



CANNA-TICS: Efficacy and safety of oral treatment with nabiximols in adults with chronic tic disorders – Results of a prospective, multicenter, randomized, double-blind, placebo controlled, phase IIIb superiority study

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ABSTRACT

Preliminary data suggest that cannabis-based medicines might be a promising new treatment for patients with Tourette syndrome (TS)/chronic tic disorders (CTD) resulting in an improvement of tics, comorbidities, and quality of life. This randomized, multicenter, placebo-controlled, phase IIIb study aimed to examine efficacy and safety of the cannabis extract nabiximols in adults with TS/CTD (n = 97, randomized 2:1 to nabiximols:placebo). The primary efficacy endpoint was defined as a tic reduction of $\geq 25\%$ according to the Total Tic Score of the Yale Global Tic Severity Scale after 13 weeks of treatment. Although a much larger number of patients in the nabiximols compared to the placebo group (14/64 (21.9%) vs. 3/33 (9.1%)) met the responder criterion, superiority of nabiximols could formally not be demonstrated. In secondary analyses, substantial trends for improvements of tics, depression, and quality of life were observed. Additionally exploratory subgroup analyses revealed an improvement of tics in particular in males, patients with more severe tics, and patients with comorbid attention deficit/hyperactivity disorder suggesting that these subgroups may benefit better from treatment with cannabis-based medication. There were no relevant safety issues. Our data further support the role of cannabinoids in the treatment of patients with chronic tic disorders.

1. Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics with childhood onset. The majority of patients suffer from psychiatric comorbidities such as obsessive-

compulsive behavior/disorder (OCB/OCD), attention deficit/hyperactivity disorder (ADHD), anxiety, depression, rage attacks, and sleeping problems. Although several lines of evidence suggest an involvement of the dopaminergic system, abnormalities in several other neurotransmitter systems have also been demonstrated including the

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glutamatergic, GABAergic, serotonergic, and the endocannabinoid systems (ECS) (Berding et al., 2004; Müller-Vahl et al., 2020; Singer and Augustine, 2019; Szejko et al., 2020). As first line treatments for tics, behavioral interventions and/or pharmacotherapy with antipsychotics are recommended (Müller-Vahl et al., 2022b). However, efficacy of available treatments is limited, antipsychotics often cause intolerable side effects, and up to 30% of patients do not respond adequately (Martino et al., 2021). In treatment-refractory cases, experimental approaches can be considered including deep brain stimulation. In patients with clinically relevant comorbidities additional treatments must be initiated, since so far, no treatments are known that improve both tics and comorbid conditions.

There is increasing evidence suggesting that cannabis-based medicines (CBM) may be a new treatment strategy that is well tolerated and improves tics and comorbidities. However, current data is limited to case reports or series, open label studies, and only three small randomized controlled trials (RCT) (Abi-Jaoude et al., 2022; Müller-Vahl et al., 2002, 2003) using pure tetrahydrocannabinol (THC), cannabis flowers, or extracts such as nabiximols (see additional literature overview in the Supplementary Material). This study aimed to examine for the first time efficacy and safety of a CBM in a large sample of adults with chronic tic disorders (CTD) by using the cannabis extract nabiximols.

2. Methods

2.1. Study design

For detailed information of the study design and methods please refer to Jakubovski et al. (2020). In brief, this study was a prospective, multicenter, randomized, double-blind, parallel group, placebo controlled, phase IIIb superiority study to demonstrate efficacy and safety of nabiximols in the treatment of adults with CTD. Patients were randomized between 4/2018 and 11/2020 at 6 study centers across Germany (Hannover, Lübeck, Aachen, München, Köln, Freiburg). The study protocol, patient consent form, and all amendments were approved by local ethics committees of the participating centers.

2.2. Patients

Main inclusion criteria were age ≥ 18 years, confirmed diagnosis of CTD according to DSM-5, at baseline, total tic score of Yale Global Tic Severity Scale (YGTSS-TTS) of ≥ 14 for patients with TS and ≥ 10 for patients with chronic motor (CMT) or vocal tic disorders (CVT) and a score on the Clinical Global Impression scale for severity (CGI-S) of ≥ 4 . Anti-tic medication had to be on a stable dose for at least 30 days before entering the study. Main exclusion criteria were: a history of schizophrenia, pervasive developmental disorders, comorbid conditions in primary need of therapy, a clinical diagnosis of substance use disorder, use of CBM in the 30 days before study entry, ongoing behavioral treatment for tics, and/or a positive delta-9-THC urine test at baseline. For further details on inclusion and exclusion criteria please refer to Jakubovski et al. (2020). Written informed consent was obtained before patients entered the study.

2.3. Randomization and masking

The study flowchart is depicted in Fig. 1. A total of 98 patients were randomized at a 2:1 ratio (nabiximols:placebo). One patient randomized to nabiximols never received any study medication and was therefore excluded from all analyses. Due to three protocol amendments, four study protocol versions were implemented. In the first amendment (11/2017, before first patient in), fitness-to-drive was defined as a key secondary endpoint and a pre-specified analysis strategy was described. The other two amendments were related to the resumption of recruitment after temporary halts due to different reasons (instability of investigational medicinal product labelling, alterations in the manufacturing chain).

At a blind review meeting involving all relevant parties, changes of the statistical analyses were defined with respect to the responder criterion, adjustment of analyses for study center, and the per protocol (PP) definition (see below).

2.4. Procedures

Medication was administered orally as a sublingual oromucosal spray with an individually flexible dose ranging from 1 to 12 puffs/day

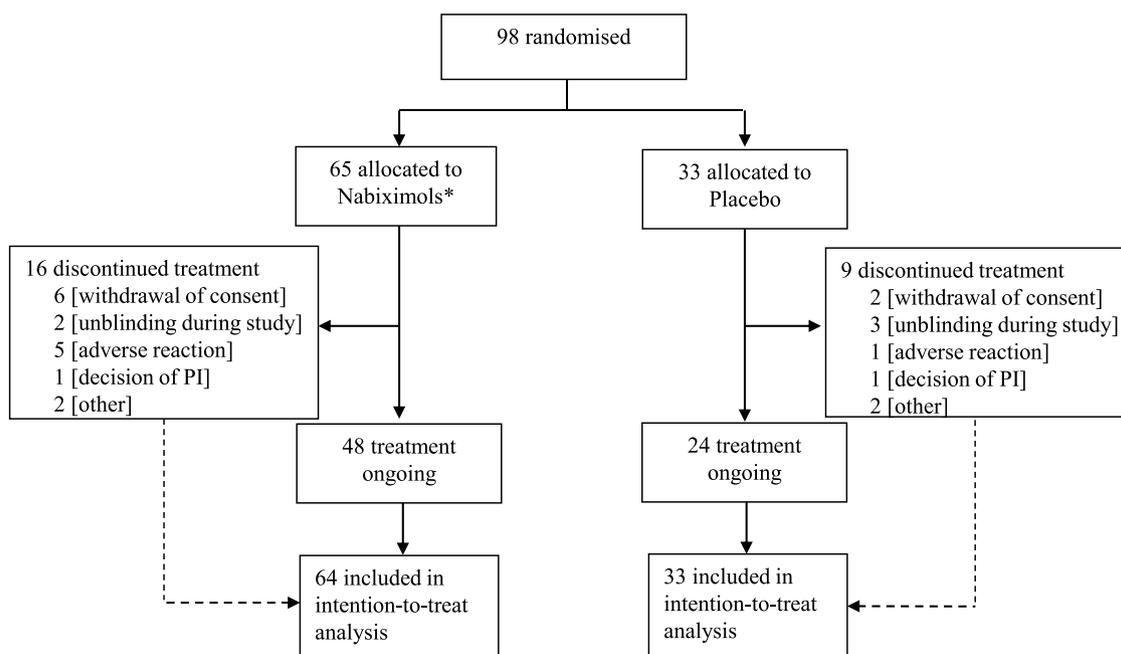


Fig. 1. Study Flowchart

*One patient never received any study medication and was therefore excluded from all analyses.

(1 puff nabiximols = 100 µl spray including 2.7 mg THC and 2.5 mg cannabidiol (CBD)) delivered flexible over the day as best suited for patients. The placebo spray was identical in visual appearance.

Patients were treated over 13 weeks including a 4-weeks titration phase continued by a treatment phase of 9 weeks with a stable dosage. For the first 4 days, dose could be increased the fasted by 1 spray every 2 days, and thereafter by 1 spray every day up to a maximum dose of 12 puffs/day (= 32.4 mg THC and 30 mg CBD or placebo). Altogether, 11 study visits were scheduled (screening, baseline, during titration phase (n = 4), during maintenance phase (n = 4), and follow-up visit 4 weeks after end of treatment).

2.5. Choice of primary measure

The primary outcome was the Total Tic Score of the Yale Global Tic Severity Scale (YGTSS-TTS) (Leckman et al., 1989). The YGTSS is the most widely used and most accepted validated rating scale for tics and is recommended as primary outcome measure in the European Guidelines for the treatment of tics (Szejko et al., 2022). Initially, the primary efficacy outcome of the study was defined as response to treatment according to a reduction in YGTSS-TTS of at least 30% after 9 weeks of stable treatment compared to baseline. At a blinded review meeting, the definition of the response criterion was changed from 30% to at least 25%, since a 25% reduction in the YGTSS-TTS has been demonstrated to be highly predictive of positive response (Jeon et al., 2013).

2.6. Secondary outcomes

As key secondary outcome, in a sub-study fitness-to-drive was investigated (results will be reported elsewhere). Further secondary endpoints included a variety of well-established psychometric scales: YGTSS, Adult Tic Questionnaire (ATQ), and Modified Rush Video-Based Tic Rating Scale (MRVS) for tics, Premonitory Urge for Tics Scale (PUTS) for premonitory urges, Gilles de la Tourette syndrome-Quality of Life Scale (GTS-QoL) for disease specific quality of life, Clinical Global Impression scale for improvement (CGI-I) for clinical global impairment, 12-item short-form Health Survey (SF-12) for general health and for psychiatric comorbidities: Conners' Adult ADHD Rating Scale (CAARS) for ADHD, Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for OCD, Beck Depression Inventory-II (BDI-II) for depression, Beck Anxiety Inventory (BAI) for anxiety, Rage Attacks Questionnaire for adults with GTS (RAQ-GTS) for rage attacks, Skala Impulsives-Verhalten-8 (I-8) for impulsivity, and Pittsburgh Sleep Quality Index (PSQI) for sleeping problems. All assessments were performed by qualified rater. To assess safety, at each study visit (serious) adverse events (AEs/SAEs) were documented, blood pressure and pulse were taken, and the Columbia-Suicide Severity Rating Scale (C-SSRS) was conducted. References for secondary and safety outcomes are given in the Supplementary Material.

2.7. Statistical analysis

The sample size calculation was based on a dataset obtained from a 1:1 randomized trial including 24 patients with TS undergoing 6 weeks of THC or placebo treatment (Müller-Vahl et al., 2003). The one-sided type-I-error was set to 2.5% and a power of 80% was presumed. Assuming that the relative reduction of YGTSS-TTS is normally distributed in each treatment group, probabilities for a reduction of at least 30% were calculated as 0.010 (placebo) and 0.294 (THC). This approach was chosen due to its higher robustness regarding the given small trial and provided similar, but slightly more conservative values than the observed responder rates of 0.00 and 0.33.

The primary analysis was conducted on the intention-to-treat (ITT) population including all patients that have been randomized and have taken at least one dosage of the study drug. The primary endpoint YGTSS-TTS was analyzed as a binary responder criterion. As determined in the blind review meeting, a patient was considered as a responder, if a

≥ 25% decrease in YGTSS-TTS at end of treatment (EoT, week 13) was observed compared to baseline. A Mantel-Haenszel estimate for the risk difference (placebo-nabiximols) and respective 95% confidence intervals (CIs) stratified by center was used. A negative risk difference means a favour for nabiximols and can directly be aligned to the results of the continuous values of YGTSS-TTS, where a larger reduction is interpreted as a favour for nabiximols. Superiority of nabiximols can be concluded if the upper boundary of the 95% CI is below 0. Since almost half of patients (55.1%) were recruited at the study center at Medical School Hannover (MHH), we decided at the blind review meeting to pool all other study centers and to analyze MHH vs. other centers. According to the pre-specification, patients with missing values of the YGTSS-TTS were equally counted as non-responders in both treatment arms. Sensitivity analyses were conducted for the initially planned responder criterion (decrease in YGTSS-TTS at EoT ≥ 30%). Both criteria were also analyzed in the PP-population comprising all patients who were compliant until EoT. Patients with reported (self-)unblinding were excluded from the PP-population if it could not be assured that the assessment of the primary endpoint was blinded. Assessment of protocol deviations was conducted in a blinded manner.

Since no prognostic variables were known, randomization and primary analysis were stratified by center only. We investigated the prognostic value of study center (MHH/other), gender (male/female), age (≤/ > median), concomitant anti-tic and psychopharmacology medication (yes/no), prior use of cannabis or other CBM (yes/no), type of tic disorder (TS/CMT/CVT), and tic severity (YGTSS-TTS < 28/ ≥ 28) on the dichotomized YGTSS-TTS-score. In addition, we examined the influence of the most common comorbidities: ADHD, depression, OCD, and anxiety. For respective definitions, please refer to the Supplementary Appendix.

Mantel-Haenszel estimate for the treatment difference was used adjusted for center (MHH/other). For the change of YGTSS-TTS an ANCOVA model was used adjusted for baseline, treatment, and center (MHH/other).

Secondary endpoints were analyzed exploratory in the ITT-population. Continuous variables at EoT were assessed as change from baseline in an ANCOVA model adjusted for the respective baseline values, center (MHH/other), and treatment group. Missing values at baseline were replaced by the overall group mean, while all other missing values were replaced by the last-observation-carried-forward method (LOCF). To examine the impact of missing values on treatment effects, we performed several sensitivity analyses (for details see Supplementary Appendix). For all models least square means (LSM) differences for the difference between nabiximols and placebo and respective 95% CIs were estimated. A negative LSM difference indicates a favour for nabiximols. Binary variables were assessed in line with the primary analysis. Improvement on the CGI-I was analyzed as a binary responder criterion. Patients were classified as "responder" if an improvement of 1-2 in the CGI-I was observed. Secondary analyses with a descriptive p-value smaller than 0.1 were assessed as a substantial trend.

The safety population included all patients who received at least one dosage of the study medication. Absolute and relative frequencies of AEs and SAEs were calculated and compared using two-sided Chi-squared tests. In addition, vital signs and suicidality as assessed by CSSRS were analyzed using two-sided t-tests and Chi-squared tests. AEs were coded according to MedDRA (Version: 22.1) and are presented by system organ class (SOC).

All analyses were performed using SAS 9.4. The trial has been registered at clinicaltrials.gov (number: NCT03087201, date of registration: March 22, 2017; last update: December 10, 2020, <https://clinicaltrials.gov/ct2/show/NCT03087201?term=canna-tics&draw=2&rank=1>).

2.8. Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, and writing of the manuscript.

3. Results

Baseline characteristics of the ITT-population in the nabiximols and placebo group showed no relevant differences (see Table 1). All 97 patients were treated as randomized.

While in the nabiximols group, 21.9% (14/64) responded to treatment, in the placebo group only 9.1% (3/33) of patients responded. The Mantel-Haenszel estimate for the risk difference (placebo-nabiximols) was -0.13 [95% CI -0.28 to 0.01; $p = 0.07$]. Results for the PP analysis and the originally planned responder criterion were in concordance with the results of the primary analysis (see Table 2). However, in all models the upper boundary of the 95%-confidence interval was not below 0. Thus, the study failed to demonstrate superiority of nabiximols with respect to the primary efficacy outcome, although descriptively clear differences between both groups were seen in Fig. 2.

To explore prognostic influence of further factors, we examined treatment effects of the responder criterion and the change in YGTSS-TTS within subgroups. Overall, we observed consistent treatment effects across all subgroups (see Fig. 3 for change in YGTSS-TTS and Supplementary Fig. 1 for the responder criterion). Interestingly, according to both the responder criterion and change in YGTSS-TTS, males (LSM difference -1.89 [95% CI -3.69 to -0.10; $p = 0.04$]) and patients with more severe tics at baseline (YGTSS-TTS ≥ 28) (LSM difference -2.06 [95% CI -4.08 to -0.05; $p = 0.04$]) benefitted more from treatment with nabiximols compared to females and patients with less severe tics. In patients with comorbid ADHD, we found a large effect in the nabiximols group ($n = 12$) on the change in YGTSS-TTS (LSM difference -6.13 [95% CI -12.02 to 0.24; $p = 0.06$]).

In line with the primary analysis, nabiximols group numerically favours for several secondary endpoints. We observed improvements when using other tic assessments with a higher mean change in (i) the YGTSS-Global Severity Score (YGTSS-GSS, LSM difference -5.38 [95% CI -11.06 to 0.03; $p = 0.06$]), (ii) the total score of the ATQ (LSM difference -8.41 [95% CI -17.24 to 0.42; $p = 0.06$]), (iii) the motoric subscale of the ATQ (LSM difference -8.72 [95% CI -14.36 to -3.07; $p = 0.003$]), and (iv) the MRVS (LSM difference -0.92 [95% CI -1.94 to 0.09; $p = 0.08$]). In addition, a trend was observed for measures of quality of life as assessed by GTS-QoL-normalization (LSM difference -4.13 [95% CI -8.65 to 0.39; $p = 0.07$]), GTS-QoL-VAS (Visual Analogue Scale) (LSM difference 5.55 [95% CI -0.69 to 11.8; $p = 0.08$]), and overall impairment according to YGTSS-Impairment (LSM difference -4.12 [95% CI -8.45 to 0.22; $p = 0.06$]). In contrast, no differences between the nabiximols and placebo group were detected with respect to general health according to SF-12 (physical and mental scores), comorbidities including ADHD according to CAARS, OCD according to Y-BOCS, depression according to BDI-II, anxiety according to BAI, rage attacks according to RAQ, sleep problems according to PSQI, impulsivity according to I-8, and premonitory urges according to PUTS (9- and 10-items versions) (see Table 3).

To assess the impact of missing values, we performed sensitivity analyses for all secondary endpoints. Importantly, findings were completely in line with above reported data with respect to YGTSS-GSS, YGTSS-Impairment, ATQ motoric subscale, MRVS, and GTS-QoL-VAS (see Supplementary Table 4). In addition, we found a clear trend for an improvement of comorbid depression (according to BDI-II) after treatment with nabiximols.

On average patients in the placebo group used significantly more puffs compared to those in the nabiximols group: 7.38 ± 2.04 versus 5.58 ± 2.36 puffs/day ($p = 0.0003$) during the titration phase and 9.19 ± 3.07 versus 7.21 ± 3.42 puffs/day ($p = 0.01$) during the maintenance phase.

Table 1

Baseline characteristics of the Intention-to-treat population.

	Nabiximols (n=64)	Placebo (n=33)
Gender		
Female	15 (23.4%)	9 (27.3%)
Male	49 (76.6%)	24 (72.7%)
Age (years)	37.4 (14.3)	34.9 (11.2)
Age at tic onset* (years)	7.9 (3.8)	9.1 (5.7)
Positive family history for tics and psychiatric disorders		
Yes	42 (65.6%)	21 (63.6%)
No	22 (34.4%)	12 (36.4%)
Concomitant anti-tic medication		
Yes	19 (29.7%)	5 (15.2%)
No	45 (70.3%)	28 (84.8%)
Concomitant psychopharmacological medication		
Yes	33 (51.6%)	11 (33.3%)
No	31 (48.4%)	22 (66.7%)
Prior use of cannabis		
Yes	22 (34.4%)	11 (33.3%)
No	42 (65.6%)	22 (66.7%)
Diagnosis according to DSM-5		
Tourette Syndrome	58 (90.6%)	31 (93.9%)
Chronic motor tic disorder	6 (9.4%)	2 (6.1%)
Chronic vocal tic disorder	0 (0%)	0 (0%)
Tic severity (YGTSS-TTS)	28.6 (8.6)	29.3 (8.8)
ADHD		
yes	12 (18.8%)	2 (6.1%)
no	52 (81.3%)	31 (93.9%)
Depression		
yes	30 (46.9%)	13 (39.4%)
no	34 (53.1%)	20 (60.6%)
OCD		
yes	13 (20.3%)	4 (12.1%)
no	51 (79.7%)	29 (87.9%)
Anxiety*		
yes	28 (46.7%)	13 (39.4%)
no	32 (53.3%)	20 (60.6%)
Rage attacks		
RAQ ≤ 9 (=median)	35 (54.7%)	18 (54.6%)
RAQ > 9	29 (45.3%)	15 (45.5%)
SF-12 - physical score*		
SF-12 psy ≤ 50 (=median)	27 (42.2%)	10 (32.3%)
SF-12 psy > 50	37 (57.8%)	21 (67.7%)
SF-12 - mental score*		
SF-12 ment ≤ 50	35 (54.7%)	14 (45.2%)
SF-12 ment > 50	29 (45.3%)	17 (31%)
Study center		
MHH	36 (56.3%)	18 (54.5%)
Others	29 (45.3%)	15 (45.5%)

Data presented in n (%), mean (SD). YGTSS-TTS-Total Tic Score of the Yale Global Tic Severity Scale. ADHD-attention deficit/hyperactivity disorder. Depression defined as BDI-II ≥ 9 . OCD-obsessive-compulsive disorder or thoughts defined as Y-BOCS ≥ 16 . Anxiety defined as BAI ≥ 8 . MHH-Hannover Medical School. *Data not available for all randomized patients.

Table 2
Primary endpoint analyses.

	Nabiximols	Placebo	RD [95% CI]	p-value
ITT, n	64	33		
25%-responder crit.	14 (21.9%)	3 (9.1%)	-0.13 [-0.28; 0.01]	0.07
30%-responder crit.	8 (12.5%)	1 (3.0%)	-0.10 [-0.19; 0.0022]	0.06
PP, n	48	24		
25%-responder crit.	11 (22.9%)	2 (8.3%)	-0.16 [-0.32; 0.005]	0.06
30%-responder crit.	5 (10.4%)	1 (4.2%)	-0.08 [-0.19; 0.03]	0.14

Responder crit. – responder criterion. ITT-intention-to-treat. PP-per-protocol. RD-risk difference. CI – confidence interval. p-value for superiority.

Numbers and type of AEs/SAEs are reported in Table 4. No suspected unexpected serious adverse event (SUSAR) occurred. No patient died and no patient experienced permanent harm. Only 2 SAEs were observed, one in each treatment group. After treatment with nabiximols, one participant experienced temporal worsening of tics (SOC: psychiatric disorders), but fully recovered. In the placebo group, a pregnancy occurred in a male participant's female partner (SOC: social circumstance). The pregnancy was terminated by uncomplicated elective abortion solely for personal reasons after the pregnant woman had been in good overall condition during all gynecological check-ups. Both events were assessed as not treatment related by the responsible investigator and sponsor's delegate for pharmacovigilance. A significantly larger proportion of patients in the nabiximols group experienced at least one AE compared to the placebo group (95.3% vs. 78.8%, $p = 0.03$). Altogether, in the nabiximols group a total of 315 AEs was observed in 61/64 patients, while in the placebo group 116 AEs in 26/33 patients occurred. No substantial differences were observed with respect to the type of AEs. All AEs were consistent with the well-known AE side effect profile of nabiximols. However, a potential causal relation to study medication for at least one AE was found in a significantly larger number of patients in the nabiximols group ($n = 58$ (90.6%), $p = 0.001$) compared to the placebo group ($n = 21$, 63.6%). For further information on SOCs of AEs per event and per patient see Supplementary Appendix (Supplementary Table 2). No substantial differences were observed between treatment groups with respect to blood pressure, pulse (see Supplementary Figs. 1, 2 and 3), and suicidality.

4. Discussion

The present study is the first large-scale RCT providing data on efficacy and safety of a CBM in the treatment of adult patients with TS or other CTD. Using the orally administered cannabis plant extract nabiximols, a larger number of patients in the nabiximols compared to the placebo group responded to treatment defined as a tic reduction of at least 25% (compared to baseline) as assessed by YGTSS-TTS (21.9% vs. 9.1%). The respective estimated treatment effect was consistent across all statistical analyses and showed a clear, but not statistically significant trend with a p -value of 0.07. Thus, we formally failed to demonstrate efficacy of nabiximols. However, sensitivity analyses as well as a supportive analysis using the YGTSS-TTS as a continuous variable in a mixed linear model were in line with the primary analysis suggesting numerical superiority of nabiximols over placebo in the reduction of tics after 9 weeks of treatment. Beneficial effects of nabiximols were further supported by trends in the YGTSS-GSS, the total and motoric subscores of the tic self-assessment ATQ, and the video tic assessment MRVS. In line with this data, we detected substantial trends towards improvement using different assessments for quality of life (GTS-QoL-VAS, GTS-QoL-normalization, and YGTSS-impairment). Our results corroborate previous data suggesting that THC containing CBM are effective in the treatment of tics and improve patients' quality of life (Abi-Jaoude et al., 2022). Since 1988 (Sandyk and Awerbuch, 1988) in several open uncontrolled case studies (see additional literature overview in the Supplementary Material) beneficial effects of cannabinoids have been reported in patients with TS either after inhalation of cannabis flowers or – in a smaller number of cases – oral intake of THC or cannabis extracts including nabiximols. So far, only three small RCTs not exceeding 24 patients, respectively, have been published suggesting that doses of up to 10 mg oral THC improve tics (Abi-Jaoude et al., 2022; Müller-Vahl et al., 2002, 2003).

Remarkably, subgroup analyses of the YGTSS-TTS revealed that males, patients with more severe tics at baseline, and those with comorbid ADHD benefitted more from treatment with nabiximols. Sex dependency is of clinical interest, since TS is three to four times more common in males compared to females. Furthermore, also in cannabinoid-mediated analgesia it has been suggested that response to

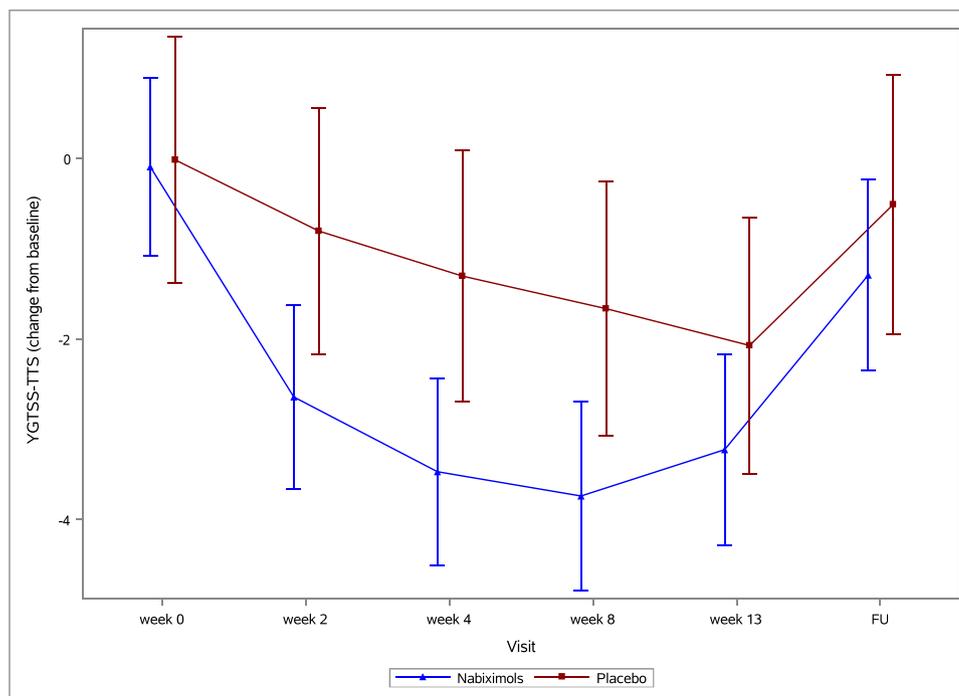


Fig. 2. Tic Severity during the course of the Study after Treatment with Nabiximols compared to Placebo

Displayed are least square means of the change from baseline to follow-up visit (FU) of the Total Tic Score of the Yale Global Tic Severity Scale (YGTS-TTS) derived from the mixed linear model. In the model repeated measures with a first-order autoregressive covariance structure, baseline values and center were included. Missing values are not replaced. FU is the follow-up visit 4 weeks after end of treatment.

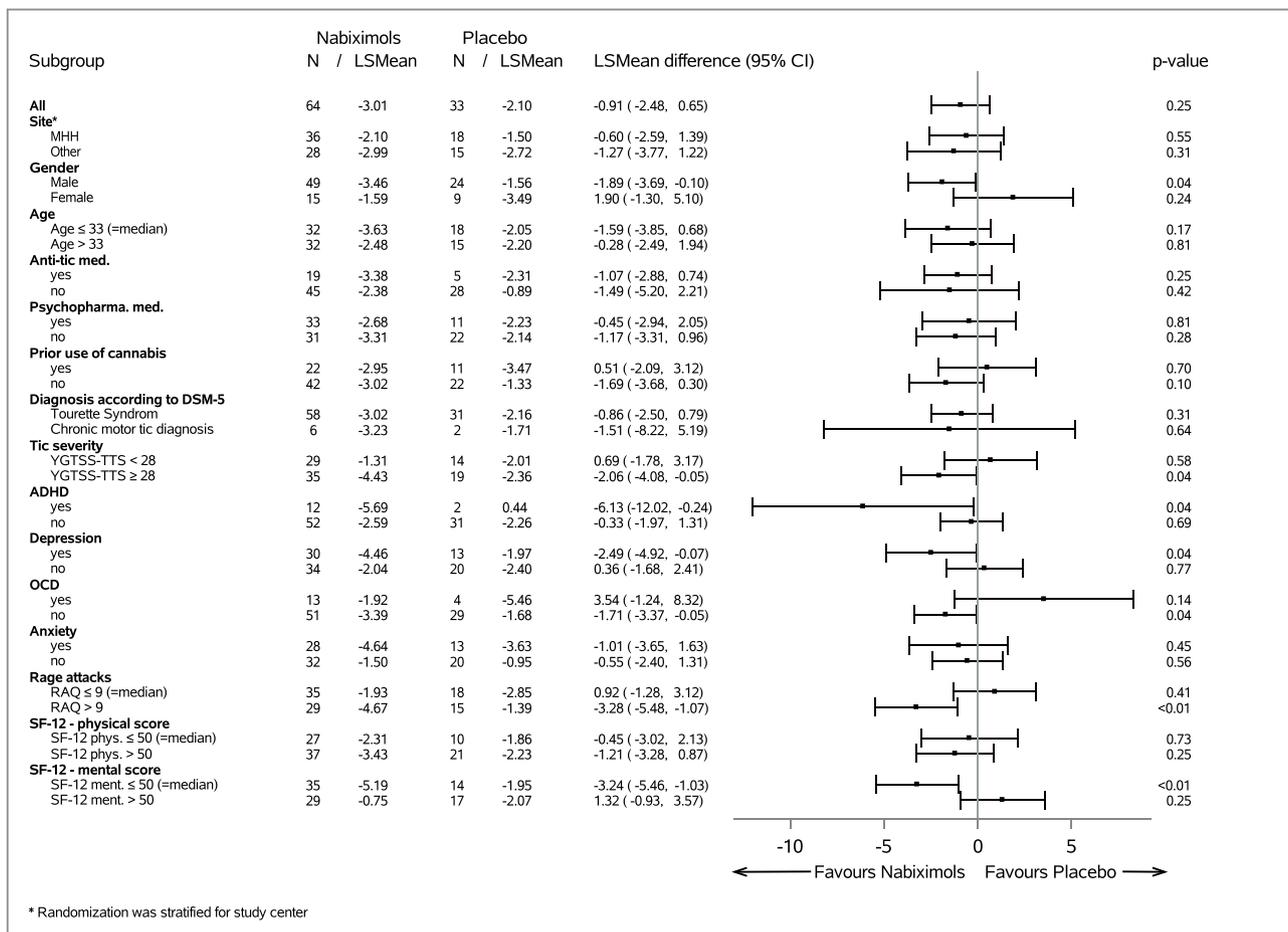


Fig. 3. Change in Tic Severity as assessed by YGTSS-TTS: Results of subgroups analyses

Displayed are LSMeans of change from baseline to end of treatment derived from the mixed linear model for the difference nabiximols-placebo. In the model different time points, baseline values and center were included. Missing values are not replaced. LSMeans-least square mean. CI-Confidence interval. MHH-Hannover Medical School. Anti-tic med.-Anti-tic medication. Psychopharma. med.-Psychopharmacological medication. DSM-Diagnostic and Statistical Manual of Mental Disorders. YGTSS-TTS-Yale Global Tic Severity Scale-Total Tic Score. ADHD-Attention Deficit Hyperactivity Disorder. OCD-Obsessive Compulsive Disorder. RAQ-Rage Attack Questionnaire. SF-12-Short Form-12.

treatment depends on sex (Blanton et al., 2021). These clinical findings are in line with preclinical data, demonstrating sex differences in cannabinoid receptor expression, function of the ECS, and response to cannabis use and to treatment with CBM (Blanton et al., 2021). Better treatment response in more severely affected patients might be related to methodological aspects, since limitations of the YGTSS in assessing tic severity are well known (Haas et al., 2021). With respect to the influence of comorbid ADHD, our data are less robust, since results obtained from change of YGTSS-TTS showed a large effect, while this was not the case for those of the responder criterion. This discrepancy might be related to the much larger group of patients with comorbid ADHD in the nabiximols group (n = 12) compared to the placebo group (n = 2). Furthermore, only one patient with comorbid ADHD was female and results might be influenced by detected sex difference. In any case, a possible influence of comorbid ADHD is of clinical relevance, since ADHD is a common comorbidity in TS occurring in about 60% of patients and is more common in males compared to females (Baizabal-Carvallo and Jankovic, 2022). Interestingly, similarly to our data using nabiximols, for α2-adrenergic receptor agonists such as clonidine it has also been suggested that comorbid ADHD may moderate efficacy in the treatment of tics in patients with TS (Weisman et al., 2013). These findings suggesting that effectiveness of anti-tic drugs depends on comorbid ADHD are in line with recent data from genetic studies demonstrating that genetic aetiology shared between TS and ADHD differs from that shared between TS and OCD (Yang et al., 2021). While in this study, we found

no beneficial effects of nabiximols on ADHD symptoms - based on very conservative diagnostic criteria for the diagnosis of ADHD (for details please refer to the Supplementary Appendix) resulting in only 14 patients with comorbid ADHD - there is evidence that nabiximols may also improve ADHD symptoms as suggested by a small RCT in 30 patients with ADHD (without TS) (Cooper et al., 2017). This observation is in line with results obtained from a study using the endocannabinoid modulator Lu AG06466 (previously ABX-1431), a highly selective inhibitor of monoacylglycerol lipase (MAGL), the primary enzyme involved in the degradation of the endocannabinoid 2-arachidonoylglycerol (2-AG). In this RCT, a non-significant reduction of ADHD symptoms was observed in patients with TS, while no beneficial effect on tics was detected (Müller-Vahl et al., 2021). Taking together, it is unlikely that in our study tics in patients with TS plus comorbid ADHD improved only secondary due to reduced hyperactivity, improved concentration, and reduced stress. In future studies using CBM in the treatment of patients with TS, possible effects on tics in relation to comorbid ADHD should be taken into consideration.

From available literature it is suggested that in patients with TS, CBM may improve not only tics, but also premonitory urges preceding the tics as well as a wide spectrum of comorbidities including ADHD, OCB/OCD, depression, anxiety, self-injurious behavior, impulsivity, rage attacks, sleeping problems, and quality of life (see additional literature overview in the Supplementary Material). In this study, we found a trend towards improvement of patients' quality of life and a significant improvement

Table 3
Exploratory secondary outcome measures.

Symptom	Measurement	Treatment		LSM difference [95% CI]	p-value
		Nabiximols (n=64) LSM	Placebo (n=33) LSM		
Tics	YGTSS-TTS	-3.01	-2.10	-0.91 [-2.48; 0.65]	0.25
	YGTSS (motoric subscale)	-1.88	-0.96	-0.93 [-2.16; 0.31]	0.14
	YGTSS (vocal subscale)	-0.91	-0.95	0.04 [-1.14; 1.22]	0.95
	YGTSS-GSS	-10.43	-5.05	-5.38 [-11.06; 0.30]	0.06
	ATQ (motoric subscale)	-9.13	-0.42	-8.72 [-14.36; -3.07]	0.003
	ATQ (vocal subscale)	-3.88	-4.73	0.85 [-3.88; 5.59]	0.72
	ATQ (total score)	-12.99	-4.58	-8.41 [-17.24; 0.42]	0.06
	MRVS	-1.10	-0.18	-0.92 [-1.94; 0.09]	0.08
Quality of life	GTS-QoL-VAS	-3.19	-2.36	5.55 [-0.69; 11.8]	0.08
	GTS-QoL-normalization	-8.11	-3.98	-4.13 [-8.65; 0.39]	0.07
	YGTSS-impairment	-7.43	-3.31	-4.12 [-8.45; 0.22]	0.06
General health	SF-12 (physical score)	0.07	-0.62	0.69 [-2.24; 3.63]	0.64
	SF-12 (mental score)	2.37	0.25	2.12 [-1.39; 5.64]	0.23
ADHD	CAARS (inattention)	-1.41	-0.98	-0.43 [-2.65; 1.78]	0.70
	CAARS (hyperactivity)	-2.18	-1.41	-0.76 [-2.56; 1.05]	0.41
	CAARS (impulsivity)	-1.59	-0.89	-0.7 [-2.88; 1.48]	0.53
	CAARS (self-concept)	-0.63	-0.43	-0.21 [-1.76; 1.35]	0.79
	CAARS (DSM-IV inattention)	-0.79	-0.36	-0.43 [-2.2; 1.35]	0.63
	CAARS (DSM-IV hyperactivity)	-1.01	-0.3	-0.7 [-2.17; 0.77]	0.35
	CAARS (DSM-IV ADHD total)	-2.08	-0.7	-1.38 [-4.2; 1.44]	0.34
	CAARS (ADHD index)	-1.94	1.71	-0.22 [-2.31; 1.86]	0.83
	Premonitory urge	PUTS-9	-1.50	-0.31	-1.19 [-3.04; 0.66]
PUTS-10		-1.64	-0.57	-1.07 [-2.99; 0.86]	0.28
OCD	Y-BOCS	-1.04	-0.43	-0.61 [-2.16; 0.93]	0.43
Depression	BDI-II	-2.48	-0.58	-1.9 [-4.29; 0.49]	0.12
Anxiety	BAI	-1.50	-2.47	0.97 [-1.77; 3.71]	0.49
Rage attacks	RAQ	-6.77	-6.23	-0.54 [-4.58; 3.51]	0.79
Sleep	PSQI	-0.31	-0.04	-0.27 [-1.72; 1.19]	0.72
Impulsivity	I8-urgency	-0.38	-0.37	-0.03 [-0.28; 0.23]	0.84
	I8-premediation	0.06	-0.04	0.09 [-0.29; 0.48]	0.63
	I8-perseverance	0.04	-0.01	0.04 [-0.28; 0.37]	0.79
	I8-sensation seeking	-0.10	-0.12	0.02 [-0.32; 0.36]	0.92

LSM-least square means. CI-Confidence interval. YGTSS-Yale Global Tic Severity Scale. YGTSS-TTS-Yale Global Tic Severity Scale-Total Tic Score. YGTSS-GSS-Yale Global Tic Severity Scale-Global Severity Score. CAARS-Conner’s Adult ADHD Rating Scale. PUTS-Premonitory Urges for Tics Scale. ATQ-Adult Tic Questionnaire. PSQI-Pittsburgh Sleep Quality Index. BDI-II-Beck Depression Inventory. BAI-Beck Anxiety Inventory. RAQ-Rage Attack Questionnaire. Y-BOCS-Yale-Brown Obsessive Compulsive Scale. GTS-QoL-VAS-Gilles de la Tourette syndrome-Quality of Life Scale (Visual Analogue Scale). MRVS-Modified Rush Videotape Rating Scale. SF-12-Short Form-12. LSM, 95% CIs and p-values are derived from the above specified ANCOVA model.

Table 4
Adverse (AE) and serious adverse events (SAE) after treatment with Nabiximols compared to Placebo.

	Nabiximols (n=64)	Placebo (n=33)	p-value
Total number of SAEs	1 (0.3%)	1 (0.9%)	NA
Total number of AEs	315	116	NA
Grade I	181 (57.5%)	66 (56.9%)	NA
Grade II	122 (38.7%)	45 (38.8%)	NA
Grade III	12 (3.8%)	5 (4.3%)	NA
At least one AE			0.03
Yes	61 (95.3%)	26 (78.8%)	
No	3 (4.7%)	7 (21.2%)	
At least one AE with potential causal relation to study medication			0.001
Yes	58 (90.6%)	21 (63.6%)	
No	6 (9.4%)	12 (36.4%)	

SAE-serious adverse event. AE-adverse event. SOC-system organ class. PT-preferred term. p-value derived from two-sided chi²-test. NA-not applicable

of comorbid depressive symptoms, but not of other symptoms. This might be related to small sample sizes, since this study was not powered for investigating improvement of comorbid conditions after treatment with nabiximols.

Similarly to recent RTCs in TS using pure THC (Abi-Jaoude et al., 2022; Müller-Vahl et al., 2002, 2003) as well as open-label studies using nabiximols in the treatment of CTD (see additional literature overview in the Supplementary Material) and large RCTs using nabiximols in other indications such as spasticity in multiple sclerosis and neuropathic

pain (Dykukha et al., 2021; Notcutt et al., 2012), nabiximols was well-tolerated in the majority of patients, although AEs were common in the nabiximols group and were reported by 95% of patients in the nabiximols group. However, the minority of AEs (3.9%) was rated as grade 3 (severe) and only 5 patients in the nabiximols group discontinued treatment due to AEs. Only two SAEs occurred and were rated as not treatment related. In line with our expectation, patients in the placebo group used on average more puffs compared to those in the nabiximols group. This result is plausible, since participants were instructed to increase the number of puffs individually based on efficacy and tolerability up to a maximum of 12 puffs/day.

So far, it is unclear, which CBM is most effective in the treatment of tics and which route of administration should be preferred (oral intake vs. inhalation). Currently, in only two studies in TS effectiveness of different CBM has been compared directly (Abi-Jaoude et al., 2022; Milosev et al., 2019). The first study was a retrospective study including 98 patients (Milosev et al., 2019). Of these, 38 patients had used different CBM and were able to compare effects directly: 66% preferred medicinal cannabis, 18% THC, 11% nabiximols, and 5% street cannabis. With respect to medicinal cannabis, strains with high THC concentrations were reported as being more effective (Milosev et al., 2019). Only recently, in a small double-blind placebo controlled single-dose trial in 12 patients with TS, effects of orally administered pure THC (10%), a combination of THC/CBD (9%/9%), and pure CBD (13%) were compared directly (Abi-Jaoude et al., 2022). While tics did not improve after any of the compounds, both THC and (to a lesser extent) THC/CBD resulted in a significant improvement of premonitory urges, distress, and clinical global impairment. Plasma levels of THC and its metabolites, but

not of CBD, correlated with the severity of tics, premonitory urges, and distress. This finding is in line with another single-dose RCT in TS using THC, where a significant correlation between plasma levels of the active THC metabolite 11-hydroxy- Δ^9 -THC (11-OH-THC) and tic severity was found (Müller-Vahl et al., 2002). The assumption that both pure THC and combinations of THC and CBD, but not pure CBD, are effective in the treatment for TS, is further supported by the fact that so far no single case report has been published describing beneficial effects of pure CBD in TS. Furthermore, in an animal model for TS and tics (1-(2, 5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced head-twitch response in mice), it could be shown that THC, but not CBD, reduces the DOI-induced head twitch response (Gorberg et al., 2021).

In this study we decided for use of nabiximols mainly because at the time, when the study was designed, nabiximols was the only officially licensed CBM in Germany. Nabiximols is an orally administered plant extract from *Cannabis sativa L.* containing THC and CBD with a roughly equivalent ratio. We believe that beneficial effects of nabiximols are primarily related to THC and not to CBD. However, based on the assumed entourage effect it can be speculated that a combination of THC and CBD is more effective than THC alone (Morgan and Curran, 2008). Similarly – and in line with the recent single-dose RCT comparing THC, CBD, and THC/CBD (Abi-Jaoude et al., 2022) – it has been suggested that the combination of THC and CBD is better tolerated than pure THC, since CBD may mitigate unwanted psychotropic effects of THC (Morgan et al., 2010). With respect to the route of administration of CBM, only limited data is available. Based on data of a retrospective study, patients with TS seem to prefer inhaled cannabis with high THC content compared to oral THC and nabiximols (Milosev et al., 2019). It is well known that the route of administration strongly influences not only the onset, peak, and persistence of effects, but also plasma levels of THC and its metabolites (Vandrey et al., 2017). In line with the observation that clinical effects correlate with levels of THC and its metabolites (Abi-Jaoude et al., 2022; Müller-Vahl et al., 2002), it can be hypothesized that inhalation of CBM may be superior to oral intake.

The following limitations of the study have to be taken into consideration: (i) during an interview performed after EoT among patients recruited at the center in Hannover, we became aware that 7/53 (13%) patients unblinded themselves intentionally or had been unblinded accidentally (Müller-Vahl et al., 2022a). Since the self-unblinding rate in the total sample is unknown, unblinding may have influenced our results more than assumed; (ii) in general, unblinding cannot entirely be excluded in studies using CBM, because of the effects of THC, although several precautions were undertaken to avoid unblinding (Jakubovski et al., 2020; Müller-Vahl et al., 2022a); (iii) the overall drop-out rate of 19.4% was larger than anticipated; and (iv) the responder rate in the placebo group was overestimated. Thus, the overall power of the study to detect a difference between nabiximols and placebo was smaller than assumed.

In conclusion, although we failed to formally demonstrate superiority of nabiximols over placebo, the number of responders in the nabiximols group was much larger compared to the placebo group. Beneficial effects of nabiximols on tics were supported by the results of several secondary endpoints. Interestingly, nabiximols was more effective in reducing tics in the subgroups of males, patients with more severe tics at baseline, and presumably in patients with comorbid ADHD. Treatment with nabiximols in addition resulted in an improvement of comorbid depressive symptoms and overall quality of life. In general, nabiximols was well tolerated. We very much hope that the promising results of our CANNA-TICS trial may facilitate initiating further RCTs to investigate the effectiveness of CMB in TS. In addition, studies further exploring the role of the ECS in the pathogenesis of TS are needed.

Data sharing

Data is available to the scientific community on request. All data requests should be submitted to the corresponding author for

consideration. Access to anonymised data might be granted following review.

CRediT authorship contribution statement

Kirsten R. Müller-Vahl: Conceptualization, Visualization, Funding acquisition, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Anna Pisarenko:** Visualization, Funding acquisition, Investigation, Data curation, Methodology, Project administration, Resources, Writing – review & editing. **Natalia Szejko:** Data curation, Investigation, Writing – original draft, Validation, Writing – review & editing. **Martina Haas:** Investigation, Data curation, Project administration, Methodology, Resources, Writing – review & editing. **Carolin Fremer:** Investigation, Data curation, Writing – review & editing. **Ewgeni Jakubovski:** Data curation, Writing – review & editing. **Richard Musil:** Investigation, Data curation, Writing – review & editing. **Alexander Münchau:** Investigation, Data curation, Methodology, Writing – review & editing. **Irene Neuner:** Investigation, Data curation, Methodology, Writing – review & editing. **Daniel Huys:** Investigation, Data curation, Writing – review & editing. **Ludger Tebartz van Elst:** Investigation, Data curation, Writing – review & editing. **Christoph Schröder:** Methodology, Writing – review & editing. **Rieke Ringlster:** Formal analysis, Investigation, Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Armin Koch:** Visualization, Funding acquisition, Formal analysis, Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Eva Beate Jenz:** Formal analysis, Investigation, Data curation, Methodology, Software, Writing – review & editing. **Anika Großhennig:** Formal analysis, Investigation, Data curation, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary materials

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