Antipsychotic maintenance treatment in schizophrenia and the importance of preventing relapse

The paper by Correll et al[1] critically reviews the literature pertaining to maintenance antipsychotic treatment in schizophrenia. This is a highly important, but poorly understood topic. The paucity of well-conducted long-term studies makes it difficult to draw firm conclusions regarding the risk to benefit ratio of ongoing antipsychotic treatment. However, this paper provides a comprehensive overview of the pros and cons of that treatment. Clinicians would do well to read the paper carefully.

Despite its demonstrated benefits, it is well recognized that long-term antipsychotic treatment is associated with substantial safety risks, adverse effects and inconveniences. For these reasons, patients and clinicians continue to entertain the possibility of stopping treatment at some stage. While the option of successfully discontinuing antipsychotics once a favourable response has been achieved would be highly desirable, the reality is that no current strategies can realistically be expected to achieve this goal. Despite our best efforts, the illness remains often characterized by chronicity, recurrence of psychotic symptoms when treatment is discontinued, and enduring deficits with negative effects on functionality, autonomy and independent living, as well as quality of life[2].

There are several important aspects concerning the nature of relapse events that clinicians and patients should be aware of when considering antipsychotic treatment discontinuation. First, relapse rates are higher than usually recognized when antipsychotics are discontinued, even after a single episode of psychosis. A recent systematic review reported a weighted mean one-year recurrence rate of 77%, and by two years the risk of recurrence had increased to over 90%[3].

Second, there are no clinically useful predictors of which individuals are likely to successfully discontinue antipsychotic treatment. Indeed, one study in a small sample found that, counterintuitively, patients who respond most favourably to treatment might be at particular risk of relapse[4].

Third, there are no reliable warning signs of imminent relapse, and early rescue medication interventions may not effectively prevent full-blown illness recurrence[5]. Evidence suggests that, once a first psychotic episode has occurred, there is a reduced threshold for illness recurrence. Unlike the first episode, where the onset of illness is frequently gradual and prodromal symptoms emerge over months and even years, the second and subsequent episodes tend to occur abruptly, with no reliable early warning signs and with rapid return of symptom severity levels similar to those of the previous episode[6]. Consequently, treatment discontinuation, even with careful follow-up and immediate re-initiation of treatment, runs the risk of exposing patients to the consequences of full-blown psychosis. This means that the often cited strategy of "targeted discontinuation" – i.e., carefully monitoring patients while treatment is reduced and discontinued, with immediate re-introduction of treatment at the first signs of recurrence – may not be effective.

Fourth, a longer period of treatment prior to discontinuation does not reduce the risk of relapse. Studies in which treatment was continued for two years before discontinuation reported similar relapse rates to those in which patients were treated for six months before discontinuation[7]. Although longer term discontinuation studies have not been conducted, there is no reason to believe that treating patients for a longer period will reduce their chance of illness recurrence once medication is discontinued.

Finally, no discontinuation strategies have been demonstrated to improve the chance of successfully stopping antipsychotic treatment. As pointed out by Correll et al[1], while psychosocial interventions are effective adjunctive therapies, they cannot be regarded as an alternative to antipsychotic medication. Furthermore, other approaches – such as gradual dose reduction followed by discontinuation of antipsychotic treatment – have not been successful.

There are serious psychosocial risks associated with illness recurrence. For example, there is a risk of self-harm and harm to others. In addition, relapses may disrupt friendships and relationships, and impact negatively on education and employment. They may also restrict autonomy, contribute to stigma, and cause patients and their families immense distress. Furthermore, relapses add hugely to the overall economic burden of treating schizophrenia.

In addition to these negative psychosocial consequences of relapse, there may be an additional risk of biological harm. While the treatment response when antipsychotics are re-initiated after relapse is variable, some patients exhibit protracted impairment of response and, importantly, treatment failure emerges in a subgroup of about one in six patients. Treatment failure occurs irrespective of whether it is the first or a subsequent relapse, and even when treatment is re-introduced immediately after the first signs of illness recurrence[8].

Given all of these potential hazards associated with illness recurrence, together with the clear-cut evidence for efficacy of antipsychotics in relapse prevention studies[9], it is understandable that clinicians continue to prioritize relapse prevention via continuous antipsychotic treatment as a treatment goal. This is despite the substantial adverse effect burden associated with antipsychotic medication. This burden can be reduced by judicious selection of the best tolerated antipsychotic according to the individual patient's profile, and at the lowest effective dose. There is also a need for the development of new antipsychotic medications that are better tolerated and at the same time more effective in providing

uninterrupted treatment, including long-acting injectable formulations.

Finally, there is an urgent need for further studies aimed at better identifying individuals who are more likely to successfully discontinue treatment, as well as at characterizing clinically useful early warning signs of impending relapse and developing treatment strategies more likely to result in successful discontinuation.

In the meantime, recommending ongoing maintenance treatment with the safest and best tolerated antipsychotic at the lowest therapeutic dose is the best option for achieving optimal outcomes.

Robin Emsley
Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

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The long-term treatment of schizophrenia with antipsychotics: a perennial debate

A number of thoughts come to mind, when revisiting the recent debate around the benefit/risk ratio of antipsychotic maintenance treatment in schizophrenia patients.

First, it appears difficult to explain why one of the best documented findings in psychiatric treatment research, namely the fact that continuous intake of antipsychotics prevents relapses with a number-needed-to-treat of 3[1], a success rate which must be seen with envy from the perspective of other medical specialties, is questioned on the basis of a handful of studies of suboptimal methodological rigor[2].

Second, one wonders why historical hypothetical constructs, such as "supersensitivity psychosis"[3], which have not proven reasonably valid ever since they were originally put forward, experience a sudden renaissance.

Third, it is interesting to note how renowned clinician researchers, when reviewing the topic based on the same datasets, come to, at least subliminally, divergent conclusions, advocating the judicious use of antipsychotics on one hand[4] and providing cautionary criticism on the other[5].

Last, I find it disconcerting that rigorously designed state of the art clinical trials, fulfilling both the demands of academic psychopharmacology and the rules and guidelines of registration agencies, are still discussed with a scepticism of an almost paranoid quality just because they are "industry sponsored".

Let me set the record straight: I am absolutely in favour of iconoclastic paradigm shattering, if it is evidence based. This is one of the guiding principles of scientific research, to either replicate or falsify. However, in my humble view, I fail to find substantial evidence from a significant number of clinical trials which convincingly puts the principle fact that antipsychotics prevent relapse in schizophrenia into question. Needless to say, this does not obviate the necessity to adjust the finer details of antipsychotic relapse prevention. More recently, treatment expectations have extended beyond the mere prevention of the recurrence of psychotic symptoms. This takes me from my more general points to issues which more specifically address Correll et al's review[6]. While the authors provide a thoughtful, balanced and clinically most useful discussion of the topic, two issues, in my mind, deserve additional attention. One of them deals with outcome assessment and the other with psychosocial outcomes.

I would like to elaborate on assessment methodology from three perspectives: diagnosis, safety monitoring and quantifying psychosocial outcomes. With respect to the first, it needs to be acknowledged that schizophrenia is still a somewhat elusive concept. Despite the efforts of the DSM-5 and the forthcoming ICD-11, the heterogeneity of the syndrome, both with respect to psychopathological presentation and neurobiological underpinnings, has left us with a certain degree of diagnostic uncertainty. Obviously, this inhomogeneity also impinges upon the quality of clinical trials, leaving us with a considerable degree of variance, even when looking at clearly defined outcome measures such as symptom recurrence. This implies that, as evidenced in basically all other fields of medicine, we are left with group findings based on mean values, which allow us only limited predictions of individual outcomes. Although personalized or precision medicine is on everybody's wish list in our field as well, it has not yet become a clinical reality, although there is some light at the end of the tunnel[7].

A problem which appears somewhat easier to solve is that of reliably assessing safety and tolerability. Many clinical trialists still rely on spontaneous reporting of adverse events. This is notoriously unreliable, especially in a disorder with well-known communicative and cognitive impairments. Standardized rating scales for all adverse events, such as those available for extrapyramidal motor side effects, need to be implemented into clinical trials, especially into phase II and phase III studies. The discrepancy between rating scale based and subjectively assessed adverse events has been well documented for motor side effects[8].