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Addressing the Evidence to Practice Gap: What to Expect From International Antipsychotic Dose Reduction Studies in the Tapering Anti-Psychotics and Evaluating Recovery Consortium

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Since the discovery of chlorpromazine’s effectiveness to diminish the severity of psychotic symptoms approximately 70 years ago, antipsychotic medication is the cornerstone of treatment of psychotic disorders.1 NICE guidelines recommend combining antipsychotic medication with psychological interventions such as family intervention and cognitive behavioral therapy.2 Furthermore, the benefits of treatment augmentation with anti-inflammatory medicine, adjunctive vitamins or dietary interventions are under investigation,3–7 and some evidence indicates that benzodiazepine treatment for early warning signs of relapse could be effective.8 However, antipsychotic medication remains the primary treatment option. Decades of research and development now offer psychiatrists a choice of many different types of antipsychotic medication to treat psychosis. While the precise mechanisms of action of specific types of antipsychotic medication remain unclear, the key mechanism of most types is largely the same, namely blockade of dopamine D2 receptors in the central nervous system. The specific receptor binding profile across medication types vary, leading to different side effect profiles.9,10 Besides being effective in treating psychotic symptoms, antipsychotic medication can also prevent relapse,11 and some evidence suggests maintenance treatment with antipsychotic medication is associated with a reduction in overall mortality rates,12 increased psychosocial functioning, higher quality of life, and more frequent clinical remission.13 Most current guidelines generally advise continued antipsychotic medication for at least 1 year after remission of a first episode of psychosis, and often even longer.14 However, there is no clear consensus about how long maintenance treatment should last. In recent years, the risk-vs-benefit debate has become increasingly heated, due to new findings on the impact of antipsychotic medication use and the growing emphasis on the patient perspective. Many alarming side effects are linked to antipsychotic exposure, such as heart disease, metabolic disease, sexual dysfunction, cognitive impairment, and a possible reduction of brain volume.11,15–19 On top of this, one of the earliest randomized studies showed that early discontinuation had a positive long-term impact on an outcome prioritized by patients: functional outcome.20 So far, subsequent studies have not replicated this.21

Meanwhile, many patients wish to discontinue their antipsychotic medication due to side effects, health concerns or stigma,16,22,23 and will even do so on their own. Within the first year of treatment, up to 58% of patients discontinue medication without consulting their professional caregivers.24–26 Importantly, abrupt discontinuation may increase the risk of both psychiatric and somatic withdrawal effects and relapse of psychosis, while gradual reduction and discontinuation on consultation with caregivers may be a better strategy.15,27,28 Horowitz et al15

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suggest gradual, even-spread reduction of medication of 5 to 10 percentage points of D2 occupancy (equivalent to a reduction of approximately 25% to 50% of the most recent dose) at intervals of 3 to 6 months and provide examples of tapering schedules for 6 types of antipsychotic medication. The main idea behind this is to minimize withdrawal effects by reducing neurotransmitter effects, such as D2 receptor antagonism, in a linear fashion, with sufficient time between dose reductions to allow gradual neuroadaptation to lower doses.

While many clinicians would consider dose reduction, there is also reluctance to do so due to a lack of evidence-based guidelines for treatment discontinuation.28,29 Whether or not to continue medication is a complex clinical decision, requiring delicate balancing of short- and long-term risks, individual patient, and family factors. A recent survey among clinicians in the Netherlands revealed significant variability in their applied treatment strategies. In patients remitted from a first psychotic episode, these clinicians favored maintenance treatment in 51.2% of cases, while they reduced dose in 33.8% of cases, and discontinued medication in 9.1% of cases.30

The numerous trials showing that maintenance treatment reduces risk of relapse provide a seemingly solid foundation for current clinical guidelines worldwide, yet an important evidence-to-treatment gap still exists. First, many of these studies ignore potential medication withdrawal effects resulting from rapid discontinuation, which may exaggerate the rate of relapse by misclassification or by precipitating genuine relapse.15,16,28 Second, studies evaluating long-term outcomes are scarce. Third, there has been little focus on more subjective outcome variables which are nonetheless important from a patient perspective, such as (social) functioning, personal recovery, and quality of life.31 Large longitudinal randomized clinical trials of gradual dose reduction and discontinuation are one approach for providing more definitive answers and have the potential to bridge the current evidence to treatment gap. This knowledge is essential when considering the delicate balance between potential detrimental effects of (longitudinal) antipsychotic medication use on the one hand and optimal recovery and relapse prevention on the other. In recent years, several of these trials were initiated.20,21,22–37 However, these trials face several challenges, including recruitment, intervention adherence, conducting long-term follow-up, and sample bias. Specifically, randomization is difficult in these trials, as patients often have a clear wish to discontinue or maintain medication when participating and do not wish to leave this decision up to randomization.38 On top of this, sample bias may complicate generalization of findings.

To further identify and overcome the challenges encountered in this field, researchers have joined forces in the Tapering Anti-Psychotics and Evaluating Recovery (TAPER) Research Consortium. This international group of researchers from Australia, China, Denmark, France, the Netherlands, Taiwan, and the United Kingdom are involved in previous and current trials investigating the effects of antipsychotic medication dose reduction and discontinuation. Based on previous and currently ongoing studies, the TAPER group aims to provide the field with evidence-based guidelines on reduction/discontinuation of antipsychotic medication after remission of first-episode and multi-episode psychosis. So far, members of the TAPER group have published relevant suggestions on how to overcome some of the issues facing the field, including the establishment of international consortia to overcome recruitment issues, and conducting clinical cohort studies and register-based studies to deal with randomization issues.38 Furthermore, while awaiting trial results, TAPER members already provided guidance on tapering antipsychotic medication based on experiences from the HAMLETT and RADAR trials, including recommendations on tapering speed, support systems, and addition of non-pharmacological interventions.39 Our upcoming projects are, among others: (1) to investigate whether discontinuation strategies offer functional benefits when compared to maintenance treatment, and at what cost to other domains, (2) to address the generalizability of future findings by evaluating sampling bias across trials, (3) to analyze heterogeneity in tapering trajectories, (4) to explore alternative analysis approaches, and (5) to map current clinician’s attitudes towards antipsychotic discontinuation across different countries. Our collective goal in current and upcoming projects is to provide meaningful, reliable, and broadly generalizable evidence on a comprehensive range of benefits and harms of antipsychotic reduction and discontinuation in the short- and long-term. Moreover, we are aiming to identify characteristics of patients associated with a favorable outcome of tapering of antipsychotic medication. Such international collaboration is crucial to fill the knowledge gap which currently leaves clinicians relatively rudderless in their medical advice and impacts the patient’s choice concerning the continued use of antipsychotic medication.

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S. Koops et al
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