American Botanical Council

A Look Inside
The ABC Clinical Guide to Herbs

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The ABC Clinical Guide to Herbs

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Learning Objectives

The information is followed by a self-test. Upon completion of this course, health professionals should be able to:

1) Identify the 29 most popular medicinal herbs available to consumers in the U.S. market.
2) Explain the common therapeutic indications of the leading herbs.
3) Provide an overview of the clinical study research of the leading herbs.
4) Identify potential drug interactions and side effects.
5) Evaluate the safety issues and contraindications.
6) Interpret product labels for indications of clinical efficacy.
7) Distinguish different types of brands on the marketplace which are backed by clinical research.
8) Understand the implications of government regulations on the clinical use of herbs.

Target Audiences

Dietitians, Naturopathic Physicians, Nurses, Pharmacists, and Physicians.

Method Instruction

Information is presented in monographs followed by test questions.

Accreditation

Dietitians

A total of 12 CE hours will be awarded to Dietitians and Registered Dietetic Technicians by the Commission on Dietetic Registration (CDR) of the American Dietetic Association, through Texas State University-San Marcos, for the successful completion of this program. The CDR program number is 075322. All requests for continuing education credit must be submitted to Texas State University-San Marcos by August 1, 2007.

Texas State University | SAN MARCOS

Naturopathic Physicians

A total of 12 CE hours will be awarded by the American Botanical Council in collaboration with the Oregon Board of Naturopathic Examiners for the successful completion of this program.

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Nurses

A total of 10 contact hours is provided by the Texas Nurses Association. Texas Nurses Association/Foundation is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation (ANCC). This activity meets Type I criteria for mandatory continuing education requirements toward relicensure as established by the Board of Nurse Examiners for the State of Texas.

TNA TEXAS NURSES ASSOCIATION

Pharmacists

A total of 1.2 CEU (12 contact hours) will be awarded to pharmacists for the successful completion of this program. Texas Pharmacy Association is approved by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The ACPE Program number is 154–999–05–723–H01 with an initial release date of December 1, 2005. All requests for continuing education credit must be submitted to Texas Pharmacy Association prior to November 30, 2008.

ACPE™

Physicians

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The University of Texas Medical Branch at Galveston and the American Botanical Council. The University of Texas Medical Branch at Galveston is accredited by the ACCME to provide continuing medical education for physicians.

UTMB Office of Continuing Education
The University of Texas Medical Branch

The University of Texas Medical Branch at Galveston designates this educational activity for a maximum of 13.5 Category 1 credits toward the AMA Physician's Recognition Award. Each physician should only claim those credits that he/she actually spent in the activity.

Expiration date: February 28, 2007

St. John's Wort

Hypericum perforatum L.

[Fam. *Clusiaceae*]

Overview

In the fifth century B.C.E., the Greek physician Hippocrates was one of the first to document therapeutic uses of St. John's wort (SJW). It rose from virtual obscurity in the U.S. to become the fifth best-selling dietary supplement in mainstream retail stores in the U.S. after major media coverage of clinical research documenting its relative safety and efficacy for treating mild to moderate depression. The National Institutes of Health's National Center for Complementary and Alternative Medicine recently funded a three-year, multi-center trial comparing the effects of a standardized extract of SJW and the selective serotonin reuptake inhibitor (SSRI), sertraline (Zoloft®). Since 1979, there have been more than 35 controlled clinical studies of SJW extracts for the treatment of mild to moderate depression. Several meta-analyses have documented the relative safety and probable efficacy of this phytomedicine. SJW is prescribed frequently by healthcare providers in Germany, where approximately 130 million preparations containing SJW were prescribed in 1999.

Primary Uses

Internal

- Depression, mild to moderate

External

- Healing wounds (acute and contused injuries)
- First-degree burns
- Myalgia (muscle pain)

Other Potential Uses

- Seasonal Affective Disorder
- Obsessive-Compulsive Disorder
- Menopause
- Fatigue
- Pediatric nocturnal incontinence
- PMS

Pharmacological Actions

Antidepressant, relaxant, improves mental performance, does not change alertness or have sedative effect; may have relaxing effect and improve concentration, memory, and receptivity.

Dosage and Administration

For depression, the onset of response to SJW is similar to that for conventional antidepressants, requiring 2–4 weeks, or as long as 6 weeks. To prevent relapse, antidepressant should be continued at full therapeutic doses for at least 6 months after remission.

Internal

Crude Preparations

Fluid extract: 1:1 (*g/ml*), 2 ml, twice daily.

Standardized Preparations

Dry extract: 5–7:1, 300 mg, 3 times daily.

Extract: Standardized to 0.3% hypericin, 900 mg daily in 3 divided doses; standardized to 2–4.5% hyperforin, 900 mg daily in 3 divided doses.

External

Oily macerate (Oleum hyperici): Fresh-flowering tops in olive oil or wheatgerm oil are macerated for several weeks, stirred often, strained through a cloth and the pulp pressed. To be applied directly to affected areas.

Contraindications

None known, according to the Commission E (1984, 1990 revision)

Pregnancy and Lactation: No known restrictions.

Adverse Effects

In general, SJW produces few adverse side effects. Between October 1991 and December 1999, over 8 million patients are estimated to have been treated with Germany's leading SJW preparation with only 95 reports of side effects. These included "allergic" skin reactions (27), increased Quick Values (prothrombin time) (16), gastrointestinal complaints (9), breakthrough bleeding (birth control pill) (8), plasma cyclosporin reductions (7), and others. Photosensitization, depicted by erythema (redness of the skin) with exposure to sunlight or other ultraviolet radiation, is possible, but relatively rare and is sometimes reported in fair-skinned individuals taking excessive dosages (1,800 mg/day). A recent review of SJW adverse reactions suggests this precaution should not constitute a general contraindication, since photosensitization is so rare and because sunlight can promote recovery from depression.

Drug Interactions

Potential drug interactions with SJW have become the primary area of concern with this popular phytomedicine. However, some of these concerns may not be supported by clinical experience. In a review of drug interactions reportedly associated with SJW, calculations show one interaction per 300,000 treatments with the leading German SJW product.

SJW should not be taken in combination with any pharmaceutical antidepressants, without professional guidance. SJW is believed to interact witsh oral contraceptives and anticoagulants (e.g., warfarin). Preliminary findings suggest that SJW does not

interact with the effects of alcohol; however, patients with depression should avoid alcohol. An uncontrolled study on 13 subjects taking SJW at normal doses (900 mg standardized extract/day), resulted in significant increases in urinary 6–beta–hydroxycortisol/cortisol ratio, suggesting that SJW is an inducer of CYP3A4, since cortisol is metabolized primarily by CYP3A4. A recent study revealed that constituents of SJW extract, especially hyperforin, are potent ligands (K(i) = 27 nM) for the pregnane X receptor, an orphan nuclear receptor that regulates expression of the cytochrome P450 (CYP) 3A4 monooxygenase. Treatment of primary human hepatocytes with SJW extracts, or hyperforin, results in a marked induction of CYP3A4 expression. CYP3A4 is involved in the oxidative metabolism of more than 50% of all drugs, and can cause a decrease in the therapeutic activity and concentration of such drugs, including contraceptives and theophylline. SJW also may increase clearance from the bloodstream of the protease inhibitor indinavir, and the anti-rejection drug cyclosporine and may also interfere with the absorption of digoxin. A recent study found that SJW induces intestinal P-glycoprotein/MDRI (in rats and humans), and induces intestinal and hepatic CYP3A4 (in humans), thereby decreasing plasma levels of cyclosporine, indinavir, and digoxin. However, a review of SJW drug interactions questions the clinical relevance of interactions based solely on pharmacokinetic measurements, with digoxin, theophylline, and amitryptaline needing to be examined critically, since reduced plasma levels are not the same as reduced active levels at the receptors. To-date there are no reported cases suggesting clinically significant weakening in effect of the three drugs cited. One 14-day study on 10 patients, using the anti-seizure drug carbamazepine (Tegretol®), found that 300 mg SJW extract, three times daily, did not increase the clearance of the drug. Sudden discontinuation of SJW after prolonged use may lead to higher plasma levels of these drugs if used simultaneously, with the risk of adverse effects.

Clinical Review

Of 24 studies outlined in the table of clinical studies on SJW (2,765 total participants), all but two studies demonstrate positive effects of SJW on depression. Five randomized, double-blind, placebo-controlled (R, DB, PC) studies (626 participants) concluded that SJW significantly benefits patients with depression without significant side effects. Five R, DB, multicenter (MC) trials (1,191 participants) found equal effectiveness to tricyclic antidepressant drugs (amitriptyline, imipramine, malprotiline) with greater tolerability, and that SJW was safer for the heart.

Three small pilot studies (60 total patients) show promising findings for fatigue and seasonal affective disorder (SAD), and one small open-label study (12 patients) indicated potential benefits for obsessive-compulsive disorder. One small pilot study of SJW for the treatment of premenstrual syndrome suggests that SJW might reduce the severity and duration of premenstrual symptoms, warranting a larger R, DB trial. A drug-monitoring study on menopausal symptoms suggests that SJW is useful for treatment of associated symptoms and increasing the sense of sexuality in middle-age women.

In a review of 17 studies on SJW and 9 studies on fluoxetine (Prozac®), researchers showed that SJW was as effective as fluoxetine in the treatment of subthreshold and mild depression. Researchers concluded that SJW may be a viable approach to avoiding the risk that mild depression becomes a full-blown disorder.

A review and meta-analysis of 23 clinical studies on SJW showed that the standardized extract was more effective than placebo in treating mild to moderate depression. A follow-up meta-analysis (27 trials; 2,291 patients) concluded that SJW was significantly superior to placebo and that short term use of SJW might be valuable in less severe forms of depression as an alternative to watchful waiting or low doses of tricyclic antidepressants with fewer short term adverse side effects. A recent trial comparing SJW with the conventional antidepressant imipramine is the largest comparison trial to date and the first to compare the two agents at the normal daily dose of imipramine (150 mg). (Previous trials used 75 mg imipramine to reduce adverse side effects and maintain patient compliance.) This study concluded that SJW is equivalent to imipramine in efficacy, and is better-tolerated by patients. A newer, larger trial (n=240) comparing SJW directly with fluoxetine concluded that SJW was equivalent to fluoxetine in efficacy, particularly in depressive patients suffering from anxiety, and was better tolerated for safety. A total of 11 studies have compared SJW preparations with conventional antidepressants (7 tricyclic; 4 SSRI) concluding that SJW is effective for mild to moderate depression with a low side effect profile.

A recently published systematic review of 8 well-controlled R, DB, controlled (C), trials suggested that SJW is more effective than placebo in the treatment of mild to moderate depression. The absolute increased response rate with SJW ranged from 23% to 55% higher than with placebo, but ranged from 6% to 18% lower compared with tricyclic antidepressants. Treatment with SJW and fluoxetine, was compared in patients with mild to moderate depression. Results showed that SJW and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although SJW may be superior in improving the responder rate, the main difference between the two treatments is safety. SJW was superior to fluoxetine in overall incidence of side effects, number of patients with side effects, and the type of side effect reported. A previous review of 15 controlled clinical trials (12 PC) reported that the only substantial documentation for the use of SJW in mild to moderate depression is for the products Jarsin® 300 (Lichtwer Pharma) and Psychotonin-M® (Steigerwald). The review concluded that SJW should not be taken for more than 6 weeks, since most trials showing efficacy have been conducted over a shorter period of time. A recent study received considerable media attention due to its negative findings on patients with severe depression; however, the study lacked an active control (no active drug was used to measure the response rate of severely depressed patients vs. SJW and placebo). The first study funded by the NIH's NCCAM (R, DB, PC, MC, 340 participants) found that neither sertraline nor SJW were effective compared to placebo for moderately severe major depressive disorder. Critics emphasize that the initial design was changed from less severely depressed patients to patients with moderately severe major depression.

St. John's wort

Hypericum perforatum
[Fam. *Clusiaceae*]

Overview

St. John's wort (SJW) rose from virtual obscurity in the U.S., to become the fifth best-selling dietary supplement in mainstream retail stores in the U.S. Its rise to fame came after the national media reported clinical research showing that SJW is safe and effective for treating mild to moderate depression. The Greek physician, Hippocrates (ca. 460-377 B.C.E.), was one of the first to speak of the health benefits of SJW. Preparations include teas, alcoholic tinctures, and tablets using either the plant in its crude form, or standardized preparation. SJW is typically standardized to contain a consistent level of hypericin (0.3%), or hyperforin (3-5%), two naturally occurring chemicals found in the plant.

Illustration © 2002 Peggy Duke

Uses

Internal

Depression (mild to moderate).

External

Wound healing; first-degree burns; muscle pain (myalgia).

Other Potential Uses

Seasonal Affective Disorder (SAD: mental depression related to certain seasons, especially winter); obsessive-compulsive disorder; menopause; fatigue; pediatric nocturnal incontinence; PMS.

Dosage

Fluid extract: 1:1 (*g/ml*), 2 ml, twice daily.

Dry extract: 5–7:1, 300 mg, 3 times daily.

Extract (standardized): standardized to 0.3% hypericin or 2–4.5% hyperforin; 900 mg daily in 3 divided doses.

Contraindications

No known contraindications.

Pregnancy and Lactation: No known restrictions.

Adverse Effects

Photosensitization (redness of the skin caused by exposure to sunlight or other ultraviolet radiation) especially in fair-skinned individuals, may occur with excessive dosages (1,800 mg/day), but this reaction is relatively rare.

Drug Interactions

SJW should not be taken in combination with any pharmaceutical antidepressants unless under professional guidance. SJW may interact with oral contraceptives, anticoagulant drugs like warfarin, the asthma drug theophylline, the anti-HIV drug indinavir, the immunosuppressant drug cyclosporine, and the cardiac medication digoxin. Abruptly stopping SJW after prolonged use may increase the concentration of drugs like carbamazepine (Tegretol®). Patients with depression should avoid alcohol. Because SJW has been shown to potentially act with these drugs, and possibly others, consumers and patients are advised to consult with a properly qualified healthcare professional before using SJW with any other over-the-counter or prescription medications.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of treatment. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement as you would any type of medication by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

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St. John's Wort

Hypericum perforatum L.

[Fam. *Clusiaceae*]

Overview

St. John's wort (SJW) has been used for various ailments since the ancient Greeks; the Greek physician Hippocrates (ca.400 B.C.E.) was one of the first to document its therapeutic use. Since the time of the Swiss physician Paracelsns (ca. 1540 C.E.) it was used to treat mental disorders (Blumenthal *et al.*, 2000; Hobbs, 1988/89). SJW rose from virtual obscurity in the United States to become the fifth best-selling dietary supplement in mainstream retail stores in the U.S. in 2000 (Blumenthal, 2001) following major media coverage of clinical research documenting its relative safety and efficacy for treating mild to moderate depression. In 1998 and 1999 it had risen to second place in mainstream sales (Brevoort, 1998), but fell to fifth place due, in part, to some adverse publicity regarding reports of its interactions with several classes of prescription drugs (Blumenthal, 2001). The National Institutes of Health's National Center for Complementary and Alternative Medicine recently funded a three-year, multi-center trial comparing the effects of a standardized extract of SJW and the selective serotonin reuptake inhibitor (SSRI) sertraline (Hypericum Depression Trial Study Group, 2002). Since 1979, there have been more than 35 controlled clinical studies of SJW extracts for the treatment of mild to moderate depression (Blumenthal *et al*., 2000). Two meta-analyses have documented the relative safety and suggested probable efficacy of this phytomedicine (Linde and Mulrow, 2001; Linde *et al.*, 1996). SJW is prescribed frequently by healthcare providers in Germany, where approximately 130 million daily doses containing hypericum were prescribed in 1999 (Schulz, 2001). SJW preparations have also been used in traditional European herbal medicine for topical antimicrobial and skin healing purposes (Reichling *et al*., 2001).

Photo © 2002 stevenfoster.com

Description

St. John's wort (*Hypericum perforatum* L., Fam. *Clusiaceae*) preparations consist of the dried above-ground parts (flowers and stems), gathered during the flowering season. Preparations include aqueous extracts (teas), standardized extracts, alcoholic tinctures, dry extracts in capsules or tablets, and oil infusions (topical) (Blumenthal *et al.*, 2000). Standardization is typically to 0.3% hypericin, or at 2–4.5% hyperforin (Bruneton, 1999). Recent research suggests that the compound hyperforin may be the main antidepressive constituent (Müller *et al*., 1998). The *German Drug Codex* formerly required that SJW preparations be standardized to hypericins content; however, this in no longer required as a chemical marker (Bühler, 1995). The *United States National Formulary* requires not less than 0.04% of total hypericins, calculated as hypericin (USP, 1999).

Primary Uses

Internal

Depression

- Mild to moderate (Harrer *et al*., 1994; Harrer and Sommer, 1994; Laakmann *et al*., 1998a; Lenoir *et al*., 1999; Linde *et al*., 1996; Linde and Mulrow, 2001; Philipp *et al*., 1999; Wheatley, 1997; WHO, 2002; Woelk, 2000)

External

- Healing wounds (acute and contused injuries) according to the German Commission E (Blumenthal *et al.*, 1998)
- First-degree burns (Blumenthal *et al.*, 1998)
- Relieving myalgia (muscle pain) (Blumenthal *et al.*, 1998)

Other Potential Uses

- Seasonal Affective Disorder (Martinez *et al*., 1994)
- Obsessive-Compulsive Disorder (Taylor and Kobak, 2000)
- Pre-menstrual syndrome (Stevinson and Ernst, 2000)
- Menopause (Grube *et al*., 1999)
- Fatigue (according to a pilot study) (Stevinson *et al*., 1998)
- Pediatric nocturnal incontinence (Weiss and Fintelmann, 2000)

Dosage

Internal

Crude Preparations

Fluid extract: 1:1 (*g/ml*), 2 ml, twice daily.

Dry extract: 5–7:1, 300 mg, 3 times daily (Blumenthal *et al*., 2000).

Standardized Preparations

Extract: Standardized to 0.3% hypericin, 900 mg daily in 3 doses of 300 mg each; or products standardized to 2–4.5% hyperforin, 900 mg/day in 3 doses (Bruneton, 1999).

External

Oily macerate (Oleum hyperici): Fresh-flowering tops in olive

oil or wheatgerm oil are macerated for several weeks, stirred often, strained through a cloth and the pulp pressed. To be applied directly to affected areas (Blumenthal *et al*., 2000).

Duration of Administration

For depression, the onset of response to SJW is similar to that for conventional antidepressants, requiring 2–4 weeks, or as long as 6 weeks. To prevent relapse, antidepressant should be continued at full therapeutic doses for at least 6 months after remission (AHCPR, 1999).

Chemistry

SJW contains 6.5–15% catechin-type tannins and condensed-type proanthocyanidins (catechin, epicatechin, leucocyanidin); 2–5% flavonoids, mostly 0.5–2% hyperoside, 0.3–1.6% rutin, 0.3% quercitrin, 0.3% isoquercitrin, quercetin, and kaempferol; bioflavonoids (about 0.26% biapigenin), phloroglucinol derivatives (up to 4% hyperforin); phenolic acids (caffeic, chlorogenic, ferulic); 0.05–1.0% volatile oils, mainly higher n-alkanes, 0.05–0.15% naphthodianthrones (hypericin and pseudohypericin); sterols (sitosterol); vitamins C and A, up to 10 ppm xanthones; and choline (Bruneton, 1999; ESCOP, 1996; Leung and Foster, 1996; Newall *et al*., 1996; Upton, 1997; Wichtl and Bisset, 1994).

Pharmacological Actions

Standardized Preparations

Human

Antidepressant (Philipp *et al*., 1999; Lenoir *et al.*, 1999; Laakmann *et al*., 1998a, 1998b; Wheatley, 1997; Linde *et al.*, 1996); relaxant (Schulz *et al.*, 2000; Schulz *et al*., 1994; Johnson *et al.*, 1994); improves mental performance (Lehrl *et al*., 1993); does not change alertness or have sedative effect (Schulz *et al*., 2000; Schulz *et al*., 1994; Johnson *et al*., 1994); may have a relaxing effect and improve concentration, memory, and receptivity (Schulz *et al*., 2000; Schulz *et al*., 1994; Johnson *et al*., 1994; Lehrl 1993).

Animal

Potentiates dopaminergic behavioral responses (alcoholic extracts), and serotoninergic effects (carbon dioxide extracts) (Bhattacharya, 1998); reduces alcohol intake (Rezvani *et al*., 1999); stimulatory and antidepressant effects on the central nervous system; prolonged sleep time; analgesic activity which reduced abdominal stretching induced by acetic acid by nearly 50% and spasmolytic activity which reduced intestinal motility (Jakovljevic *et al.*, 2000).

In vitro

There has been confusion about the potential monoamine oxidase (MAO) inhibiting effect of SJW. Earlier research suggested that SJW possibly inhibits MAO, using 80% pure hypericin (Suzuki *et al*., 1984). However, a more recent study suggests that 95% pure hypericin does not inhibit MAO, but a crude ethanolic extract (Herb Pharm, Williams, OR) does, at 2 mcg/ml (Cott, 1995). MAOI activity has *not* been reported *in vivo* in animals or in humans (Cott, 1997). SJW unspecifically inhibits biogenic amine and amino acid neurotransmitter uptake (serotonin, dopamine, noradrenaline, GABA, L-glutamate) (Chatterjee *et al*., 1998; Butterweck *et al*., 1997); inhibits serotonin reuptake (Perovic and Müller, 1995; Müller and Rossol, 1994; Holzl, 1989); is antiretroviral (using purified hypericin) (Lavie *et al*., 1990; Meruelo *et al*., 1988); modulates interleukin-1x (hypericin) (Panossian *et al*., 1996) and interleukin-6 (SJW) (Thiele *et al*., 1994); is antiviral (influenza and herpes simplex type 1) (Serkedjieva *et al.*, 1990), and is antimicrobial (primarily hyperforin) toward methicillin-resistant *Staph. aureus* but not against gram-negative bacteria or *Candida albicans* (Reichling *et al*., 2001). Isolated hypericin from SJW extracts showed highest phototoxicity *in vitro*, but this was controlled by the flavonoid fraction, particularly quercitrin (Wilhelm *et al*., 2001).

Mechanism of Action

- Bind at $GABA_A$, $GABA_B$, adenosine, benzodiazepine, inositol, triphosphate, and MAO-A and MAO-B receptors (Cott, 1997).
- May inhibit uptake of several neurotransmitters (Müller and Rossol, 1994; Perovic and Müller, 1995; Holzl, 1989; Chatterjee *et al*., 1998; Raffa, 1998; Butterweck *et al*., 1997).
- May inhibit uptake of neuropeptides and neurosteroids (Perovic and Müller, 1995; Holzl *et al*., 1989; Chatterjee *et al*., 1998; Raffa, 1998; Butterweck *et al*., 1997).
- May inhibit 5-hydroxzytryptamine (5HT, serotonin) receptor expression resulting in inhibition of 5HT reuptake (Müller and Rossol, 1994).
- Antidepressant effects may be mediated mainly through changes in serotonin and dopamine neurotransmission but not noradrenaline (in humans) (Franklin and Cowen, 2001).
- May act on information substances (shared components of immune and nervous systems) such as leukotriene B4 and interleukin-1a inhibiting release of arachidonic acid, leukotriene B4, production of IL–1α, and activating NO synthesis (Panossian *et al*., 1996; Thiele *et al.*, 1994).
- Hyperforin, but not hypericin, in SJW induces CYP3A4 expression in human hepatocytes and activates the steroid X receptor, possibly suggesting a mechanism for drug interactions (Moore *et al.*, 2000; Wentworth *et al.*, 2000).
- Hyperforin from SJW leads to an elevation of Na^+, thus explaining its effect on serotonin uptake into platelets and synaptozomes but also the non-selective profile on many neurotransmitter transport systems which are all driven by Na^+ gradient membranes (Müller *et al*., 2001).

Contraindications

The Commission E stated "none known" in 1984 and in 1990 revision (Blumenthal *et al*., 1998). Recent drug interaction reports suggest professional guidance when certain conventional pharmaceuticals may be simultaneously administered (see Drug Interactions).

Pregnancy and Lactation: No known restrictions. Animal reproductive studies did not produce mutagenicity at relatively high doses (Upton *et al*., 1997). Due to lack of available data, the WHO monograph recommends that SJW not be administered during pregnancy or nursing without advice of a healthcare provider (WHO, 2002).

Adverse Effects

In general, SJW produces few adverse side effects. Between October 1991 and December 1999, over 8 million patients are estimated to have been treated with Germany's leading SJW preparation (Jarsin® or Jarsin®300); during this period only 95

reports of side effects were received by the German Adverse Drug Reaction Recording System. These included "allergic" skin reactions (27 reports), increased Quick Values (prothrombin time) (16), gastrointestinal complaints (9), breakthrough bleeding (birth control pill) (8), plasma cyclosporin reductions (7), and others (Schulz, 2001). Photosensitization, depicted by erythema (redness of the skin) with exposure to sunlight or other ultraviolet radiation is possible, although this is relatively rare and is sometimes reported in fair-skinned individuals taking excessive dosages (1,800 mg/day) (Brockmuller, 1997; Blumenthal *et al.*, 1998). A recent review of SJW adverse reactions suggests that this precaution should not constitute a general contraindication, since the incidence of photosensitization is so rare and because sunlight can promote recovery from depression (Schulz, 2001).

Drug Interactions

Potential drug interactions with SJW have become the primary area of concern with this popular phytomedicine. However, one source suggests that some of these concerns may not be borne out by clinical experience. In a review of drug interactions reportedly associate with SJW, the author calculates one interaction per 300,000 treatments with the leading German SJW product (Jarsin®).

SJW should not be taken in combination with any pharmaceutical antidepressants (Gordon, 1998; Prost *et al.*, 2000), unless under professional guidance. SJW is believed to interact with oral contraceptives and anticoagulants (e.g., warfarin) (TGA, 2000; Di Carlo *et al*., 2001; Lantz *et al*., 1999; McGuffin *et al*., 1997). Preliminary findings suggest that SJW does not interact with the effects of alcohol; however, patients with depression should avoid alcohol (Schmidt, 1993). An uncontrolled study on 13 subjects taking SJW at normal doses (900 mg of the standardized extract/day), resulted in significant increases in urinary 6–beta–hydroxycortisol/cortisol ratio, suggesting that SJW is an inducer of CYP3A4, since cortisol is metabolized primarily by CYP3A4 (Roby *et al*., 2000). A recent study (Moore, 2000) revealed that constituents of SJW extract, especially hyperforin, are a potent ligand (K(i) = 27 nM) for the pregnane X receptor, an orphan nuclear receptor that regulates expression of the cytochrome P450 (CYP) 3A4 monooxygenase. Treatment of primary human hepatocytes with SJW extracts, or hyperforin, results in a marked induction of CYP3A4 expression. CYP3A4 is involved in the oxidative metabolism of more than 50% of all drugs, and can cause a decrease in the therapeutic activity and concentration of such drugs, including contraceptives (Moore, 2000) and theophylline (Baede-van Dijk *et al.*, 2000). SJW also may increase clearance from the bloodstream of the protease inhibitor indinavir, and the anti-rejection drug cyclosporine (Piscitelli *et al*., 2000; Ruschitzka *et al*., 2000), and may also interfere with the absorption of digoxin (Tatro, 2000). A recent study found that SJW induces intestinal P-glycoprotein/MDRI (in rats and humans), and induces intestinal and hepatic CYP3A4 (in humans), thereby decreasing plasma levels of cyclosporine, indinavir, and digoxin (Dürr *et al.*, 2000). However, a review of SJW drug interactions questions the clinical relevance of interactions that are postulated solely on the basis of pharmacokinetic measurements, with digoxin, theophylline, and amitryptaline needing to be examined critically, since reduced plasma level are not the same as reduced active levels at the receptors. The author states that to-date there are no reported cases suggestive of a clinically significant weakening in effect of the three drugs cited (Schulz, 2001). One 14-day study on 10 patients, using the anti-seizure drug carbamazepine (Tegretol®), found that 300 mg St. John's wort extract, three times daily, did not increase the clearance of the drug (Burstein *et al*., 2000). Sudden discontinuation of SJW after prolonged use may lead to higher plasma levels of these drugs if used simultaneously, with the risk of adverse effects (Baede-van Dijk *et al.*, 2000).

American Herbal Products Association (AHPA) Safety Rating

Class 2d: Based on earlier *in vitro* research and the Commission E monograph, AHPA cautioned that SJW may potentiate pharmaceutical MAO-inhibitors (McGuffin *et al*., 1997), although there are no animal or human data to support this.

Regulatory Status

Australia: Complementary medicine available without prescription from pharmacies, health food shops, supermarkets, and complementary medicine practitioners (TGA, 2000). Required label warning: "St. John's wort affects the way some prescription medicines work. Consult your doctor." (Trickey, 2000).

Canada: Non-prescription drug for internal or external use classified as either "Schedule OTC Herbs and Natural Products" or "Schedule Homeopathic Products," in either case requiring premarketing authorization and assignment of Drug Identification Number (DIN) by the Therapeutic Products Programme (TPP) (Health Canada, 2001a). In January 2001, added to "Drugs of Current Interest (DOCI) List" maintained by the Canadian Adverse Drug Reaction Monitoring Program (Health Canada, 2001b). Potential drug-interaction warning statement required.

European Union: Whole or cut, dried, flowering tops harvested during flowering time, containing no less than 0.08% total hypericins, official in the *European Pharmacopoeia* (Ph.Eur., 2001).

France: Dried flowering top or aerial part official in *French Pharmacopoeia* approved only for external use but not prior to sun exposure (Bruneton, 1999; ESCOP, 1996).

Germany: Approved by Commission E as a nonprescription drug for internal and external use (Blumenthal *et al*., 1998). Whole or cut aerial parts, collected just before or during the flowering period, official for internal or external use in the *German Drug Codex* supplement to the *German Pharmacopoeia* (DAC, 1998). Whole, fresh, flowering plant for preparation of mother tincture is official in German Commission D monographs and corresponding *German Homeopathic Pharmacopoeia* (BAnz, 1985; GHP, 1993).

Italy: No information available.

Sweden: Classified as Natural Remedy, requiring premarket authorization. As of January 2001, nine SJW-containing products are listed in the Medical Products Agency (MPA) "Authorised Natural Remedies," and a monograph is published with the approved indication: "Traditionally used in case of slight mood lowering and for minor nervous tension" (MPA, 1999; 2001a; Tunón, 1999). St. John's wort homeopathic preparations are also registered drugs (MPA, 2001b).

Switzerland: Official in *Swiss Pharmacopoeia* (Upton *et al*., 1997; Wichtl, 1997). Herbal medicine with positive classification (List D) by the *Interkantonale Konstrollstelle für Heilmittel* (IKS) and corresponding sales Category D with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; Ruppanner and Schaefer, 2000). Numerous SJW phytomedicines and homeopathic preparations are listed in

the *Swiss Codex 2000/01* (Ruppanner and Schaefer, 2000).

U.K.: Licensed product for internal use; *General Sale List* (GSL), Table B (external use only), Schedule 1 (requires full product license) (GSL, 1994). A recent article reviewed the benefits and risks of SJW and their regulatory implications in the U.K. (McIntyre, 2000).

U.S.: Dietary supplement (USC, 1994). Dried, flowering tops gathered shortly before or during flowering, containing no less than 0.04% total hypericins, official in *U.S. National Formulary*, 19th edition (USP, 1999).

Clinical Review

Twenty-four studies are outlined in the following table, "Clinical Studies on St. John's Wort", including a total of 2,765 participants. All but three of these studies (Lenoir *et al*., 1999; Shelton *et al.*, 2001) demonstrate positive effects of SJW on depression. Five randomized, double-blind, placebo-controlled (R, DB, PC) studies have been performed on 626 participants, concluding that SJW significantly benefits patients with depression without significant side effects (Philipp *et al*., 1999; Laakmann *et al*., 1998a, 1998b; Harrer and Sommer 1994; Hübner *et al*., 1994; Hänsgen *et al*., 1994). Five R, DB multicenter trials, with 1,191 participants, found equal effectiveness to tricyclic antidepressant drugs (amitriptyline, imipramine, malprotiline) with greater tolerability (Wheatley, 1997; Vorbach *et al*., 1994; Harrer *et al.*, 1994), and that SJW was safer for the heart than tricyclic antidepressants (Czekalla *et al*., 1997).

Three small pilot studies on a total of 60 patients show promising findings for the conditions of fatigue and seasonal affective disorder (SAD) (Stevinson *et al.*, 1998; Kasper, 1997; Matinez *et al*., 1994), and one small open-label study on 12 patients indicated the potential benefits of SJW for obsessive-compulsive disorder (Taylor and Kobak, 2000). One small pilot study of SJW for the treatment of premenstrual syndrome suggests that SJW might improve the severity and duration of premenstrual symptoms, warranting a larger R, DB trial (Stevinson and Ernst, 2000). A drug-monitoring study on menopausal symptoms suggests that SJW is useful for treatment of associated symptoms, and increasing the sense of sexuality in middle-age women (Grube *et al*., 1999).

In a review of 17 studies on SJW and 9 studies on fluoxetine (Prozac®), researchers showed that SJW was as effective as fluoxetine in the treatment of subthreshold and mild depression (Volz, 2000). Researchers concluded that SJW is effective in subthreshold depression exhibiting very few or no side effects, easy availability, and may be a viable approach to avoiding the risk that mild depression becomes a full-blown disorder.

A review and meta-analysis of 23 clinical studies on SJW showed that the extract was more effective than placebo in treating mild to moderate depression (Linde *et al*., 1996). Based on the evidence available at the time, the same review concluded that further studies were needed to establish whether SJW is as effective as conventional antidepressant drugs (Linde *et al*., 1996). A follow-up meta-analysis by the Cochrane Center of 27 trials with 2,291 patients concluded that SJW was significantly superior to placebo (Linde and Mulrow, 2001). The review concluded that the short term use of SJW might be valuable in less severe forms of depression as an alternative to watchful waiting or the commonly used approach to low doses of tricyclic antidepressants and that SJW has less short term adverse side effects than tricyclics. A recent trial comparing SJW with the conventional antidepressant imipramine is the first to compare the two agents at the normal daily dose of imipramine (150 mg) (Woelk, 2000). Previous trials used only 75 mg imipramine in order to reduce adverse side effects and maintain patient compliance. This study is the largest comparison trial to date and concluded that the SJW extract used in the study (Remotiv® marketed by Bayer in Germany) is equivalent to imipramine in efficacy, and is more well-tolerated by patients. A newer, larger trial (n=240) comparing SJW (Ze 117) directly with fluoxetine concluded that SJW was of equivalent efficacy as fluoxetine, particularly in depressive patients suffering from anxiety, and was better tolerated for safety than the SSRI (Friede *et al*., 2001). A total of 11 studies have compared SJW preparations with conventional antidepressants (7 tricyclic; 4 SSRI) concluding that SJW is effective for mild to moderate depression with a low side effect profile (Kasper, 2001).

A recently published systematic review of R, C, DB trials selected, and assessed for methodological quality, eight well-controlled studies (Gaster and Holroyd, 2000). The results suggest that SJW is more effective than placebo in the treatment of mild to moderate depression. The absolute increased response rate with the use of SJW ranged from 23% to 55% higher than with placebo, but ranged from 6% to 18% lower compared with tricyclic antidepressants. The treatment with SJW and the commonly used selective serotonin reuptake inhibitor (SSRI) fluoxetine (Prozac®), was compared in patients with mild to moderate depression. The results showed that SJW and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although SJW may be superior in improving the responder rate, the main difference between the two treatments is safety. SJW was superior to fluoxetine in overall incidence of side effects, number of patients with side effects, and the type of side effect reported (Schrader, 2000). A previous review of 15 controlled clinical trials (12 placebo-controlled) reported that the only substantial documentation for the use of SJW in mild to moderate depression is for the products Jarsin® 300 (Lichtwer Pharma) and Psychotonin-M® (Steigerwald) (Volz, 1997). The review concluded that SJW should not be taken for more than 6 weeks, since most trials showing efficacy have been conducted over a shorter period of time. A recent study by Shelton *et al.* (2001) received considerable media attention due to its negative findings on patients with severe depression. The study was noted for its lack of an active control (no SSRI or other active drug was used to measure the response rate of severely depressed patients vs. SJW and placebo) (Cott *et al*., 2001).

Results were recently published for the first study funded by the NIH's NCCAM. This long awaited and much publicized R, DB, PC, MC, 3 arm study (340 participants) found that neither sertraline nor SJW were effective compared to placebo for moderately severe major depressive disorder. Critics emphasize that the initial design included only less severely depressed patients (HAMD score ≥15) but was later changed to patients with moderately severe major depression (HAMD score ≥ 20). Widespread publicity on this trial focused on the failure of SJW without equally noting the failure of sertraline which was given a slight edge over SJW because of sertraline's better performance on a secondary measure (a Clinical Global Impression scale that included partial responders). (Outcomes on secondary measurements are not considered appropriate measures for ascribing success or failure.) The authors of this study acknowledged that 35% of clinical trials on known anti-depressant drugs failed. More than 50% of trials with investigational antidepressant drugs fail (Robinson and Rickels, 2000).

BRANDED PRODUCTS*

Hyperiforce™: Bioforce AG / 437 Rt. 295 / Chatham, NY 12037 / U.S. / Tel.: (800) 641-7555 x100 / Fax: (518) 392-8794 / Email: info@bioforceUSA.com / www.bioforceUSA.com. 275 mg/tablet of a 1:9.0 ethanol/water extract of fresh tips of shoots. One tablet 3 times/day after meals provides 1 mg hypericin/day.

Jarsin® 300: Lichtwer Pharma / Wallenroder Strasse 8-14 / 13435 Berlin / Germany / Tel.: +49-30-40-3700 / Fax: +49-30-40-3704-49 / www.lichtwer.de. 300 mg St. John's wort extract/capsule in coated tablets standardized to 0.3% total hypericins.

Kira®: Lichtwer Pharma, c/o ABKIT, Inc., New York, New York. 300 mg dried methanolic extract produced from leaves, stems, and flowers standardized to 300 mcg total hypericin.

LI 160: Lichtwer Pharma, Berlin: 300 mg St. John's wort extract/capsule in coated tablets standardized to 0.3% total hypericins.

Neuroplant® (WS 5572; a.k.a. Perika®): Dr. Wilmar Schwabe GmbH & Co / International Division / Willmar Schwabe Str. 4 / D-76227 Karlsruhe / Germany / www.schwabepharma.com / Each 300 mg capsule contains dry SJW extract standardized to 5.0% hyperforin.

Perika®: Dr. Wilmar Schwabe GmbH & Co., U.S. distributor: Nature's Way Products, Inc. / 10 Mountain Spring Parkway / Springville, Utah 84663 / U.S. / Tel.: (801) 489-1500 / www.naturesway.com. Each 300 mg capsule contains dry SJW extract standardized to 5.0% hyperforin.

Remotiv® (Ze117): Bayer Vital GmbH & Co. / Consumer Care / Welser Strasse 5 – 7 / 51149 Köln / Germany / Tel.: + 49-01-30-82-6301 / www.bayer-ag.de. Each 250 mg film-coated tablet of St. John's wort extracted in 50% alcohol, standardized to 2% hypericins.

STEI 300: Steiner Arzneimittel / Postfach 450520 / 12175 Berlin / Germany / Tel.: +49-03-07-1094-0 / Fax: +49-03-07-1250-12 / www.steinerarznei-berlin.de Each 350 mg capsule contains 0.2%–0.3% hypericin, and 2%–3% hyperforin.

WS 5570: Dr. Wilmar Schwabe GmbH & Co, Karlsruhe, Germany. An 80% *v/v* hydroalcoholic extract of St. John's wort, drug to extract ratio 3–7.1.

WS 5572: see Neuroplant® and Perika®.

WS 5573: Dr. Wilmar Schwabe GmbH & Co, Karlsruhe, Germany. Each 300 mg capsule contains dry SJW extract standardized to 0.5% hyperforin.

Ze 117: Zeller Medical / Seeblickstrasse 4 / CH-8590 Romanshorn 1 / Switzerland / www.zellerag.ch. St. John's wort extracted in 50% alcohol, standardized to 2% hypericins in a 250 mg tablet, drug to extract ratio 4–7:1.

*American equivalents are found in the Product Table on page XXX.

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Clinical Studies on St. John's wort (*Hypericum perforatum* L.)

Depression

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Hypericum Depression Trial Study Group, 2002	Major depression	R, DB, PC, MC n=340 adults with baseline total HAMD score ≥ 20.	8–18 weeks	900–1500mg SJW/day or 50–100mg sertraline/day or placebo; divided into 3 doses/day	LI-160 SJW extract standardized to between 0.12% and 0.28% hypericin; sertraline (Zoloft®)	Initial treatment phase = 8 weeks. Patients responding positively were given respective treatments for additional 18 weeks. On the 2 primary outcome measures neither sertraline nor SJW performed significantly differently from placebo, based on HAMD or CGI scale. Full response occurred in 31.9% placebo group, 24.8% sertraline group (p=0.26), and 23.9% SJW group (p=0.21). Sertraline was better than placebo on a secondary measure: a CGI improvement scale that included partial responders (p=0.02). Authors concluded that the study does not support the efficacy of SJW in moderately severe major depression, acknowledging the low assay sensitivity of this trial, and the fact that 35% of trials on known antidepressants result in failure.
Friede *et al*., 2001	Mild to moderate depression	R, DB, MC n=240 (HAMD scores 16–24)	6 weeks	500 mg/day Ze 117 vs. 20 mg/day fluoxetine	Ze 117	SJW extract is equivalent in efficacy (p=0.09) to fluoxetine for both overall depressive symptoms and the main symptoms of depressive disorders. SJW is particularly effective in depressive patients suffering from anxiety symptoms. Tolerability for SJW revealed better safety (p<0.001) than for fluoxetine.
Shelton *et al*., 2001	Severe depression	R, DB, PC, MC n=200 patients with baseline HAMD ≥ 20	SJW for 4 weeks (n=98) or placebo (n=102) for 8 weeks	900 mg/day increased to 1200 mg/day or placebo	SJW standardized extract (LI 160) or placebo	The number of patients with a remission of depression was significantly higher with SJW than placebo (p=0.2), but they had low rates 14.3% with SJW vs. 4.9% for placebo in the full intention-to-treat analysis. SJW was well tolerated, with the only adverse effect being headaches (41% vs. 25%). The random analyses for the HAMD, HAMA, CGI-S, and CGI-I showed significant effects for time but not for treatment or time-by-treatment interaction. The study concluded that SJW was not effective in treating major depression (no active control used).
Brenner *et al*., 2000	Mild to moderate depression; comparison of SJW and selective serotonin reuptake inhibitors (SSRIs)	R, DB, C n=30	7 weeks	600 mg per day of standardized SJW extract or 50 mg per day of sertraline for 1 week, followed by 900 mg per day of SJW or 75 mg per day of sertraline	LI 160 or sertraline	Severity of symptoms, as measured by HAMD and the Clinical Gobal Impression scale was significantly reduced in both treatment groups (p<0.01). The difference in clinical response, based on reduction in HAMD for each group, was not statistically significant. SJW extract was found to be at least as effective as sertraline in treating mild to moderate depression.
Woelk, 2000	Mild to moderate depression without suicidal ideation (ICD-10)	R, DB, PG, MC (40 centers) n=324 HAMD scale >18. Mean HAMD 22.4 (SJW); 22.1 (imipramine) (ages >18 years)	6 weeks	250 mg SJW extract, 2x/day; 75 mg imipramine, 2x/day	Remotiv® (Ze 117) vs. imipramine	157 subjects on SJW had HAMD scores drop from mean or 22.4 at baseline to 12.00 at 12 weeks end, compared to 167 imipramine patients' scores of 22.1 dropping to 12.75 (no statistical difference between groups). CGI scores at end were mean of 2.22 of 7 for SJW group and 2.42 for imipramine group (no statistical difference between groups). In self-assessment, mean scores were 2.44 for SJW and 2.60 for imipramine (no statistical difference between groups). Tolerability scores were better for SJW (1.65) than drug (2.35); (no statistical difference between groups). Researchers concluded that SJW is therapeutically equal to imipramine for mild to moderate depression and tolerated better. This is largest trial on SJW comparing it to imipramine at standard dose (150 mg/day).
Philipp *et al*., 1999	Moderate depression	R, DB, MC, PG, PC, Cm n=262	2 months	1050 mg/day SJW , 350 mg, 3x/day vs. daily dosing of 50 mg, 25 mg, then 25 mg (100 mg total/day) imipramine	STEI 300 vs. imipramine	SJW was more effective than placebo and as effective as 100 mg/day imipramine in the treatment of depression as measured by HAMD, HAMA, and Clinical Global Impression scales. Improved quality of life also demonstrated in Zung self-rating depression scale. Proven safe with less adverse effects than imipramine.

KEY: C – controlled, **CC** – case-control, **CGI** – clinical global impression scale, **CGI-I** – clinical global improvement impression scale, **CGI-S** – clinical global severity impression scale, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** - cross-sectional, **DB** – double-blind, **D-S** – von Zerssen depression severity scale, **DSM** – Diagnostic and Statistical Manual of Mental Disorders, **E** – epidemiological, **HAMA** – Hamilton Anxiety Scale, **HAMD** – Hamilton Depression Scale, **ICD** – International Classification of Disease, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, n – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on St. John's wort (*Hypericum perforatum* L.) (cont.)

Depression (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Lenoir *et al*., 1999	Mild to moderate depression (ICD-10)	R, DB, PG, Cm, MC n =260 (over 20 years old)	6 weeks	1 tablet 3x/day (1 mg total hypericin/day or 33 mg total hypericin/day or 17 mg total hypericin/day)	Hyperiforce™ tablets containing approximately 60 mg SJW extract (4–5:1) of shoot tips standardized to 0.33 mg total hypericin content/tablet (controls standardized to 0.11 mg or 0.055 mg total hypericin/ tablet)	At the end of the treatment period, a reduction of about 50% in Hamilton Depression scores was observed in all groups. No significant differences between dosages. SJW was determined to be effective in all 3 doses and is well tolerated.
Laakmann *et al*., 1998a	Mild to moderate depression	R, DB, PC, MC, PG n=145 (mean age, 51 years placebo; 48.7 years WW5573 group; 47.3 years SJW group)	7 weeks	900 mg/day (300 mg, 3x/day)	WS 5573 (0.5% hyperforin) or WS 5572 (5% hyperforin) or placebo	Study demonstrated relationship between hyperforin dose and antidepressant efficacy. 5% hyperforin SJW product enhanced patients' quality of life by producing appreciable relief from symptoms compared to 0.5% (p=0.017) and placebo (p=0.004). No statistical difference between 0.5% and placebo. Study suggests hyperforin is a therapeutically active constituent with antidepressant activity.
Wheatley, 1997	Mild to moderate depression (DSM-IV),	R, DB, PG, MC n=156 (HAMD score between 17–24, mean score SJW=20.6 amitriptylline= 20.8) (ages 20–65 years)	6 weeks	900 mg/day SJW extract (300 mg, 3x/day) or amitriptyline (3x25 mg in a fixed dose manner)	LI 160 vs. amitriptyline	Comparable efficacy to amitriptyline with clear tolerability advantage. No statistically significant difference in response rate was shown between SJW and amitriptyline (p=0.064). In the CGI item "side-effects of drugs," greater tolerability for SJW was apparent (p<0.001 at week 2, p<0.05 at weeks 4 and 6).
Schrader *et al*., 1998	Mild to moderate depression	R, P, DB, PC, MC n=159	6 weeks	One, 250 mg tablets SJW extract 2x daily (1 mg hypericin daily)	Ze 117 SJW extract standardized to 0.5 mg hypericin/ tablet	Of SJW patients, 56% were deemed responsive to treatment compared to 15% on placebo.There were few adverse effects: 5 placebo, 6 SJW (mostly minor gastrointestinal upsets in SJW group). Researchers noted that the good tolerability profile contributed to the high compliance of the SJW group.
Vorbach *et al*., 1994	Typical depression with single episode, recurrent episode, neurotic depression, and adjustment disorder with depressed mood (DSM-III-R).	R, DB, Cm, MC n=130 (Mean HAMD score 20.2 SJW group, 19.4 imipramine group) (ages 18–75 years)	6 weeks	900 mg/day SJW extract (300 mg, 3x/day) vs. imipramine (3x25mg daily)	LI 160 vs. imipramine	SJW showed equal effectiveness to and better tolerability than imipramine. Improved HAMD total score by 56% on SJW and 45% on imipramine. SJW caused less frequent and less severe side effects than imipramine.
Harrer *et al*., 1994	Depression (ICD-10)	R, DB, Cm, MC n=102 (HAMD score >16) (ages 25–65 years)	4 weeks	900 mg/day SJW extract (300 mg, 3x/day), maprotiline, (25 mg 3x/day)	LI 160 vs. maprotiline	Showed roughly equal efficacy to maprotiline. No significant difference between groups on HAMD, D-S, and CGI scores (HAMD score >16). 25% in SJW group and 35% in maprotiline group reported adverse drug effects.

KEY: C – controlled, **CC** – case-control, **CGI** – clinical global impression scale, **CGI-I** – clinical global improvement impression scale, **CGI-S** – clinical global severity impression scale, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** - cross-sectional, **DB** – double-blind, **D-S** – von Zerssen depression severity scale, **DSM** – Diagnostic and Statistical Manual of Mental Disorders, **E** – epidemiological, **HAMA** – Hamilton Anxiety Scale, **HAMD** – Hamilton Depression Scale, **ICD** – International Classification of Disease, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, n – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on St. John's wort (*Hypericum perforatum* L.) (cont.)

Depression (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Harrer and Sommer, 1994	Mild to moderate depression (ICD-9)	R, DB, PC, MC n=89 (HAMD score <20) (ages 20–64 years)	1 month	900 mg/day (300 mg, 3x/day)	LI 160 vs. placebo	Significantly ($p<0.05$) reduced depressive symptoms after 2 weeks and even further after 4 weeks ($p<0.01$) compared to placebo. No notable side effects were reported.
Hübner *et al*., 1994	Mild depression and somatic symptoms (ICD-09).	R, DB, PC n=39 (Mean HAMD score 12.55 SJW group, 12.37 placebo group) (ages 20–64 years)	4 weeks	900 mg/day (300 mg, 3x/day)	LI 160 vs. placebo	Significant reduction in HAMD score in SJW group compared to placebo ($p<0.01$). Final score=7.17. Significant reduction in falling asleep compared to placebo ($p<0.01$). Benefited patients with good tolerability and high compliance ($p<0.05$). By week 4, 5% statistical difference level in HAMD between placebo and SJW groups. No adverse effects reported.
Hänsgen *et al*., 1994	Major depression and temporary depressive neurosis (DSM-III-R)	R, DB, PC, MC n=72 (HAMD score >16) (ages 18–70 years)	6 weeks	900 mg/day (300 mg, 3x/day)	LI 160 vs. placebo	Significantly improved all 4 psychometric tests vs. placebo, with no serious side effects reported: Hamilton depression scale ($p<0.001$), depression scale of von Zerssen ($p<0.001$), complaint inventory, Clinical Global Impression Scale.

Fatigue and Seasonal Affective Disorder

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Stevinson *et al*., 1998	Fatigue	O, U, pilot n=20 (mean age, 44.4 years)	6 weeks	900 mcg/day hypericin (300 mcg 3x/day)	Kira®	Significantly lowered perceived fatigue after 2 weeks ($p<0.05$) and reduced significantly more after 6 weeks ($p<0.01$) . Significantly ($p<0.05$) reduced mean scores of depression and anxiety.
Kasper, 1997	Seasonal affective disorder (SAD) (DSM-IV)	O n= 20 (ages 18–65 years)	1 month	900 mg/day (300 mg 3x/day)	LI 160 vs. light therapy	Significantly reduced depression scores when given with or without bright light therapy. Tolerated well by patients.
Martinez *et al*., 1994	Seasonal affective disorder (SAD) (DSM-III-R) HAMD scale>16	R, SB n=20 (ages 29-63 years)	4 weeks	900 mg/day (300 mg, 3x/day)	LI 160 with bright light (3000 lux) vs. LI 160 with dim light (<300 lux)	Significant improvement in symptoms over time with SJW and bright light ($p=0.001$). No adverse drug reactions reported.

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Shüle *et al*, 2001	Effect of SJW on cortisol, growth hormone, and prolactin	R, PC, CO n=12 healthy males between 20 and 35 years old	5 hours	300 mg WS 5570, 600 mg WS 5570, or placebo	WS 5570 SJW extract or placebo	No prolactin stimulation was observed ($p>0.05$) in SJW or placebo. A small but statistically significant ($p<0.05$) increase in growth hormone occurred after 300 mg SJW. After 600 mg SJW, cortisol stimulation was clearly observed ($p<0.05$) from 30 to 90 minutes after application.
Schempp *et al*., 2001	Phototoxicity of SJW in treatment of depression (UV-B, UV-A, visible light, solar-simulated radiation)	R, P n=72	Single-dose or Steady-state 7 days	Single dose: 6 or 12 coated tablets, 3x daily (containing 5400 or 10,800 mcg of total hypericins). Steady-state trial: initial dose of 6 tablets (1800 mcg of hypericins) followed by 3 x 1 tablets (2700 mcg) per day for 7 days	LI 160	No significant changes were observed (erythema and melanin index) in either the single or multiple doses administered, with the exception of a slight, ($p=0.50$) influence on UV-B-induced pigmentation. The authors concluded that this study did not indicate phototoxic potential in the oral administration of higher than therapeutic doses (2–4 times) of SJW for depression.

KEY: C – controlled, **CC** – case-control, **CGI** – clinical global impression scale, **CGI-I** – clinical global improvement impression scale, **CGI-S** – clinical global severity impression scale, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** - cross-sectional, **DB** – double-blind, **D-S** – von Zerssen depression severity scale, **DSM** – Diagnostic and Statistical Manual of Mental Disorders, **E** – epidemiological, **HAMA** – Hamilton Anxiety Scale, **HAMD** – Hamilton Depression Scale, **ICD** – International Classification of Disease, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, n – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on St. John's wort (*Hypericum perforatum* L.) (cont.)

Other (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Burnstein *et al*., 2000	SJW effects on steady state carba-ma-zepine and carbama-zepine-10,11-epoxide phar-maco-kinetics	U n=8	21 days	100 mg 2x daily for 3 days, then 200 mg, 2x daily for 3 days, then 400 mg once daily for 14 days; then 300 mg SJW with carba-maze-pine, 3x daily for 14 days	St. John's wort (0.3% stan-dardized tablet) or car-bama-zepine (brand not stated)	The study concluded that SJW did not increase clear-ance of carbamazepine.
Taylor and Kobak, 2000	Obsessive-compulsive disorder (OCD)	O n=12 patients with 12 months diag-nosis of OCD (DSM-IV)	12 weeks	450 mg SJW extract, 2x/day	450 mg SJW extract stan-dardized to 0.3% hypericin (brand not stated)	Significant change from baseline, with mean change in Yale-Brown Obsessive-Compulsive Scale of 7.4 points (p=0.01). At end of trial, 5 patients were rated much or very much improved on clinician CGI, 6 were minimally improved, and 1 had no change. Side effects included diarrhea (3 subjects) and restless sleep (2 subjects). Improvements noted in first week. Results warrant placebo-controlled study of SJW for obsessive-compul-sive disorder.
Grube *et al*., 1999	Menopausal symptoms	O Drug moni-tori-ng study n=106 Women 43–65 years old with symp-toms charac-teristic of pre- and post-menopause	12 weeks	One, 300 mg tablet, 3x/day	Kira®	Self-assessment by Menopause Rating Scale for assessing sexuality and CGI. Psychological, psychosomatic, and vasomotor symptoms recorded at baseline, 5, 8, and 12 weeks. Significant improvement in psychological and psy-chosomatic symptoms. Menopausal symptoms reduced or disappeared in majority (76.4% by patient assess-ment; 79.2% by physician assessment). About 80% of women considered sexuality was improved with SJW
Czekalla *et al*., 1997	Electro-car-diogram effects in patients with depression	R, DB, Cm, MC n=209	6 weeks	1800 mg/day or 150 mg/ day imipramine	Jarsin® 300 vs. imipramine	SJW did not delay conduction through the atria or depolarization and repolarisation in the ventricles. Imipramine increased heart rate and can cause patho-logical repolarisation. High-dose SJW extract (i.e., 2x normal daily dose) produced fewer cardiac conduction defects than tricyclic antidepressants for treating elderly patients or patients with a pre-existing conductive dys-function, and should be considered safer than tricyclic antidepressants, especially in patients with pre-existing conduction disorders.

KEY: C – controlled, **CC** – case-control, **CGI** – clinical global impression scale, **CGI-I** – clinical global improvement impression scale, **CGI-S** – clinical global severity impression scale, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** - cross-sectional, **DB** – double-blind, **D-S** – von Zerssen depression severity scale, **DSM** – Diagnostic and Statistical Manual of Mental Disorders, **E** – epidemiological, **HAMA** – Hamilton Anxiety Scale, **HAMD** – Hamilton Depression Scale, **ICD** – International Classification of Disease, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, n – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

ERRATA to *The ABC Clinical Guide to Herbs*

April 15, 2003

The editors detected the following errors after printing had been completed. Corrections are indicated by SMALL CAPITAL TEXT. **Updates and any additional corrections to *The ABC Clinical Guide to Herbs* will be posted on the American Botanical Council's Web site www.herbalgram.org/.**

BLACK COHOSH

p. 19: Monograph, Branded Products

Remifemin®: GlaxoSmithKline / One Franklin Plaza / Philadelphia, PA 19102 / U.S.A. / Tel: (800) 366-8900. One tablet contains black cohosh extract WITH MONITORING OF ACTIVE COMPOUNDS (TRITERPENE GLYCOSIDES) CORRESPONDING TO 20 MG OF CRUDE DRUG.

p. 19: Monograph, Branded Products

Remifemin® drops: Schaper & Brümmer GmbH & Co. KG. / Bahnhofstrasse 35 / 38259 Salzgitter / Ringelheim / Germany / Tel: +49-5341-30-70 / Fax: +49-5341-30-71-24 / Email: info@schaper-bruemmer.de / www.schaper-bruemmer.com/. Twenty drops correspond to 20 mg of crude drug. [DELETE "THIS PRODUCT IS NO LONGER AVAILABLE."]

ECHINACEA

p. 92: Monograph, Branded Products

Esberitox® (NAME AND FORMULATION prior to 1985): Schaper and Brümmer GmbH & Co. KG. / Bahnhofstrasse 35 / 38259 Salzgitter / Ringelheim / Germany / Tel.: +49-5341-30-70 / Fax: +49-5341-30-71-24 / Email: info@schaper-bruemmer.de / www.schaper-bruemmer.com. One tablet contains 0.215 ml of an alcoholic-aqueous extract (1:11) corresponding to 2 mg *Thuja occidentalis* (white cedar) leaf, 7.5 mg Echinacea (*E. purpurea* and *E. pallida* 1+1) root, 10 mg *Baptisia tinctoria* (wild indigo) root and homeopathic dilutions of Apis mell. (D4), Crotalus (D6), Lachesis (D4), and Silicea (D4).

p. 92: Monograph, Branded Products

Replace Esberitox®N1 and Esberitox®N2 entries with the following:

Esberitox® N (NAME AND FORMULATION 1985–PRESENT): Schaper and Brümmer GmbH & Co. KG. One tablet contains 0.215 ml of an alcoholic-aqueous extract (1:11) corresponding to 2 mg *Thuja occidentalis* (white cedar) leaf, 7.5 mg Echinacea (*E. purpurea* and *E. pallida* 1+1) root, and 10 mg *Baptisia tinctoria* (wild indigo) root (homeopathic ingredients removed). PRIOR TO 1990 THIS PRODUCT WAS REPORTED TO CONTAIN *E. ANGUSTIFOLIUS* AND *E. PALLIDA* (MELCHART *ET AL.*, 1994); HOWEVER, IT REALLY CONTAINED *E. PURPUREA* AND *E. PALLIDA* (LISKE, 2003).

p. 93: Monograph, References

Add the following reference:

LISKE E [HEAD OF INTERNATIONAL MEDICAL DEPARTMENT, SCHAPER & BRÜMMER GMBH & CO. KG]. PERSONAL WRITTEN COMMUNICATION. MARCH 25, 2003.

p. 94: Monograph, Table of Clinical Studies

Henneicke-von Zepelin *et al.*, 1999:

Preparation: ESBERITOX®N [DELETE "2"] tablet vs. placebo

p. 95: Monograph, Table of Clinical Studies

Reitz, 1990:

Dosage: 3 TABLETS 3x/day or placebo (vitamin C)

Preparation: ESBERITOX®N [DELETE "1"] tablet vs. placebo

Vorberg, 1984:

Dosage: 2 TABLETS 3x/day

Preparation: Esberitox® tablet (INCLUDES HOMEOPATHIC INGREDIENTS) vs. placebo

p. 96: Monograph, Table of Clinical Studies

Forth and Beuscher; 1981:

Dosage: 25 drops 3x/day or 1 [DELETE MG] tablet 3X/DAY or placebo

Preparation: Esberitox® (INCLUDES HOMEOPATHIC INGREDIENTS)

PROPIETARY PRODUCTS

p. 375: Esberitox®, Monograph

Title: Esberitox® / ESBERITOX®N

Contents: [EDITORS' NOTE: THIS PRODUCT WAS ORIGINALLY NAMED ESBERITOX®. IN 1985 THE PRODUCT WAS REFORMULATED TO REMOVE THE HOMEOPATHIC INGREDIENTS AND THE NAME WAS CHANGED TO ESBERITOX®N.] ONE TABLET CONTAINS 0.215 ML OF AN ALCOHOLIC-AQUEOUS EXTRACT (1:11) CORRESPONDING TO 2 MG *THUJA OCCIDENTALIS* (WHITE CEDAR) LEAF, 7.5 MG ECHINACEA (*E. PURPUREA* AND *E. PALLIDA* 1+1) ROOT, AND 10 MG *BAPTISIA TINCTORIA* (WILD INDIGO) ROOT. NOTE: PRIOR TO 1985 THE PRODUCT ALSO CONTAINED HOMEOPATHIC DILUTIONS OF *APIS MELL.* (D4), CROTALUS (D6), LACHESIS (D4), AND SILICEA (D4). PRIOR TO 1990 THE PRODUCT WAS DECLARED TO CONTAIN *E. ANGUSTIFOLIA* AND *E. PALLIDA* (MELCHART *ET AL.*, 1994); HOWEVER, IT REALLY CONTAINED *E. PURPUREA* AND *E. PALLIDA* (LISKE, 2003).

Duration of Administration: DEPENDS ON THE CONDITION BEING TREATED.

p. 375: Esberitox®, Table of Clinical Studies

Henneicke-von Zepelin *et al.*, 1999:

Dosage: 3 TABLETS 3x/day

Preparation: ESBERITOX®N [DELETE "2"]

Reitz, 1990:

Dosage: 3 TABLETS 3x/day or placebo (vitamin C)

Preparation: ESBERITOX®N [DELETE "1"]

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ERRATA to *The ABC Clinical Guide to Herbs* continued

April 15, 2003

p. 375: Esberitox®, Table of Clinical Studies (cont.)

Vorberg, 1984:

Dosage: 2 TABLETS 3x/day

Preparation: Esberitox® (INCLUDES HOMEOPATHIC INGREDIENTS)

Forth and Beuscher; 1981:

Preparation: Esberitox® (INCLUDES HOMEOPATHIC INGREDIENTS)

p. 381: Mastodynon®, Table of Clinical Studies

Kubista *et al.*, 1986:

Results/Conclusion: 74.5% [INSTEAD OF 74.55]

p. 391: References

Add the following reference:

LISKE E [HEAD OF INTERNATIONAL MEDICAL DEPARTMENT, SCHAPER & BRÜMMER GMBH & CO. KG]. PERSONAL WRITTEN COMMUNICATION. MARCH 25, 2003.

TABLE OF PRODUCTS USED IN CLINICAL STUDIES LISTED IN SINGLE HERB MONOGRAPHS

p. 398: Black Cohosh

Remifemin® drops (Schaper & Brümmer GmbH & Co. KG) [DELETE "(PRODUCT NO LONGER AVAILABLE)"]

p. 398: Chaste Tree

Products Used in Clinical Studies: BNO 1095 Capsules (Bionorica AG) (EXTRACT USED IN RETAIL PRODUCTS) [DELETE: "PRODUCT NOT DISTRIBUTED"]

Other Names: AGNUCASTON® FILM COATED TABLETS (BIONORICA AG)

p. 399: Echinacea

Esberitox® (PRE-1985) (Schaper & Brümmer GmbH & Co. KG) (PRODUCT WITH HOMEOPATHIC INGREDIENTS NO LONGER AVAILABLE)

[DELETE ENTIRE ENTRY "Esberitox®N1 (1985 formulation based on Esberitox®) (Schaper & Brümmer GmbH & Co. KG)"]

ESBERITOX®N [DELETE "2"] (1985–PRESENT) (Schaper & Brümmer GmbH & Co. KG); Esberitox® (US: Enzymatic Therapy, Inc.)

TABLE OF PRODUCTS USED IN CLINCAL STUDIES LISTED IN PROPRIETARY HERBAL MONOGRAPHS

p. 404: Esberitox®

Proprietary Product: Esberitox® (Schaper & Brümmer GmbH & Co. KG) (pre-1985 formulation, PRODUCT WITH HOMEOPATHIC INGREDIENTS NO LONGER AVAILABLE)

Ingredients: *Echinacea pallida* root, *E. purpurea* root, *Thuja occidentalis* LEAF, *Baptisia tinctoria* root, AND HOMEOPATHIC DILUTIONS OF APIS MELL., CROTALUS, LACHESIS, AND SILICEA

p. 404: Esberitox®N1

[DELETE ENTIRE ENTRY]

p. 404: Esberitox®N2

Proprietary Product: Esberitox®N [DELETE "2"] (Schaper & Brümmer GmbH & Co. KG) (1985–PRESENT formulation)

Ingredients: *Echinacea pallida* root, *E. purpurea* ROOT, *Thuja occidentalis* LEAF, *Baptisia tinctoria* root

p. 404: Mastodynon®

Other Names:

Not marketed in the U.S.

BNO 1020 (Bionorica AG) (EXTRACT USED IN RETAIL PRODUCTS) NOT MARKETED IN THE U.S.

p. 404: Sinupret®

Other Names:

(U.S. Distributor: Mountain Home Nutritionals)

BNO 1015 (BIONORICA AG) (EXTRACT USED IN RETAIL PRODUCTS) NOT MARKETED IN THE U.S.

CONTINUING MEDICAL EDUCATION FOR NATURIOATHIC PHYSICIANS APPLICATION

p. 435

TO QUALIFY FOR 12 HOURS [NOT 10] of approved CE for Naturopaths, complete this original application form (copies will not be accepted), the answer sheet, include a check for $20, and mail to:

Updates and any additional corrections to *The ABC Clinical Guide to Herbs* will be posted on the American Botanical Council's Web site www.herbalgram.org/.

Author Disclosure of Commercial Affiliations

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The authors have asked that we advise readers that by law dietary supplement uses are not listed on product labels. Each monograph will discuss uses and clinical studies conducted using herbs and herbal products.

The following authors have asked that we advise participants in this activity that they have an affiliation with the following organization(s).

Mark Blumenthal	employee, American Botanical Council
	chairman, Board of Trustees, American Botanical Council
Tara Hall	employee, American Botanical Council
Alicia Goldberg	former contractor, American Botanical Council
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FDA Issues Final Rule Banning Ephedra

Sales of Ephedra Supplements Must Cease by April 12, 2004

By Rakesh M. Amin

On Friday, February 6, 2004, the United States Food and Drug Administration (FDA) announced that it was publishing its final rule banning the sales of all dietary supplements containing the controversial herb ephedra (*Ephedra sinica* Stapf, Ephedraceae) and any ephedra group alkaloids (e.g., ephedrine, pseudoephedrine).[1] The final rule was published in the *Federal Register* on February 11, 2004, and will take effect sixty days following publication on April 12, 2004.[2] The final rule is a culmination of FDA's 1997 proposed rule requiring that warning labels be placed on dietary supplements containing ephedra.[3] It also follows FDA's December 30, 2003, consumer alert on the safety of dietary supplements containing ephedra and the agency's notice to manufacturers of its intention to publish a final rule stating that dietary supplements containing ephedra alkaloids creates an "unreasonable risk of illness or injury" for consumers.[4]

The previous issue of *HerbalGram* (#61) contained an extensive article summarizing many of the issues dealing with FDA's announcement in December of the proposed ban and the banning of ephedra by California, Illinois, and New York.[5] The FDA's ban follows the current trend of state legislation restricting the sale and use of dietary supplements containing ephedrine alkaloids. Currently three states, Illinois, California, and New York, have developed and placed into effect legislation outlawing the retail sale of dietary supplements containing ephedra and/or any of its alkaloids.[6,7,8] The states do allow a narrow exception to an otherwise almost total ban on the sale of products containing ephedra. Illinois banned the sale of ephedra as a dietary supplement and does not allow an exception for healthcare practitioners like acupuncturists to use ephedra in their clinical practice.[6] However, Illinois does permit the sale of FDA approved ephedrine alkaloid-containing products marketed under an over-the-counter (OTC) drug monograph or the prescription of ephedra alkaloid-containing drugs by conventional health professionals as explicitly approved by the FDA (i.e., for FDA-approved medical uses).[6] California's bill made sales of dietary supplements in California that contain any amount of "ephedrine group alkaloids" a crime as of January 1, 2004, effectively making any dietary supplement containing the herb illegal for any purpose unless sold by medical prescription.[7] New York law prohibits the sale of dietary supplements containing ephedra and violators can face fines up to $500.00.[8] The only exceptions to New York's prohibition include the sale of the herb to licensed, certified, and accredited practitioners of Traditional Chinese Medicine (TCM) for appropriate purposes within the scope of their practice and for products that receive explicit safe and effective approval for their intended use according to the Federal Food, Drug, and Cosmetic Act or lawfully marketed under an OTC monograph.[8] The new FDA ban preempts inconsistent existing state regulations that are more permissive but will not preempt those state regulations that are more stringent.

The FDA's recent final rule came under the authority granted to it by the Dietary Supplement Health and Education Act of 1994 (DSHEA).[9] Under DSHEA, the FDA determined that dietary supplements containing ephedra are "adulterated because they present an unreasonable risk of illness or injury under the conditions of use recommended, suggested or recommended in labeling, under ordinary conditions of use."[9] The FDA chose not to use or define the "*significant* risk of illness or injury" safety standard under DSHEA, relying instead on the "*unreasonable* risk" safety standard. The FDA concluded that "unreasonable risk represents a relative weighing of the product's known and reasonably likely risks against its known and reasonably likely benefits. In the absence of a sufficient benefit, the presence of even a relatively small risk of an important adverse health effect to a user may be unreasonable."[9] The FDA determined a "reasonably likely benefit" is one that is supported by a meaningful totality of the evidence given the current state of scientific knowledge though not the level of information required for prescription drug approval.[9]

To meet its burden of proof, the FDA gathered and reviewed evidence concerning the following: (1) ephedra's pharmacology; (2) peer-reviewed scientific literature on the safety and effectiveness of ephedra; (3) adverse event reports; and (4) an independent seminal report on the safety and efficacy of ephedra supplements issued by the RAND Corporation.[10,11] Based upon the best available scientific data and the known pharmacology of ephedrine alkaloids, the FDA determined that dietary supplements containing ephedrine alkaloids do not provide a meaningful health benefit and the risks of use were not outweighed by the known or reasonable likely benefits.[12] The FDA's sweeping approach and ability to trump up safety concerns potentially places at risk all dietary supplements including herbals without strong and substantiated benefits. Therefore, it is essential for the industry to address both safety and effectiveness in product testing and to stay abreast of adverse events while striving for solid methodology and strong substantiation to prove a product's effectiveness.

The FDA listed a range of botanicals containing ephedrine alkaloids that would be part of the ban: ma huang (the Chinese name for ephedra), country mallow (*Sida cordifolia* L., Malvaceae; also known as *bala*), the Chinese herb *ban xia* (*Pinellia ternata* [Thunb.] Makino, Araceae), and most members of the genus *Ephedra* that contain the ephedra alkaloids, e.g., *E. sinica*, *E. equisetina* Bunge, *E. intermedia* var, *tibetica* Stapf, and *E. distachya* L.

The ephedrine alkaloids that appear to be pharmacologically active in plants and which are covered by the ban include l-ephedrine, d-pseudoephedrine, 1-norephedrine, 1-methylephedrine, d-norpseudoephedrine, and d-methylpseudoephedrine. The final rule does not apply to conventional foods (such as herbal teas) that contain ephedrine alkaloids, nor does it apply to OTC and prescription drugs. The FDA also stated that most American species of ephedra do not contain ephedrine alkaloids (e.g., Mormon tea [*E. viridis* Coville,]) and are therefore not part of the ban.

The rule will also not affect preparations prepared under TCM because they are intended for episodic (e.g., temporary respiratory infections) rather than chronic use (e.g., long-term use for weight loss). Thus, Chinese practitioners wishing to sell ephedra-containing products will have to remove the "Dietary Supplement" statement of identity

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Amin R. M. "FDA Issues Final Rule Banning Ephedra: Sales of Ephedra Supplements Must Cease by April 12, 2004" *HerbalGram* 2004;62:63-64, 67.

from the products they sell. However, TCM practitioners importing products containing ephedra may be subjected to heightened regulatory scrutiny from U.S. Customs and the FDA because it is uncertain whether premarket approval and/or other documentation will be required.

There are several notable consequences of the FDA's final rule.

First, manufacturers, retailers, and distributors selling ephedra supplements after April 12, 2004, will be subject to civil and/or criminal enforcement, and likely serious product liability exposure.

Second, all dietary supplements, not just ephedra, will now be subject to a risk/benefit safety analysis for the first time as opposed to only risk of injury analysis which was relevant in the past. The FDA's risk/benefit analysis weighs the quality, persuasiveness, and seriousness of the presence of risks associated with the supplement against the quality and importance of the related benefits, with an emphasis on long-term health outcomes opposed to temporary measures such as feeling or looking better.[12] The FDA indicated its determination did not rely on adverse event reporting because such reports are not indicative of a determination of unreasonable risk.[12]

Third, the FDA will act proactively and the industry can expect further rule-making instead of waiting for case-by-case enforcement when an ingredient safety issue arises. One of these proactive measures is indicated by the FDA adding a new section to the Code of Federal Regulations for "Dietary Supplements that Present a Significant or Unreasonable Risk."[2]

Fourth, the FDA has substantially raised the bar on safety substantiation. It is significant to note for future safety studies that the FDA rejected the previously published ephedra safety trials because they were either too small or designed to detect serious effects in susceptible individuals. Warning labels, says FDA, are insufficient. The implications of this ruling with respect to the sale of other herbs are not clear. Since few herbs on the market possess the relatively strong pharmacological activity as ephedra, the stringent warnings that would have pertained to ephedra if FDA's warnings previously proposed in February 2003 had stood are now moot.[13] Finally, various state ephedra laws that conflict with the FDA's final rule will be preempted.

Predictably, while many elements of the supplement industry accepted FDA actions, the FDA's final rule has not received totally positive reactions and several companies in opposition continue to defend ephedra's use. Metabolife International, Inc. issued a statement maintaining the safety of ephedra products "if taken as directed as a safe, inexpensive and effective means by which to support weight loss."[14] On the other hand, several manufacturers see the FDA's ban as a way to remove a level of controversy over the industry. Nonetheless, this is the first time the FDA has ordered a ban on a dietary supplement ingredient, which is strong evidence that most of the popular dietary supplements on the market when taken according to suggested use and labeling or under ordinary conditions of use are safe.

On March 4, 2004, NVE Pharmaceuticals, Inc. (NVE) became the first dietary supplement company to sue the federal government for banning ephedra (*NVE v. Dept. of HHS, et al.*, 04 CV 00999). NVE filed suit against the Department of Health and Human Services (HHS) in the U.S. District Court for the District of New Jersey on the grounds the ban is in violation of the 1994 DSHEA law. NVE requests the Court to set aside the government ban thereby stalling the April 12, 2004 deadline and to consider new evidence challenging the government's claims that ephedra can dangerously raise blood pressure.

Various trade associations of the dietary supplement industry—the Council for Responsible Nutrition, the National Nutritional Foods Association, and the Utah Natural Products Alliance— recently announced they will not challenge the FDA's final rule banning dietary supplements containing ephedrine alkaloids.[15] The associations noted that the agency's action demonstrates that the DSHEA provides FDA with the legal authority to take strong evidence-based regulatory action. While the associations do not agree with every point in FDA's justification of the final rule, they believe the FDA's discussion of the rule indicates that the agency supports access to dietary supplements that are safe, beneficial, made to high quality standards, properly labeled, and in compliance with the law.

For more information on the FDA's first-ever ban on the sale of a dietary supplement ingredient, visit http://www.fda.gov/ ohrms/ dockets/98fr/1995n-0304-nfr0001.pdf. Further inquiries or comments can be directed to Rakesh M. Amin at (312) 327-3382 or e-mail to Rakesh@amin-law.com.

Rakesh M. Amin is a registered pharmacist and attorney at Amin Law, LLC. He is also an adjunct professor teaching Food & Drug Law at the DePaul University College of Law.

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1. U.S. Food and Drug Administration. Sales of Supplements Containing Ephedrine Alkaloids (Ephedra) Prohibited, February 6, 2004. 69 Fed. Reg. 6788 (February 11, 2004). Available at <http://www.fda.gov/oc/initiatives/ephedra/february2004/>.
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