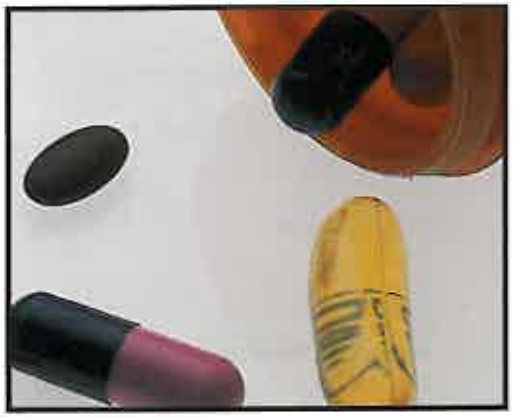

OPTOMETRICALLY-RELEVANT SIDE EFFECTS OF THE SYSTEMIC DRUGS MOST FREQUENTLY PRESCRIBED IN 1991

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ABSTRACT

The 10 drugs most frequently dispensed by retail pharmacies in the United States during 1991 are briefly described. Each has been reported to cause side effects which impact the practice of optometry. Reference sources used to obtain this information are identified and recommended to optometrists. A free-standing computer database program containing summaries of 250 drugs with reported ocular side effects (ODIS) has been written by the author. ODIS exists in both IBM and Macintosh versions, and is offered on a complimentary basis to practicing optometrists.

KEY WORDS

prescription drugs, ocular side effects, computer database, visual side effects

Optometrists who were trained after 1970 are probably unaware of the pioneering role played by the Optometric Extension Program (OEP) in encouraging the pharmacological education of their profession. Starting in October, 1968, Prof. James Koetting authored the monthly series, "Pharmacology for Optometrists," for OEP *Curriculum II* for three years.[1] Together, these 36 articles comprise a comprehensive and nearly definitive statement of those aspects of pharmacology essential to the background of every practicing optometrist. Dr. Koetting expressed the need for optometrists to be pharmacologically literate in the first paragraph of his first article:

> *This series ... is intended to assist the optometrist in becoming more proficient in ... those aspects of pharmacology relevant to optometric practice. It is primarily concerned with the ocular and medical side effects of systemic medication ...*

The appropriateness of those words was demonstrated to me when I was developing a course in Optometric Pharmacology for the Pacific University College of Optometry in the early 1970s. I decided to include a section on the ocular side effects of systemic drugs. In that context I consulted the National Prescription Audit[a] to identify which drugs had been most commonly prescribed the previous year. Then I researched those drugs to determine whether any had been reported to cause ocular side effects. I was surprised to find that of the 10 most frequently prescribed drugs[2] all had been reported to be linked to ocular side effects.[3]

The following year, Stanfill, Traylor and Smith published the results of a survey of practicing optometrists: 86% of their sample encountered at least one patient each month whose vision was affected by prescription or non-prescription drugs, and nearly half (44%) uncovered such patients once a week or more.[4]

It is obvious that many patients seen by optometrists are using systemic medicines prescribed by medical practitioners and many of these drugs can cause optometrically-relevant side effects. Awareness of these facts and knowledge of where to obtain information about specific drugs is, to complete Dr. Koetting's introductory paragraph, "... what the practitioner needs to know to practice optometry."

THE 10 MOST FREQUENTLY DISPENSED DRUGS IN 1991

The 10 prescription drugs which were dispensed most frequently in the United

Table 1. The 10 drugs which were most frequently dispensed by retail pharmacies in the United States during 1991. Drugs are listed in descending order by brand names with generic names and manufacturers also included. Based on a summary of data from the National Prescription Audit by Walsh America/PDS published in American Druggist, February 1992.

Brand Name	Generic Name	Manufacturer
1. Amoxil	amoxicillin	Beecham
2. Premarin	estrogens	Ayerst
3. Zantac	ranitidine	Glaxo
4. Lanoxin	digoxin	Burroughs Wellcome
5. Xanax	alprazolam	Upjohn
6. Synthroid	thyroxine	Boots
7. Ceclor	cefaclor	Eli Lilly
8. Seldane	terfenadine	Marion Merrell Dow
9. Procardia	nifedipine	Pfizer
10. Vasotec	enalapril	Merck, Sharp & Dohme

States in 1991 are listed by their brand names in Table 1, along with their generic names and manufacturers.[5] It is worth noting that three of the drugs are used primarily for treatment of cardiovascular disorders (Lanoxin, Procardia and Vasotec), and two are used primarily for hormonal deficiencies (Premarin and Synthroid). The principal indications for these five drugs are chronic conditions which require continuing drug therapy. In general, prolonged usage of drugs increases the risk of occurrence and the intensity of possible side effects.

The remaining five drugs include two antibiotics (Amoxil and Ceclor), two antihistamines (Seldane and Zantac), and one anti- anxiety agent (Xanax).

Ocular side effects have been reported for all 10 drugs.

DESCRIPTIONS OF THE INDIVIDUAL DRUGS

Each of the 10 most frequently prescribed drugs is briefly described below, with special attention to reported ocular side effects. Some side effects are relevant because they hamper the optometric examination or cause erroneous findings (e.g., cataracts, decreased accommodation) and may result in misdiagnosis or inappropriate treatment. Other side effects are of interest because they impair the biological health of the visual system (e.g., retinal vascular disorders, optic atrophy) and may warrant referral to a medical specialist for co-management. To maximize the usefulness of this information to the practicing optometrist, I have attempted to correlate the reported side effects to phases of the optometric examination:

1. external eye and adnexa
2. internal eye
3. oculomotor system
4. accommodation
5. refractive system
6. sensory dysfunction, including decreased vision, photophobia, dyschromatopsia, asthenopia, visual hallucinations, and diplopia

1. *Amoxil* is the brand name for amoxicillin and is manufactured by Beecham Laboratories. It is a semi-synthetic, broad spectrum antibiotic of the penicillin family which acts by inhibiting bacteria cell wall synthesis. Principal indications are the treatment of infections due to *H. influenzae, E. coli, P. mirabilis, N. gonorrhoeae, D. pneumoniae, Streptococci,* and non-pencillinase-producing *Staphylococci.* These infections include acute otitis media, acute sinusitis, acute bacterial cystitis and other urinary tract infections, and uncomplicated gonorrhea.

Reported side effects correspond to:

- *external eye and adnexa:* allergic reactions, blepharoconjunctivitis, edema, angioneurotic edema, urticaria, erythema multiforme, exfolia dermatitis, photosensitivity, subconjunctival hemorrhages, ptosis
- *internal eye:* retinal hemorrhages
- *oculomotor system:* myasthenic neuromuscular blocking effects (paralysis or paresis of extraocular muscles, ptosis, diplopia)
- *sensory dysfunction:* diplopia

2. *Premarin* is the brand name under which Wyeth-Ayerst Laboratories market this mixture of six conjugated estrogens (mostly estrone and equilin). Estrogens are female sex hormones which are involved in the development and maintenance of the reproductive system and secondary characteristics. Therapeutically, estrogens are administered to supplement insufficient natural production (menopause), to correct an imbalance with progesterone (dysfunctional bleeding), to ameliorate aberrant growth patterns, and to prevent or retard osteoporosis. The principal indications for the use of Premarin are menopausal vasomotor symptoms, atrophic vaginitis, atrophic urethritis, and osteoporosis.

Many ocular side effects have been associated with the use of estrogens. However, most reports derive from use of oral contraceptives. Many of these also contain a progestin in addition to an estrogen so that it is not always possible to identify which drug is responsible for the reported effect.

Reported side effects of Premarin are:

- *external eye and adnexa:* allergic reactions, edema, photosensitivity, angioneurotic edema, urticaria, lupoid syndrome, erythema multiforme, mydriasis, decreased hard contact lens tolerance, ptosis
- *internal eye*: retinal vascular disorders (spasms, occlusions, hemorrhages, and retinal or macular edema), retrobulbar or optic neuritis, papilledema (secondary to pseudotumor cerebri), uveitis
- *oculomotor system:* myasthenic neuromuscular blocking effects (paralysis or paresis of extraocular muscles, ptosis, diplopia), nystagmus
- *refractive system:* myopia
- *sensory dysfunction:* decreased vision, diplopia, field changes (scotomas, hemi- or quadrantanopsia, and constrictions)

3. *Zantac*, manufactured by Glaxo Pharmaceuticals, is the brand name for ranitidine, an antihistamine. Unlike the classical type of antihistamines, such as #8 Seldane, ranitidine is a competitive antagonist of the H_2, rather than the H_1, histamine receptors. H_2 receptors are found in the stomach and, when stimulated by histamine, increase the secretion of gastric acid. Zantac blocks this process and thereby reduces gastric acid secretion. Its principal indications are duodenal and gastric ulcers, pathological hyper-

secretory disease, and gastroesophageal reflux disease (GERD).

Reported side effects correspond to:

- *external eye and adnexa:* erythema, non-specific conjunctivitis, angioneurotic edema, urticaria, loss of eyelashes and/or eyebrows, and subconjunctival hemorrhage
- *internal eye:* retinal hemorrhages, possible acute angle closure
- *sensory dysfunction:* decreased vision, color vision defect, visual hallucinations

4. *Lanoxin* is the Burroughs Wellcome brand name for their form of digoxin. It is a cardiac glycoside of the digitalis family, which has both direct and indirect actions on the heart muscle. These result in an increased force of ventricular contraction, reduction of impulse propagation through the A-V node and slowing of the heart rate. The principal indications for its use are chronic heart failure and cardiac arrythmias such as atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia.

   Dosage adjustment with digoxin is critical, since there is a very small safety margin between therapeutic and toxic doses. Digoxin overdose, which is potentially life-threatening, is therefore not uncommon. Some of the earliest signs and symptoms of digitalis intoxication involve the visual system. Optometrists noting any of the listed side effects in patients using digoxin should contact the patient's cardiologist or responsible physician promptly and without fail.

Reported side effects correspond to:

- *external eye and adnexa:* allergic reactions and angioneurotic edema, mydriasis
- *internal eye:* decreased IOP, abnormal ERG, retrobulbar neuritis
- *sensory dysfunction:* decreased vision, dyschromatopsia (blue-yellow defect), blue halos around lights, "glare" phenomenon, scintillating scotomas, central or paracentral scotomas, diplopia, visual hallucinations

5. *Xanax* is the brand name under which the Upjohn Company markets alprazolam, one of the benzodiazepine family of central nervous system (CNS) depressants. The principal inhibitory transmitter in the CNS is γ-amino butyric acid (GABA). $GABA_A$ receptors are found in high densities in cortical and subcortical parts of the limbic system. The benzodiazepines bind with a subunit of $GABA_A$ receptors, which greatly enhances the binding of GABA, and thus intensifies its inhibitory action. As a family, the benzodiazepines are used as antianxiety, sedative, hypnotic, muscle relaxant, and antiepileptic agents. In particular, Xanax is recommended for management of generalized anxiety disorder, panic disorder and agarophobia, and as an antidepressant.

Reported side effects correspond to:

- *external eye and adnexa:* allergic reactions, erythema, photosensitivity, angioneurotic edema, urticaria, purpura, erythema multiforme, mydriasis, decreased pupillary light reflex, blepharospasm, non-specific conjunctivitis, burning sensation, lacrimation, and subconjunctival hemorrhage
- *internal eye:* retinal hemorrhages, possible acute angle closure
- *oculomotor system:* oculogyric crisis, decreased spontaneous movements, abnormal conjugate deviations, jerky pursuit movements, decreased saccadic movements, nystagmus, paralysis or paresis
- *accommodation:* decreased amplitude
- *sensory dysfunction:* decreased vision, diplopia, photophobia, dyschromatopsia, visual hallucinations, ocular pain

6. *Synthroid* is the brand name under which Boots Pharmaceuticals, Inc. markets synthetic thyroxine (T4). Indications for Synthroid are as replacement or supplemental therapy for all forms of hypothyroidism, and for treatment or prevention of euthyroid goiters.

Reported side effects correspond to:

- *external eye and adnexa:* edema of eyelids and conjunctivae, blepharospasm, hyperemia, exophthalmos
- *internal eye:* papilledema secondary to pseudotumor cerebri
- *oculomotor system:* myasthenic neuromuscular blocking effects (paralysis or paresis of extraocular muscles, ptosis, diplopia)
- *sensory dysfunction:* decreased vision, diplopia, photophobia, visual hallucinations

7. *Ceclor* is marketed by Eli Lilly and Company and contains cefaclor, a second generation cephalosporin antibiotic (there are now three generations). The cephalosporins are wide-spectrum bactericidal agents with a large safety factor, but are usually regarded as alternatives to antibiotics of first choice. Cefaclor is indicated in the treatment of acute otitis media and acute sinusitis caused by ampicillin-resistant strains of Haemophilus influenzae and Moraxella catarrhalis. It is also used to treat infections of the upper and lower respiratory tract, the urinary tract, and skin caused by susceptible microorganisms. As with Drug #1, Amoxil, Ceclor acts by inhibiting bacterial cell wall synthesis.

Reported side effects correspond to:

- *external eye and adnexa:* allergic reactions, edema, erythema, angioneurotic edema, urticaria, exfolia dermatitis, subconjunctival hemorrhages
- *internal eye:* retinal hemorrhages
- *oculomotor system:* nystagmus
- *sensory dysfunction:* visual hallucinations

8. *Seldane* is the brand name of Marion Merrell Dow Inc. for the antihistamine, terfenadine. One of a newer generation of "nonsedating" H_1-receptor antagonists, terfenadine differs from traditional antihistamines in that it does not readily cross the blood brain barrier. Therefore, at therapeutic doses, terfenadine exerts less intense CNS effects than traditional H_1 antagonists. Nonsedating antihistamines also show a lower incidence of anticholinergic effects than do traditional agents. Seldane is indicated for symptomatic relief in seasonal allergic rhinitis, urticaria, and pruritis of contact dermatitis. Desired effects occur without the drowsiness and anticholinergic side effects often associated with traditional antihistamines.

   Ocular side effects associated with terfenadine have not yet appeared in standard reference sources, but the National Registry of Drug-Induced Ocular Side Effects has received reports of a variety of adverse reactions (personal communication), which are summarized below.

Reported side effects correspond to:

- *external eye and adnexa:* allergic reactions, loss of eyelashes and/or eyebrows, blepharospasm, corneal lesion, keratoconjunctivitis,

mydriasis, photosensitivity, blepharitis, abnormal tear flow
- *internal eye:* increased IOP, optic neuritis, retinal degeneration, optic atrophy, branch artery occlusion, retinal pigment
- *oculomotor system:* strabismus, paralysis of extraocular muscles
- *accommodation:* abnormal accommodation
- *sensory dysfunction:* decreased vision, diplopia

9. *Procardia* is the brand name (Pfizer, Inc.) for nifedipine, a calcium channel blocker. Procardia moved up from #13 last year, and dropped Cardizem (Marion Merrell Dow, Inc.), a different calcium channel blocker, from #7 in 1990 to #11 in 1991. Calcium channel blockers inhibit one of the critical steps in excitation- contraction coupling of vascular smooth muscle. This results in vascular smooth muscle relaxation and vasodilatation. This increases blood flow in the case of constricted coronary vessels and lowers vascular resistance and arterial pressure systemically. These actions are the basis for the widespread use of calcium channel blockers as anti-anginal and anti-hypertensive agents. In 1988, the Committee for the Detection, Evaluation, and Treatment of High Blood Pressure listed calcium channel blockers as one of four classes of drugs recommended for the initial therapy of hypertension.[6]

Reported side effects correspond to:
- *external eye and adnexa:* erythema, non-specific conjunctivitis, photosensitivity, angioneurotic edema, urticaria, purpura, erythema multiforme, exfolia dermatitis, increased tear flow, loss of eyelashes/eyebrows, edema, and subconjunctival hemorrhages
- *internal eye:* retinal thrombosis and hemorrhages, increased IOP, and cataracts
- *oculomotor system:* rotary nystagmus
- *sensory dysfunction:* visual hallucinations, photophobia, ocular pain, decreased vision

10. *Vasotec*, marketed by Merck, Sharp and Dohme, is generically enalapril, a so-called ACE-inhibitor indicated for the treatment of chronic hypertension and congestive heart failure. Like the calcium channel blockers, ACE-inhibitors are one of the four classes of drugs recommended by the Committee for the Detection, Evaluation, and Treatment of High Blood Pressure for the initial therapy of hypertension.[6] ACE is an acronym for angiotensin converting enzyme, which catalyzes the conversion of the inactive form of angiotensin to the active angiotensin II. Angiotensin II stimulates vascular smooth muscle, causing arteriolar constriction, and it increases the secretion of aldosterone, which promotes sodium and water reabsorption, both of which cause increased blood pressure. The angiotensin converting enzyme also causes degradation of bradykinin, which is a powerful vasodilator. Enalapril blocks the conversion of angiotensin I to angiotensin II and prevents destruction of bradykinin. These effects result in widespread vasodilatation, leading to increased coronary blood flow and decreased arterial pressure.

Reported side effects correspond to:
- *external eye and adnexa:* erythema, blepharoconjunctivitis, edema, brown discoloration, photosensitivity, angioneurotic edema, urticaria, lupoid syndrome, erythema multiforme, subconjunctival hemorrhages
- *internal eye:* retinal hemorrhages
- *accommodation:* decreased accommodation
- *sensory dysfunction:* decreased vision, visual hallucinations

DISCUSSION

Based on the statistics cited earlier, most optometric practices will include a significant number of patients who are using prescription medicines for systemic conditions. Many of these patients will be using one (or more) of the 10 most frequently prescribed drugs, and many will be using these agents in an ongoing manner. This article documents the ocular side effects that have been reported for all 10 of these drugs. These realities confirm Prof. Koetting's earlier-quoted point: the informed practice of optometry requires an awareness that side effects involving the visual system may occur with many systemic drugs.

Several points that were made in an earlier article[3] bear rephrasing here:

1. Information about side effects comes mostly from the medical literature and reflects a non-optometric orientation.
2. Many non-ophthalmological physicians have modest training in visual physiology and ocular disease and report ocular side effects in general or vague language (e.g., decreased vision, diplopia).
3. Side effects are more likely to have been detected and reported the more vision-threatening they are. Side effects which are of importance to the optometrist, such as a change in refraction or tear flow, may be unobserved by a physician or unreported by a patient if they are not disconcerting or prove transient.
4. Possible side effects involving the ocular muscles (both intrinsic and extrinsic) should be especially noted by optometrists, since they may operate below the level of patient awareness but have great significance for the optometric examination (e.g., reduced amplitude of accommodation, regression of the nearpoint of convergence, reduced fusional reserve).
5. Many reported side effects are transient or reversible upon discontinuation of the drug. Optometric findings taken when side effects are present, as well as any diagnosis or therapy based on those findings, would be invalid when the side effects subside or disappear.

It is noteworthy that six of the 10 most frequently prescribed drugs (Amoxil, Premarin, Xanax, Vasotec, Synthroid and Seldane) include, as possible side effects, adverse reactions affecting accommodation, convergence, or both. Awareness of these associations, while of considerable interest to all optometrists, should be of special significance to those whose practices emphasize vision therapy. This is particularly important for those examining and treating Medicare-eligible and traumatic brain-injured patients.

USEFUL PROFESSIONAL SOURCES OF INFORMATION ABOUT DRUGS

Optometrists should know where to find information about the ocular side effects possible with specific drugs that their patients are using.

The data on which the preceding drug summaries are based were obtained in large part from an optometric drug

Table 2. The five standard reference sources which were used to research systemic drugs in this article and in ODIS and which are recommended for inclusion in optometric libraries. .

1. Gilman AG et al. Goodman and Gilman's The pharmacological basis of therapeutics, 8th ed., New York: Pergamon Press, 1990.
2. Drug Evaluations Annual 1992. Chicago: AMA, 1992.
3. Physicians' Desk Reference (PDR), 46th ed. Springfield, NJ: Medical Economics, 1992.
4. Grant WM. Toxicology of the eye, 3rd ed. Springfield, MA: Charles C. Thomas, 1986.
5. Fraunfelder F. Drug-induced ocular side effects and drug interactions, 3rd ed. Philadelphia: Lea & Febiger, 1989.

database which has been accumulating at the Pacific University College of Optometry for 15 years. Entries in this database are derived from student reports which are completed in satisfaction of a pharmacology course requirement. Drugs to be researched are assigned to at least three students in different years. Each student must submit a standard report based on information obtained from five authoritative reference sources (see Table 2). The submitted reports are then collated, confirmed (if necessary), and edited before being entered into the database.

These five standard reference works which the students use comprise a minimal pharmacological collection which should be familiar to practicing optometrists and should either be in their professional libraries or be easily accessible to them.

A COMPUTER DATABASE OF DRUGS WITH OCULAR SIDE EFFECTS

Several years ago a computer program (ODIS) was developed to make the Pacific University College of Optometry database available to practicing optometrists.[7] The program was designed for speed and ease of use. The generic or brand name of a drug is selected from an alphabetical list (by clicking with a mouse or pressing the Return key). ODIS then retrieves the corresponding record and displays it on screen. Each record identifies a drug by its official (generic) name and by as many as four brand names and manufacturers, gives its pharmacological class, briefly describes its actions, lists its principal indications, and outlines its reported medical and optometric side effects. A hard copy of any record may be printed out for inclusion in a patient's file, if desired. ODIS has undergone several revisions as the database has expanded. In 1991, ownership was transferred to Pacific University, which has agreed to continue the author's original intention of making ODIS available to members of the optometric profession without charge. The database currently contains approximately 250 different drugs, including almost all of the 200 most frequently prescribed, under nearly 700 different generic and brand names.

Any practicing optometrist or optometry student may obtain a copy of ODIS and the complete database by writing to the present author. Requests should indicate whether the Macintosh or IBM version is desired and, if IBM, whether a 3.5 or 5.25 inch disc is preferred. Please include a check in the amount of $15.00, payable to Pacific University to cover the costs of materials, processing and shipping.

FOOTNOTES

a. Conducted annually by Walsh America/PDS for the pharmaceutical industry in the United States, and summarized in journals such as *Pharmacy Times and American Druggist.*

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