EDITORIAL

LONG ACTING INJECTABLE ANTIPSYCHOTICS – WHERE ARE WE?

Phani Prasant Mulakaluri
Consultant Psychiatrist, Chetana Hospital, Secunderabad, 500003. Telangana.

Globally, schizophrenia is a leading cause of years lost to disability, with a particularly large burden among adolescents and young adults.[1] Although antipsychotic medications reduce psychotic symptoms and greatly decrease the risk of relapse, their effectiveness in real-world practice is decreased by non-adherence.[2] Non adherence rates have been reported up to 40-60% in the literature.[3] Despite this high prevalence, providers are often unaware of this issue and generally overestimate medication adherence in their patients.[4]

The first Long Acting Injectable (LAI), Fluphenazine enanthate and decanoate, were introduced in 1966 in the context of large-scale de-institutionalization of patients with serious mental illnesses and the consequent need for effective community-based treatment. There was an initial enthusiasm and wide spread use of these depots but slowly with the invention of new oral second generation antipsychotics with better side effect profile, the use of the LAIs, declined. It is time for understanding where we are in our knowledge of the LAIs, as new second generation LAIs, with Risperidone in 2002, followed by Paliperidone and Olanzepine are being made available in India. The newer LAIs Aripiprazole and once in three months Paliperidone are likely to be available here soon.

Clinicians who consider using LAIs in their practice want to know: Do LAIs improve patient outcomes compared with oral antipsychotics and if so, which outcomes? Are newer LAIs more effective than the older ones? Who should receive a LAI?

Examining the research about the efficacy of the LAIs, one makes a basic presumption that LAI are expected to be more efficacious basically due to improved adherence and less side effects due to stable Pharmacokinetics. The literature on adherence and efficacy of LAI has no definite answers. It is found that there is no difference in LAIs versus Oral agents in Randomized Controlled Trials. The two meta-analyses done by Leucht et al gave conflicting results, the first one favoring LAI and the second one showing no difference.[5,6] However the Observational studies, both prospective and retrospective studies have shown the efficacy of LAIs.[7,8] There has been a good argument on which is the right method to assess the efficacy and adherence of LAIs, as the main aim of LAI is to improve the care in the community setting where as RCTs cannot represent the population who might benefit from such intervention. In short, if LAI clinical trials select patients who are relatively adherent and stable, then it is possible that LAIs might have a different effect in the real world patients with unstable illness who are often prescribed LAIs.[9] A meta-analysis to this effect has shown that study design influences the outcome in the case of LAI versus Oral.[10] They describe a possible 'Hawthorne effect'—where behavior is affected by the awareness of being observed—that would lead study subjects to have greater adherence to oral medications than they would have in real-world practice because of their knowledge that their adherence is being monitored; They concluded that these aspects of RCTs attenuate the advantages of LAIs over oral medications that are seen in observational studies.

The second question to address is whether Second Generation (SGA) LAIs are better than the First Generation (FGA) LAIs? The second Generation antipsychotics starting with Clozapine came with big promises of greater efficacy, more in treating negative symptoms and less neurological side effects compared to the first generation antipsychotics. There has been considerable research into this area and large famous studies like CATIE[11] and CUTLASS[12] have shown that there is no difference and that the SGA have more metabolic side effects and less neurological side effects than FGAs. A recent Meta-analysis[13] however shows that four SGAs (Amisulpiride, Clozapine, Olanzepine and Risperidone) were better than FGAs on overall efficacy with small to medium size effect. The other SGA's were no better even for the negative symptoms. Additionally, increasing evidence suggests that there is

Address for correspondence:
Dr Phani Prasant Mulakaluri
Director and Consultant Psychiatrist,
Chetana Hospital, Minister Road,
Secunderabad-500003, Hyderabad, Telangana, India
Mobile: 9849807740
Email: editoroftjp@gmail.com

considerable variability among the older and newer drugs, which calls into question the validity of the 'generation' categories.

Few studies have looked at how newer LAIs are compared with older LAIs. Initial study comparing patients with Schizophrenia and co-morbid substance use showed Risperidone LAI to be more efficacious in reducing the substance use and PANSS score than Zuclopenthixol LAI.[14]Later one more observational study on Risperidone LAI versus FGA LAI showed no difference.[15] However two recent multisite RCT one comparing Risperidone LAI[16] and other Paliperidone LAI[17] with FGA LAI Haloperidol and Fluphenazine found no benefit of the SGA instead found more weight gain and increased prolactin level than the FGA.

We find similar issues with the research on whether LAIs are more tolerable than oral, and whether the SGA LAIs have lesser side effects. There are no studies comparing equivalent oral doses to LAI and, SGA LAI have not proven to be having lesser side effects.[18] We need to be aware of the new side effects due to the route of administration like PDSS(Post injection Delirium Sedation Syndrome) that warrants three hours compulsory monitoring with Olanzepine LAI.[19]

While researchers argue about the reason why there are no definitive answers to the efficacy of the LAI and specifically SGA LAIs, the clinicians have to take an individualistic approach to prescribing LAI, looking at the previous response, tolerability and affordability.

Now addressing the last question, who needs to be given LAI? Some have argued that LAIs may be most beneficial when used for people experiencing a first episode of psychosis, when knowledge about the illness is low and ambivalence about medications is high. The large sample study of the Finnish Registry showed that in the follow up, patients on LAI were 59% were more likely to be continued and 36% less likely to be hospitalized compared to the oral counterparts.[20] Two open label studies[21,22] and recent RCT[23] comparing Risperidone in both the forms showed that those on LAI were more compliant and relapsed less often. Patients in first episode of schizophrenia accepted LAI as a good option. In summary even though the research is meager and more on Risperidone LAI it shows that might be a definite benefit in using LAI in these group of patients who will benefit the most from continued treatment.

There is also a definite population that might not be benefited from LAI. Whenever a new drug is released clinicians commonly prescribe it to their treatment refractory patients, who have already been tried on multiple antipsychotics. These individuals may not be the right ones for LAIs. A trial of LAI is warranted if the patient has been Resistant to treatment (that is, not compliant to treatment prescribed), but true treatment resistant Schizophrenia will not benefit from LAI.

Before concluding we need to focus on an important practical issue in prescribing LAI. LAI administration is a combination of Art and Science. Research has shown adequately that poor knowledge among the clinicians as one of the reason for not prescribing a LAI. As clinicians we need to learn the science i.e., the pharmacodynamics and pharmacokinetics and art i.e. How to address the optimal dose and duration of the LAI and tailor it to the needs of the patient. We need to know the does equivalents of the LAI vs oral (for E.g. – Risperidone LAI 25mg = 2mg/d, 37.5=3mg/d and 50mg=4mg/d), and also pharmacokinetics; like when the peak level and steady states are reached, how long to overlap with the oral antipsychotics, what to do if a dose is missed. Most of the LAI can be prescribed once in a month except the Risperidone LAI and Olanzepine LAI (if given at equivalent to 20mg/d dose).[24] Some of the additional information might add to the art of giving LAI for example if a patient develops mild EPS when given a dose of Paliperidone, giving the next dose through the gluteal region than the deltoid region might reduce it and reverse is true if even after reaching the maximum dose if there is partial response.[25] Cultural variation and knowledge about fast metabolizers is very essential if someone is neither showing response nor side effects. Clinicians need to update themselves regularly with the knowledge of LAI to feel more comfortable to prescribe them.

CONCLUSIONS

While the researchers are still trying to find the best study design and type of patients who will show definite benefits of LAI, we need long term follow up studies in naturalistic environment to prove the efficacy (indirectly due to adherence) over the oral agents. That said, a good study of LAIs would be of long duration since the most salient outcomes go beyond efficacy in terms of symptom control and extend to relapse prevention, re-hospitalization and mortality. Clinicians still need answers to the questions posed at the beginning: Do LAIs improve patient outcomes compared to oral antipsychotics and if so, which outcomes? Are certain LAIs more effective than others? Who should receive LAIs?

In clinical practice LAI are an important part of the armamentarium and need to be used in patients who are considered to be at risk of Non adherence, such as; a history of non-adherence, severe symptoms, co-morbid

substance use, cognitive impairment, ambivalence or negative attitudes towards medications and poor insight.[26] LAI reduce the effort of taking the medication daily for the patients and help clinicians by alerting promptly on onset of non-adherence.

Research to date is clear on no superior efficacy of SGA LAIs to FGA LAIs, so the clinicians should consider patient's preferences, prior experience with antipsychotics, health status and the specific side-effect profiles and cost of the medications when selecting an LAI antipsychotic.[27]

First episode of Schizophrenia is an important opportunity to improve the outcomes of the illness if adherence is ensured; clinicians should consider it as one of the options earlier in the treatment rather than after multiple failures. However caution should be used as the first encounter with the medication needs to be positive and if LAI induces side effect then the dose adjustments cannot be made immediately, therefore for all new patients stabilizing on the oral medication before shifting them to LAI is mandatory.

In treatment resistance cases if true resistance is established, in which patients take medication for adequate duration but do no benefit from the treatment LAIs are not the first choice and Clozapine is the recommended drug in such cases.

In summary, in spite of equivocal evidence to support LAI usage over the orals, LAIs have a legitimate and potentially important role in clinical practice. However LAI are only a part of the comprehensive treatment and without adequate psychosocial interventions the comprehensive care is incomplete to achieve the desired goals.

Box 1 Summary of clinical perspective on long-acting injectable (LAI) antipsychotic medications

- Consider LAIs for patients with recent-onset schizophrenia and those with risk factors for medication non-adherence: history of non-adherence, severe symptoms, comorbid substance use, cognitive impairment, ambivalence or negative attitudes towards medications, and poor insight.
- When selecting an LAI, consider patient's preferences, health status, experience with prior antipsychotic medication trials, and the side-effect profiles of different medications.
- The effectiveness of newer LAIs and older LAIs is similar.
- Clozapine rather than LAIs should be tried for those whose clinical instability is due to treatment-resistant illness rather than medication non-adherence

Adapted from Enrico G Castillo, T Scott Stroup Evid Based Mental Health 2015[27]

REFERENCES

1. Gore FM, Bloem PJ, Patton GC, et al. Global burden of disease in young people aged 10–24 years: a systematic analysis. Lancet 2011;377:2093–102.
2. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 2012;379:2063–71.
3. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry 2002;63:892–909.
4. Byerly M, Fisher R, Whatley K, et al. A comparison of electronic monitoring vs.clinician rating of antipsychotic adherence in outpatients with schizophrenia. Psychiatry Res 2005;133:129–33.
5. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. The Lancet. 2013 Sep 20;382(9896):951-62.
6. Kishimoto T, Robenzadeh A, Leucht C, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophr Bull 2014;40:192–213.
7. EmsleyR, Oosthuizen P, Koen L et al. Oral versus Injectable antipsychotic treatment in early Psychosis: post hoc comparison of two studies. ClinTher. 2008;30(12):2378-86.
8. Tiihonen J, Wahlbeck K, Lonnqvist J et al. Effectiveness of antipsychotic treatments in nationwide cohort of patients in community care after first hospitalization due to schizophrenia and schizoaffective disorder: observational follow-up study, BMJ. 2006. 333(7561):224.
9. Shi L, Ascher-Svanum H, Zhu B, et al. Characteristics and use patterns of patients taking first-generation depot antipsychotics or oral antipsychotics for schizophrenia. PsychiatrServ 2007;58:482–8.
10. Kirson NY, Weiden PJ, Yermakov S, et al. Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs. J Clin Psychiatry 2013;74:568–75.
11. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res2005;80:45–53.
12. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 2006;63:1079–87.
13. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373:31–41.
14. Rubio G, Martinez I, Ponce G, et al. Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. Can J Psychiatry 2006;51:531–9.
15. Lammers L, Zehm B, Williams R. Risperidone long-acting injection in schizophrenia spectrum illnesses compared to first generation depot antipsychotics in an outpatient setting in Canada. BMC Psychiatry 2013;13:155.
16. Covell NH, McEvoy JP, Schooler NR, et al. Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone

microspheres: an open-label, randomized controlled trial. J Clin Psychiatry 2012;73:669–7.
17. McEvoy JP, Byerly M, Hamer RM, et al. Effectiveness of paliperidonepalmitatevs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. JAMA 2014;311:1978–87.
18. Gentile S Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comprehensive systematic review. Pharmacotherapy. 2013 Oct;33(10):1087-106. doi: 10.1002/phar.1313. Epub 2013 Jun 17.
19. Tiihonen J, Haukka J, Taylor M, et al. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 2011;168:603-9.
20. Kim B, Lee SH, Choi TK, et al. Effectiveness of risperidone long-acting injection in first-episode schizophrenia: in naturalistic setting. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1231-5.
21. Emsley R, Oosthuizen P, Koen L, et al. Remission in patients with first-episode schizophrenia receiving assured antipsychotic medication: a study with risperidone long-acting injection. Int Clin Psychopharmacol 2008;23:325-31.
22. Weiden PJ, Schooler NR, Weedon JC, et al. A randomized controlled trial of long-acting injectable risperidone vs. continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial adherence outcome. J Clin Psychiatry 2009;70:1397-406.
23. Byerly MJ, Nakonezny PA, Lescouflair E. Antipsychotic medication adherence in schizophrenia. Psychiatr Clin North Am 2007;30:437–52.
24. John J Sheehan, Kristin R. Reilly, Dong-Jing Fu et al. Comparison of the peak-totrough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. Innovclinneurosci. 2012;9(7–8):17–23.
25. Alexandre González-Rodríguez, Rosa Catalán, Rafael Penadés et al Profile of paliperidonepalmitate once-monthly long-acting injectable in the management of schizophrenia: long-term safety, efficacy, and patient acceptability – a review Patient Preference and Adherence 2015:9 695–706.
26. Goff DC. Maintenance treatment with long-acting injectable antipsychotics: comparing old with new. JAMA 2014;311:1973–4.
27. Castillo EG, Stroup TS. Effectiveness of long-acting injectable antipsychotics: a clinical perspective. Evid Based Ment Health. 2015 May;18(2):36-9. doi: 10.1136/eb-2015-102086. Epub 2015 Apr 8.

How to cite the article: Phani Prasant M. Long acting injectable antipsychotics- Where are we?. TJP 2015; 1(1): 1-4.