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**Introduction:** As the use of medical cannabis continues to increase <sup>1</sup>, prescribers and other healthcare professionals need to continually update their knowledge of patients' characteristics that may affect treatment, such as age, co-occurring use of other drugs, and sex. **Aims:** To provide the necessary basis for further research on sex differences in medicinal cannabis treatment. **Methods:** Literature review of publications addressing how sex affects metabolism and effects of medical cannabis. Internet databases were searched for relevant terms (i.e. "sex

differences THC") and reviewers reached a final consensus on the inclusion of studies. **Results:** Preliminary data from the first large German non-interventional survey of medical cannabis users suggests that males and females respond differently to medicinal cannabis.<sup>2</sup> There is a significant gender difference in density of the cannabinoid receptor CB1 in several brain areas; availability of CB1 increases in women with age in basal ganglia, limbic regions, lateral temporal cortex, and hippocampus, but not in males; males and females exhibit differences in metabolism of 11-OH-THC, the primary metabolite of THC.<sup>3</sup> Animal research suggests a reduction in NMDA receptors in females after adolescent THC exposure; males respond with a higher expression of

NMDA receptors.<sup>4</sup> Furthermore, sex differences were found in the gene expression patterns across different brain regions.<sup>5</sup> **Conclusions:** Our literature review indicates that there are significant gender differences in response to medical cannabis therapy. These could be due to differences in THC metabolism and receptor expression. Future analyses of data from clinical studies and non-interventional surveys should examine phenotypic differentiation between the sexes in cannabis efficacy for treating different symptoms, side-effects, and pharmacokinetics, in order to enable patient- and sex-specific therapies with medicinal cannabis. **Keywords:** THC, Sex Differences, Cannabinoids, Literature Review, Precision Medicine. **Acknowledgements:** none

# Males and females respond differently to THC; differences are evident, though not confined to density and availability of CB1 receptors, 11-OH-THC metabolism, and NMDA receptors dynamics.

# Practitioners should be aware of sex differences in responses to THC in order to provide the best cannabinoid therapy to patients.

## References

1. Fasesan, O. A. (2022). Legalisation and Liberalisation of Cannabis: The Benefits and Drawbacks of the Global Trend. *Annals of Health Research*, 8(3), 165-176.
2. Schmidt-Wolf, G., & Cremer-Schaeffer, P. (2021). Three years of cannabis as medicine-preliminary results of the survey accompanying the prescription of medical cannabis in Germany. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz*, 64(3), 368-377.
3. Calakos, K. C., Bhatt, S., Foster, D. W., & Cosgrove, K. P. (2017). Mechanisms underlying sex differences in cannabis use. *Current addiction reports*, 4(4), 439-453.
4. Zamberletti, E., Prini, P., Speziali, S., Gabaglio, M., Solinas, M., Parolaro, D., & Rubino, T. (2012). Gender-dependent behavioral and biochemical effects of adolescent delta-9-tetrahydrocannabinol in adult maternally deprived rats. *Neuroscience*, 204, 245-257.
5. Zuo, Y., Iemolo, A., Montilla-Perez, P., Li, H. R., Yang, X., & Telesse, F. (2022). Chronic adolescent exposure to cannabis in mice leads to sex-biased changes in gene expression networks across brain regions. *Neuropsychopharmacology*, 1-10.