Drug-Induced OCULAR SIDE EFFECTS

Seventh Edition

Frederick T. **Fraunfelder**
Frederick W. **Fraunfelder**
Wiley A. **Chambers**

ELSEVIER
SAUNDERS

Drug-Induced Ocular Side Effects

Content Strategist: *Russell Gabbedy*
Content Development Specialist: *John Leonard*
Project Manager: *Joanna Souch*
Design: *Christian Bilbow*
Illustration Manager: *Brett MacNaughton*
Marketing Manager(s) (UK/USA): *Brian McAllister*

Drug-Induced

OCULAR

SIDE EFFECTS

Seventh Edition

Frederick "Fritz" T. Fraunfelder, MD
Professor
Department of Ophthalmology
Oregon Health and Science University
Casey Eye Institute
Portland, OR

Frederick "Rick" W. Fraunfelder, MD, MBA
Professor and Chair Department of Ophthalmology
Roy E. Mason and Elizabeth Patee Mason Professor
University of Missouri – Columbia School of Medicine
Mason Eye Institute
Columbia, MO

Wiley A. Chambers, MD
Clinical Professor of Ophthalmology
Adjunct Assistant Professor of Computer Medicine
George Washington University School of Medicine
Washington, DC

Associate Editor:
Bree Jensvold-Vetsch, BS
National Registry of Drug-Induced Ocular Side Effects
Department of Ophthalmology
Oregon Health and Science University
Casey Eye Institute
Portland, OR

For additional online content visit expertconsult

ELSEVIER
SAUNDERS

London New York Oxford Philadelphia St Louis Sydney Toronto

ELSEVIER
SAUNDERS

SAUNDERS an imprint of Elsevier Inc.

First edition 1976
Second edition 1982
Third edition 1989
Fourth edition 1996
Fifth edition 2000
Sixth edition 2008

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.
Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.
With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.
To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-323-31984-3
e-book ISBN: 978-0-323-31985-0

Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

Contents

Preface vii
List of Contributors viii
Dedication ix
Instructions to Users x

Part 1 Principles of Therapy 1
Focke Ziemssen, MD
Manfred Zierhut, MD

Part 2 Ocular Drug Delivery and Toxicology 9
Frederick T. Fraunfelder, MD

Part 3 Methods for Evaluating Drug-Induced Visual Side Effects 15
Wiley A. Chambers, MD

Part 4 The Role of Electrophysiology and Psychophysics in Ocular Toxicology 21
Eberhart Zrenner, MD

Part 5 National Registry of Drug-Induced Ocular Side Effects 41
Frederick W. Fraunfelder, MD
Frederick T. Fraunfelder, MD

Part 6 Herbal Medicines and Dietary Supplements – An Overview 43
Frederick W. Fraunfelder, MD

Part 7 Drug-Induced Ocular Side Effects 47

Section 1: Anti-infectives
Amebicides 47
Anthelmintics 48
Antibiotics 51
Antifungal Agents 74
Antileprosy Agents 76
Antimalarial Agents 78
Antiprotozoal Agents 83
Antitubercular Agents 85

Section 2: Agents Affecting the CNS
Analeptics 92
Anorexiants 95
Antianxiety Agents 97
Anticonvulsants 98
Antidepressants 104
Anti–Multiple Sclerosis Agents 111
Antipsychotic Agents 111
Depressants 119
Psychedelic Agents 121
Sedatives and Hypnotics 124

Section 3: Analgesics, Narcotic Antagonists and Agents Used to Treat Arthritis
Agents Used to Treat Gout 126
Antirheumatic Agents 127
Mild Analgesics 136
Narcotic Antagonists 140
Strong Analgesics 140

Section 4: Agents Used in Anesthesia
Adjuncts to Anesthesia 144
General Anesthesia 147
Local Anesthetics 151
Therapeutic Gases 153

Section 5: Gastrointestinal Agents
Agents Used to Treat Acid Peptic Disorders 155
Antacids 156
Antiemetics 156
Antilipidemic Agents 157
Antispasmodics 159
Gastrointestinal and Urinary Tract Stimulants 162

Section 6: Cardiac, Vascular and Renal Agents
Agents Used to Treat Migraine 163
Antianginal Agents 164
Antiarrythmic Agents 168
Antihypertensive Agents 173
Bronchodilators 179
Diuretics 180
Osmotics 183
Peripheral Vasodilators 184
Vasopressors 184

Section 7: Hormones and Agents Affecting Hormonal Mechanisms
Adrenal Corticosteroids 188
Androgens 193
Antithyroid Agents 195
Erectile Dysfunction Agents 196
Estrogens and Progestogens 198
Ovulatory Agents 201
Thyroid Hormones 203

Section 8: Agents Affecting Blood Formation and Coagulability
Agents Used to Treat Deficiency Anemias 203
Anticoagulants 206
Blood Substitutes 211

Contents cont

Section 9: Homeostatic and Nutrient Agents

Agents Used to Treat Hyperglycemia 212

Section 10: Agents Used to Treat Allergic and Neuromuscular Disorders

Agents Used to Treat Myasthenia Gravis 216
Antihistamines 216
Anti-Parkinsonism Agents 219
Cholinesterase Reactivators 222
Muscle Relaxants 223

Section 11: Oncolytic Agents

Antineoplastic Agents 224

Section 12: Heavy Metal Antagonists and Miscellaneous Agents

Agents to Treat Alcoholism 259
Calcium-Regulating Agents 259
Chelating Agents 261
Diagnostic Aids 266
Immunosuppressants 268
Retinoids 272
Solvents 276
Vaccines 278

Section 13: Agents Used in the Management of Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome

Antiretroviral Agents 287

Section 14: Drugs Used in Ophthalmology

Agents Used to Treat Age-Related Macular Degeneration 290
Agents Used to Treat Allergies 295
Agents Used to Treat Glaucoma 296
Antiviral Agents 311
Carbonic Anhydrase Inhibitors 314
Decongestants 317
Miotics 318
Mydriatics and Cycloplegics 323
Neurotoxins 324
Ophthalmic Dyes 326
Ophthalmic Implants 330
Ophthalmic Preservatives and Antiseptics 332
Proteolytic Enzymes 336
Topical Local Anesthetics 336
Topical Ocular Nonsteroidal Anti-inflammatory Drugs 340
Topical Osmotic Agents 342
Viscoelastics 342

Part 8 Herbal Medicine and Dietary Supplement–Induced Ocular Side Effects 345

Frederick W. Fraunfelder, MD

Index of Side Effects 353

Subject Index 399

Preface

This is the 7th edition of *Drug-Induced Ocular Side Effects*. The 6th edition was *Clinical Ocular Toxicology*. Major revisions include changing over 80% of the parts and sections with additions or significant edits. We attempted to add the probability of the adverse ocular event being due to the agent, in part, based on the World Health Organization (WHO) classification system. Dr. Chambers has not taken part in the WHO classification system due to his affiliation with the U.S. Food and Drug Administration (FDA), and this text has no relationship to the FDA.

As with previous editions, we continue to incorporate the most recent data from the spontaneous reporting systems of the FDA (Bethesda, Maryland), WHO (Uppsala, Sweden) and the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Oregon Health and Science University, Portland, Oregon). The National Registry contains case reports from clinicians in many countries and includes the world literature in its database. Data in this book have been accumulated from numerous physicians and scientists who have suspected adverse drug reactions and reported their suspicions to the FDA, WHO or the National Registry.

This book is intended as a guide to help the busy clinician decide whether a visual problem is related to a medication. The clinician's past experience, the known natural course of the disease, the adverse effects of similarly structured compounds, and previous reports all help physicians make their decisions. Unfortunately, there have been only limited attempts to apply rigorous science to the clinical ocular toxicology of marketed products. There are many variables, and there is a paucity of research dollars available to assess cause-and-effect relationships between drugs and visual adverse events. The clinician needs to keep in mind the marked variability of how each human metabolizes or reacts to the drug or its metabolites. A change in the expected course of a disease after starting a drug should heighten the physician's suspicion of a drug-related event. Peer review journals have difficulty in accepting papers on potential visual side effects of drugs because causation, once the agent is marketed, is usually difficult to prove by scientific parameters. At this stage, medical case reports and spontaneous reporting systems and their inherent pitfalls are left as significant factors of clinical ocular toxicology. While we have made an attempt to classify a suspected adverse event with our impression as to causality (i.e. certain, probable, possible, unlikely, conditional/unclassified, unassessable/unclassifiable), one needs to remember that this is not based on science. This is only a guide for the busy clinician and will always be a work in progress. We welcome your input.

F.T. Fraunfelder, MD
F.W. Fraunfelder, MD, MBA
Wiley A. Chambers, MD

List of Contributors

Focke Ziemssen, MD, FEBO
Professor of Ophthalmology
Centre for Ophthalmology
Eberhard Karis University
Tuebingen, Germany

Manfred Zierhut, MD
Professor of Medicine
Centre for Ophthalmology
Eberhard Karls University
Tuebingen, Germany

Eberhart Zrenner, MD
Distinguished Professor of Ophthalmology
Centre for Ophthalmology
Eberhard Karls University
Tuebingen, Germany

Dedication

Frederick "Fritz" T. Fraunfelder, MD
To: Yvonne and our grandchildren: Matthew, Kara, Courtney, J.D., Brooke, Mikayla, Nicolette, Jake, Gracie-Anne, Rees, Connor, Asher, Sara-Jane, Keilan and Piper

Frederick "Rick" W. Fraunfelder, MD, MBA
To: Wendee, Mikayla, Jacob, Gracie-Anne and Sara-Jane

Wiley A. Chambers, MD
To: Jayne and Wes

Bree Jensvold-Vetsch, BS
To: Mom, Dad, Richard and Ava

The basic format used in each section of ocular side effects is:

Class: The general category of the primary action of the drug, chemical or herb is given.

Generic Name: The recommended International Nonproprietary Name (rINN) for each drug is listed, which is designated by the World Health Organization. In parentheses is the United States National Formulary name or other commonly accepted names.

Proprietary Name: The United States trade names are given but this is not an all-inclusive listing. In a group of drugs, the number before a generic name for both the systemic and ophthalmic forms corresponds to the number preceding the proprietary drug. International trade names and multiingredient preparations are not listed unless indicated.

Primary Use: The class of medicine and its current use in the management of various conditions are listed.

Ocular Side Effects:

Systemic Administration: Ocular side effects are reported from oral, nasal, intravenous, intramuscular, or intrathecal administration.

Local Ophthalmic Use or Exposure: Ocular side effects are reported from topical ocular application, subconjunctival, retrobulbar or intracameral injection.

Inadvertent Ocular Exposure: Ocular side effects are reported due to accidental ocular exposure.

Inadvertent Systemic Exposure: Ocular side effects are reported due to accidental systemic exposure from topical ophthalmic medications.

Systemic Absorption from Topical Application to the Skin: Ocular side effects are reported secondary to topical dermatologic application.

The ocular side effects are listed as certain, probable, possible and conditional/unclassified. This classification is based, in part, on the system established by the World Health Organization. There are debatable scientific bases for our opinions. They are only intended as guides for the clinician and are the results of "educated" conjectures from the authors, F.T. Fraunfelder and F.W. Fraunfelder. The name of the preparation in the parentheses adjacent to an adverse reaction indicates that this is the only agent in the group reported to have caused this side effect.

Systemic Side Effects:

Systemic Administration: Systemic side effects are reported from ophthalmic medications administered by an oral, intravenous or intramuscular route.

Local Ophthalmic Use or Exposure: Systemic side effects are reported from topical ocular application or subconjunctival or retrobulbar injection.

The listing as to certainty of causality is the same as used by systemic medication.

WHO Classification System

Where data is available (i.e. published or submitted for publication), we have classified medication adverse reactions according to the following World Health Organization Causality Assessment of Suspected Adverse Reactions Guide.

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration, which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/Unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction about which more data is essential for a proper assessment or the additional data are under examination.

Unassessable/Unclassifable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

Clinical Significance: A concise overview of the general importance of the ocular side effects produced is given.

References: References have been limited to the most informative articles, the most current or those with the most complete bibliography.

Recommendations: For specific medications, we make recommendations on following patients for probable related effects on the visual system. This was often done in consultation with other coworkers interested in the specific drug; however, this is only intended as a possible guide.

Index of Side Effects: The lists of adverse ocular side effects due to preparations are intended in part to be indexes in themselves. The adverse ocular reactions are not separated in this index as to route of administration; however, this can be obtained by going to the text.

This page intentionally left blank

PART 1

Principles of therapy

Focke Ziemssen, MD and Manfred Zierhut, MD

PHARMACODYNAMICS

"Pharmacodynamics" can be defined as the quantitative relationship between the observed tissue concentration of the active drug and its pharmacologic effects. In contrast to pharmacokinetics, which describe how the body interacts with a drug, pharmacodynamic models predict what the drug does to the body. Ocular pharmacodynamics is therefore not just an abstract issue. Knowing how a substance causes the response, which pathways are involved and which cell will be affected is of the utmost importance not only in drug development, but also when applying a drug. Exact understanding of the concentration-dependent response for an individual patient provides more precise information for deciding how to dose. The main challenge in designing a drug dosage regimen is the variability that exists from patient to patient.

Extensive studies and clear specifications have to be made during the approval process of a drug. The effect of a formulation might vary with its dosage, the affected tissue and confounding comorbidity. Because some of the different reactions to a molecule are not known at the time of approval, caution is important when treating understudied populations such as women, minorities and patients who have multiple health problems or preexisting medication.

Initially, the term "receptor" was introduced as an abstract model, before any molecular structure had been exactly identified (Langley 1904). The leading aspect of the receptor is the quantitative relationship between drug dose and the pharmacological effect.

Where does the drug act?

The target of the active agent is not necessarily the body itself but e.g. a foreign organism, as is the case in antibiotics. The action of the drug can be initiated either by extracellular localization or by intracellular binding. Very often, membrane proteins, forming receptors (beta-blockers) and ion channels (glutamate receptor antagonists), are the target structures of a drug. There are also examples of drugs targeting structures of the intracellular compartment, e.g. the cytoskeleton (taxanes).

Many drugs make an impact on enzymatic activity (inhibitors of carboanhydrase). However, more and more substances are developed that influence promoter regions of the DNA or directly interfere with transcriptional activity. By binding the messenger RNA, small aptamers can prevent syntheses of new proteins.

Biotechnological engineering enables the design of drugs that are specifically directed against a cytokine, a surface receptor or a key step in signal transduction. The invention of the so-called "biologicals" has revolutionized the opportunity to intervene more specifically with particular reactions by focusing on single pathophysiological sequences. In terms of toxicity, these treatment modalities bear the risk of antigenicity. When using fully humanized proteins, specific autoantibodies can provoke loss of function. If biotechnological synthesis leaves residuals of different species, anaphylactic reactions can occur during treatment with foreign proteins.

Besides the receptor-mediated effects, mechanisms that are caused by chemical or physical interaction also have to be considered. Ophthalmologic examples are the rinsing solutions neutralizing the ocular surface after alkali burn injuries.

In reality, some drugs may have several mechanisms of actions; e.g. it is possible to distinguish a fast from a slower effect. For example, the delayed decline in the intraocular pressure by prostaglandins seems to be related to collagen degradation after the activation of metal-matrix proteases. In contrast, the early decrease in intraocular pressure within the first hours was assigned to relaxation of the trabecular meshwork after inhibition of a Ca^{2+}-dependent contraction (Thieme et al 2006).

Nonspecific effects are typically mediated through a generalized effect in many organs, and the response observed depends on the distribution of the drug. It must be appreciated that many drugs exist whose sites of action have not been elucidated in detail. Furthermore, many drugs are known to bind to plasma proteins as well as to various cellular compartments, without producing any obvious physiological effect.

How does a drug interact with its target?

A variety of different types of drug actions exists. Accordingly, drugs can be classified into specific categories such as agonists, antagonists, partial agonists, inverse agonists, allosteric modulators and enzyme inhibitors or activators.

Agonists bind to a receptor or site of action and produce a conformational change, which mimics the action of the normal physiological binding ligand. At low concentrations, the activity of the drug can be additive to the natural ligand. The affinity of the drug to the receptor ultimately determines the concentration necessary to produce a response. The presence of *spare receptors* becomes an important point when considering changes in the numbers of available receptors resulting from adaptive responses in chronic exposure or irreversible binding. The effect of a drug is thought to be proportional to the number of occupied receptors. Drug antagonists bind either to the receptor itself or to a component of the effector mechanism, which then prevents the agonist's action. If the antagonist-mediated inhibition can be overcome by increasing agonist concentration, ultimately reaching the same maximal effect, the antagonist is termed *competitive* (Fig. 1.1). In contrast, a *noncompetitive* agonist will prevent the agonist from producing a maximal effect. If the antagonist is reversible and binds at the active site, the inhibition will be competitive.

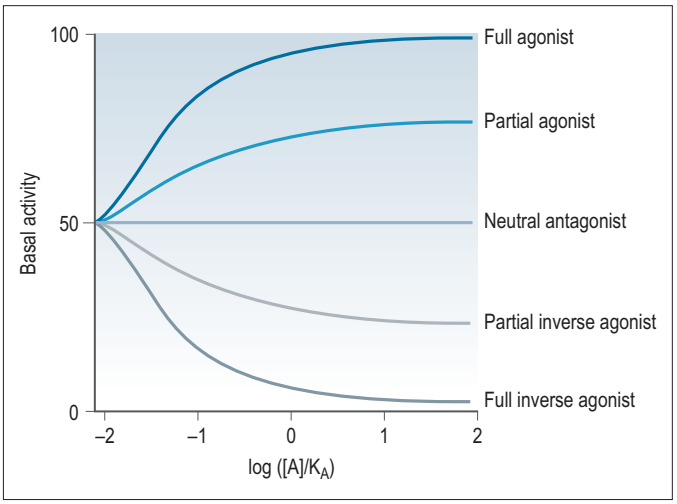

Fig. 1.1. In a constitutively active system, an antagonist modulates the activity and is defined as a full or partial inverse agonist depending on the degree of inhibition.

However, often the rate of binding/dissociation is not so important in determining the onset or termination of the elicited effect because such behavior mostly depends on the delivery and distribution.

Antagonists bind to the receptor without eliciting the necessary conformational changes required to produce the response effect. These drugs block access to the receptor. Most antagonists shift the dose-response curve to the right but do not alter the magnitude of the maximum response. *Functional antagonism* is defined as antagonism of tissue response that is unrelated to blockade at receptors but instead represents blockade at a site distal to receptors. Functional antagonists may affect second messenger production. Nonspecific antagonism might depress all cellular excitability, e.g. by energy charge.

Receptors and signal cascades

A receptor is a macromolecule whose biological function changes when a drug binds to it. Most drugs produce their pharmacological effects by binding to specific receptors in target tissues. *Affinity* is the measure of the propensity of a drug to bind to a receptor and depends on the force of attraction between drug and receptor. There are different structural and functional classifications of receptors, but generally speaking there are just a few functional families whose members share both common mechanisms of action and similarities in molecular structure. There are at least four main types.

Type 1 receptors are typically located in a membrane and are directly coupled to an ion channel. Receptors for several neurotransmitters send their signals by altering a cell's membrane potential or its ionic composition. This group includes nicotinic cholinergic receptors and γ-aminobutric acid receptors. These receptors are all multiple subunit proteins arranged symmetrically to form a channel.

Type 2 receptors are also located in a membrane and are coupled by a G protein to an enzyme or channel. There is a large family that utilizes heterotrimeric guanosine 5′-triphosphate (GTP)-binding regulatory proteins. Ligands for G-protein receptors include eicosanoids and biogenic amines. Second messengers include adenyl cyclase, phospholipase C, Ca^{2+} currents and phosphatidyl inositol-3-kinase. G-protein-coupled receptors span the cell membrane and exist as a bundle of seven helices.

Type 3 receptors, usually located in membranes, are directly coupled to an enzyme. Receptors with inherent enzymatic activity are most commonly cell-surface protein kinases. These receptors demonstrate their regulatory activity by phosphorylating various effector proteins at the inner face of the cell membrane. Phosphorylation changes the structures, biological properties and, hence, the biological activity.

Finally, *type 4 receptors* are located in the nucleus or cytoplasm and are coupled via DNA to gene transcription. Receptors for steroid hormones, thyroid hormones, retinoids, vitamin D and other molecules are soluble proteins and can bind DNA. These transcription factors are regulated by phosphorylation, association with other proteins, binding metabolites or regulatory ligands.

Drug-receptor binding triggers a cascade of events known as *signal transduction*, through which the target tissue responds. Within a physiologic entity there are myriad possible chemical signals that can affect multiple different processes. Subsequently, a very important, but not totally understood, property of a receptor is its specificity or the extent to which a receptor can recognize, discriminate and respond to only one signal. Some receptors demonstrate a very high degree of specificity and will bind only a signal endogenous ligand, while other receptors are less specific. In most cases the binding is transient and each binding triggers a signal. Furthermore, there may be different subtypes of a given receptor, each of which recognizes or binds to the same specific ligand but generates different intracellular responses. Spatial organization is one possible explanation why cross talk between the pathways does not lead to tremendous confusion.

The magnitude of receptor-mediated responses can decrease with repeated drug administration, thus after exposure to catecholamines there is a progressive loss of the ability of the target site to respond. This phenomenon is termed *tachyphylaxis*. The receptor desensitization is usually reversible.

Spare receptors allow maximal response without total receptor occupancy by increasing the sensitivity of the system. Spare receptors can bind extra ligands, preventing an exaggerated response if too much ligand is present.

A question of quantity – dose response

Characterizing the dose-response relationship in populations often is not informative enough when the inter-subject variation is relatively high. The response can vary across subjects who achieve the same concentration. In the majority of cases, the effect of a drug is dependent on the number of bound receptors, although mostly there is no linear relationship.

It is necessary to differentiate between efficacy and potency. From the clinician's point of view, the *efficacy* is more important as it stands for the maximum effect achievable (ED_{max}). ED_{50} indicates the dose of a drug that produces 50% of the maximal response. In contrast, the *potency* is a measure of the affinity and indicates which concentration has to be provided at the site of action (Fig. 1.2).

Graphically, potency is illustrated by the relative position of the dose-effect curve along the dose axis. Because a more potent drug is not necessarily clinically superior, potency has little clinical significance for a given therapeutic effect. However, low potency is a disadvantage only if it is so large that it is awkward to administer. Potency is determined by the affinity and intrinsic activity of a drug.

Pharmacodynamics is very tightly connected with toxicodynamics, both showing a very similar dose-response curve. The

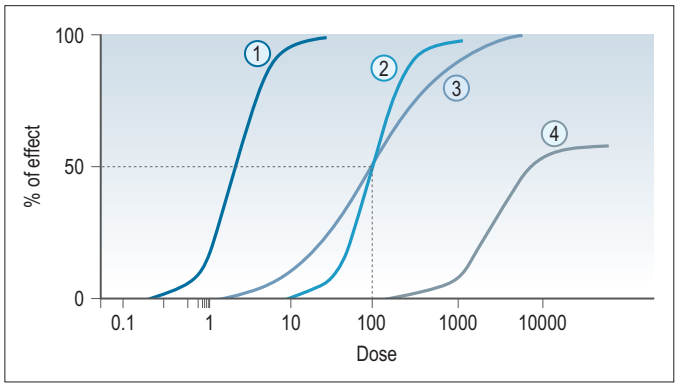

Fig. 1.2. The potency of drug 1 is higher than that of drug 2, according to a superior binding affinity. The efficacy and potency of drugs 2 and 3 are the same, but the mode of action differs. Drug 4 is less effective and less potent.

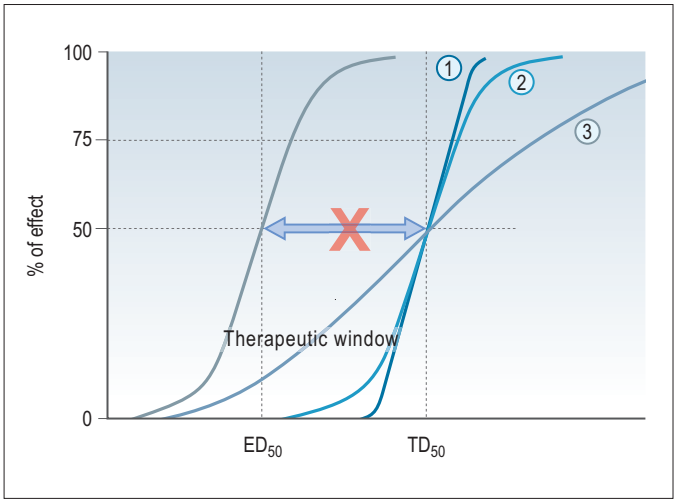

Fig. 1.3. Therapeutic width is characterized by the distance of both sensitivity curves, the therapeutic (ED_{50}, left) effect vs. the toxic (TD_{50}, right) effect. For toxicity, curves 1, 2 and 3 illustrate the different toxic responses of rise, shown by the rates of rise. If the ratio of TD_{50}/ED_{50} is used to estimate the therapeutic width, the same value would be wrongly assumed for all three curves. In reality, the therapeutic index TD_5/ED_{95} more exactly represents the safety of a drug. The therapeutic window is sometimes given as the difference $TD_5–ED_{95}$.

curve progression is characterized by the concentration where 50% (95% for LD_{95}) of the effect appears. For many years, the LD_{50} (median lethal dosage) was tested in rodents before approval of new drugs. Since 1991, LD_{50} estimations in animals have become obsolete and are no longer required for regulatory submissions as a part of preclinical development. In addition to the effect level, the relationship between time and response is crucial.

In practice, the therapeutic window is much more relevant than the maximum efficacy (treatment dosage in g or mg). Drugs with a narrow margin are more difficult to dose and administer, and may require therapeutic drug monitoring. The more innocuous a drug is, the higher is its therapeutic width (Fig. 1.3). Side effects can be classified by the dosage or the cause. *Adverse drug reactions* (ADRs) can be seen following overdose or therapeutic dose. The intended pharmacological action, effects which are independent from the primary effect or interactions with other drugs can cause the undesired effects. Correspondingly, ADRs can be classified as *type A* (augmented) or *type B* (bizarre) reactions. Withdrawal reactions, which may occur with abrupt withdrawal of some drugs, and delayed onset were assigned to type A reactions.

In overdose, increased development of the therapeutic effect often occurs. Although the patient may be prescribed a dose within the normal recommended range, impaired organ function affects clearance and may result in adverse effects. However, when the level is accordingly further increased, nearly every drug shows toxicity.

Examples of undesired effects unrelated to the primary effect are hemolytic anemia following sulfonamides, atropine-like effects in the use of tricyclic antidepressives and thrombophilia induced by contraceptives. Some serious side effects do not occur before longer-lasting therapy, e.g. osteoporosis in chronic steroid treatment.

Various type B reactions are unexpected because they are unrelated to the known pharmacological action of the drug. Many of these reactions have an immunological basis, e.g. anaphylaxis with antibiotics. Others are due to genetic abnormalities such as drug-induced hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency when given oxidative drugs. Allergic reactions are idiosyncratic and normally unrelated to dosage. Management of such ADRs usually requires stopping the offending drug.

Some ocular reactions (miosis, mydriasis or intraocular pressure) show a very reproducible pattern of the pharmacodynamic response. Ophthalmic pharmacological responses are therefore often used to investigate the administration and pharmacokinetics of a drug with special interest in the quantitative response.

PHARMACOKINETICS

Because a later part of this book concentrates on ocular pharmacokinetics and drug delivery in detail, only some general considerations are given here.

The *bioavailability* describes the proportion of the unchanged drug delivered to the site of potential action regardless of the route of administration. To facilitate the calculation of absorption and elimination rates, a compartment is usually postulated as a space where the drug is supposed to be homogeneously distributed. *First-order kinetics* are found when the rates (absorption, elimination) are proportional to the concentration. However, usually *zero-order kinetics* are detectable for most eye drops because the rates are independent of the concentration but proportional to the functional capacity of the body.

It has been estimated that only 1–5% of the active drug enclosed in an eye drop penetrates the eye (Schoenwald 1997). The maximum bioavailability is afforded by a drop size of 20 µL. An increase in volume or number of drops only leads to systemic toxicity due to increased lacrimal outflow and mucosal absorption of the drug. Up to 80% may reach the general circulation. Otherwise, after intraocular penetration there is no first-pass metabolism. Tissue binding has to be taken into consideration, reducing the elimination process by retention.

Barriers of the eye

Despite its apparent easy accessibility, the eye is well protected against the absorption of foreign materials, including therapeutic agents. The corneal epithelium acts as a trilaminar barrier

to the penetration of topical drugs. Absorption of drugs depends on their solubility; lipophilic substances seem to penetrate readily in the corneal epithelium.

Drugs administered topically will drain into the nasolacrimal duct and be absorbed through the epithelial mucosa lining into the systemic circulation. One of the reasons for this behavior is that the fornix of the lower eyelid can hold only the volume of one drop of topical medication, which is approximately 40 µl at most. Most ophthalmic drugs are adapted from other therapeutic applications and were not specifically developed for the treatment of eye disease; hence, they are not well suited to provide eye-specific effects.

For maximal corneal drug penetration, a molecule must have an optimized ratio of hydro- and lipophilicity, as nonionized molecules penetrate the epithelium/endothelium well and ionize the stroma. The clinical state of the eye also strongly determines ocular pharmacokinetics. Transcorneal drug penetration is greater when the epithelium is altered or the corneal stroma is edematous (Ueno et al 1994). Similarly, preservatives improve the penetration of the drug (Ramselaar et al 1982). The blood ocular barrier is based on tight junctions of the nonpigmented ciliary epithelium, the retinal pigment epithelium and the retinal capillary endothelial cells. Intraocular structures are also shielded by these barriers from systemic toxins. However, these natural ocular barriers may also act as drug depots and can play an important role in the pathogenesis of drug-induced ocular toxicity.

The retinal pigment epithelium (RPE) is metabolically very active and can participate in the detoxification of various drugs. As chlorpromazine and chloroquine have an affinity to the melanin of the pigment epithelium, both drugs are metabolized by the RPE and are, therefore, retinotoxic (Koneru et al 1986).

Factors affecting the availability of drugs

Surfactants increase the solubility of hydrophilic drugs by altering the permeability of epithelial membranes. Solutions with high viscosity increase the contact time of a drug on the cornea. The pH determines the degree of ionization of a drug. Because the pH of tears is slightly alkaline (7.4), many ocular drugs are weak bases (alkaloids) existing in both their charged and uncharged forms at that pH. However, if the pH of the solution is made more basic, then more uncharged forms of the molecule are present, resulting in increased lipid solubility and epithelial penetration.

After systemic administration, the ability of blood-borne agents to reach the globe depends on the lipid solubility, the plasma protein binding (only the unbound form is bioavailable) and the molecular weight. Calculating the *loading dose* of a drug is similar to calculating the amount of drug required to achieve a desired concentration in a predefined volume. This ratio can also be used to estimate the top-up dose that may be required if the drug is already present but the concentration is too low. Drugs start to be eliminated as soon as they are absorbed. Target drugs can, therefore, be maintained only if doses are given at a rate that balances the clearance rate. *Maintenance dosage* regimens are designed to achieve this balance. The time to reach this steady state depends only on the *half-life* of the drug.

Understanding the reasons for pharmacokinetic variability and adjusting drug doses accordingly can make major impacts on risk management and patient care. Besides the genetic background, we know many sources for variability related to observable clinical characteristics. Age, gender, weight and hormonal status are important. The elimination of the drug and therefore renal and liver function are determinant factors.

When describing the pharmacokinetic properties of a chemical, the four points of absorption, distribution, metabolism and excretion (ADME) are considered. A pharmacokinetic system can be determined to be linear or nonlinear and time-invariant or time-varying with respect to the modeling.

Many of the clinically significant interactions between drugs are pharmacokinetic in origin. Not only can induction/inhibition of metabolizing enzymes occur, but also direct competition for transport mechanisms can influence tissue distribution and accumulation. Drugs competing for albumin are phenylbutazone and warfarin; therefore each affects the distribution of the other. Thyroxine influences the absorption of calcium. Probenecid vies with penicillin for renal excretion.

Important pathways, such as the microsomal cytochrome P_{450} monooxygenase, are known to be inducible, but also genetically determined. These enzymes act on structurally unrelated drugs. In phase I of biotransformation, drugs are made more polar by oxidation, reduction and hydrolytic reactions, before phase II reaction results in drug inactivation by conjugation (glucuronidation, sulfation, acetylation). Mutations in the cytochrome P_{450} monooxygenase lead to slower metabolizing of drugs. The application of pharmacogenetics therefore holds great promise for an optimized, individualized therapy. However, there is little clinical impact at present because of the complex variability of the pharmacology (different pathways, active metabolites), leading to a high level of operating expense. The benefits of prospective testing still need to be weighed against the costs.

PHARMACOLOGY PRINCIPLES

When designing drug regimens, it is important to consider the risks and limitations of medical treatment. We recommend paying attention to the following 10 reminders of what to not to do.

1) Do not be ignorant of the pharmacology

General pharmacology often is not an exciting issue. Complicated and unusual names of agents, difficult schemes of dosages and biochemical pathways do not invite the study of the basics of pharmacologic treatment. However, the effective therapy is intimately connected with the pathophysiology of a disease as designing selective inhibitors to a cytokine or receptor has become feasible. Although it is often not a simple story, the knowledge of the background facilitates the choice of the appropriate therapeutic approach.

In terms of legal advice, a physician's liability is based on negligence, the legal equivalent of malpractice. Professional negligence means that a professional person (physician, pharmacist) acting within the scope of his or her reputation has performed in a substandard fashion, causing a person to suffer damages. Physicians may be negligent in two ways – by failing to do something or by doing something incorrectly (Francisco 1990). When a physician has not been obviously negligent by inappropriately prescribing a drug, many considerations are examined to determine whether a physician's conduct fell below the requisite standard of care.

Some questions are raised before a legal proceeding: Was the physician aware of the risks involved prescribing the medication; and, if the physician was not aware, should he or she have been? Were there warnings included in the pharmaceutical

manufacturer's literature that were not followed? Would a physician read the literature in exercising reasonable care? Were the expected benefits of use of that particular drug sufficient to justify exposing the patients to the risks? Were specific tests recommended in the literature that the physician failed to perform before initiating the drug? Should the physician have noticed the adverse effect of the drug when it occurred and taken countermeasures? Could the medication have been stopped in time to avoid injury?

2) Do not mix too many drugs

Maintaining an overview of the situation can be difficult, especially in challenging situations. If the therapeutic benefit is still missing in the presence of psychological strain, the physician is at risk of escalating the therapeutic regimen by just adding further drugs.

Blind polypragmasia ("*If a little is good, more is better*") rarely achieves an improvement. If combining too many remedies, it is not possible to differentiate between the effects of several drugs and acknowledge the exact agent responsible for the observed side effects or therapeutic response. Do not prescribe any medication unless it is absolutely needed, and discontinue use of the drug as soon as possible.

Most drugs are available in different formulations, e.g. as eye drops and ointments at the same time. Different therapies have different advantages and disadvantages. Drops allow faster visual rehabilitation because of the effect on the precorneal tear film and visual acuity is less pronounced. In the presence of corneal ulcers or erosions, eye drops do not interfere with reepithelialization. Preservative-free drops can even be used together with bandage contact lenses. In contrast, ointments have the advantage of increased drug contact time. If the administration is difficult, prolonged concentration can be maintained. Ointments may, however, also act as barriers to the penetration of other drops. The slow release of some agents from the ointment may result in subtherapeutic levels of the drug. In contrast, preservatives and antibiotics (e.g. aminoglycosides) can cause damage to the corneal epithelium if contained in the ointment (Napper et al 2003).

3) Do not forget the aim of treatment

The strategy of the approach should always include a clear definition of the therapeutic target. Even though the therapy sometimes makes the diagnosis, it is important to clarify the suspected problem before looking for the solution. Waiting for a further course of the disease and defining the suspected diagnosis exactly might be wiser in some situations before intensified treatment is considered. For example, in the case of intraocular lymphoma, (steroid) treatment should be stopped before diagnostic vitrectomy in order to harvest enough significant cells.

Controlling the success of therapy is essential. Although only a few drugs need special biomonitoring, the drug concentration has to be assessed if the high variability of bioavailability fails to meet the therapeutic window, e.g. in systemic cyclosporine therapy. Other agents only require additional safety assessment. Because tamoxifen, chloroquine, amiodarone and cetirizine are reported to produce ocular toxicity, clinicians are usually careful to note their particular toxicities.

Control of the outcome is also important in general treatment for several reasons. First, nonresponders would otherwise not be detected. Second, it should not be forgotten that most patients expect a final examination giving them positive feedback. Telling patients that their disease has been cured or at least stability has been achieved can give an additional feeling of safety. This may be of major importance in improving individual compliance in chronic diseases. Finally, recognizing potential adverse events (and reporting them to the US FDA or equivalent) is the physician's responsibility (Kaufman et al 1994). Without looking for side effects, the physician would not identify toxicity. Systemic adverse effects of topical ocular treatment are not easy to recognize. We need an optimum level of alertness and an interdisciplinary comprehension.

4) Do not taper anti-infective drugs

For many drugs it is mandatory to adjust the dosage in accordance with the development of the disease. Immunosuppressives are prime examples, where tapering reduces side effects but can result in inflammatory activity developing over time. If dose reduction is too fast, tapering may lead to recurring activity (rebound phenomena).

To a certain extent, varying the frequency at which eye drops are administered provides an additional tool for adapting dosage. For example, the use of repeated applications is able to achieve the same levels in aqueous humor as a subconjunctival injection. However, in antibiotics the therapeutic range usually is very limited. The width of the therapeutic window is restricted by the required effective dosage (Mattie 1993).

Using antibiotic agents for too long and with an insufficient dosage is not only the reason for ineffective treatment, but can increase the risk of developing resistance (Gaynor et al 2005). Anti-infective drugs should be always stopped abruptly and never tapered.

5) Do not overestimate patient compliance

"Real world" conditions are often very different from theoretical considerations. Although a combination of multiple drugs might be necessary in the advanced stage of a disease and frequent administration can achieve higher drug concentrations, the ability to apply drugs as frequently as prescribed may be restricted for the average patient.

Blinded prospective studies have evaluated application behavior in detail and have shown that noncompliance is very often the limiting factor (Stewart et al 2004; Herrmann et al 2006). The issue is even more relevant in permanent treatment, e.g. with antiglaucomatous drugs.

With higher frequency dosing and an increasing number of drugs, a growing number of patients do not comply with drug therapy recommendations. However, there are ways of overcoming these problems. An exact written plan helps the patient to follow the prescription. This should explain how to administer the drug and discuss side effects clearly. Administration is an important issue especially for older or disabled patients. The dose regimen should be critically optimized for the individual patient to address administration issues. Explaining the background and convincing the patient of the necessity of the planned treatment and its aim can strongly improve the acceptance of the drug.

6) Do not disregard patients' warnings

Incompatibility and allergic predisposition mostly arise with clear symptoms. Nearly all symptoms related to adverse effects are recognized by the patient. It therefore seems wise to listen carefully to the (sometimes bizarre) reports of the patients' experiences. Depending on what they say, the medication can be adapted.

Drug-induced allergy remains a relatively rare situation, occurring in a small percentage of patients, mostly in the early course of treatment. For the ocular surface, preservatives are major sources of allergic reaction (Baudouin 2005).

Other clinical manifestations may also be related to the toxicity of the drug without the occurrence of allergic reactions. Corneal punctate staining can occur regardless of the agent. Previous studies have illustrated the importance of discriminating early, acute allergic reactions from often more-delayed toxic and nonspecific inflammatory mechanisms that may require some time to occur or result from indirect inflammatory mechanisms.

7) Do not underestimate drug interactions

Because the tear turnover is 30%/min (following 1 drop, nonirritated eye 15%/min), drops wash out in approximately 5 minutes. This is the minimum time interval between drops. Concurrent use of individual preparations has shown much lower concentrations than achieved with a fixed combination.

Using pharmacodynamics, the interaction between different antiglaucomatous drugs is very well studied. There are many examples where combined treatment does not induce additive or synergistic effects; e.g. pilocarpine added to prostaglandins does not seem to produce an additive decrease in intraocular pressure effect (Toor et al 2005). When the interacting drug has a long elimination half-life, the interaction may persist for some time after the drug has been discontinued. It is important to consider potential interactions not only when two drugs are given together but also when one is stopped.

8) Do not to forget whom to treat

We have to keep in mind that several subgroups of patients are at higher risk of developing side effects. A very important example is treatment during pregnancy, when toxicity and placental transfer must be evaluated in addition to other factors (Chung et al 2004). Data are very limited as large-scale population surveillance is needed to detect individual drug teratogenicity. Researchers are often not willing to invest funds in research that will most likely give a negative association between the two variables studied.

Reasonable care must also be used in children. Besides absolute contraindications (e.g. brimonidine), some drugs have to be weighted in the individual situation (Bowman et al 2004). Topical application offers lower systemic exposure and sometimes enables the use of drugs that are not harmless when applied systemically in children (e.g. chinolones). However, recent FDA warnings for children include some topical medications (e.g. pimecrolimus/tacrolimus ointment because of the potential cancer risk). Changes in clearance vary with age. When there is a special need for dose adjustment, we strongly recommend consultation with pediatricians.

Because of the increasing longevity of the population, a growing number of very old people are exposed to medications. The average number of drugs is five per patient for patients over 65 years old. Geriatric dosing is problematic because of possible drug interactions. Drug therapy in this population is also difficult because changes in body composition, malnutrition and renal failure can cause drug accumulation and toxicity. Liver function and P_{450} metabolism can also be affected. Physicians should therefore always be particularly careful when prescribing drugs to pregnant women, children or elderly patients.

9) Do not disregard alternative approaches and recommendations of how to behave in daily life

The acceptance of drug treatment is much higher if if patients are given the impression that they are able to actively fight the disease. In contrast, if they experience a loss of control, patients find it more difficult to cope with the treatment burden. The extent to which any patient adheres to a medical regimen is an essential determinant of clinical success.

Although the perception of disease depends on many different factors, it is possible to satisfy individual demands. A holistic perspective also takes psychosomatic complaints and factors seriously.

There is not a great deal of evidence for the effectiveness of alternative treatment options. Nonetheless, if a patient insists on an alternative treatment attempt, it is important to keep contact and perform control examinations regularly. In terms of toxicity, there is not a great difference between approved drugs and homespun remedies (Fraunfelder et al 2003). Because of their widespread use, ophthalmologists should be aware of nutritional supplements and herbal medicines (West et al 2006) and their side effects.

10) Do not overlook signs of a causal relationship when discussing potential adverse events

Most physicians react in an irritated manner when patients mention any side effects they have found in the patient information leaflet. Although the necessity and in particular the extent and modalities to provide information of potential drug reactions can be controversial, a greater awareness can help identify a potential toxicity.

On the one hand, warnings can also become self-fulfilling prophecies (Witthoeft et al 2013). That is often the reason why diffuse statements and unobjectifiable symptoms are rated critically or considered to trace back to the medical consultation. The so-called *nocebo* phenomenon is seen after use of formulations containing no active ingredients, though nonmedicated, negative effects similar to diseases were reported by the persons affected. The symptoms were mainly attributable to the psychosomatic disorders (nausea, headache, exhaustion); however, objective manifestations like skin rash, hypertension or tachycardia also were reported (Hahn et al 1997).

On the other hand, the complaints and history of patients can be of high relevance in order to identify so far unknown side effects, both for the individual patient and the knowledge of the general connection. The single observation can be useful and superior in the systematic analysis of higher-evidence trials (Aagaard et al 2009). Nevertheless, many examples such as the floppy iris syndrome caused by α1-antagonists exemplify the difficulties in recognizing the causal relationship between a medicinal drug and any signal that might also be associated with the treated disease or the person treated (Chang et al 2005). Contaminated, falsified agents or cheap quality are more frequently placed on the global market (Sun et al 2011). Therefore, still facing a high incidence of adverse drug reactions, it is necessary to have a good practice in detecting the signals and a predefined strategy to assess the causal relationship.

While a deterministic approach such as laboratory diagnostics is usually missing, rarely can it be said for sure whether the event observed is causally connected to the intake of a medication. Most approaches to analyzing the causality focus

Table 1.1 – WHO Causality Assessment Criteria (Rehan et al 2009)

Causality Categories	Time Sequence	Other Drugs/Disease Ruled Out	Dechallenge	Rechallange
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No
Unclassified				
Not appraisable				

Table 1.2 – Naranjo Probability Scale (Rehan et al 2009)

	Yes	No	Not Sure
Presence of previous conclusive report on adverse reaction?	+1	0	0
Did adverse event appear subsequent to administration of suspected drug?	+2	–1	0
Did adverse event improve on drug discontinuation or on administration of specific antagonist?	+1	0	0
Did the adverse event reappear when the drug was readministered?	+2	–1	0
Are there any alternative causes other than the suspected drug that could have caused the reaction on their own?	–1	+2	0
Did the adverse event reappear when a placebo was administered?	–1	+1	0
Was the incriminated drug detected in toxic concentrations in blood (fluids)?	+1	0	0
Did the adverse event worsen on increasing the dose or decrease in severity with lower doses?	+1	0	0
Past history of any similar reaction to the same or similar drugs?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0
Total score: 0, doubtful; 1–4, possible; 5–8, probable; ≥9, definite			

on three parameters: the chronological relationships between the exposure and the adverse event, the probability of competing factors and the pharmacologic plausibility. Valuable instruments in the assessment are the WHO classification scheme and the likelihood scale of Naranjo (Table 1.1 and Table 1.2; Rehan et al 2009 UMC).

In addition, the nine criteria of the English epidemiologist Sir Austin Bradford Hill can be used to evaluate the quality of the data and potential signals (strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, analogy).

REFERENCES AND FURTHER READING

Aagaard L, Hansen EH: Information about ADRs explored by pharmacovigilance approaches: a qualitative review of studies on antibiotics, SSRIs and NSAIDs, *BMC Clin Pharmacol* 9:4, 2009.

Baudouin C: Allergic reaction to topical eyedrops, *Curr Opin Allergy Clin Immunol* 5:459–463, 2005.

Bowman RJ, Cope J, Nishal KK: Ocular and systemic side effects of brimonidine 0.2% eye drops in children, *Eye* 18:24–26, 2004.

Buller A, Hercules BL: Should patients choose their own eyedrops? *Acta Ophthalmol Scan* 84:150–151, 2006.

Chang DF, Campbell JR: Intraoperative floppy iris syndrome associated with tamsulosin, *J Cataract Refract Surg* 31:664–673, 2005.

Chung CY, Kwok AK, Chung KL: Use of ophthalmic medications during pregnancy, *Hong Kong MeJ* 10:191–195, 2004.

Francisco CJ: Liability for adverse drug reactions, *Tex Med* 86:42–46, 1990.

Fraunfelder FW, Fraunfelder FT, Goetsch RA: Adverse effects from over-the-counter lice shampoo, *Arch Ophthalmol* 121:1790–1791, 2003.

Gardiner SJ, Begg EJ: Pharmacogenetics, drug-metabolizing enzymes and clinical practice, *Pharmacol Rev* 58:521–590, 2006.

Gardiner P, Dvorkin L: Promoting medication adherence in children, *Am Fam Physician* 74:793–798, 2006.

Gaynor BD, Chidambaran JD, Cevallos V, et al: Topical ocular antibiotics induce bacterial resistance at extraocular sites, *Br J Ophthalmol* 89:1097–1099, 2005.

Hahn RA: The nocebo phenomenon: concept, evidence, and implications for public health, *Prev Med* 26:607–611, 1997.

Herrmann MM, Diestelhorst M: Microprocessor controlled compliance monitor for eye drop medication, *Br J Ophthalmol* 90:830–832, 2006.

Kaufman MB, Soukides CA: Physician's liability for adverse drug reactions, *South Med J* 87:780–784, 1994.

Koneru PB, Lien EJ, Koda RT: Oculotoxicities of systemically administered drugs, *J Ocul Pharmacol* 2:385–404, 1986.

Labetoulle M, Frau E, LeJeune C: Systemic adverse effects of topical ocular treatments, *Presse Med* 34:589–595, 2005.

Langley JN: On the sympathetic system of birds, and on the muscles which move the feathers, *J Physiol* 30:221–252, 1904.

Mattie H: The importance of pharmacokinetics and pharmacodynamics for effective treatment of infections, *Clin Invest* 71:480–482, 1993.

Meibohm B: The role of pharmacokinetics and pharmacodynamics in the development of biotech drugs. In Meibohm B, editor: *Pharmacokinetics and Pharmacokinetics of Biotech Drugs: Principles and Case Studies in Drug Development*, Weinheim, 2006, Wiley-VSH GmbH & Co, pp 3–13.

Moorthy RS, Valluri S: Ocular toxicity associated with systemic drug therapy, *Curr Opin Ophthalmol* 10:438–446, 1999.

Napper G, Douglass I, Albietz J: Preservative and antibiotic toxicity to the ocular surface, *Clin Exp Optom* 86:414–415, 2003.

Olson MK: Are novel drugs more risky for patients than less novel drugs? *J Health Econ* 23:1135–1158, 2004.

Ramselaar JA, Boot JP, van Haeringen NJ, et al: Corneal epithelial permeability after instillation of ophthalmic solutions containing anaesthetics and preservatives, *Curr Eye Res* 7:947–950, 1982.

Rehan HS, Chopra D, Kakkar AK: Physician's guide to pharmacovigilance: terminology and causality assessment, *Eur J Intern Med* 20:3–8, 2009. http://www.sciencedirect.com/science/article/pii/S0953620508001295.

Schoenwald RD: Ocular pharmacokinetics. In Zimmermann TJ, Koonerm KS, Sharir M, et al, editors: *Textbook of Ocular Pharmacology*, ed 9, Philadelphia, 1997, Lippincott-Raven, pp 119–138.

Stewart WC, Konstas AG, Pfeiffer N: Patient and ophthalmologist attitudes concerning compliance and dosing in glaucoma treatment, *J Ocul Pharmacol* 20:461–469, 2004.

Sun X, Xu X, Zhang X: Counterfeit bevacizumab and endophthalmitis, *N Engl J Med* 365:378–379, 2011.

Thieme H, Schimmat C, Munzer G, et al: Enodthelin antagonism: effects of FP receptor agnonists prostaglandin F2alpha and fl uprostenol on trabecular meshwork contractility, *Invest Ophthalmol Vis Sci* 47:938–945, 2006.

Toor A, Chanis RA, Polikoff LA, et al: Additivity of pilocarpine to bimatoprost in ocular hypertension and early glaucoma, *J Glaucoma* 14:243–248, 2005.

Ueno N, Refojo MF, Abelson MB: Pharmacokinetics. In Albert DA, Jakobiec FA, editors: *Principles and Practice of Ophthalmology 74, Basic Sciences*, Philadelphia, 1994, WB Saunders Company, pp 916–926.

The Uppsala Monitoring Centre: The use of the WHO-UMC system for standardised case causality assessment, 2012. http://who-umc.org/Graphics/24734.pdf.

West AL, Oren GA, Moroi SE: Evidence for the use of nutritional supplements and herbal medicines in common eye diseases, *Am J Ophthalmol* 141:157–166, 2006.

Witthoeft M, Rubin GJ: Are media warnings about the adverse health effects of modern life self-fulfilling? An experimental study on idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF), *J Psychosom Res* 74(3):206–212, 2013.

Worakul N, Robinson JR: Ocular pharmacokinetics/pharmacodynamics, *Eur J Pharmac Biopharm* 44:71–83, 1997.

Wotquenne P, Petermanns J, Scheen AJ: Drug therapy in the elderly. What should we know? *Rev Med Suisse* 23:1878–1883, 2006.