



# St. John's Wort Interactions: What's New?

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Although the popularity of St. John's wort has slipped a bit lately, it is still among the more widely used herbal products in the United States. Moreover, because St. John's wort induces the most important drug-metabolizing cytochrome P-450 isozyme (CYP3A4), one would expect St. John's wort to interact with more than half of all medications used by patients. Limited clinical evidence suggests that St. John's wort may also induce CYP2C9 and perhaps other cytochrome P-450 isozymes. In addition, St. John's wort increases the activity of P-glycoprotein, a transporter that pumps drugs out of cells. Inhibition of P-glycoprotein can increase absorption of some drugs. Recently published information has provided more solid evidence upon which to make decisions about St. John's wort drug interactions.

## Alprazolam

Alprazolam, a commonly used anxiolytic, is metabolized almost exclusively by CYP3A4. When alprazolam was given to healthy subjects with and without pretreatment for 14 days with St. John's wort, alprazolam plasma concentrations were decreased by more than half with St. John's wort pretreatment.<sup>1</sup> This is a large enough effect to substantially reduce the effect of alprazolam, but it also is compelling evidence that St. John's wort is an effective CYP3A4 inducer. Our recommendation is that pharmacists be alert for evidence of a reduced effect of alprazolam (or other

benzodiazepines) when St. John's wort is taken concomitantly.

## Oral Contraceptives

Two recent studies have dramatically increased one's knowledge about the impact of St. John's wort on oral contraceptives. Although there have been isolated case reports of unintended pregnancy when St. John's wort was used with oral contraceptives, little hard evidence has been available. That situation is changing, however.

In 1 recent study of 12 women on norethindrone 1 mg/ethinyl estradiol 0.035 mg, the addition of St. John's wort resulted in a substantial reduction in ethinyl estradiol serum concentrations and an increase in breakthrough bleeding from 17% to 58%.<sup>2</sup> Another study of 18 women on low-dose oral contraceptives found a dramatic increase in breakthrough bleeding when St. John's wort was given concurrently (occurring in 88% of women taking St. John's wort 3 times a day).<sup>3</sup> Our recommendation is that patients on oral contraceptives be counseled that taking St. John's wort may reduce the efficacy of their contraceptive.

## Antiretroviral Drugs

HIV-positive patients taking antiretroviral drugs may be adversely affected by concurrent use of St. John's wort. That herbal product has been shown to substantially reduce serum concentrations of indinavir and nevirapine.<sup>4,5</sup> Many other antiretroviral drugs also are substrates for CYP3A4 and/or P-glycoprotein. Our recommendation is that patients taking antiretroviral drugs should generally avoid taking St. John's wort concurrently. If they do take St. John's wort, they should be carefully monitored for reduced antiviral effect.

## Immunosuppressants

Immunosuppressants—such as cyclosporine, sirolimus, and tacrolimus—are substrates for both CYP3A4 and P-glycoprotein, and thus they would be expected to interact with St. John's wort. Indeed, there are numerous reports of subtherapeutic cyclosporine concentrations and rejection of transplanted organs following the use of St. John's wort.

A recent report showed large reductions in tacrolimus serum concentrations with concurrent St. John's wort administration.<sup>6</sup> Sirolimus is very likely to interact with St. John's wort as well. Our recommendation is that patients on cyclosporine, sirolimus, or tacrolimus should be warned to avoid St. John's wort. This warning is especially important because depression is common in patients with organ transplants, and St. John's wort can be obtained without a prescription.

## Conclusion

St. John's wort clearly increases the activity of CYP3A4 and P-glycoprotein and thus can reduce the effects of a large number of drugs. Although it may be possible to adjust the dose of the affected drug to achieve an adequate serum concentration in the presence of St. John's wort, excessive fluctuations in drug concentrations still may occur. These fluctuations occur because different preparations of St. John's wort (or even different lots of the same brand) may differ with respect to the amount of active ingredients. 

*For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. D. Ryan, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: [dryan@mwc.com](mailto:dryan@mwc.com).*