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Review article

A critical appraisal of long acting injectable antipsychotics: Translating research to clinics

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ABSTRACT

Long acting injections (LAI) are an effective alternative mode of administration of antipsychotics, less commonly used in clinical practice. Gap in knowledge base is an important source of attitudinal bias. Current article is focused on reviewing the literature for the principles underlying the choice, initiation, maintenance, switch and termination of an LAI; historical, pharmacological and clinical factors implicating the rationale of using LAI against oral agents and older against newer LAIs. Evidences available in clinical and basic psychopharmacological researches are critically appraised, highlighting the lacunae in our understanding. It is endeavored to open the window for the studies to be carried forward in the future answering critical questions which could lay a stronger base for clinical utility of different LAIs. Thus, this article tries to acquaint clinicians with the translatable knowledge imparted from the research and riposte queries for the researchers to explore in relation to LAI.

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1. Introduction

Introduction of chlorpromazine in 1952 brought a paradigm shift in the management of psychosis. Within few years, it became clear that dose reduction or stopping neuroleptics caused re-emergence of symptoms as much as, if not more, than life events. Thus, concept of continued treatment started emerging and in

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parallel, the problems related to adhering to the treatment. A huge rate as high as 24–86% of patients were noted to be poorly adherent on oral antipsychotics (Young et al., 1986). The need for easier dosing regimens became the focus of further progress in this area; in turn, these developments culminated towards need for longer acting antipsychotics. G. R. Daniel, was the pioneer who initiated this endeavor and came out with the first Long Acting Injectable Antipsychotic (LAI), fluphenazine enanthate in 1966 (Johnson, 2009); about 18 months later, the same group of researchers developed fluphenazine decanoate. Flupenthixol decanoate was the next in line introduced by a Danish pharmaceutical company. Long acting formulations of Haloperidol (Granger and Albu, 2005) and zuclopenthixol (Buschmann et al., 2007) followed the lane.

Inflexible, non-individualized dosing of long acting injectable first generation antipsychotics (FGA LAI) led to intolerability due to extrapyramidal side effects. This warranted add-on anticholinergic medications that had to be administered orally; hence, the basic idea of avoiding oral medications failed. The physician so used it as a back-up along with oral antipsychotics, to protect against non-adherence (Johnson, 2009). Thus the acceptance of LAI among psychiatrists as well as patients had been through a bumpy track.

With emergence of oral second generation antipsychotics (SGA), the tolerance problems (especially due to extrapyramidal symptoms) decreased to some extent (although some of the second generation antipsychotics like risperidone, when prescribed in higher doses, can cause extrapyramidal symptoms comparable to that of haloperidol (Marder and Meibach, 1994)). The improved tolerability of oral SGAs led to widespread reduction in usage of oral and LAI FGAs. Nonetheless, the issue of non-adherence and relapse persisted (Naber and Lambert, 2009). Need of long acting agents were reconceived and SGA LAIs are being invented with newer technologies. Risperidone microspheres, paliperidone palmitate [once monthly and 3-monthly injections] (Gopal et al., 2015), olanzapine pamoate injections and freeze dried aripiprazole are already in clinical use in different countries. Recently iloperidone LAI has also been found to be safe and efficacious in preclinical trials and is in the verge of getting approval of regulatory bodies (Tonin et al., 2016). Now eleven of the 65 antipsychotics are available in LAI preparation (Bruijnzeel et al., 2014). In the context of increasing number of newer antipsychotics in LAI formulation, this narrative review aims at summarizing varied aspects of LAI research and elucidates a critical appraisal focusing on the clinical needs.

2. Clinical efficacy of antipsychotics: long acting injectable vs oral formulation?

2.1. Adherence as a modulator of efficacy

Traditionally, LAIs are recommended for patients with poor adherence to treatment. It also helps to an extent, in distinguishing poor adherence from poor response. In a regular clinical situation, any relapse raises the doubt of adherence; it is usually very difficult to ascertain adherence objectively. Serum drug level monitoring is an ideal approach, but not cost effective. The reduced frequency of dosing along with guaranteed supervised administration is the chief advantage of LAI in improving adherence. Indirectly, treatment with LAI facilitates contact of patient with the health system which by itself may improve the adherence. This also will enable the caring team to intervene at the earliest, on patient failing to turn up for the scheduled injection (Morrissette and Stahl, 2012). The enhanced supervision almost avoids one from overdosing as a mean of deliberate self-harm. The longer action reduces the chances of covert non adherence (skipping of dose due to forgetfulness) as well as overt non-adherence resulting from poor insight (Patel et al., 2009).

Adherence is a dynamic issue which fluctuates across spectrum from good to poor. Adherence has bidirectional relationship with efficacy. Studies have shown that adherence improves with better effectiveness of drugs as well as lower side effects (Valenstein et al., 2004). Continuous availability of drug improves symptomatic and functional outcome which in turn favors good adherence (Brissos et al., 2014). The improvement noted in acute phase is also not static. Progressive improvement has been reported up to 4 years of starting antipsychotic treatment (Morrissette and Stahl, 2012). It is highly likely that adherence might play a critical role in maintaining this trajectory; nonetheless, there might be additional mechanisms that can lead to enhanced outcome in patients treated with LAIs.

2.2. Potential pharmacological factors of the LAIs influencing the clinical decisions

Pharmacokinetic factors of longer action give an advantage of time to relapse in case of delay in follow-up visits. The elimination half-life of most LAIs are significantly greater than oral. Thus, a minimal therapeutic level could be maintained for few weeks if dosing schedule is missed. Bioavailability tends to be high because of parenteral route of administration, being associated with lesser first pass metabolism (8). This will reduce the total dose of the therapeutic agent to be administered. Inherently associated with the longer half-life and longer action is the more consistent, less frequent and less intense fluctuations of blood levels. Lower difference between peak and trough levels results in lower side effect risk which further enhances treatment adherence (Zhornitsky and Stip, 2012). This also minimizes the risk of sudden withdrawal or rebound phenomenon. The predictability of plasma level could be more accurate with less inter-individual variations. All these factors are likely to increase the comfort level of clinician with the standard dosing regimens of LAIs.

Intriguingly, despite the fact that the active pharmacological moiety is similar, there can be differential pharmacodynamic effects between oral and LAI formulations. Of course, this is implicated upon the variations of blood levels of drugs and their subsequent effects on receptor sensitivity related side effects of antipsychotics. For instance, dystonia has been found to occur more frequently during the trough levels and hence LAI formulation has lesser risk for dystonia (Yamamoto and Inada, 2012). The frequent fluctuations in blood levels of antipsychotics over a period of time risks the change in dopamine receptor sensitivity. Tardive dyskinesia and dopamine supersensitivity psychosis are few of the clinically significant phenomena linked with heightened sensitivity of dopamine receptors (Kimura et al., 2016, 2013). In supersensitivity psychosis, dopamine receptors develop tolerance to antipsychotics so that higher doses gradually fail in controlling the symptoms. Acute exacerbation occurs on sudden discontinuation of drug and/or relapse happens with minor stressor, ultimately leading on to treatment resistance. It has been suggested that as much as about 50% of treatment resistance in schizophrenia might be resultant of dopamine receptor supersensitivity (Kimura et al., 2014). In supersensitivity phenomenon the density of D2 receptors are hypothesized to increase with need for more antipsychotics to occupy the receptor for effective blocking. The constant elimination half-life in the presence of higher receptor occupancy leads to higher fluctuations in blood levels across the borders of therapeutic window. Thus, the resultant higher doses of short acting antipsychotics can potentially cause more side-effects, however with less effectiveness (Seeman and Seeman, 2011). Risperidone LAI was found to improve by stabilizing the therapeutic blood levels leading to continuous optimal percentage in D2R occupancy (Kimura et al., 2014) and has now been recommended as a potential option to be explored (and thus the