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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 This is based on the increased relapse rates in patients who have their previous antipsychotic medication withdrawn, often abruptly or very rapidly, compared to those who remain on treatment (Moncrieff, Gupta, & Horowitz, 2020). However, the extent of antipsychotics' relapse prevention properties is uncertain, because withdrawal problems (including withdrawal-induced relapse) with short-term follow-up might partly explain these results (Leucht et al., 2012; Moncrieff et al., 2020).

Furthermore, many patients report aversive effects of taking long-term antipsychotics. In a meta-analysis of 41 qualitative articles, patients were largely positive about acute and short-term use, but were more ambivalent about long-term use, especially highlighting negative effects on functional and social recovery (Bjornestad et al., 2019). Patients perceived that long-term antipsychotic use disrupted their individual efforts to overcome their condition and undermined their sense of agency. They also expressed concern about irreparable bodily damage caused by the drugs (Bjornestad et al., 2019; Thompson et al., 2020). Others perceived long-term use more positively, and described adapting their use to minimize their side-effects. In one qualitative survey conducted online, most respondents (70%) had tried to stop taking antipsychotics at least once, mainly due to unpleasant side effects (64%) and worries about long-term physical health (52%), while 35% reported that their quality of life was improved by antipsychotics and 56% thought that the drugs reduced the problems that they were prescribed for (Read & Williams, 2019).

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, while the majority restarted medication at the same or reduced dose (Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013). After decades of trying to identify people who are more likely to relapse following antipsychotic withdrawal, no consistent findings have emerged, and so it has been suggested that all patients should have the opportunity to try to discontinue medication if this is what they want and if risks allow (Sommer, Oomen, & Hasan, 2019; Wunderink, 2018). Ongoing work to try to determine who may benefit and who may not, might contribute further clarity to this area. 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; Weller 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. 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); 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: 4, 3, 2, 1.5, 1, 0.75, 0.5, 0.375, 0.25, 0.1875, 0.125, 0.063, 0 mg) (Horowitz et al., 2021). While these final doses may seem very small, it should be noted that 0.063 mg still causes 8% D_2 occupancy and so this final dose reduction represents the same reduction in D_2 occupancy as reducing from 10 to 4 mg 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 self-limiting – although sometimes they can persist for weeks or months – and may spontaneously resolve without any change in medication dose. Although, this has not been the subject of rigorous scientific study to date, this is a phenomenon that has been previously identified as fitting a rebound pattern, analogous to withdrawal dyskinesia (Cosci & Chouinard, 2020).

Clozapine

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 more 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 25 mg (or less) even at higher doses, or as little as 6.25 mg 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 may tolerate an increased risk of relapse to benefit from

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reduced adverse effects of medication. Therefore, patients who experience reoccurrence of symptoms during discontinuation should not necessarily be considered to have 'failed'. When they have re-stabilized, 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. Others may prioritize symptom control and avoidance of relapse and therefore find their quality of life is improved by maintaining antipsychotics. Moreover, antipsychotic medication may reduce the chance of a dramatic reduction in quality of life that can be the consequence of a psychotic relapse.

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.

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References

Begemann, M. J. H., Thompson, I. A., Veling, W., Gangadin, S. S., Geraets, C. N. W., van 't Hag, E., … Sommer, I. E. C. (2020). To continue or not to continue? Antipsychotic medication maintenance versus dose-reduction/discontinuation in first episode psychosis: HAMLETT, a pragmatic multicenter single-blind randomized controlled trial. *Trials*, *21*(1), 147. https://doi.org/10.1186/s13063-019-3822-5

Bjornestad, J., Lavik, K. O., Davidson, L., Hjeltnes, A., Moltu, C., & Veseth, M. (2019). Antipsychotic treatment – a systematic literature review and meta-analysis of qualitative studies. *Journal of Mental Health*, *0*(0), 1–11. https://doi.org/10.1080/09638237.2019.1581352

Bogers, J. P. A. M., Hambarian, G., Michiels, M., Vermeulen, J., & de Haan, L. (2020). Risk factors for psychotic relapse after dose reduction or discontinuation of antipsychotics in patients with chronic schizophrenia: A systematic review and meta-analysis. *Schizophrenia Bulletin Open*, *1*(1), 1–12. https://doi.org/10.1093/schizbullopen/sgaa002.

Borison, R. L., Diamond, B. I., Sinha, D., Gupta, R. P., & Ajiboye, P. A. (1988). Clozapine withdrawal rebound psychosis. *Psychopharmacology Bulletin*, *24*(2), 260–263. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3212159

Bowtell, M., Eaton, S., Thien, K., Bardell-Williams, M., Downey, L., Ratheesh, A., … O'Donoghue, B. (2018). Rates and predictors of relapse following discontinuation of antipsychotic medication after a first episode of psychosis. *Schizophrenia Research*, *195*(13–14), 231–236. https://doi.org/10.1016/j.schres.2017.10.030

Cooper, R. E., Laxhman, N., Crellin, N., Moncrieff, J., & Priebe, S. (2019). Psychosocial interventions for people with schizophrenia or psychosis on minimal or no antipsychotic medication: A systematic review. *Schizophrenia Research*, *225*, 15–30. https://doi.org/10.1016/j.schres.2019.05.020.

Cosci, F., & Chouinard, G. (2020). Acute and persistent withdrawal syndromes following discontinuation of psychotropic medications. *Psychotherapy and Psychosomatics*, *89*(5), 283–306. https://doi.org/10.1159/000506868

Horowitz, M. A., Jauhar, S., Natesan, S., Murray, R. M., & Taylor, D. M. (2021). A method for tapering antipsychotic treatment that may minimize the risk of relapse. *Schizophrenia Bulletin*, *47*(4), 1116–1129.

Horowitz, M. A., Murray, R. M., & Taylor, D. (2020). Tapering antipsychotic treatment. *JAMA Psychiatry*, *78*(2), 125–126. https://doi.org/10.1001/jamapsychiatry.2020.2166.

Kahn, R. S., Winter van Rossum, I., Leucht, S., McGuire, P., Lewis, S. W., Leboyer, M., … Sommer, I. E. (2018). Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): A three-phase switching study. *The Lancet. Psychiatry*, *5*(10), 797–807. https://doi.org/10.1016/S2215-0366(18)30252-9

Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., & Davis, J. M. (2012). Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: A systematic review and meta-analysis. *The Lancet*, *379*(9831), 2063–2071. https://doi.org/10.1016/S0140-6736(12)60239-6

Moncrieff, J., Gupta, S., & Horowitz, M. A. (2020). Barriers to stopping neuroleptic (antipsychotic) treatment in people with schizophrenia, psychosis or bipolar disorder. *Therapeutic Advances in Psychopharmacology*, *10*, 1–10. https://doi.org/10.1177/2045125320937910.

Moncrieff, J., Lewis, G., Freemantle, N., Johnson, S., Barnes, T. R. E., Morant, N., … Priebe, S. (2019). Randomised controlled trial of gradual antipsychotic reduction and discontinuation in people with schizophrenia and related disorders: The RADAR trial (Research into Antipsychotic Discontinuation and Reduction). *BMJ Open*, *9*(11), e030912. https://doi.org/10.1136/bmjopen-2019-030912

Pitschel-Walz, G., Leucht, S., Bäuml, J., Kissling, W., & Engel, R. R. (2001). The effect of family interventions on relapse and rehospitalization in schizophrenia – A meta-analysis. *Schizophrenia Bulletin*, *27*(1), 73–92. https://doi.org/10.1093/oxfordjournals.schbul.a006861

Read, J., & Williams, J. (2019). Positive and negative effects of antipsychotic medication: An international online survey of 832 recipients. *Current Drug Safety*, *14*(3), 173–181. https://doi.org/http://dx.doi.org/10.2174/1574886314666190301152734.

Shimomura, Y., Kikuchi, Y., Suzuki, T., Uchida, H., Mimura, M., & Takeuchi, H. (2020). Antipsychotic treatment in the maintenance phase of schizophrenia: An updated systematic review of the guidelines and algorithms. *Schizophrenia Research*, *215*, 8–16. https://doi.org/https://doi.org/10.1016/j.schres.2019.09.013

Sommer, I. E. C., Oomen, P. P., & Hasan, A. (2019). Maintenance treatment for patients with a first psychotic episode. *Current Opinion in Psychiatry*, *32*(3), 147–156. https://doi.org/10.1097/YCO.0000000000000494

Thompson, A., Singh, S., & Birchwood, M. (2016). Views of early psychosis clinicians on discontinuation of antipsychotic medication following symptom remission in first episode psychosis. *Early Intervention in Psychiatry*, *10*(4), 355–361. https://doi.org/10.1111/eip.12244

Thompson, J., Stansfeld, J. L., Cooper, R. E., Morant, N., Crellin, N. E., & Moncrieff, J. (2020). Experiences of taking neuroleptic medication and impacts on symptoms, sense of self and agency: A systematic review and thematic synthesis of qualitative data. *Social Psychiatry and Psychiatric Epidemiology*, *55*(2), 151–164. https://doi.org/10.1007/s00127-019-01819-2

https://doi.org/10.1017/S0033291721003299 Published online by Cambridge University Press

Verghese, C., DeLeon, J., Nair, C., & Simpson, G. M. (1996). Clozapine withdrawal effects and receptor profiles of typical and atypical neuroleptics. *Biological Psychiatry*, *39*(2), 135–138. https://doi.org/10.1016/0006-3223(95)00215-4

Weller, A., Gleeson, J., Alvarez-Jimenez, M., McGorry, P., Nelson, B., Allott, K., … Killackey, E. (2019). Can antipsychotic dose reduction lead to better functional recovery in first-episode psychosis? A randomized controlled-trial of antipsychotic dose reduction. The reduce trial: Study protocol. *Early Intervention in Psychiatry*, *13*(6), 1345–1356. https://doi.org/10.1111/eip.12769

Wunderink, L. (2018). Who needs antipsychotic maintenance treatment and who does not? Our need to profile and personalize the treatment of first episode psychosis. *Schizophrenia Research*, *197*, 65–66. https://doi.org/10.1016/j.schres.2017.11.007

Wunderink, L., Nieboer, R. M., Wiersma, D., Sytema, S., & Nienhuis, F. J. (2013). Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry*, *70*(9), 913–920. https://doi.org/10.1001/jamapsychiatry.2013.19

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