# Anxiolytics, Adrenergic Agents, and Naltrexone

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**ABSTRACT**

**Objective:** To review extant data on the efficacy and safety of anxiolytic medications (benzodiazepines, buspirone, and other serotonin 1A agonists), adrenergic agents (β-blockers and $\alpha_2$-adrenergic agonists clonidine and guanfacine), and the opiate antagonist naltrexone that have been used to treat various psychopathologies in children and adolescents. To identify critical gaps in our current knowledge about these agents and needs for further research. **Method:** All available controlled trials of these medications in children and adolescents published in English through 1997 were reviewed. In addition, selected uncontrolled studies are included. **Results:** The major finding, that there are virtually no controlled data that support the efficacy of most of these drugs for the treatment of psychiatric disorders in children and adolescents, is both surprising and unfortunate. For some drugs, e.g., buspirone and guanfacine, this is because no controlled studies have been carried out in children and/or adolescents. For other drugs, e.g., clonidine and naltrexone, most of the placebo-controlled studies have failed to demonstrate efficacy. **Conclusions:** The strongest recommendations for controlled studies of safety and efficacy in children and adolescents can be given for the following drugs: benzodiazepines for acute anxiety; buspirone (and newer serotonin 1A agonists as they become available) for anxiety and depression; β-blockers for aggressive dyscontrol; guanfacine for attention-deficit/hyperactivity disorder; and naltrexone for hyperactivity, inattention, and aggression in autistic disorder. *J. Am. Acad. Child Adolesc. Psychiatry,* 1999, 38(5):546–556. **Key Words:** psychopharmacology, pediatric, drugs.

This review examines safety and efficacy data for several groups of medications that are used to treat psychiatric disorders in children and adolescents. Classes of medications reviewed are the anxiolytics (benzodiazepines, buspirone, and other serotonin [5-HT] 1A agonists), adrenergic agents (the β-blockers and the $\alpha_2$-adrenergic agonists clonidine and guanfacine), and the opiate antagonist naltrexone. Other classes of drugs that are used as anxiolytics, e.g., the tricyclic antidepressants and the selective serotonin reuptake inhibitors, are reviewed elsewhere in this Special Section (see Emslie et al., 1999; Geller et al., 1999).

All controlled trials of the selected medications in children and adolescents published in English through 1997 are included in this review. In addition, selected uncontrolled studies are included.

Each section follows a consistent format: background, efficacy, safety, and conclusions with recommendations for further research.

*Accepted December 3, 1998.*

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## BENZODIAZEPINES

### BACKGROUND

Benzodiazepines have muscle relaxant, anticonvulsant, hypnotic, and antianxiety effects (Dantzer, 1985). Benzodiazepines have been studied widely in adults, but only a few controlled studies in children and adolescents have been reported and conclusions are limited by small sample sizes, short duration of medication trials, low dosages, and high placebo response rates. Benzodiazepines are in general absorbed and metabolized more rapidly in children than in adults (Siméon, 1993), but no specific

pharmacokinetic data in children and adolescents are available for any of the benzodiazepines except diazepam (Clein and Riddle, 1995).

## EFFICACY

### Anxiety Disorders

*Open-Label Studies.* Of 18 children and adolescents with separation anxiety disorder treated with alprazolam (0.5–6 mg/day), 89% were rated improved by psychiatrists, 82% by parents, 65% by self-reports, and 64% by teachers (R. Klein, personal communication, 1991, cited by Kutcher et al., 1992). In another study, 4 adolescents with panic disorder improved on clonazepam 0.5 mg twice a day (Kutcher and MacKenzie, 1988). Somatic symptoms of anxiety improved more quickly than psychological symptoms of anxiety.

*Placebo-Controlled Studies.* In an 8-week double-blind study comparing alprazolam (mean daily dosage of 1.4 mg/day), imipramine (mean dosage of 135 mg/day), and placebo in children and adolescents with anxiety and/or depressive disorders, there was a trend in favor of the active medication groups (Bernstein et al., 1989). However, it was unclear whether the results were affected by baseline differences in symptom severity between the groups. In a double-blind, placebo-controlled study of alprazolam (mean dosage 1.6 mg/day, range 0.5–3.5 mg/day) for 4 weeks in 30 children and adolescents with overanxious disorder or avoidant disorder, 88% of the completers on alprazolam improved versus 62% in the placebo group, but this difference was not statistically significant (Siméon et al., 1992). A double-blind crossover study evaluated 4 weeks of clonazepam (0.5–2.0 mg/day) versus 4 weeks of placebo in 15 children with anxiety disorders, mainly separation anxiety disorder (Graae et al., 1994), without finding a significant difference between treatment arms. A double-blind, placebo-controlled study of clonazepam for adolescents with panic disorder demonstrated benefit with active medication (Kutcher and Reiter, personal communication, 1996). Those treated with clonazepam showed improvement on measures of generalized anxiety, frequency of panic attacks, and school and social disability.

### Anxiety Associated With Medical Procedures

In 13 pediatric oncology patients, an open-label study of low-dose alprazolam (0.125–1.0 mg) showed the drug to be effective in decreasing anticipatory and acute situational anxiety associated with bone marrow aspirations and spinal taps (Pfefferbaum et al., 1987b). A double-blind, placebo-controlled study evaluated 0.2 mg/kg of oral midazolam, a high-potency, short-acting benzodiazepine, in preschool children undergoing laceration repair (Hennes et al., 1990). Midazolam is currently available only as a parenteral injection solution. Seventy percent in the midazolam group (21/30) improved versus 12% (3/25) in the control group ($p < .0001$). There were no respiratory or other adverse events.

## SAFETY

As in adults, drowsiness and sedation are the most common side effects observed in children. These side effects are dose-related and generally resolve as tolerance develops (DuPont and Saylor, 1992). Other potential side effects include incoordination, diplopia, tremor, and decreased mental acuity (Biederman, 1991; Kutcher et al., 1992). Behavioral disinhibition in children is manifested by irritability, tantrums, and aggression (Graae et al., 1994), and in adolescents as irritability and behavioral outbursts (Reiter and Kutcher, 1991). In a report of 4 children with behavioral disinhibition on clonazepam, 3 of the children had underlying structural brain damage (Commander et al., 1991). These authors suggested that brain injury may be a risk factor for developing this adverse effect. Psychotic reactions or exacerbation of psychotic symptoms have also been reported. Pfefferbaum and colleagues (1987a) described 2 cases of exposure to low-dose benzodiazepines which were associated with psychotic symptoms, which resolved upon discontinuation of benzodiazepines.

Tolerance of and dependence on benzodiazepines occur in adults (Salzman, 1989). No data have been published regarding the risk of physiological and psychological dependence in children and adolescents. However, it is recommended that benzodiazepines be prescribed for youth on a short-term basis (i.e., weeks rather than months) because of the theoretical potential for dependence. Discontinuation of the benzodiazepines can be associated with recurrence of anxiety, rebound anxiety, and withdrawal symptoms such as anxiety, malaise, irritability, headache, sweating, gastrointestinal symptoms, insomnia, and muscle tension (Coffey, 1993; Salzman, 1990). Gradual tapering of the drug reduces the risk of developing these symptoms (Coffey, 1993; DuPont and Saylor, 1992; Kutcher et al., 1992). Abrupt discontinuation of benzodiazepines can result

in seizures, especially in patients with a history of seizures. For clonazepam, a discontinuation rate of less than 0.04 mg/kg per week was found to be safe in a prospective study (Sugai, 1993). Benzodiazepines are relatively safe in overdose (Kutcher et al., 1992), yet these drugs have additive effects with other sedative and hypnotic drugs, including alcohol (Green, 1995). The rate of absorption of the benzodiazepines and the magnitude of their CNS depression effects are also increased by alcohol (Rall, 1990).

Unprescribed use of benzodiazepines occurs in adolescence. In a longitudinal study of 1,230 teenagers in Sweden, 10% had taken anxiolytic and/or hypnotic medications in the previous year (Pedersen and Lavik, 1991). The majority gave sleep disturbance, depression, or minor life stressors as explanations for taking the drugs. Two thirds of the teenagers received the benzodiazepines from their parents, primarily their mothers. On the other hand, 13% of the males and 20% of the females reported intoxication as the purpose for taking these drugs. In this group, the benzodiazepines were obtained from peers and illegal sources. There was a strong association between use by parents and unprescribed use by the adolescents, suggesting that the teenagers were modeling their parents' use.

### RECOMMENDATIONS FOR FURTHER RESEARCH

Future work should focus on controlled studies with adequate sample size, dosage, and duration of treatment to address efficacy of the benzodiazepines for anxiety disorders in children and adolescents. For those benzodiazepines that demonstrate clinical efficacy, pharmacokinetic studies need to be conducted. In addition, studies that evaluate medication in combination with psychosocial treatment are desirable, as they more closely mimic treatment in the real world. It is also important to study tolerance and dependence so that clinicians will be guided regarding which youth are candidates for benzodiazepines and how long treatment should last. The long-term safety of this class of medication needs to be addressed.

## BUSPIRONE AND OTHER 5-$HT_{1A}$ AGONISTS

### BACKGROUND

The 5-$HT_{1A}$ receptor agonists enhance the tonic activation of postsynaptic 5-HT receptors by acting to desensitize the 5-$HT_{1A}$ receptor located on the somatodendritic portion of the presynaptic neuron (Blier et al., 1990). This receptor is part of a negative feedback loop that limits release of 5-HT from the presynaptic neuron as synaptic 5-HT concentrations rise. In studies of adults, buspirone and other azaperone partial agonists at the 5-$HT_{1A}$ receptor have been shown to have both anxiolytic and antidepressant properties. Controlled trials have shown that buspirone is effective for major depression (Rickels et al., 1991; Robinson et al.,1989) and generalized anxiety disorder (Ansseau et al., 1990; Enkelmann, 1991). Unlike gepirone (Pecknold et al., 1993), buspirone does not appear to be effective for panic disorder (Sheehan et al., 1993) or for obsessive-compulsive disorder as a primary agent (Pato et al., 1991) or as an augmentor (McDougle et al., 1993). Buspirone is the only 5-$HT_{1A}$ agonist currently marketed in the United States (for generalized anxiety disorder in adults). Despite lack of controlled studies, buspirone is used in children and adolescents for indications as diverse as oppositional behavior, anxiety, and depression, in part because it is remarkably free of side effects (Kutcher et al., 1995). Other compounds active at pre- and postsynaptic 5-$HT_1$ receptors also are under development (Dubovsky, 1993; Mosconi et al., 1993). For example, flesinoxan (Rodgers et al., 1994), gepirone (McGrath et al., 1994), ipsapirone (Cutler et al., 1994), and tandospirone (Evans et al., 1994) have shown promise in adults.

### EFFICACY

No pharmacokinetic, dose-finding, or controlled safety and efficacy studies of buspirone or any other 5-$HT_{1A}$ agonist in mentally ill children or adolescents have been reported (Hughes and Preskorn, 1994; Kutcher et al., 1995). On the basis of open data, clinical experience, and age-downward extension of studies in adults, buspirone has been used for children with generalized anxiety (Coffey, 1990; Kutcher et al., 1992, 1995; Maletic et al., 1994; Popper, 1993). Moreover, it has been used in the following contexts: anxiety mixed with mild depression; affect-driven aggression in association with oppositional symptoms; pervasive developmental disorders, where affect dysregulation, aggression, and cognitive rigidity are problematic; and occasionally, attention-deficit/hyperactivity disorder (ADHD) refractory to more conventional treatments. However, until controlled studies are available, the use of buspirone for these indications must be considered preliminary.

In an open trial, Siméon (1993) treated 15 patients (aged 6–14 years) with anxiety disorders with buspirone for 4 weeks (18.6 mg mean maximum daily dose) and reported significant improvement in anxiety, behavior, and hyperactivity. Adverse events were infrequent and mild. Case reports of children and adolescents also suggest benefit in overanxious disorder (Kranzler, 1988), depression and obsessive-compulsive disorder (Alessi and Bos, 1991), and social phobia (Zwier and Rao, 1994). An interesting literature also has grown up around the use of buspirone in aggressive children (Gross, 1995; Mandoki, 1994; Stanislav et al., 1994), where speculation has it that benefit may accrue from dopamine antagonist properties seen at high doses as well as from modulation of serotonergic activity, and in autistic children (Realmuto et al., 1989), where attention, impulse control, and hyperactivity have reportedly decreased in some patients. A recently published open-label study in 25 prepubertal children with anxiety and aggression tested doses of up to 50 mg/day for up to 9 weeks: 6 children showed increased aggression or mania, and of the 19 who completed the study only 3 had sufficient benefit to continue buspirone after the study (Pfeffer et al., 1997). Buspirone is usually started at 5 mg 3 times per day and gradually increased to 30, 60, and 90 mg/day in 3 divided doses every 2 weeks. The need for thrice-daily dosing limits feasibility and compliance. Time will tell whether compounds such as gepirone, with higher potency at the 5-$HT_{1A}$ receptor than buspirone; transdermal (patch) delivery of buspirone, which allows much higher serum levels without excessive side effects and which one investigative group (Conners and March, personal communication, 1998) is studying for the treatment of ADHD; or longer-lived 5-$HT_{1A}$ agonists may show greater benefit than the tablet form of buspirone in this regard.

### SAFETY

Side effects across trials of patients with different disorders using different 5-$HT_{1A}$ agonists have been uniformly mild: light-headedness, stomach upset, dizziness, sedation, asthenia, or headaches. Furthermore, the 5-$HT_{1A}$ agonists cause no withdrawal symptoms even after prolonged administration (Rakel, 1990) and have no addictive potential (Murphy et al., 1989).

### RECOMMENDATIONS FOR FURTHER RESEARCH

There is a need for rigorous, controlled studies of buspirone in children and adolescents with various anxiety disorders. In addition, the newer 5-$HT_{1A}$ agonists, such as flesinoxan and gepirone, should be assessed for safety and efficacy in children with anxiety disorders. All of these agents are potentially attractive for use in children because of their favorable side effect profile.

## β-BLOCKERS

### BACKGROUND

The β-adrenergic blocking agents ("β-blockers") have been used for children and adolescents with anxiety disorders or aggressive dyscontrol, although systematic studies have not been done. The largest body of work actually exists for their use in children for treatment of nonpsychiatric disorders, such as migraine headache and neurally mediated syncope. For example, 36 children and adolescents with neurally mediated hypotension were treated with β-blockers, and the investigators concluded that they were safe and efficacious (Scott et al., 1995). Their role in prophylaxis of migraine headaches has been reported since the early 1980s (Forsythe et al., 1984).

There are essentially no pharmacokinetic data in children. β-Blockers differ on type (specificity) of β-receptor blockade, lipophilicity, elimination, and half-life. Propranolol and nadolol are nonselective β-blockers (at both $\beta_1$ and $\beta_2$ receptors), whereas atenolol and metoprolol are selective for $\beta_1$ receptors. These drugs differ on exerting central and peripheral effects, although it is not clear which may play a more important role in moderating anxiety symptoms. Propranolol and metoprolol have both central and peripheral effects, whereas nadolol and atenolol have very little central action. Propranolol and metoprolol undergo hepatic metabolism, whereas atenolol and nadolol are cleared by renal elimination. Propranolol is highly protein-bound, which has clinical import in terms of drug interactions. Drug–drug interactions have been reported in which β-blockers may increase the levels and effects of certain drugs, as well as decrease those of others, generally through competitive inhibition mechanisms. Gillette and Tannery (1994) reported on 2 children with nearly toxic plasma levels of imipramine when taking concomitant propranolol.

### EFFICACY

#### Anxiety Disorders

Studies in adults have not shown significant effects of β-blockers over placebo in the treatment of social phobia,

panic disorder, performance anxiety, or posttraumatic stress disorder (PTSD) (Liebowitz et al., 1992; Turner et al., 1994), yet these agents are commonly prescribed for such disorders. Data in children are even more limited.

*Open-Label Studies.* Famularo and colleagues (1988) reported some improvement in 11 children with PTSD openly treated with propranolol up to 2.5 mg/kg per day using an on-off-on design. Joorabchi (1977) reported that propranolol (up to 30 mg/day) helped 13 of 14 adolescents with hyperventilation syndrome and suggested that this drug might be effective in treating panic disorder.

*Placebo-Controlled Studies.* No systematic studies of a β-blocker have been completed for any pediatric anxiety disorder.

#### Aggressive Dyscontrol

*Open-Label Studies.* Williams and colleagues (1982) reported that open treatment of propranolol in 30 patients (age ranged from 7 to 35 years) with organic brain dysfunction resulted in moderate to marked improvement of the aggression using high dosages (50–1,600 mg/day). Subsequent open trials have reported symptom improvement. Recently, a case report of a 14-year-old, multiply handicapped adolescent with severe self-injury reported a positive response to 300 mg of propranolol per day over a 12-month period (Lang and Remington, 1994). The authors hypothesized that individuals with mental retardation whose symptoms are characterized by overactivity, overarousal, poor frustration tolerance, and self-injurious behavior may be the target population, but more studies are needed.

*Placebo-Controlled Studies.* No placebo-controlled studies have been reported.

### SAFETY

Side effects reported in children are generally similar to those in adults: sedation, mild hypotension, lowered heart rate, bronchoconstriction, hypoglycemia (in diabetic patients), dizziness, Raynaud phenomenon, and sleep disruption (Coffey, 1990). Major concerns in children are potential bradycardia, hypotension, and bronchoconstriction in asthmatic patients. Rebound hypertension is reported in adults upon abrupt withdrawal, so this risk can be avoided by a gradual discontinuation.

One possible effect that has received little attention is that of β-blockers on growth hormone (GH) regulation. Catecholamines inhibit GH secretion through β-adrenergic receptors. β-Blockers do not appear to stimulate GH when given alone, but a controlled study found that long-term administration of atenolol potentiated the growth-promoting effects of GH-releasing hormone therapy in growth-deficient children (Cassorla et al., 1995). β-Blockers can also suppress melatonin (Riddle et al., 1988). This effect has provided the rationale to treat winter depression with propranolol or atenolol (Schlager, 1994). The long-term effects of these neuroendocrine manipulations in children are unknown, and additional studies are needed.

### RECOMMENDATIONS FOR FURTHER RESEARCH

This class of drugs needs further investigation regarding safety, efficacy, and pharmacokinetics. Controlled studies in patients with brain damage and aggression are particularly needed.

## α-ADRENERGIC AGONISTS: CLONIDINE AND GUANFACINE

### BACKGROUND

Since the 1960s, clonidine has been used to treat hypertension in adults (see Wilber, 1980). In the late 1970s, the psychiatric use of clonidine was initiated by Cohen and colleagues (1979) for the treatment of children with Tourette's and other tic disorders. Later this use was extended by Leckman and Cohen (1983) and Hunt and colleagues (1985) as an alternative to stimulant medications for the treatment of children with ADHD, alone or comorbid with Tourette's disorder. By the early 1990s, approximately 200,000 prescriptions per year were written in the United States (Swanson et al., 1995) for clonidine at doses of 0.05 to 0.10 mg administered multiple times during the day to treat children with ADHD (Hunt et al., 1990) and sometimes at night to treat spontaneous or stimulant-related sleep problems (Rubinstein et al., 1994; Wilens et al., 1994). At these doses, clonidine is considered to have agonist effects on presynaptic $\alpha_2$-adrenergic receptors, which result in a net negative effect on noradrenergic activity by reducing its release (Svensson et al., 1975). At peak times, 2 to 6 hours after administration, this produces decreased sympathetic and increased para-

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