

CANNA-TICS: Efficacy and Safety of Nabiximols in the Treatment of Adults with Chronic Tic Disorders

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Background

New treatment strategies are urgently needed for patients with Tourette Syndrome (TS) and chronic tic disorders (CTD), since current first-line therapies have several limitations. Based on case studies and two small randomized controlled trials (RCT), it has been suggested that cannabis-based medicines might be a promising new treatment option resulting not only in a reduction of tics, but also an improvement in a variety of comorbidities such as attention deficit/hyperactivity disorder (ADHD). This study aimed to examine for the first time efficacy and safety of the cannabis extract nabiximols (a complex botanical mixture containing THC, CBD (at a 2.7:2.5 ratio) and other cannabinoid and non-cannabinoid components that was provided by GW Pharmaceuticals Ltd.) in an investigator-initiated, multicenter, placebo-controlled, parallel-group, phase IIIb RCT funded by the German Research Foundation (DFG).

Criteria for Inclusion

- Age ≥18 years
- Total Tic Score of the Yale Global Tic Severity Scale (YGTSS-TTS) > 14 for patients with TS or YGTSS-TTS > 10 for patients with chronic motor or vocal tics only
- Clinical Global Impression–Severity Score (CGI-S) ≥ 4
- Stable Medication for tics and comorbidities for at least 30 days and during the study
- Prevention of pregnancy

Criteria for Exclusion

- Comorbidity when unstable and/or in need of an therapy
- Ongoing behavioral treatment for tics
- History of schizophrenia, psychotic, severe personality, pervasive developmental disorder, suicidal ideation with intent to act or a plan to act in the 12 months
- Current clinical diagnosis of substance abuse or dependence and compulsive disorder
- Secondary tic disorders
- Severe somatic diseases
- Pregnancy or lactation period
- Use of cannabis or cannabinoid-based medicine in the 30-day period prior to study entry

Methods

A total of 98 patients with TS or CTD were randomized across 6 study sites with a 2:1 ratio into a nabiximols and a placebo arm. The primary efficacy endpoint was defined as tic reduction of at least 25% according to the YGTSS-TTS after 9 weeks of stable treatment. As a key secondary endpoint, in 2 study sites fitness to drive was investigated with respect to a non-inferiority margin of -32%. The primary as well as the key secondary analysis were performed with a center-stratified Mantel-Haenszel estimate for the risk difference (nabiximols – placebo). To examine effects on tics (as assessed by YGTSS-TTS) in specific subgroups at different time points, mixed linear models were used. Adverse and severe adverse events were analyzed.

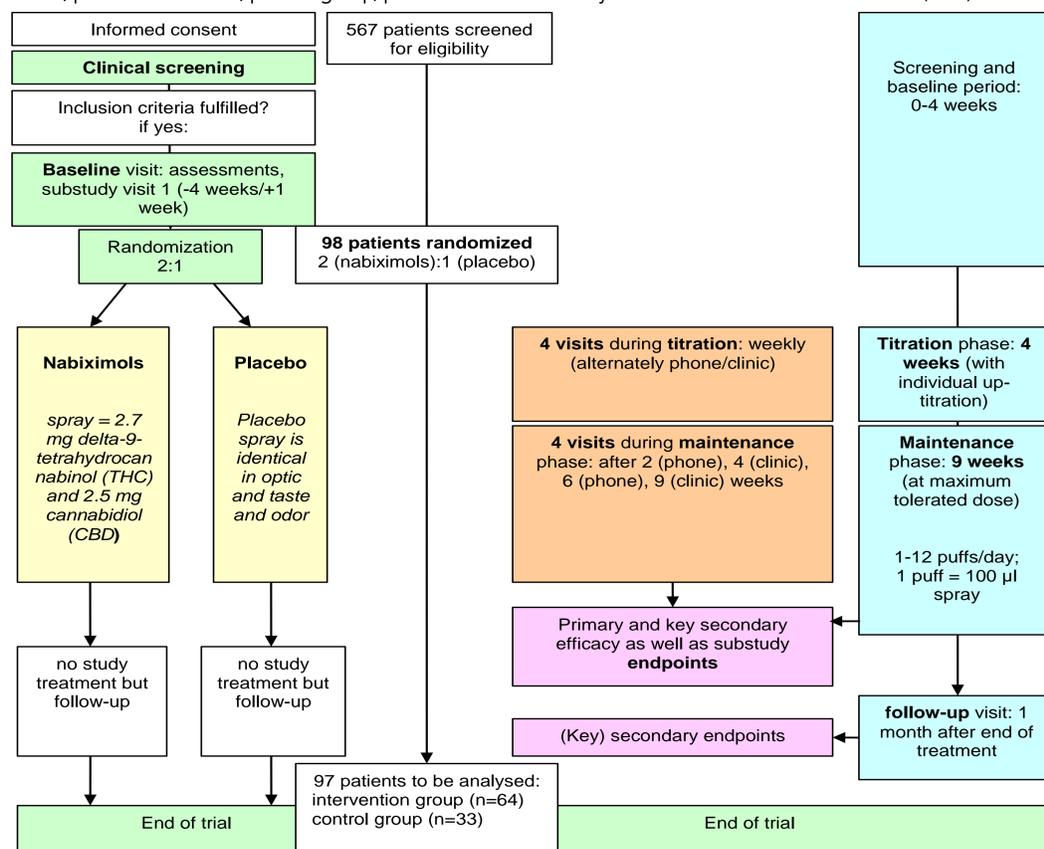


Fig. 1: Trial Flow

Results

Sample: 97 patients (75.3% males, mean age=36.6 years (SD=13.3)) received treatment and were analyzed

Endpoints: In the primary analysis, 14/64 (21.9%) patients in the nabiximols, but only 3/33 (9.1%) in the placebo group met the responder criterion. However, in the intention-to-treat population (ITT), we failed to demonstrate superiority of nabiximols over placebo with respect to tic reduction according to YGTSS-TTS (-0.13 [-0.28; 0.01], $p=0.07$). Further subgroup analyses, however, showed differences depending on patients' sex and comorbidities with larger tic reduction in males (-1.9 [-3.7; -0.1], $p=0.04$) compared to females (1.9 [-1.3; 5.1], $p=0.24$) and patients with comorbid ADHD (-6.1 [-12.0; -0.2], $p=0.04$) compared to those without (-0.33 [-2.0; 1.3], $p=0.69$). 25/35 (71.4%) patients in the nabiximols and 9/16 (56.3%) in the placebo group met the criterion for fitness to drive in the per-protocol population (PPP). Thus, non-inferiority of the nabiximols group compared to the placebo group could be demonstrated (risk difference 0.14 [-0.15; 0.42]).

Safety Analyses: Safety analyses did not show any substantial differences between nabiximols and placebo. However, after treatment with nabiximols, a higher number of drug-specific adverse events (e.g. dry mouth) was reported.

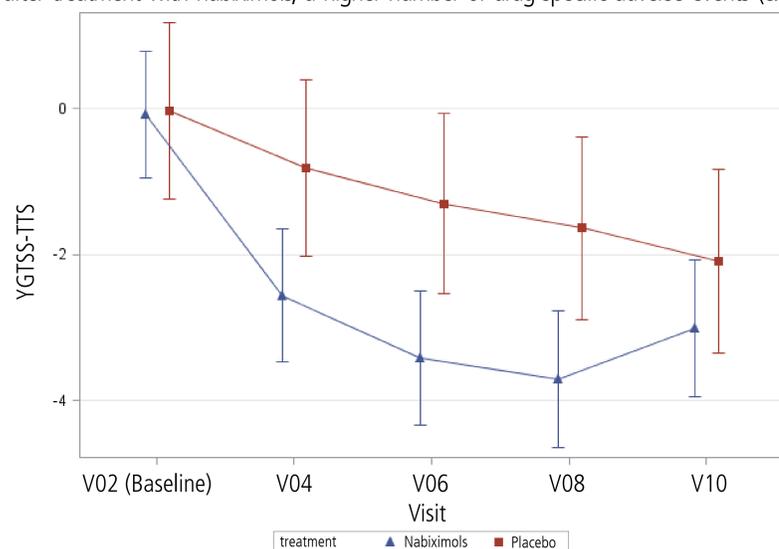


Fig. 2: Change from Baseline (YGTSS-TTS); Least Square (LS) Means derived from a Mixed Model Repeated Measures (ITT Population); V02 (Baseline)=Baseline Visit; V04=Titration Phase (+2 weeks); V06=Titration Phase (+4 weeks); V08=Maintenance Phase (+8 weeks); V10=Ende of Treatment (+13 weeks)

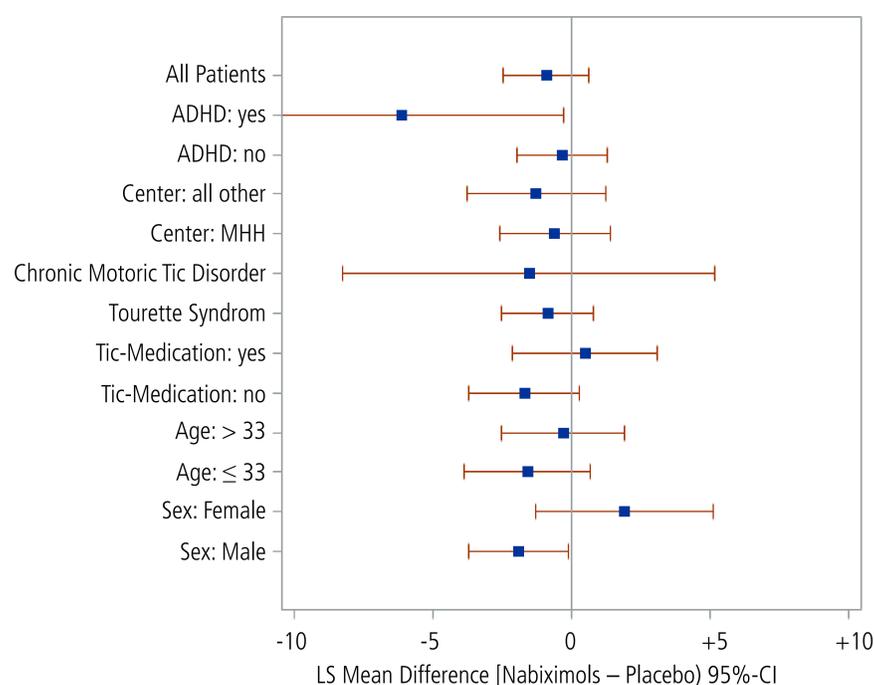


Fig. 3: Subgroup Analyses; Change from Baseline (YGTSS-TTS); Least Square (LS) Mean Difference (Nabiximols – Placebo) derived from a Mixed Model Repeated Measures (ITT Population)

Conclusion

Although the number of responders is larger in the nabiximols group compared to placebo, the CANNA-TICS study failed to demonstrate superiority. However, first results indicate that male patients and patients with ADHD benefit more than others. Most important for use of cannabinoids in clinical routine practice, the results suggest that fitness to drive was not impaired by use of nabiximols. Based on our data, nabiximols can be regarded as a safe treatment.

References

- Bhikram, T., Elmaghraby, R., Abi-Jaoude, E., & Sandor, P. (2021). An International Survey of Health Care Services Available to Patients With Tourette Syndrome. *Frontiers in Psychiatry*, 12(February), 1–9. <https://doi.org/10.3389/fpsy.2021.621874>
- Müller-Vahl, K. R., Koblenz, A., Jöbges, M., Kolbe, H., Emrich, H. M., & Schneider, U. (2001). Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. *Pharmacopsychiatry*, 34(1), 19–24. <https://doi.org/10.1055/s-2001-15191>
- Müller-Vahl, K. R., Schneider, U., Prevedel, H., Theloe, K., Kolbe, H., Daldrup, T., & Emrich, H. M. (2003). Delta 9-Tetrahydrocannabinol (THC) is Effective in the Treatment of Tics in Tourette Syndrome. *The Journal of Clinical Psychiatry*, 64(4). <https://doi.org/10.4088/JCP.v64n0417>
- Müller-Vahl, K. R., Szejko, N., Verdellen, C., Roessner, V., Hoekstra, P. J., Hartmann, A., & Cath, D. C. (2021). European clinical guidelines for Tourette syndrome and other tic disorders: summary statement. *European Child & Adolescent Psychiatry*. <https://doi.org/10.1007/s00787-021-01832-4>
- Pringsheim, T., Holler-Managan, Y., Okun, M. S., Jankovic, J., Piacentini, J., Cavanna, ... Oskoui, M. (2019). Comprehensive systematic review summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*, 92(19), 907–915. <https://doi.org/10.1212/WNL.00000000000007467>
- Szejko, N., Jakubovski, E., & Müller-Vahl, K. R. (2018). Possible Role of the Endocannabinoid System in Tourette Syndrome. In W. J. Costain (Ed.), *Recent Advances in Cannabinoid Research* (pp. 119–136). IntechOpen. <https://doi.org/10.5772/intechopen.79895>