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REVIEW ARTICLE

Deprescribing Antipsychotic Medications in Psychotic Disorders: How and Why?

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Abstract: ***Background*:** Standard guidelines for the management of chronic psychoses recommend the rapid initiation of treatment with antipsychotic medications (APs) and often, indefinite continuation. Ongoing treatment with APs is based primarily on evidence from AP discontinuation studies, which have several crucial flaws. Due to this equivocal evidence for continued treatment with APs and owing to their serious side effects, there is a critical need for considering controlled reduction and/or discontinuation of APs in persons with chronic psychoses.

***Discussion and Conclusion*:** Deprescribing has been defined as the systematic process of medication reduction and or discontinuation when current or potential harms outweigh current or potential benefits, taking into account a patient's medical condition, functional status and their values and preferences. In this paper, we utilize the framework of deprescribing to answer the questions of why and how to reduce and/or discontinue treatment with APs. We first approach the complex issue of assessing the risk-benefit ratio of APs by examining the evidence for their continued benefit and their side effects. We emphasize deprescribing as a patient-centered process, using shared-decision making, psychosocial interventions and a flexible approach while prescribing. Finally, we present some of the limitations and challenges of using this approach in AP reduction and discontinuation.

Keywords: Antipsychotic, neurological, hallucinations, chronic psychoses, deprescribing, psychosocial.

1. INTRODUCTION

Current guidelines for the treatment of patients with schizophrenia and other psychoses state that Anti Psychotic medications (APs) are critical to symptom control and the prevention of relapse [1]. Treatment with APs is initiated to control disruptive and distressing positive symptoms such as delusions and hallucinations in addition to reducing agitation and improving sleep. It is recommended that they be started as quickly as possible after psychotic symptoms emerge and then continued indefinitely, at the lowest dose possible. The recommendation to continue APs indefinitely is based on evidence that is flawed and equivocal at best. In addition to unclear benefit with chronic use, both first and second-generation APs are known to cause serious neurological and metabolic side effects thereby skewing the risk-benefit ratio with increasing age and medical comorbidities. Finally, in clinical practice APs are often used in combinations with each other and for off-label indications such as insomnia and post-traumatic stress disorder unsupported by any evidence. Thus, there is a critical need for developing a systematic method for periodically evaluating the risk-benefit ratio and deprescribing APs when indicated.

The term deprescribing has been described in geriatric and palliative care medicine, and refers to the "systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits taking into account medical status, current level of functioning, patient values and preferences" [2]. This concept has only recently been applied to psychiatry [3] and lends itself particularly well to the field for several reasons. In psychopharmacology, the risk-benefit ratio is sensitive to numerous parameters including the natural course of the disorder for a given individual, the individual's psychosocial environment and psychosocial treatments. Deprescribing provides an excellent framework for both, a periodic re-examination of AP prescriptions and for subsequent action. Psychotropic medications, especially APs are known to have serious neurological and metabolic side effects thus rendering the consideration of a patient's medical status even more important. Lastly, in the absence of clear evidence-based guidelines, a patient's values and preferences for the treatment of a psychotic disorder assume a greater weight in the decision-making process than for the treatment of coronary heart disease or hypertension.

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Table 1. Systematic reviews / meta-analysis of studies examining relapse rates following AP discontinuation in schizophrenia.

S. No.	Refs.	Methodology	Findings	Conclusions	Limitations
1.	Gilbert *et al*. 1995 [5]	Systematic review of 66 studies of AP withdrawal in schizophrenia.	Over a mean follow-up period of 9.7 months the relapse rate was 53% in patients who discontinued AP and 17% in those who did not.	Risk-benefit of neuroleptic continuation Vs taper must be considered carefully.	AP withdrawn in one day in 42 studies, 24 studies had a taper duration between 2-60 days 22 studies did not provide a definition of relapse No mention of psychosocial interventions.
2.	Viguera *et al*. 1997 [4]	Systematic review of AP discontinuation in studies 1210 patients with schizophrenia.	After abrupt discontinuation, the risk of relapse reached 50% within six months.	The risk of relapse was highest within 6 months of discontinuing AP. Subjects who remained stable in the first six months were more likely to remain stable after.	In 1006 of the 1210 patients, AP was discontinued abruptly No mention of psychosocial interventions.
3.	Chen *et al*. 2010 [8]	178 patients with first episode psychosis maintained on quetiapine Vs placebo for one year.	Relapse at 12 months was 41% (95% confidence interval 29% to 53%) for the quetiapine group and 79%(68% to 90%) for the placebo group.	Quetiapine treatment substantially reduced the risk of relapse in first episode psychosis patients.	No mention of psychosocial factors or treatments.
4.	Leucht *et al*. 2012 [9]	Meta-analysis of 65 trials involving 6500 patients.	APs significantly reduced relapse rates at 1 year (drugs 27% *vs* placebo 64%). Fewer patients given APs than placebo were readmitted (10% *vs* 26%) but less than a third of relapsed patients had to be admitted. In a meta-regression, the difference between drug and placebo decreased with study length.	APs benefit patients with schizophrenia. More data needs to be obtained about the long-term morbidity and mortality of APs.	The funnel plot was asymmetrical and may represent a small trial effect Time to relapse data was not available for most studies Method of AP withdrawal was not described No mention of psychosocial interventions.
5.	Zipursky *et al*. 2014 [6]	Systematic review of six studies of AP discontinuation in first episode psychosis patients, after they had achieved symptomatic remission.	Recurrence rates in the AP discontinuation group were 77% and 90% at the end of 1 and 2 years. Recurrence rates in the AP continuation group were 3%.	Trial off AP medications in first episode psychosis patients is not recommended as the risk of recurrence is very high.	Three studies discontinued AP over a maximum of 3 months, two studies stopped depot AP, one did not specify the rate of discontinuation Variable definitions of recurrence.

1.1. The Evidence for Indefinite Treatment with APs is Flawed

The recommendation for continued treatment is based on the evidence that AP discontinuation causes relapse in a much higher proportion of patients with chronic psychotic disorders than in those who continue on the drugs [4-6]. However, these studies have several limitations. Many of the studies do not individualize the medication taper, stop the medications abruptly, have no mention of additional psychosocial interventions, or have unclear or varying definitions of relapse. None of the studies attempt to identify factors that would differentiate those who relapsed from those who did not. Furthermore, almost all studies conclude that there is a percentage of patients with psychosis that could remain well without medications and these studies recommend further investigations to identify such patients. A more recent paper re-analyzing the chronic use of APs concludes that up to 40% of patients whose symptoms remit after a first episode, may have a good outcome with either no, or minimal AP treatment [7] (Table **1**).

1.2. There is Emerging Evidence for Better Functional Outcomes with Controlled AP Reduction and / or Discontinuation

The management of schizophrenia has typically focused on remission of symptoms rather than on recovery. Remission has been defined as an improvement in the core symptoms of psychosis to the point that they no longer interfere with behavior and are at a threshold lower than the one used for the initial diagnosis of schizophrenia [10]. However, recovery is a broader concept emphasizing a person's capacity to have hope and lead a meaningful life including maximization of 1) each patient's autonomy based on that patient's desires and capabilities, 2) patient's dignity and self-

respect, 3) patient's acceptance and integration into full community life, and 4) resumption of normal development. The concept of recovery focuses on increasing the patient's ability to successfully cope with life's challenges, and to successfully manage their symptoms and has been strongly supported by the American Psychiatric Association in a position statement [11]. Accordingly, some AP reduction trials have focused on functional as opposed to symptomatic outcomes. For instance, Wunderink *et al*. [12] conducted a randomized clinical trial of maintenance treatment with APs versus dose reduction / discontinuation in persons with remitted first episode psychosis. After 6 months of remission on drugs, they followed subjects for an additional 18 months and found that the relapse rate in the dose reduction group was twice that in the maintenance group. Additionally, dose reduction did not show better functional outcomes. Of note was the result that 20% of the patients remained well despite AP discontinuation. When the same sample was followed for seven years after the initiation of the study, those persons in the dose reduction arm, experienced twice the functional recovery rates as those in the maintenance arm [13]. The symptomatic recovery was the same between groups. The Chicago follow-up study which tracked individuals after they experienced an initial psychotic episode for twenty years provides an additional reason to question the role of long-term APs for recovery in persons with schizophrenia [14]. They report that, on average, individuals who were not on antipsychotic drugs had much better functional outcomes than those who continued to take them. Commenting on these studies, Thomas Insel in his blog states that "although these symptoms *(of psychosis)* can be frightening and dangerous for patients, family members, and providers, antipsychotics safely and effectively help people through the crisis of acute psychosis. However, the long-term management of chronic mental illness is another matter. Recently, results from several studies have suggested that these medications may be less effective for the outcomes that matter most to people with serious mental illness: a full return to well-being and a productive place in society".

AP reduction and/or discontinuation in first episode psychosis becomes a particularly contentious issue as several studies have demonstrated high rates of relapse following AP reduction [6, 8]. At the same time, Wunderink, Nieboer *et al*. 2013 [13] demonstrated better recovery rates when AP was reduced or discontinued in a guided fashion following treatment for first episode psychosis. The strongest argument for early treatment of psychosis with APs comes from the 'toxic psychosis' hypothesis that states that the experience of psychosis can itself be 'toxic' to the brain and make it more susceptible to another episode of psychosis but animal studies have stated that APs may cause brain volume loss [15]. A recent review of the usefulness of APs in schizophrenia concluded that the efficacy of antipsychotics for the initial treatment of psychosis is well established. However, they add that more research is needed to determine whether some individuals may respond to alternative pharmacologic or non-pharmacologic treatments for a first episode of psychosis and if so, how to identify them [16].

1.3. The Increasing Rates of Polypharmacy

The pharmacological treatment of psychoses has witnessed an alarming rise in AP polypharmacy in the past two decades [17, 18]. The current clinical practice commonly involves combining antipsychotics to improve treatment of patients with sub-optimally controlled symptoms of schizophrenia, despite the lack of robust evidence for this approach, the increased risk of side effects, and the cost implications. In addition to the lack of evidence for efficacy, there are no guidelines for the duration for which these combinations should be continued. As a result, AP combinations may be continued indefinitely [19]. Recent studies have shown that a large proportion of patients can be safely transitioned from AP polypharmacy to a single AP without clinical deterioration [20] although one study demonstrated an increase in hospitalizations in persons who were on one antipsychotic versus two [21]. Finally, a meta-analysis of sixteen studies of AP polypharmacy concluded that AP polypharmacy did not confer any additional clinical benefit with the sole exception of aripiprazole in some persons with prominent negative symptoms [22].

1.4. Off-label use of APs

Another reason to be concerned about deprescribing APs is that their indications have broadened. Although once considered primarily for individual diagnosed with schizophrenia spectrum disorders, they are now widely prescribed to individuals with behavioral problems and even for children and adolescents with behavioral disruption [23] that occurs independently of a mood disorder or psychosis diagnosis. The use of quetiapine for insomnia [24] and second-generation APs for post-traumatic stress disorder [25] have become increasingly common despite clear evidence for the lack of efficacy.

1.5. The Risk-benefit Ratio Grows Unfavorable with Increasing Age and Duration of Illness

As mentioned above, although APs have efficacy in acute psychosis, their utility in long-term management of psychosis is questionable. In the absence of reliable indicators of a propensity for relapse, well-intentioned prescribers may err on the side of treatment and perhaps even overtreatment for all patients. This situation would be acceptable if APs did not have serious long-term side effects. However, it has been unequivocally demonstrated that long-term use of APs can have serious neurological and metabolic consequences and even increase the mortality rate [26]. With increasing age and medical comorbidities, the risks of continuing the AP unchanged may outweigh their projected benefits. In this scenario, repeated, periodic analysis of the risk benefit ratio of the AP for a given patient needs to be performed and when appropriate, deprescribing needs to be considered.

1.6. Applying the Steps of Deprescribing to the Reduction and/or Discontinuation of Antipsychotic Medications

Reeve *et al*. 2014 [27] have described a patient-centered, five-step deprescribing process that has been expanded and tailored for use in psychiatry (3). Using the principles of 1) patient-centered care 2) Shared decision-making 3) Family involvement and other psychosocial interventions in psychosis and 4) flexible and sensitive prescribing we propose the following steps for deprescribing APs.

1.6.1. Review of Psychiatric History

This step will include reviewing the person's history of hospitalizations, suicide and homicide risk and response to medications, including the outcome of past papers, if any. Collating information from multiple sources including the patient's old charts is essential. An individualized list of early signs of relapse can also be generated through a chart review and early interventions can be tailored to the person's past history.

1.6.2. Solicit Preferences from the Patient, Friends, Family and Clinical Care Team

This step is critical to ensure the success of deprescribing intervention. For a patient and their family, who have repeatedly received the message that medications are essential to their safety and survival, it can be very disconcerting to even consider the idea of medication reduction or discontinuation. Further, the patient and their immediate social circle will be critical to reducing the risk for relapse through various psychological interventions and should a relapse occur, the same people will be critical to its early identification and management. It is important to remember that although the reemergence of psychotic symptoms may constitute an emergency for some patients, this does not hold true for all. Patients may assign different values to different outcomes and the same patient's preferences and values may change depending on their circumstance. For instance, a patient may accept an increased risk of hospitalization, whereas another patient may want to avoid hospitalization at all costs. If a patient should choose to continue medications unchanged for fear of relapse, despite understanding the risks and benefits, this decision should be respected by the psychiatrist.

1.6.2.1. Develop a Plan for Monitoring Changes in Mental State before Initiating a Taper

The person might experience withdrawal symptoms, or prodromal symptoms such as insomnia, transient hallucinations, anxiety, fleeting paranoid thoughts. It is important to Individualize this list of relapse symptoms. For instance, one patient described a reduction in her ability to concentrate as 'when I start reading magazines instead of novels, I know I'm getting sick' and another, speaking about increasing irritability and paranoia said 'I start getting irritated with my brother because I feel like he wants to see me miserable.' As noted above, the medical record can be an invaluable source of a given patient's prodromal symptoms. Whenever a patient has family and friends involved, they can provide collateral information to this end.

A useful tool for creating a relapse prevention plan or to offer direction and support in the event of an increase in symptoms is a Wellness Recovery Action Plan (WRAP) [28] which assists a person in identifying daily wellness strategies as well as early warning signs of relapse and a crisis plan. WRAP is one approach among many which seek to assist in empowering a person to be self-monitoring and empowered to intervene and seek help early on and avoid worsening of symptoms or hospitalization if possible.

1.7. Initiate Potentially Useful Psychotherapeutic Interventions before the Taper

Psychotherapeutic interventions may be targeted at treating factors that increase the risk of relapse such as substance abuse, environmental stress and expressed emotions. Psychotherapy may also be able to address some of the early symptoms of relapse such as insomnia and transient delusions and hallucinations. For instance, the use of CBT to manage insomnia, anxiety or depressive symptoms and even positive symptoms may go a long way in preventing relapse.

Comorbid substance use is one of the strongest predictors of relapse in chronic psychotic disorders [29] and addressing the use of cannabis, cocaine and alcohol constitutes a critical intervention in preventing relapse in schizophrenia. This may be done by using pharmacological strategies such as naltrexone or disulfiram [30] or motivation interviewing, CBT or family interventions [31, 32].

High expressed emotions have been shown to predict relapse in schizophrenia (relapse rate in a high expressed emotion environment compared with low is 48% to 21%) [33]. Hence focusing on the family to minimize interpersonal stress and to enhance the stress management capacity of the patient may yield useful results in terms of relapse prevention. Falloon [34] in a nine-month trial, showed that family therapy was an effective method for relapse prevention. In a later trial, Hogarty [35] demonstrated that a novel family psychoeducational approach and an individual social skills training approach designed for patients living in high—expressed emotion households each reduced schizophrenic relapse by one-half when compared with medication controls in the 1st year after hospital discharge. The combination of

Table 2. Non-pharmacological intervention with demonstrated benefit in functioning outcomes in schizophrenia.

Type of Intervention	Level of Evidence	References
Cognitive behavior therapy	Meta-analysis	Pilling, Bebbington *et al*. 2002 [37]
Family therapy	Meta-analysis	Pilling, Bebbington *et al*. 2002 [37]
Cognitive remediation	Controlled trials	McGurk, Twamley *et al*. 2007 [38]
Psychoeducation	Meta-analysis	(McFarlane, Dixon *et al*. 2003) [39]
Open dialogue	Narrative reports	Seikkula 2001 [40]
Hearing voices networks	Narrative reports	Corstens, Longden *et al*. 2014 [41]

Table 3. Withdrawal symptoms of antipsychotic medications and how to manage them.

Symptom	Mechanism	Management
Nausea, malaise, diaphoresis, vomiting, insomnia [49, 50]	Cholinergic rebound	No specific treatment may be needed, continue anticholinergic medication for a week after discontinuing AP
Withdrawal emergent dyskinesia [46, 50, 51]	Dopamine supersensitivity	Lower the rate of taper
Decreased REM latency, REM sleep and total sleep time [52]	Dopamine supersensitivity	Other measures for management of insomnia such as low dose benzodiazepines, antihistaminics or trazodone
Withdrawal akathisia [53]	Dopamine supersensitivity	Slow the rate of taper

treatments resulted in no relapse [36]. By 24 months, a persistent and significant effect of the family intervention on forestalling relapse was observed, but the effect of social skills training was lost late in the 2nd year.

Open Dialogue (OD) approaches crisis intervention and ongoing care for young people experiencing psychosis by engaging the individual and family (or other supports) in meetings and conducting open discussions of all aspects of the clinical situation and decision making. This approach has been shown to result in good clinical outcomes, higher satisfaction with care and shared decision-making (Table **2**).

1.7.1. Small Reductions with one Drug at a Time

This step requires following all the tenets of good prescribing; Making small changes in only one medication at a time. The step also requires a great deal of flexibility from the prescribers' part. The change needs to be presented as a trial to the patient and they need to be offered a reversal of the change should an adverse event occur.

Standard guidelines for treatment of schizophrenia agree on dosage requirement for the acute phase but vary widely in their recommendations as far as maintenance treatment is concerned. For instance, The American Psychiatric Association [1] and the World Federation of Societies of Biological Psychiatry [42] recommended continuing the same regimen with which the patient had improved for at least six months, and the International Psychopharmacology Algorithm Project [43] recommended maintaining the dose that was effective in the acute phase during the first few months. Three guidelines recommended chlorpromazine equivalent maintenance dose of typical antipsychotics of 600 mg/day or less [1, 42, 44] and one guideline suggested the use of 8 mg/day or less haloperidol equivalents which is roughly equivalent to chlorpromazine equivalent dose of 400 mg.

Guidelines with regard to AP tapering are very sparse and conflicting. One review comparing the rates of relapse in a slow medication taper versus a rapid medication taper showed distinct benefits of a slow taper [4]. This finding was not supported by a more recent systematic review and meta-analysis that concluded that there was no difference in relapse rates between slow versus a rapid taper [45]. Both conclusions could be flawed because the AP tapers were not individualized in any of the studies included in the review.

Another consideration while reducing APs is the appearance of withdrawal symptoms. Table **3** presents a list of possible withdrawal symptoms and their management. A special consideration is the appearance of a "withdrawal psychosis or a "dopamine supersensitivity psychosis" which may be confused for a relapse of the underlying illness. Supersensitivity psychosis has been described as the appearance of new psychotic symptoms or psychotic symptoms of greater severity in a patient who has been taking APs over a long period of time and abruptly discontinues or reduces them. It is hypothesized that chronic antagonism of post-synaptic dopaminergic D2 receptors causes their upregulation, thereby making the post-synaptic neuron "supersensitive" to dopamine. Dopamine supersensitivity psychosis has been described by Chouinard as early as 1991 [46]. A more recent review examining the dopamine supersensitivity hypothesis in both animal and human studies concluded that dopamine supersensitivity could be final common pathway leading to psychosis and although APs treated it acutely, long-term AP use could enhance dopamine sensitivity, thereby making a person more vulnerable to developing psychosis in the face of environmental or neurochemical stress [47]. Another review concluded that there was sufficient evidence for a withdrawal psychosis to warrant research into interventions to reduce its occurrence. Further, a possibility was raised that treatment with APs could compound the primary hyperdopaminergic state in psychosis by producing a secondary dopamine supersensitivity [48]. The latter is of particular relevance to the decision of whether to initiate APs in a patient with first episode psychosis.

1.7.2. Regular Follow-up and Re-adjustment of Rate of Taper

Regular follow-up is an essential component of deprescribing. In addition to monitoring for early symptoms of relapse and adjusting the rate of taper accordingly, follow-up visits can serve as an opportunity to initiate wellness initiatives such as a wellness recovery action plan [28] and also obtain support from peers.

2. CHALLENGES

A prescriber may face both systemic and individual challenges while considering deprescribing antipsychotic medications. Some of the systemic challenges include the lack of guidelines and training for the process and often, the lack of peer support. Such a situation may compel the prescriber to not "rock the boat" by changing any medications for fear of symptom reappearance, relapse or even litigation. From the perspective of the patient, it can be extremely unsettling to

think about a life without medication when they have already given up on that hope. These issues can be addressed by funding more research on AP discontinuation studies and including deprescribing as an essential part of training. At an individual level, it is important to have a discussion about the potential duration of treatment with APs with each patient, perhaps even at the time the AP is initiated.

CONCLUSION

Prescribers have historically almost never considered the discontinuation of AP medications in persons with chronic psychotic disorders but a growing recognition of their side effects in addition to questionable long-term efficacy warrants an effort in this direction. Deprescribing provides an excellent framework for the repeated re-evaluation of AP risk-benefit ratio and the steps for their reduction and discontinuation.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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