

# Adverse effects and drug interactions relating to use of St. John's wort

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THE BOTANICAL NAME OF ST. JOHN'S WORT IS *HYPERICUM PERFORATUM* L. and it is in the family Clusiaceae (also known as Guttiferae or Hypericaceae). St. John's wort is widely used in Canada, the United States, and Europe.<sup>1,2</sup>

## Uses

St. John's wort (SJW) has been researched extensively for the treatment of psychiatric conditions such as seasonal affective disorder and mild to moderate depression. Substantial research exists on the efficacy of this product for this level of depression.

## FIRST IN A SERIES ON DRUG INTERACTIONS AND NATURAL HEALTH PRODUCTS

For example, a systematic review and meta-analysis of 23 randomized controlled trials demonstrated that St. John's wort was more effective than a placebo for mild to moderate depression.<sup>3,4</sup> Furthermore, SJW may be as effective as tricyclic antidepressants and selective-serotonin reuptake inhibitors (SSRIs) for mild to moderate depression.<sup>3</sup> However, there are limited data to support its use in major depression.<sup>3,5</sup>

St. John's wort has also been used for minor skin inflammation, and muscle and nerve pain. Under the newly implemented Nat-

tribution, metabolism, and excretion of conventional pharmaceuticals. Effective knowledge transfer to our patients about these potential concerns is vital in providing appropriate care.

## Addressing adverse effects in natural health products

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IN CANADA, THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE, specifically natural health products (NHPs), is significant. More than 70% of Canadians report regular NHP use and up to 31% of Canadians use three or more.<sup>1,2</sup> Such products are frequently used by patients with chronic or recurrent conditions; these patients are also the most likely to be prescribed conventional medications.<sup>3</sup> For example, 58% of patients taking narrow therapeutic index cardiovascular medications reported concurrent NHP use.<sup>4</sup> As the likelihood of an adverse event increases with the number of products used, patients who use prescription medications in combination with NHPs are potentially at greater risk for an adverse event than if they were using either product on its own.<sup>5</sup>

Patients often use these "natural" therapies without the appropriate knowledge of how they may affect their underlying medical condition(s) and/or conventional medications. While many natural health products, such as echinacea, have a relative lack of serious adverse effects and drug interactions, others may be highly toxic and have significant effects on the absorption, dis-

A critical step toward providing patients with accurate information about natural health products is to change health care provider behaviour. In particular, pharmacists, physicians, and nurses need to routinely ask about NHP use as part of history-taking. Only a minority of patients spontaneously report such use to their conventional health care professionals, in part because they are concerned about how this information will be accepted. There is also widespread public perception that natural products are "safe" and therefore do not need to be disclosed. Since many patients are taking these products as part of self-care, health care professionals need to ask about NHP use and counsel patients with the best available safety and efficacy information. Although formal rigorous evaluation of these products has been fairly limited to date, research in this field is expanding rapidly.

Beginning in this issue, we will be writing a series of clinical letters on natural health products commonly used in Canada and

ural Health Products Regulations,<sup>6</sup> the Natural Health Products Directorate of Health Canada has approved the following traditional uses of St. John's wort:<sup>7</sup>

- Orally: Sedative for relief of restlessness or nervousness
- Topically: Minor inflammation of the skin, blunt injuries, wounds, and burns

St. John's wort has been used to treat a number of other conditions, such as premenstrual syndrome, neuropathy, bronchitis, enuresis, gastritis, hemorrhoids, hypothyroidism, insect bites, insomnia, and scabies. However, only anecdotal evidence exists to support treatment of these conditions.

### Safety

Research demonstrates that St. John's wort is generally well tolerated, with adverse effects occurring in 1% to 3% of users.<sup>8</sup> Commonly occurring adverse effects include headache, fatigue, restlessness, photosensitivity, dry mouth, and nausea.<sup>9</sup> Recent meta-analysis suggests that these side effects are similar to those that occurred with placebo.<sup>5</sup>

purchased in community pharmacies. The focus of these articles will be on information about safety and potential drug interactions. Our goal is to assist community pharmacists in helping patients weigh the relative risks and benefits of starting or continuing with a natural health product. As over 65% of NHPs are purchased in community pharmacies, it is imperative that community pharmacists be aware of the issues involved with their use.<sup>6</sup> Unlike the staff in health food stores, pharmacists have access to accurate prescription information for patients purchasing NHPs as well as specific training in the pathophysiology of disease and pharmacotherapeutics. This affords community pharmacists an excellent opportunity to review their patient's medication profile, and identify potential concerns for discussion.

Fortunately, there are a number of reputable sources of information. Throughout this series, we will identify evidence-based resources for pharmacists to access. We hope this series will help remind pharmacists to ask patients about NHP use, side effects experienced, and potential drug interactions. Pharmacists are encouraged to report any adverse events or drug interactions with NHPs to Health Canada ([www.hc-sc.gc.ca/dhp-mps/med-eff/report-declaration/form/ar-ei\\_form\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/med-eff/report-declaration/form/ar-ei_form_e.html)), as there con-

### Knowledge into practice

In order to provide patients with appropriate safety information, pharmacists should review the profiles of patients inquiring about St. John's wort.

- Potential drug interactions should be discussed with patients, and appropriate management options for these should be offered.
- Patients should be encouraged to discuss use of this product with their physician, in case further investigations or follow-up is needed.
- Pharmacists can be proactive with patients taking some of the most widely prescribed medications mentioned above, such as triptans, OCs, and SSRIs.



tinues to be a critical lack of information on this topic.

Community pharmacists can play a vital role in helping advance understanding about the nature and frequency of adverse events related to natural health products, and thereby improve the safety and well-being of Canadians. We hope this series will assist them in this endeavour.

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Case reports suggest serious but rare adverse effects can occur with use, such as induction of mania, serotonin syndrome (see Table 1), and hypertension. If these adverse effects occur, a health practitioner should be consulted.

**Drug interactions**

A number of drug interactions have been identified with St. John’s wort. Caution should be used when it is combined with anticoagulants, anticonvulsants, SSRIs, monoamine oxidase inhibitors, sympathomimetics (amphetamine, methyl dopa), and oral contraceptives.<sup>10</sup> Until more information is available, concurrent use of St. John’s wort and the following particular drugs should be avoided: triptans, digoxin, cyclosporine, and warfarin.<sup>10</sup> Patients with HIV/AIDS taking nonnucleoside reverse transcrip-

tase inhibitors and protease inhibitors should not take St. John’s wort because of the potential for reduced antiviral concentration.<sup>10</sup> Also, in theory, this product may worsen photosensitization if used in combination with other photosensitizing drugs. Pharmacists should monitor the health status of patients taking SJW concurrently with these medications. Table 1 provides an evidence summary of St. John’s wort–drug interactions with commonly used medications.

**Precautions/contraindications**

St. John’s wort should be avoided in people with a history of mania or bipolar affective disorder due to case reports of manic episodes. Also, sudden discontinuation may cause withdrawal symptoms, as with SSRIs and other antidepressants.

**TABLE 1 Summary of evidence for drug interactions with St. John’s wort**

Drug	Evidence	Finding	Study recommendation	Pharmacist management recommendations
Oral contraceptives (OC)	Pilot study <sup>11</sup> International case reports <sup>12</sup>	Concurrent use of SJW and OC can lead to greater chances of breakthrough bleeding than placebo and increased metabolism of the OC.  Unwanted pregnancies upon concurrent use of SJW and OC.	Authors recommend that women should be warned that taking SJW might lessen the effectiveness of OC.  More research is required to determine the clinical significance of these findings.	Patients should be advised to use an alternative method of birth control while on SJW and OCs concurrently. Alternatively, advise patient not to take SJW while on OC.  Patients should be advised regarding the risk of breakthrough bleeding.
SSRIs	Case series and case reports <sup>8</sup>	Serotonin syndrome (nausea, vomiting, dizziness, confusion, or anxiety) can occur with concomitant use of SSRIs and SJW.	Not available	Patients taking SSRIs as well as SJW should be cautioned about risk of serotonin syndrome. Pharmacists should monitor for signs/symptoms of serotonin syndrome.
Drugs metabolized by cytochrome P450 3A4	Systematic review, clinical reports <sup>13-15</sup>	SJW can induce CYP 3A4 when taken long term and may inhibit metabolism of medications with short-term use.	SJW may affect drug metabolism and serum concentration of drugs depending on length of use.	Patients may require increased laboratory monitoring for some medications. Patients should be recommended to discuss this with their physician and avoid concurrent use if possible. Drugs to monitor: cyclosporin, carbamazepine, protease inhibitors, nonnucleoside reverse transcriptase inhibitors.
Warfarin	Case reports <sup>14,15</sup>	Decrease in INR with co-administration of warfarin and SJW possibly due to induction of CYP 2C9 or p-glycoprotein	SJW should not be used concurrently with warfarin.	Patients should be counselled to avoid concurrent use of warfarin and SJW. If they do use these concurrently, they should be advised to follow up with their physician for increased frequency of INR testing, and potential adjustment of warfarin dose.

**Use in special populations**

Caution should be used in pregnant and lactating women, given the lack of available data in this population. An observational study of maternal use of St. John's wort suggests that the infant's weight and mother's milk production do not statistically vary from breastfeeding mothers who do not consume St. John's wort.<sup>16</sup> Although surveys show that children use St. John's wort, little evidence exists to recommend this use.

**Useful websites**

Health Canada Food and Drug Regulations:  
[www.hc-sc.gc.ca/fn-an/legislation/acts-lois/fdr-rad/index\\_e.html](http://www.hc-sc.gc.ca/fn-an/legislation/acts-lois/fdr-rad/index_e.html)  
 Natural Standard: [www.naturalstandard.com](http://www.naturalstandard.com)  
 Health Canada monographs of natural health products:  
[www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono\\_list\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_list_e.html)  
 CAMline: [www.camline.org](http://www.camline.org)

**Conclusion**

St. John's wort is effective for treating mild to moderate depression. In addition, Health Canada has approved this product for the treatment of minor inflammation of the skin. However, serious drug interactions have been shown, warranting an active role for pharmacists in monitoring drug interactions and adverse events related to the use of St. John's wort. ■

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