Use of Stimulants in Very Young Children


Concerns have been raised regarding the use of psychotropic drugs in children and adolescents with emotional or behavioral disorders. In a February 23, 2000 JAMA article by Zito, et al. it was stated that psychotropic medication prescriptions for preschoolers had increased dramatically between 1991 and 1995. Based on these concerns, OMAP conducted an internal review of stimulant prescribing patterns in this young population. In addition, the Oregon DUR Board recommended to the State of Oregon Office of Medical Assistance Programs (OMAP) that the prescribing physician's OMAP performing provider number must be included on all claims for psychotropic drugs (e.g. stimulants) prescribed for children less than 6 years of age.

The use of stimulant medications, including Ritalin, Cylert, Adderall and Dexedrine, is poorly studied in children under six years of age. While the FDA has approved the use of dextroamphetamine, magnesium pemoline and Adderall in children as young as 3 years of age, there are only 6 published controlled studies that include preschoolers aged 4 to 6 years. Methylphenidate is not approved for use in children less than 6 years of age. With this in mind, it is surprising that non-FDA approved uses of stimulants are steadily increasing.

OMAP Report

All outpatient care prescriptions for stimulants (classes 10 and 12) issued in 1997 and 1999 to patients aged 0-19 years were reviewed. Medical claims data from the same time period were also used to identify patients with a diagnosis of "hyperkinetic syndrome of childhood," which includes attention deficit hyperactivity disorder (ADHD). Average prevalence rates of "hyperkinetic syndrome of childhood" in 1997 and 1999 for children aged 0-9 years were 2.26% and 2.76% respectively. The prevalence rates in 10-14 year olds were 4.2% and 5.5% respectively. These rates compare to the medical literature which reports that 3-5% of the nation's school age children are diagnosed with ADHD.

Turning to the prescription claims data, Figure 1 depicts the prevalence rates for patients prescribed stimulant drugs versus patient age for 1997 and 1999. Overall, prevalence rates increased by 15% between 1997 and 1999. This increase occurred primarily in patients over 7 years of age. No stimulant claims were identified for Oregon Medicaid patients below two years of age in either 1997 or 1999.

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ADDRESS CHANGES:

Addresses for distribution of the Oregon DUR Board Newsletter are gathered from OMAP provider files. Update your address by contacting the OREGON OMAP PROVIDER ENROLLMENT UNIT in writing, by fax or e-mail. Inform the Enrollment Unit which provider number the change affects. Request to change the physical address. Changes of the mailing address will affect where checks are sent. For questions, call 1-800-422-5047.

Email: susie.fraser@state.or.us
Fax: 503-947-1177

OxM Provider Enrollment
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Salem, OR 97301-1079
Treatment Recommendations

A review of Oregon’s FFS Medicaid population demonstrates that the use of stimulants in the 2-4 year age group in both 1997 and 1999 was lower than in either of the two Medicaid populations studied by Zito et al. While this is encouraging, the ongoing use of stimulants in some members of this population still remains questionable. Given the controversy surrounding the use of stimulant medication in very young children, consultation with a developmental/behavioral specialist is strongly recommended for all children under 6 years of age who present with behavioral problems suggestive of ADHD so that other diagnoses can be ruled out before treatment is initiated.

Meeting the Needs of Parents and Children

Despite the lack of a definitive diagnosis and with the encouragement of multi-million dollar advertising campaigns, parents may continue to request a prescription for stimulant medications. It is important to thoroughly educate parents on the diagnosis of ADHD, as well as medication side effects, behavior management skills, and other treatment options. The following resources provide useful information for the parent and medical provider.

Sources of ADHD information

2. http://www.p-a-r.org
3. National Attention Deficit Disorder Association (ADDA)
P.O. Box 972
Mentor, Ohio 44061; (803) 487-2282
4. Children and Adults with Attention Deficit Disorder (CHADD)
459 N.W. 70th Ave., Suite 101
Plantation, Florida 33317; (800) 233-4050

References

Table 1. Currently Approved Acetylcholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Rate</th>
<th>Max Daily Dose</th>
<th>Reversibility</th>
<th>Enzymes Inhibited</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>tacrine</td>
<td>10mg PO QID between doses for 4-6 weeks;</td>
<td>160mg</td>
<td>Yes</td>
<td>ACHE, BChE</td>
<td>Liver toxicity, GI,</td>
</tr>
<tr>
<td>Cognex</td>
<td>1 q 8h up to a max of 40mg QID</td>
<td></td>
<td></td>
<td></td>
<td>diarrhea</td>
</tr>
<tr>
<td>donepezil</td>
<td>5mg PO QHS for 1 week; dose may be</td>
<td>10mg</td>
<td>Yes</td>
<td>ACHE</td>
<td>NIVD, gastric upset, constipation</td>
</tr>
<tr>
<td>Anexiact</td>
<td>1 q 2wk as needed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rivastigmine</td>
<td>1.5mg PO BID w/food; dose may be</td>
<td>12mg</td>
<td>Yes</td>
<td>ACHE, BChE</td>
<td>NIV, anorexia, diarrhea</td>
</tr>
<tr>
<td>Exelon</td>
<td>1 q 3mg BID, max 4-6mg BID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recently, focus has shifted to the use of cholinesterase inhibitors (ChEIs), the only FDA approved medications for the treatment of AD. Table 1 provides a summary of the available ChEIs.

Cholinesterase Inhibitors

- Mechanism of Action
  ChEIs prevent the degradation the ACh in the synaptic cleft, resulting in an increase in ACh concentration. There are two major classes of enzymes with cholinesterase activity: butyrylcholinesterase (BChE) and acetylcholinesterase (ACHE), both of which are present in the central and peripheral compartments. ACHE is found to a lesser extent in the periphery, relative to BChE. Therefore, agents that selectively inhibit ACHE over BChE tend to exhibit fewer peripheral cholinergic side effects.

Table 2. Contraindications and Precautions of Cholinesterase Inhibitors

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CONTRAINDICATIONS</th>
<th>PRECAUTIONS</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ChEIs</td>
<td>* Hypersensitivity to anticholinesterase agents</td>
<td>* Anesthesia with succinylcholine-type muscle relaxants</td>
<td>May enhance muscle relaxation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Asthma with exercise, exercise intolerance</td>
<td>1 q 8h of acetaminophen</td>
</tr>
<tr>
<td>tacrine</td>
<td></td>
<td>* Recent or current use of beta blocker</td>
<td>May cause bradycardia</td>
</tr>
<tr>
<td>Cognex</td>
<td></td>
<td>* Recent or current use of fluoxetine</td>
<td>May cause bradycardia</td>
</tr>
<tr>
<td>donepezil</td>
<td></td>
<td>* See Above</td>
<td>May cause bradycardia</td>
</tr>
<tr>
<td>Anexiact</td>
<td></td>
<td>* Pregnancy</td>
<td>May cause bradycardia</td>
</tr>
<tr>
<td>rivastigmine</td>
<td></td>
<td>* Pregnancy</td>
<td>May cause bradycardia</td>
</tr>
<tr>
<td>Exelon</td>
<td></td>
<td>* Recent or current use of antihistamines</td>
<td>May cause bradycardia</td>
</tr>
</tbody>
</table>

DRUG SPECIFIC

- Previous tacrine-induced hepatotoxicity
- History of or current liver disease
- Pregnancy
- Parkinson's disease (PD)
- High incidence of nausea/vomiting with the possibility of weight loss
- Pregnancy
reintroduce and continue treatment. Rogers, et al. concluded that there was no evidence that patients who were on active treatment (donepezil) which was abruptly discontinued did any worse than those who were on placebo throughout the study.13 Patients eligible for trial discontinuation include those showing either no improvement or a mild deterioration after 12 weeks of active treatment.14

**Conclusion**

Currently, providers are faced with limited drug therapy options for Alzheimer’s disease. Despite having only moderate efficacy, ChEIs are presently considered the mainstay of treatment. Patients eligible for treatment with these agents include those without contraindications and with the potential for accomplishing treatment goals. Ongoing therapy with ChEI may or may not continue to prevent disease progression. Drug-free trials provide a safe method of evaluating ChEI efficacy. Practitioners are further encouraged to utilize nonpharmacological treatment methods such as behavioral therapy as a first-line recommendation. 

**References**


OxyContin is a Drug of Abuse

By Joseph Jordan, Pharm.D.

Controlled-Release Oxycodeone

Approved in 1996, OxyContin is currently the only available form of controlled-release oxycodeone and is sold in strengths of 10, 20, 40, 80, and 160 mg.1,3 OxyContin, a C-II controlled substance with a relative potency close to that of oral morphine, is indicated for the treatment of moderate to severe pain when continuous analgesia is required for more than several days.1,3 The recommended dosing interval is every 8 to 12 hours. OxyContin has gained popularity for pain relief because of its long duration of action and its lack of acetaminophen, found in many combination products. Sales of OxyContin in 1999 reportedly increased 95% in 1 year, with sales of $900 million annually.2

Abuse of OxyContin

Oxycodeone abuse is growing as a health-risk in the United States. There were 3,190 emergency room (ER) visits nationwide (1.4 per 100,000 population) related to oxycodeone use in 1996, when OxyContin was released.3 By 1999, the latest year for which data are available, the number of visits had climbed to 6,429 (2.6 per 100,000 population).4 In 1989, 1.2% of drug-related emergency room visits involved oxycodeone, fewer than heroin/morphine (15.2%), but more than codeine (0.2%) or LSD (0.9%).5 The statistics for Oregon follow the same trend. The Oregon Poison Center recorded 21 cases of OxyContin exposure in 1999, which doubled to 46 exposures in 2000. (S. Giffin, Oregon Poison Center, personal communication, Jan 18, 2001)

OxyContin contains an acrylic and polymer matrix which allows for the controlled-release of the active ingredient. Product literature warns that tablets should not be chewed or crushed, as this could lead to the rapid release and absorption of oxycodeone.8 This fact has been utilized to make OxyContin a popular drug of abuse, reportedly achieving extensive use in some parts of the United States.9 Drug abusers can smash OxyContin tablets, destroying the controlled-release mechanism and leaving only a dose of immediate-release oxycodeone plus remnants of the original inert matrix. The oxycodeone can then be inhaled nasally or injected, for an euphoric effect reportedly comparable to that of heroin.5 Oxycodeone is rapidly and effectively absorbed from the nasal mucosa with intranasal administration.8

OxyContin provides the largest dose of oxycodeone available in a single tablet. Immediate-release oxycodeone is only available as 5, 10, and 30 mg tablets and combination formulations include aspirin or acetaminophen, making these less attractive for this kind of abuse. Abuse of combination products is still a concern because of both the opioid and the acetaminophen or aspirin component.

Health Risks

The abuse of oxycodeone has the inherent risks expected from high doses of an opioid, including central nervous system and respiratory depression, which can lead to respiratory arrest, coma and death. Unique problems from oxycodeone abuse have been reported, such as several Australian patients developing granulomatous granulomereuphrisis, leading to the need for hemodialysis, following the intravenous injection of oxycodeone derived from suppositories.5 The granulomas were believed to develop from a component of the suppositories. The intravenous injection or inhalation of the acrylic/polymer matrix found in OxyContin could lead to problems such those seen with the suppository form, or other serious health problems.

Conclusion

OxyContin is becoming a popular drug of abuse. Healthcare providers should be aware of this situation and evaluate patients receiving long-term pain medication for their potential to abuse it. Evaluating a patient’s drug abuse potential may be as simple as asking them about their drug use habits. A recent survey of primary care physicians and psychiatrists found that 32% of physicians do not routinely ask patients about illicit drug use, despite the willingness of many patients to discuss such sensitive information with their physicians.10 Healthcare providers may be able to assess if a patient is manipulating the system to receive prescriptions from multiple providers and/or fill them at multiple pharmacies. Another potential sign of medication abuse is recurring requests for early refills of pain medications. Following the determination that a patient is abusing medications, providers should counsel the patient and offer referral to a treatment program. The previously mentioned survey found that only about half of physicians routinely recommended formal addiction treatment programs to drug abusing patients, in spite of good evidence of their effectiveness.10

Prescribers of pain medications are encouraged to seek a second opinion when patients require relief from long-term pain. Pain management specialists are one group that may be of help in assessing a patient’s treatment options. Oregon law supports this practice when treating intractable pain, as well as having patients sign an informed consent when using pain medications long-term.1,2,4

Article Reviewers: Paul Bascom, M.D., FACCP, Director, Comfort Care Team, OHSU Division of General Internal Medicine & Brett Stoevy, M.D., Director, Pain Management Center, Associate Professor, OHSU Department of Anesthesiology

References

Topiramate (Topamax): a Review of Evidence for Off-Label Uses

By: Joseph Jordan, Pharm.D.

Topiramate (Topamax) is approved for use as an adjunctive therapy for partial-onset and generalized tonic-clonic seizures in adults and children over age 2. It may also be useful for controlling therapy-resistant partial seizures.1,2

Topiramate, a sulfamate-substituted monosaccharide, is actually a derivative of fructose.3,4 The exact mechanism of action for seizure control by topiramate is unknown, but it does block the spread of seizures, and it may have efficacy as adjunct therapy in treating both convulsive and absence seizures.5

Topiramate is increasingly being employed in the treatment of various off-label or non-FDA-approved uses, often without any supporting evidence. Off-label uses mentioned in case reports include binge-eating, acute mania, and cluster-headaches.6,7 A study using topiramate to treat childhood onset epilepsy showed moderate benefit, but the usefulness of topiramate was limited by a high incidence of adverse effects, primarily cognitive dulling.8

Topiramate has been employed as a mood stabilizer for bipolar disorder in several small, open-label studies.9-11 In a study of 54 bipolar patients, those treated for manic symptoms showed significant reductions in standard rating scores, while patients who were depressed or euthymic showed no significant benefit.9 Topiramate was discontinued by 18% of study patients due to adverse effects. In an open-label, retrospective study of 56 patients with psychiatric disorders, 23 of 44 bipolar patients (52%) showed at least moderate improvement.12 No long-term or placebo-controlled studies have been conducted for this indication.

Obesity may occur 2 to 5 times more often in mentally ill patients taking medications than in the general public.13 While many anti-seizure medications cause weight gain, topiramate has been noted to occasionally induce weight loss. This property has been employed by some healthcare providers treating obese patients, and several case reports have been published on this population.14-18 Weight loss has averaged 1-6 kg, and has occurred in 7-13% of topiramate study patients. The most likely cause of weight loss is a reduction of appetite.13,19 Weight loss has usually peaked within 3-12 months of the initiation of topiramate, with patients then returning to pre-topiramate weight levels, even with prolonged therapy.20,21 The case reports did not address the long-term effects of topiramate use.

Pharmacokinetics & Drug Interactions

Topiramate has favorable pharmacokinetics, with rapid absorption and good bioavailability.4 Elimination of topiramate is primarily renal, with 50-80% excreted unchanged in the urine.2 The elimination half-life is 20-30 hours, allowing for once- or twice-daily dosing.4 It appears that the clearance of topiramate is 50% higher in pediatric patients.19 The recommended dose for adjunctive therapy for seizures is 400 mg/day in 2 divided doses.19 The manufacturer recommends titrating the dose upwards slowly, starting with 50 mg/day, and increasing by 50 mg/day each week until the desired dose is reached.20 Monitoring plasma concentrations is not necessary.1

Topiramate has a few important drug-drug interactions. The enzyme-inducing antiepileptic drugs phenytoin and carbamazepine can decrease topiramate plasma concentrations by up to 50%.20 Valproic acid and topiramate may decrease each other’s plasma concentrations by 10-15%.15 Topiramate can decrease plasma estrogen levels by 30% in women taking oral contraceptives concomitantly, necessitating the use of either oral contraceptives with a high estrogen content or an alternative form of contraception.20 Topiramate is in the pregnancy-risk category C.22

Adverse Effects

Other than weight loss, the most common adverse effects seen with topiramate are CNS symptoms, including dizziness, mental slowing or cognitive impairment, somnolence, ataxia, headache, fatigue, impaired concentration and parasthesia.14 Adverse effects have been described as mild, but up to 28% of study patients have discontinued therapy due to adverse effects.1 Adverse effects experienced most often include ‘abnormal thinking’ or cognitive dysfunction in 25-33% of study patients, somnolence in 25-30% and fatigue in 11-30%.15,18 CNS adverse effects are more common with high doses and rapid dose escalation.2

Topiramate is a weak carbonic anhydrase inhibitor and so has a risk of inducing kidney stone formation in approximately 1-2% of patients.24 The majority of the stones that formed in study patients passed spontaneously, however, some did require lithotripsy. Stone formation does not appear related to length of topiramate therapy.2 Increasing a patient’s fluid intake may reduce the likelihood of stone formation.2

Cost

The average single-patient OMAP monthly drug costs for several anticonvulsants and mood stabilizers are provided in Table 1.25 Newer drugs are often priced higher than older drugs in the same class or with the same indication, and topiramate is no exception, with an average OMAP cost of $165 per month. It should be mentioned that the treatment of obesity is not covered by the Oregon Health Plan.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average OMAP Monthly Drug Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium carbonate</td>
<td>$15.19</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>$20.51</td>
</tr>
<tr>
<td>Eskalith ( lithium )</td>
<td>$20.67</td>
</tr>
<tr>
<td>Lithiod ( lithium )</td>
<td>$28.31</td>
</tr>
<tr>
<td>Tegretol XR (carbamazepine)</td>
<td>$45.75</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>$48.39</td>
</tr>
<tr>
<td>Depakote (valproic acid)</td>
<td>$91.67</td>
</tr>
<tr>
<td>Topamax (topiramate)</td>
<td>$165.32</td>
</tr>
</tbody>
</table>

Conclusions/Recommendations

Topiramate is reported to be beneficial for patients with therapy-resistant partial seizures. It has also been used off-label for several other indications with some success, but often without strong supporting evidence. There appears to be little or no justification in using topiramate for weight loss, since it is not likely to be permanent. Studies have indicated weight loss will occur in only 7-13% of patients, and patients will eventually return to baseline weight.20,21 Like most drugs, topiramate has adverse effects associated with its use, with CNS effects and kidney stone formation being the most worrisome. Patients are more likely to experience the cognitive adverse effects of topiramate, than the weight loss effects.2

Article Reviewer: Jonathan M. Meyer, M.D., Psychopharmacology Research, Adult Treatment Services, Oregon State Hospital.

References

4. Scheidmann JH. Topiramate: pharmacokinetics and
Newly Approved Drug from 2000 - Testosterone 1% gel (AndroGel)

By: Joseph Jordan, Pharm.D.

Introduction
AndroGel was approved in February 2000 as replacement therapy for conditions of deficiency or absence of endogenous testosterone in males. AndroGel, a gel formulation containing 1% testosterone for transdermal delivery, is the fourth transdermal testosterone preparation marketed in the U.S. The other 3 products, all patch formulations, have had problems with adherence or local skin reactions. The injectable form of testosterone causes dramatic peaks and troughs in serum testosterone levels and the oral form of the drug has been associated with hepatic toxicity, leaving topical formulations as the best option for delivery.

Supplied in packets of 2.5 and 5 grams, AndroGel is applied as 5 grams, 7.5 grams, or 10 grams of gel, which provide 50 mg, 75 mg, or 100 mg of testosterone respectively. When applied to clean, dry skin, 10% of the topical dose of testosterone is absorbed into the skin over a 24 hour period. The skin acts as a reservoir, slowly releasing testosterone into the bloodstream. Once-daily applications of AndroGel should maintain serum testosterone concentrations within the normal range. Serum testosterone levels should be checked 2 weeks after initiation of therapy to ensure proper dosing.

Clinical Studies
Clinical trials showing the efficacy of AndroGel are limited to one unpublished, 6-month study of 227 hypogonadal men randomized to receive AndroGel or a testosterone transdermal patch. Patients treated with the gel reported improvements in libido, erectile function, mood, and energy and 67% had testosterone levels within the normal range at the end of the trial. No information was provided on the comparator group. A second study was performed comparing the application of testosterone gel repeatedly at one site versus application to four different sites. This 21-day crossover study (7 days each - drug washout/drug) of nine men showed that changing the area of application caused a modest (non-significant) increase of serum testosterone compared to using a single site. Study subjects reported no skin irritation or adverse events with the gel formulation.

Adverse Effects
Adverse effects seen with the use of AndroGel include acne, application site reactions, and prostate disorders. The administration of androgens in diabetic patients may decrease blood glucose and insulin requirements. Androgens may also decrease levels of thyroxine-binding globulin, resulting in decreased total T4 serum levels, however, free thyroid levels may remain unchanged. While 10% of a topical dose reaches the blood stream, the remaining 90% stays on the skin. A study of skin-to-skin contact showed that 15 minutes of vigorous contact allowed the transfer of drug to another person, which led to the doubling of testosterone levels in female partners. It is recommended that the application site be covered with clothing to minimize the potential of drug transfer. Residual testosterone is removed from the skin by washing with soap and water.

Comparative Cost of Therapy
The average monthly costs to OMAP for treatment of a single patient with the 4 topical testosterone formulations are compared in Table 1. AndroGel is the most costly of the products, but may be the most effective and least problematic for some patients.

<table>
<thead>
<tr>
<th>Testosterone Formulation</th>
<th>Average OMAP Monthly Cost for a Single Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testoderm Transdermal (patches)</td>
<td>$91.90</td>
</tr>
<tr>
<td>Testoderm TTS System (patches)</td>
<td>$97.02</td>
</tr>
<tr>
<td>Androderm (patches)</td>
<td>$100.34</td>
</tr>
<tr>
<td>AndroGel (package)</td>
<td>$138.03</td>
</tr>
</tbody>
</table>

Conclusion
AndroGel is the most expensive of the available topical testosterone formulations, but it does have some advantages over the competition, which are all in patch formulation. Patients have reported problems with the patch products including poor adherence and local skin reactions. With AndroGel, the skin serves as a reservoir, slowly releasing testosterone into the bloodstream. One problem encountered with AndroGel is that skin-to-skin contact may allow transfer of the drug to another person, which may be dangerous for some people, such as pregnant women.

References
4. 2000 OMAP Drug Claims Database.