



World of Drug Information

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CURRENT CLINICAL ISSUES

Safety and Efficacy of Medications Used to Treat Primary Open-Angle Glaucoma

GOAL:

To increase awareness of the general safety and efficacy of medications used for the treatment of primary open-angle glaucoma.

OBJECTIVES:

1. Describe the treatment options for primary open-angle glaucoma (POAG).
2. Identify the five major classes of medications used to treat POAG.
3. List the common and unique adverse effects for each class of medication used to treat POAG.
4. Identify long-term safety issues associated with topical antiglaucoma medications.
5. Describe the relative efficacy of the medications used to treat POAG.

Glaucoma is an optic neuropathy characterized by changes in the optic nerve head leading to the loss of optic-nerve tissue. This loss is progressive and may lead to visual field losses and eventual blindness. Glaucoma is the second leading cause of blindness worldwide and has been estimated to affect nearly 66.8 million people worldwide by the year 2000 (Coleman, 1999). The disease can be classified into three categories according to the reason for poor aqueous humor outflow: open-angle, closed-angle, or congenital. Open-angle glaucoma is the most common form of the disorder and affects approximately 3 million Americans and accounts for over 4.5 million visits to physicians each year. The disorder is often asymptomatic and about half of those with open-angle glaucoma are unaware they have the disease (National Eye Institute, 1999).

Primary open angle glaucoma (POAG) typically has an adult onset, is bilateral and has few or no noticeable symptoms in most patients until the loss of central vision occurs in later stages of the disease. The exact pathogenesis of the disease remains unknown; however, increased intraocular pressure (IOP) is one of many factors associated with the development and progression of glaucoma (Lesar 1999).

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The increased IOP in open-angle glaucoma is a result of the decreased outflow of aqueous humor through the trabecular meshwork. Current diagnosis and treatment options concentrate on the reduction of IOP as a means of slowing the progression of the disease. Significant advances in the discovery of glaucoma-causing genes, defining the molecular and biochemical mechanisms that lead to retinal ganglion cell death, and neuroprotective strategies may lead to additional therapies in the coming years.

Treatment for primary open-angle glaucoma generally consists of either surgical or pharmacological interventions. Medications are considered first-line therapy, although surgery is becoming increasingly common (Lewis 1999, Alward 1998). Surgical procedures, such as argon-laser trabeculoplasty and surgical trabeculectomy, attempt to physically improve aqueous humor outflow and decrease IOP. Medications lower IOP by either limiting the production of aqueous humor in the ciliary body and/or enhancing aqueous humor outflow through the trabecular meshwork or uveoscleral pathways.

Pharmacologic treatment consists of a stepped approach by which a single topical agent is titrated to effect or to its maximum dosage before an additional agent(s) is added or an altogether different agent is used. Pharmacological options for the treatment of open-angle glaucoma can be divided into five basic classes: beta-adrenergic antagonists, cholinergic agonists, carbonic anhydrase inhibitors, prostaglandin analogues, and adrenergic-receptor agonists. Traditionally, topical beta-adrenergic antagonists have been given as initial therapy due to excellent pressure-lowering efficacy, adequate duration of action, and relatively few ocular side effects. Additional medications from remaining classes were then added or substituted as needed.

In the last few years, several new medications indicated for the treatment of POAG have been introduced. The advent of new treatment

options, and the continuous release of new information concerning their use, presents clinicians with increasingly complex therapeutic decisions. To best care for patients with POAG, it is necessary for healthcare professionals to be aware of the efficacy and safety differences of the multiple classes of medications.

TOPICAL BETA-ADRENERGIC-RECEPTOR ANTAGONISTS

Topical beta-adrenergic-receptor antagonists have been an important part of glaucoma therapy for more than twenty years and are traditionally considered the initial treatment of choice for POAG. These medications reduce IOP primarily by decreasing the production of aqueous humor in the ciliary body of the eye. Topical beta-adrenergic-receptor antagonists include the beta₁-adrenergic-selective medication, betaxolol, the nonselective beta-adrenergic-receptor antagonist with intrinsic sympathomimetic activity (ISA), carteolol, and the nonselective beta-adrenergic-receptor antagonists, timolol, metipranolol, and levobunolol. These agents differ in potency, selectivity, lipophilicity, and ISA; however, all reduce IOP to a similar degree of between 20% and 30% in most patients.

The choice of which topical beta-adrenergic-receptor antagonist to use in a patient with POAG is based on differences in side-effect potential and individual response. Various ocular side effects, though minimal, have been associated with the short-term use of beta-adrenergic-receptor antagonists including: ocular burning, stinging, transient blurred vision, aching, redness, photophobia, foreign-body sensation, and dry eyes. Long-term use of these agents (≥ 1 year) has produced adverse tissue effects on the conjunctiva, damage to the mucous layer of the tear film, corneal anesthesia, superficial punctate keratitis associated with corneal anesthesia, reductions in endothelial cell counts, and dendritic keratopathy. Both timolol and carteolol are thought to produce relatively similar types of ocular side effects. Both medications produce

fewer ocular side effects than the other medications in the class. Metipranolol has the most ocular side effects of the class and has been associated with the development of uveitis (Patel 1997, Watanabe 1997). The occurrence of long-term drift, or tachyphylaxis due to the up-regulation of beta-adrenergic receptors is an additional problem with the use of topical beta-adrenergic-receptor antagonists.

Topically applied beta-adrenergic-receptor antagonists have also been associated with systemic effects. These systemic side effects are the most important adverse effects of the beta-adrenergic-receptor antagonists and include: asthma exacerbation, worsening congestive heart failure, heart block, depression, sleep disturbance, fatigue, anorexia, dysarthria, tinnitus, alterations in test perception, impotence, masking of the signs of hypoglycemia, alteration of serum lipids, dermatologic reactions, and even sudden death. Due to its cardioselectivity, betaxolol is potentially associated with fewer pulmonary side effects than the other medications in the class. Because of the potential for these systemic side effects, all medications in this class should be used with caution in patients with pulmonary diseases, sinus bradycardia, second- or third-degree heart block, congestive heart failure, peripheral vascular disease, diabetes, myasthenia gravis, and in elderly patients.

CHOLINERGIC AGENTS

The cholinergic medications, also referred to as parasympathomimetic or miotic medications, reduce IOP by increasing aqueous humor outflow. These agents, having been utilized for over 100 years, are the oldest medications being used to treat POAG patients. The relatively recent availability of better tolerated and more effective classes of medications has caused the cholinergic classes of medication to be used much less frequently and primarily in patients intolerant of the newer medications. This class of medications includes the direct acting parasympathomimetics, pilocarpine and

carbachol, and the cholinesterase inhibitors physostigmine, demecarium, and echothiophate.

Pilocarpine is the most commonly used cholinergic agonist and is the agent of choice for treating POAG with cholinergic medications. Pilocarpine produces reductions in IOP similar to those seen with beta-adrenergic-receptor antagonists of between 20% and 30%. Treatment with pilocarpine solution 4% given four times daily is approximately equivalent to pilocarpine 4% gel given once daily or timolol 0.5% given twice daily (Lesar 1999). Carbachol is a potent agent in this class with a duration of action longer than that of pilocarpine due to resistance to hydrolysis by cholinesterases. Cholinesterase inhibitors are more potent than the direct cholinergic agonists and cause a greater reduction of IOP.

In general, the side effects caused by the cholinesterase inhibitors are more severe than those caused by the direct-acting cholinergic agonists. Ocular side effects of cholinergic agonists include fixed, small pupils, induced myopia, cataracts (cholinesterase inhibitors), frontal headache, browache, periorbital pain, blurred vision, eyelid twitching, conjunctival irritation, superficial punctate keratitis, retinal tears or detachment, allergic reaction, permanent miosis, precipitation of angle-closure glaucoma, and rarely, miotic cysts of the pupillary margin. These local effects are often intolerable for many patients and may be responsible for as many as 20% of patients discontinuing pilocarpine therapy (Zimmerman 1982, Edwards 1997).

Systemic side effects of the cholinergic agonists are seen relatively infrequently and include symptoms of cholinergic stimulation such as excessive salivation, lacrimation, sweating, nausea, vomiting, diarrhea, pulmonary edema, and symptoms of shock. Heart block has been thought to occur secondary to using high concentrations of topical pilocarpine (Littmann 1987). Long-term use of cholinergic medications has been associated with conjunctival tissue changes, reduction of tear

production, allergic dermatitis, and hyperplasia of the mucous layer of the tear film. Prolonged use of cholinesterase inhibitors is associated with a high frequency of cataracts as well as other serious ocular and systemic side effects and thus these agents are typically reserved for patients who are without lenses, have artificial lenses and are not responding or are intolerant to other therapies.

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase inhibitors (CAIs) lower IOP by decreasing ciliary body aqueous humor secretion. The CAIs can be divided into two separate groups of medications: oral and topical. Oral medications were the first CAIs to be developed and have been used for more than 40 years. Oral CAIs include acetazolamide, methazolamide, and dichlorphenamide. These preparations are more effective than topically applied CAIs, with reductions in IOP ranging from 25% to 40%; however, the oral CAIs have low site specificity and frequently produce intolerable side effects. Because of their side effect profiles, the oral CAIs are considered second or third-line agents in the treatment of POAG.

Two topical CAIs were approved for use in the United States in 1994, dorzolamide and brinzolamide. These topical medications have greater site specificity, considerably fewer side effects, and a reduced IOP-lowering ability of between 15% to 26%. Due to their improved side effect profiles, these topical CAIs provide a useful replacement or addition to a patient with an inadequate response to other medications.

Oral CAI formulations can produce serious and possibly fatal idiosyncratic systemic side effects including aplastic anemia, pancytopenia, Stevens-Johnson syndrome, and severe allergic reactions (mainly due to the fact that they are sulfonamide derivatives). Other side effects caused by oral CAIs include systemic or metabolic acidosis, decreased libido, organic impotence, altered taste, renal failure, renal

calculi, increased serum uric acid levels, gouty arthritis, diuresis, hemorrhagic gastritis, hepatitis, and hirsutism.

Topical CAIs, though less effective at reducing IOP, are generally well tolerated. Ocular side effects experienced by patients receiving topical CAIs include blurred vision, tearing, photophobia, transient burning and stinging, and eyelid inflammation. One study (Adamson 1998) found the most common ocular drug-related side effects of 164 patients receiving dorzolamide monotherapy for 2 years to be conjunctival hyperemia (20.7% of patients), blepharitis (11.6%), follicular conjunctivitis (6%), superficial punctate keratitis (6%), and eyelid erythema (6%). Systemic side effects for these agents are rare, but this may be due to the short duration of experience with using these newer topical agents. Systemic side effects seen with dorzolamide include renal stones (Carlsen 1999), hypotony and ciliochoroidal detachment in patients with previous filtration surgery (Fineman 1996), depression, anorexia, and dementia (Rusk 1998, Schwartzberg 1999). Taste disturbances have been reported in 14% and 13% of patients receiving dorzolamide for 3 months and for 1 year respectively (Rusk 1998, Lass 1998) and in 5% and 13% of patients receiving brinzolamide twice and 3 times daily respectively for 3 months (Silver 1998).

PROSTAGLANDIN ANALOGUES

The newest class of agents available to treat POAG are the topical prostaglandin analogues. While the class includes several medications, latanoprost (available in the United States since 1996) is the most widely available and best studied medication of this class. Prostaglandin analogues reduce IOP by increasing uveoscleral outflow of aqueous humor. Latanoprost is a topical prodrug that produces clinical effects similar to the other classes of medications (IOP reduction of between 30% and 35%) with a favorable ocular and systemic side effect profile. Latanoprost 0.005% one drop daily has been shown to produce a similar or greater reduction of IOP than that of timolol 0.5% twice

daily (Camras 1996, Watson 1996, Mishima 1996, Alm 1995). Latanoprost has not been approved by the United States Food and Drug Administration as a first-line agent for POAG; however, due to its efficacy and side effect profiles, latanoprost represents an additional option for monotherapy or adjunctive therapy in patients not tolerating or responding to other medications.

Several side effects have been shown in clinical trials and reported in community-based use. Ocular side effects of latanoprost include mild conjunctival hyperemia, iris and eyelash hyperpigmentation, cystoid macular edema, anterior uveitis, herpes simplex keratitis, hypertrichosis, punctate corneal erosions, hypotony with choroidal detachment, iris cyst, and pseudodendrites. The unique effect of iris hyperpigmentation is due to an increased production of melanin and not to increased melanocyte division within the iris. This is the most common side effect of latanoprost therapy and occurs in between 7% and 19% of patients treated over 3 to 24 months (Alm 1995, Watson 1998). A vast majority of these pigmentation changes occur in patients with mixed-color irises and are thought to be irreversible upon discontinuation of the medication. The long-term consequences of these pigmentation changes remain unknown. Some patients also develop longer, thicker, and more heavily pigmented eyelashes after treatment with latanoprost (Johnstone 1997). Systemic side effects seen with latanoprost therapy are rare and include muscle and joint pain, allergic skin reaction, and hypertension.

ADRENERGIC-RECEPTOR AGONISTS

Topical adrenergic-receptor agonists may be divided into non-selective agents (alpha- and beta-receptor stimulation) and selective agents (alpha₂-receptor stimulation). Non-selective adrenergic-receptor agonists include epinephrine and dipivefrin (an epinephrine prodrug) and are thought to lower IOP through increased outflow of aqueous humor. These

agents provide less reduction in IOP than is seen with topical beta-adrenergic-receptor antagonists or cholinergic medications. Because of this inferior IOP reduction and a poor side effect profile, these medications are typically used in patients not able to tolerate other therapies or needing mild reductions in IOP.

A high frequency of ocular side effects limits the use of epinephrine in many patients. Dipivefrin may be used in much lower effective concentrations than epinephrine and produces less frequent ocular and systemic side effects; however, dipivefrin use is becoming less common due to the development of the selective topical adrenergic-receptor agonists. Ocular and allergic side effects of epinephrine include mydriasis, burning, allergic blepharoconjunctivitis, eyelid edema, severe conjunctival vascular hyperemia, punctate keratopathy, stenosis of the nasolacrimal duct, corneal staining, excessive tearing, headache, cystoid macular edema in aphakic eyes, and black corneal and conjunctival deposits. Long-term use of non-selective adrenergic-receptor agonists can reduce corneal endothelial cell densities and corneal thickness, cystoid macular edema in aphakic eyes, pigment deposits, allergic dermatitis, and conjunctival inflammation. The development of black, melanin-containing pigment deposits can occur on the cornea, conjunctiva, contact lenses, and in the nasolacrimal duct as cast plugs after long-term use of epinephrine (and to a lesser extent dipivefrin). Acute systemic reactions to epinephrine can include severe hypertension, tachycardia, arrhythmias, tremor, anxiety, and headache. Long-term side effects from epinephrine have been reported and include the development of premature ventricular contractions (Becker 1977) and anorexia (Dantes 1972).

The selective adrenergic-receptor agonists, apraclonidine and brimonidine, decrease IOP by suppressing the productions of aqueous humor. Brimonidine also increases the outflow of aqueous humor via the uveoscleral pathway. Both agents produce IOP reductions similar to

those of 0.5% timolol (between 18% and 27% at peak concentration 2 to 5 hours post-dose and 10% at 8 to 12 hours). The combination of selective adrenergic-receptor agonists with beta-adrenergic-receptor antagonists, latanoprost, or CAIs produces additional IOP reduction.

Apraclonidine has been labeled for use in the management of transient IOP elevations after ocular surgery; however due to a high incidence of tachyphylaxis and central nervous system effects, its use in POAG is limited. Ocular side effects seen with brimonidine therapy include blepharitis, conjunctival edema and hyperemia, conjunctival follicles, photophobia, foreign-body sensation, and stinging. Due to a greater selectivity for the α_2 -receptor, fewer α_1 -receptor reactions such as mydriasis, vasoconstriction, and lid retraction occur with brimonidine use when compared to apraclonidine use. Interestingly, brimonidine

therapy has not been associated with the tachyphylaxis or high incidences of allergic reactions seen with apraclonidine (nor has there been a cross-reactive allergic response shown). Systemic side effects such as respiratory symptoms, muscular pain, headache, dry mouth, mild systemic hypotension (due to its ability to cross the blood-brain barrier), and fatigue have been seen with brimonidine. In clinical trials, very few patients have discontinued therapy with brimonidine due to ocular side effects (Schuman 1997, LeBlanc 1998, Melamed 2000) and relatively few experienced systemic side effects compared to topical beta-adrenergic-receptor antagonists (LeBlanc 1998, Melamed 2000). As more experience and knowledge is gained from the community-based use of brimonidine, increased awareness of its complete side effect profile should become apparent.

CONCLUSION

Newer topical agents for treating POAG such as dorzolamide, brinzolamide, brimonidine and latanoprost appear to have similar efficacy to traditional agents, however their advantage is in improved safety and tolerability. Current studies are assessing the capacity of these newer therapies to influence visual field preservation as well as attempting to ascertain more a complete understanding of the efficacy and safety profiles not apparent in previous clinical trials. As the world's population continues to expand and the number of elderly adults grows with it, healthcare professionals will come into contact with increasing numbers of patients with primary open-angle glaucoma. An increased awareness and general knowledge of medications used to treat these patients will enable appropriate care for this growing population.

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Christopher Robinson, R.Ph., Pharm.D.

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Certificates will be issued to those who score 70% or higher. Those who score below 70% will be notified, and no credit will be recorded. Allow four weeks for processing.

1. Which of the following medications is NOT one of the five major classes of medications used to treat POAG?
 - A. Alpha-adrenergic antagonists
 - B. Carbonic anhydrase inhibitors
 - C. Prostaglandin analogues
 - D. Adrenergic-receptor agonists
2. Which of these is NOT a treatment option for the therapy of POAG?
 - A. Topical application of the carbonic anhydrase inhibitor dorzolamide
 - B. Argon-laser trabeculoplasty
 - C. Oral treatment with the prostaglandin latanoprost
 - D. Oral treatment with the carbonic anhydrase inhibitor acetazolamide
3. Which of the following medications is typically associated with a hyperpigmentation of the iris in patients with mixed-color irises?
 - A. Brimonidine
 - B. Timolol
 - C. Latanoprost
 - D. Pilocarpine
4. Which of these four classes of medications is the oldest class of medications being currently used to treat patients with POAG?
 - A. Alpha-adrenergic antagonists
 - B. Adrenergic-receptor agonists
 - C. Prostaglandin analogues
 - D. Cholinergic agents
5. In general, what percent IOP reduction can a patient expect to achieve when using the selective adrenergic-receptor agonist, brimonidine?
 - A. 10%
 - B. 20%
 - C. 35%
 - D. 45%
6. Which of the following side effects appears to be more common in patients taking the topical carbonic anhydrase inhibitor, dorzolamide?
 - A. Taste disturbances
 - B. Eyelid erythema
 - C. Superficial punctate keratitis
 - D. Conjunctival hyperemia
7. Systemic side effects are often considered the most important adverse effects of the beta-adrenergic-receptor antagonists. Caution should be used when administering one of these medications to a patient with:
 - A. Obstructive airway disease
 - B. Sinus bradycardia
 - C. Second- or third-degree heart block
 - D. All of the above
8. Which of the following side effects has been seen with the long-term treatment of POAG using cholinergic agents such as pilocarpine, carbachol, or the cholinesterase inhibitors?
 - A. Conjunctival tissue changes
 - B. Long, thick, heavily-pigmented eyelashes
 - C. Reduction of tear production
 - D. Allergic dermatitis
9. Carbonic anhydrase inhibitors lower IOP primarily through which of the following mechanisms?
 - A. Decrease formation/secretion of aqueous humor
 - B. Increased outflow of aqueous humor through the trabecular meshwork
 - C. Increased constriction of the ciliary muscle of the eye
 - D. Decreased resistance to aqueous outflow
10. Which topical beta-adrenergic-receptor antagonist produces the most ocular side effects?
 - A. Timolol
 - B. Betaxolol
 - C. Carteolol
 - D. Metipranolol

ANSWER SHEET

Circle the most appropriate answer

- | | | | | | | | | | |
|----|---|---|---|---|-----|---|---|---|---|
| 1. | a | b | c | d | 6. | a | b | c | d |
| 2. | a | b | c | d | 7. | a | b | c | d |
| 3. | a | b | c | d | 8. | a | b | c | d |
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There are two 'Look-up' buttons located on the Main Search screen which are extremely useful in conducting a search. These buttons can be found on the right hand side of the screen, one beside the Descriptor field and one beside the Journal field. To choose one or more descriptors, click on the Look-up button for the Descriptor field and make your selection. Click in the box to the left of each descriptor that you wish to use. A second click in the box will delete the checkmark. When finished with your selections click on OK. This will take you back to the Main Search screen with all of your selections appearing in the Descriptor field. Note that the default Boolean term is OR, so if in your search strategy you want to use "AND", click the "AND" button under "CONNECTOR" before clicking "OK". For instance, if you select "**STUDY RANDOMIZE ADULT 135**", "**ADM PARENT INTRAVENOUS 66**", and "**DOSAGE 43**", select "AND" to include all of these descriptors in your search.

The same process applies to the Look-up button associated with the Journal field, though in this field it is less likely that you would want to use multiple entries. However, the Look-up button does provide a quick and easy way to select the valid term for whichever journal you wish to search.



Nicola Sarrazin, R.Ph., Pharm.D.

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Perspective from an *IDIS* Subscriber



Late Occurring Nausea/Abdominal Pain in an Elderly Female on Maintenance Lithium Carbonate Therapy. Chronic Lithium Toxicity at "Therapeutic Serum Levels"?

Re: A 70 year old female who was admitted to psychiatry service on 3/15 with recent plan to commit suicide by overdose with severe leg pain and worsening depression with gradual loss of the ability to care for herself over the preceding few months. On 3/23 transferred to the GEM (Geriatric Evaluation and Management) Unit for further work up and discharge planning.

CHIEF COMPLAINT:

Severe pain in legs; did not want to live anymore.

PRIOR MEDICAL/SURGICAL HISTORY:

Coronary artery disease, insulin dependent diabetes mellitus, duodenal ulcer and mild antral gastritis; s/p acute myocardial infarction; hypercholesterolemia with elevated triglycerides; vertigo; chronic right ear otitis media; endometrial cancer; urinary incontinence; past surgeries include: total hysterectomy; bladder suspension placement; cholecystectomy; and esophageal dilation.

PRIOR PSYCHIATRIC HISTORY:

History of generalized anxiety disorder (onset and pattern vague); history of bipolar affective disorder (for > 20 years). Has been stable on Proloxin™ and lithium for about 20 years. Over the past six months she had become increasingly depressed, with sadness, decreased energy, nausea, anorexia, diarrhea, about a 10 pound weight loss, anhedonia and memory problems. She also complained of significant extrapyramidal symptoms including: tremors, bradykinesia, and cramping (dystonias?) in the legs.

HOSPITAL COURSE:

While on Psychiatry Service on 3/16 Proloxin™ was discontinued and lithium dose was reduced

(decreasing the serum lithium level from 1.1 to 0.7 mEq/L). Within a few days she reported

improvement in her energy level, tremor, leg cramps, and resolution of any suicidal ideation. She remains depressed, pessimistic and continues to complain of poor appetite and nausea. Mini-mental state examination on 3/1 score 23/30.

After transfer to GEM she often refused to participate in her assigned rehabilitation visits, offering nausea or fatigue as the reason(s) for her refusal. She made minimal progress during her time on GEM unit.

DATA:

(3/24) BUN/s.cr 25/0.9; NA 139; CA9.3; Cholesterol 178; WBC 11.7 glucose 98; Lithium serum level 3/15 = 1.1; 3/22 - 0.7;

Physical Examination:

(3/23) 66", 135 lbs., 97.9 F; respiration 18; pulse 51; BP 146/53 DTR's absent both upper and lower extremities;

Medications:

Insulin Reg. Human 10u.bid; Insulin Lente human 48u AM & 32u PM; levothyroxine 0.025mg qd; lansoprazole 30 mg qd; quinine 325mg bid; lithium carbonate 450mg @ hs; thiamine 100mg po qd (prior to admission was on lithium carbonate 300 mg bid and Proloxin™ 1mg bid for several years).

EDITOR'S NOTE: From time to time, we publish articles contributed by *IDIS* subscribers. An article from Dave Mace, B.S.Pharm., is included in this issue. Dave Mace is from an institution that is a long-standing *IDIS* subscriber, utilizing the database on a regular basis. His consult illustrates *IDIS* database use contributing directly to patient care outcomes. The responsibility for errors is the author's alone. The consult does not necessarily represent hospital views and recommendations. We hope you find the information interesting and useful and welcome comments. If you are interested in sharing your experiences using the *IDIS* database, please contact donna-brus@uiowa.edu.



Donna Brus, Editor

FOLLOW UP:

She was discharged to her home on 5/5, her nausea, abdominal pain, fatigue and mental sluggishness were unresolved. However she was considered sufficiently improved to be alone in her son's home for a few hours each day. Her son and daughter will be providing her care in their home. The psychiatric consultant and attending physician both considered her current therapeutic benefit (depression improved) from lithium too important to risk completely withdrawing the drug, to determine if any of the features of her current syndrome might resolve.

LITERATURE:

Schou recently commented of the risks involved with long term combinations of lithium and neuroleptics. He concluded that the lithium level should be $< 0.8\text{mEq/L}$. In 4,900 patient years of follow up data from his clinic only nine cases of lithium intoxication occurred at therapeutic doses. One of them occurred because of lowered intake of food and fluid. None of his cases of lithium toxicity at therapeutic levels were unexplained.⁸

Lewis reported the emergence of impaired coordination with lead to several falls and two motor vehicle accidents in a 58 year old male on chronic

lithium therapy. His 12-16 hour post dose lithium levels had ranged from (0.7 to 0.9 mEq/L). On admission his EEG was consistent with cerebellar dysfunction of unknown etiology. Because his syndrome was severe, he was discharged to a nursing home and for three months his syndrome persisted. He was then admitted to a neurology service where his persistent ataxia and dysarthria were thought to be the result of a cerebellar infarction. On discharge his serum lithium level was 0.7mEq/L. A short time later, he was admitted to an inpatient psychiatry service. On admission he was considered to have mild depressive symptoms and a cerebellar syndrome of known etiology. Lithium was discontinued to determine if it had been the cause of his cerebellar dysfunction. During the next 10 days his dysarthria and ataxia gradually resolved. He was able to walk unassisted, had substantial improvement in intellectual function, and his EEG cleared. On discharge he was able to resume independent living. Eight months later he had no recurrence of the previous syndrome. His syndrome was present for six months (had been on lithium for 24 months) when his serum lithium levels were 0.7-0.9 mEq/L. When lithium therapy was discontinued the syndrome resolved suggesting lithium was the cause.⁶



Smith and Helms compared the incidence of lithium adverse effects in fifteen patients 65 years of age or older with a control group of forty-one younger patients. They reported the incidence of adverse effects in both groups as:

Symptom:	<65 years	>65 years
Gastrointestinal		
Nausea	22.0%	33.3%
Vomiting	19.5%	13.3%
Abdominal Pain	4.9%	13.3%
Diarrhea	9.8%	13.3%
Anorexia	0	6.7%
CNS - General		
Dizziness	2.4%	0
Slurred Speech	0	13.3%
Aphasia	0	6.7%
CNS - Mental		
Memory Impairment	2.4%	0
Confusion	4.9%	33.3%
Disorientation	2.4%	26.7%
Neuromuscular		
Tremor	29.3%	40.0%
Hyperreflexia	2.4%	0
Weakness	4.9%	6.7%
Ataxia	0	6.7%
Dystonia	0	13.3%
Miscellaneous		
Lethargy	4.9%	33.3%

The mean serum lithium level was below 1.5 mEq/L in the elderly patients who developed adverse reactions thought to be caused by lithium maintenance therapy.⁹

Bassingthwaighe and Rumman published a case of lithium toxicity, in an elderly woman, which developed gradually after fifteen years of lithium maintenance therapy. Serum lithium levels were consistently around 0.8 mEq/L. During the past year she had become more forgetful. A few weeks before admission she became more active, talkative and intrusive. On admission she was oriented only to person and year and refused to cooperate with formal cognitive evaluation. She was dehydrated, had upper extremity tremors, and was unable to walk without support due to generalized weakness and possibly ataxia. Her serum lithium level was 1.2 mEq/L and her EEG showed moderate nonspecific slowing. It was thought she was suffering from a manic exacerbation of her bipolar disorder. She was rehydrated and given haloperidol for eight days; her symptoms only worsened. On the eighth day she began to vomit and have diarrhea. Lithium was withheld. Over the next three days her mental status improved. Within five days she was oriented, more conversant, cooperative and eating and sleeping better. Lithium toxicity had mimicked mania, only the emergency of physical signs and symptoms of lithium toxicity allowed the proper diagnosis. The diagnosis of lithium toxicity becomes obscured by the similarity of toxic symptoms to symptoms of the underlying illness. The emergence of physical changes such as: tremor, dysarthria, ataxia, nausea, vomiting, and diarrhea should alert the clinician to the possibility of drug toxicity. In the elderly, medically compromised patient, previously psychologically stable, who is taking lithium, lithium toxicity must be considered if a change in mental status occurs.¹

Foster has recently reviewed the use of lithium in elderly psychiatric patients. He concluded that lower lithium daily doses and blood levels (0.4-0.7 mEq/L) are recommended and that non-toxic side effects are common and may occur late in treatment. The prevalence rates of specific common side effects, associated with maintenance lithium therapy in the elderly, based on three small case series referenced by him were: polydipsia (50-74%); polyuria (25-58%); tremor (33-58%); nausea (33%); memory impairment (32-33%); weight gain (32%); restlessness (32%); constipation (32%); confusion (11-33%); disorientation (16%); ataxia (11%).⁵

Tueth, Murphy and Evans have recently commented on the special needs of elderly lithium patients. They suggest that doses of 300 to 900 mg of lithium carbonate daily often result in lithium serum levels of 0.4-0.8 mEq/L in very old, frail, medically ill, or cognitively impaired patients. Physically healthy elderly patients are said to generally tolerate lithium well and have only a few mild side effects. However, discernible subgroups including the very old, physically ill, or cognitively impaired, experience lithium side effects and toxicity more commonly. The most prominent side effects in these groups are: polyuria, gastrointestinal abnormalities, trauma, ataxia and cognitive impairment. They emphasized the side effects can occur at both therapeutic as well as higher serum lithium levels.¹³ There are other published reports of lithium toxicity at so called normal therapeutic levels including those by:

Bell², Brown⁴, Speirs¹¹, Strayhorn¹², and Muniz⁷. Case reports describe three elderly patients who developed a state of rapidly deteriorating dementia both early and late in lithium treatment (usually with elevated lithium levels) whose clinical and EEG data suggested a Creutzfeld-Jacob like syndrome.

Fortunately in each case the syndrome reversed over several weeks after lithium was withdrawn.^{10, 3}

COMMENT:

The clinical presentation in this case is consistent with the possibility of lithium toxicity. It can be assumed the intoxication evolved gradually with classic prodromal symptoms including anorexia, nausea, and diarrhea. Other symptoms consistent with lithium toxicity were muscle fasciculations (cramping) in the lower extremities and her recently decreased energy, worsening memory and ability to care for herself. The literature is consistent in recommending the complete withdrawal of lithium therapy with signs and symptoms consistent with the possibility of lithium toxicity are present.

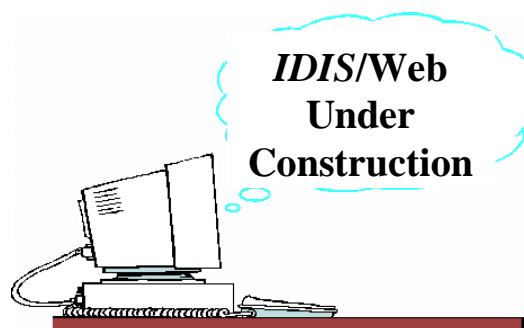
Features of this case which favor the possibility of lithium toxicity include: serum lithium levels ranged from 0.7-1.1 mEq/L; rapid clinical improvement when lithium dose was reduced from 600 mg to 450 mg daily; no other obvious explanation for her rapid decline over the past few months.

PROGRESS REPORT...

IDIS/Web WILL BE AVAILABLE SOON!

Many of you have asked when we will have the *IDIS* database available via the World Wide Web (WWW). We are most pleased to be able to say "very soon." The programming is underway and we have begun in-house testing.

IDIS/Web will offer even more features than the current *IDIS/CD-ROM*. Linkage will be available to pdf's of each full-text article from 1997. Information Technology Services of the University of Iowa will host the database. Subscribers may select single or multiple concurrent user access and will have the ability to customize both administrative access and technical features of database access.



We are optimistic that subscribers will have access to *IDIS/Web* later this summer. All subscribers will be given a logon identification and password to use for the balance of 2000. For 2001 subscribers may choose *IDIS/Microfiche*, *IDIS/CD-ROM* or *IDIS/Web*. Specific information will be sent to each subscriber as soon as *IDIS/Web* is open for use. *IDIS/Web* offers valuable enhancements to the database — we look forward to showing them to you.



Hazel H. Seaba, R.Ph., M.S.
Director, *IDIS*/Clinical Professor

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4. Brown AS and Rosen J. Lithium-induced delirium with therapeutic serum lithium levels: A case report. *J Geriatr Psychiatry Neurol* 1992;5:53-55.
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6. Lewis DA. Unrecognized chronic lithium neurotoxic reactions. *JAMA* 1983;250:2029-2030. (IDIS Article Number 176633)
7. Muniz C, Forman AJ, Wilder BJ, and Ramsey RE. Lithium toxicity with low serum levels: Report of a case. *Clin Electroencephalography* 1976;7:31-34.
8. Schou M. Lithium prophylaxis: myths and realities. *AM J Psychiatry* 1989;146:573-576. (IDIS Article Number 253914)
9. Smith RE and Helms PM. Adverse effects of lithium therapy in the acutely ill elderly patient. *J Clin Psychiatry* 1982; 43:94-99. (IDIS Article Number 145633)
10. Smith SJK, Kocen RS. A Creutzfeldt-Jacob like syndrome due to lithium toxicity. *J Neurol Neurosurg Psychiatry* 1988;51:120-123.
11. Speirs J and Hirsch SR. Severe lithium toxicity with "normal" serum concentrations. *Br Med J* 1978; 1:815-816. (IDIS Article Number 82869)
12. Strayhorn JM and Nash JJ. Severe neurotoxicity despite "therapeutic" serum lithium levels. *Dis Nerv Syst* 1977; (Feb):107-111.
13. Tueth MJ, Murphy TK, and Evans DL. Special considerations: Use of lithium in children, adolescents, and elderly populations. *J. Clin Psychiatry* 1998; 59:66-73. (IDIS Article Number 409776)

Dave Mace, R.Ph., Drug Information Specialist, prepared this article. Mace graduated from the University of Iowa College of Pharmacy in 1967. Since 1982 he has served as the Director of the Drug Information Center at BPVAMC, 10,000 Bay Pines Blvd., Bay Pines, FL 33744. His responsibilities include serving as a preceptor for drug information and Pharm.D. clerkship programs and responding to complex drug information requests from clinical staff.

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Federation Internationale Pharmaceutique (FIP)

Pharmacy World Congress and International Congress of FIP
Vienna, Austria
August 26-31

American College Clinical Pharmacy (ACCP)

Annual Meeting
Los Angeles, California
November 5-8

American Society of Health-System Pharmacists (ASHP)

Midyear Clinical Meeting (MCM)

**FDA DRUG/BIOLOGIC
APPROVALS**

Generic Name (FDA Therapeutic Classification) Trade Name	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)*	Indication/Use	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Alosetron Hydrochloride (1P)** <i>Lotronex</i>	Glaxo Wellcome (February 9)	ALOSETRON 56220027 (6 citations)	Treat irritable bowel syndrome in women whose predominant symptom is diarrhea	Irritable Colon 564.1
Articaine HCl Epinephrine (1S)*** <i>Septocaine</i>	Deproco (April 3)	ARTICAINE 72000069 EPINEPHRINE 12120002 (2 citations)	For infiltration or nerve block anesthesia for dentistry	Anesthesia/Paresthe sia 782.0 Removal/Restor, Teeth NEC 23. Or- Teeth/Gum/Alveoli NEC 24.
Insulin Glargine (1S) <i>Lantus</i>	Aventis (April 20)	INSULIN GLARGINE 68200817 (2 citations)	For one-daily subcutaneous administration in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for the control of hypoglycemia	Diabetes Mellitus 250.
Linezolid (1P) <i>Zyvox</i>	Pharmacia and Upjohn (April 18)	LINEZOLID 8122935 (18 citations)	Treatment of vancomycin- resistant enterococcus faecium, hospital-acquired pneumonia and complicated skin and skin structure infections and community acquired pneumonia	Infection, Streptococcus D 041.04 Pneumonia, Streptococcus 482.3 Infection, Skin/Sq NEC 686.
Meloxicam (1S) <i>Mobic</i>	Boehringer Ingelheim (April 13)	MELOXICAM 28080526 (51 citations)	For relief of the signs and symptoms of osteoarthritis	Osteoarthritis 715.

FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) Trade Name	Sponsor (Approval Date)	Valid IDIS Drug Term Drug Number (IDIS Citations)*	Indication/Use	Valid IDIS Disease Term Modified ICD-9-CM Number
Oxcarbazepine (1S) <i>Trileptal</i>	Novartis (Jan 14)	OXCARBAZEPINE 28122011 (106 citations)	For use as monotherapy or adjunctive therapy in the treatment of partial seizures in children ages 4-16 with epilepsy	Epilepsy, Part No Impair Consc 345.5 Epilepsy, Part W Impair Consc 345.4
Pantoprazole Sodium (1S) <i>Protonix</i>	Wyeth Ayerst (February 2)	PANTOPRAZOLE 56400023 (98 citations)	For short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis	Esophagitis 530.1
Rivastigmine (1S) <i>Exelon</i>	Novartis (April 21)	RIVASTIGMINE 12040020 (35 citations)	Treatment of mild to moderate dementia of the Alzheimer's type	Alzheimer's Disease 331.0 Psychosis, Organic NEC 294.
Verteporfin (1P) <i>Visudyne</i>	QLT Photo Therapeutics (April 12)	VERTEPORFIN 10120166 (8 citations)	For the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choioidal neovascularization	Degeneration, Macula/Pole 362.5
Zonisamide (1S) <i>Zonegran</i>	Elan (March 27)	ZONISAMIDE 28122004 (59 citations)	For adjunctive therapy in the treatment of partial seizures in adults with epilepsy	Epilepsy, Part W Impair Consc. 345.4 Epilepsy, Part No Impair Consc 345.5

* Through May 2000 Update. Complete bibliographic citations will be provided upon request.

** (1P) New Molecular Entity given priority review by FDA

*** (1S) New Molecular Entity given standard review by FDA

New Drug Selected Bibliography



KEY REFERENCES

This new drug selected bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA January through April 2000. *IDIS/CD-ROM* was searched to retrieve key articles relevant to the new drugs and their approved uses.

Linezolid

Chien JW, Kucia ML, Salata RA. Use of linezolid, an oxazolidinone, in the treatment of multidrug-resistant gram-positive bacterial infections. *Clin Infect Dis* 2000;30:146-151. (*IDIS* Article Number 442532). ***Investigators report their experience in treating fifteen patients who had vancomycin-resistant enterococcus infections and were treated with linezolid 600mg every 12 hours for 5-24 days (mean +/-SE, 20.5+/-3.5 days).***

Dresser LD and Rybak MJ. The pharmacologic and bacteriologic properties of oxazolidinones, a new class of synthetic antimicrobials. *Pharmacotherapy* 1998;18:456-462. (*IDIS* Article Number 414871). ***This is a comprehensive review on the oxazolidinones that includes linezolid.***

Meloxicam

Prouse PJ, Bevis PJ, Bluhmki E et al. Evaluation of the safety, tolerability, and efficacy of meloxicam tablets in patients with osteoarthritis. *Clin Ther* 1996;18:429-439. (*IDIS* Article Number 370948). ***In an open-label, multi-center 12 week study, investigators assessed the efficacy, tolerability, and safety of meloxicam 15 mg once daily in 139 patients with confirmed osteoarthritis of the hip or knee.***

Schoenfeld P. Gastrointestinal safety profile of meloxicam: a meta-analysis and systematic

review of randomized controlled trials. *Am J Med* 1999;107:48S-54S. (*IDIS* Article Number 442217). ***This review is a meta-analysis of adverse gastrointestinal events reported in 10 randomized controlled studies of 20,374 patients (19,643 with osteoarthritis) taking either meloxicam (7.5 mg or 15 mg/day) or another NSAID .***

Kaplan-Machlis B and Storyk Klostermeyer B. The cyclooxygenase-2 inhibitors: safety and effectiveness. *Ann Pharmacotherapy* 1999;33:979-988. (*IDIS* Article Number 436184). ***This article provides a comprehensive review of COX-2 inhibitors and continuing education credit for pharmacists.***

Oxcarbazepine

Schachter SC, Vazquez B, Fisher RS et al. Oxcarbazepine. double-blind, randomized, placebo control, monotherapy trial for partial seizures. *Neurology* 1999;52:732-737. (*IDIS* Article Number 424300). ***Investigators conducted a ten day double-blind, randomized, placebo-controlled multi-center trial to evaluate the efficacy and safety of oxcarbazepine 1200 mg twice daily in 102 hospitalized patients with refractory partial seizures.***

Houtkooper MA, Lammertsma A, Meyer JWA et al. Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine? *Epilepsia* 1987;28:693-698. (*IDIS* Article Number 236766). ***Investigators conducted a double-blind randomized crossover study (8 week titration period followed by a 12 week steady state) comparing carbamazepine and oxcarbazepine in 48 patients with epilepsy (10 patients with partial seizures and 29 with both generalized and partial).***

Pantoprazole

Holtmann G, Cain C, Malfertheiner P. Gastric *Helicobacter pylori* infection accelerates healing of reflux esophagitis during treatment with the proton pump inhibitor pantoprazole.

Gastroenterology 1999;117:11-16. (IDIS Article Number 430126). ***In a cohort study of 971 patients with endoscopically verified reflux esophagitis, investigators compared the efficacy of pantoprazole 40 mg orally once daily for at least 4 weeks in patients with and without H. pylori-infected patients.***

Rivastigmine

Rosler M, Anand R, Cicin-Sain A et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled. *BMJ* 1999;318:633-638. (IDIS Article Number 420701). ***In a 26 week, randomized, multi-center, double-blind study, investigators evaluated the efficacy and safety of two fixed dosage ranges of rivastigmine (1-4 mg/day or 6-12 mg/day) compared to placebo in 725 patients with mild to moderately severe probable Alzheimer's disease.***

Jann MW. Rivastigmine, a new-generation cholinesterase inhibitor for the treatment of Alzheimer's disease. *Pharmacotherapy* 2000;20:1-12. (IDIS Article Number 439273). ***This is a comprehensive review of the new-generation cholinesterase inhibitor, rivastigmine, used in the treatment of patients with Alzheimer's disease.***

Verteporfin

Arnold J, Blumenkranz M Bressler NM et al et al. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one year results of 2 randomized clinical trials – TAP report 1. *Arch Ophthalmol* 1999;117:1329-1345. (IDIS Article Number 436688). ***Two multi-center, double-blinded, placebo-controlled randomized clinical trials involving 609 patients were conducted by investigators to determine if photodynamic therapy with verteporfin (6 mg/m² body surface area I.V.) can safely***

reduce the risk of vision loss in patients with subfoveal choroidal neovascularization caused by age-related macular degeneration.

Miller JW, Schmidt-Erfurth U, Sickenberg M et al. Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of a single treatment in a phase 1 and 2 study. *Arch Ophthalmol* 1999;117:1161-1173. (IDIS Article Number 434839). ***In a multi-center non-randomized, open label study, varying light doses with either 6 mg/m² or 12 mg/m² I.V. of verteporfin were evaluated for safety and short-term visual/fluorescein angiographic effects in 128 patients with choroidal neovascularization caused by age-related macular degeneration.***

Zonisamide

Shimizu A, Yamamoto J, Yamada Y et al. The antiepileptic effect of zonisamide in patients with refractory seizures. *Curr Ther Res* 1987;42:147-155. (IDIS Article Number 233204). ***Investigators assessed the efficacy of zonisamide (dose initiated at 100 mg/day and increasing up to 600mg daily for an average duration of 9.5 months treatment) in 45 patients with refractory seizures, of whom 28 had complex partial seizures.***

Additional information on these newly approved drugs will be available in the Summary Basis of Approval (an official United States Food and Drug Administration [FDA] document) that is compiled for each new drug being reviewed. This document includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. Following the FDA approval of a new drug, these documents are requested from the FDA and are then indexed and included as part of the IDIS database. Use descriptor 155 SUMMARY BASIS OF APPROVAL in combination with the valid drug term to retrieve these documents from the database.





**STAFF
PROFILE**

Amy Boyse joined the DDIS staff as a Clerk Typist II in January of 2000. Her duties include processing orders in the accounting office and providing assistance for DDIS subscribers. She previously worked at Iowa State Bank in Iowa City as a Loan Servicer. Amy resides in Kalona, Iowa where she enjoys spending time with her family, reading a good book, and listening to music.

Amy Boyse

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Editor Donna Brus
Production/Design Coordinator ... Julie Tomash
Photographer.....David Luck

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Iowa Drug Information Service

Telephone: 319-335-4800
U.S. Toll-Free: 800-525-IDIS
Fax: 319-335-4440
E-mail: IDIS@uiowa.edu
Web Site: <http://www.uiowa.edu/~idis>



Iowa Drug Information Network

Telephone: 319-335-4199
U.S. Toll-Free: 800-791-7055
Fax: 319-335-4440
E-mail: IDIN@uiowa.edu
Web Site: <http://idin.idis.uiowa.edu>

Division of Drug Information Service
The University of Iowa, 100 Oakdale Campus N330 OH
Iowa City, IA 52242-5000 USA