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A Risk-Benefit Assessment of Pharmacotherapy for Anxiety Disorders in Children and Adolescents

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Contents

Abstract

Few pharmacotherapy trials have been undertaken in young people with anxiety disorders. Of those conducted, few are placebo-controlled or blinded, and often sample size is small, making interpretation of the data difficult.

Case report and uncontrolled trial data generally support the efficacy of pharmacotherapy in many of the anxiety disorders seen in young people. However, most attempts to confirm these impressions in controlled trials have not been as encouraging. Further controlled studies in larger, diagnostically homogeneous samples are needed. At present, the decision as to whether or not to use medication in this patient population must be made on clinical grounds. Evidence is accumulating to suggest that anxiety disorders in young people can become chronic and cause at least moderate functional impairment in some individuals. This possibility has to be weighed against the potential for adverse effects of many of the drugs used clinically. Serious adverse effects appear only in a minority of

patients; however, there does not seem to be a reliable method of predicting which patients might be at risk.

Benzodiazepines are used to treat anxious children, notwithstanding concerns about dependence, behavioural disinhibition, cognitive impairment and mood changes. The tricyclic antidepressants (TCAs) are generally well tolerated, but their effects on cardiac conduction at higher plasma concentrations are well documented and there have been sporadic reports of sudden death associated with their use in children. Toxicity in overdose is an added concern.

The use of selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors in children and adolescents is widespread, but few rigorous supportive trials have been conducted. The occurrence of both potentially serious adverse effects and other less serious, but troublesome, adverse effects and a possible discontinuation syndrome may complicate the use of these agents in younger patients. However, their relative safety in overdose and the apparent reversibility of adverse effects may favour their use over the TCAs.

Other drugs used in this setting include buspirone and β-blockers. No controlled trials are available at this time, but their adverse effect profiles appear to be relatively favourable and further study is warranted, given the promising nature of the uncontrolled data. The reversible monoamine oxidase inhibitors may be useful in younger anxious patients, but controlled data are needed.

The decision to use pharmacotherapy should be made after consideration of multiple factors, and firm recommendations for the use of drug therapy in anxiety disorders in children and adolescents await more rigorous data.

In recent decades there have been substantial advances in our understanding and management of the anxiety disorders in adults. Epidemiological studies have demonstrated that these disorders are among the most prevalent of the psychiatric disorders.[1] Nosologists have succeeded in separating out 'anxiety neurosis' into various discrete entities with reliable diagnostic criteria. Rigorous controlled trials have led to the introduction of therapies which demonstrate a clear risk-benefit advantage in the drug treatment of these conditions.

However, despite the recognition that the anxiety disorders frequently have their onset in childhood or adolescence, there has been relatively little work on anxiety disorders in this population.

Several factors have impeded research in this area. They include: rapid changes in diagnostic classifications of childhood and adolescent anxiety disorders; the uncertain reliability of rating instruments for anxiety disorders in this population; and, the relatively high comorbidity of other psychiatric disorders, particularly depressive,[2] attention deficit/-hyperactivity[2] and substance use disorders,[3] in children with anxiety disorders.

Given the possible severity and chronicity of many childhood and adolescent anxiety disorders,[2] and the relative safety of the newer pharmacotherapeutic agents, there may well be risk-benefit advantages in the use of medication for these conditions. Researchers have gradually begun to gather rigorous data in this area. In a 1995 review, Allen and colleagues[4] found 13 controlled trials of medication for children and adolescents, and some additional trials have been undertaken since that time. Increasingly, it is being recognised that ethical concerns about research in this population also need to include consideration of the importance of developing effective treatments.[5]

In this paper we selectively review the English language literature on pharmacotherapy of anxiety disorders in children and adolescents, focusing in particular on risk-benefit assessments. The review is divided into 3 sections. The first approaches the topic by focusing on the treatment of the various

anxiety disorders seen in children and adolescents. The second examines the most commonly used medications in these conditions. The third is concerned with risk-benefit assessment and factors influencing choice of drug by a clinician.

1. Anxiety Disorders in Children and Adolescents

The incidence of clinically significant anxiety in children and adolescents has been found by some authors to be as high as 20% in a non-referred population,[6] far greater than the number of cases which come to the attention of the medical and psychological professions. This discrepancy may be contributed to by spontaneous remission, social attitudes concerning the seriousness of emotional, nondisruptive symptoms in children, lack of parental attunement to children's mental states,[7] comparatively low levels of clinician awareness and the tendency of younger children to somatise symptoms.

Keller et al.[2] found a lifetime history of childhood or adolescent anxiety disorder in 14% of participants in a community- and clinic-based study (n = 275), with average age of onset of 10 years and a spontaneous remission rate of 34%. A recent twin study in Virginia, US, has documented a 3-month point prevalence of any Diagnostic and Statistical Manual of Mental Disorders (DSM)-III[8] emotional disorder in 8- to 16-year-olds of 35.8%, but found that the presence of moderate impairment was limited to 14.2%.[9] However, an increased incidence of interpersonal difficulties, academic impairment, somatic symptoms, poor self-esteem and depression in children and adolescents with prominent anxiety symptoms has been described,[6] and in an 8-year prospective study, young adults with a history of childhood-onset anxiety disorder were found to be less likely to be living independently than young adults with no history of psychiatric illness.[10] The importance of effective management of childhood onset anxiety disorders early in their course may lie in the possibility of prevention of secondary and associated psychopathology.

Establishing reliable diagnostic criteria for childhood and adolescent anxiety disorders is an important step in facilitating their appropriate recognition and treatment. There is a growing trend towards conceptualising the anxiety disorders seen in children as the first onset of disorders usually recognised only later in adults. Of the previously listed Anxiety Disorders of Childhood or Adolescence in the DSM-III-R,[11] only 'separation anxiety disorder' and 'reactive attachment disorder' remain as child-specific diagnoses in DSM-IV.[12] 'Overanxious disorder' has been subsumed under 'generalised anxiety disorder' and 'avoidant disorder of childhood or adolescence' now falls under 'social phobia'. The adult criteria have required only minimal modification to accommodate most childhood onset cases.[12]

While the 'anxious child' has traditionally been treated with psychotherapy alone, the introduction of apparently well tolerated new medications has precipitated a review of the use of psychotherapy as the sole modality of treatment. Although controlled studies of the efficacy of individual, play and family therapies in anxious children are admittedly scarce, there are many studies supporting the use of cognitive-behavioural psychotherapy for anxiety disorders in young patients.[13,14] In addition, a retrospective review of 763 young patients treated at the Anna Freud Centre in London, England, suggested that intensive psychoanalytic therapy over at least 6 months was effective in the treatment of younger children with anxiety disorders, particularly phobic disorders.[15] Most child psychiatrists are likely to agree that the current approach to childhood and adolescent anxiety disorders is ideally multimodal, with attention paid to family intervention, individual psychotherapy and environmental manipulation, as well as pharmacological treatment where indicated. The use of other or combined modalities is beyond the scope of this review.

1.1 Separation Anxiety Disorder

Separation anxiety disorder in children and adolescents has significant comorbidity with de-

pression,[16] and a history of separation anxiety disorder has been found in up to half of adult study participants with panic disorder and agoraphobia.[17] There is also a strong familial occurrence of these disorders.[18] These findings have led to the hypothesis that the disorders are variants with a common underlying pathophysiology. This offers an explanation for the overlap of the syndromes and also their documented positive response to the same psychotropic agents, namely the antidepressants.[17]

Early studies, however, focused on the use of benzodiazepines. In an open trial, children with psychiatric disorders were treated with chlordiazepoxide. It was found to be effective in 77% of those with school phobia (n = 50), a heterogeneous group in whom separation anxiety disorder is commonly the primary diagnosis.[19] A smaller open label study of 9 children with school phobia (again with prominent symptoms of separation anxiety) found chlordiazepoxide 10 to 30 mg/day to be a useful adjunct to psychotherapy, enabling 8 of the children to return to school within 2 weeks without serious discomfort.[20]

There have been 4 placebo-controlled studies of the efficacy of tricyclic antidepressants (TCAs) in separation anxiety and school refusal with separation anxiety. An early study using imipramine 100 to 200 mg/day (mean = 152 mg/day) plus behavioural treatment for 6 weeks showed an 81% return to school (n = 16), which was significantly better than a 47% return rate in the group receiving placebo plus behavioural treatment (n = 19). Of interest is that at 3 weeks there was still no difference between the drug group and the placebo group in terms of return to school.[21] However, an attempt to replicate this study in children who had not responded to 4 weeks of behavioural treatment (21 of 45) failed to show any superiority of imipramine over placebo, with an overall improvement rate of 50% in both groups.[22] It should be noted that the number of individuals is small in this last study, making interpretation of the results difficult. Similarly, in a 12-week, double-blind trial comparing clomipramine (40 to 75 mg/day) with placebo in 51 children and adolescents with school refusal (87% with separation anxiety), clomipramine was not found to be superior to placebo in alleviating anxiety/depression symptoms or facilitating a return to school.[23] It is possible that higher doses of clomipramine might have been more effective.

The high potency benzodiazepine clonazepam, given as a daily dose of 0.5 to 3mg, was found to be effective in 3 children with separation anxiety and panic-like symptoms who had not responded adequately to other forms of therapy, including imipramine (n = 2) and alprazolam (n = 1).[24] Nevertheless, results from a controlled study were more ambiguous. An 8-week double-blind crossover trial of clonazepam (up to 2 mg/day) versus placebo was carried out on 12 children with anxiety disorders, 11 of whom had separation anxiety disorder and 10 of whom had more than 1 diagnosis, including generalised anxiety disorder, oppositional defiant disorder, avoidant disorder/social phobia and attention deficit/hyperactivity disorder. At the end of the study, 50% of those who completed the trial no longer met the criteria for an anxiety disorder, but there was no significant improvement relative to the baseline for either group according to the brief psychiatric rating scale (BRPS) or clinical global impression scale (CGI). The authors suggested that a longer duration of treatment may be required for improvement.[25]

An open trial of imipramine (mean dosage = 135 mg/day) versus alprazolam (mean dosage = 1.43 mg/day) in 17 children refusing to attend school showed a 50 and 55% return to school, respectively,[26] but a subsequent controlled trial of alprazolam (mean dosage = 1.82 mg/day) versus imipramine (mean dosage = 164 mg/day) versus placebo in 24 different children refusing to attend school did not find significant intergroup differences in outcome. However, at week 8 there were significantly greater reductions in both anxiety and depression symptoms for the children taking imipramine or alprazolam, with alprazolam somewhat superior to imipramine. Six children completed the study in each group and all except 1 placebo group participant returned to school with improved atten-

dance.[26] Both studies included a high percentage of individuals with comorbid depression.

In an open label study of 21 children, 15 of whom had separation anxiety disorder in addition to overanxious disorder and/or social phobia, fluoxetine (mean dosage 25.7 mg/day) was found to be effective in achieving a marked to moderate reduction in anxiety symptoms in 81%.[27] Initial dosages were low (10mg 3 times per week) and therapeutic effect was noted to begin after 6 to 8 weeks of drug treatment. The medication was well tolerated. In another open study, 10 out of 10 patients with separation anxiety disorder responded to treatment with fluoxetine (mean dosages: children = 24 mg/day; adolescents = 40 mg/day).[28]

In summary, while there is only 1 early controlled trial which strongly points to the efficacy of medication for separation anxiety disorder, it seems clear that benzodiazepines and TCAs may be useful in some children. Given their relative safety and promising efficacy, the use of selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) should also be considered. Further controlled studies of these agents in larger diagnostically distinct groups are necessary to establish efficacy in this disorder.

1.2 Panic Disorder With or Without Agoraphobia

Data on the treatment of childhood and adolescent panic disorder are predominantly limited to case reports and small open trials. TCAs (imipramine and desipramine), for example, were found to be effective in 3 adolescents with panic disorder,[29] and in an 8-year-old boy.[30] An earlier report described 3 children (8 to 13 years) whose panic disorder with agoraphobia responded to imipramine 75 to 125 mg/day with or without alprazolam 1mg twice daily.[31]

Similarly, clonazepam 0.5 to 3 mg/day has been described as effective in 3 prepubertal children with panic-like symptoms.[24] A report of 4 adolescents with panic disorder showed clonazepam 0.5mg twice daily to result in a decrease of mean panic attack frequency from 3 per week to 0.25 per week. There was also a decrease in the mean anxiety score, as measured on the Hamilton Anxiety Rating Scale (HARS), from 32 to 5.7 over 2 weeks of treatment.[32]

In addition, results of a double-blind study of 12 adolescents with panic disorder treated with clonazepam showed that 80% of patients receiving clonazepam achieved a moderate or marked improvement on the CGI scale versus 20% of the patients receiving placebo. The mean panic attack frequency fell from 2 to 0.5 per week in the group receiving clonazepam and from 2 to 1.8 per week in the placebo group. Mean HARS score fell from 25 to 10 in the group receiving clonazepam and from 29 to 21 in the placebo group.[33]

Propranolol has been reported to be useful in the treatment of paediatric hyperventilation syndrome, a possible panic disorder variant. Of 14 patients in an open label series, 13 responded positively to propranolol 30 to 60 mg/day, but relapse occurred within 5 days of cessation of treatment in 8 of the 13 responders.[34]

There are clearly inadequate controlled data to indicate the efficacy of any medication in panic disorder in children, but the 1 controlled trial suggests that clonazepam is an effective treatment in adolescents. It is notable that in adults with panic disorder, clinical recommendations to begin treatment with SSRIs were made before controlled data became available. The addition of a high potency benzodiazepine in the initial stages of treatment may be useful, although the potential adverse effects and complications warrant caution. Additional research is necessary before clinical guidelines can be given with certainty.

1.3 Social Phobia

Black and Uhde[35] described the case of a 12-year-old patient with elective mutism and social phobia who did not respond to 10 weeks of desipramine 200 mg/day, but did respond to fluoxetine 20 mg/day within 4 weeks. Subsequently, an open study of fluoxetine for elective mutism with comorbid overanxious disorder or social phobia in 21 children found that the response was better in those

patients under 10 years of age.[36] In a recent open trial of fluoxetine in the treatment of social phobia, 8 out of 10 children and adolescents showed an improvement, with younger patients who had only 1 anxiety disorder diagnosed tending to respond to lower dosages than those with more than 1 anxiety disorder (i.e. 0.49 versus 0.8 mg/kg/day).[28]

However, a 12-week, placebo-controlled study of fluoxetine 12 to 27 mg/day in the treatment of 15 children and adolescents with selective mutism and social phobia or avoidant disorder showed only 1 significant difference: the parents' rating of global improvement and mutism improvement was greater in those participants receiving fluoxetine.[37] Campbell and Cueva[38] have questioned the significance of this result, as selective mutism is characteristically not prominent in the home environment.

There has been 1 case report of the successful use of buspirone 20 mg/day in an adolescent with social phobia complicating schizotypal/schizoid personality disorder.[39]

A double-blind, placebo-controlled trial over 4 weeks of alprazolam 0.5 to 3.5 mg/day in the treatment of 30 children and adolescents with avoidant or overanxious disorder showed a slightly greater improvement in those with avoidant disorder treated with alprazolam, but this result failed to reach statistical significance.[40]

In adults, monoamine oxidase inhibitors (MAOIs) such as phenelzine[41] have been shown to be effective in the treatment of generalised social phobia. These agents have not been well studied in children. In 1 case report, a 7-year-old girl with selective mutism was successfully treated with phenelzine 60 mg/day.[42]

Limited social phobia or performance anxiety has been successfully treated with a single dose of a β-blocker given prior to the anticipated stressor (e.g. exam, performance, etc) in the vast majority of studies in adults.[43] In 1 study of students, oxprenolol proved more effective than diazepam in reducing anxiety and improving examination performance.[44] However, no specific data on the use of these agents for performance anxiety in children or adolescents were found in the literature.

Given the increasing successful use of SSRIs in adults with social phobia[45] and the possibility that these agents may be helpful in the treatment of social phobia symptoms in children, it seems reasonable to consider their use in this somewhat resistant condition. Once again, this a field in which rigorous controlled trials are necessary.

1.4 Simple Phobia

To our knowledge, no studies on the pharmacotherapy of simple phobia have been conducted to date. Behavioural/cognitive-behavioural therapy remains the treatment of choice,[46] although there are indications that intensive psychoanalytical therapy may also be effective.[15]

1.5 Obsessive-Compulsive Disorder

While there is controversy as to whether or not obsessive-compulsive disorder (OCD) is appropriately placed amongst the anxiety disorders in the DSM system, it is included in this review because it is currently so placed and because the drug treatments used for OCD are similar to those used in other anxiety disorders.

The finding that serotonin reuptake inhibitors were useful in adults with OCD encouraged trials of these agents in children and adolescents. Clomipramine 140 to 200 mg/day[47-49] and fluoxetine 20 mg/day[50] have been established as well tolerated and superior to placebo in the treatment of OCD in children and adolescents in controlled trials. A retrospective review of 20 children and 18 adolescents treated with fluoxetine for OCD showed similar responses in both age groups at similar bodyweight-adjusted dosages (mean dosage 50 mg/day).[51] Fluvoxamine was found to be effective and well tolerated in an open trial,[52] as was sertraline.[53] The phenomenology and the pharmacotherapy of OCD in children and adults with OCD appear to have much in common. Thus, despite possible concerns about their long term efficacy and safety, serotonin reuptake inhibitors

should be considered in younger patients, particularly when other treatment modalities have failed.

It is likely that pharmacotherapy in both children and adults needs to be maintained for some time, as relapse may follow discontinuation of medication.[54] While it is probable that combining medication with behaviour therapy allows earlier or more successful tapering of medication, this remains to be proven in controlled trials. Cognitive behavioural therapy has been concluded to be an effective treatment for the disorder, alone or in combination with drug therapy.[55] Further long term studies are needed, as well as studies of pharmacotherapy versus psychotherapy versus combination therapy.

In adults with OCD, the presence of comorbid tics has been associated with relative failure to respond to serotonin reuptake inhibitors.[56] For example, 11 patients with comorbid Tourette's disorder and obsessive-compulsive symptoms did not show a significantly better response to fluoxetine than to placebo.[57] However, in a retrospective study, 76% of 30 patients with Tourette's disorder and comorbid obsessive-compulsive behaviours responded to fluoxetine 20 to 40 mg/day.[58] Such comorbidity in children and adolescents may require combined therapy with both serotonin reuptake inhibitors and dopamine blockers.[59]

The pharmacotherapy of disorders postulated to fall on a spectrum of OCD-related disorders is not well studied in children and adolescents. Further attention to the pharmacotherapy of disorders such as body dysmorphic disorder, trichotillomania and possibly related conditions in this age group is warranted.

1.6 Post-Traumatic Stress Disorder

A report of the use of propranolol to treat agitation in 11 children with post-traumatic stress disorder (PTSD) following abuse indicated a reduction in symptoms on this medication.[60] There are also some promising preliminary data on the use of clonidine in the treatment of severe PTSD in 7 preschool children.[61]

Although the SSRIs are receiving increased attention in adults with PTSD,[62] there is relatively little data on their use in children with this condition. Once again, given the adult data and given the relative safety of these agents, in clinical practice they should be considered in children and adolescents with PTSD. Further work is necessary to establish efficacy and safety in this population.

1.7 Generalised Anxiety Disorder

Previously referred to as overanxious disorder of childhood, this disorder is one of the more common anxiety disorders in children, with the incidence in a community study ranging from 8.6% in 8-year-olds to 17.1% in 17-year-olds.[6] Despite this, and possibly because it is often comorbid with other anxiety disorders (>50%), there are few studies of the specific pharmacotherapy of this condition.

An 11-week, single-blind study of alprazolam 0.5 to 1.5 mg/day in 12 children and adolescents with overanxious and/or avoidant disorder showed a significant improvement in CGI, and anxiety and depression ratings during the active phase of treatment, but nonresponse and relapse during the placebo phases.[63] However, a subsequent 6-week, double-blind, placebo-controlled study using a larger sample (n = 30) showed no significant superiority of alprazolam 0.5 to 3.5 mg/day over placebo.[40]

In an open trial of fluoxetine 10 to 60 mg/day in 21 children and adolescents with overanxious disorder, separation anxiety disorder and/or avoidant disorder, and excluding OCD and panic disorder, there was moderate to marked improvement in 81% after 6 to 8 weeks.[27] There is a lack of controlled trials of antidepressants in children and adolescents with generalised anxiety disorders. However, these agents may be useful in at least some of these patients.

A single case report of an adolescent treated with buspirone 7.5 to 15 mg/day, started after adverse effects had limited the use of desipramine 125 mg/day, suggested that this agent might be a useful treatment for generalised anxiety disorder in

adolescents.[64] Furthermore, an open label study of adolescents with generalised anxiety disorder/overanxious disorder showed significant reduction of anxiety symptoms after 6 weeks of buspirone 15 to 30 mg/day.[33] Given the efficacy of buspirone in adults with generalised anxiety disorder and its apparently favourable adverse effect profile, this agent appears to be a useful choice in children and adolescents with this disorder and deserves further study in controlled trials.

In summary, there is, at present, no incontrovertible evidence supporting the use of benzodiazepines, antidepressants or buspirone in the treatment of generalised anxiety disorder in young patients. Controlled trials are imperative, given the frequency of the disorder and the widespread empirical use of such medications in its treatment.

1.8 Anxiety Disorder due to Substance Use or to General Medical Conditions

Anxiety disorder due to substances or to general medical conditions is not uncommon in certain clinical settings. Nevertheless, these disorders have not been well researched. In clinical practice, treatment involves addressing the underlying substance abuse disorder or general medical condition and the use of short term benzodiazepines where necessary. Where prescription medication at therapeutic doses is the cause, review of drug choice is indicated.

1.9 Anxiety Symptoms in Other Psychiatric Disorders

There are several case reports and open trials suggesting that serotonin reuptake inhibitors may be beneficial in the treatment of obsessive-compulsive behaviours or anxiety symptoms in children or adolescents with developmental disorders.[65-68] In a 10-week, double-blind, placebo-controlled trial, clomipramine (mean dosage = 152 mg/day) was found to be superior to desipramine (mean dosage = 127 mg/day) and placebo in the treatment of stereotypies and obsessive-compulsive symptoms in 24 autistic children (6 to 18 years).[69] Propranolol[70] and imipramine[71] have also been reported as beneficial in single case reports.

2. Drugs Used to Treat Anxiety in Children: Adverse Effects and Efficacy

2.1 Benzodiazepines

Benzodiazepines have long been established as useful in decreasing the symptoms of anxiety.[19,72] Nevertheless, the literature concerning adults has emphasised the risk of dependency on benzodiazepines. Additional important adverse effects that require consideration in children and adolescents include cognitive impairment, disinhibition and depression.[19]

For example, in an early open trial of chlordiazepoxide 30 to 110 mg/day in divided doses in 130 children with various diagnoses, 41% were rated as having a 'good' to 'excellent' response. Drowsiness and dizziness occurred in about 20%, although this was transient and responsive to dosage reduction in most. A 'paradoxical reaction' of hyperactivity, rage and dyscontrol occurred in 10%. Of these 13 children, 5 had abnormal electroencephalograms, suggesting that this may be a risk factor for adverse behavioural reactions to benzodiazepines. Depression which necessitated withdrawal of the medication occurred in 2 patients.[19]

Similar kinds of adverse events have been reported in controlled trials of benzodiazepines in children and adolescents. For example, in a double-blind study of clonazepam in 12 adolescents with panic disorder, minimal adverse effects were reported, most commonly mild transient drowsiness, but increasing irritability and restlessness caused 1 person to withdraw from the study.[33] In a placebo-controlled study of clonazepam at a dosage of up to 2 mg/day in 12 children with anxiety disorders (11/12 had separation anxiety disorder and 10/12 had more than 1 diagnosis), mild to severe adverse effects (drowsiness, irritability/lability and oppositional behaviour) were experienced by 83% of those receiving clonazepam and 58% of those receiving placebo, the difference not reaching significant levels. However, 3 boys had to be withdrawn

from the trial during the active phase owing to serious disinhibition with marked irritability, tantrums and aggressive behaviour. The authors suggested that the rather steep induction rate (0.25mg every 3 days to 1mg then every 2 days to 2mg) may have contributed to the adverse effects.[25] Toxicity with psychotic symptoms has been reported in 2 cases.[73]

Recent findings on the effect of some benzodiazepines on the immune system may raise concerns about the potential dangers of these drugs, particularly in immune-compromised individuals.[74] However, further research in this area is needed before definitive conclusions can be reached.

In summary, while the benzodiazepines may be useful for the short term treatment of anxiety symptoms in some children and adolescents, the potential for dependence and other adverse effects makes them less than ideal agents. Benzodiazepines should therefore be used with caution and for as short a time as possible.

2.2 Tricyclic Antidepressants

The emergence of self-destructive behaviour in a child with Tourette's disorder and OCD treated with clomipramine 20 to 50 mg/day,[75] and paranoid and aggressive behaviour in 2 adolescents with OCD treated with clomipramine 75 to 200 mg/day,[76] has been reported.

The potentially dangerous cardiovascular adverse effects of imipramine and desipramine, particularly at high doses, have long been a subject of concern to clinicians. Increased heart rate,[77] PR interval prolongation, QTc lengthening and QRS widening[78] have all been reported in children and adolescents. Of 16 children, aged 7 to 12 years, 3 developed first degree atrioventricular block while receiving imipramine 50 to 150 mg/day, and plasma levels above 225 ng/ml were consistently shown to produce slowed intracardiac conduction.[79] In a series, 6 of 30 patients aged 6 to 17 years developed a right bundle branch block-type conduction defect while receiving desipramine at a dosage of up to 5 mg/kg/day (mean = 2.7) and 1 developed an atrioventricular block.[78]

In a review of the pre- and intratreatment electrocardiograms of 39 children given imipramine or desipramine, 11 showed an increase of 0.02 seconds or more in the PR interval, and a new first degree atrioventricular block developed in 2 participants. Those with pretreatment conduction abnormalities were more likely to develop an increase in the PR interval of 0.02 seconds or more. Intratreatment abnormalities did not correlate with the choice or dosage of drug. However, none of the participants showed any clinical adverse cardiovascular responses.[80]

The most disturbing adverse event associated with treatment with desipramine is the intermittent reporting of sudden death in young children taking the drug, often at relatively low dosages.[81] It remains unclear whether these deaths reflect preexisting cardiac dysfunction or are a direct consequence of pharmacotherapy with this agent. Nevertheless, given these findings, the use of TCAs, in particular desipramine, in children and adolescents seems warranted only when psychopathology is severe, and when it is relatively likely they will be efficacious. When the decision to use these agents is made, careful electrocardiogram monitoring is required.

2.3 Selective Serotonin Reuptake Inhibitors

In a study of 24 children and adolescents with OCD or depression treated with fluoxetine 20 to 40 mg/day, Riddle et al.[82] found a 50% incidence of agitation, motor restlessness and sleep disturbance. A second report in the same year from the same group of researchers detailed the emergence of self-destructive behaviour in 6 patients aged 10 to 17 years who were treated with fluoxetine for OCD. Of these patients, 4 required hospitalisation for their symptoms. Whether these adverse events were coincidental or drug-related is not yet established beyond doubt, but there are 2 hypotheses – either the behaviour emerges as a result of the activation of specific mechanisms in vulnerable indi-

viduals, or the drug has a specific effect on the regulation of aggression.[83]

Additional evidence of troublesome adverse effects of the SSRIs emerged in a series of 20 adolescents treated with fluvoxamine for OCD or depression and included hyperactive behaviour, excitement and increased anxiety in 3 patients (severe in 1), hypomania in 1, dermatitis in 3, nausea in 3, drowsiness in 2 and insomnia in 4. More serious adverse effects included hallucinations and delirium (1 each), but these appear to have been limited to 2 debilitated girls with anorexia nervosa.[52] Sertraline used in the treatment of anxiety symptoms in autistic children caused deterioration in behaviour at higher dosages in 2 of 9 children,[68] but in a larger study the major adverse effect reported was gastric discomfort.[53] Sporadic case reports of mania[84] and extrapyramidal symptoms[85] as a complication of treatment with SSRIs in adolescence have appeared.

In an open trial of fluoxetine over 10 months, 21 children and adolescents with overanxious disorder, social phobia or separation anxiety disorder were treated with a mean dosage of 27.5 mg/day, starting with 10mg every second day. Reported adverse effects included insomnia (3 cases), nausea (3), stomach-ache, mild headache and anorexia (1 each). There were no reports of agitation, hypomanic behaviour or suicidal ideation. 81% showed moderate to marked improvement.[27] Similar adverse effects were recorded in an earlier study[86] and in a later open trial.[28]

These contradictory findings may be related to the different initial doses used in the studies. It is possible that low initial doses with slow increments may avoid the behavioural adverse effects seen in earlier studies. The disparate findings may also reflect differences in the underlying neurobiology of the different disorders studied by these groups. Studies of fluoxetine in children and adolescents with depression, for example, suggest that the adverse effect profile of this agent in this population is favourable.

In addition, there is the potential for sexual dysfunction, an adverse effect of the SSRIs that is well known in adults,[87] to limit compliance in older adolescents, and 1 case of hypersexuality has been reported in a 15-year-old boy.[88] Memory impairment has been described as a rare adverse effect of fluoxetine in adults and there is at least 1 report of similar difficulties complicating fluoxetine treatment of an adolescent.[89] There is also recent concern about a discontinuation syndrome following use of SSRIs in adults.[90] There are no available data in this regard for children and adolescents, but there is no reason to believe that they are exempt from this phenomenon. If it does occur in the younger patient, it may complicate termination of treatment with these agents.

Certainly, caution is always required when using antidepressants in children and adolescents. Furthermore, studies to date have primarily focused on fluoxetine, fluvoxamine and sertraline and detailed data on other SSRIs remain to be collected. Nevertheless, in clinical practice the largely favourable adverse effect profile of these agents makes them a useful choice and there is increasing evidence of their efficacy in a number of childhood and adolescent anxiety disorders. Further studies with larger samples are needed to establish firm guidelines for their use.

2.4 Other Agents

Buspirone is a 5-HT_{1A} receptor agonist that has been shown to be effective for generalised anxiety disorder in adults and that appears to have an acceptable adverse effect profile. Furthermore, preliminary data on the safety of this agent in adolescents with generalised anxiety disorder are favourable.[91] However, there has been 1 report of psychotic deterioration in 2 children treated with buspirone for anxiety disorders.[92] Additional research on buspirone in children and adolescents would seem particularly worthwhile.

β-Blockers have been used with good effect for symptomatic relief in anxious younger patients with performance anxiety, hyperventilation syndrome and PTSD, as well as in an adolescent with multiple disabilities and self-injurious behaviour. However, they have been described as inhibiting

Table I. Controlled pharmacotherapy trials in anxiety disorders of childhood and adolescence

Reference	Diagnosis	n	Medication(s) and dosage (mg/day) [approx mean/range]	Duration	Outcome
Gittelman-Klein & Klein[21]	School phobia	35	Imipramine 100-200 *vs* placebo	6 wks	Imipramine > placebo
Berney et al.[23]	School phobia	46	Clomipramine 40-75 *vs* placebo	12 wks	No statistical difference
Flament et al.[47]	OCD	19	Clomipramine 140 *vs* placebo	10 wks	Clomipramine > placebo
Leonard et al.[48]	OCD	48	Clomipramine 150 *vs* desipramine 155	10 wks	Clomipramine > desipramine
Bernstein et al.[26]	School refusal	24	Alprazolam 1-3 *vs* imipramine 150-200 *vs* placebo	8 wks	Alprazolam > imipramine > placebo on clinician rating only
Kutcher et al.[33]	Panic disorder	12	Clonazepam 1-2 *vs* placebo	?	Clonazepam > placebo
Leonard et al.[54]	OCD	26	Clomipramine 140 *vs* imipramine 125	8 mos	Clomipramine > imipramine
DeVeaugh-Geiss et al.[49]	OCD	60	Clomipramine 75-200 *vs* placebo	8 wks	Clomipramine > placebo
Klein et al.[22]	Separation anxiety disorder	21	Imipramine 75-275 *vs* placebo	6 wks	No statistical difference
Riddle et al.[50]	OCD	14	Fluoxetine *vs* placebo	20 wks	Fluoxetine > placebo on clinical global impression scale
Simeon et al.[40]	Overanxious or avoidant disorder	30	Alprazolam 0.5-3.5 *vs* placebo	4 wks	No statistical difference
Gordon et al.[69]	Stereotypes in autistic disorder	12	Clomipramine 150 *vs* placebo	10 wks	Clomipramine > placebo
		12	Clomipramine 150 *vs* desipramine 125	10 wks	Clomipramine > imipramine
Kurlan et al.[57]	Obsessive-compulsive symptoms in Tourette's disorder	11	Fluoxetine 20-40 *vs* placebo	4 mos	No statistical difference
Black & Uhde[37]	Elective mutism	15	Fluoxetine 12-27 *vs* placebo	12 wks	Fluoxetine > placebo on parent ratings
Graae et al.[25]	Separation anxiety	15	Clonazepam 0.5-2 *vs* placebo	8 wks	No statistical difference
Bouvard et al.[91]	Generalised anxiety disorder	42	Buspirone 30 *vs* placebo	6 wks	No statistical difference

n = number of patients; **OCD** = obsessive-compulsive disorder; **?** = not stated; **>** = more effective than.

TCA metabolism in 2 children who received propranolol 30 and 400 mg/day in combination with imipramine 75 and 80 mg/day, respectively.[93] Concentrations of imipramine were found to be near-toxic in both cases.

MAOIs and several other classes of antidepressants have also not been well studied in children and adolescents. While the difficulties of adhering to a strict diet makes the irreversible MAOIs an unlikely choice except in the most refractory of cases, the introduction of the reversible MAOIs, with their apparently favourable adverse effect profile, encourages research on the use of these agents in children and adolescents. Caution would have to be exercised with respect to sequential treatment with SSRIs, in view of the reported occurrence of the serotonin syndrome in such situations.[94]

Clonidine, an α_2-adrenergic agonist, has been used in the treatment of PTSD. Concerns have been expressed about electrocardiogram changes and rebound hypertension following abrupt cessation of clonidine treatment.[95] However, transient sedation appears to be the most commonly reported adverse effect when the medication is used in children with PTSD.[61]

3. Discussion

The usefulness of open trials and case reports is limited by several factors, including the possibility of spontaneous recovery from the conditions under consideration, noted to be 34% in the 1992 study

by Keller et al.[2] However, even in the controlled trials which have been conducted, the number of study participants is low, usually around 20 and very seldom more than 50 (table I). This seriously limits the statistical power of the studies and thus their usefulness in establishing generalisable data concerning the outcome of anxiety disorders treated with pharmacotherapy in young patients.

Should a clinician decide that the potential benefit outweighs the potential risk in any particular case, the choice of which agent to use remains problematic. Such decisions are frequently made on the basis of the cost of individual drugs. However, in the longer term, multiple trials of cheaper, but less effective, medications may be just as costly as treatment with a more expensive, but more effective, drug. Predicting which drug is likely to be the most effective for a particular child is not currently possible, but some trends are suggested by the available literature.

As a point of departure, it appears to be the consensus of clinicians treating children and adolescents with anxiety disorders that, should resources and symptom severity allow, psychotherapeutic treatment, usually cognitive-behavioural in nature, should be the initial intervention. Supportive and psycho-educational intervention with the family as well as the patient would appear to be mandatory whatever treatment regimen is used.

If there is a need for immediate relief of symptoms, or should psychotherapeutic treatment have failed to ameliorate the condition after an adequate trial, the addition of medication must be considered. Factors to be considered in the choice of medication should include age, safety data for that age-group, documented efficacy for the particular disorder in that age group, medical and psychiatric comorbidity, inpatient or outpatient status, lethality in overdose, degree of supervision of medication if an outpatient, previous response to a particular type of medication and, all else being equal, financial implications.

The drugs discussed in sections 2 and 3 act on different neurotransmitter systems: adrenergic, serotonergic and γ-aminobutyric acid (GABA)-ergic, and thus have their effects at different levels of symptom production. There is evidence in adult panic disorder research that benzodiazepines are useful in relieving anticipatory anxiety, while TCAs and SSRIs act at the locus ceruleus level in preventing acute episodes of anxiety as well as the generalisation of associated anxiety.[96] It may be that the same rationale can be applied to the choice of drug for children and adolescents, depending on the nature of the most disabling symptoms. Drug combinations may be required on the same basis.

Further detailed elaboration of the mechanism of the action of drugs in children and adolescents, as well as rigorous controlled studies as to safety and efficacy with documentation of adverse effects, is necessary before evidence-based decisions can be made in clinical practice.

4. Conclusion

In children and adolescents with psychiatric disorders, the immediate morbidity as well as the possible long term consequences of nontreatment need to be emphasised. Increasingly, the anxiety disorders are being understood to have a significant impact on social and occupational functioning in some young patients. Furthermore, while there are relatively few long term follow-up studies of children and adolescents with anxiety disorders, a number of those published emphasise the persistence of original symptoms and the development of additional comorbid disorders.

Conversely, in considering pharmacotherapy of psychiatric disorders in children and adolescents, several risks come to mind. In particular, the adverse cardiovascular effects of the TCAs and the risk of dependency on benzodiazepines have been emphasised in the literature. The dearth of controlled clinical trials showing efficacy of medication over placebo also makes their use problematic in many cases. Certainly, the high costs of many newer agents makes the need for studies of efficacy and cost-efficiency paramount.

Overall, given the relative seriousness of disorders such as OCD and panic disorder in children and adolescents and the relative safety of newer

agents such as the SSRIs in the treatment of these disorders, in current clinical practice it is often prudent to consider the use of such agents in these disorders. Additional controlled trials to establish the efficacy and cost-efficacy of such interventions are, however, clearly necessary in order to make firm pharmacotherapy recommendations in this population.

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