Tapering antipsychotic medication: practical considerations

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Antipsychotic medications are the gold-standard treatment for psychotic patients, and their efficacy is evident (Kahn et al., 2018). Most guidelines recommend long-term, continuous treatment with antipsychotic medication to prevent relapse (Shimomura et al., 2020). This is based on the increased relapse rates in patients who are switched to placebo in discontinuation studies (Moncrieff, Gupta, & Horowitz, 2020). However, the extent of their relapse prevention properties is uncertain, because withdrawal problems (including withdrawal-induced relapse) with short-term follow-up might partly explain these results (Moncrieff et al., 2020), as these properties are inferred from discontinuation studies of antipsychotics in which oral antipsychotics are tapered over four weeks, or depot medication is stopped abruptly (Leucht et al., 2012).

Furthermore, over half (54%) of patients in a large survey reported that their quality of life worsened after treatment with antipsychotic medication (Williams, 2019). Around 90% reported adverse effects, such as drowsiness, feeling tired and sedation, loss of motivation, slowed thoughts, and emotional numbing. Most respondents (70%) had tried to stop taking these drugs at least once, mainly due to unpleasant side effects (64%) and worries about long-term physical health (52%) (Williams, 2019). There was also a counterpoint to this finding with 35% finding that their quality of life was improved by antipsychotics and 56% thought that the drugs reduced the problems that they were prescribed for. As these findings are derived from online surveys it is possible that people with negative experiences of antipsychotics were more motivated to participate, however systematic investigation of representative patient cohorts has not been conducted.

Many patients want to try to reduce or discontinue their antipsychotic medication.

Moreover, 75% of respondents in a UK-based survey among 172 clinicians working with first episode patients (Thompson, Singh, & Birchwood, 2016), thought that early discontinuation of antipsychotic medication after remission was beneficial for most patients. Previous studies have demonstrated that some patients can stop their medications associated with an improvement in their functional capacity (Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013). Preliminary studies examining which characteristics of patients might predict relapse on discontinuation have identified two factors: cannabis abuse and a longer duration of antipsychotic treatment (Bowtell et al., 2018). However, there still remains considerable uncertainty as to who might benefit from reduction and discontinuation (Wunderink, 2018). To fill the gap in understanding the benefits and disadvantages of antipsychotic reduction, several large-scale trials are currently being undertaken (Begemann et al., 2020; Moncrieff et al., 2019).

However, in the meantime, little guidance is available on how to best taper antipsychotic medication. Below, we discuss several considerations based on our experience in tapering medication in patients with first- and multi-episode psychosis from the HAMLETT (Begemann et al., 2020), and RADAR (Moncrieff et al., 2019) studies to assist clinicians in this task.

Involve family

As with all major changes in treatment, it is important to consider the individual's circumstances when initiating antipsychotic reduction, including their social support and the attitudes of family and caregivers. It is crucial to involve key persons providing support,

including family psychoeducation which has been shown to reduce the risk of relapse by 20% (Pitschel-Walz, Leucht, Bäuml, Kissling, & Engel, 2001).

Add non-pharmacological interventions

Non-pharmacological interventions may be useful to enable people to manage emerging symptoms during the withdrawal process and to re-adapt to a 'new normal' following medication reduction/cessation, including more intense emotions. A recent systematic review has found that non-pharmacological interventions, like cognitive-behavioural therapy, Needs Adapted Treatment and Soteria have outcomes, including relapse, similar to usual care (Cooper, Laxhman, Crellin, Moncrieff, & Priebe, 2019), with encouraging but inconsistent findings for other non-pharmacological interventions. Psychoeducation has been shown to decrease relapse rates (Xia, Merinder, & Belgamwar, 2011). These approached may therefore be useful to support patients, though they have not been formally evaluated in the withdrawal process.

The longer antipsychotics have been used, the longer tapering should take

Long-term antipsychotic use causes adaptations in the brain to the presence of the medication, including up-regulation of post-synaptic D_2 dopaminergic receptors (Horowitz, Murray, & Taylor, 2020). Indeed, one study found that longer duration of antipsychotics treatment produced a small increase in risk of relapse on antipsychotic discontinuation(Bowtell et al., 2018), consistent with the notion of increased adaptation to the drug over time. The rationale behind tapering is therefore to reduce the drug slowly

enough to allow the brain to re-adapt incrementally to lowered levels of neurochemical effects (Horowitz, Jauhar, Natesan, Murray, & Taylor, 2021). These adaptations may take years to normalize after long-term use and therefore tapering may also need to last a year or longer in these situations (Moncrieff et al., 2019). However, less prolonged tapering schedules may be tolerable for patients with shorter term use (Begemann et al., 2020). As higher doses take longer to taper, initial dose should be kept as low as possible, and reduction considered as soon as acute disturbance settles.

Motivate patients for gradual tapering

Patients may want to stop their antipsychotics rapidly, as initial reductions may make them feel more energized and motivated. However, abruptly stopping medication is most likely to cause relapse, as will be familiar to many patients and clinicians (Bogers, Hambarian, Michiels, Vermeulen, & de Haan, 2020). Patients therefore should be encouraged to reduce more cautiously. Although prolonged tapering may be unappealing for many patients, the benefit of a slow rate, especially when down to lower doses, should be emphasized, as it may decrease their risk of relapse, need for future re-instatement and ongoing treatment (Bogers et al., 2020).

Dose reduction following a hyperbolic pattern

Like many other pharmacological compounds, the relationship between dose of antipsychotic and its effect on target receptors is hyperbolic (Horowitz et al., 2021, 2020); at low doses, there is a very steep relationship between drug-dose and receptor occupancy; at

higher doses, this relationship flattens out. Tapering antipsychotics according to a hyperbolic pattern produces linear reductions of D_2 occupancy and other antipsychotic-induced changes. In other words, dose reductions should get smaller as total dose becomes lower (e.g. a pharmacologically-informed haloperidol dose regimen would entail the following sequential reductions: 4mg, 3mg, 2mg, 1.5mg, 1mg, 0.75mg, 0.5mg, 0.375mg, 0.25mg, 0.1875mg 0.125mg, 0.063mg, 0mg) (Horowitz et al., 2021). While these final doses may seem very small, it should be noted that 0.063mg still causes 8% D_2 occupancy and so this final dose reduction represents the same reduction in D_2 occupancy as reducing from 10mg to 4mg of haloperidol. As tablets of most antipsychotic drugs do not enable this type of tapering, the use of liquid formulations is recommended, which are available for many antipsychotics.

An individual approach

Despite the overall patterns, there are large individual differences regarding dose occupancy, symptoms, self-management skills and people's social networks, which are reflected in variations in the tolerability of patients to different rates of tapering. A reasonable approach, therefore, is to start with a small decrease in dose, perhaps equal to 5-10 percentage of D_2 receptor occupancy (equivalent to about a 25% dose reduction, depending on the starting dose (Horowitz et al., 2021)), monitor the effects on the patient for approximately two months and then proceed based on the tolerability of this first step. There are other considerations that should be taken into account as well such as interactions with other medications (e.g. plasma levels might change as antipsychotics are lowered due to overlapping metabolic pathways). It is advisable to generate a list of early warning signs

(e.g. insomnia) with the patient before commencing the reduction. We have also observed in the course of conducting our antipsychotic reduction trials that some symptoms (e.g. insomnia, psychotic symptoms), that arise on reducing medications can be transitory - although sometimes they can persist for weeks or months – and may spontaneously resolve without any change in medication dose. This is a phenomenon that has been previously identified as fitting a rebound pattern, where original symptoms rapidly return after dose reduction sometimes above pre-treatment levels, thought to be short-lasting and reversible, analogous to withdrawal dyskinesia (Cosci & Chouinard, 2020).

Clozapine is distinct from other antipsychotics

Clozapine has a well-defined withdrawal syndrome, which is known to include psychotic symptoms (Cosci & Chouinard, 2020; Verghese, DeLeon, Nair, & Simpson, 1996), and it is reported to be difficult to withdraw than other antipsychotics (Borison, Diamond, Sinha, Gupta, & Ajiboye, 1988; Verghese et al., 1996), which matches our clinical experience. It is particularly important to identify a tolerable rate of dose reduction, and to warn patients about the possible occurrence of withdrawal symptoms, which may include temporary worsening of psychotic symptoms (Borison et al., 1988; Cosci & Chouinard, 2020; Verghese et al., 1996). It may be prudent to taper clozapine by as little as 25mg (or less) even at higher doses, or as little as 6.25mg at lower doses depending on how the patient tolerates the reduction, made practical by widely available small dose formulations.

Definitions of success

For some people relapse may be important to avoid at all costs, yet others prioritise quality of life and functioning. Therefore, patients who experience reoccurrence of symptoms during discontinuation should not be considered to have 'failed'. When they have re-stabilised, it may be reasonable to try reduction again, more gradually (smaller dose reductions spaced out at greater time periods) or with enhancement of non-pharmacological coping strategies. Some patients will see the process of relapsing as part of the process of determining a tolerable rate to taper the medication. Some patients may conclude that reaching the lowest possible dose is preferable to complete cessation. Other patients may find that their quality of life is improved by maintaining antipsychotics.

Conclusion

For reducing antipsychotic medication, it is important to motivate patients to taper gradually, rather than precipitously especially those who have been on medication for years. Gradual reductions might reduce the chance of withdrawal effects like insomnia, and possibly relapse. Prepare the patient for the "new normal", including increased intensity of perceptions and emotions. As there are large individual differences in receptor occupancy, the effect of the first few steps needs to be monitored closely to determine tapering velocity for each patient.

As dose reduction should be done in a hyperbolic pattern, fluid preparations are convenient for the final small steps. Clozapine is different, as initial steps should already be small. Finally, success can be defined in different ways and the optimal situation may not be zero, but a low dose.

Author Contribution

IS conceived the manuscript idea. MH and IS wrote the initial manuscript. JM, LdH, JB, SG, MK, WV all substantially revised and edited the manuscript and contributed substantially to the concepts outlined.

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Conflict of Interest

JM is the Chief Investigator of the National Institute of Health Research funded RADAR trial, co-chairperson of the Critical Psychiatry Network and board member of the Centre for Evidence-based Psychiatry. MH, LdH, JB, SG, MJ, WV and IS have no conflicts of interest.

Ethical standards

As no patients were involved in this research, no ethical clearance was required for this Commentary article.

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