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## Use of Stimulants in Very Young Children

*By: **Ann Hamer**, Pharm.D. and **Helen Varley**, B.Pharm., Dip. Clin. Pharm., M.R. Pharm.S.*

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.[1] 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.[2] 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 2.28% 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.[3]

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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## Cholinesterase Inhibitors: Use in Alzheimer's Disease

*By: **Ann Hamer,** Pharm.D. and **Cisco Jorgensen**, B.S. Pharmacy Clerkship Student*

Alzheimer's disease (AD) is a neurodegenerative process most commonly associated with the progressive loss of cognitive and memory functions. AD is a devastating disorder associated with large economic and emotional burdens. When the costs of medical and long-term care, home care and lost productivity for caregivers are tallied, the direct and indirect costs approach $100 billion each year in the United States.[1]

### Cholinergic Neurotransmission

The etiology of AD is unknown, but significant advances have been made in the understanding of its pathogenesis. Characteristic morphological brain lesions and neurochemical changes, particularly within cortical cholinergic systems occur in AD patients. Without dismissing the importance of other pathological features, this article will focus on those mechanisms responsible for the development of current pharmacologic therapy.

Early AD is marked by the degeneration of a select group of neurons, those transmitting acetylcholine (ACh) from the basal forebrain to the cerebral cortex and hippocampus.[2] As the disease progresses, so does the degeneration of neuronal systems. Pharmacologic research in AD is based on the hypothesis that memory and cognitive deficits are caused by decreased neurotransmitter activity in cholinergic pathways.

### Treatment

Several strategies, with mild to moderate results, have been used in the treatment of ACh deficits in AD patients. Initial attempts focused on administering precursors of ACh, such as choline (Ch) and phosphatidylcholine (lecithin). No clinically significant improvements in cognitive function were shown with these treatments and they are no longer considered focal points of interest.[3] Another attempt to correct ACh deficits involved the use of cholinergic muscarinic agonists. Unfortunately, clinical trials did not show benefit and the use of these drugs was associated with multiple adverse effects (including diarrhea, nausea, vomiting, hypotension, diaphoresis and hypersalivation).[3]

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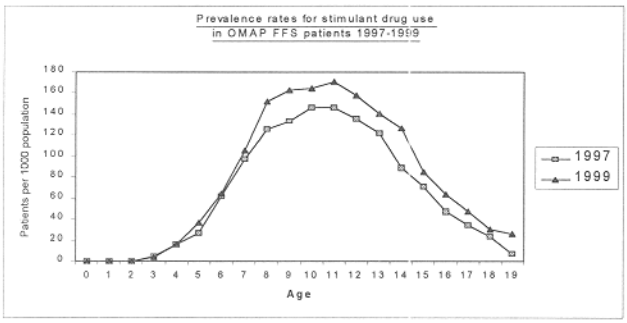


Figure 1

When patients were grouped by age, the prevalence of stimulant use in Oregon Medicaid fee-for-service (FFS) patients was highest in 10-14 year olds. In 1999 the prevalence rate for this age group was 153 patients per 1000, a 19% increase compared to 1997. Use in the 5-9 year age group also increased by 19% in the two year period. Figure 2 shows that use of stimulants increased most in the 15-19 year age group between 1997 and 1999 with a 36% increase in prevalence rates. Use in the 2-4 year age group had a 7.3% reduction in prevalence. These results are more encouraging than those reported by Zito, et al. where use of methylphenidate in 2 to 4 year olds increased as much as 3.1-fold.[1]

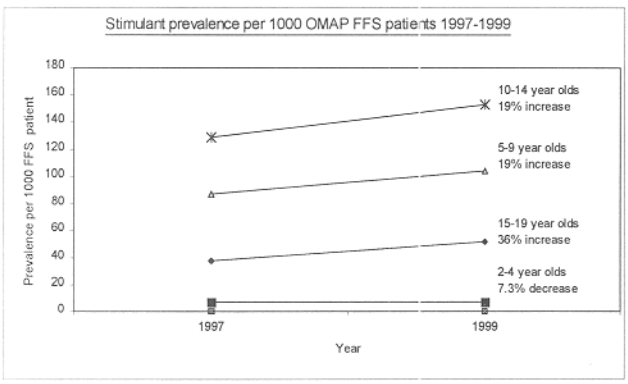


Figure 2

There are two OMAP drug classes that contain stimulant drugs, class 10 and class 12. Class 10 contains methylphenidate and pemoline with 95.6% of prescriptions in this class for methylphenidate in 1999. Class 12 includes amphetamine and dextroamphetamine. Overall 71% of patients prescribed a stimulant in 1999 were prescribed a class 10 drug and 37% were prescribed a class 12 drug. This was a change from 1997 when 85% of patients were prescribed stimulants from class 10 and only 20% were prescribed class 12 drugs. Figures 3 and 4 illustrate the changes in drug selection that have occurred between 1997 and 1999.

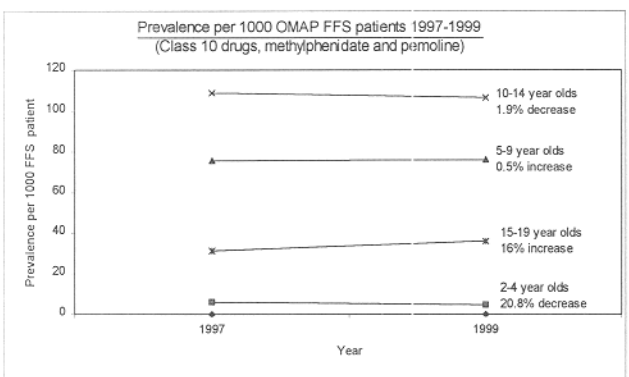


Figure 3

### 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.[1] 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.

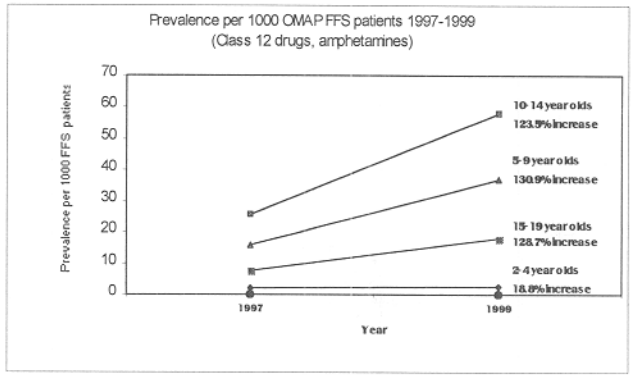


Figure 4

### 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

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

**Article Reviewer**: Robert McKelvey, M.D., OHSU Department of Child and Adolescent Psychiatry, Doernbecher Children's Hospital & Mark Ruggiero, M.D., Assistant Professor, OHSU Department of Developmental and Behavioral Pediatrics, Child Development and Rehabilitation Center

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**Table 1. Currently Approved Acetylcholinesterase Inhibitors**

| Drug | Dose Rate | Max Daily Dose | Reversible | Enzymes Inhibited | Adverse Effects |
|---|---|---|---|---|---|
| tacrine Cognex | 10mg PO QID between meals for 4-6 weeks; ↑ by 40mg/day q 4-6 wks up to a max of 40mg QID | 160mg | Yes | AChE BChE | ↑ liver enzymes, GI distur-bances |
| donepezil Aricept | 5mg PO QHS for 1 week; dose may be ↑ to 10mg QD | 10mg | Yes | AChE | N/V/D, gastric upset, consti-pation |
| rivastigmine Exelon | 1.5mg PO BID w/food; dose may be ↑ q 2 wks as needed to 3mg BID. Max=6mg BID | 12mg | Yes | AChE BChE | N/V, anorexia, dizziness |

Recently, focus has shifted to the use of cholinesterase inhibitors (ChEI), 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.[4]

- Tacrine

Currently, there are three cholinesterase inhibitors approved for use in the United States. Galantamine, a fourth cholinesterase inhibitor, is currently awaiting FDA approval. The first, tacrine (Cognex), was approved in September of 1993. Several double-blind, placebo-controlled trials with parallel group comparisons have been conducted and have involved more than 2,000 patients.[5] The efficacy of tacrine is considered moderate at best. An average improvement on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) does not exceed 3 to 4 points.[6] It has been recognized that a dose-response relationship is present, often necessitating maximal doses for patients to see optimal benefit (120 to 160mg QID). Often these higher doses are not tolerable, with patients routinely experiencing nausea, vomiting and diarrhea. Less commonly, patients have reported dyspepsia, anorexia, increased agitation and confusion.[5] Tacrine has also been associated with hepatotoxicity. Frequent and consistent monitoring of liver enzymes is required. Baseline liver function (AST, ALT, bilirubin) should be obtained prior to the initiation of therapy. ALT levels should be drawn every other week for the first 16 weeks of therapy. If the levels are normal, the ALT should be drawn monthly for two months and then every three months thereafter. If the ALT level is above the normal limit, then weekly tests are recommended. Dose reductions may be warranted as well.[5]

Tacrine's effect on behavior and emotional symptoms, unlike cognition, is less well studied. While benefit may be seen in some patients, a meta-analysis of tacrine trials failed to report significant improvement. In fact, patients are often excluded from drug trials if behavioral symptoms are present.[7]

- Donepezil

The second cholinesterase inhibitor approved for use was donepezil (Aricept) in November 1996. Like tacrine, donepezil is indicated for the treatment of patients with mild to moderate AD, but it has significant advantages in dosing and adverse effects. Donepezil has a higher selectivity for AChE in the CNS versus the periphery resulting in fewer cholinergic side effects.[8] In addition, donepezil has a longer inhibitory action; once-a-day dosing is appropriate. In clinical trials, donepezil appears to be well tolerated, but only moderately effective. Nausea, vomiting, diarrhea and constipation were commonly reported, and generally diminished as therapy was continued. Donepezil is not associated with hepatotoxicity. Improvement in ADAS-cog scores ranged from 2.49 to 4 points.[4]

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**Table 2. Contraindications and Precautions of Cholinesterase Inhibitors[10]**

| DRUG | CONTRAINDICATIONS | PRECAUTIONS | EXPLANATION |
|---|---|---|---|
| **GENERAL** | | | |
| All ChEIs | * Hypersensitivity to anticholinesterase agents | * Anesthesia with succinylcholine-type muscle relaxants<br>* Active GI disease, history of ulcer disease, or patients receiving NSAIDs<br>* Pre-existing conduction defects, bradyarrhythmias, or sick sinus syndrome<br>* Asthma or obstructive pulmonary disease<br>* Seizure disorders<br>* Pregnancy | ▸ May enhance muscle relaxation<br>▸ ↑ gastric acid secretion, ↑ risk of ulceration<br>▸ May cause bradycardia<br>▸ Cholinomimetic<br>▸ Potential to induce seizures |
| **DRUG SPECIFIC** | | | |
| tacrine (Cognex) | * Previous tacrine-induced hepatotoxicity | * History of or current liver disease<br>* Pregnancy | ▸ Risk of hepatotoxicity<br>▸ Pregnancy category C |
| donepezil (Aricept) | * See Above | * Pregnancy<br>* Parkinson's disease (PD) | ▸ Pregnancy category C<br>▸ May exacerbate PD |
| rivastigmine (Exelon) | * Known hypersensitivity to carbamate derivatives or other components | * High incidence of nausea/vomiting with the possibility of anorexia and weight loss<br>* Pregnancy | ▸ Associated with a higher incidence of GI side effects<br>▸ Pregnancy category B |

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• Rivastigmine

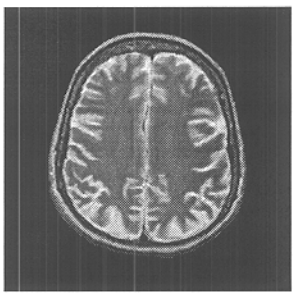
The most recent cholinesterase inhibitor to reach the market, rivastigmine (Exelon), was approved for use in April 2000. Rivastigmine was proven effective in two randomized, double-blind, placebo-controlled studies in patients with mild to moderate AD (n=699; n=725).[9] In both studies, patients on 6-12mg/day produced statistically significant clinical improvement with both the ADAS-cog and the Clinician's Interview-Based Impression of Change (CIBI-plus) compared to the 1-4mg/day and placebo groups. Rivastigmine is associated with a high incidence of GI side effects. Nausea and vomiting have been reported by up to 42% of patients.[9] In addition, patients may experience anorexia and weight loss while taking this drug. Like tacrine, although higher doses may be required for an optimal response, patients may not tolerate the elevated dose.

**When Should Treatment be Started?**

• Who should receive ChEI treatment?

This is a question best answered by first deciding who should not receive ChEI therapy. Based on the contraindications and precautions of the cholinesterase inhibitors, it is easy to determine who is not eligible. See table 2 for a listing of contraindications and precautions.

Trials with all three ChEIs have been conducted with patients diagnosed with "probable AD," or those with a mini-mental status exam (MMSE) score between 10 and 26. The practice of evidence-based medicine would therefore imply that only patients with "probable AD" should receive therapy. Yet, ChEIs can only compensate for ACh deficits as long as the cholinergic system remains intact. Therefore, it can be presumed that the earlier a patient is started on ChEI therapy, the better. One of the difficulties in initiating early treatment is that the rating scales used to monitor patients are not extremely sensitive to small changes, nor are they commonly used in everyday practice.[11] It is not uncommon for clinicians to see patients whose cognitive function is neither clearly normal nor abnormal. As a result, a definitive diagnosis of early AD is difficult to ascertain, and referral may be necessary.



Clearly the decision to initiate treatment will depend upon each individual patient. First, treatment goals should be established between the clinician, patient and caregiver. At best, studies have shown that ChEIs will improve cognitive ability by approximately 3 to 4 ADAS-cog points. Based on the limited efficacy of ChEIs, it should then be realistically determined whether drug therapy will enable achievement of the preestablished treatment goals. Patients with advanced disease are not appropriate candidates for treatment. It should also be recognized that patients on ChEIs will only have a limited duration of improvement. Studies have shown that patients will return to baseline function or worse after 26 weeks of ChEI treatment.[12]

**When Should Treatment be Stopped?**

Another question that arises with the use of ChEIs is when, if at all, should these medications be discontinued. Those who are poorly tolerating or poorly complying with treatment should be withdrawn. The difficult decision involves those patients receiving uncertain benefit from the medication. There is no definitive answer to this piece of the question. Some experts recommend the discontinuation of drug therapy if there is a lack of clinical improvement after 3 to 6 months, yet, the definition of clinical improvement in AD patients is highly ambiguous and subjective. Most would agree that prevention of disease progression is a reasonable outcome, and that true clinical improvement is highly unlikely. To that end, an evaluation of patient response should be undertaken. Drug-free periods may offer the best means of evaluation. It is suggested that symptomatic deterioration during a drug-free period of up to 6 weeks might be used as an indication to 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 behavior therapy as a first-line recommendation. ❖

**Article Reviewers:** Douglass Stennett, Pharm.D., Professor of Pharmacy Practice, Oregon State University; Jonathan M. Meyer, M.D., Psychopharmacology Research, Adult Treatment Services, Oregon State Hospital; Harry Krulewitch, M.D., Providence Elderplace & Kevin Smith, M.D., OHSU Department of Psychiatry

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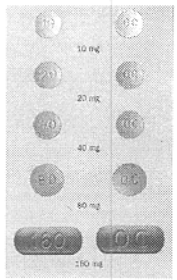
# OxyContin is a Drug of Abuse

*By:* ***Joseph Jordan****, Pharm.D.*

### Controlled-Release Oxycodone



Approved in 1996, OxyContin is currently the only available form of controlled-release oxycodone and is sold in strengths of 10, 20, 40, 80 and 160 mg.[1,2] 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.[3,4] The recommended dosing interval is every 8 to 12 hours. OxyContin has gained popularity for pain relief because of its potency, its duration of pain relief and its lack of acetaminophen, found in many combination products. Sales of OxyContin in 1999 reportedly increased 95% in 1 year, with sales of $600 million annually.[5]

### Abuse of OxyContin

Oxycodone 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 oxycodone use in 1996, when OxyContin was released.[6] 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).[6] In 1999, 1.2% of drug-related ER visits involved oxycodone, fewer than heroin/morphine (15.2%), but more than codeine (0.2%) or LSD (0.9%).[7] 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 oxycodone.[1] This fact has been utilized to make OxyContin a popular drug of abuse, reportedly achieving extensive use in some parts of the United States.[5] Drug abusers can smash OxyContin tablets, destroying the controlled-release mechanism and leaving only a dose of immediate-release oxycodone plus remnants of the original inert matrix. The oxycodone can then be inhaled nasally or injected, for a euphoric effect reportedly comparable to that of heroin.[5] Oxycodone is rapidly and effectively absorbed from the nasal mucosa with intranasal administration.[8]

OxyContin provides the largest dose of oxycodone available in a single tablet. Immediate-release oxycodone is only available as 5, 15 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 oxycodone 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 oxycodone abuse have been reported, such as several Australian patients developing granulomatous glomerulonephritis, leading to the need for hemodialysis, following the intravenous injection of oxycodone derived from suppositories.[9] 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 recommend 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.[11,12] ❖

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

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

*By:* ***Joseph Jordan****, Pharm.D.*

Topiramate (Topamax) is approved for use as 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.[2]

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.[5-7] 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.[9,10] 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 58 patients with psychiatric disorders, 23 of 44 bipolar patients (52%) showed at least moderate improvement.[10] 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.[11] 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.[12-14] 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.[3,15] 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.[2,15] 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.[3] The recommended dose for adjunctive therapy for seizures is 400 mg/day in 2 divided doses.[3] 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.[3] Monitoring plasma concentrations is not necessary.[3]

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%.[3,4] Valproic acid and topiramate may decrease each other's plasma concentrations by 10-15%.[3] 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.[4] Topiramate is in the pregnancy-risk category C.[3]

### 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.[1,2] Adverse effects have been described as mild, but up to 28% of study patients have discontinued therapy due to adverse effects.[3] 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%.[3,15] CNS adverse effects are more common with high doses and rapid dose escalation.[3]

Topiramate is a weak carbonic anhydrase inhibitor and so has a risk of inducing kidney stone formation in approximately 1-2% of patients.[1] 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.[3]

### Cost

The average single-patient OMAP monthly drug costs for several anticonvulsants and mood stabilizers are provided in Table 1.[16] 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 1**

| Average OMAP Monthly Drug Costs for Anticonvulsants and Mood Stabilizers | |
|---|---|
| lithium carbonate | $15.19 |
| carbamazepine | $20.51 |
| Eskalith (lithium) | $20.57 |
| Lithobid (lithium) | $28.31 |
| Tegretol XR (carbamazepine) | $45.75 |
| valproic acid | $48.39 |
| Depakote (valproic acid) | $91.57 |
| Topamax (topiramate) | $165.32 |

### 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.[2,3] 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. ❖

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

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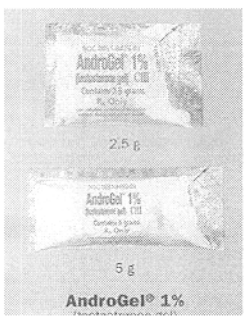
# Newly Approved Drug from 2000 - Testosterone 1% gel (AndroGel)

*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.[1]




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.[2] The skin acts as a reservoir, slowly releasing testosterone into the blood. 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.[2]

### 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.[2] Patients treated with the gel reported improvements in libido, erectile function, mood, and energy and 87% 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.[3] Study subjects reported no skin irritation or adverse events with the gel formulation.[3]

### Adverse Effects

Adverse effects seen with the use of AndroGel include acne, application site reactions, and prostate disorders.[2] The administration of androgens in diabetic patients may decrease blood glucose and insulin requirements. Androgens may also decrease levels of thyroxin-binding globulin, resulting in deceased 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.[2] 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.[1] 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.[4] AndroGel is the most costly of the products, but may be the most effective and least problematic for some patients.

**Table 1**

| Average OMAP Monthly Cost for a Single Patient | |
|---|---|
| Testoderm Transdermal (patches) | $91.90 |
| Testoderm TTS System (patches) | $97.02 |
| Androderm (patches) | $100.34 |
| AndroGel (packet) | $138.03 |

### Conclusion

AndroGel is the most expensive of the 4 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. ❖

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We hope you found this issue of the Oregon Drug Use Review Board Newsletter useful as well as thought-provoking and interesting. We welcome your questions, concerns, comments or ideas regarding the newsletter. Address correspondence to the managing editor:

**Joseph E. Jordan, Pharm.D.**

OSU College of Pharmacy, 840 SW Gaines, Mail Code: GH212, Portland, OR 97201-3098

E-mail: jordanjo@ohsu.edu; Phone: (503) 494-1637; Fax: (503) 494-8797



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840 SW Gaines Street, MC: GH212
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