Treatment of Childhood and Adolescent Anxiety Disorders with Tricyclic Antidepressants

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ABSTRACT

Children and adolescents suffering from anxiety disorders may require pharmacotherapy. Tricyclic antidepressants are often prescribed in these instances. Unfortunately, most clinical research analyzing the effectiveness of tricyclic antidepressants on anxiety disorders has focused exclusively on adult patients. This critical review examines those studies that have investigated the effects of tricyclic antidepressants on childhood and adolescent anxiety. Double-blind placebo-controlled trials have been conducted on patients suffering from school phobia, separation anxiety, and obsessive-compulsive disorder. Case studies have highlighted the use of tricyclic antidepressants in panic disorder. To date, there have been mixed results. Attention is also given to the potential adverse effects of tricyclic antidepressants, including anticholinergic effects, as well as cases of sudden death in young patients.

INTRODUCTION

Anxiety disorders are a serious form of psychopathology, which can have a debilitating effect on children and adolescents. These disorders are often associated with social problems at home and in school, somatic distress, depression, low self-esteem, and substance abuse. Moreover, children with anxiety are likely to have similar disorders into adulthood, along with other adjustment problems (Birmaher et al., 1994).

As childhood anxiety disorders take many forms, the DSM-III-R (American Psyciatric Association, 1987) provides two sections relevant to their diagnoses. The "anxiety disorders" section lists criteria for panic disorder, agoraphobia, social phobia, simple phobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder, generalized anxiety disorder, and anxiety disorder not otherwise specified. These diagnoses can be used for all age groups. Additionally, a category devoted to "anxiety disorders of childhood or adolescence," includes separation anxiety disorder, overanxious disorder, and avoidant disorder. In the more recently published DSM-IV (American Psyciatric Association, 1994), these childhood categories are subsumed under other categories of childhood or adult disorders[1].

Recent studies have shown that the prevalence of anxiety disorders in young people are remarkably high. For example, Benjamin et al. (1990) in a study of children aged 7 to 11 years reported a 15.4% prevalence rate of anxiety disorders. Working with another sample of children in that same age group, Costello (1989) found that 9.2% suffered from simple phobias, 4.6% from overanxious disorder, 4.1% from separation anxiety, and an additional 1% to 2% each from avoidant disorder, agoraphobia, and social phobia.

Studies of adolescents have found prevalence rates that were even higher. Kashani and Orvaschel (1988) discovered that 17.3% of a sample of 150 adolescents met the criteria for at least one anxiety disorder with 8.7% demonstrating clinical dysfunction required treatment. In their subsequent study (Kashani and and Orvaschel 1990) of 210 subjects, 3 groups of 70 adolescents each aged 8, 12, and 17 years, 21% suffered from an anxiety disorder. Among the female population, prevalence of anxiety was an astonishing 28.6%. Furthermore, anxiety was the most common type of psychopathology reported in all three age groups.

Since psychiatric drugs typically have side effects, individual or family therapy is often considered first-line treatment. However, in many cases a clinician may determine that a medical approach is necessary. Recent studies relating to pharmacological treatments for childhood and adolescent anxiety disorders have almost entirely focused on benzodiazepines and antidepressants, and to a much lesser extent, on antihistamines, beta-blockers, and buspirone.

The class of drugs known as antidepressants is composed of several different types. Among those tested in childhood and adolescent anxiety disorders are the selective serotonin reuptake inhibitors (SSRIs) (for a review, see Birmaher et al., 1994). However, the majority of investigators have concentrated on the use of tricyclic antidepressants (TCAs), such as imipramine, clomipramine, desipramine, and nortriptyline[2]. Like SSRIs, TCAs act by preventing the reuptake of serotonin, though they are also known to prevent the reuptake of norepinephrine and acetylcholine (Riddle et al., 1993; Walsh, 1999).

1. See Rabian and Silverman (2000) for a detailed description of these changes. In this article, references will be made to the pre-DSM-IV childhood categories, since most extant studies were performed by diagnosing subjects using the previous terminology.

2. There is also one study (Frommer, 1967), which examined the effects of a monoamine oxidase inhibitor on anxious and depressed youth.

Some theorists justify the use of antidepressants to treat childhood anxiety by claiming that anxiety disorders in children are really forms of depression (Gittelman and Koplewicz, 1986). Furthermore, TCAs in particular have been shown to be an effective treatment for adults with panic disorder and social phobia (Kutcher, 1992), but their role in the treatment of childhood and adolescent anxiety is not yet clear. Studies of TCA treatment for childhood and adolescent anxiety disorders have focused exclusively on school phobia, separation anxiety, panic disorder, and OCD.

SEPARATION ANXIETY

The first such study that was both double-blind and placebo-controlled was reported by Gittelman-Klein and Klein (1971, 1973). Children aged 6 to 14 years, who had not been able to attend school for 2 weeks or had "marked distress" in school, were accepted for 6 weeks of multidisciplinary treatment. All participants received psychosocial therapy along with either imipramine or placebo. While dosage for individuals in the imipramine group was altered periodically, after 6 weeks it ranged from 100 to 200 mg/day, with a mean of 152 mg/day.

Results showed that imipramine was significantly more therapeutic than the placebo. Of the 35 children (mean age of 10.8 years) who completed the study, 13 of the 16 (81%) on imipramine returned to school, as opposed to only 9 of the 19 (47%) on placebo. Furthermore, the imipramine-treated participants were rated as having demonstrated significantly more improvement on measures of anxiety than did the placebo-treated participants. The authors concluded that imipramine diminished the children's separation anxiety and with the help of counseling enabled them to return to school.

In a similar study, Berney et al. (1981) reached contrary results. Forty-six 9 to 14 year-old school refusers completed 12 weeks of psychosocial therapy coupled with clomipramine treatment (n=27) or a placebo (n=19). Dosages of clomipramine were gradually increased until the generally accepted dose for the subject's age was achieved, (i.e. 40 mg/day for 9 to 10 year olds, 50 mg/day for 11 to 12 year olds, and 75 mg/day for 13 to 14 year olds.) No significant difference emerged between the clomipramine-treated group and the placebo-treated group on a series of measures of anxiety and neurotic behavior.

Another study supported these latter findings. Bernstein et al. (1990) examined 24 children and adolescents (mean age of 14.12 years) with a record of poor school attendance, coupled usually with depression or anxiety. All participants were treated with weekly psychotherapy aimed at school reentry. However, pharmacotherapy was dependent on random assignment to one of three groups. The first group received the benzodiazepine, alprazolam. The second group received the TCA, imipramine. The third group received a placebo. For the first 2 weeks, dosages of the medications were gradually increased until the maximum dosages were achieved, (0.03 mg/kg/day for alprazolam and 3 mg/kg/day for imipramine). Since five participants dropped out at various points, each group had five to seven participants by the end of the eighth week when final evaluations were conducted. Results showed no significant difference between the medicated and nonmedicated groups on anxiety symptoms[3].

It should be noted that there are important differences between the latter two studies where TCAs did not seem effective and the contrary findings by Gittelman-Klein and Klein (1971, 1973). Perhaps the most critical difference was in the dosages used. Although it is difficult to compare between drugs, Berney et al. (1981) estimate that the dosages they used of clomipramine were less potent than the amounts of imipramine employed by Gittelman-Klein and Klein (1971, 1973)[4]. This is aside from the possibility that clomipramine, rather than, imipramine, is inappropriate for this disorder at any dosage. Similarly, while it is not known what the imipramine mg/kg ratio was in the Gittelman-Klein and Klein (1971, 1973) study, judging by the ages of the participants, Bernstein et al. (1990) speculate that it was higher than that employed in their study.

Variation in the concurrent psychosocial therapies provided to participants in each of the studies also warrants consideration. For example, the Gittelman-Klein and Klein (1971, 1973) study offered participants "persuasive and desensitization techniques," while Berney et al. (1981), used "concurrent individual psychotherapy and casework for the parents." By contrast, Bernstein et al. (1990) placed participants in an individually tailored "school reentry plan" and also provided psychotherapy by "a child psychologist or a child psychiatry resident under the supervision of a child psychiatrist" (Bernstein et al., 1990). Furthermore, especially in the Bernstein et al. (1990) study, it is even questionable whether participants in a given study received identical treatments. Bernstein et al. (1990) recommend that future studies use a therapy manual to increase the likelihood that each patient received similar interventions.

Many other issues have also been raised. For example, the Bernstein et al. (1990) study has been criticized for its small sample size, high dropout rate, and diagnostic heterogeneity (Klein et al., 1992). Bernstein et al. (1990),

3. Their negative findings for alprazolam stand in contrast to many other studies of benzodiazephines, which have demonstrated an anxiolytic effect in children and adolescents. See Coffey (1993) and Kutcher et al. (1992) for a review.

4. Kutcher et al. (1992) agrees with this assessment. Ryan and Puig-Antich (1987) go so far as to say that the dosages in the Berney et al. (1981) study were "almost certainly insufficient for clinical effect."

in turn, argue that Berney et al. (1981) used participants who were older and showed comparatively greater depression, yielding results that might not have been relevant to the Gittelman-Klein and Klein (1971, 1973) study.

More recently, Klein et al. (1992) tested the findings of Gittelman-Klein and Klein (1971, 1973) and their contention that TCAs are significantly effective for separation anxiety in a double-blind placebo-controlled experiment. In selecting participants, this study used criteria for separation anxiety without regard for school refusal. Although all the aforementioned studies dealt exclusively with school refusers, 93% of the participants in the Gittelman-Klein and Klein (1971, 1973) study and 87% of the participants in the Berney et al. (1981) study did, in fact, have moderate or severe separation anxiety. As such, the authors hypothesized that this study could still provide support for, and even extend, the findings of the original studies.

In the first phase of the study, 45 children diagnosed with separation anxiety were provided with behavioral treatment only. This phase was meant to eliminate participants who were not in need of pharmacological treatment as well as rapidly remitting patients, who would respond to nonspecific treatment and decrease the power of the experiment to detect treatment effects.

At the conclusion of phase one, 24 children displayed symptom reductions of adequate clinical magnitude to warrant excluding them from pharmacological treatment. The 21 remaining children (mean age of 9.5 years), who still met the criteria for separation anxiety, entered the 6 week experimental phase of the study. They continued behavioral therapy, while one group was also treated with imipramine (n=11) and another with placebo (n=10, although one dropped out because of an unrelated illness.) By the end of the study, the average dosage was 153 mg/day (4.67 mg/kg).

Results showed imipramine to be no better than placebo on dozens of clinical measures. The only significant difference between the two groups was on a mother-rated fear of danger scale, where the placebo group fared better. There was also a trend in favor of the placebo on a mother-rated scale of "obsessional" factors.

This study is a particularly strong blow to the findings of Gittelman-Klein and Klein (1971, 1973) since the senior author and investigator was the same in both cases. Rachel G. Klein personally saw almost all the children in both experiments and affirms that diagnostic standards, drug levels, and non-pharmacological treatment features were consistent throughout both. Nevertheless, this study's comparatively small sample size weakens the strength of its findings. Additionally, since patients that did not necessarily display school avoidant behavior were included here, this research may merely demonstrate that in milder forms of separation anxiety imipramine is not more effective than placebo (Klein et al., 1992). In sum, this study, and the series which motivated it, casts considerable doubt on the practice of prescribing TCAs for childhood and adolescent school avoidance and separation anxiety disorder[5].

PANIC DISORDER

There is a substantial body of literature demonstrating that children with separation anxiety disorder and panic attacks may be different symptoms of the same underlying disorder. For example, panic attacks are strikingly similar to symptoms displayed by children with separation anxiety disorder when parting from parents. Moreover, children and adults with panic disorder frequently avoid separation from attachment figures (see Black and Robbins, 1990 for a review of the relevant literature). As such, it is no surprise that another type of anxiety disorder where TCAs have been examined in children and adolescents, albeit not nearly as extensively, is panic disorder. Treatment studies have already shown TCAs to be effective in adult panic disorders, but there are only case studies relating to their use for this disorder in children and adolescents (Ballenger et al., 1989; Black and Robbins, 1990; Garland and Smith, 1990).

Taken together, however, the extant series of case studies seems promising[6]. Accordingly, further research in the form of double-blind placebo controlled studies of TCAs in childhood and adolescent panic disorder seems to be indicated.

OBSESSIVE-COMPULSIVE DISORDER

Another area where TCAs have been studied for use in children and adolescents is during the treatment of OCD.

5. It is noteworthy that Bernstein et al. (2000) found that imipramine in combination with cognitive-behavioral therapy (CBT) was significantly more effective in treating adolescent school refusers than CBT alone. Nevertheless, their study participants all had comorbid anxiety and major depressive disorder. Thus, the authors point out that their results are likely not relevant to adolescents who are not depressed, as was the case in the aforementioned studies.

6. It should be noted, however, that uncontrolled data might be particularly misleading when young people are being investigated. For example, Simeon et al. (1990), in a study of the antidepressant fluoxetine in adolescents, found stronger placebo effects than have been reported in similar adult studies. McLeer and Wills (2000) assert that this is not an isolated finding relating specifically to fluoxetine or even antidepressants, but an example of the "fact that children have a consistently higher placebo effect in drug studies than do adults." They do not support that assertion with any other data. However, Simeon and Wiggins (1993) report that in many types of short-term clinical trials the placebo benefits about 30% to 50% of children and adolescents. Furthermore, they quote many studies that illustrate that "pediatric psychopharmacology is full of examples where the initial positive results of open drug studies are contradicted or questioned by the findings of placebo-controlled double-blind studies."

While early studies of OCD patients treated with clomipramine had seen largely positive results (see Flament et al., 1985 for a review), these investigations had focused on adult populations.

Flament et al. (1985) were the first to conduct a double-blind placebo-controlled study to examine the effects of clomipramine on younger OCD patients. As this study employed a crossover design, both groups received clomipramine and placebo, the only variation being the order. Nineteen subjects, their ages ranging from 10 to 18 years (mean age of 14.5 years), completed the 10 week trial. Dosages of the drug were gradually increased to 3 mg/kg/day, as tolerated. The children were provided with individual psychotherapy (but no behavioral therapy) throughout the study, and their parents received feedback counseling when necessary.

Results demonstrated that clomipramine was significantly better than placebo in relieving the symptoms of OCD. Seventy-four percent experienced at least moderate improvement when taking clomipramine. However, when placebo followed the drug, relapse was typical.

For several reasons, the authors assumed that clomipramine's antiobsessional action was direct, and not merely a result of an antidepressant effect. Firstly, patients with major depression were excluded from the study. (While secondary depression was not an exclusion criterion, most subjects did not suffer from it.) Additionally, initial depression did not correlate with drug response. Lastly, clomipramine treatment in this study did not seem to significantly reduce depressive symptoms.

A study performed by DeVeaugh-Geiss et al. (1992) on a larger population provides corroboration for these results. Their study was similar to that of Flament et al. (1985) in the dosages of clomipramine used, the length of treatment, the age and diagnoses of the subjects, and their concomitant psychotherapy. Aside from the fact that this double-blind placebo-controlled study had 60 patients, the only major difference from the Flament et al. (1985) study was that DeVeaugh-Geiss et al. (1992) did not use a crossover design.

Results of the DeVeaugh-Geiss et al. (1992) study showed that in comparison with those in the placebo group, the patients receiving clomipramine showed significantly greater clinical improvement. It is noteworthy that DeVeaugh-Geiss et al. (1992) conducted a one-year open-label extension to the study which 25 patients completed. Efficacy was perpetuated during the long-term treatment.

Following the publishing of the Flament et al. (1985) study, Leonard et al. (1989) pointed out two possible weaknesses in it. Firstly, since TCAs cause anticholinergic side effects, patients may have known when they were taking clomipramine and when they were taking the placebo. Since most patients fared comparably worse on the placebo when it followed the drug, as opposed to when it preceded the drug, it is not unreasonable to suggest that they had learned to discriminate the drug from the placebo. Secondly, the Flament et al. (1985) study did not show conclusively that the antiobsessional effects were not caused by a nonspecific anxiolytic or antidepressant effect.

To address these issues, Leonard et al. (1989) conducted another 10 week double-blind crossover comparison with 48 children and adolescents suffering from OCD, similar to that performed by Flament et al. (1985). However, this experiment compared the effects of clomipramine to desipramine, instead of to a placebo. Since desipramine, another TCA, is likewise known to cause antidepressant, anxiolytic, and anticholinergic effects, it would be a superior experimental control in determining whether clomipramine is indicated for OCD in young patients.

Leonard et al. (1989) found that clomipramine produced a remarkable decrease in OCD symptoms, but desipramine did not. Furthermore, when desipramine was given after clomipramine, patients experienced a rate of relapse similar to the rate experienced by the subjects of Flament et al. (1985) when placebo followed clomipramine. Since desipramine is an effective antidepressant, this study further confirms that clomipramine's effectiveness for OCD is not mediated by an antidepressant effect. It also suggests that when patients respond to clomipramine it is not merely a placebo effect, since the authors assumed that the side effects of clomipramine were similar enough to those of desipramine to prevent a patient's distinguishing between the two.

Having further established the effectiveness of clomipramine for childhood and adolescent OCD, Leonard et al. (1991) performed a follow-up study to examine the necessity of maintenance treatment with this drug. As experimental participants, they used 26 patients from their original study who were then undergoing long-term treatment (mean treatment duration 17.1 months) with clomipramine. Leonard et al. (1991) followed these patients for eight months. During months four and five, half of the patients were randomly selected to receive desipramine as a substitute for clomipramine. The substitution was double-blind. As in their previous experiment, it was hoped that substituting desipramine instead of a placebo would prevent patients from detecting the change in medication from the disappearance of side effects.

In the substituted group, 89% experienced relapse, as opposed to only 18% in the nonsubstituted group. These results suggest that long-term clomipramine therapy may be required for children and adolescents with OCD.

Leonard et al. (1991) did note that this study has impor-

tant limitations. Firstly, the experimental population was self-selected in that those who had experienced remission were not included. As such, this study only shows that a certain subset of OCD sufferers will relapse if clomipramine treatment is discontinued. Furthermore, there is the possibility that patients could distinguish between clomipramine and desipramine based on the greater anticholinergic side effects of the former. (This reasoning would also compromise the findings of their earlier experiment.) Although no patient claimed an ability to distinguish between the two drugs, there was no way to resolve this issue from the available data.

In sum, it seems that TCAs may be an effective treatment in childhood and adolescent OCD. Moreover, long-term treatment may be required for maintenance of the therapeutic effect.

ADDITIONAL CONSIDERATIONS

A physician contemplating TCA treatment for an anxious child or adolescent must also consider the adverse effects that this drug may cause. Reviewers associate TCAs with a wide range of negative side effects including lowered seizure threshold, sedation or insomnia, nightmares, sexual dysfunction, rashes, photosensitivity, confusion, incoordination, dizziness, and changes in pulse, blood pressure, and weight as well as anti-cholinergic effects (e.g., constipation, blurred vision, and dry mouth). In some rare cases, which will be addressed later, sudden death has been reported (Husain and Kashani, 1992; Kutcher et al., 1992; McLeer and Wills, 2000; Waterman and Ryan, 1993).

Gittelman-Klein and Klein (1971, 1973) and Klein et al. (1992) did find that significantly more imipramine-treated children had side effects than those on placebo. Yet it should be noted that of the dozens of side effects that Gittelman-Klein and Klein (1971, 1973) reported, only one (dry mouth) significantly differentiated the two groups. Moreover, in a heretofore unmentioned double-blind placebo controlled study of desipramine in depressed adolescents, Buolos et al. (1991) also did not find any specific side effect or specific subcategory of side effect which differentiated the two groups.

In the Buolos et al. (1991) study, however, an uncharacteristically high one third of the desipramine-treated participants discontinued treatment on account of various serious side effects. By contrast, Bernstein, et al. (1990), note that no participant "had any side effect rated higher than 'mild, does not interfere with functioning.'" In summary, it is unclear to what extent adverse effects are actually caused by TCAs.

Of greater concern, however, are the reported cases of youths experiencing sudden death while undergoing TCA treatment. As with many drugs, acute overdose of TCAs can cause death[7]. Yet, there have been seven reported sudden deaths that do not seem attributable to acute overdose.

Two of the instances of sudden death involved imipramine (Saraf et al., 1974; Varley and McClellan, 1997). However, it is questionable whether these particular cases actually implicate TCAs. Ostensibly more disconcerting are the five reported cases (Abramowicz, 1990; Popper and Zimnitzky, 1995; Riddle et al., 1991; Riddle et al., 1993) of sudden death in children and adolescents taking desipramine. It seems that all five had been taking appropriate dosages of the drug and had not been on any other prescription medication that might conceivably have interacted with it. It has been widely speculated that desipramine might have caused cardiac irregularities or at least have aggravated preexisting cardiac abnormalities.

Using this hypothesis, Riddle et al., (1993) explain why desipramine would be more lethal than other TCAs. While all TCAs inhibit the reuptake of norepinephrine and serotonin, desipramine is the most selective for norepinephrine. By increasing noradrenergic neurotransmission, desipramine adds to cardiac sympathetic tone. There is already a developing literature that suggests that an increase in cardiac sympathetic tone puts vulnerable individuals at risk for syncope, ventricular tachyarrhythmias, and sudden death[8].

While sudden deaths involving TCAs are very rare, the existence of such cases makes the use of TCAs as a first line treatment in children and adolescents somewhat questionable. Nevertheless, more research is necessary before any definite judgment can be reached regarding when and if there is a lethal potential to these drugs.

CONCLUSION

In conclusion, TCAs are widely prescribed for children and adolescents with anxiety disorders even in the absence of extensive testing in these younger populations. Nevertheless, there is a growing literature surrounding their use in the treatment of children and adolescents suffering from separation anxiety and school phobia, panic disorder, and OCD. However, many doubts still remain as to the effectiveness of TCAs even in these disorders. Coupled with the possibility that TCAs may have even a lethal potential in children, medical practitioners should be cautious in considering them for young patients.

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7. For description of a clinical example and review of several other cases of overdose, see McCgiles (1963).

8. See *The Lancet* (1991) and Verrier and Hagestad (1985).

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