Non-hormonal Systemic Medications and Dry Eye

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ABSTRACT **Many drugs used for chronic illnesses can contribute to dry eye syndrome, and elderly patients who have dry eye may concurrently be on systemic medications that worsen the condition. Such medications include anticholinergic drugs, eg, antidepressant, antipsychotic, anti-Parkinson's disease, and antihistamine drugs. Other drugs such as anti-acne preparations and antihypertensives can also cause dry eye. In some cases, the adverse effects of the drug on dry eye is dose-related and can be relieved by reducing the dosage. Alternatively, a different drug within the same drug family may alleviate the dry eye problem. Awareness of the drugs that contribute to dry eye will allow ophthalmologists and other physicians to better manage patients who have this common problem.**

KEY WORDS **anticholinergic agents, antidepressants, antihistamines, antipsychotics, anxiolytics, chemically induced dry eye, dry eye syndrome, isotretinoin, overactive bladder, Parkinson's disease**

I. INTRODUCTION

Dry eye syndrome is a multifactorial disorder of the tear film and ocular surface that results in eye discomfort, visual disturbances, and potential damage to the ocular surface.[1] Many patients with dry eye syndrome seen in ophthalmology clinics also have systemic diseases that require chronic medications. This is especially true in the elderly population, as both dry eye and systemic diseases have increased prevalence in older people.[2]

Many drugs used to treat chronic illnesses can contribute to dry eye syndrome.[3] The 10-year incidence of dry eye has been reported to be greater in people using antidepressants, anxiolytics, antihistamines, steroids, and vitamins, after adjusting for age.[4] In the Blue Mountains study (1,174 participants), dry eye syndrome, after adjustment for age and sex, was associated with antidepressants, corticosteroids and hormone replacement therapy.[5] Physicians are often unaware of this side effect of systemic medications, and, because most patients with multiple chronic illnesses are seen by various specialists in different clinics, the physicians involved may be unaware of a patient's complete drug history. The lack of communication may be compounded by the fact that elderly patients are more likely to lack understanding and knowledge of the details of their own drug history.

The purpose of this review is to describe classes of systemic medications associated with dry eye syndrome. Because hormonal drugs comprise an extremely large category of such drugs, space limitations preclude their inclusion in this review; they will be separately addressed in a future review. This review compares drugs from within other classes of commonly used medications with regard to their ocular drying effects. It is often possible to alleviate distress from drug-related dry eye syndrome by altering the drug dose, changing the patient's prescription to a drug with less ocular drying effect from within the same class or switching to a different class of drugs. For this reason, communication among all physicians involved in a patient's care is crucial.

II. PATHOPHYSIOLOGY OF DRY EYE AS AN ADVERSE EFFECT OF SYSTEMIC MEDICATIONS

Dry eye syndrome is caused by the disturbance of components of the tear film, ie, lipid, aqueous and mucous layers, produced by meibomian, lacrimal and accessory lacrimal glands, and the conjunctival goblet cells, respectively.[6] These structures are anatomically distinct and regulated by distinct physiological mechanisms.[7] Systemic medica-

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tions, when consumed at therapeutic doses, may achieve significant doses in these glands or indirectly affect these glands through regulatory neurological innervation. This is likely because these structures are highly vascularized and therefore subject to high penetration rates once drugs are absorbed into the systemic circulation. Through their effects on one or more of the components of the tear film, systemic medications can induce dry eye.

III. DRUGS WITH ANTICHOLINERGIC EFFECTS

Anticholinergic agents are substances that block the neurotransmitter acetylcholine in the central and peripheral nervous system. These agents act at the muscarinic or nicotinic receptors. Most anticholinergic drugs are antimuscarinic agents. Drugs that act on nicotinic anticholinergic receptors are usually neuromuscular blocking drugs and are not within the scope of this article. In this review, anticholinergic drugs, for all intents and purposes, refer to the antimuscarinic agents.

Anticholinergic drugs are postulated to affect the aqueous and mucous secretions.[8] Stimulated secretion of tears occurs via release of the neurotransmitter acetylcholine from parasympathetic nerves, which interact with G-protein coupled muscarinic (**M3**) receptors in the lacrimal gland acini and conjunctival mucus-producing cells.[9] The G-protein coupled receptors activate two main signalling pathways, ie, the Ca2+/protein kinase C-dependent and cyclic adenosine monophosphate (**cAMP**)-dependent pathways. These pathways then produce efflux of tear fluid. Systemic anticholinergics compete with acetylcholine at the post-synaptic M3 receptors, blocking the action of acetylcholine and reducing the signalling that produces the aqueous and mucous tear component secretion.[10] These alterations in tear film constituents result in tear film instability, contributing to dry eye syndrome.[7,9,11] A mouse model of dry eye documented that reduced tear production was induced via transdermal delivery of scopolamine.[12,13] Scopolamine, an anticholinergic agent, induced a significant decrease in cotton thread wetting and tear clearance, demonstrating that these drugs decrease tear function in animals.

The major evidence for association of anticholinergic medications and dry eye is summarized in Table 1.[14-24] This includes clinical trials on antidepressants, antihistamines, and drugs that reduce bladder overactivity. Although few studies have addressed dry eye *per se*, a number of studies have reported the association of dry mouth with these systemic medications, which may possibly suggest concurrent dry eye.

A. Antidepressant Drugs

Nine sub-classes of antidepressants commonly encountered in clinical use are shown in Table 2.

1. Epidemiology and Clinical Indications

Two studies in Singapore found the prevalence of depression to be 8.6% in adults[25] and 5.7% in the elderly.[26] In the United States, up to 1 in 8 people may require treatment for depression during their lifetime.[27] Either tricyclic antidepressants (**TCA**s) or selective serotonin reuptake inhibitors (**SSRI**s) may be used as first line medications.[27] They are effective in the treatment of all forms of depression,[28] and there is comparable efficacy between and within classes.[29,30] Antidepressants are also used for anxiety disorders, obsessive compulsive disorders, and chronic pain management.[8]