complications such as difficulty urinating, urinary retention, impotence, cavernosa fibrosis, and gangrene (Yealy and Hogya 1988). In addition, the high level of sedation associated with trazodone is intolerable for some patients (Haria et al. 1994). There is also some concern about the arrhythmogenic potential of trazodone (Barry and Schatzberg 1995).

While mild insomnia associated with depression can generally be ignored in the initial stages of treatment until improvement is observed with the primary (antidepressant or psychosocial) treatment, a sedating antidepressant might be considered in cases of severe insomnia and in treatment-resistant cases requiring rapid relief from insomnia (Ambrosini et al. 1995). A sedating antidepressant administered at bedtime may also be useful when daytime fatigue is disabling or when insomnia is exacerbated by a nonsedating antidepressant (Nierenberg et al. 1994, Neylen 1995). Even in these situations, trazodone cannot be recommended as the antidepressant of choice. Given the paucity of data on other sedating antidepressants (such as nefazodone or doxepin) for insomnia associated with adolescent depression, it is not possible to offer any specific recommendations. However, nefazodone (a compound related to trazodone) was recently reported to be well tolerated by seven youths with mood disorders, who seemed to benefit from the antidepressant (Wilens et al. 1997).

CONCLUSIONS

Given the methodological limitations of this study, its conclusions are only tentative and heuristic. Our data are consistent with the hypothesis that trazodone is significantly faster than fluoxetine in the resolution of insomnia associated with depression in adolescents, but this faster onset is probably not a clinically significant advantage in management of insomnia in most adolescents with depressive disorders. The findings of this study might justify a prospective double-blind placebo-controlled study that focuses on numerous sleep (including days to insomnia resolution) and other clinical differences in the effects of trazodone and fluoxetine. Further, the sleep-related effects of other antidepressants need to be investigated also.

Trazodone is not indicated as a first-line antidepressant in adolescent depression because it has never been tested in depressed adolescents, it can produce priapism and potentially irreversible complications, and it is quite sedating. Fluoxetine has a mixed picture in its controlled trials in youth with depressive disorders (Simeon et al. 1990, Emslie et al. 1997), and it can induce sedation as well as behavioral activation. According to Graham Emslie, (personal communication, 1997), treatment with fluoxetine (20 mg) in adolescents is initially associated with complaints of troubled sleep; however, after 8 weeks of treatment, there appears to be an improvement in insomnia along with improvement in other depressive symptoms (on the Children's Depression Rating Scale—Revised). Choice of an antidepressant does not necessarily require consideration of insomnia and should generally be based on an understanding of the multidimensional differences among antidepressants and among patients.

At present, definitive guidelines cannot be offered for antidepressant selection in youth. The controversies and opinions involved in selecting a sequence of antidepressants have been addressed by five recognized experts in adolescent depression (Ambrosini et al. 1995). They point out that antidepressant selection is a complex decision with little available research data to support the difficult medication choices and that the factors that can modify pharmacological decisions are multiple and varied. Even predicting whether an antidepressant will be activating or sedating is difficult. Above all, the choice of antidepressants is based on consideration of side effects and therapeutic effects in individual patients (Preskorn 1994, Guile 1996).

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