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Authors' reply

Carsten Hjorthøj and colleagues question the extent to which the effects of cannabidiol as a pharmacological treatment for cannabis use disorder might be clinically meaningful. As they pointed out, and as discussed in our Article,¹ the phase 2a trial was not designed to estimate the magnitude of efficacy. However, phase 2a trials can be valuable when testing a novel indication with no previous evidence on what doses might be efficacious or safe. We found that cannabidiol 400 mg and cannabidiol 800 mg were more efficacious than placebo according to both primary endpoints (reduced urinary 11-nor-9-carboxy- δ -9-tetrahydrocannabinol:creatinine ratio and increased days with abstinence from cannabis during treatment) based on a priori Bayesian criteria. We did not make inferences about clinical relevance in our Article and it would be premature to do so because our phase 2a trial was not intended to address this question. Larger phase 2b or phase 3 trials are needed to determine how efficacious and clinically meaningful the effects of cannabidiol are at the doses we identified in our trial.

We used a 4-week treatment design, similar to the first randomised clinical trial of cannabidiol for the treatment of psychosis. More research is needed to test different dosing durations and formulations. Three randomised clinical trials have investigated nabiximols (low dose cannabidiol and tetrahydrocannabinol).²⁻⁴ Only one trial found a reduction in cannabis use compared with placebo,⁴ and none of the trials reported increases in sustained abstinence compared with placebo.

Hjorthøj and colleagues believe that a change in paradigm is needed in the treatment of cannabis use disorder, away from a focus on reduction in use and towards complete abstinence. Their views contrast with expert consensus on clinical outcomes for cannabis use disorder trials, published in 2020:⁵ the primary recommendation is that sustained

abstinence from cannabis should not be considered the primary outcome for all cannabis use disorder clinical trials because it has multiple limitations. Furthermore, given the absence of any recommended pharmacotherapies at present, a treatment that consistently reduces cannabis use would represent a major achievement towards decreasing the global burden of cannabis use disorders.

We declare no competing interests.

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Panel sampling in health research

In *The Lancet Psychiatry*, Matthias Pierce and colleagues^{1,2} identify the importance of sampling in studying mental health effects of

COVID-19. We found that a mental health survey³ using a commercial panel (of approximately 20 000 people) overrepresented mentally unhealthy respondents by approximately 2.5 times. This overrepresentation occurred despite multiple measures to ensure representativeness: prespecified demographic and geographical sampling quotas; post-collection checks on the distribution of socio-economic parameters; and adjustments for mismatches between clinical psychological scores and use of health-care services. Further random subsampling, before analysis, was required to correct for this sampling bias.

It seems that self-selected commercial survey panels in general might be biased towards mentally unhealthy or unhappy individuals. Commercial survey organisations operate through networks of subcontractors who hold customer contact lists. Individuals self-select to take part, for a small financial incentive. This might create bias towards people who are in difficult financial circumstances, and hence are under mental stress. The turnover in these self-selected panels is high.

It is now easy to target precise population segments using social media, but difficult to obtain random representative population samples. Political⁴ and personality⁵ representativeness have been tested. Surveys measuring mental health specifically can correct for bias during analysis.³ However, commercial surveys are also widely adopted in physical and social health research, and these might risk invalid results if they omit mental health measures.

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Discontinuation of antipsychotic medication—time to rethink trial design

There is a pressing need for knowledge about the effects of discontinuing antipsychotic medication in patients with remitted psychosis. Patients usually ask how long they will have to continue, and many stop taking medication, hoping that they can manage without it. As health-care professionals, we are responsible for providing evidence-based counselling for the initiation and discontinuation of medication, to help patients make informed choices. However, the two randomised trials^{1,2} that have compared a maintenance strategy with an early dose reduction strategy after remission in patients with first-episode psychosis, have reported contradictory results. The Dutch MESIFOS study¹ found that more patients achieved long term functional remission in the group who were assigned to early discontinuation of antipsychotic medication after 6 months of remission, compared with those who were assigned to maintenance treatment. However, a recent study² from Hong Kong did not replicate this finding in a larger sample.

The pressure to find answers has been felt worldwide and three large randomised clinical trials (EudractCT 2016–000565–23, EudractCT 2017–00246–12, ACTRN12617000870358) have been initiated by the authors of this Correspondence. However, none of these trials are progressing as expected.

The first problem is insufficient recruitment. Despite great interest in the discontinuation of antipsychotic medication, few individuals can equally accept either treatment group in a randomised discontinuation trial, because the decision to maintain or discontinue is too important to be left to randomisation. Low recruitment leads to small sample sizes with a high risk of type 2 errors and excludes the possibility of developing personalised risk profiles. The second problem is poor adherence to the treatment arm. Despite agreeing to participate, participants' strong personal preferences lead to high rates of crossover between the treatment groups. Poor adherence to the allocated treatment arm leads to data with less clinical use because describing differences in outcomes between similar treatment arms has no real value to the patient. In fact, weak adherence to treatment might create data that are approaching observational, where confounding is a major limitation for causal inference.

We suggest four recommendations using alternative designs for future research that could shed light on the questions about maintenance treatment with antipsychotic medication. First, to reach a sufficient number of participants in randomised clinical trials, international consortia should be established to enable recruitment within a reasonable timeframe. Second, clinical cohort studies including individuals who discontinue antipsychotic medication should be done to generate precise knowledge about the proportion and

characteristics of participants who successfully adhere to the treatment, those who start medication again without relapse, and those who have a severe relapse and irreversible consequences such as treatment resistance and functional decline.

Third, observational data such as nationwide population-based registers could be used to emulate a hypothetical target trial if randomisation is not feasible.³ A target protocol describes the ideal, but unachievable randomised clinical trial. This trial can be emulated by exploiting the natural variation in observational data, which would allow causal inference by adjustment for confounders and selection bias. The concept has been increasingly applied in pharmaco-epidemiology and provides reliable answers in the comparative effectiveness of research.⁴ Fourth, n-of-1 trials should be used to develop personalised decision making. These recommendations are proposed to avoid pitfalls of the current approach to precision medicine.⁵ A common pitfall is to split variance around an estimate, in the so-called responders and non-responders, using arbitrary definitions on a continuous outcome. Using these arbitrary categories as true, and looking for prognostic factors predicting the response, is a simplistic and often misleading way to develop personalised risk models because all control conditions are completely ignored. By using the n-of-1 design, the same individual is acting as their own control by comparing periods when on medication with periods when not on medication.

In conclusion, we know from cohort studies that a substantial proportion of individuals can manage without antipsychotic medication, and will not relapse. Therefore understandably, many try to stop medication at some point to find out if they belong to this group. The duty of clinicians is to provide knowledge about the risks