



The DUR Discovery

Exploring ways to improve pharmacotherapy

Antipsychotics in Patients with Dementia and Behavioral Disturbances

by Heather Brandt PharmD
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Atypical antipsychotics are FDA approved for the treatment of schizophrenia and for mania in patients with bipolar disorder, but have also been found effective in the treatment of a variety of related conditions, including behavioral disturbances associated with dementia. Although this off-label use is widespread and may result in clinical improvement for many elderly patients with dementia, accumulating safety data for more than two years may have significant impact on this practice. Specifically, an increased risk of cardiovascular, cerebrovascular, and other adverse events has been reported in dementia patients treated with atypical antipsychotics.¹

On April 11, 2005, the FDA issued a public health advisory concerning all atypical antipsychotic medications. This alert advised health care providers, patients, and caregivers of safety concerns when using these medications for unapproved or "off-label" indications and applied to all atypical antipsychotics, including Abilify (aripiprazole), Clozaril (clozapine), Geodon (ziprasidone), Risperdal (risperidone), Seroquel (quetiapine), and Zyprexa (olanzapine). In addition, a black box warning has been added to the product labeling of these agents.

Seventeen placebo-controlled trials were cited in which 5,106 elderly patients with dementia were enrolled. These safety trials included aripiprazole, risperidone, quetiapine, and olanzapine. Several analyses showed an increased mortality rate (relative risk of 1.6 - 1.7) in elderly patients with dementia who were users of atypical antipsychotics vs. placebo. The main causes of death were identified as either heart-related (heart failure or sudden death) or infectious disease (pneumonia).

Behavioral disturbances in patients with dementia represent a significant source of emotional distress on the part of caregivers, are a leading cause of institutionalization, and are often very difficult to manage medically. While atypical antipsychotics have benefit in the treatment of these symptoms with an acceptable safety profile for many patients, recent cautionary information suggests that this treatment option may need to be reevaluated. Specifically, cardiovascular and cerebrovascular risks should be carefully considered and documented before initiating treatment with an atypical antipsychotic in a patient with a previous history of stroke, transient ischemic attack, or myocardial infarction. Consideration should also be given to other risk factors including hypertension, diabetes, current smoking, and atrial fibrillation.

As with most medications in this at-risk population, treatment should be commenced at the lowest possible dose and monitored and titrated carefully with regular reviews. In the case of atypical antipsychotics in dementia patients with psychosis, there are a variety of factors to be considered with benefit to patients and caregivers weighed carefully against the risk of adverse events and increased mortality.

References

1. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. FDA Public Health Advisory. Available at: <http://www.fda.gov/cder/drug/advisory/antipsychotics.htm> (accessed 4/05)
2. Motsinger CD, Perron GA, Lacy TJ. Use of Atypical Antipsychotic Drugs in Patients with Dementia. *Am Fam Physician*. 2003 Jun 1;67(11):2335-40.

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Depo-Provera® and Bone Loss

By Kelli Sommers-Nielsen, PharmD Candidate

Since its approval in 1992, Depo-Provera (depo medroxyprogesterone) has become a popular form of birth control due to its ease of use (given IM every 3 months) and low failure rate. A progestin only product, Depo-Provera has been shown to have a lower incidence of estrogen-related adverse events, such as thromboembolism, severe headache and hypertension. However, recent studies warn that Depo-Provera can cause significant decreases in bone mineral density (BMD).

In November 2004, Pfizer issued a similar warning, citing two post-marketing studies, one in adults and one in adolescents, showing a decrease in BMD of 1-2% a year. Bone loss is greatest with increasing duration of use and appears to be only partly reversible. Women under 21 years of age are at greatest risk due to high rates of bone accretion during adolescence and early adulthood. In response to this data, Pfizer issued a black box warning to be added to prescribing information outlining the risk of Depo-Provera use and stating "Depo-Provera contraceptive injection should be used as a long-term birth control method only if other birth control methods are inadequate".

Women should be advised not to use Depo-Provera for more than two years unless other methods are inadequate. It is particularly important to assess the risks/benefits of using Depo-Provera in patients with other risk factors for osteoporosis (ie: smoking, anorexia nervosa, family history of osteoporosis, etc). Physicians and pharmacists should recommend bone mineral density monitoring in long-term users and encourage sufficient calcium and vitamin D intake in all women using Depo-Provera.

Alternatives to Depo-Provera include progestin-only oral contraceptives, estrogen/ progestin combination products and extended cycle oral contraceptives. For women who do not wish to take a pill everyday, NuvaRing® (ethinyl estradiol 15 mcg/day + etonogestrel 0.120 mg/day) and Ortho Evra™ (ethinyl estradiol 20 mcg/day + norelgestromin 0.15 mg/day) are cost-effective, equally-efficacious alternatives.

Table I: Hormone Based Contraception Options

Method	Cost	Onset	Duration	Return to Fertility	Efficacy Perfect	Efficacy Typical
Depo-Provera	\$75/q3mo	0-7 days	3 months	12-18 months	0.3	0.3
Combination Pills	\$15-40/ mo	7 days	Daily	Weeks to months	0.1	5
Progestin-only Pills	\$30-40/ mo	48 hours	Daily	Rapid	0.5	5
Ortho Evra	\$45/ mo	7 days	1 week	6 weeks	1	*
NuvaRing	\$42/ mo	7 days	3 weeks	Weeks to months	1-2	*

* Data not available at this time

NuvaRing® is a small ring inserted vaginally for three weeks then removed for one week. It may be removed for up to three hours per day with no change in efficacy. Ortho Evra™ is a patch applied once weekly for three weeks to the abdomen, buttock, upper outer arm or upper torso then removed for one week. Single replacement patches are available if a patch falls off or is lost.

References

1. Dear Healthcare Professional Letter (Pfizer Inc.) Available at: http://www.fda.gov/medwatch/SAFETY/2004/DepoProvera_deardoc.pdf. Accessed 03/15/2005.
2. Dickey RP. Managing Contraceptive Pill Patients. Millenium Ed. Durant OK: EMIS Medical Publishers 2000.
3. Product Information: Depo-Provera Contraceptive Injection®, medroxyprogesterone acetate suspension. Pharmacia S Upjohn Company, Kalamazoo, MI, (PI revised 03/1999) reviewed 09/2001.
4. Product Information: Nuvaring®, etonogestrel/ethinyl estradiol vaginal ring. Organon Inc., West Orange, NJ, US, 10/2001.
5. Product Information: Ortho Evra™, norelgestromin/ethinyl estradiol. Ortho McNeil Pharmaceutical, Inc., Raritan, NJ, (PI revised 11/2001) reviewed 3/2002.

Cost Corner: Treatments for Allergic Rhinitis

by Scott Sloan, PharmD Candidate and Chris Owens, PharmD

Allergic rhinitis is the sixth most common medical condition in the United States, affecting approximately 40 million people. While not life-threatening, it is associated with lost work days and productivity as well as significant quality of life issues. The total direct and indirect costs for the condition are estimated at more than \$5 billion annually.¹ Common symptoms of allergic rhinitis include rhinorrhea, sneezing, congestion, and pruritis and are due to hypersensitivity of the nasal mucosa to allergens such as pollen, dust mites, and mold. By convention, allergic rhinitis is treated predominantly with antihistamines and nasal corticosteroids, but recent FDA approval of montelukast

of montelukast to Idaho Medicaid totaled \$49,000. In January 2003, montelukast received FDA approval for the treatment of seasonal allergic rhinitis in patients age 2 years and older and by the end of that year spending had increased to over \$1.6 million. By the end of 2004, spending for the agent reached nearly \$2.3 million.

The use of montelukast in the treatment of allergic rhinitis has been evaluated in recent clinical trials. These trials show that montelukast is more effective than placebo, as effective as loratadine, and less effective than a nasal steroid in the treatment of seasonal

Table II: Comparison of Allergy Treatments

Class	Medication	Dosing Interval	Monthly Cost
Sedating antihistamines	Diphenhydramine(Benadryl®)	3-4 times daily	\$12.99
	Clemastine (Tavist®)	Twice daily	\$18.99
	Chlorpheniramine(Chlor-Trimeton®)	Twice daily	\$7.99
Non-sedating antihistamines	Cetirizine (Zyrtec®)	Once daily	\$58.99
	Desloratadine (Clarinx®)	Once daily	\$68.99
	Fexofenadine (Allegra®)	Once daily	\$68.99
	Loratadine (Claritin OTC®)	Once daily	\$19.99
Nasal Steroids	Beclomethasone(Beconase AQ®)	1-2 inhalations each nostril daily	\$76.99
	Budesonide (Rhinocort®)	1 spray/nostril once daily	\$69.99
	Flunisolide (Nasalide®)	2 sprays in each nostril twice daily	\$37.99
	Fluticasone (Flonase®)	2 sprays/nostril daily or 1 spray/nostril twice daily	\$61.99
	Mometasone (Nasonex®)	2 sprays per nostril daily	\$67.99
Mast Cell Stabilizer	Triamcinolone (Nasacort®)	1 spray in each nostril daily	\$67.99
	Cromolyn sodium (NasalCrom®)	2 puffs 3-4 times/day	\$65.39
Leukotriene Inhibitor	Montelukast (Singulair®)	Once in the evening	\$89.99

*Based on AWP per Redbook 2005

(Singulair) for this indication has led to large increases in spending for this agent and clinical debate regarding its appropriate place in therapy.^{1,2}

Montelukast was the second drug in a new class of agents called 'leukotriene inhibitors' approved in February 1998 as a long-term control medication for the prevention of asthma exacerbations. In 1998, the cost

allergic rhinitis. It was likewise less effective than a nasal steroid even when used in combination with loratadine. Available data do suggest, however, that montelukast alone or in combination with antihistamines is perhaps more effective for alleviating congestion symptoms in allergic rhinitis suffers than antihistamines alone.^{2,3,4,5}

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When both clinical and economic issues are considered, antihistamines remain the best first-line treatment for most patients with allergic rhinitis. *Over-the-counter loratadine is an important, cost-effective option that should be considered first-line for patients with allergic rhinitis. It is covered by Idaho Medicaid with a written prescription, provided that patients have a diagnosis of allergic rhinitis coded prior to filling the prescription.*

Nasal corticosteroids alone or in combination with antihistamines are appropriate for individuals with an inadequate response or contraindications to antihistamine therapy. Montelukast may be useful for a subset of patients with significant congestive symptoms; however, combination antihistamine decongestants (loratadine-D) are likely equally effective. At this time, clinical trial data does not support the use of montelukast over antihistamines or nasal steroids, and is best reserved for patients who fail other treatment modalities or for individuals with concomitant asthma.^{1,6}

References

1. Javed Sheikh. "Allergic Rhinitis." *eMedicine*; located at: http://www.emedicine.com/med/topic104.htm#section~author_information (cited 6/02/05)
2. Jeanenne Valli. "The Use of Leukotriene Receptor Antagonists to Treat Allergic Rhinitis." *PharmaNote* 2003;18:9.
3. Nathan RA et al. Pharmacotherapy for allergic rhinitis: A critical review of leukotriene receptor antagonists compared with other treatments. *Ann Allergy Asthma Immunol.* 2003; 90: 182-189.
4. Ratner PH et al. Fluticasone propionate aqueous nasal spray provided significantly greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with Montelukast. *Ann Allergy Asthma Immunol.* 2003 May;90(5): 466-8.
5. Pulleritis T et al. Comparison of nasal glucocorticoid, antileukotriene, and a combination in the treatment of allergic rhinitis. *J Allergy Clin Immunol.* 2002; 109(6): 949-955.
6. Leukotriene Inhibitor Criteria for Use in Veteran Patients: VHA Pharmacy Management Strategic Healthcare Group and the Medical Advisory Group. Located at: <http://www.vapbm.org/criteria/Leukotriene.pdf> (cited 6/8/05)

