Herbal Products

Toxicology and Clinical Pharmacology

Second Edition

Edited by
Timothy S. Tracy, PhD
Richard L. Kingston, PharmD

Humana Press

Herbal Products

FORENSIC SCIENCE AND MEDICINE

Steven B. Karch, MD, SERIES EDITOR

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999 Riverview Drive, Suite 208
Totowa, New Jersey 07512
www.humanapress.com

This publication is printed on acid-free paper. ∞

ANSI Z39.48-1984 (American Standards Institute) Permanence of Paper for Printed Library Materials.

Production Editor: Amy Thau

Cover design by Nancy K. Fallatt

Cover Illustration: Fig. 1, Chapter 13, "Hawthorn," by Timothy S. Tracy

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Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN 10-digit: 1-59745-383-8
eISBN 13-digit: 978-1-59745-383-7

Library of Congress Cataloging in Publication Data
Herbal products : toxicology and clinical pharmacology / edited by
Timothy S. Tracy, Richard L. Kingston. -- 2nd ed.
p. ; cm. -- (Forensic science and medicine)
Rev. ed. of: Toxicology and clinical pharmacology of herbal
products / edited by Melanie Johns Cupp. c2000.
Companion to: Dietary supplements / edited by Melanie Johns Cupp
and Timothy S. Tracy. c2003.
Includes bibliographical references and index.
ISBN 10-digit: 1-58829-313-0 (alk. paper)
ISBN 13-digit: 978-1-58829-313-8 (alk. paper)
1. Herbs--Toxicology. 2. Materia medica, Vegetable--Toxicology.
I. Tracy, Timothy S. II. Kingston, Richard L. III. Toxicology and
clinical pharmacology of herbal products. IV. Dietary supplements.
V. Series.
[DNLM: 1. Plants, Medicinal. 2. Phytotherapy--adverse effects.
3. Plant Extracts--pharmacology. 4. Plants, Medicinal--adverse
effects. QV 766 H5347 2007]
RA1250.T68 2007
615.9'52--dc22

2006017680

Preface

Herbalists and laypersons have used herbs for centuries. Interest in and use of herbal products was revitalized in the late 1990s with the passage of the Dietary Supplement Health and Education Act, which allowed dietary supplements to be marketed without enduring the FDA-approval process required of drugs. Thus, despite the widespread use of herbal products, information about their safety and efficacy is generally sparse compared with the information available about prescription drugs. *Toxicology and Clinical Pharmacology of Herbal Products* was published in 2000 to help fill this information void. Since its publication, additional scientific information has come to light, and the public's interest in particular herbs has changed. *Herbal Products: Toxicology and Clinical Pharmacology, Second Edition* updates the information presented in *Toxicology and Clinical Pharmacology of Herbal Products.* Herbs were chosen for inclusion in the current volume based on their popularity, toxicity, and quantity and quality of information available. A companion volume, *Dietary Supplements: Toxicology and Clinical Pharmacology*, covers nonherbal dietary supplements.

The aim of this book is to present, in both comprehensive and summative formats, objective information on herbal supplements from the most reliable sources, with an emphasis on information not readily available elsewhere (i.e., detailed descriptions of case reports of adverse effects, pharmacokinetics, interactions, etc.). It is not designed to be a "prescribers handbook;" the intended audience is both forensic and health care professionals, particularly researchers and clinicians interested in more detailed or context-oriented clinical information than is available in most "herbal" or "natural product" references.

Although information about dietary supplements is widely available on the Internet, it is usually provided by product distributors, and is designed to sell products rather than to provide objective information about product efficacy and toxicity. Even reviews of dietary supplements in journals, newsletters, books, and electronic databases can be biased or incorrect. In compiling information to be included in *Herbal Products: Toxicology and Clinical Pharmacology, Second Edition*, emphasis was placed on the use of original studies published in reputable, peer-reviewed journals. Older studies, as well as more current literature, were utilized for completeness, with an emphasis on newer literature and double-blind, controlled trials. Where appropriate, information was obtained

from meta-analyses, systematic reviews, or other high-quality reviews, such as those authored by recognized experts. Case reports of adverse effects and interactions, although anecdotal in nature, were used to identify and describe uncommon but potentially serious adverse events that may not have been noted in controlled studies because of small sample size or short duration.

Each of the chapters in this volume includes an Introduction, which contains a review of the product's history and a description of the plant. This is followed by sections on Commonly Promoted Uses, Sources and Chemical Composition, and descriptions of Products Available, which is kept general because of the myriad and ever-changing products on the market. Product quality is also discussed in this section. The Pharmacological/Toxicological Effects section focuses on in vitro data and animal studies chosen to provide an explanation for the herb's mechanism of action, clinical effects in humans, and rationale for clinical studies. It should be noted that because of the nature of herbal supplement claims (*see* Regulatory Status section), some promoted product uses might not have been studied in humans; conversely, known pharmacological and therapeutic effects might not be promoted commercially as a result of limitations in the ability of manufacturers to make "health claims" related to known pharmacological effects of various herbs. As a result, there is generally a mismatch among the nature of the information presented in the Commonly Promoted Uses and Pharmacological/Toxicological Effects sections. However, emphasis is placed on inclusion of basic science data and clinical studies that relate to the promoted uses.

The Pharmacokinetics section of each chapter covers absorption, tissue distribution, elimination, and body fluid concentrations. Such pharmacokinetic information is usually not included in other sources and may be useful in forensic investigations or in the clinical setting regarding use of the product in patients with renal or hepatic insufficiency. A section on Adverse Effects and Toxicity follows and includes detailed information on case reports of adverse reactions to the herb. The Interactions section includes discussions of interactions between the supplement and drugs or foods. The Reproduction section follows and is generally limited because of lack of information. Each chapter ends with a discussion of Regulatory Status of the product. The amount of information included in each of these sections varies according to availability.

Adverse reactions to herbals appear uncommon compared with those attributed to prescription drugs. This may be a function of health care and forensic professionals' unfamiliarity with the products' pharmacology and toxicology or assumption that the products are "natural" and therefore safe. Thus, an adverse reaction may go unrecognized or be attributed to a prescription medication.

It is hoped that the information in *Herbal Products: Toxicology and Clinical Pharmacology, Second Edition* will be used to solve clinical or forensic problems involving dietary supplements, promote dialogue between health care professionals and patients, and stimulate intellectual curiosity about these products, fostering further research into their therapeutic and adverse effects.

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Contents

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Chapter 1

Ma Huang and the Ephedra Alkaloids

Steven B. Karch

Summary

Ephedra has been used as a natural medicine for thousands of years by numerous cultures with very little concern about toxicity. Its most recent popularity is related to its purported "weight loss" or "performance enhancing" attributes. In spite of that in 2004, concerns over safety resulted in the banning of all over-the-counter (OTC) sales of ephedra-containing dietary supplements by the Food and Drug Administration.

All ephedra plants contain phenylalanine-derived alkaloids, including ephedrine, pseudoephedrine, methylephedrine, and trace amounts of phenylpropanolamine. Previously marketed herbal supplements typically stated total ephedra alkaloid content, although actual levels of individual alkaloid varied depending on raw material and production runs.

A double-blind, placebo-controlled trial by Boozer et al. examined issues of long-term safety and efficacy of ephedra, demonstrating its ability to reduce body weight and body fat while improving blood lipids without significant adverse events. Although other studies have documented a favorable adverse effect profile for appropriately administered doses of ephedra-containing supplements, there have been numerous anecdotal reports of adverse effects. Abuse and misuse of ephedra-containing products likely contributed to spontaneously reported adverse effects and increased concerns over safety.

As with other sympathomimetic agents, theoretical drug interactions with ephedra alkaloids are possible. Despite this potential, only a handful of adverse drug interactions have been reported. This is especially pertinent when considering the extensive use of both ephedra-containing supplements and ephedrine- or pseudoephedrine-containing OTC products. The most notable interaction exists between nonselective monoamine oxidase inhibitors and ephedra- or ephedrine-containing products.

From Forensic Science and Medicine:
Herbal Products: Toxicology and Clinical Pharmacology, Second Edition
Edited by: T. S. Tracy and R. L. Kingston © Humana Press Inc., Totowa, NJ

With the ban of ephedra-containing dietary supplements and severe restrictions in access to ephedrine-containing OTC products, the landscape of clinical use associated with agents of this nature has been dramatically changed forever. Interest in further clinical study will likely be severely limited.

Key Words: Herbal stimulants; weight loss; phenylalanine; alkaloids; bronchodilator; athletic performance.

1. HISTORY

Ephedra, and other medicinal plants have been identified at European neanderthal burial sites dating from 60,000 BCE *(1)*. Thousands of years later, Pliny accurately described the medicinal uses of ephedra. But thousands of years before Pliny, traditional Chinese healers used ephedra extracts. Chinese texts from the 15th century recommended ephedra as an antipyretic and antitussive. In Russia, around the same time, extracts of ephedra were used to treat joint pain; and though recent laboratory studies confirm that ephedra might be useful for that purpose *(2)*, additional trials and studies have not been forthcoming. In the 1600s, Indians and Spaniards in the American Southwest used ephedra as a treatment for venereal disease *(3)*. That idea might also have had some merit, as some studies show that ephedra contains compounds with antibiotic activity called transtorines *(4)*. Whether the transtorines will prove to be clinically useful has not been determined.

In 1885, Nagayoshi Nagi, a German-trained, Japanese-born chemist, isolated and synthesized ephedrine. Nagi's original observations were confirmed by Merck chemists 40 years later *(5)*. Merck's attempts at commercializing ephedrine were unsuccessful, at least until 1930, when Chen and Schmidt published a monograph recommending ephedrine as the treatment of choice for asthma *(3)*. During the 1920s and 1930s, epinephrine was the only effective oral agent for treating asthma. Epinephrine, which had been available since the early 1900s was (and still is) an effective bronchodilator, but it has to be given by injection, or administered with special nebulizers. Ephedrine was nearly as effective as epinephrine, and could be taken orally. As a result, ephedrine became the first-line drug against asthma. It was displaced from that front during the late 1970s and early 1980s, when aerosolized synthetic β-agonists were introduced.

Unlike most of the other alkaloids contained in ephedra (methylephedrine and cathinone are both psychoactive, but the amount contained in unadulterated ephedra is too low to be of clinical significance), ephedrine is also a

potent central nervous system (CNS) stimulant *(6)*. Injections of ephedrine, called philopon (which means "love of work") were given to Japanese kamikaze pilots during World War II. A major epidemic of ephedrine abuse occurred in postwar Japan, when stockpiles of ephedrine accumulated for use by the Army were dumped on the black market. Abusers in Tokyo, and other large Japanese cities, injected themselves with ephedrine (then referred to as hirapon), in much the same way that methamphetamine is injected today *(7)*. In the Philippines, a mixture of ephedrine and caffeine called shabu was traditionally smoked for its stimulating effect. In the late 1980s, shabu smoking gave way to the practice of smoking methamphetamine ("ice"). In what is perhaps a tribute to the past, some "ice" is sold under the philopon name.

The chemistry and nomenclature of these compounds are somewhat confusing, and are best understood by reference to the synthetic route used by plants to make ephedrine. All ephedra plants contain phenylalanine-derived alkaloids. Plants use phenylalanine as a precursor, but incorporate only seven of its carbon atoms. Phenylalanine is metabolized to benzoic acid, which is then acetylated and decarboxylated to form pyruvic acid. Transamination, results in the formation of forms (–)-cathinone.

Reduction of one carbonlyl group leads to the formation of either (–)-norephedrine (phenylpropanolamine is the name used to refer to the synthetic mixture of ± norephedrine), or norpseudoephedrine (called cathine). N-methylation of (–)-norephedrine results in the formation of (+)-ephedrine. N-methylation of cathine leads to the formation of (+)-pseudoephedrine *(8)*.

2. Current Promoted Uses

Physicians routinely used intravenous ephedrine for the prophylaxis and treatment of hypotension caused by spinal anesthesia particularly during caesarean section *(9)*. In the past, ephedrine was used to treat Stokes–Adams attacks (complete heart block), and was also recommended as a treatment for narcolepsy. Over the years, ephedrine has been replaced by other, more effective agents *(10)*, and the advent of highly selective β-agonists has mostly eliminated the need to use ephedrine in treating asthma.

European medical researchers have, for several years, used ephedrine to help promote weight loss, at least in the morbidly obese *(11,12)*, and nutritional supplements containing naturally occurring ephedra alkaloids are sold in the United States for the same purpose. Clinical trials confirm that, taken

as directed, use of these supplements does result in weight loss, though whether such losses are sustained has not been determined *(13,14,15)*.

Prior to its banning by the Food and Drug Administration (FDA) in 2004, ephedra was found in many "food supplements," used by bodybuilders. Generally, it was compounded with other ingredients such as vitamins, minerals, and amino acids in products, which are said to increase muscle mass and enhance endurance *(16)*. Performance improvement secondary to ephedrine ingestion has been established in a controlled clinical trials *(17,18,19)*, and use of ephedrine has been prohibited by the International Olympic Committee.

Ephedra was also sold in combination with many other herbs in obscure combinations. Labels frequently listed 10 or 15 different herbs, but, analysis usually disclosed only the ephedra alkaloids and caffeine as present in sufficient quantities to be physiologically active. After several well-publicized accidental deaths, products clearly intended for abuse, such as "herbal ecstasy," and other "look-alike drugs" (products usually containing ephedrine or phenylpropanolamine designed to look like illicit methamphetamine, but in concentrations higher than recommended by industry or the FDA) were withdrawn from the market. Labels on these products were frequently misleading. For example, one might suppose that a product called "Ephedrine 60™ " contained 60 mg of ephedrine when, in fact, the actual ephedrine content was 25 mg.

3. Sources and Chemical Composition

Ephedra (*ephérdre du valais* in French and *Walliser meerträubchen* in German) is a small perennial shrub with thin stems. It rarely grows to more than a foot in height, and at first glance, the plant looks very much like a small broom. Different, closely related species are found in Western Europe, southeastern Europe, Asia, and even the Americas. Some of the better known species include *Ephedra sinica* and *E. equisentina* from China (collectively known as ma haung), as well as *E. geriardiana, E. intermedia,* and *E. major,* which grow in India and Pakistan, and countless other members of the family Ephedraceae that grow in Europe and the United States (*E. distachya, E. vulgaris*) *(20)*.

Ephedra species vary widely in their ephedrine content. One of the most common Chinese cultivars, known as "China 3," contains 1.39% ephedrine, 0.361% pseudoephedrine, and 0.069% methylephedrine *(21)*. This mix is fairly typical for commercially grown ephedra plants. Noncommercial varieties of ephedra may contain no ephedrine at all *(22)*, while others may contain more

pseudoephedrine than ephedrine. Depending on the variety, trace amounts of phenylpropanolamine, (–) norephedrine, and methylephedrine may also be present, however (+) norephedrine does not occur naturally, and its presence is proof of adulteration.

Labels on herbal supplements listed total ephedra alkaloid content, usually 10 or 11 mg per serving. Depending on the raw materials used, different production runs of the same product contained ephedrine and pseudoephedrine in varying proportions. Occasionally, supplement makers were accused of adulterating their product by adding synthetic ephedrine or pseudoephedrine. Unlike with (+)-norephedrine, these compounds occur naturally and product adulteration should not have been alleged just because alkaloids other than ephedrine were detected in trace amounts, or because the ratio of ephedrine to pseudoephedrine was close to, or even greater than, 1:1. Of course, if one of the minor alkaloids, such as methylephedrine, were found to be present in concentrations approaching those of ephedrine, the ratio could only be explained by adulteration.

4. Products Available

Prior to its ban in 2004, no one government agency was tasked with tracking production of ephedrine-containing products. Nor were these products indexed by any industry or trade organization. Ephedrine-containing supplement products were mostly purchased at health food stores or over the Internet. Claims made by some of the Internet vendors were quite outrageous and totally unsupported by any scientific research. The large supplement makers, of course, had web pages, many of which contained, or had links to, the most recent peer review studies. But in addition to the established names, hundreds of other, smaller manufacturers also advertised and sold over the Internet. These companies came into and went out of existence so rapidly that a detailed listing of their web sites would likely be outdated before the links were published. Even today, a simple search using the word "ephedrine," will disclosed numerous off-shore vendors, along with numbers of attorneys soliciting for ephedra-related class action legal cases.

In addition to selling their own proprietary mixture, many of these same web sites sold the same popular products as the herbal and general retail outlets, such as a previous Twin Labs best seller "Ripped Fuel™ ," which contained ephedrine in the form of ma huang, combined with guarana, L-carnitine, and chromium picolinate. Metabolife 356™ contained guarana (40 mg caf-

feine), 12 mg ephedrine as ma huang, chromium picolinate 75 mg, and several other ingredients. Ever since ephedrine became the precursor of choice for making methamphetamine, federal regulators have severely restricted bulk sales of ephedrine, but these restrictions have been bypassed in some cases by illegally ordering from a foreign web site *(23)*.

In most products, ephedrine content ranged anywhere from 12 to 80 mg per serving, with the majority of products falling into the lower range. Industry standards called for a total dose of ephedrine of less than 100 mg/day. The FDA, however, allowed a maximum daily dose of 150 mg/day of synthetic ephedrine. Unless fortified, the expected ephedrine content of ma huang capsules was generally less than 10%. Thus, a capsule said to contain 1000 g of ephedra would probably have contained no more than 80 mg of ephedrine.

In the United States, (+)-norpseudoephedrine, in its pure form, is considered a Schedule IV controlled substance. However, because of the small amounts of this alkaloid in ephedra plants or extracts, the Drug Enforcement Administration (DEA) had never stated or proposed that ephedra products were subject to the scheduling requirements of the Controlled Substances Act. Quite the contrary, DEA published a proposed rule in 1998 that stated DEA's intent to exempt legitimate ephedra products in finished form from regulation even as "chemical mixtures." Other regulatory sanctions and actions on ephedra rendered action on this regulation moot.

5. *Pharmacological Effects*

Studies have shown that resultant effects are similar, regardless of whether pure synthetic ephedrine or naturally occurring ephedra is ingested *(24,25)*. There are, however, significant enantioselective differences between the enantomers in both pharmacokinetic and pharmacodynamic effects. All of the ephedra alkaloids have important effects on the cardiovascular and respiratory systems, but not to the same degree.

Ephedrine, the predominant alkaloid in ephedra, is both an α and β stimulant. It directly stimulates α_2 and β_1; receptors and, because it also causes the release of norepinephrine from nerve endings, it also acts as a β_2 stimulant. The resultant physiological changes are variable, depending on receptor distribution and receptor regulation *(26)*. Tolerance to ephedrine's β agonist actions emerges rapidly, which is why ephedrine is no longer the preferred agent for treating asthma; receptor downregulation quickly occurs and the bronchodilator effects are lost *(27,28)*.

Receptor distribution probably explains why ephedrine has no effect on diastolic pressure, and only minimal effect on systolic. β_2 Stimulation of vessels in peripheral muscles results in peripheral vasodilation and "diastolic runoff," which more than cancels ephedrine's other inotropic effects *(29)*. The absence of any significant effect on blood pressure was firmly established during the late 1970s and early 1980s in dozens of double-blind, placebo-controlled studies performed to compare the effectiveness of ephedrine with that of newly synthesized adrenergic agents *(30–60)*.

The pharmacokinetic and toxicokinetic behavior of any isomer cannot be used to predict that of any other ephedrine isomer. The (+) isomer of methamphetamine, for example, is a potent CNS stimulant, but the (–)-isomer is merely a decongestant. There is a tendency in the literature to lump together all "ephedrine alkaloids" and use the term "class effect" to assume that all the different drugs in that class exert the same effects on the same biological targets. In fact, some of the drugs in the class will be similar in some regards and different in others.

The affinity of the various ephedrine isomers for human β-receptors has been measured and compared (as indicated by the amount of cyclic adenosine monophosphate produced compared to that of isoproterenol) in tissue culture. Activity of the different isomers is highly stereoselective, i.e., the different isomers had very different receptor-binding characteristics. For β_1-receptors, maximal response (relative to isoproterenol = 100%) was greatest for ephedrine (68% for 1R,2S-ephedrine and 66% for the 1S,2R-ephedrine isomer). Both of the pseudoephedrine isomers had much lower affinities (53%). When binding to β_2-receptors was measured, the rank order of potency for 1R,2S-ephedrine was 78%, followed by 1R,2R-pseudoephedrine (50%), followed by 1S,2S-pseudoephedrine (47%). The 1S,2R-ephedrine isomer had only 22% of the activity exerted by isoproterenol, but was the only isomer that showed any significant agonist activity on human β_3-receptors (31%) *(61)*. Stimulation of β_3-receptors, which are thought to be located only in fat cells, may account for ephedrine's ability to cause weight loss *(62–64)*.

Ephedrine is also an α agonist and, as such, is capable of stimulating bladder smooth muscle. At one time, it was used to promote urinary continence *(65,66)*. In animal models, when compared to norepinephrine, ephedrine is a relatively weak α-adrenergic agonist, possessing less than one-third the activity of norepinephrine *(67)*. Ephedrine's usefulness as a bronchodilator is limited by the number of β-receptors on the bronchi. The number of β-

receptors located on human lymphocytes (which correlates with the number found in the lungs) decreases rapidly after the administration of ephedrine; the density of binding sites drops to 50% after 8 days of treatment and returns to normal 5 to 7 days after the drug has been withdrawn *(27)*.

6. Clinical Studies

6.1. Bronchodilation

Banner et al. summarized studies where the effects of ephedrine and ephedra were compared to placebo in controlled studies in humans. None of the controlled trials disclosed any evidence of cardiovascular toxicity when ephedrine was given in doses as high as 1 mg/kg, even when it was administered to severe asthmatics with known cardiac arrhythmias *(57)*. The trial reported by Banner et al. studied the respiratory and circulatory effects of orally administered ephedrine sulfate, 25 mg, aminophylline, 400 mg, terbutaline sulfate, 5 mg, and placebo in 20 patients with ventricular arrhythmia by a double-blind crossover method. The study was comprised of 20 patients, with an average age of 60 years and a preexisting history of both asthma and heart disease (as evidence by the presence of frequent premature ventricular contractions). The bronchodilator effect of terbutaline was similar to that of aminophylline over 4 hours but superior to ephedrine at hour 4. Both terbutaline and ephedrine exhibited chronotropic effects, with the effect of terbutaline greater than that of ephedrine at hour 4. The effect of aminophylline on heart rate (HR) did not differ from placebo. Only terbutaline was associated with an increase in ventricular ectopic beats. Ventricular tachycardia occurred in three patients treated with terbutaline and in one patient with ephedrine (which occurred before he was given ephedrine). There were no significant changes in blood pressure. Orally administered terbutaline should not be regarded as safer than orally administered ephedrine or aminophylline in patients with arrhythmias.

In 1992, Astrup studied the effects of ephedrine and caffeine in a group of obese patients *(68)*. In a randomized, placebo-controlled, double-blind study, 180 obese patients were treated by diet (4.2 mJ/day) and either an ephedrine/caffeine combination (20 mg/200 mg), ephedrine (20 mg), caffeine (200 mg), or placebo three times a day for 24 weeks. Withdrawals were distributed equally in the four groups, and 141 patients completed the trial. Mean weight losses was significantly greater with the combination than with placebo from week 8 to week 24 (ephedrine/caffeine, 16.6 ± 6.8 kg vs placebo, 13.2 ± 6.6

kg [mean ± standard deviation {SD}], $P = 0.0015$). Weight loss in both the ephedrine and the caffeine groups was similar to that of the placebo group. Side effects (tremor, insomnia, and dizziness) were transient and after 8 weeks of treatment they had reached placebo levels. Systolic and diastolic blood pressure fell similarly in all four groups.

6.2. Weight Loss

The most recent of the studies examining weight control were designed to address concerns about long-term safety and efficacy for weight loss using a mixture containing 90 mg of ephedrine (from ephedra) and 192 mg of caffeine, derived from cola nuts *(15)*. A 6-month randomized, double-blind, placebo-controlled trial was performed, in which a total of 167 subjects (body mass index 31.8 ± 4.1 kg/m^2) were randomized to receive either placebo (n = 84) or herbal treatment (n = 83). The primary outcome measurements were changes in blood pressure, heart function, and body weight. Secondary variables included body composition and metabolic changes. It was found that herbal vs placebo treatment decreased body weight (–5.3 ± 5.0 vs –2.6 ± 3.2 kg, $P < 0.001$), body fat (–4.3 ± 3.3 vs –2.7 ± 2.8 kg, $P = 0.020$), and low-density lipoprotein cholesterol (–8 ± 20 vs 0 ± 17 mg/dL, $P = 0.013$), and increased high-density lipoprotein cholesterol (+2.7 ± 5.7 vs –0.3 ± 6.7 mg/dL, $P = 0.004$). Herbal treatment produced small changes in blood pressure variables (+3 to –5 mmHg, $P \leq 0.05$), and increased HR (4 ± 9 vs –3 ± 9 beats per minute, $P < 0.001$), but cardiac arrhythmias were not increased ($P > 0.05$). By self-report, dry mouth ($P < 0.01$), heartburn ($P < 0.05$), and insomnia ($P < 0.01$) were increased and diarrhea decreased ($P < 0.05$). Irritability, nausea, chest pain, and palpitations did not differ, nor did numbers of subjects who withdrew. CONCLUSIONS: In this 6-month placebo-controlled trial, herbal ephedra/caffeine (90/192 mg/day) promoted body-weight and body-fat reduction and improved blood lipids without significant adverse events.

6.3. Athletic Performance

In a series of studies, Bell et al. assessed the effects of ephedrine mixtures on performance, and found measurable improvement. One and one-half hours after ingesting a placebo (P), caffeine (C) (4 mg/kg), ephedrine (E) (0.8 mg/kg), or caffeine and ephedrine, 12 subjects performed a 10-km run while wearing a helmet and backpack weighing 11 kg. The trials were performed in a climatic suite at 12–13°C, on a treadmill where the speed was regulated by the subject. VO_2, VCO_2, V(E), HR, and rating of perceived exer-

tion were measured during the run at 15 and 30 minutes, and again when the individual reached 9 km. Blood was sampled at 15 and 30 minutes and again at the end of the run and assayed for lactate, glucose, and catecholamines. Run times (mean ± SD), in minutes, were for C (46.0 ± 2.8), E (45.5 ± 2.9), C + E (45.7 ± 3.3), and P (46.8 ± 3.2). The run times for the E trials (E and C + E) were significantly reduced compared with the non-E trials (C and P). Pace was increased for the E trials compared with the non-E trials over the last 5 km of the run. VO_2 was not affected by drug ingestion. HR was elevated for the ephedrine trials (E and C + E), but the respiratory exchange ratio (a measure of maximal exertion) remained similar for all trails. Caffeine increased the epinephrine and norepinephrine response associated with exercise and also increased blood lactate, glucose, and glycerol levels. Ephedrine reduced the epinephrine response but increased dopamine and free fatty acid levels. Bell concluded previously that the effects of caffeine, when taken with ephedrine, were not additive, and that all of the observed improvement could be accounted for by the presence of ephedrine *(19)*.

7. *Pharmacokinetics*

Phenylpropanolamine is readily and completely absorbed, but pseudoephedrine, with a bioavailability of only approx 38%, is subject to gut wall metabolism, and absorption may be erratic *(69)*. Pure ephedrine is well absorbed from the stomach, but absorption is much slower when it is given as a component of ma huang, rather than in its pure form *(70)*. Ephedrine ingested in the form of ma huang has a t_{max} of nearly 4 hours, compared to only 2 hours when pure ephedrine is given. Like its enantiomers, ephedrine is eliminated in the urine largely as unchanged drug, with a half-life of approx 3–6 hours.

The rate at which any of the enantiomers is eliminated depends upon the urinary pH. At high pHs, excretion time is prolonged. At low pH ranges, excretion is accelerated. In controlled laboratory studies, where volunteer subjects were given either bicarbonate or ammonium chloride, the higher the urine pH, the more slowly the ephedrine and pseudoephedrine were excreted. Conversely, when the urine pH is low, excretion is accelerated *(71)*. The importance of these observations is hard to assess, because without the addition of bicarbonate, urine pH values in the general population rarely approach 8.0. A study of pseudoephedrine pharmacokinetics in 33 volunteers who were not treated with drugs to alter urine pH found that these parameters could not be

correlated to urine pH, mainly because there was little difference in pH between the different participants *(72)*. Excretion patterns may be much more rapid in children, and a greater dosage may be required to achieve therapeutic effects. Patients with renal impairment are at special risk for toxicity.

Peak concentrations for the other enantiomers, specifically phenylpropanolamine and pseudoephedrine, occur earlier (0.5 and 2 hours, respectively) than for ephedrine, but all three drugs are extensively distributed into extravascular sites (apparent volume of distribution between 2.6 and 5.0 L/kg). No protein-binding data in humans are available. Peak ephedrine levels after ingestion of 400 mg of ma huang, containing 20 mg of ephedrine, resulted in blood concentrations of 81 ng/mL—essentially no different than the peak ephedrine levels observed after giving an equivalent amount of pure ephedrine *(70,25)*. In another study, 50 mg of ephedrine given orally to six healthy, 21-year-old women produced mean peak plasma concentrations of 168 ng/mL, 127 min after ingestion, with a half-life of slightly more than 9 hours *(73)*. The results are comparable to those obtained in studies done nearly 30 years earlier *(74)*.

Very high levels of methylephedrine have been observed in Japanese polydrug abusers taking a cough medication called BRON. Concentrations of methylephedrine less than 0.3 mg/L, the range generally observed in individuals taking BRON for therapeutic rather than recreational purposes *(75)*, appear to be nontoxic and devoid of measurable effects. Methylephedrine is a minor component of most ephedra plants, but in Japan (where, unlike in the United States, methylephedrine is legally sold) it is produced synthetically, and is used in cough and cold remedies, especially BRON *(76–78)*. In terms of catecholamine stimulation, methylephedrine appears comparable to ephedrine; however, it does not react with most standard urine screening tests for ephedrine *(75)*. This can be a cause of some forensic confusion, because 10–15% of a given dose of methylephedrine is converted to ephedrine *(75)*.

Although the issue has been raised in litigation, the amounts of methylephedrine and norephedrine contained in naturally occurring ephedra are so low as to be of no clinical consequence. For example, the study by Gurley et al. found that most of the commercial products tested had no methylephedrine whatsoever, but when it was present, it was usually in quantities of less than 1 mg per serving (range 0.2 to 2.2 mg). If the volume of distriution (Vd) of methylephedrine is assumed to be 3.5, approximately the same as ephedrine, then a 70-kg man ingesting a 2-mg serving of methylephedrine would produce a blood concentration of (dose = kg weight ×

blood concentration × Vd) 0–0.06 mg, undoubtedly below most laboratories' minimum level of detection, and a clinically insignificant finding. Similar considerations apply to the small amounts of norephedrine found in these products.

8. Adverse Effects and Toxicity

8.1. General Overview

Two journal articles analyzing adverse event reporters (AERs) have been published in the peer-reviewed literature, and both reports have received wide publicity *(79,80)*. The reports are, however, of limited use in assessing toxicity, because they are comprised of passively collected anecdotal data, which is often incomplete and unreliably reported. For example, one of the FDA ephedrine AERs "analyzed" in an article published in the *New England Journal of Medicine* described the sudden death of a teenage girl who had been born with a lethal cardiac malformation who died while playing volleyball *(79)*. Postmortem blood and tissue tested negative for ephedrine, and the article failed to mention the existence of the cardiac malformation. In other AERs, massive doses of ephedrine were consumed (as with products intended for abuse, such as "herbal ecstasy," now withdrawn from the market). Toxicology testing was rarely performed in any of these cases, and it is not known with any certainty whether ephedrine was even taken. Even the authors of the two papers concede that anecdotal reports cannot be used to prove causality, stating that "Our report does not prove causation, nor does it provide quantitative information with regard to risk" *(79)*. There is little point in reviewing material that cannot be used to prove causality, and it is not included in the summaries that follow, which are comprised only of published, peer-review case reports, epidemiological surveys, and controlled clinical trials. An additional review of the utility of spontaneously reported adverse events involving supplements and, more specifically, ephedra was published by Kingston et al. *(81)*. The review discussed the limitations of spontaneously reported data in assessing supplement safety and determining causality between exposure and adverse effects.

Despite conflicting data regarding the safety of ephedra from clinical studies and conclusions drawn from spontaneously reported adverse events, FDA banned the sale of ephedra-containing supplements in 2004 (*see* Regulatory Status).

8.2. Neurological Disorders

Many strokes attributed to ephedrine have actually been caused by the ingestion of ephedrine enantiomers, pseudoephedrine *(82–85)*, phenylpropanolamine *(86–93)*, and even methylephedrine *(77)*. Two cases of ischemic stroke have been reported *(94,95)*, but in neither case was their any toxicological testing to confirm the use of ephedrine. A decade-old report described the autopsy findings in three individuals with intracerebral hemorrhage and positive toxicology testing for ephedrine; however, one had hypertensive cerbrovasular disease and the other had a demonstrable ruptured aneurysm *(96)*. Intracerebral hemorrhage has also been described in suicide and attempted suicide victims who took overdoses of pseudoephedrine *(97,98)*. There is also a report describing a patient who developed described arteritis following the intravenous administration of ephedrine during a surgical procedure *(99)*. On the other hand, a large study to assess risk factors for stroke in young people (age 20–49) over a 1-year period was carried out in Poland, a country where ephedra-based products are widely used. Nearly one-half the cases of stroke were associated with preexisting hypertension, another 15% had hyperlipidemia, and 6% were diabetic *(100)*. None of the individuals were ephedrine users.

Sometimes, especially in Japan and the Philippines, ephedrine is taken specifically as a psychostimulant. In Japan, BRON, the OTC cough medication containing methylephedrine, dihydrocodeine, caffeine, and chlorpheniramine, is very widely abused, and transient psychosis commonly results *(76–78)*. Reports of ephedrine-related psychosis following prolonged, heavy use are fairly common *(101–105)*. In general, psychosis is only seen in ephedrine users ingesting more than 1000 mg/day, and it resolves rapidly once the drug is withdrawn *(106)*. Ephedrine psychosis closely resembles psychosis induced by amphetamines: paranoia with delusions of persecution and auditory and visual hallucinations, even though consciousness remains unclouded. Typically, patients with ephedrine psychosis will have ingested more than 1000 mg/day. Recovery is rapid after the drug is withdrawn *(103)*. The ephedrine content per serving of most food supplements is on the order of 10–20 mg, making it extremely unlikely that, in recommended doses, use of any of the products would lead to neurological symptoms.

8.3. Renal Disorders

Reports, particularly in the European literature, have described the occurrence of renal calculi in chronic ephedrine users *(107–111)*. A review of cases

from a large commercial laboratory specializing in the analysis of kidney stones found that 200 out of 166,466, or 0.064%, of stones analyzed by that laboratory, contained either ephedrine or pseudoephedrine. Unfortunately, the analytic technique used could not distinguish ephedrine from pseudoephedrine, and because pseudoephedrine is used so much more widely than ephedrine, it seems that the risk of renal calculus associated with ephedrine use must be quite small *(110)*. There have been no new reports of ephedrine-related nephrolithiasis since 1999. Direct toxicity, with altered renal function and demonstrable kidney lesions related to ephedrine use, has never been demonstrated. Urinary retention, occurring as a consequence of drug overdose, was occasionally reported *(112,113)*, but additional cases have not been described in more than a decade. The FDA and Commission E both warn against the possibility of urinary retention in patients with prostatic enlargement, but the theoretical basis for this concern is unclear, and, in any case, retention in patients with prostate disease has not been reported.

Small amounts of ephedrine are oxidized in to norephedrine and norpseudoephedrine in the liver *(24,73)*. In patients with diminished renal function, these drugs may accumulate and have the potential to cause serious toxicity. None of the ephedrine enantiomers are easily removed by dialysis, and treatment of overdose remains supportive, using pharmacological antagonists to counter the α- and β-adrenergic effects of these drugs *(114)*. Because excretion is pH-dependent, patients with renal tubular acidosis are also at risk *(115)*. The FDA reports having received a number of accounts of hematuria after use of ephedra-based products, but no such cases have ever appeared in the peer-reviewed literature, and review of the reports published by the FDA shows that all of the affected individuals were taking multiple remedies, some capable of causing interstitial nephritis.

8.4. Cardiovascular Diseases

Ephedrine and pseudoephedrine share properties with cocaine and with the amphetamines because they: (1) stimulate β-receptors directly, and (2) also cause the increased release of norepinephrine. Chronic exposure to abnormally high levels of circulating catecholamines can damage the heart. This is certainly the case with cocaine and methamphetamine *(116,117)*, but ephedrine-related cardiomyopathy is an extremely rare occurrence, occurring only in individuals who take massive amounts of drug for prolonged periods of time. Only two papers have ever been published on the subject *(118,119)*.

The two existing reports are uninterpretable, because histological findings were not described in either report, and angiography was not performed, thereby making it impossible to actually establish the diagnosis of cardiomyopathy.

Similar considerations apply to the relationship (if any) between myocardial infarction and ephedrine use. The report by Cockings and Brown described a 25-year-old drug abuser who injected himself with an unknown amount of cocaine intravenously *(120)*. The only other published reports involved a woman in labor who was receiving other vasoactive drugs *(121)*; and two pseudoephedrine users, one of whom was also taking bupropion, who developed coronary artery spasm *(122,123)*. Three cases of ephedra-related coronary spasm in anesthetized patients have also been reported, but multiple agents were administred in all three cases, and the normal innervation of the coronary arteries was disrupted in two of the cases where a high spinal anesthetic had been administered *(121,124)*. One case of alleged ephedrine-related hypersensitivity myocarditis has been reported *(125),* but the patient was taking many other herbal supplements, and the responsible agent is not known with certainty. Although there are no reasons why ephedra alkaloids should not cause allergic reactions, the incidence appears to be extremely low.

Although clinical trials or epidemiological studies are lacking, it has been suggested that maternal use of OTC cold medication may result in fetal arrhythmias *(126,127)*, but linkage between ephedrine and isomers and arrhythmia has never been demonstrated. The literature contains one case report *(128)* describing arrhythmias occurring in a 14-year-old who overdosed on cold medications. The child had taken a total of 3300 mg of caffeine, 825 mg of phenylpropanolamine, and 412 mg of ephedrine. Clearly, large doses of ephedrine, and its enantiomers, are capable of exerting toxicity.

The paucity of peer-reviewed studies describing cardiovascular complication with ephedra alkaloids suggests that few such cases are occurring. This notion is support by the studies of Porta et al., who performed a follow-up study of more than 100,000 persons below age 65 years who filled a total of 243,286 prescriptions for pseudoephedrine. No hospitalizations could be attributed to the drug. There were no admissions within 15 days of filling a prescription for pseudoephedrine for cerebral hemorrhage, thrombotic stroke, or hypertensive crisis. There were a small number of hospitalizations for myocardial infarction, seizures, and neuropsychiatric disorders, but the rate of such admissions among the pseudoephedrine users was close to the expected rate in the population at large.

8.5. Workplace Drug Testing

Ephedra alkaloids, even when used in the recommended amounts, can cause positive urine screening tests for methamphetamine *(129,130)*, sometimes yielding surprisingly high concentrations.

8.6. Postmortem Toxicology

Very few fatalities have ever been reported (or studied), but it appears that the therapeutic index for ephedrine is very great. A 1997 case report described a 28-year-old woman with two prior suicide attempts, who died after ingesting amitriptyline and ephedrine. The blood ephedrine concentration was 11,000 ng/mL, and the liver concentration was twice that value (kidney, 14 mg/kg; brain, 8.9 mg/kg). The amitriptyline concentration was 0.33 mg/kg in blood and 7.8 mg/kg in liver *(131)*. Values in a second case report (where methylephedrine concentrations were nearly 6000 ng/mL) may or may not be relevant to the problem of ephedrine toxicity, as the individual in question took massive quantities of a calcium channel blocker, and it is not known whether methylephedrine exerts all the same effects as ephedrine *(132)*. Baselt and Cravey mention the case of a young woman who died several hours after ingesting 2.1 g of ephedrine combined with 7.0 g of caffeine, but tissue findings were not described. Her blood ephedrine level was 5 mg/L, whereas the concentration in the liver was 15 mg/kg *(133)*.

A report from the European literature describes the findings in a 19-year-old woman who committed suicide by taking 40 Letigen® tablets (200 mg of caffeine and 20 mg of ephedrine) amounting to 10 g of caffeine and 1 g of ephedrine. She developed severe toxic manifestations from the heart, CNS, muscles, liver, and kidneys leading to several cardiac arrests, and died subsequently of cerebral edema and incarceration on the fourth day of hospitalization. Postmortem blood concentrations were not given *(134)*.

Pseudoephedrine concentrations, but not measurements for ephedrine or any of the other enantiomers, have been published by the National Association of Medical Examiners in their Annual Registry report. In 15 children diagnosed with sudden infant death syndrome, the mean blood pseudoephedrine concentration was 3.55 mg/L, the median 2.3 mg/L, with a range of 0.07–13.0 mg/L (SD = 3.36 mg/L). The authors of the study take pains to point out that "The data do not allow definitive statements about the toxicity of pseudoephedrine at a given concentration" *(129)*.

In the only autopsy study yet published *(135)*, all autopsies in the San Francisco Medical Examiner's jurisdiction from 1994 to 2001 where ephedrine or any its isomers (E+) were detected were reviewed. Cases where ephe-

drine or its isomers were detected were compared with those in a control group of drug-free trauma victims. Of 127 ephedrine-positive cases identified, 33 were the result of trauma. Decedents were mostly male (80.3%) and mostly Caucasian (59%). Blood ephedrine concentrations were less than 0.49 mg/L in 50% of the cases, with a range of 0.07–11.73 mg/L in trauma victims, and 0.02–12.35 mg/L in nontrauma cases. Norephedrine was present in the blood of only 22.8% (mean concentration of 1.81 mg/L, SD=3.14 mg/L) and in the urine of 36.2% of the urine specimens, with a mean concentration of 15.6 mg/L, SD=21.50 mg/L). Pseudoephedrine (PE) was detected in the blood of 6.3% (8/127). More than 88% (113/127) of the decedents who tested positive for ephedrine or one of its isomers also tested positive for other drugs, the most common being cocaine (or its metabolites) and morphine. The most frequent pathological diagnoses were hepatic steatosis (27/127) and nephrosclerosis (22/127). Left ventricular hypertrophy was common, and coronary artery disease was detected in nearly one-third of the cases. The most common findings in the ephedrine-positive deaths reviwed were those generally associated with chronic stimulant abuse. There were no cases of heat stroke and no cases of rhabdomyolysis.

8.7. Methamphetamine Manufacture

Either (–)-ephedrine or (+)-pseudoephedrine can be used to make methamphetamine by reductive dehalogenation using red phosphorus as a catalyst. If (–)-ephedrine is used as the starting material, the process will generate (+)-methamphetamine. If psuedoephedrine is used, the result will be dextromethamphetamine *(136)*. As this synthetic route has become nearly universal, both state and federal governments have enacted laws limiting the amount of pure ephedrine or pseudoephedrine that can be purchased.

9. Drug Interactions

The ephedra alkaloids are all sympathomimetic amines, which means that a host of drug interactions are theoretically possible. In fact, only a handful of adverse drug interactions have been reported in the peer-reviewed literature. The most important of these involve the monoamine oxidase inhibitors (MAOI). Irreversible, nonselective MAOIs have been reported to adversely interact with indirectly acting sympathomimetic amines present in many cough and cold medicine. In controlled trials with individuals taking moclobemide, ephedrine's effects on pulse and blood pressure were potentiated, but only at higher doses than those currently provided in health supplements *(137)*. Ephedrine-MAOI interaction may, on occasion, be severe enough to mimic pheo-

chromocytoma *(138)*. In addition, there is decreased metabolic clearance of pseudoephedrine when MAOIs are administered concurrently *(139)*. At least one case report suggests that selective serotonin reuptake inhibitor antidepressants can react with pseudoephedrine, leading to the occurrence of "serotonin syndrome" *(140)*. Bromocriptine, the ergot-derived dopamine agonist can interact with pseudoephedrine, and would presumably interact with ephedrine as well *(141)*. Surgical patients being treated with clonidine have an enhanced pressor response to ephedrine, apparently a result of clonidine-induced potentiation of α_1-adrenoceptor-mediated vasoconstriction *(142,143)*. In some clinical trials, the coadministration of ephedrine with morphine has been shown to increase analgesia *(144)*, but this approach to pain relief remains somewhat controversial.

10. Reproduction

Use of ephedra-containing products is likely unsafe during pregnancy because of reports of psychoses and cardiovascular effects *(79,104,145)*.

11. Regulatory Status

In 2004, the FDA issued a final rule prohibiting the sale of dietary supplements containing ephedrine alkaloids (ephedra), citing concerns over safety and potential risk of illness or injury.

The FDA reviewed evidence about ephedra's pharmacology: peer-reviewed scientific literature on ephedra's safety and effectiveness, adverse event reports, and a seminal report by the RAND Corporation, an independent scientific institute. Spontaneously reported adverse effects with high-profile sports figures and others raised public awareness and fueled the debate over safety. Subsequent to the ban, various trade groups and supplement companies have criticized the ban, and an appeal of the decision with temporary suspension of sanctions in some jurisdictions, pending further review, has occurred. Regardless of the regulatory outcome, reintroduction of OTC ephedra-containing supplements is not likely to occur.

Although banned in the United States, use of ephedra in other countries is likely to continue.

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