



Herbal detox – Benzodiazepine withdrawal treatment with the help of St. John's Wort?



Dear editor,

Benzodiazepine (BZD) use disorder has a high prevalence (Blanco et al., 2018). Frequent use can lead to physical and mental dependence and tolerance (Fluyau et al., 2018).

Withdrawal of BZD is challenging and may pose the risk of adverse events, e.g. seizures and delirium (Fluyau et al., 2018). Pharmacological management, e.g. anticonvulsants, antidepressants (Muller et al., 2012) and even plant-based derivatives (Fluyau et al., 2018) reduces craving. However, data of effectiveness are heterogeneous. So far, there are no reports of using St. John's wort (SJW) to reduce craving in BZD withdrawal. In rats, SJW attenuated physical signs of opium withdrawal due to receptor interactions (Khan et al., 2014). However, there are neither in vitro nor in vivo data for the use of SJW in benzodiazepine withdrawal treatment. Several studies demonstrated a significant affinity of SJW for GABA(A) and GABA(B) which are the main targets of BZDs (Schmidt and Butterweck, 2015).

A 49-year-old patient presented with a four year history of BZD use disorder. He was otherwise healthy. The patient started taking BZD after being a passenger in an airplane that had to make an emergency landing because it caught fire. He continued and increased the consumption of alprazolam. The patient usually took approximately four milligrams per day during the last nine months. The patient took 900 mg of *Hypericum perforatum* (SJW) for at least three months prior to hospitalization. Pharmacological withdrawal treatment was done

using administration of clonazepam covering with woodruff that the patient was not able to know how much of the BZD he got. He first obtained four times a day one milligram clonazepam. The reduction steps of the BZD included a decrease of approximately 0.4 mg per day within two weeks (Fig. 1). We off-label administered SJW three times a day 425 mg. During his hospitalization, only once at the beginning of the stay mild withdrawal symptoms, i.e. tachycardia and mild tremor of the hands occurred. The patient was discharged from hospital symptom-free after 18 days. In a follow-up visit three month after discharge from the hospital the patient was still clean and continued his SJW medication.

SJW could be a promising tool in the psychiatric armamentarium involving BZD withdrawal. SJW has comparable antidepressant properties like tricyclic antidepressants and selective serotonin reuptake inhibitors (Zirak et al., 2018). Usually, it is used for mild and moderate forms of depression (Zirak et al., 2018). His compounds, e.g. hyperforin as the major antidepressant component in the extract of SJW (Zanoli, 2004), inhibit the re-uptake of GABA (Butterweck, 2003). Moreover, Baureithel et al. showed that SJW extracts inhibited flumazenil binding to benzodiazepine binding sites on the GABA-A receptor (Baureithel et al., 1997). Thus, the potential of SJW of reduced craving during BZD discontinuation might be related to the affinity to the central GABA-ergic system. However, there are still many unanswered questions about its pharmacology and its exact mechanism of action (Zirak et al., 2018).

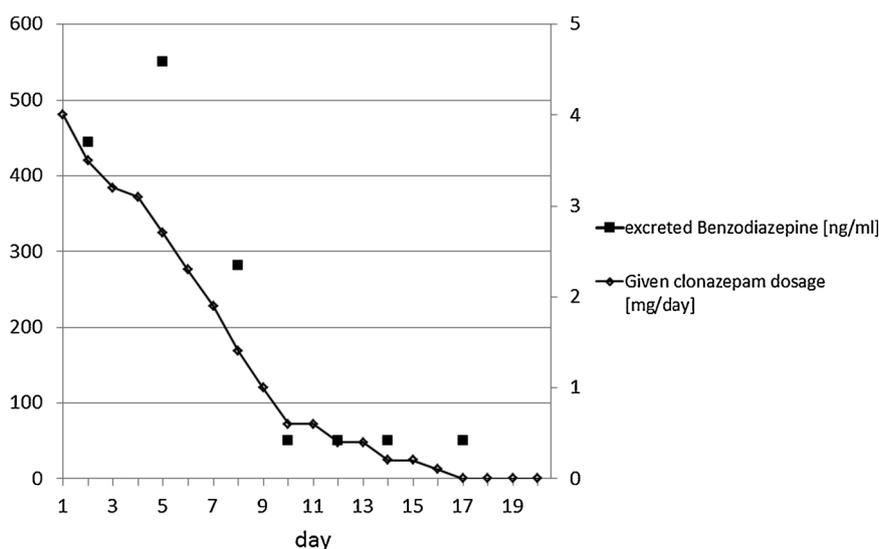


Fig. 1. Amount of ingested clonazepam, amount of benzodiazepines in urine during the hospital stay of the patient.

SJW is a strong inductor of cytochrome P450-enzymes and P-glycoprotein transporter, and thus, affects the pharmacokinetics of various drugs (Soleymani et al., 2017). Consequently, the additional administration of SJW to the regular withdrawal treatment might induce faster metabolism of clonazepam with subsequent lower clonazepam level in the blood. The course of our illustrated case suggests that the affinity to the GABA receptors and the enzyme induction effect of SJW in BZD withdrawal treatment may be beneficial. Milder withdrawal symptoms could be based on sedating and/or anti-craving effects (Zirak et al., 2018). We have now described for the first time that SJW may be beneficial for GABA-mediated addictive diseases. To test this hypothesis, it requires double-blind randomized and laboratory-relied studies.

Authors' contributions

All authors were directly involved in the care of the patient. S. Moeller, A. Olek and H.H.O. Müller wrote the manuscript. A. Sitter, R. Wang, U. Darrelmann and A. Philipsen reviewed and revised the manuscript. No medical writer.

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Declaration of Competing Interest

None declared.

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References

- Baureithel, K.H., Buter, K.B., Engesser, A., Burkard, W., Schaffner, W., 1997. Inhibition of benzodiazepine binding in vitro by amentoflavone, a constituent of various species of Hypericum. *Pharm. Acta Helv.* 72, 153–157.
- Blanco, C., Han, B., Jones, C.M., Johnson, K., Compton, W.M., 2018. Prevalence and correlates of benzodiazepine use, misuse, and use disorders among adults in the United States. *J. Clin. Psychiatry* 79.
- Butterweck, V., 2003. Mechanism of action of St John's wort in depression: what is known? *CNS Drugs* 17, 539–562.
- Fluyau, D., Revadigar, N., Manobianco, B.E., 2018. Challenges of the pharmacological management of benzodiazepine withdrawal, dependence, and discontinuation. *Ther. Adv. Psychopharmacol.* 8, 147–168.
- Khan, M., Subhan, F., Khan, A.U., Abbas, M., Ali, G., Rauf, K., Gilani, A.H., 2014. Nature cures nature: Hypericum perforatum attenuates physical withdrawal signs in opium dependent rats. *Pharm. Biol.* 52, 586–590.
- Muller, H., Seifert, F., Maler, J.M., Kornhuber, J., Sperling, W., 2012. Agomelatine reduces craving in benzodiazepine addicts: a follow-up examination of three patients. *Singapore Med. J.* 53, e228–230.
- Schmidt, M., Butterweck, V., 2015. The mechanisms of action of St. John's wort: an update. *Wien. Med. Wochenschr.* 165, 229–235.
- Soleymani, S., Bahramsoltani, R., Rahimi, R., Abdollahi, M., 2017. Clinical risks of St John's Wort (*Hypericum perforatum*) co-administration. *Expert Opin. Drug Metab. Toxicol.* 13, 1047–1062.
- Zanoli, P., 2004. Role of hyperforin in the pharmacological activities of St. John's Wort. *CNS Drug Rev.* 10, 203–218.
- Zirak, N., Shafiee, M., Soltani, G., Mirzaei, M., Sahebkar, A., 2018. Hypericum perforatum in the treatment of psychiatric and neurodegenerative disorders: Current evidence and potential mechanisms of action. *J. Cell. Physiol.* 234 (6), 8496–8508.

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