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
• PM S

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 with 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 pregnant 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 may also 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/M D R I (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 amitriptyline 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 Overview**

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 (M C) trials (1,191 participants) found equal effectiveness to tricyclic antidepressant drugs (amitriptyline, imipramine, m dalfontline) 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 was 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, M C, 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.

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; PM S.

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.

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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 Paracelsus (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).

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 hypericin content; however, this is 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., 1998; 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 (AH C PR, 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% quercitin, 0.3% isoquercitin, quercetin, and kaempferol; bioflavonoids (about 0.26% biapigenin), phloroglucinol derivatives (up to 4% hyperforin); phenolic acids (caffic, chlorogenic, ferulic); 0.05–1.0% volatile oils, mainly higher n-alkanes, 0.05–0.15% naphthodianthrones (hypercin and pseudohy- percin); sterols (stigmasterol); 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 serotonergic effects (carbon dioxide extracts) (Bhattacharya, 1998); reduces alcohol intake (Reviani 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 spasmylytic 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, O.R.) does, at 2 mcg/ml (Cott, 1995). MAO-I 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; Muruolo 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) (Serkedjiev et al., 1990), and is antimicrobial (primarily hyperforin) toward methicillin-resistant Staph. aureus but not against gram-negative bacteria or Candida albicans (Rächling 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 to GABA_{A} and 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-hydroxytryptamine (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 (Moor 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 synaptosomes 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 pharmacotherapies 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 associated 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 pharmacological antidepressants (Gordon, 1998; Prost et al., 2000), unless under professional guidance. SJW is believed to interact with oral contraceptives and antiocoagulants (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 (M oreo, 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 monoxygenase. 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 (M oreo, 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/M D R 1 (in rats and humans), and induces intestinal and hepatic CYP3A4 (in humans), thereby decreasing plasma levels of cyclosporine, indinavir, and digoxin (D ürr 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 pharmacological 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 (DOC1) 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 (BAAnz, 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 (M PA) “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; Tunon, 1999). St. John’s wort homeopathic preparations are also registered drugs (M PA, 2001b).

**Switzerland:** Official in Swiss Pharmacopoeia (Upton et al., 1997; Wichtl, 1997). Herbal medicine with positive classification (List D) by the Interkantonale Kontrollstelle für H eilmittel (IKS) and corresponding sales Category D with sale limited to pharmacies and drugstores, without prescription (M orant and Ruppanner, 2001; Ruppanner and Schaefer, 2000). Numerous SJW phytomedicines and homeopathic preparations are listed in
The studies have been performed on 626 participants, concluding that SJW has less short-term adverse side effects than tricyclics. A recent clinical trial compared 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 SSRIs) 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, placebo-controlled study (Linde et al., 2001) did not meet the criteria for a valid comparison trial to date and concluded that the SJW extract used in the study (Removit® marketed by Bayer in Germany) is equivalent to imipramine in efficacy, and is more well-tolerated by patients. A larger study (n=240) comparing SJW (Ze 117) directly with fluoxetine concluded that SJW was as effective 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 SSRIs) concluding that SJW is effective for mild to moderate depression with a low side effect profile (Kasper, 2001).

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**BRANDED PRODUCTS**

Hyperforce™: 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. O ne tablet 3 times/day after meals provides 1 mg hypericin/day.

Jarins®: 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.


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 250 mg film-coated tablet of St. John's wort extracted in 50% alcohol, standardized to 2% hypericins.

WS 5572: see Neuroplant® and Perika®.

WS 5572: Dr. Willmar 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 extract 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.

**REFERENCES**


AH CPT. See Agency for Health Care Policy and Research.


BANZ. See Bundesanzeiger.


Bühler. Communication from BfarM (German Federal Institute for Drugs and Medical Devices) to German Non-prescription Drug Association (BAH), Sept. 11, 1999.


DAC. See Deutscher Arzneimittel-Codex.


ESC O P. See European Scientific Cooperative on Phytotherapy.


### Clinical Studies on St. John’s wort (Hypericum perforatum L.)

<table>
<thead>
<tr>
<th>Author/Year</th>
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<tbody>
<tr>
<td>Friede et al., 2001</td>
<td>Mild to moderate depression</td>
<td>R, DB, MC n=240</td>
<td>6 weeks</td>
<td>500 mg/day Ze 117 vs. 20 mg/day fluoxetine</td>
<td>Ze 117</td>
<td>SJW extract was 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&lt;0.001) than for fluoxetine.</td>
</tr>
<tr>
<td>Shelton et al., 2001</td>
<td>Severe depression</td>
<td>R, DB, PC, MC n=200</td>
<td>8 weeks</td>
<td>900 mg/day increased to 1200 mg/day or placebo</td>
<td>SJW standardized extract (LI 160) or placebo</td>
<td>The number of patients with a remission of depression was significantly higher with SJW than placebo (p=0.02), 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).</td>
</tr>
<tr>
<td>Brenner et al., 2000</td>
<td>Mild to moderate depression; comparison of SJW and selective serotonin reuptake inhibitors (SSRIs)</td>
<td>R, DB, C n=30</td>
<td>7 weeks</td>
<td>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</td>
<td>LI 160 or sertraline</td>
<td>Severity of symptoms, as measured by HAMD and the Clinical Global Impression scale was significantly reduced in both treatment groups (p&lt;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.</td>
</tr>
<tr>
<td>Woelk, 2000</td>
<td>Mild to moderate depression without suicidal ideation (ICD-10)</td>
<td>R, DB, PG, MC (40 centers) n=324</td>
<td>6 weeks</td>
<td>250 mg SJW extract, 2x/day; 75 mg imipramine, 2x/day</td>
<td>Remotiv® (Ze 117) vs. imipramine</td>
<td>157 subjects on SJW had HAMD scores drop from mean of 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-I 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).</td>
</tr>
<tr>
<td>Philipp et al., 1999</td>
<td>Moderate depression</td>
<td>R, DB, MC, PG, PC, Cm n=262</td>
<td>2 months</td>
<td>1050 mg/day SJW, 350 mg 3x/day vs. daily dosing of 50 mg, 25 mg then 25 mg (100 mg total/day) imipramine</td>
<td>STEI 300 vs. imipramine</td>
<td>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.</td>
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<tbody>
<tr>
<td>Lenoir et al., 1999</td>
<td>Mild to moderate depression (ICD-10)</td>
<td>R, DB, PG, Cm, MC, n=260 (over 20 years old)</td>
<td>6 weeks</td>
<td>1 tablet 3x/day (1 mg total hypericin/day or 33 mg total hypericin/day or 17 mg total hypericin/day)</td>
<td>Hyperforce™ tablets containing approximately 60 mg SJW extract (4-5:1) of shoot tips standardized to 0.33 mg total hypericin content/tablet</td>
<td>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.</td>
</tr>
<tr>
<td>Laakmann et al., 1998a</td>
<td>Mild to moderate depression</td>
<td>R, DB, PC., MC, PG, n=145 (mean age, 51 years) placebo; 48.7 years W W 5573 group; 47.3 years SJW group</td>
<td>7 weeks</td>
<td>900 mg/day (300 mg, 3x/day)</td>
<td>W S 5573 (0.5% hyperforin) or W S 5572 (5% hyperforin) or placebo</td>
<td>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.</td>
</tr>
<tr>
<td>Wheatley, 1997</td>
<td>Mild to moderate depression (DSM-IV)</td>
<td>R, DB, PG, MC, n=156 (HAMD score between 17-24, mean score SJW=20.6 amitriptyline=20.8) (age 20-65 years)</td>
<td>6 weeks</td>
<td>900 mg/day SJW extract (300 mg, 3x/day) or amitriptyline (3x25 mg in a fixed dose manner)</td>
<td>LI 160 vs. amitriptyline</td>
<td>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 &quot;side-effects of drugs,&quot; greater tolerability for SJW was apparent (p&lt;0.001 at week 2, p&lt;0.05 at weeks 4 and 6).</td>
</tr>
<tr>
<td>Schrader et al., 1998</td>
<td>Mild to moderate depression</td>
<td>R, P, DB, PC., MC, n=159</td>
<td>6 weeks</td>
<td>0.06, 250 mg tablets SJW extract 2x daily (1 mg hypericin daily)</td>
<td>Ze 117 SJW extract standardized to 0.5 mg hypericin/tablet</td>
<td>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.</td>
</tr>
<tr>
<td>Vorbach et al., 1994</td>
<td>Typical depression with single episode, recurrent episode, neuropsychiatric, and adjustment disorder with depressed mood (DSM-III-R)</td>
<td>R, DB, CM, MC, n=130 (Mean HAMD score 20.2 SJW group, 19.4 imipramine group) (ages 18–75 years)</td>
<td>6 weeks</td>
<td>900 mg/day SJW extract (300 mg, 3x/day) vs. imipramine (3x25mg daily)</td>
<td>LI 160 vs. imipramine</td>
<td>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.</td>
</tr>
<tr>
<td>Harrer et al., 1994</td>
<td>Depression (ICD-10)</td>
<td>R, DB, CM, MC, n=102 (HAMD score &gt;16) (ages 25–65 years)</td>
<td>4 weeks</td>
<td>900 mg/day SJW extract (300 mg, 3x/day), maprotiline (25 mg, 3x/day)</td>
<td>LI 160 vs. maprotiline</td>
<td>Showed roughly equal efficacy to maprotiline. No significant difference between groups on HAMD, D-S, and CGI scores (HAMD score &gt;16). 25% in SJW group and 35% in maprotiline group reported adverse drug effects.</td>
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</table>

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

#### Depression (cont.)

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<tr>
<th>Author/Year</th>
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<tbody>
<tr>
<td>Harrer et al, 2001</td>
<td>Mild to moderate depression (ICD-9)</td>
<td>R, D, B, PC, MC</td>
<td>1 month</td>
<td>900 mg/day (300 mg, 3x/day)</td>
<td>LI 160 vs. placebo</td>
<td>Significantly (p&lt;0.05) reduced depressive symptoms after 2 weeks and even further after 4 weeks (p&lt;0.01) compared to placebo. No notable side effects were reported.</td>
</tr>
<tr>
<td>Hübner et al, 1994</td>
<td>Mild depression and somatic symptoms (ICD-09)</td>
<td>R, D, B, PC</td>
<td>4 weeks</td>
<td>900 mg/day (300 mg, 3x/day)</td>
<td>LI 160 vs. placebo</td>
<td>Significant reduction in HAMD score in SJW group compared to placebo (p&lt;0.01). Significant reduction in falling asleep compared to placebo (p&lt;0.01). Benefited patients with good tolerability and high compliance (p&lt;0.05). By week 4.5% statistical difference level in HAMD between placebo and SJW groups. No adverse effects reported.</td>
</tr>
<tr>
<td>Hänsgen et al, 1994</td>
<td>Major depression and temporary depressive symptoms (DSM-III-R)</td>
<td>R, D, B, PC, MC</td>
<td>6 weeks</td>
<td>900 mg/day (300 mg, 3x/day)</td>
<td>LI 160 vs. placebo</td>
<td>Significantly improved all 4 psychometric tests vs. placebo, with no serious side effects reported: Hamilton depression scale (p&lt;0.001), depression scale of von Zersen (p&lt;0.001), complaint inventory, Clinical Global Impression Scale.</td>
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#### Fatigue and Seasonal Affective Disorder

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<tr>
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<tr>
<td>Stevinson et al, 1998</td>
<td>Fatigue</td>
<td>O, U, pilot</td>
<td>6 weeks</td>
<td>900 mcg/day hypericin (300 mcg 3x/day)</td>
<td>Kira®</td>
<td>Significantly lowered perceived fatigue after 2 weeks (p&lt;0.05) and reduced significantly more after 6 weeks (p&lt;0.01). Significantly (p&lt;0.05) reduced mean scores of depression and anxiety.</td>
</tr>
<tr>
<td>Kasper, 1997</td>
<td>Seasonal affective disorder (SAD) (DSM-IV)</td>
<td>0 n=20 (mean age 44.4 years)</td>
<td>1 month</td>
<td>900 mg/day (300 mg, 3x/day)</td>
<td>LI 160 vs. light therapy</td>
<td>Significantly reduced depression scores when given with or without bright light therapy. Tolerated well by patients.</td>
</tr>
<tr>
<td>Martinez et al, 1994</td>
<td>Seasonal affective disorder (SAD) (DSM-III-R)</td>
<td>R, SB n=20 (ages 29-63 years)</td>
<td>4 weeks</td>
<td>900 mg/day (300 mg, 3x/day)</td>
<td>LI 160 with bright light (3000 lux) vs. LI 160 with dim light (&lt;300 lux)</td>
<td>Significant improvement in symptoms over time with SJW and bright light (p=0.001). No adverse drug reactions reported.</td>
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#### Other

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<tr>
<td>Shüle et al, 2001</td>
<td>Effect of SJW on cortisol, growth hormone, and prolactin</td>
<td>R, PC, CO n=12 healthy males between 20 and 35 years old</td>
<td>5 hours</td>
<td>300 mg W S 5570, 600 mg W S 5570, or placebo</td>
<td>WS 5570 SJW extract or placebo</td>
<td>No prolactin stimulation was observed (p&gt;0.05) in SJW or placebo. A small but statistically significant (p&lt;0.05) increase in growth hormone occurred after 300 mg SJW. After 600 mg SJW, cortisol stimulation was clearly observed (p&lt;0.05) from 30 to 90 minutes after application.</td>
</tr>
<tr>
<td>Schempp et al, 2001</td>
<td>Phototoxicity of SJW in treatment of depression (UV-B, UV-A, visible light, solar-simulated radiation)</td>
<td>R, P n=72</td>
<td>Single-dose or Steady-state 7 days</td>
<td>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 hypericin) followed by 3 x 1 tablets (2700 mcg) per day for 7 days</td>
<td>LI 160</td>
<td>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.</td>
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<td>Burnstein et al., 2000</td>
<td>SJW effects on steady state carbamazepine and carbamazepine-10,11-epoxide pharmacokinetics</td>
<td>U</td>
<td>21 days</td>
<td>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 carbamazepine, 3x daily for 14 days</td>
<td>St. John's wort (0.3% standardized tablet) or carbamazepine (brand not stated)</td>
<td>The study concluded that SJW did not increase clearance of carbamazepine.</td>
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<tr>
<td>Taylor and Kobak, 2000</td>
<td>Obsessive-compulsive disorder (OCD)</td>
<td>0</td>
<td>12 weeks</td>
<td>450 mg SJW extract, 2x/day</td>
<td>450 mg SJW extract standardized to 0.3% hypericin (brand not stated)</td>
<td>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-compulsive disorder.</td>
</tr>
<tr>
<td>Grube et al., 1999</td>
<td>Menopausal symptoms</td>
<td>0 Drug monitoring study</td>
<td>n=106 women 43-65 years old with symptoms characteristic of pre- and postmenopause</td>
<td>12 weeks</td>
<td>0ne, 300 mg tablet, 3x/day</td>
<td>Kira®</td>
</tr>
<tr>
<td>Czekalla et al., 1997</td>
<td>Electrocardiogram effects in patients with depression</td>
<td>R, DB, Cm</td>
<td>6 weeks</td>
<td>1800 mg/day or 150 mg/day imipramine</td>
<td>Jarsin® 300 vs. imipramine</td>
<td>SJW did not delay conduction through the atria or depolarization and repolarisation in the ventricles. Imipramine increased heart rate and can cause pathological 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 dysfunction, and should be considered safer than tricyclic antidepressants, especially in patients with pre-existing conduction disorders.</td>
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</table>

**KEY:** C - controlled, CC - case-control, CGI - clinical global impression scale, CGIH - clinical global improvement impression scale, CGIS - 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.