

Q. What is St. John's Wort?

A. St. John's Wort (SJW) or *Hypericum perforatum* is a flowering plant used for its antidepressant properties. SJW is most commonly used and studied for depression in the form of a liquid extract standardized to either hypericin (0.1–0.3%) or hyperforin (1–6%) as active ingredients.

Q. What are the potential mechanisms of action underlying SJW for the treatment of major depressive disorder (MDD)?

A. Research has suggested hyperforin compounds are responsible for the effect of SJW on mood by affecting neurotransmitter levels, including serotonin, norepinephrine and dopamine. SJW is an over the counter dietary supplement and is not regulated by the U.S. Food and Drug Administration (FDA). Given this limited oversight, SJW dosing and formulations may vary across different manufacturers.

Q. Is SJW recommended as a treatment for MDD in the Military Health System (MHS)?

A. **Yes.** The 2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder suggests standardized extract of SJW as medication monotherapy for patients with mild MDD who prefer herbal treatments, with a “Weak For” strength of recommendation. The guideline cautions against using SJW for moderate to severe MDD, women who are pregnant or breastfeeding, or in combination with another antidepressant to avoid drug-herb interactions.

The MHS relies on the VA/DoD clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

Q. Do other authoritative reviews recommend SJW as a treatment for MDD?

A. **Yes.** Other authoritative reviews have provided some evidence substantiating SJW for MDD.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: A 2015 comparative effectiveness review of nonpharmacological versus pharmacological treatments for adults with MDD included SJW as a complementary and alternative medicine (CAM) intervention (Gartlehner et al., 2015). Meta-analysis of nine trials comparing SJW to a second-generation antidepressant (SGA) indicated similar response rates, with a low strength of evidence. It is important to note that the SGA regimens used in these trials were lower than the approved dose range. SGAs were associated with higher rates of discontinuation and higher risk of adverse events, with a moderate strength of evidence.
- Cochrane: A 2008 systematic review of SJW for major depression included 29 trials comparing SJW to placebo or standard antidepressants (Linde, Berner, Kriston, 2008). The included studies varied with regards to country and type of SJW extract, and included subjects with mostly mild to moderate depression. Overall, the authors found SJW to be superior to placebo and similarly effective to standard antidepressants with fewer side effects. The authors cautioned that studies from countries with a tradition of physician prescribing of SJW may report overoptimistic results.

Q. Is there any recent research on SJW as a treatment for MDD?

A. A search conducted in August 2020 identified two meta-analyses on the efficacy of SJW for the treatment of depression published in the time period since the search conducted for the 2016 VA/DoD *Clinical Practice Guideline for the Management of Major Depressive Disorder*. One meta-analysis (Cui & Zheng, 2016) included 27 trials and 3,126 patients with depression, finding that SJW was not significantly different from selective serotonin reuptake inhibitors (SSRIs) in treatment response or remission. SJW had a significantly lower rate of adverse events and fewer withdrawals. A second meta-analysis (Ng, Venkatanarayan, & Ho, 2017) of 27 trials, for a total of 3,808 patients, found that SJW showed comparable treatment response and remission, with a significantly lower dropout rate compared to standard SSRIs. The authors noted that the duration of the included studies ranged from 4 to 12 weeks, limiting any conclusions on long-term effectiveness.

Q. What conclusions can be drawn about the use of SJW as a treatment for MDD in the MHS?

A. SJW standardized extract is safe and effective as monotherapy for mild MDD, for patients who are not pregnant or breastfeeding. SJW is not recommended for moderate to severe forms of MDD. Providers should exercise caution when recommending SJW due to common drug-herb interactions. SJW is not regulated by the FDA, and dosing and formulations may vary across different manufacturers.

References

- Cui, Y. H., & Zheng, Y. (2016). A meta-analysis on the efficacy and safety of St John's wort extract in depression therapy in comparison with selective serotonin reuptake inhibitors in adults. *Neuropsychiatr Dis Treat*, 12, 1715–1723.
- Department of Veterans Affairs/Department of Defense. (2016) *VA/DoD clinical practice guideline for management of major depressive disorder. Version 3.0*. Washington (DC): Department of Veterans Affairs/Department of Defense.
- Gartlehner, G., Gaynes, B. N., Amick, H. R., Asher, G., Morgan, R. C ... Lohr, K. N. (2015). Nonpharmacological versus pharmacological treatments for adults patients with major depressive disorder (AHRQ Publication No. 15(16)-EHC031-EF). Rockville, MD: Agency for Healthcare Research and Quality.
- Linde, K., Berner, M. M., & Kriston, L. (2008). St. John's wort for major depression. *Cochrane Database of Systematic Reviews*, 4.
- Ng, Q. X., Venkatanarayanan, N., & Ho, C. Y. (2017). Clinical use of *Hypericum perforatum* (St John's wort) in depression: A meta-analysis. *Journal of Affective Disorders*, 210, 211–221.

