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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 study[1] 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 study[2] 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

and benefits associated with stopping antipsychotic medication and to support each individual's decision. To improve the evidence base, we suggest that researchers should consider how observational data could be exploited and use n-of-1 designs to develop personalised medicine. Further, we suggest that funding agencies need to call for large-scale international research and provide funding to build international consortia, which would enable necessary research to fill the knowledge gap on discontinuing medication in psychiatry.

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