nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The software "secuTrial“ version 6.8.0.11 was used to capture and store patients data.
Data analysis	All statistical analyses were performed with the use of R version 4.5.1 or higher.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Individual participant data (IPD), including de-identified datasets, data dictionaries, and relevant supporting documents can be made available for academic research purposes. Access will be granted following review and approval of a research proposal by the sponsor (Charité – Universitätsmedizin Berlin) and the principal investigator (Stefan Roepke), and will be subject to a data use agreement, applicable data protection regulations, and other relevant legal or contractual requirements. Data will be available beginning 6 months after publication and for a period of 5 years. Requests should be directed to the first author

(stefan.roepke@charite.de). Proposals will be evaluated based on scientific merit, feasibility, and compliance with ethical and legal requirements. A decision on data access requests will be made within 6 weeks of receipt of a complete application. Approved applicants will receive access to the data via a secure data-sharing environment.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	All analyses were performed using sex assigned at birth. Data on participant-reported gender identity are presented in the footnote to Table 1. Prespecified subgroup analyses according to sex attributed at birth showed no evidence of heterogeneity of treatment effects across the studied population.
Reporting on race, ethnicity, or other socially relevant groupings	The study was conducted in Germany, Europe, and included predominantly participants of White European ancestry. As is common in many European studies, race and ethnicity were not systematically collected. Sociodemographic variables are presented in Table 1.
Population characteristics	Sociodemographic variables are presented in Table 1. Comorbid psychiatric disorders are presented in Table S2. Table S3 presents concomitant Medication Across Groups Based on ATC Level 2 Classification.
Recruitment	Participants were recruited from help-seeking populations at the participating university medical centers, at cooperating outpatient psychiatric and psychotherapeutic treatment centers, through advertisements on websites, printed materials, and via social media.
Ethics oversight	The protocol was approved by the ethics committee of the federal state of Berlin, by the local ethics committee at each site, and by the federal regulatory authority (BfArM reference number: 61-3910-40473825).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Given a standardized mean difference (Cohen's d) on the CAPS-IV B2 score at 10 weeks of 0.45 (supported by a meta-analysis), a sample size of 158 patients (79 per group) provides 80% power to detect a significant difference at a two-sided significance level of 5%. Allowing for 10 % attrition, 176 patients were planned for enrolment. The sample size was determined using nQuery version 8.2.1.0 and R including rpact version 4.2.0.
Data exclusions	The primary analysis was done in the full analysis set (N = 169) based on the intention-to-treat principle, which included all randomized patients who received at least one dose of study medication and provided data on efficacy post-baseline.
Replication	Codes for statistial analysis are presented in the statistical analysis plan in the supplement of the manuscript.
Randomization	Patients were randomized at baseline in a 1:1 ratio using block randomization with fixed block lengths of four, stratified by study center. The block size was not disclosed to investigators, raters, site personnel, or other staff involved in participant enrolment or assessment. Concealed allocation was ensured using randomization sequences generated by the pharmacy with SAS, version 9.4 (PROC PLAN).
Blinding	Patients, investigators and study site personnel were blinded to treatment assignement. Concealed allocation was ensured using randomization sequences generated by the pharmacy with SAS, version 9.4 (PROC PLAN); the sequence was not accessible to the sponsor or investigators. Allocation concealment was ensured through centralized randomization and dispensing by an independent pharmacy, with identical packaging, labeling, appearance, and titration procedures for active drug and placebo.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	The trial was registered at ClinicalTrials.gov (NCT04448808) and in the EU Clinical Trials Register (EudraCT 2019-002211-25).
Study protocol	The first and final versions of the protocol, including descriptions of all modifications, are provided in the Supplementary Information.
Data collection	The THC-PTSD trial was an investigator-initiated, randomized, double-blind, placebo-controlled, parallel-group trial conducted at four university medical centers in Germany. From October 1, 2020 (first patient in) to January 2, 2025 (last patient out), 213 patients were screened at 4 centers; 171 underwent randomization, 87 to dronabinol and 84 to placebo.
Outcomes	The primary end point was the change in nightmare frequency and intensity on the CAPS-IV B2 item (range, 0 to 8) from baseline to Week 10. Key secondary end points were the change from baseline to Week 10 in the total CAPS-5 score (a measure of overall PTSD symptom severity during the preceding week); the change in depressive symptoms (assessed with the MADRS); and the Patient Global Impression of Change (PGIC) (capturing participants' overall subjective improvement, range 1 to 7). Responder and remitter analyses were included as secondary end points, with responders defined as participants showing at least a 50% reduction in the CAPS-IV B2 score from baseline to Week 10 and remitters as those with complete nightmare cessation (CAPS-IV B2 = 0). Additional secondary end points included PTSD-related sleep disturbances assessed with the Pittsburgh Sleep Quality Index-Addendum (PSQI-A, range 0 to 21) and self-reported PTSD symptoms measured with the PTSD Checklist for DSM-5 (PCL-5, range 0 to 80). General sleep quality was assessed with the PSQI (range 0 to 21), and sleep parameters—total sleep time, sleep-onset latency, time awake at night, perceived recuperation, and nightmare frequency and intensity—were recorded daily using patient sleep-diaries. Further secondary end points included health-related quality of life assessed with the EQ-5D-3L utility index generating a preference-based index score derived from time trade-off (TTO) valuation and the EQ-5D-3L visual analogue scale (VAS, range 0 to 100), and Social and Occupational Functioning Assessment Scale (SOFAS, range 0 to 100). Symptoms of borderline personality disorder were measured with the Borderline Symptom List-23 (BSL-23, range 0 to 92) and symptoms of complex PTSD were evaluated with the International Trauma Questionnaire (ITQ, range 0 to 72). Withdrawal symptoms were monitored with the Marijuana Withdrawal Checklist (MWC, range 0 to 45) at baseline, week 10, and week 12. A detailed description of the outcome measures is provided in the Supplement.

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a