Antipsychotic maintenance treatment versus dose reduction: how the story continues

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In this issue of *The Lancet Psychiatry*, Giovanni Ostuzzi and colleagues[1] evaluated the effect of different antipsychotic treatment strategies on risk of relapse by combining 98 randomised controlled trials (RCTs) in meta-analysis (n=13 988 individuals). Compared with discontinuation, the risk for relapse was largely reduced when continuing at standard doses (relative risk [RR] 0·37, 95% CI 0·32–0·43) or when switching antipsychotics (RR 0·44, 0·37–0·53) and moderately reduced when lowering dose (RR 0·68, 0·51–0·90). The large number of patients on which their analyses are based provide their findings great credibility and the authors argue that these results should support updating the evidence-based treatment guidelines for patients with schizophrenia-spectrum disorders. Indeed, the findings regarding relapse prevention are trustworthy and important, yet only tell part of the story.

10 years ago, a meta-analysis by Leucht and colleagues[2] already demonstrated that the chance for relapse at 7–12 months is reduced by more than half when continuing antipsychotic medication (27% relapse rate) compared with placebo (64% relapse rate). Accordingly, most guidelines recommend maintenance treatment for at least 1 year after remission. However, the past decade has shown that patients have quite a different perspective on treatment outcome, with functional recovery as their main goal.[3] The same research group[4] extended their work towards quality of life and social functioning, which were both better in patients on medication (standardised mean difference [SMD] −0·32, 95% CI −0·57 to −0·07 at 3 months to 18 months follow-up, seven RCTs, low-certainty evidence; SMD −0·43, 95% CI −0·53 to −0·34 at 1 month to 15 months, 15 RCTs, moderate-certainty evidence). Ostuzzi and colleagues[1] reached similar results, not surprisingly also with a substantially lower number of RCTs for those outcomes. This is an important finding, contradicting an earlier report suggesting higher social functioning with the dose-reduction strategy.[5]

Even when discussing relapse prevention, the findings from Ostuzzi and colleagues[1] warrant cautious interpretation. The dose reduction or stopping modalities that were used in the RCTs they analysed are not as slowly decreasing as has recently been advised.[6] Although tapering information was often missing, antipsychotic discontinuation was probably abrupt for about two thirds of the included studies. Their meta-regression comparing studies that gradually reduce dosage to studies that taper medication off abruptly showed no significant difference. In contrast, a review clearly showed the effect of tapering speed on relapse rate; tapering antipsychotic medication over months was linked to half the relapse rate versus tapering quickly.[7] Gradual dose reduction instead of abrupt discontinuation can also mitigate the risk of new somatic and psychiatric effects, as found in an individual patient meta-analysis.[8] Although not necessarily withdrawal effects, these effects can arise even after short-term treatment and could include psychotic symptoms per se or emerging symptoms, such as insomnia or anxiety that can lead to a genuine relapse.[6,8] Although the work from Ostuzzi and colleagues[1] provided important information, the issue of slow versus swift tapering is not yet settled, as there is a scarcity of RCTs that provide very gradual tapering over several months.

To fill this gap, several randomised trials have been initiated across the globe, to specifically address the effects of gradual tapering or discontinuation versus antipsychotic maintenance treatment on functional recovery,[9] currently collaborating as the Tapering AntiPsychotics and Evaluating Recovery group. Awaiting future results, the ongoing HAMLETT trial[4] investigated antipsychotic treatment practices among Dutch psychiatrists specialised in early psychosis; within the first year after remission, they already taper medication in 33·8% of patients having a first episode and discontinue medication in 9·1% of patients.[10] These findings might reflect the practice of shared-decision making, in which patients' preferences are an important factor in choosing treatment strategies, and the patients often have a strong wish to stop medication earlier and will do so on their own when not supported by their physician.

Time is pressing, as patients, their families, and clinicians need evidence-based data to weigh up the

risks and benefits of maintaining, switching, or reducing medication with respect to a range of outcomes that are important to them, including social functioning, cognition, physical health, sexual health, and quality of life, thus going well beyond relapse prevention. Discontinuation studies applying appropriate tapering methods that seek to minimise withdrawal-associated effects can help this field move forward by focusing on outcomes prioritised by patients. Yet the evidence needed will involve more than strategy-wise comparisons. Schizophrenia-spectrum disorders are heterogeneous with a largely unpredictable course, and we have known for a long time that a substantial proportion of patients who experienced a first psychosis can manage without antipsychotic medication.[6] The challenge for future research is therefore to identify this subgroup on the basis of individual characteristics and guide them in tapering medication safely.

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Intensive home treatment in different settings

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Randomised controlled trials of models of acute mental health care that provide generalisable results are hard to conduct. On the one hand, service users, their informal supporters, and health professionals have preferences regarding hospital admission versus an alternative, making randomisation difficult where such an option is already available. On the other hand, where the intervention of interest is newly provided through the research, subsequent fidelity can be difficult to achieve. The trial by Cornelis and colleagues[1] is an important contribution to the literature on intensive home treatment; based on their review of previous literature, it is only the third trial on the topic, and the intensive home treatment teams concerned were already in operation. Their solution to the existing availability of intensive home treatment was a Zelen procedure, such that informed consent was sought after randomisation within 14 days once the service user had the capacity to consent. However, they were required to make intensive home treatment available to controls, leading to loss from the trial of 14 (7·4%) control patients.

Based on intention-to-treat analysis, Cornelis and colleagues found that at 12 months, the mean number of admission days in the intensive home treatment condition was 42·47 (SD 53·92) versus 67·02 days (79·03) for treatment as usual, a reduction of 24·55 days (10·73) or 36·6% (p=0·033). This finding is consistent with the earlier trials in the UK[2] and Switzerland,[3] as was their null finding regarding involuntary admissions. Adverse event numbers and service user satisfaction did not differ significantly between the two groups. This lack of difference in satisfaction is interesting given the preference among some of the control group to switch