The place of long-acting injectable antipsychotics in the treatment of schizophrenia

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Most experts and guidelines recognize the importance of antipsychotic medications in the short- and long-term treatment of schizophrenia.[1–3] It is imperative to emphasize at the outset that the diagnostic indication for antipsychotic maintenance is for schizophrenia, but not necessarily for related disorders (e.g. schizophreniform, substance-induced psychosis). This clarification seems necessary, since data derived from trials including psychotic disorders other than schizophrenia, such as the influential Wunderink study,[4] are used in the literature to argue against the need for maintenance treatment in schizophrenia.[5,6] A seminal meta-analysis[7] indicated that antipsychotic medications are superior to placebo in preventing relapse among patients experiencing schizophrenia, with a number needed to treat of 3. Since then, analogous data derived from a national registry have corroborated the critical role of antipsychotic maintenance in relapse prevention.[8] The effect size revealed from this research is among the largest in psychiatry and comparable to the most effective interventions in other areas of medicine.[9] Thus, consistent evidence from the treatment of schizophrenia and a robust effect size strongly support maintenance treatment with antipsychotics.

Treatment adherence is a critical yet often an underappreciated factor in the management of chronic conditions.[10] Recent data show that the annual adjusted disease-specific avoidable cost of non-adherence per person ranged from $5271 to $52,341,[11] with non-adherence rates ranging, for example, between 25% and 75% in asthma, or between 40% and 50% in coronary heart disease treatments.[12] In schizophrenia, stigma, cognitive symptoms, lack of insight, economic disadvantage, and lack of social support, among other factors, only make continuous adherence even more challenging, although, remarkably, non-adherence rates are comparable (i.e. about 50%).[12,13] Poor adherence in schizophrenia is associated with greater risk of relapse, and consequently greater risk of rehospitalization, suicidal and aggressive behavior, poorer functioning, increased healthcare costs, and premature death.[7,8,14,15] In addition to direct or indirect sequelae from the greater risk of relapse, there is mounting evidence that upon reintroduction, antipsychotics will be less effective,[16,17] which ultimately could lead to treatment resistance. Clinical assessment has poor accuracy in predicting or detecting non-adherence,[18] and no method is 'ideal', a trade-off existing between reliability and applicability.[13] Thus, the reality is that most often clinicians are mostly unaware as to whether or not their patients take the medicine that they prescribe.

In our opinion, the first approach to tackle the issue of poor adherence and its consequences is to normalize and de-stigmatize non-adherence and acknowledge it as common human behavior. Clinicians should not rely too heavily on clinical impression about adherence for any given individual – given the evidence that prescribers are often wrong[18] – and instead assume that most of our patients will be non-adherent at some point. Clinicians should deliver psychoeducation on this issue in a patient-centric and non-judgmental way, actively avoiding stigmatizing language, such that a patient is 'bad' if they are not able to follow the prescribed regimen. Concepts such as the high prevalence of non-adherence, contributing factors, and it being 'normal' behavior, as well as its consequences, should be elements of such psychoeducation. Beyond psychoeducation, there is an array of interventions that have been tried to mitigate non-adherence, such as various forms of reminders, but there is limited evidence for their effectiveness.[19] Given the imperfect tools available to address poor adherence with oral medication,

long-acting injectables (LAIs) have obvious advantages, since they deliver the treatment continuously and adherence can be easily monitored in medical records by checking injection dates. However, despite having existed for decades, there are broad disparities in the extent of LAI utilization and their role in treatment remains controversial in some quarters.

The potential advantages of LAI antipsychotic medications include greater certainty that a patient will receive continuous medication and that the treatment team will be immediately aware of a missed injection, providing valuable time for appropriate intervention before symptoms recur.[20] Other advantages of LAI antipsychotics include a decreased risk of treatment discontinuation, work disability, relapse, hospitalization, and mortality, as well as better functional outcomes over time.[8,21–23] In addition, LAIs can reduce conflict with family members or significant others related to medication-taking concerns.[24] It has also been recommended by an international panel of experts that a trial of an LAI be used to confirm the presence of treatment-resistant schizophrenia, by ruling out those with 'pseudo resistance' resulting from inadequate drug exposure.[25]

Although some patients may initially be concerned about the discomfort or stigma associated with receiving injections, this is not a major barrier for most patients. For instance, discomfort can often be minimized using second generation antipsychotics (SGA) LAIs rather than first generation antipsychotics (FGA) LAIs, (the latter having pain-inducing sesame oil–based vehicles), or using a formulation with a smaller injection volume or lower administration frequency. In addition, subcutaneous injections are now available as an alternative to intramuscular routes of administration.[20]

Despite these potential advantages, many guidelines provided by national and international societies remain, in our view, illogically conservative. For example, the American Psychiatric Association (APA)[1] *suggests* (2B) that patients receive treatment with a long-acting injectable antipsychotic medication 'if they prefer such treatment or if they have a history of poor or uncertain adherence'.

Preference must be informed by awareness and understanding. Patients would 'prefer' not to be ill and 'prefer' not to have to take any medication. Psychoeducation is key, as is shared decision making. Yet many patients and families feel uninformed about the potential use of LAIs. In addition, clinicians are often not trained in presenting the treatment alternatives in an appropriate fashion.[26] Training clinical staff can help, and our research has shown that even young, early phase patients will have a very high rate of LAI acceptance if clinicians are adequately trained.[27] And among first-episode and early-phase patients, we found a significant advantage of LAIs over usual care – reducing the incidence rate of hospitalization by 44% over 2 years.[28]

Given the fact that most patients will have some difficulty with adherence over time and that clinicians are limited in being able to predict if and when this will happen, shouldn't LAIs be used more routinely? Claims data in the United States show that LAIs are most often used in reaction to relapse, rather than proactively to prevent them.[29] Why should we wait until someone relapses to use an appropriate relapse prevention strategy? Answering this question requires an appreciation of benefits and risks of LAIs. The benefits have been previously addressed. What are the risks? Are adverse effects more common, or more severe? Meta-analyses of numerous studies comparing oral and LAI formulations of the same medication indicate that this is not the case.[30] If anything, this is a conclusion based on unequal samples given there was likely some degree of nonadherence among those taking oral medication. A recent report indicates that in the case of tardive dyskinesia, one of the major risks associated with long-term antipsychotic treatment, the risk with oral medication was actually higher than with LAIs.[31] Another concern might be the risks associated with adverse effects that would be cause for rapid drug discontinuation. Even in the case of neuroleptic malignant syndrome, where rapid discontinuation of the offending agent is desirable, there does not appear to be a significant difference in fatality rates between those developing neuroleptic malignant syndrome (NMS) on oral or LAIs.[32] Yet another potential obstacle is the negative perception of LAIs: their being associated with a sense of coercion and loss of autonomy or with stigma. In our opinion, such interpretation is often biased and stems from various factors, such as the generalization of specific scenarios (e.g. use of injectable antipsychotics for management of agitation or in court mandated treatment), the emphasis of the method of drug

delivery (i.e. injection) over the goal of treatment (i.e. relapse prevention), or the underappreciation of the importance of health literacy and insight about non-adherence and relapse to make an informed decision about treatment. These potential biases in thinking about LAIs should be assessed, and if present should be addressed with the appropriate psychoeducation within a shared decision-making framework.

As was emphasized at the outset, we are discussing individuals with a diagnosis of schizophrenia for whom the indication for antipsychotic treatment is clear. We still hear clinicians say, 'What if the patient doesn't need the medication?' as a reason for not considering LAIs. The choice between oral medicine and an LAI does not depend on the indication. It is a matter of the delivery method. Once we have decided on the most appropriate treatment the task becomes, how do we best assure that the patient derives the intended benefit.

Given the evidence of benefits and risks coupled with the consequences of psychotic relapse, in our view, we should less frequently be asking 'why?' we should use an LAI and more frequently be asking 'why not?'

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Consent for publication
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