PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the Children's Medical Center at the University of Virginia

Volume 8 Number 4 April 2002

New Agents and Second-line Therapies for Attention-Deficit/Hyperactivity Disorder

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This is the third in a series of articles in *Pediatric Pharmacotherapy* focusing on new pharmacologic approaches to the treatment of attention-deficit/hyperactivity disorder (ADHD).[a] While approximately 70 to 80% of children with ADHD respond favorably to treatment with either methylphenidate or amphetamines, the remaining patients continue to have symptoms or develop adverse effects requiring discontinuation of their stimulant.[1] This issue will cover alternative choices for the treatment of ADHD, including a new medication, atomoxetine, and second-line therapies such as clonidine, antidepressants, and anxiolytics.

Atomoxetine: A New Choice

Approval for atomoxetine, a unique new agent for ADHD, is expected within the year. Unlike methylphenidate and amphetamines, it is not a stimulant. It is believed to act indirectly, through blockade of the presynaptic norepinephrine transporter in the brain, resulting in inhibition of norepinephrine reuptake. Atomoxetine was originally called tomoxetine; the name was changed to avoid confusion with tamoxifen. In 1998, Spencer and coworkers conducted a double-blind, placebo-controlled crossover study of atomoxetine in 22 adults with ADHD.[2] At an average dose of 76 mg per day over 3 weeks, 11 of the 21 evaluable patients showed a positive response (> 30% reduction in symptoms). With placebo, only two showed improvement.

In a subsequent study, Spencer's group evaluated the efficacy and safety of atomoxetine in children.[3] Thirty patients between 7 and 14 years of age were enrolled in this 11-week, open-label, dose-ranging study. Therapy was initiated at a dose of 0.1-0.4 mg/kg/day, given in two divided doses. Doses were increased at weekly intervals by 0.25 mg/kg/day as needed. The average dose used during the trial was 1.9 mg/kg/day. Twenty-two patients (73%) completed the study. Statistically significant reductions in ADHD symptoms were found at 1 and 3 weeks of treatment. The mean reduction in symptoms compared to baseline was 38.6% at 11 weeks. Only one patient failed to respond to therapy. The most commonly reported adverse effects were rhinitis (33%), headache (20%), anorexia (17%), and dizziness (17%). None of the patients withdrew because of adverse effects.

In a multicenter study of 297 children (ages 8-18 years) published in *Pediatrics* last year, Michelson and colleagues found that atomoxetine was superior to placebo in reducing ADHD symptoms and improving social functioning.[4] The average effective dose in this 8-week trial was 1.2 mg/kg/day, given in two divided doses in the morning and afternoon. Atomoxetine was well tolerated by most of the subjects. Anorexia, somnolence, and pruritus were the most common drug-related adverse effects, occurring in 6-12% of patients. Only 7 of the 213 patients given atomoxetine withdrew from the study because of adverse effects.

Clonidine

Among the current non-stimulant medications used for ADHD, clonidine is becoming one of the most frequently prescribed. Clonidine, an alpha$_2$-adrenergic agonist, is believed to act through regulation of norepinephrine release from the locus ceruleus. It has been found to be effective in reducing ADHD symptoms alone or in combination with stimulants. Clonidine may also reduce symptoms of aggression and reduce the insomnia associated with stimulants.[5,6] A meta-analysis of 11 studies from 1980-1999, revealed a moderate clonidine effect size of 0.58 ± 0.16, with a 95% confidence interval of 0.27-0.89, on symptoms of ADHD and ADHD with comorbid conduct disorder, developmental delay, and tic disorders.[7]

The typical dosing regimen for clonidine in ADHD is 0.05 mg given orally once daily (usually at bedtime to minimize sedation and any potential orthostatic hypotension), with titration

up to 0.4 mg/day (4-5 mcg/kg/day). The dose may be divided if response is inadequate by the end of the day.[5] Once stabilized, children on larger doses may be switched to the transdermal clonidine patch. The patch is available in sizes to release 0.1, 0.2, or 0.3 mg/day for 7 days. In younger children, clonidine tablets may be made into an extemporaneous oral suspension.[8]

The use of clonidine and methylphenidate in combination continues to be controversial. Both agents can adversely affect cardiac conduction, and this effect may be worsened when the drugs are given in combination. In the early 1990's, four deaths of children receiving both drugs were reported to the Food and Drug Administration (FDA). These cases formed the basis for revised product labeling to caution practitioners about the risk for arrhythmias. Questions remain, however, about the true degree of risk. Although the combination is being used with increasing frequency in the ADHD population, there has not been a parallel increase in the number of cases of arrhthymias.[9] In addition, recent clinical trials of the combination have failed to identify cardiovascular disturbances.[10] Despite these assurances, close monitoring is still warranted. Screening for a patient or family history of rhythm disturbances and periodic monitoring of blood pressure, heart rate and rhythm is recommended. Because of the rarity of this adverse effect, the utility of electrocardiograms remains unclear.[5,11]

Tricyclic Antidepressants and SSRIs

Over two dozen studies have documented the benefits of the tricyclic antidepressants and their successors, the selective serotonin reuptake inhibitors (SSRIs) in patients with ADHD. While they may not be as effective as stimulants, these agents are often beneficial in refractory cases, as combination therapy in patients failing single-agent therapy, or in patients with psychiatric comorbidities. Traditionally, imipramine and desipramine have been chosen for this patient population. The recommended starting dose for both agents in children with ADHD is 2 mg/kg/day (divided into two doses) titrated weekly up to 5 mg/kg/day. While these low doses have been effective for controlling ADHD symptoms, they are usually too low to treat comorbid depression or anxiety.[12] However, they may improve other comorbidities, such as tic disorders.

Patients receiving tricyclic antidepressants should be monitored for adverse cardiovascular effects. Five cases of sudden cardiac death in children receiving tricyclic antidepressants were reported in the 1980's and 1990's, although causality could not be clearly established. Prior to starting therapy and periodically during treatment, a history and physical examination should be obtained to identify any changes in heart rate or rhythm. Other disadvantages to their use include tolerance with long-term use, the need for multiple daily dosing, and the risk for severe toxicity in the event of an overdose.

Because of their selectivity for serotonin, the SSRIs offer several advantages over the tricyclics, primarily fewer adverse effects and reduced toxicity with overdose. Their selectivity, however, may limit their usefulness in ADHD, where inhibition of norepinephrine reuptake may also be needed. In 1991, Barrickman and colleagues reported the results of an open-label trial of fluoxetine in 19 children (ages 7-15 years) with ADHD.[13] All were considered resistant to standard treatment. The average dose after titration was 27 mg/day (range 20-60 mg). Eleven patients (58%) showed at least moderate improvement over six weeks. Adverse effects were minimal. Based on their results, the authors recommended fluoxetine as an alternative for refractory ADHD.

In 1993, Gammon and Brown conducted a second open-label trial of fluoxetine.[14] In their study, 32 patients (9-17 years of age), were given doses up to 20 mg/day over 12 weeks, in addition to their baseline methylphenidate regimen. Thirty patients (94%) showed significant improvement in ADHD symptoms. As in the earlier trial, fluoxetine was well tolerated. With a lack of comparison trials, the role of the SSRIs in ADHD remains undefined. Further research is needed to explore the potential utility of this therapeutic class.

Bupropion

Other antidepressants may also be useful in the treatment of ADHD. Since the late 1980's, over a dozen studies and case series have demonstrated the efficacy of bupropion (Wellbutrin® or generic) in improving ADHD symptoms.[15-20] One of the most frequently cited studies was published by Conners and coworkers in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 1996.[17] In this multicenter trial, 109 children between 6 and 12 years of age were randomized to receive bupropion, at a dose of 3 to 6 mg/kg/day, or placebo for 6 weeks. The authors found significant improvement in both teacher and parent ratings with bupropion, sometimes as early as day 3 of treatment.

Bupropion may offer a distinct advantage over traditional stimulant therapy in patients with

comorbid depression, conduct disorder, or substance abuse. In 2001, Daviss and colleagues evaluated the efficacy of sustained release bupropion in an open-label trial of 24 adolescents (ages 11-16 years) with ADHD and depression.[19] The patients were treated for 8 weeks with doses titrated up to a maximum of 3 mg/kg twice daily. Clinician evaluations of both ADHD and depressive symptoms were favorable in 14 (58%) of the teens. In seven, there was improvement in depression only, and in one patient, only ADHD symptoms improved. Parent and subject evaluations showed improvement in both depression and ADHD symptoms, but teacher evaluations failed to show benefit in ADHD behaviors. As in other clinical trials, bupropion was well tolerated; no patients withdrew because of adverse effects.

While bupropion does not have the cardiovascular risks associated with the tricyclic antidepressants or the substance abuse potential of the stimulants, it does have use-limiting adverse central nervous system effects in some patients. Bupropion may also exacerbate tic disorders and increase seizure frequency in patients with underlying seizure disorders.[12]

Buspirone

Buspirone (BuSpar® or generic), typically used in the management of anxiety and obsessive-compulsive disorders, may also be useful in ADHD. Malhotra and Santosh reported the use of buspirone as the sole treatment in 12 children with ADHD.[20] The patients were 6-12 years of age and had no comorbid disease. They were treated with 0.5 mg/kg/day (range 15 to 30 mg/day) in two divided doses. Treatment was continued for 6 weeks. Mean Conners Parent Abbreviated Index (CPAI) score showed a reduction in ADHD symptoms from 24.75 at baseline to 11.25 at 6 weeks. The mean Children Global Assessment Scale (CGAS) score improved from 36.6 to 67.1. The only adverse effect reported was dizziness in two of the children during the first week. Based on this response, the authors concluded that buspirone may be a useful alternative for ADHD.

Additional research with buspirone in ADHD is expected within the next several years. A transdermal delivery system, a buspirone patch, is currently under review by the FDA for use in patients with ADHD.

Pemoline-associated Hepatotoxicity

Although previously considered an alternative first-line stimulant, pemoline (Cylert®) is no longer recommended for most patients. Pemoline was first marketed in the United States in 1975, following nearly a decade of use in Europe.[21] In December 1996, a letter was sent from Abbott Laboratories, the maker of Cylert®, to health care professionals, alerting them to a potential link between pemoline and hepatotoxicity.[22] In the years between 1975 and 1996, 193 cases of liver dysfunction were reported to the FDA. There were 13 cases of acute hepatic failure. Of those cases, 11 resulted in death or liver transplantation. In all cases, hepatic transaminases were markedly elevated. The development of hepatotoxicity was so rapid in several of these cases, they were not detected with the recommended periodic assessment of liver function.[21,23]

Based on these cases, the wording on pemoline labeling has been changed to highlight the risk of hepatotoxicity and to remove pemoline as a consideration for first-line therapy in ADHD. In recent treatment guidelines from both the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry, pemoline is no longer recommended as a first-line treatment. It has been suggested that pemoline be restricted to patients failing stimulants and the second-line agents.[5,24] The United Kingdom has removed pemoline from the market.[21] In Canada, pemoline is now available only through Health Canada's Special Access Program to better track its use.[25]

Summary

There are a number of useful alternatives for children with ADHD who fail to respond to methylphenidate and amphetamines. While pemoline, the remaining stimulant, has lost popularity because of its link to hepatotoxicity, the use of non-stimulant medications as second-line therapies continues to increase. Clonidine, antidepressants, and anxiolytics may provide significant benefit as an alternative to stimulants in children who are refractory to or are unable to tolerate them, or as combination therapy in children with comorbidities.

[a]These reviews have been developed for a workshop on therapies for behavioral illnesses in children to be given at the 22nd Annual University of Virginia McLemore Birdsong Pediatric Conference from May 17th through 19th. For more information, please contact Shirley P. Newman, Conference Coordinator at 434-924-2554.

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Pharmacology Literature Review

Hepatic complications of parenteral nutrition

This timely review focuses on the hepatic complications associated with the use of parenteral nutrition in children. The authors discuss risk factors, possible mechanisms of injury, and propose several methods for reducing the likelihood of hepatic complications. Btaiche IF, Khalidi N. Parenteral nutrition-associated liver complications in children. **Pharmacotherapy 2002;22:188-211.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/22/02:

1. Moxifloxacin (Avelox®), an IV quinolone antibiotic, was added to the Formulary, replacing gatifloxacin. There are currently no dosing guidelines for its use in children.
2. Ertapenem (Invanz®), a broad-spectrum carbapenem antibiotic, was added. It is currently indicated only for adults. Imipenem/cilastatin was removed from the Formulary. Meropenem remains on the Formulary.
3. Cefotetan (Cefotan®) was added to the Formulary. Cefoxitin was removed.
4. Sodium chondroitin sulfate/sodium hyaluronate (Viscoat®) was added for use during ocular surgery.
5. Brimonidine (Alphagan P®) was added for the treatment of open-angle glaucoma or ocular hypertension. This product contains a stabilized oxychloro compound as a preservative; it replaces the original Alphagan® product containing benzalkonium chloride.
6. Tenofovir disproxil fumarate (Viread®), a prodrug of tenofovir, was approved for management of HIV infection.
7. The restriction on the use of valganciclovir was amended to include CMV prophylaxis following solid organ transplantation.
8. A number of drugs were removed because of lack of use or product discontinuation. For a complete listing, see the P&T Forum newsletter: http://www.hsc.virginia.edu/pharmacy-services/Newsletters/Topic%20listings.html#P&T

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