

## Does St John's Wort interact with combined and progestogen only hormonal contraception?

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### Background

St John's Wort (SJW) is the common name for the plant *Hypericum perforatum* and is a popular herbal remedy for the management of mild to moderate depression [1, 2].

Hormonal contraception includes combined hormonal contraception and progestogen only contraception. Combined hormonal contraception contains an oestrogen and progestogen and preparations includes tablets, transdermal patches and vaginal rings. Progestogen only contraception is available as tablets, injections, implants and intra-uterine devices [3].

### Answer

SJW has several active constituents including hypericin, hyperforin and adhyperforin. *In vitro* studies have shown that hyperforin is a potent inducer of the cytochrome P450 enzymes, particularly CYP3A4, CYP1A2 and CYP2C9, as well as affecting the P-glycoprotein cellular transport system [1]. Clinically important interactions between SJW and CYP3A4 substrates have been reported in with SJW wort products containing hyperforin 1 mg or more [2, 4]. The isoenzyme CYP3A4 appears to be the major route for inactivation of most contraceptive steroids, meaning concomitant use with enzyme inducers can cause a decrease in serum hormone levels [1].

In 2014, the Medicines and Healthcare products Regulatory Agency (MHRA) published a drug safety alert regarding the use of SJW alongside contraceptives. This is in response to 19 reports of unplanned pregnancy (15 reports) and breakthrough bleeding without pregnancy (4 reports) between 2000 and 2013. Out of these reports, 15 were in relation to contraceptive pills and 4 were in relation to progestogen-only implants. The MHRA recommends for women taking hormonal contraception for pregnancy prevention should not take herbal products that contain SJW. They apply this to all hormonal contraceptives with exception to intra-uterine devices [5].

Most of the clinical evidence regarding an interaction between SJW and hormonal contraceptives, relates to women who were taking a combined oral hormonal contraceptive, although there have been a few anecdotal reports with other formulations [6, 7]. It has also been reported that SJW can decrease norethindrone and ethinylestradiol levels by 13% and 15%, resulting in breakthrough bleeding, irregular menstrual bleeding or unplanned pregnancy. Bleeding irregularities usually occur within a week of starting SJW and regular cycles return when SJW is discontinued [1].

Several studies have assessed the effect of SJW extracts on oral contraceptives. The effect of SJW 300mg three times daily (TDS) in 12 healthy premenopausal women receiving a combined oral contraceptive pill containing norethindrone and ethinylestradiol was assessed over 3 consecutive 28 day menstrual cycles. SJW was associated with increased clearance of norethindrone (8.2 L/h to 9.5L/h,  $p=0.04$ ) and a reduction in the half life of ethinylestradiol (23.4 to 12.2,  $p=0.02$ ). Serum concentrations of follicle stimulating hormone, luteinising hormone and progesterone were not significantly affected by SJW. Breakthrough bleeding occurred in 17% (2/12 women) on COC alone vs 58% (7/12) women when on COC and SJW together [8].

In another study, 17 women who had received a low dose oral contraceptive containing ethinylestradiol and desogestrel for one menstrual cycle, randomly received either 300mg SJW twice daily (BD) or 300mg SJW TDS for one cycle. The groups were then crossed over. There was no

significant change in follicle maturation, serum estradiol or progesterone concentrations. More subjects reported intra-cyclic bleeding in the SJW treatment groups, (77% and 88% in the BD and TDS groups;  $p < 0.001$  respectively versus 35% in the COC alone group). The study authors concluded that there was no evidence of ovulation during concomitant treatment with SJW, but intra-cyclic bleeding episodes increased which could affect compliance and lead to unintended pregnancies [9].

In a non-randomised, single blind, sequential trial, 16 healthy women received a low dose COC, containing ethinylestradiol and norethindrone acetate for 21 days and placebo for 7 days for 2 consecutive 28 day cycles. SJW 300mg TDS was then taken concomitantly for 2 additional 28 day cycles. The Area under the Curve (AUC) decreased, resulting in a 13-15% reduction in dose exposure to the oral contraceptives. Breakthrough bleeding occurred in more subjects during the SJW treatment phase than during the control phase (56% vs. 31%;  $p = 0.05$ ). One patient was thought to have ovulated during the control phase compared with 6 patients in the SJW cycle. The study authors concluded that SJW is associated with increased metabolism of norethindrone and ethinylestradiol, breakthrough bleeding, follicle growth and ovulation [10].

In 1999, 3 cases of breakthrough bleeding were reported in patients taking ethinylestradiol and desogestrel and were attributed to lowered plasma ethinylestradiol concentrations caused by SJW [11, 12]. By 2000, the Swedish Medical Products Agency, had received 8 reports of inter-menstrual bleeding and 1 report of changed menstrual bleeding in women on oral contraceptive tablets who started taking SJW [13, 14].

An unplanned pregnancy in a 36 year old woman taking a regular ethinylestradiol plus dienogestrel oral contraceptive, was reported by Schwarz et al in 2003 [15]. The woman self-medicated with up to 1700mg of hypericin extract daily for approximately 3 months prior to conception.

Despite limited documentation of interaction between SJW and progestogen only contraceptives, there have been case reports and case series of reduced serum hormone concentration and subsequent contraception failure when women took other enzyme inducers (e.g. carbamazepine, efavirenz and rifampicin) alongside progestogen only pills and implants [7, 16]. Also, studies regarding interactions between SJW and combined hormonal contraceptives have shown a decrease in the serum level of the progestogen component as well the oestrogen component [6]. As such, guidelines advise against the use of these contraceptive methods alongside SJW [17, 18].

With respect to progestogen only injections, medroxyprogesterone acetate (contained within Depo-Provera and Sayana press injections) clearance is approximately equal to the rate of hepatic blood flow. As such, it is unlikely that enzyme induction will significantly affect the pharmacokinetic profile of medroxyprogesterone acetate [19]. Small studies investigating the effect of enzyme inducing nucleotide reverse transcriptase inhibitors (efavirenz, nevirapine and nelfinavir) have confirmed this. Therefore, no dose adjustment is recommended in patients receiving enzyme inducers and is a suitable for women who continue to take SJW [20]. There have been no interaction studies between enzyme inducers and norethisterone enantate injections (Noristerate). A theoretical interaction is possible based on data showing that some rifamycins and carbamazepine can decrease the exposure to norethisterone when it is used as a component of an oral combined hormonal contraceptive [20, 21].

Enzyme inducers have been shown to reduce serum levonorgestrel levels when used as a component of combined oral contraception, and it has been theorised these inducers may reduce the systemic exposure to levonorgestrel from the intra-uterine devices. However, the efficacy of levonorgestrel intra-uterine devices is thought to derive from local effects as opposed to systemic effects of levonorgestrel, meaning that the efficacy of intra-uterine devices may not be significantly affected by concurrent use of enzyme inducers such as SJW. In one pilot study, 47 patients taking

enzyme inducers (mostly anti-epileptics) used levonorgestrel intra-uterine devices. The total number of months this method was used across all patients was 1075 months. During this time, 1 apparent contraceptive failure resulting in pregnancy was documented. The failure rate calculated was 1.1 per 100 women-years, whereas the usual quoted failure rate of the levonorgestrel intra-uterine system is 0.2 per 100 women-years. Although there is a rise, it is not considered significant enough to recommend women to not use levonorgestrel intra-uterine devices whilst on enzyme inducers [22].

The Faculty of Sexual and Reproductive Healthcare recommends the following regarding SJW use (and use of enzyme inducers in general) alongside hormonal contraceptives:

- Women on short term treatment with SJW (defined arbitrarily as  $\leq 2$  months) may continue using the combined patch, ring or standard strength combined pill, but they should be advised to use additional contraceptive precautions (e.g. condoms) while taking SJW and for 28 days after stopping [23].
- Women taking combined hormonal contraceptives (including pills, patches and vaginal rings) alongside SJW are advised to switch to an alternative method of contraception (e.g. progestogen only injection or intra-uterine device) [23].
- If a woman wishes to use combined oral contraception concomitantly with an enzyme-inducing drug (with the exception of rifampicin or rifabutin) use of a minimum 50mcg (30mcg pill + 20mcg pill) ethinylestradiol monophasic combined pill may be considered during use of the enzyme-inducer and for a further 28 days after stopping. A continuous or tricycling regimen plus a shortened pill-free interval of 4 days should be used. Dose of ethinylestradiol can exceptionally be increased up to a maximum of 70mcg after specialist advice. It is not known how such usage affects risk of venous thromboembolism. The use of two patches or two rings is not recommended [23].
- Women on short term treatment with SJW may continue using the progestogen only pill, but they should be advised to use additional contraceptive precautions (e.g. condoms) while taking SJW and for 28 days after stopping [24].
- For women on long term SJW, progestogen only pills are not recommended. These women should be advised to switch to the progestogen-only injectable or intrauterine contraception. Women wishing to start the progestogen only pill after stopping enzyme-inducing drugs should be advised to use condoms until 28 days after the last dose of enzyme-inducing drug [24].
- Women using progestogen only implants should be advised to switch to a method unaffected by enzyme-inducing drugs or to use additional contraception (e.g. condoms) until 28 days after stopping the treatment [25].
- Appropriate forms of hormonal contraception in patients taking SJW are intra-uterine devices and progestogen-only injections [17, 26, 27].

## Summary

- The interaction between combined oral contraceptives and SJW appears to be established. Its incidence is not known, but cases of breakthrough bleeding, menstrual irregularity and unplanned pregnancy have been reported. The MHRA has advised that SJW should not be used with hormonal contraceptives, except intrauterine devices, as there is a risk of contraceptive failure and unplanned pregnancy.
- Health professionals supplying hormonal contraception should ask women about their current and previous drug use including prescription, over the counter, herbal, recreational drugs and dietary supplements.
- Women using hormonal contraception should be informed about the potential for interactions with other drugs and the need to seek the advice of a health professional before starting any new drugs including herbal or dietary supplements.

- The FSRH in the UK, advise that women taking combined hormonal contraceptives, progestogen only pills or progestogen only implants should either avoid SJW or they should use an alternative form of contraception, unaffected by enzyme inducers e.g. progestogen only injection, intra-uterine devices (copper or levonorgestrel containing) or additional barrier methods.
- If St John's Wort is continued, the general guidelines, produced by the FSRH for the use of liver enzyme inducers with hormonal contraceptives should be followed.

### Limitations

This Q&A does not discuss the potential for SJW to interact with emergency hormonal contraception. A separate Q&A that addresses this can be found [here](#).

### References

1. Jellin J, Gregory P, Batz F, Bonakdar R, editors. Natural Medicines Database. St John's Wort. Last reviewed 13/04/2020. Accessed 14/04/2020 via <http://www.naturaldatabase.com>
2. Taylor D, Paton C, Kerwin R. The South London and Maudsley NHS Foundation Trust & Oxleas NHS Foundation Trust Prescribing Guidelines. 13th ed. London: Informa Healthcare; 2018: 355-7.
3. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press; Contraceptives, hormonal. April 2020 edition. Accessed 08/04/2020 via <http://bnf.nice.org.uk>
4. Chrubasik-Hausmann S, Vlachojannis J, McLachlan AJ. Understanding drug interactions with St John's wort (*Hypericum perforatum* L.): impact of hyperforin content. *Journal of Pharmacy and Pharmacology* 2019; 71 (1): 129-138.
5. Medicines and Healthcare product Regulatory Agency. St John's wort: interaction with hormonal contraceptives, including implants. Published 11/12/2014. Accessed 08/04/2020 via <https://www.gov.uk/drug-safety-update/st-john-s-wort-interaction-with-hormonal-contraceptives-including-implants>
6. Baxter K (ed). Stockley's Drug Interactions online. Combined Hormonal Contraceptives + St John's wort (*Hypericum perforatum*). Last updated 20/04/2017. Accessed 08/04/2020 via [www.medicinescomplete.com](http://www.medicinescomplete.com)
7. Baxter K (ed). Stockley's Drug Interactions online. Progestogen only contraceptives; oral + enzyme inducers. Last updated 24/04/2017. Accessed 08/04/2020 via [www.medicinescomplete.com](http://www.medicinescomplete.com)
8. Hall SD, Wang Z, Huang, SM et al. The interaction between St John's Wort and an oral contraceptive. *Clinical Pharmacology and Therapeutics* 2003; 74: 525-535.
9. Pfrunder A, Schiesser M, Gerber S et al. Interaction of St John's Wort with low dose oral contraceptive therapy: a randomised controlled trial. *British Journal of Clinical Pharmacology* 2003; 56: 683-690.
10. Murphy PA, Kern SE, Stanczyk FZ et al. Interaction of St John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinylestradiol, ovarian activity and breakthrough bleeding. *Contraception* 2005; 71: 402-408.
11. Madabushi R, Frank B, Drewelow B et al. Hyperforin in St. John's Wort drug interactions. *European Journal of Clinical Pharmacology* 2006; 62: 225-233.
12. Ernst E. Second thoughts about safety of St John's Wort. *Lancet* 1999; 354: 2014-2015.
13. Izzo AA. Drug interactions with St John's Wort (*Hypericum perforatum*): a review of the clinical evidence. *International Journal of Clinical Pharmacology and Therapeutics* 2004; 139-148.
14. Yue QY, Bergquist C. Safety of St John's Wort. *Lancet* 2000; 355: 576-577.
15. Schwarz UI, Buschel B, Kirch W et al. Unwanted pregnancy on self medication with St John's Wort despite hormonal contraception. *British Journal of Clinical Pharmacology* 2003; 55:112-113.
16. Baxter K (ed). Stockley's Drug Interactions online. Progestogen only contraceptives; implants + enzyme inducers. Last updated 28/06/2017. Accessed 08/04/2020 via [www.medicinescomplete.com](http://www.medicinescomplete.com)

17. Faculty of Sexual and Reproductive Healthcare. Clinical Effectiveness Unit Guidance: Drug Interactions with Hormonal Contraception. Last reviewed 01/12/2019. Accessed 08/04/2020 via <https://www.fsrh.org/>
18. NICE Clinical Knowledge Summaries. Contraception - progestogen-only methods. Last reviewed 11/2019. Accessed 08/04/2020 via <https://cks.nice.org.uk/>
19. Summary of Product Characteristics. Depo-Provera 150mg/ml Injection Sterile suspension for injection. Pfizer Ltd. Last updated 11/02/2020. Date accessed 08/04/2020 via <https://www.medicines.org.uk>
20. Baxter K (ed). Stockley's Drug Interactions online. Progestogen only contraceptives; injections + enzyme inducers. Last updated 28/06/2017. Accessed 08/04/2020 via [www.medicinescomplete.com](http://www.medicinescomplete.com)
21. Summary of Product Characteristics. Noristerat 200mg, solution for intramuscular injection. Bayer plc. Last updated 23/10/2019. Accessed via <https://www.medicines.org.uk>
22. Baxter K (ed). Stockley's Drug Interactions online. Progestogen only contraceptives; intra-uterine system + enzyme inducers. Last updated 18/05/2017. Accessed 08/04/2020 via [www.medicinescomplete.com](http://www.medicinescomplete.com)
23. Faculty of Sexual and Reproductive Healthcare. Clinical Guideline: Combined Hormonal Contraception. Last reviewed 07/2019. Accessed 08/04/2020 via <https://www.fsrh.org/>
24. Faculty of Sexual and Reproductive Healthcare. Clinical Guideline: Progestogen-only Pills. Last reviewed 30/04/2019. Accessed 08/04/2020 via <https://www.fsrh.org/>
25. Faculty of Sexual and Reproductive Healthcare. Clinical Guideline: Progestogen-only Implant. Last reviewed 01/02/2014. Accessed 08/04/2020 via <https://www.fsrh.org/>
26. Faculty of Sexual and Reproductive Healthcare. Clinical Guideline: Progestogen-only Injectables. Last reviewed 01/04/2019. Accessed 08/04/2020 via <https://www.fsrh.org/>
27. Faculty of Sexual and Reproductive Healthcare. Clinical Guideline: Intrauterine contraception. Last reviewed 26/09/2019. Accessed 08/04/2020 via <https://www.fsrh.org/>

## Quality Assurance

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### Search strategy

- References checked: BNF, EMC, NHS Evidence, Martindales: the Complete Drug Reference, AFHS Drug Information, Drugex, Stockley's Drug Interactions, Natural Medicines Database, Herbal Medicines, MHRA, NICE Clinical Knowledge Summaries, FSRH, Maudsleys
- Embase: Hypericum Perforatum AND (exp Contraception). Limited to 2016-2020
- Medline: Hypericum AND (exp Contraceptive Agents). Limited to 2016-2020