St. John's Wort and S-Adenosyl Methionine as "Natural" Alternatives to Conventional Antidepressants in the Era of the Suicidality Boxed Warning: What is the Evidence for Clinically Relevant Benefit?

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Abstract
INTRODUCTION: A boxed-warning in antidepressant labeling now informs prescribers of the potential for treatment-emergent suicidality to occur. Consequently, alternative "natural" antidepressant therapies widely viewed to be devoid of this risk, such as St. John's wort (SJW) and s-adenosyl methionine (SAM-e), may experience a resurgence in popularity and expansion of use beyond mild forms of depressive illness. The purpose of this article is to critically assess whether the clinical evidence supports the use of SJW and SAM-e as alternatives to conventional antidepressants in the treatment of major depressive disorder (MDD). In addition, this article evaluates whether the behavioral adverse event profiles of SJW and SAM-e suggest an increased risk for suicidality, like their conventional counterparts. METHODS: A comprehensive literature review was performed (Jan 1975-July 2010) to identify all English language reports of placebo-controlled studies of SJW and SAM-e conducted for psychiatric indications. MDD studies were categorized as "positive" or "negative" based on statistical superiority to placebo on prospectively-defined, primary, clinician-rated efficacy parameters (e.g., change in Hamilton Depression scores [HAM-D] or Montgomery-Asberg Depression Rating Scale [MADRS] total). Treatment effect size (Cohen's *d*) was also calculated in each case to assess the clinical relevance of the findings. Behavioral-related adverse events were summarized by treatment. RESULTS: Ten of 14 (71%) SJW studies in mild-to-moderate MDD were positive. The mean and median effect sizes for HAM-D change in those studies were 0.64 and 0.48, respectively, indicative of a moderately-large treatment effect. In the few studies that included patients with severe symptoms, however, or which evaluated long-term maintenance of effect, SJW did not differentiate from placebo. The majority of SAM-e studies in MDD were also positive (8/14, 57%); however, most were methodologically flawed to some extent. Based on the magnitude of the treatment-effect size in a number of positive studies, SJW appears to be useful for the short-term treatment of mild-to-moderate depressive illness in adults. Existing data do not support the use of SJW in more severely depressed individuals. The SAM-e clinical data also are strongly suggestive of antidepressant efficacy; however, until more rigorously generated data become available it is not possible to reach a more definitive conclusion. There are no long-term treatment data that convincingly demonstrate long-term maintenance of effect for either product. The reviewed studies did not reveal evidence of treatment-emergent suicidality, suggesting that this risk for either product is low. However, the studies examined were not prospectively designed to detect such events and therefore were likely unable to reliably assess this risk.
(*Altern Med Rev* 2011;16(1):17-39)

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Introduction

The suicide rate in the United States fell approximately 14 percent from 1985 to 1999.[1] The decline was largely attributed to the increased use of selective serotonin reuptake inhibitor (SSRI) antidepressants during this same period.[1] In 2004, however, labeling for SSRIs, as well as all prescription antidepressants in the United States, began to include warnings of an *increased* risk for suicidal thinking or behavior with use in children and adolescents. This "boxed" warning also cautioned prescribers, other healthcare providers, and families to be vigilant for behavioral changes (e.g., hostility, agitation) in those taking antidepressants, as these behaviors could be precursors to suicidality. This class labeling change was based on a meta-analysis conducted by the U.S. Food and Drug Administration (FDA) that revealed a greater incidence of possible suicidality (behavior or ideation) in clinical trials of pediatric patients treated with antidepressants, compared to

placebo.[2] In 2007, following further analyses, the FDA expanded the warning to include young adults (18-24 years) among those potentially at risk.

Although not the intent, the initial regulatory actions resulted in reduction of antidepressant prescriptions to those less than age 18 years.[3-6] Given the seriousness of suicidality, and the pronounced media attention that this issue garnered, this outcome was not necessarily surprising. Diagnoses of pediatric depression also declined during this period (a significant change from the historical trend)[7] and, for the first time in decades, the incidence of adolescent suicide reversed trend and began to rise.[4] While it is impossible to know whether the recent increase in adolescent suicide was related to reduced antidepressant use, the temporal relationship suggests the regulatory warnings, while well-intentioned, may have been partially responsible. One notion that most experts seem to agree on is that untreated depression carries a significant risk for suicide.[8,9] Depression diagnoses and antidepressant use in adults also reportedly declined after the initial pediatric warnings were issued.[10,11] Whether the expansion of the "boxed" warning to encompass young adults will further reduce antidepressant use in adults, particularly in young adults, remains to be seen.

Major depressive disorder (MDD) is among the most frequently diagnosed psychiatric illnesses, with a lifetime prevalence approaching 20 percent.[12] It is well-established that if left untreated MDD is associated with substantial morbidity and mortality,[13,14] including an increased risk for suicide.[8,9] The widely-communicated potential link between antidepressant use and suicidality, together with the recognition that the greatest risk for depression-related morbidity and mortality lies with no treatment, may prompt greater numbers of prescribers and patients to turn to alternative treatment options. Pharmacotherapies perceived to be devoid of the suicidality risk are likely to attract the most interest. Candidate therapies include "natural" mood-enhancing dietary supplements, which include herbal as well as non-herbal products/nutraceuticals. These are available "over-the-counter" (OTC) in the United States. Although many dietary supplements are purported to have mood-enhancing properties, the two most widely-used are the herbal product St. John's wort (SJW) and the nutraceutical s-adenosyl methionine (SAM-e).

Alternative medicine use continues to rise in people of all ages.[15] Between 1990 and 1997, the percentage of the U.S. population that had used an herbal medicine increased almost five-fold (from 2.5% to 12.1%).[16] In 2007, according to the U.S. Centers for Disease Control, 18 percent of adults and four percent of children used natural herbal products.[17] Consumers are turning to these products to treat a variety of ailments, from relatively benign conditions such as acne and male pattern baldness, to more serious disorders such as cancer, heart disease, and depression. Why do these products hold such appeal? Proposed reasons include their wide distribution and ready availability, their lower cost and purported efficacy advantage over conventional medications (e.g., "faster-acting"), and the widely-held but misguided perception that they are always inherently safe.[18]

A greater percentage of individuals with mental illness use alternative medicine than the general population.[19] Simon et al reported that approximately 10 percent of visits to a complementary/alternative medicine (CAM) practitioner were for a mental health-related complaint.[20] A large survey by Druss et al indicated that self-reported mental conditions were associated with increased use of CAM treatments.[21] Despite its well-recognized morbidity, mortality, and associated disease burden, MDD is frequently treated with unproven alternative medicines.[22] In a primary care study, the use of herbal products was specifically associated with a depression diagnosis.[23] Although consumers are self-medicating for mild depressive symptoms, those with severe depression or anxiety reportedly use alternative treatments the most often, with 41 percent of severely depressed patients using at least one nonconventional treatment for depression, compared to general CAM use in 28 percent of the overall adult population.[17] According to another U.S. survey, approximately nine percent of those with severe depression specifically used alternative pharmacotherapy as a treatment approach.[22] Similarly, in a study conducted in German pharmacies, patients who purchased SJW reported pronounced and persistent depressive symptoms.[24] Benefit in pediatric patients is also implied.[25] The topic clearly remains an area of interest, as new review articles and meta-analyses describing SJW and/or SAM-e as potential first-line alternatives to conventional antidepressants continue to appear in the literature.[26-32] In addition, there is a multitude of internet websites touting the benefits of both products.

Key Words:
St. John's wort, SJW, hypericum, S-adenosylmethionine, SAM-e, SAM, SAMe, antidepressant, depression, suicidality, suicide, depressive

With the potential for increased popularity of CAM antidepressant products on the horizon, several questions should be foremost in the minds of healthcare professionals prescribing or recommending these products. First, have these products demonstrated reproducible, clinically relevant efficacy, such that they can be viewed as suitable alternatives to conventional antidepressants? Second, what is the evidence for efficacy in individuals with more severe symptoms? Third, should the recommendations in the antidepressant "boxed" warning also apply to these "natural" antidepressants? In other words, should health care providers and families of individuals taking CAM antidepressant products be similarly vigilant for the potential behavioral changes associated with suicidality that may be seen with conventional antidepressants?

For both SJW and SAM-e, a relatively voluminous amount of clinical trial data potentially helps to answer these questions. Since limitations of many early trials for both products are well-documented, a fair amount of skepticism exists as to efficacy.[18,33-36] In brief, major weaknesses included small sample sizes, insufficient study durations, lack of experience among investigators, lack of a placebo-control, lack of a strict definition of MDD, diagnostic heterogeneity of the participants, inclusion of subjects with only mild illness, failure to use standard rating instruments (such as the Hamilton Depression Rating Scale [HAM-D] or Montgomery-Asberg Depression Rating Scale [MADRS]), and questionable analytic approaches (i.e., not limited to "intention to treat"). Publication bias (e.g., the exclusion of less favorable study data from meta-analyses) has also been a common concern, as has been the case for conventional antidepressants.[37]

Figure 1. St. John's Wort

SJW and SAM-e are widely perceived to be exceedingly well-tolerated. Of current relevance, both are considered to be largely devoid of risk for inducing behavioral changes associated with suicidality and described in the antidepressant boxed warning.[26,38] However, case reports of neuropsychiatric adverse events (AEs) associated with these products, including mania, suicidal and/or homicidal thoughts, agitation, psychosis, or acute anxiety, although infrequent, have been reported.[39-43] Such events have also not been limited to psychiatric patients. For example, mania and suicidal ideation were reported in a healthy volunteer shortly after starting SAM-e.[44] Past reviewers of the safety/tolerability of SJW and SAM-e have typically taken a broad-based approach, focusing primarily on only the more commonly occurring AEs, and have not specifically examined whether these products resulted in behavioral changes associated with suicide ascribed to conventional antidepressants.

This systematic review takes an evidenced-based approach to addressing these specific questions regarding SJW and SAM-e. The focus of this effort will be to examine the treatment effect sizes generated from randomized, double-blind, placebo-controlled studies. The following is some brief background information on the two substances.

St. John's Wort

St. John's wort (*Hypericum perforatum*) is a flowering plant that has been used as a medicinal herb for centuries (Figure 1). It is particularly popular in parts of Europe where it has attained regulatory approval for use as an antidepressant – in Germany for example. Despite its widespread use, lingering controversy persists regarding its effectiveness. The most appropriate dosage is not well-characterized, nor is its mechanism of action entirely clear, in part because the question of which of its constituents are responsible for its mood-enhancing effect is still largely unanswered. The plant contains a number of constituents thought to be pharmacologically active, including hypericin and hyperforin.[45] Recent research suggests that Hypericum extract exhibits a "broad spectrum of action," reportedly inhibiting the reuptake of as many as five neurotransmitters (serotonin, dopamine, norepinephrine, L-glutamate, and gamma-aminobutyric acid [GABA]).[46] A new species of Hypericum (*Hypericum enshiense*) identified in China has been reported to also have potential antidepressant activity based on animal behavioral models; however, there are currently no clinical data.[47]

Consistent findings of benefit have generally emerged from meta-analyses of SJW in depression.[27,48-52] However, one relatively recent efficacy meta-analysis of SJW in MDD produced less than convincing results, particularly when the analysis was restricted to "larger, more precise" studies.[53]

Other ongoing concerns with SJW, as well as most herbal products, relate to inconsistent product quality (e.g., poor batch-to-batch reproducibility with respect to the amount of active constituent, and/or the presence of adulterants).[54,55] Despite these issues, as well as a well-established potential for causing clinically relevant drug interactions,[56,57] SJW remains widely and extensively used.

S-Adenosyl Methionine (SAM-e)

SAM-e is a naturally occurring, endogenous substance produced from adenosine triphosphate and the amino acid methionine (Figure 2).[58] It is involved in a broad range of important biochemical pathways, including those affecting the central nervous system (CNS), where it functions as a methyl donor.[59] While its antidepressant mechanism of action is not entirely clear, it is thought that its ability to function as a methyl donor increases brain levels of serotonin, dopamine, and norepinephrine. Serum and cerebrospinal fluid levels of SAM-e are reportedly low in depressed patients[60,61] and increases in serum SAM-e levels have been correlated with improved treatment response.[62] As was the case for SJW, meta-analyses[63,64] and systematic reviews[65-67] of SAM-e studies have consistently concluded that SAM-e is effective for treating depression. However, the rigor and quality of many of the individual studies comprising those reviews is potentially suspect (even more so than the SJW studies). Most studies are quite dated (1970s or 1980s), of short treatment duration, of small sample size (n < 50), and not necessarily restricted to major depression. Like SJW, the most appropriate daily dosage for SAM-e is also not well established. Its oral bioavailability is low, likely due to a significant first-pass effect. For this reason many of the earlier SAM-e studies utilized parenteral formulations (intramuscular or intravenous), which may limit the clinical relevance of those studies. SAM-e is also reportedly unstable at room temperature when exposed to air.[68] Therefore, depending on manufacturing and storage conditions, tablets may contain less than the labeled amount of active constituent.

Surveys have demonstrated that many healthcare professionals, both in the United States and elsewhere,[69] admit to a lack of knowledge regarding dietary supplements, both with respect to the scientific evidence supporting their use as well as the regulations that govern their manufacture, sale, and marketing.[70] Therefore, the goal of this systematic review is to provide prescribers, pharmacists, and other clinician healthcare professionals with a sound understanding of the published findings from randomized, double-blind, placebo-controlled clinical trials of these two popular OTC antidepressant products.

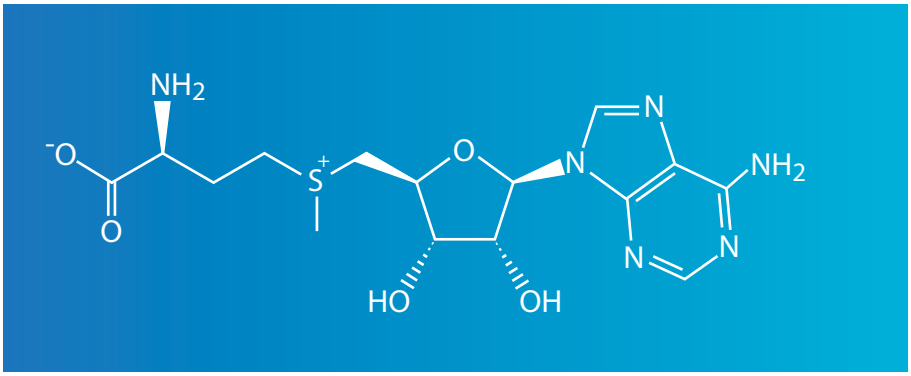
Methods

Overview

The efficacy of conventional antidepressants is typically established via well-powered, randomized, placebo-controlled trials that enroll patients with moderate-to-severe MDD. To assess retrospectively, whether natural antidepressants are suitable alternatives to conventional antidepressants, performance should be evaluated based on clinical studies that utilized similar methodological approaches. In addition, it has become fairly commonplace to also establish the magnitude or size of any observed treatment effect (the effect size) rather than relying only on the presence of a statistically significant difference from placebo.[71] Although somewhat arbitrary, an effect size of 0.2 is typically considered small, 0.5 is considered medium, and 0.8 or greater is considered to be a large effect size.

A computerized search of electronic databases (Medline, PubMed, Cochrane Library, TrialTrove) was performed, using the following text search strategy, to retrieve all English language reports (full manuscript or abstract) of placebo-controlled studies of each compound published between January 1975 and July 2010: St. John's wort, hypericum, hypericin, hyperforin, herbal remedies,

Figure 2. S-Adenosyl Methionine



SAM-e, s-adenosylmethionine, ademetionine, alternative therapy, depression, MDD, and antidepressant.

Reference lists from all articles identified by the electronic searches were also manually reviewed for other relevant papers/studies.

Study Selection

For the efficacy review, the search outputs were scrutinized to identify all SJW or SAM-e studies that met the following criteria:

- Randomized, double-blind, placebo-controlled, parallel group design
- Minimum of 20 subjects per SJW or SAM-e treatment arms
- Limited to patients with MDD defined by DSM and/or ICD as their predominant psychiatric illness
- Use of traditional clinician-rated assessments for rating depression severity (e.g., HAM-D, MADRS)
- Used standard approaches for assessing treatment effect (i.e., change from baseline, or standard response or remission criteria)
- Product tested alone (not a combination treatment) and compared to placebo
- Presented data from an intention-to-treat (ITT) dataset

Studies that enrolled subjects representing all levels of MDD symptom severity were included in the review. If the depression severity level was not stated (i.e., mild, moderate, severe), then depression severity was based on any identified HAM-D (or other suitable scale) cutoff criteria for entry. In the absence of that, the actual mean HAM-D total score at entry was used (e.g., 17-item HAM-D total scores of ≤ 16 were classified as mild, 17-24 as moderate, and > 24 as severe).[72] The studies could involve acute (short-term) or long-term dosing. If long-term, in order to have been included, the study must have utilized a re-randomization relapse-prevention design, as opposed to simply continuing subjects on the same acute study treatment for an extended length of time.

SJW and SAM-e as monotherapies have also been evaluated in placebo-controlled trials in psychiatric disorders other than depression. These studies were not utilized for the systematic review of efficacy in depression; however, they were considered appropriate for the safety-related review. Placebo-controlled studies in disorders other than depression that evaluated SJW or SAM-e as adjunctive treatment or in combination with another alternative product were not included in either the efficacy or safety reviews.

Determination of Effect Size

Studies were categorized as positive or negative based on statistical superiority to placebo at endpoint on one or more prospectively defined, clinician-rated, primary efficacy parameter. Effect size was also calculated if sufficient information was available. In some cases this required visual inspection of a graphical figure to determine an estimate of the mean value(s). The Cohen's *d* approach to calculating effect size was used, where effect size *d* was defined as the difference between the two mean changes from baseline (i.e., SJW or SAM-e change minus the placebo change) divided by the pooled standard deviation for those mean changes.[71] The pooled standard deviation was derived by taking the square root of the mean of the two squared standard deviations at endpoint. If variance was presented as standard errors (SE), the SE was converted to standard deviation to allow for determination of the effect size.

Evaluation of Behavioral-related Safety/Tolerability

The objective of this assessment was to informally assess whether SJW or SAM-e may produce suicidality or other behavioral changes thought to represent potential precursors of suicidality. To accomplish this, each relevant publication was scrutinized for evidence of any of the following behavioral-related AEs (derived from the antidepressant boxed warning language): worsening of depression, suicidal ideation and/or behavior, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or other unusual changes in behavior.

All placebo-controlled SJW and SAM-e monotherapy studies in depressed patients or in patients with other psychiatric illnesses identified by the searches were utilized in this safety review.

Results

SJW Efficacy in MDD

The searches identified 25 English language citations of placebo-controlled studies of SJW in the treatment of adult depression.[73-97] No placebo-controlled studies of SJW in pediatric depression patients were identified. Of these 25 studies, 17 met all or most of the predefined study selection criteria and were included in the efficacy review.[73-89]

Table 1. Randomized, Double-blind, Acute, Placebo-controlled Studies of SJW in the Treatment of Mild-to-Moderate Depression

Study (total n)	Treatment Arms/n	Mean Baseline HAM-D[2] (±SD)	Study Duration	Primary Outcome	Primary Efficacy Results/ p-value (SJW vs Placebo)		Effect Size
					Positive	Negative	
Lecrubier Y, et al (2002) (n=375)	a. SJW 900 mg/day; n=186 b. Placebo; n=189	21.9 (1.7) 21.9 (1.7)	6 weeks	HAM-D Total Change	p=0.03		0.26
Kasper S, et al (2006) (n=332)	a. SJW 600 mg/day; n=123 b. SJW 1200 mg/day; n=127 c. Placebo; n=82	22.8 (3.3) 22.6 (3.8) 23.6 (4.2)	6 weeks	HAM-D Total Change	a. p<0.001 b. p<0.001		0.74 0.62
Uebelhack R, et al (2004) (n=140)	a. SJW 900 mg/day; n=70 b. Placebo; n=70	22.8 (1.1) 22.6 (1.2)	6 weeks	HAM-D Total Change	p<0.001		1.83
Phillip M, et al (1999) (n=263)	a. SJW 1050 mg/day; n=106 b. Imipramine 100 mg/day: n=110 c. Placebo; n=47	22.7 (4.2) 22.2 (4.2) 22.7 (4.0)	6 weeks	HAM-D Total Change	p<0.05		0.44
Kalb R, et al (2001) (n=72)	a. SJW 900 mg/day; n=37 b. Placebo; n=35	19.7 (3.4) 20.1 (2.6)	6 weeks	HAM-D Total Change	p<0.001		0.83
Fava M, et al. 2005 (n=135)	a. SJW 900 mg/day; n=45 b. Fluoxetine 20 mg/day; n=47 c. Placebo; n=43	19.6 (3.5) 19.6 (3.1) 19.9 (2.9)	12 weeks	HAM-D Total Change		[3]p=0.096	0.31
Bjerkenstedt L, et al (2005) (n=163)	a. SJW 900 mg/day; n=54 b. Fluoxetine 20 mg/day; n=54 c. Placebo; n=55	24.9* (4.8) 23.8* (3.6) 25.2* (2.9)	4 weeks	HAM-D Total Change		[3]p=0.90	0.03
Gastpar M, et al (2006) (n=388)	a. SJW 900 mg/day; n=131 b. Citalopram 20 mg/day; n=127 c. Placebo; n=130	21.9 (1.2) 21.8 (1.2) 22.0 (1.2)	6 weeks	HAM-D Total Change	p<0.0001		0.40
Schrader E, et al (1998) (n=159)	a. SJW 500 mg/day; n=80 b. Placebo; n=79	16-24* (NAV) 16-24* (NAV)	6 weeks	HAM-D Total Change	p< 0.001		NAV
Montgomery SA, et al (2000) (n=248)	a. SJW 900 mg/day; n=124 b. Placebo; n=124	NAV NAV	12 weeks	HAM-D Responder rate		p value not reported	NAV
Laakman G, et al (1998) (n=147)	a. SJW 900 mg/d (0.5%): n=49 b. SJW 900 mg/d (5.0%): n=49 c. Placebo; n=49	20.3 (2.7) 20.9 (3.1) 21.2 (3.3)	6 weeks	HAM-D Total Change	a. p = NS b. p=0.004		0.11 0.49
Moreno RA, et al (2006) (n=66)	a. SJW 900 mg/day; n=20 b. Fluoxetine 20 mg/day; n=20 c. Placebo; n=26	~15* (NAV) ~15* (NAV) ~16* (NAV)	8 weeks	HAM-D Response and remission rates		[+]p<0.05	NAV
Volz HP, et al (2000) (n=140)	a. SJW (NAV); n=NAV b. Placebo; n=NAV	21.0* (2.0) 20.7* (1.9)	6 weeks	HAM-D Total Change	p=0.0046		0.47
Mannel M, et al (2010) (n=200)	a. SJW 600 mg/day; n=100 b. Placebo; n=100	12.4 (4.4) 12.0 (3.8)	8 weeks	HAM-D Total Change	p<0.05		0.35

[1]St. John's wort dose strength given as mg hypericum; [2] Based on the 17-item HAM-D unless otherwise specified; [3]Technically a failed trial, as the active comparator was not superior to placebo; *Based on the 21-item HAM-D; NAV = data not available or could not be calculated; +In favor of placebo vs SJW for both response and remission

Of the remaining eight studies, three were excluded from consideration regarding efficacy because the publication did not include an ITT analysis,[90-92] two were excluded because the studies did not enroll subjects specifically with major depressive disorder,[93,94] two were excluded because each evaluated a combination product (SJW plus other herbal products),[95, 96] and one was excluded because it was a long-term extension study that did not involve re-randomization of subjects in the relapse-prevention phase.[97] Of the 17 studies selected for efficacy assessment, 16 were short-term (ranging from 4-12 weeks) and one was long-term (six-week, single-blind phase followed by a 26-week relapse-prevention phase).[89] Of the 16 short-term studies, 14 included subjects with mild-to-moderate depression (Table 1), and two included subjects with moderate-to-severe depression (Table 2). The lone long-term study enrolled subjects with moderate depressive symptoms (Table 3). Six of the 17 identified studies included an active comparator treatment arm (fluoxetine, citalopram, sertraline, or imipramine); 13 of the 17 studies, including the one long-term study, were conducted in Europe. The two studies in more severely depressed patients were conducted in the United States.

Ten of the 17 relevant studies (59%) produced results significantly favoring SJW over placebo on the prospectively defined primary efficacy endpoint; therefore, they were deemed positive. All 10 positive studies were in patients with mild-to-moderate depression. Of the seven negative studies, five were in mild or moderately depressed patients and two were in more severely depressed subjects. Three of these studies are better described as "failed," including one of the two studies with subjects with severe symptoms. This is because they included an active treatment arm that also did not separate from placebo, raising questions about the assay sensitivity of those trials.

The effect size in the 10 positive studies ranged from 0.26-1.83 (mean 0.64; median 0.48). Per clinical convention, mean values in the 0.6-0.7 range reflect a moderately large effect size. Excluding the two outlier studies (the highest and lowest effect sizes from the group of 10 positive studies) reduces the mean effect size only slightly (to 0.54), a figure that is still consistent with a moderate-to-moderately large effect size. Both SJW studies in subjects with moderate-to-severe depression were negative. One of those two studies included a sertraline arm that also did not separate from placebo on the primary endpoint.[87] In the one long-term efficacy study, while SJW produced a longer time to relapse and a lower relapse rate than placebo, the differences from placebo failed to achieve statistical significance.[89]

In only one of the six selected SJW studies that included an active comparator arm was the active comparator statistically superior to placebo on the primary endpoint (Table 1, Gastpar et al). In that study, SJW was also superior to placebo, with efficacy essentially equivalent to citalopram. In two of the other five active-controlled studies, SJW was statistically superior to fluoxetine (but not placebo)

Table 2. Randomized, Double-blind, Acute, Placebo-controlled Studies of SJW in the Treatment of Moderate-to-Severe Depression

Study (total n)	Treatment Arms/n	Mean Baseline HAM-D[2] (±SD)	Study Duration	Primary Outcome	Primary Efficacy Results/ p-value (SJW vs Placebo)		Effect Size
					Positive	Negative	
Shelton RC, et al (2001) n=200	a. SJW 900-1200 mg/day; n=98 b. Placebo; n=102	~22 (NAV) ~23 (NAV)	8 weeks	HAM-D Total Change		p=0.58	-0.05
Hypericum Depression Trial Study Group (2002) n=340	a. SJW 900-1500 mg/day; n=113 b. Sertraline 50-100mg/day; n=111 c. Placebo; n=116	23.1 (2.7) 22.7 (2.7) 22.5 (2.5)	8 weeks	HAM-D Total Change		[3]p=0.59	-0.08

[1]St. John's wort dose strength given as mg hypericum; [2] Based on the 17-item HAM-D unless otherwise specified; [3]Technically a failed trial, as the active comparator was not superior to placebo; NAV = data not available or could not be calculated

in one (Table 1, Fava et al) and was statistically superior to placebo in the other (Table 1, Philipp et al). In another study, fluoxetine was not statistically superior to placebo but was superior to SJW (Table 1, Moreno et al). Despite failing to achieve statistical superiority versus placebo in the "failed" study in moderate-to-severe depression, sertraline was numerically superior to both placebo and SJW on all endpoints (Table 2, Hypericum Depression Trial Study Group).[87]

as serious adverse events (denoted as "partial" AE reporting for this review) , or (3) no specific AE information was included in the paper. In this latter case, either no AE information was included or only general, nonspecific AE incidence by body system class was included. For example, overall incidence of psychiatric-related AEs was provided, but not the incidence of any specific psychiatric symptom (denoted as AEs "not available" for this review).

Table 3. Randomized, Double-blind, Placebo-controlled Study of SJW in the Long-term Treatment of Major Depression Disorder

Study (total n)	Treatment Arms/n	Mean Baseline HAM-D[2] (±SD)	Study Duration	Primary Outcome	Primary Efficacy Results/ p-value (SJW vs Placebo)		Effect Size
					Positive	Negative	
Kasper S, et al (2008) n=570	a. SJW 900 mg/day; n=376 b. Placebo; n=194	23.8 (2.8)	32 weeks	Time to relapse		[3]P=0.034	NAV

[1]St. John's wort dose strength given as mg hypericum; [2] Based on the 17-item HAM-D unless otherwise specified; [3]Technically a negative trial, as the primary endpoint was analyzed by means of a log-rank test using a one-side type 1 error of alpha=0.025; NAV = data not available or could not be calculated

SJW Behavioral-related Adverse Effects

The results of the behavioral adverse event review for the SJW studies are summarized in Tables 4 and 5. A total of 32 study publications were identified and reviewed for this purpose, derived from the 23 placebo-controlled monotherapy SJW depression studies identified by the searches plus an additional nine placebo-controlled monotherapy studies on other psychiatric conditions: social anxiety disorder (1),[98] obsessive compulsive disorder(1),[99] somatoform disorders (2),[100,101] climacteric symptoms (1),[102] premenstrual syndrome/symptoms (2),[103,104] irritable bowel syndrome (1),[105] and smoking cessation (1).[106]

The publications relating to all 32 studies were scrutinized for reports of the AEs of interest (i.e., suicidality-related or other behavioral-related events, per the list above). In most instances, minimal information on AEs was included in the publication. Authors generally took one of three approaches in describing the specific AEs that occurred: (1) all reported AEs were included in the paper (denoted as "complete" reporting for this review), (2) only the incidence of selected specific AEs were included in the manuscript, typically the most common or those of particular interest, such

Nine of the 32 SJW publications (28%) that were reviewed provided complete AE information, 13 manuscripts (41%) included partial AE information, and in the case of 10 (31%) the AE information was not available. Overall, few behavioral-related AEs were reported in the 22 studies that provided specific AE information. There were no events of suicidal behavior or ideation reported, except for one subject who had received placebo. Table 4 presents the behavioral AEs from the 17 studies comprising the efficacy review, while Table 5 presents the behavioral AEs from the other SJW placebo-controlled studies identified by the search strategy. Four reports of worsening depression (described as symptom aggravation, depression aggravation, or acute deterioration of mental state) and one report of acute stress/anxiety occurred in depressed patients who received SJW. There were no similar reports for placebo. In the OCD study (Kobak et al, 2005), the incidence of agitation in the SJW-treated subjects was reported to be significantly greater than for the placebo group (p=0.03).

Table 4. Specific Behavioral-related Adverse Events in Placebo-controlled Trials of SJW in Major Depressive Disorder (17 Trials Meeting Criteria for the Efficacy Review)

Study	Approach to Including Specific AEs ("Complete"/"Partial"/or "Not Available")	St. John's Wort n/N (%)	Placebo n/N (%)
Lecrubier et al (2002)	Partial (AEs occurring in at least 3 patients in either group)	Insomnia 3/186 (1.6%) 2 patients (1.1%) withdrawn due to "symptom aggravation"	Insomnia 2/189 (1.1%)
Kasper et al (2006)	Partial (AE incidence provided by body system class only, along with any serious AEs)	Psychiatric AEs 4/250 (1.6%); 1 patient with SAE of "depression aggravation"; 1 patient with SAE of "acute stress disorder"	Psychiatric AEs 0/82 (0.0%)
Uebelhack et al (2004)	Partial ("Most common" [not defined] AEs reported)	No behavioral AEs mentioned	No behavioral AEs mentioned
Phillip et al (1999)	Partial (AEs with >3% incidence and of possible relationship to study drug in either group)	No behavioral AEs mentioned	1 subject with suicide attempt
Kalb et al (2001)	Complete	No behavioral AEs mentioned	No behavioral AEs mentioned
Fava et al (2005)	Partial (AEs with > 10% incidence in either arm)	Insomnia 7/45 (16%) 1 SAE of heroin overdose	Insomnia 6/43 (14%)
Bjerkenstedt et al (2005)	Not Available (AE incidence by body system class only)	Psychiatric AEs 2/57 (3.5%)	Psychiatric AEs 3/57 (5.3%)
Gastpar et al (2006)	Partial (AE incidence provided by body system class only, along with any serious AEs)	No behavioral AEs mentioned	1 SAE of anxiety disorder
Schrader et al (1998)	Complete	1 case of "acute deterioration of mental state"	No behavioral AEs mentioned
Montgomery et al (2000)	Not Available (abstract format only, no AE results)	Data not provided/not available	Data not provided/not available
Laakman et al (1998)	Partial (AEs occurring in more than one subject)	No behavioral AEs mentioned	No behavioral AEs mentioned
Moreno et al (2005)	Not Available	Data not provided/not available	Data not provided/not available
Volz et al (2000)	Not Available (abstract format only, no AE results)	Data not provided/not available	Data not provided/not available
Hypericum Dep. Study Group (2002)	Partial (AEs with significantly difference incidence by treatment)	No behavioral AEs mentioned	No behavioral AEs mentioned
Shelton et al (2001)	Partial (AEs with > 10% incidence in either arm)	No behavioral AEs mentioned	No behavioral AEs mentioned
Kasper et al (2008)	Partial (Most common AEs presented)	No behavioral AEs mentioned	No behavioral AEs mentioned
Mannel et al (2010)	Not Available (AE incidence by body system class only)	No behavioral AEs mentioned	No behavioral AEs mentioned

Table 5. Specific Behavioral-related Adverse Events in Placebo-controlled Trials of SJW in Depression (trials not meeting efficacy review criteria) or in other Psychiatric Disorders (n=15 studies)

Study	Approach to Including Specific AEs ("Complete"/"Partial"/or "Not Available")	St. John's Wort n/N (%)	Placebo n/N (%)
Sommer, et al (1994)	Complete	No behavioral AEs mentioned	1 case "psychological vulnerability"
Hübner, et al (1994)	Complete	No behavioral AEs mentioned	No behavioral AEs mentioned
Hänsgen, et al (1994)	Complete	1 case "sleep disturbance"	No behavioral AEs mentioned
Randlov, et al (2006)	Partial (Most common AEs presented)	No behavioral AEs mentioned	No behavioral AEs mentioned
Winkel, et al (2000)	Not Available (Abstract format only, no AE results)	Data not provided/not available	Data not provided/not available
Kasper, et al (2007)	Not Available (only overall AE rate provided by group)	Data not provided/not available	Data not provided/not available
Kobak, et al (2005) (SAD)	Partial (Most common AEs presented)	No behavioral AEs mentioned (other than that similar rates of insomnia were reported for SJW and placebo)	No behavioral AEs mentioned
Kobak, et al (2005) (OCD)	Partial (Most common AEs presented)	Agitation 4/28 (14.3%; p=0.03 vs placebo) Sleep disturbance 3/28 (10.7%)	Agitation 0/30 (0.0%) Sleep disturbance 0/30 (0.0%)
Müller, et al (2004)	Not Available (AE incidence by body system class only)	Psychiatric AEs (not otherwise specified) 4/87 (4.6%)	Psychiatric body system AEs 0/88 (0.0%)
Volz, et al (2002)	Complete	No behavioral AEs mentioned	No behavioral AEs mentioned
Al-Akoum et al (2009)	Complete	No behavioral AEs mentioned	No behavioral AEs mentioned
Ryoo JG, et al (2010)	Not Available (Abstract format only, no AE results)	Data not provided/not available	Data not provided/not available
Hicks, et al (2004)	Complete	No behavioral AEs mentioned	No behavioral AEs mentioned
Saito YA, et al (2009)	Partial	No behavioral AEs mentioned	No behavioral AEs mentioned
Parsons A, et al (2009)	Complete	Insomnia (31.3%) Irritation (50.0%) Mood changes (56.3%)	Insomnia (38.7%) Irritation (46.8%) Mood changes (59.7%)

SAM-e Efficacy

Fourteen English language citations of placebo-controlled studies of SAM-e monotherapy for the treatment of depressive symptoms were identified.[107-120] Study quality was a common issue; no study met all of the study selection criteria outlined, with most being deficient in regards to more than one selection criterion. Nevertheless, because these studies represent the only placebo-controlled data identified by the searches, they were utilized for this efficacy examination.

Nine of 14 identified studies included subjects with mild-to-moderate depressive symptoms (Table 6) and five included subjects with moderate-to-severe symptoms (Table 7). Only six of the 14

Table 6. Randomized, Double-blind, Placebo-controlled Studies of SAM-e in the Treatment of Mild-to-Moderate Depression

Study (total n)	Treatment Arms/n	Mean Baseline HAM-D[2] (±SD)	Study Duration	Primary Outcome	Primary Efficacy Results/ p-value (SAM-e vs Placebo)		Effect Size
					Positive	Negative	
Agnoli A, et al (1976) n=30	a. SAM-e 15 mg IM TID; n=20 b. Placebo; n=10	21.6 (1.26 SE) 19.1 (2.42 SE)	15 days	HAM-D Total Change	p<0.05		1.6
Fava M, et al (1992) n=39	a. SAM-e 1600 mg/day PO; n=17 b. Placebo; n=21	27.2** (4.8) 24.6** (4.3)	6 weeks	HAM-D Total Change		p= NS	0.16
Thomas CS, et al (1987) n=20	a. SAM-e 200 mg/day IV bolus; n=9 b. Placebo; n=11	26.6* (4.2) 25.2* (4.6)	2 weeks	HAM-D Total Change		p= NS	0.12
Salmaggi P, et al (1993) n=80	a. SAM-e 1600 mg/day PO; n=40 b. Placebo; n=40	24.4* (3.0) 23.5* (3.0)	30 days	HAM-D Total Change	p<0.01		0.33
De Leo D (1987) n=40	a. SAM-e 200 mg IM QD; n=20 b. Placebo; n=20	NAV NAV	4 weeks	Zung Self-Rating Depression Scale	p<0.05		0.61
Ancarani E, et al (1993) n=51	a. SAM-e 400 mg/QOD IV; n=41 b. Placebo; n=10	25.73* (8.58) 20.66* (8.60)	3 weeks	IPAT-DS[2] Change	p value for comparison between groups not provided		NAV
Cerutti R, et al (1993) N=60	a. SAM-e 1600 mg/day PO; n=30 b. Placebo; n=30	NAV NAV	30 days	Kellner Symptom Questionnaire	p value for comparison between groups not provided		NAV
Janicak PG, et al (1989) n=15	a. SAM-e 400 mg/day IV; n=7 b. Imipramine 150 mg/day IV: n=3 c. Placebo; n=5	33.6** (9.0) 33.3** (6.9) 32.9** (5.9)	15 days	HAM-D Total Change	p<0.02		1.46
Carrieri PB, et al. (1990) n=21	2 period crossover design: a. SAM-e 1000 mg/day → PBO; n=11 b. PBO→ SAMe 1000 mg/day; n=10	~26* (NAV) ~24* (NAV)	15 days (per x-over arm)	HAM-D Total Change	p<0.05		NAV

[1]Based on the 17-item HAM-D unless otherwise specified; [2]IPAT-DS=Institute for Personality and Ability Testing – Depression Scale; *Based on the 21-item HAM-D; **Based on the 24-item HAM-D; NAV = data not available or could not be calculated

studies were restricted to subjects with MDD (three in mild-moderate MDD, three in moderate-severe MDD). All 14 studies enrolled only adults; no placebo-controlled studies of SAM-e in pediatric patients with depression were identified. Only one study included an active comparator arm (imipramine).[114] Eleven of the 14 studies were conducted in Europe and three were conducted in the United States. All 14 studies were short-term, ranging from 2-6 weeks. No placebo-controlled studies were identified that assessed the long-term antidepressant efficacy of SAM-e.

Five of the nine studies in mild-to-moderate depressives were "positive", i.e., they reported statistically significant results favoring SAM-e on the prospectively defined primary endpoint. Two other studies in mild-to-moderate depression also produced numerically favorable results for SAM-e; however, a statistical comparison between groups was not provided. The mean treatment effect size in the positive studies was 1.0 (range 0.33-1.6), by convention a large effect size.

Table 7. Randomized, Double-blind, Placebo-controlled Studies of SAM-e in the Treatment of Moderate-to-Severe Depression

Study (total n)	Treatment Arms/n	Mean Baseline HAM-D[2] (±SD)	Study Duration	Primary Outcome	Primary Efficacy Results/ p-value (SAM-e vs Placebo)		Effect Size
					Positive	Negative	
Kagan BL, et al (1990) n=15	a. SAM-e 1600 mg/day PO; n=9 b. Placebo; n=6	26.6* (5.5) 31.0* (8.5)	3 weeks	HAM-D Total Change	p<0.05		0.79
Caruso I, et al (1987) n=60	a. SAM-e 200 mg IM QD; n=30 b. Placebo; n=30	45.1*** (6.7) 42.4*** (5.1)	3 weeks	HAM-D Total Change	p<0.01		1.4
Delle Chiaie R, et al (1997) n=75	a. SAM-e 800 mg/day IV; n=40 b. Placebo; n=35	29.9 (4.0) 30.0 (3.2)	3 weeks	HAM-D Total Change	p=0.05		0.43
Muscettola G, et al (1982) n=20	a. SAM-e 150 mg IM QD; n=10 b. Placebo; n=10	23.2**** (NAV) 22.2****(NAV)	15 days	HAM-D Total Change	p<0.05		NAV
Carney MWP, et al (1986) n=32	a. SAM-e 200 mg/day IV; n=16 b. Placebo; n=16	26.5* (5.3) 25.5* ($.7)	2 weeks	HAM-D Total Change		p=tNS	0.36

[1]Based on the 17-item HAM-D unless otherwise specified; *Based on the 21-item HAM-D; **Based on the 24-item HAM-D; ***Based on the 28-item HAM-D; ****Based on the 14-item HAM-D; NAV = data not available or could not be calculated

Four of the five SAM-e studies in subjects with more severe symptoms were also positive. The mean effect size for these studies was 0.87 (median 0.79), again consistent with a large effect size. In the study with an active comparator, SAM-e produced a reduction in HAM-D score that was essentially equivalent to the reduction produced by imipramine. As previously noted, all SAM-e studies identified were methodologically flawed to some extent. These shortcomings are briefly summarized in Table 8.

SAM-e Behavioral-related Adverse Effects

In addition to the 14 placebo-controlled studies in patients with depressive symptoms, three placebo-controlled studies in fibromyalgia were identified.[121-123] All 17 publications were scrutinized for reports of AEs of interest (i.e., suicidality or other behavioral-related events). The results are summarized in Table 9. Again, as was the case with most SJW studies, generally very little specific AE information was included. Using the previously described approaches for including AE findings, five of 17 studies included complete AE reporting, five included partial AE information, and seven did not provide any specific AE information. Only a few instances of specific behavioral-related AEs were mentioned, with no evidence for the occurrence of treatment-emergent suicidality detected. Four study publications mentioned AEs of mania/hypomania or psychomotor excitation following SAM-e administration (no similar AEs were reported for placebo in those studies). In two studies, a greater incidence of anxiety-related AEs was reported for SAM-e than for placebo.

Discussion

Given current concerns surrounding conventional antidepressant therapy and suicidality, which led to the boxed warning in labeling, it is conceivable that use of "natural" antidepressant therapies will rise. Recently available data suggesting that some antidepressants may be associated with teratogenicity may also increase the use of CAM treatments for treating perinatal depression, despite the fact that no systematic information exists regarding the safety of Hypericum or SAM-e use during pregnancy.[124-126] The objective of this

systematic review was to determine whether the scientific evidence regarding antidepressant efficacy actually justifies wider use.

Numerous clinical studies, reviews, and meta-analyses have examined the antidepressant efficacy of SJW and SAM-e. Most authors have concluded that both products appear to be superior to placebo, generally as effective as conventional antidepressants, and better tolerated than their conventional counterparts, leading many to conclude that both products are viable alternative options for the treatment of depressive patients.[48,49,53,63,127-130] For many clinicians, however, the jury is still out regarding the effectiveness of these two therapies, particularly for moderate-to-severe depressive illness. Meta-analyses can be subject to over-interpretation and, therefore, should not necessarily be considered definitive, given the varying designs, sample sizes, power, entrance/diagnostic criteria, and depression assessment approaches utilized in

Table 8. Design/Analysis Limitations of Placebo-controlled Trials of SAM-e in Depression

Study	Limitations
Agnoli et al (1976)	Diagnostic heterogeneity, not restricted to MDD (analysis pools responses of endogenous, reactive and neurotic depression)
Fava et al (1992)	Small sample size (< 20 per SAM-e treatment arm)
Thomas et al (1987)	Small sample size (< 20 per SAM-e treatment arm)
Salmaggi et al (1993)	Diagnostic heterogeneity, not restricted to MDD (analysis combines patients with MDD with patients with dysthymia); does not present an ITT analysis
De Leo (1987)	Diagnostic heterogeneity, not restricted to MDD (analysis combines patients with MDD with patients with dysthymia); does not present an ITT analysis; primary endpoint was a self-rating scale rather than clinician-rated
Ancarani et al (1993)	Does not present an ITT analysis, primary endpoint (IPAT-DS) not a standard instrument
Cerutti et al (1993)	Primary endpoint (Kellner self-rated SQ) not a standard clinician rated approach; nonstandard patient population (postpartum depression) not restricted to MDD
Janicak et al (1989)	Does not present an ITT analysis; small sample size (< 20 per SAM-e treatment arm); not restricted to MDD
Carrieri et al (1990)	Does not present an ITT analysis; not a parallel group design; small sample size, not restricted to MDD
Kagan et al (1990)	Does not present an ITT analysis; small sample size (< 20 per SAM-e treatment arm)
Caruso et al (1987)	Does not present an ITT analysis; nonstandard patient population (depression secondary to rheumatoid arthritis)
Delle Chiaie et al (1997)	Does not present an ITT analysis
Muscettola et al (1982)	Diagnostic heterogeneity, not restricted to MDD (analysis combines patients with unipolar depression with patients with bipolar depression); does not present an ITT analysis; small sample size (<20 per SAM-e treatment arm)
Carney et al (1986)	Diagnostic heterogeneity, not restricted to MDD (analysis pools responses of endogenous and reactive depression); does not present an ITT analysis; an interim report with small sample size (< 20 per SAM-e treatment arm)

Table 9. Behavioral-related Adverse Events in All Placebo-controlled Trials of SAM-e (Depressive Disorders and Fibromyalgia)

Study	Approach to Including Specific AEs ("Complete"/"Partial"/or "Not Available")	SAM-e n/N (%)	Placebo n/N (%)
Agnoli A, et al (1976)	Not Available	Data not provided/not available	Data not provided/not available
Fava M, et al (1992)	Not Available	Data not provided/not available	Data not provided/not available
Thomas CS, et al (1987)	Not Available	Data not provided/not available	Data not provided/not available
Salmaggi P, et al (1993)	Not Available	Data not provided/not available	Data not provided/not available
De Leo D (1987)	Complete	Anxiety 5/20 (25%)	No behavioral AEs mentioned
Ancarani E, et al (1993)	Complete	Psychomotor excitation 6/41 (14.6%) Sleeplessness 5/41 (12.2%)	No behavioral AEs mentioned
Cerutti R, et al (1993)	Not Available	Data not provided/not available	Data not provided/not available
Janicak PG, et al (1989)	Partial: AEs leading to withdrawal discussed	1 case psychotic decompensaton leading to withdrawal	No behavioral AEs mentioned
Carrieri PB, et al (1990)	Complete	Elation/hypomanic switch 3/21 (14.3%) Insomnia 1/21 4.8%)	No behavioral AEs mentioned
Kagan BL, et al (1990)	Partial	1/9 (11%) with hyperkinetic, manic symptoms with insomnia	No behavioral AEs mentioned
Caruso I, et al (1987)	Complete	No behavioral AEs mentioned	No behavioral AEs mentioned
Delle Chiaie R, et al (1997)	Not Available (abstract format, no AE results)	Data not provided/not available	Data not provided/not available
Muscettola G, et al (1982)	Complete	1/10 (10%) with AEs of anxiety, insomnia and hostility	No behavioral AEs mentioned
Carney MWP, et al (1986)	Partial	"hypomanic/manic reactions in a small number of patients. . .a few others displayed severe anxiety" (N's not provided)	No behavioral AEs mentioned
Volkmann H, et al (1997)	Partial: AEs leading to withdrawal discussed	No behavioral AEs mentioned	No behavioral AEs mentioned
Tavoni A, et al (1987)	Not Available	Data not provided/not available	Data not provided/not available
Jacobson S, et al (1991)	Partial: Discussion of AEs by body system class	No behavioral AEs mentioned	No behavioral AEs mentioned

the component studies. This review attempted to focus on data from individual randomized, double-blind, placebo-controlled, sufficiently-sized studies, with an emphasis on treatment effect sizes to provide further perspective regarding the clinical relevance of the findings.

SJW demonstrated antidepressant efficacy in 10 of 14 studies (71%) of mild-to-moderate MDD. The primary measure of efficacy in each positive study was change in HAM-D total score. Despite its known flaws, the HAM-D is still considered a clinically relevant tool for assessing antidepressant

efficacy. The mean and median effect sizes for HAM-D change in these studies (0.64 and 0.48, respectively) were indicative of moderately large treatment effects, further supporting the relevance of these findings.

In patients with more severe illness the results were not so favorable. Neither study in moderate-to-severe depression differentiated SJW from placebo, tempering the generally positive findings observed in the studies of mild-to-moderate depression. It had been anticipated that the two large, rigorously conducted U.S. studies in more severely ill patients would help resolve the lingering questions regarding the efficacy of SJW, but the negative findings probably raised more questions than answers. Following release of these findings, much speculation ensued regarding what factors might have contributed to the poor results (e.g., low assay sensitivity, study design issues, treatment resistant populations, or sponsor bias).[54] The general lack of any clear trends for SJW efficacy in both studies suggests that it simply is not effective in more severely depressed patients. The lone long-term SJW relapse-prevention study also did not produce a statistically significant difference between SJW and placebo on the primary endpoint. Therefore, while SJW appears to be a suitable alternative to conventional antidepressants for short term use in mild-to-moderate depression, there are currently no data from placebo-controlled studies demonstrating acute efficacy in more severe depression or convincing data to demonstrate the long-term maintenance of its antidepressant effects.

The SAM-e efficacy findings, while very intriguing, are more difficult to interpret. On the one hand, the majority of studies reported positive results, including in subjects with more severe symptoms, and produced impressive effect sizes. On the other hand, all studies exhibited methodological flaws – some extensive. The lack of rigor was evidenced by poorly-defined diagnostic approaches, inadequate sample sizes, and questionable approaches to identifying primary datasets. Many studies included data from "completer" datasets only. Thus, patients dropping out for any reason (e.g., lack of efficacy, poor tolerability) were excluded from the efficacy analyses. Studies exhibiting such deficiencies often produce exaggerated or inflated treatment effects, which can be further magnified by the very small sample sizes to begin with. Therefore, these data must be interpreted with caution. In addition, there are no long-term studies that adequately assess the maintained treatment effect for SAM-e in any depressed population. Although a U.S. Department of Health and Human Services report concluded that "SAMe is more effective than placebo for relief of symptoms of depression…and was equivalent to standard therapy for depression,"[64] until further data are generated from more rigorously controlled and analyzed studies, it would seem premature to conclude it is a suitable alternative to conventional antidepressant therapy. This is particularly true for more severe illness. The authors of that commissioned report acknowledged the need for caution in interpreting their findings, noting that possible publication bias was identified that might "temper the strength of the conclusions we report."[64]

Scant clinical data exist for either SJW or SAM-e in children and adolescents. Placebo-controlled studies utilizing either product in depressed pediatric patients appear to be nonexistent. For SJW, open-label data[131,132] and "post-marketing" surveillance data[133] in depressed pediatric patients exist. For SAM-e, only a case series summarizing experience in three depressed pediatric patients was identified.[134] Despite the paucity of data supporting their use in children and adolescents, both products are widely utilized in these populations, particularly SJW. In Germany, SJW is labeled for adolescent use and is the most commonly used antidepressant in that population.[135] Advocates for the pediatric use of these products point to their long-standing use in folk remedies as evidence of their overall safety and tolerability. In their view, natural antidepressants should be preferred to synthetic antidepressants in pediatric patients due to a gentler side effect profile.[25,136] The open-label study of SJW in juvenile depression reported by Findling found that approximately 75 percent of participants responded favorably.[131] A similar response rate was seen in the open-label SJW study in adolescent depression reported by Simeon.[132] While these preliminary findings suggest that SJW may be an appropriate treatment for depressed pediatric patients, more rigorously conducted research, including placebo-controlled studies, clearly are needed before SJW can be routinely recommended for this population.

The literature contains numerous double-blind studies comparing SJW to a conventional antidepressant, but without utilizing a placebo control. The majority of these studies concluded that SJW was as at least as effective as the conventional product, following short-term (e.g., Szegedi[137]) or

long-term (e.g., Anghelescu[138]) use. Other like-designed studies have reached similar conclusions regarding SAM-e (e.g., Pancheri[139]). Without a placebo control, however, such trials arguably lack scientific validity. Consequently, it is difficult to interpret how either product realistically compares to conventional agents.

The four placebo- *and* active-controlled SJW studies examined in this review that demonstrate assay sensitivity are not overly informative, although they do generally suggest that SJW is as efficacious in treating mild-to-moderate MDD as conventional antidepressants. More specifically, SJW was essentially equivalent to citalopram in one study (Gastpar et al, 2006; Table 1), numerically or statistically superior to fluoxetine in two studies (Fava et al, 2005; Philipp et al, 1999; Table 1), and not as effective as fluoxetine in the fourth study (Moreno et al, 2005; Table 1). In a U.S. study in patients with more severe depression, which included an active comparator, neither sertraline nor SJW was statistically superior to placebo; however, sertraline was numerically superior to SJW on all primary and secondary efficacy endpoints. In the only placebo-controlled SAM-e study that included an active comparator, both SAM-e and imipramine were superior to placebo, producing similar reductions in depressive symptoms. Therefore, while placebo-controlled evidence exists supporting the claims that SJW and SAM-e are as effective as conventional antidepressants, it is limited to a handful of studies in patients with only mild-to-moderate depression.

With respect to efficacy, this review examined whether SJW and SAM-e provide clinically relevant benefit when utilized as antidepressant monotherapy. Whether either product is potentially useful in an augmentation or combination approach along with a conventional antidepressant was not addressed. Sarris et al, in their review, report that either product, when used in combination with conventional antidepressants, has the potential to enhance response or limit side effects (by allowing lower doses of the conventional antidepressant to be prescribed).[140] Results from a recent randomized, placebo-controlled study support the notion that SAM-e can be an effective, well-tolerated adjunctive treatment in depressed patients who have not responded to SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) therapy.[141] In that study, non-responding depressed patients taking an SSRI or SNRI who were treated with adjunctive SAM-e achieved two- to three-fold greater response and remission rates than nonresponding depressed patients taking an SSRI or SNRI who were treated with adjunctive placebo. While this finding needs to be replicated, it suggests the greatest promise for a product like SAM-e may lie with adjunctive use rather than as monotherapy treatment. The adjunctive treatment approach using SJW is potentially problematic given its propensity for causing pharmacokinetic drug interactions.

Natural antidepressants are widely perceived to exhibit more favorable side effect profiles than conventional antidepressants,[18,25,26,38,142] and the publications examined for this review tend to support this view. However, claims[143] that these alternative products are completely benign and devoid of side effects are not supportable. The activity of these products is rooted in the same pharmacological principles underlying the activity of conventional antidepressants. SJW is thought to exert its mood-enhancing effects as a result of "broad spectrum" reuptake inhibition of as many as five neurotransmitters.[46] SAM-e is likewise believed to act ultimately via some of these same neurotransmitters. Therefore, it would seem logical that their AE profiles at higher doses, particularly for SJW, might resemble those of more conventional pharmacotherapies, such as the SSRIs, as some have reported.[144] Generally speaking, the more nonspecific the pharmacological activity of an antidepressant, the more diverse its AE profile is likely to be. For example, tricyclic antidepressants fell out of favor because they exhibited less favorable safety and tolerability than newer, more selective agents (such as the SSRIs). The studies examined in this review do suggest that increased anxiety, agitation, and (in rare instances) mania may be associated with either product, as is the case with conventional antidepressants. Expectation bias of study subjects may also contribute to the low incidence of side effects reported with these products. Freeman et al[145] demonstrated that the discontinuation rate due to adverse events in subjects receiving placebo is generally lower in studies in which a CAM treatment is compared to placebo, compared to studies in which a conventional antidepressant is compared to placebo. A quick review of the available AE data from studies examined for this review show a similar pattern (data not shown). There was generally insufficient information included within the publications examined to allow for a thorough assessment of the risk for treatment-emergent suicidality to occur with these products. Whether this was because events did not occur that were

suggestive of emergent suicidality, or because such events, if they occurred, were simply considered a symptom of the underlying disorder rather than an AE, is not clear. The latter scenario is conceivable, given that the majority of these studies were conducted well before the issue of treatment-emergent suicidality became widely recognized. Of potential relevance to this issue, Gryzlak recently reported that 13 percent of adverse events associated with SJW reported to poison control centers were suspected suicidal cases, further noting that this raises the possibility that SJW, similar to conventional antidepressants, could worsen depression or increase the risk for suicidality.[146]

When weighing the specific findings presented here, or those related to other alternative pharmacotherapies, there are other issues that clinicians should consider. Key among them is that the regulations that govern the manufacture and sale of dietary supplement products are less restrictive than those overseeing the manufacture and sale of conventional antidepressants.[147] It was only relatively recently (June 2007) that legislation was enacted that requires dietary supplement manufacturers to verify the identity, purity, strength, and composition of their products. Many consumers, as well as more than a third of physicians in one survey (37%),[148] are unaware that the safety and efficacy of dietary supplements are not systematically evaluated before they hit store shelves. Generally these products routinely enter the U.S. marketplace without undergoing FDA review, because they are considered food supplements under the provisions of the Dietary Supplement Health and Education Act (DSHEA) of 1994. DSHEA limits FDA's ability to regulate their manufacture and marketing. As a result, unsubstantiated claims of effectiveness are commonly implied in product messaging, as is a lack of balanced information pertaining to the potential for side effects. Until the recent implementation of the Dietary Supplement Nonprescription Drug Consumer Protection Act (January 1, 2008), there was no provision under any law or regulation that the FDA enforced that required a marketer of a dietary supplement to disclose to FDA (or to consumers) any important safety information regarding their product. As a result, it is conceivable that adverse effects associated with dietary supplement use have been historically underreported and underestimated. It has been estimated that FDA learns of fewer than one percent of adverse events involving these products.[149] Contributing factors to such under-reporting include physicians often being unaware that their patients are using dietary supplements[150,151] and that general practitioners are not familiar with the risk profiles of CAM therapies.[152,153]

While SJW and SAM-e products appear to be safe and at least as well-tolerated as conventional antidepressants such as the SSRIs,[154] it has become increasingly clear that herbal or "natural" does not always mean safer.[155] Questionable adherence to good manufacturing processes and quality control measures in the supplement industry has led to undisclosed product adulterations and to preparations that can vary substantially in content from batch to batch, potentially putting consumers at risk.[149] While recent legislative actions are clearly a step in the right direction, as long as manufacturers of these products are not required to prove that their products are relatively effective, consumer safety will continue to be impacted.[156]

Consumers have a right to know which dietary supplement products may provide real health benefits, which may be associated with side effects, and which may be essentially nothing more than placebos. They will often turn to the internet to seek information related to dietary supplements; however, studies have shown that the quality of the content on internet sites and in the media about herbal products is generally poor.[157,158] A sizable portion of the dietary supplements purchased in the United States are sold in pharmacies. Pharmacists therefore, given their training in pharmacology, therapeutics, and drug interactions are well-suited to serve as a primary point of contact for consumers searching for reliable information regarding these products. Pharmacists can also play a needed role as the first line of defense against the indiscriminate use of these products. Relying on product labeling will not be particularly helpful, however, as studies have shown that the vast majority of dietary supplement labeling fails to adequately address key clinically relevant issues.[159] To best assist consumers regarding these products, pharmacists, physician prescribers, psychologists, and other health professionals should have an adequate understanding of relevant pharmacology and be reasonably familiar with the key evidenced-based findings from the clinical literature. This can present a challenge, given the relatively scarce reliable literature and often inconclusive findings published for many of these products. Clinicians also need to be aware that consumers who inquire about natural antidepressant products are likely to already be taking one or more alternative products,

even though this may not be reflected in their chart/profile. These patients therefore might be at a greater risk for adverse drug-nutrient/herb interactions. Useful strategies for approaching patient consultations regarding the use of alternative/herbal therapies have been proposed.[160]

It is important that these two products, as well as other potentially useful alternative agents for mood disorders such as omega-3 fatty acids, continue to undergo rigorous, well-controlled trials. Further data from randomized, double-blind, placebo-controlled (and ideally also active-controlled), well-powered clinical trials would clearly be most useful.

Limitations of this Review

The literature search focused on English language studies only. As a result, important publications may have been omitted, given that substantial clinical investigation of both compounds has taken place outside the Unites States.

The initial intent was to base this review only on studies meeting all the predefined study selection criteria. However, given the pervasiveness of potentially flawed studies for both products, some studies of lesser quality (meeting some, but not all, selection criteria) were included out of necessity (particularly for SAM-e).

This review only examined studies in which SJW and SAM-e were utilized as antidepressant monotherapy. As mentioned, preliminary results (from one randomized, well-controlled trial) suggest the greatest potential benefit (at least for SAM-e) may lie with adjunctive use rather than as monotherapy.

Regarding examination of the publications for evidence of possible treatment-emergent suicidality, none of the studies examined were prospectively designed to look at this issue. Therefore, they may have been unable to reliably detect such events.

Similarly, the limited attention paid to addressing safety and tolerability in the studies did not allow for a thorough assessment of the incidence of the potential suicidality precursor behavioral AEs of interest. Many studies reported extremely low AE incidence rates, or reported that no AEs occurred at all, which leads one to question the rigor with which those safety data were collected.

Conclusions

Based on the evidence examined in this review, both SJW and SAM-e appear to be potentially useful for the short-term treatment of mild-to-moderate depressive symptoms. When considering these data one should keep in mind that the majority of studies examined were not of the quality typically used to establish the efficacy of conventional antidepressants from a regulatory standpoint. The evidence for SJW appears to be the more reliable of the two, given the methodological weaknesses characteristic of most of the SAM-e studies. It is the opinion of this author, after reviewing the data, that neither product can be recommended in place of conventional antidepressants for patients with moderate-to-severe depression, in patients less than age 18 years, or for long-term monotherapy treatment of depression of any severity level, without physician supervision.

Both products appear to be generally well-tolerated from a behavioral AE standpoint. No publication examined in this review revealed evidence of treatment-emergent suicidality for either product. However, these studies were not prospectively designed to assess the suicidality issue specifically. Consequently, whether these products have the potential to increase the risk of suicidality in adolescents or young adults (like conventional antidepressants) remains an unanswered question. Until more data are available, it would be prudent to apply the recommendations of the antidepressant boxed warning to all individuals being treated pharmacologically for depressive illness, irrespective of treatment modality (i.e., conventional or alternative).

Despite the lack of rigorous regulatory oversight of the manufacture, testing, and marketing of dietary supplements, the use of alternative products should not be categorically discouraged. Some products, including SJW, represent potentially legitimate treatment options. It is important that clinicians and other healthcare practitioners recommend natural/herbal antidepressant products, including SJW and SAM-e, judiciously and with a sound understanding of the data that exists to support such a recommendation.

Disclosures

David Carpenter is an employee of Helicon Therapeutics, Inc., and a shareholder in GlaxoSmithKline (GSK). However, the views expressed in this manuscript are offered in his private capacity as a health professional and are not necessarily the views of either company or their employees. No official support or endorsement of the content by Helicon or GSK is intended nor should be inferred.

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