The International Journal of Indian Psychology
ISSN 2348-5396 (Online) | ISSN: 2349-3429 (Print)
Volume 8, Issue 4, Oct- Dec, 2020
DIP: 18.01.110/20200804, DOI: 10.25215/0804.110
http://www.ijip.in

Research Paper

Role of long acting injection in treatment of schizophrenia: literature review

Aditi Rana[1]*

ABSTRACT

Schizophrenia, prevalent in approximately 1% of the UK adult population, characterized by severe and chronic symptoms remains a challenge for the health care services providers, health researchers and policy-makers. Antipsychotic therapy has been indicated as the primary choice of treatment for schizophrenia, supported by leading American Psychological Association, National Institute of Mental Health and National Institute for Clinical Excellence. However, absolute non-compliance or partial compliance to antipsychotic therapy is common in schizophrenia and is a strong predictor of worsening symptoms, augmented chance of relapse, hospitalization and further resistance to antipsychotic treatment. The administration of depot by the clinicians provides an advantage of being in close contact with the patients and provide follow-up if an appointment is missed, which is likely to increase adherence to treatment, and consequently reduce relapse and hospitalization. The potential advantages of Long-Acting Injection (LAI/Depot) antipsychotic therapy look promising in reducing the economic burden of this big budget problem. However, inconsistencies in the results of studies comparing cost effectiveness of oral and depot antipsychotic therapy limits our understanding of any true benefit of using depot antipsychotics.

Keywords: *Schizophrenia, Long-Acting Injections, Oral antipsychotics, Treatment Cost, Benefit Analysis*

Schizophrenia, a debilitating mental illness marked by severe positive, negative and cognitive symptoms is a common psychiatric disorder, affecting approximately 1% of the adult UK population. A systematic review by McGrath[52] et al addressed the question of prevalence of schizophrenia. The review included 128 studies in 33 countries with 1,457 reported rates. The results from the study reported an estimate of 15.2 per 100,000 individuals (SD: 7.7- 43.0/100 000) as the median incidence rate. This soaring incidence rate is an estimate of only the reported schizophrenia cases in the population.[52] This indicates that the true prevalence of schizophrenia is underestimated.

Due to early onset, chronicity, severity of symptoms consequently leading to high rate of relapse and frequent need for hospitalization, schizophrenia is associated with major

[1]Research Assistant, Department of Psychiatry, AIIMS, New Delhi, India
*Responding Author

Received: September 13, 2020; Revision Received: December 02, 2020; Accepted: December 31, 2020

economic burden on not the patients, caregivers, close relatives and employers but also the health services and broader society in general. Treatment of schizophrenia is not only expensive in terms of direct cost of treatment inclusive of psychiatric care, hospitalization cost, pharmacological cost and others, but also the indirect costs. In addition to the loss of productivity in patients' due to severity of symptoms, the burden associated with providing constant care to the patient in care giver is liked to deteriorated life quality and decreased productiveness.[53]

Meta-analysis conducted by Kavanagh et al, 1995 reported that the average cost incurred by the insurance agencies for the treatment of schizophrenia in England per year is approximated to be £1905 Million. Furthermore, treatment of schizophrenia has been reported to account for approximately 3%of the total National Health Services cost.[56] Inconsistency in results of cost-of-illness studies due to heterogeneity in population, differences in methodology used and availability of service utilization across countries limits our understanding of the true economic estimates of schizophrenia. EPSILON study, comparing the economics of schizophrenia treatment, conducted in 5 different countries, Denmark, England, Italy, Spain, The Netherlands, found extreme variance in the mean total annual cost per site. Despite these differences, developed countries reportedly have an augmented overall cost of treatment.[57] Similarly, the estimated total cost of schizophrenia treated approximates to US$ 65 Billion/annum in United States. Despite the variance in the estimated cost of individual, a unanimous agreement exists that schizophrenia is a persistent big budget problem elevating at a rapid rate.

NICE guidelines[54] consider antipsychotic therapy to be the fairly favorable and acknowledges it as the first step in schizophrenia treatment A major shift in the treatment of schizophrenia has also been observed with the introduction of novel atypical antipsychotics. Supported by the National Institute for Clinical Excellence, American Psychiatric Association and National Institute of Mental Health, atypical antipsychotics are indicated as the primary treatment choice for patients with recent diagnosis of schizophrenia due to good efficacy and potential to reduce relapse and extrapyramidal side effects. However, due to graveness of symptoms in schizophrenia, non-adherence to treatment is not uncommon. The failure to comply to antipsychotic treatment is a good predictor of relapse and deteriorated long term prognosis of illness.

A great deal of economic burden associated with schizophrenia is accounted by the augmented rates of relapse and exorbitant hospitalization costs. Long acting injections are popularized to decrease total treatment cost by reducing relapse and burden. The aim of this literature review is to assess the effectiveness of using two different administration approaches in antipsychotic therapy: Long Acting Injections and Oral Antipsychotics, in reducing the costs of treatment associated with schizophrenia.

LITERATURE REVIEW

Cost Drivers in Treatment of Schizophrenia

The cost of treatment in schizophrenia can be broadly split into two categories: Direct treatment cost and indirect treatment cost.

Direct cost can be simply put as costs that are associated with the disease and the treatment, such as admission costs, pharmacy and drug costs, outpatient services, laboratory testing costs etc. On the other hands, indirect costs are the non-medical costs that are the

consequence costs of the disease, such as decrease in work productivity, unemployment, chronic and permanent disability, social impairment in patients and caregivers.
The patients diagnosed with schizophrenia require care and support from the relatives. Thus, the burden placed on the caregivers to provide support often leads to decrease in productivity of the caregivers, the caregivers may be required to take extra days off work or even quit their job. Both the direct and the indirect costs are the contributory factor to the expensiveness of the disease.

Cost-of-illness studies are likely to exclude the measures of indirect cost in schizophrenia as they often extract data from medical records and datasets. The indirect costs are more challenging to report and require the use of self-report questionnaire assessing the health care cost utilization. Indirect cost such as lost productive and unemployment are also depended upon the severity of symptoms and improvement in disease prognosis. The patients with moderate symptom severity may have less problem in terms of productively as compared to patients with comparatively more severe symptoms. Hence, this may vary with the symptom severity. None the less, inclusion of indirect cost is an important factor to predict the total economic burden of the disorder.[62]

In a paper review[63], Knapp addressed the cost of schizophrenia, one of the largest contributing factor to the indirect cost was the rate of unemployment among the patients diagnosed with schizophrenia due to severity of illness and augmented morbidity rate associated with schizophrenia (Allebeck, 1989; Anderson et al, 1991). Further, only 20% of people diagnosed with psychosis were paid employees. This was consistent with unemployment rate of other studies (Foster et al, 1996). Additionally, the study reported that the annual indirect cost in England, using the estimates of annual average wage in the general population, accounted by lost productivity was approximately 1.2 Billion in 1992/1993. Another factor affecting the indirect cost of schizophrenia was the care provided by the relatives to patients with schizophrenia. An estimate from a study in North American population approximated the cost related to the time committed by relatives of the patients with schizophrenia as 11, 519 dollars/ family. (Rice et al, 1991), though this was highly variable, but the estimated cost gave an indication of the magnitude of indirect cost associated with the caregiver burden. (McGuire, 1991). Other factors reported by Knapp were the effect of the illness on quality of life of the patients and caregivers. In conclusion, the indirect costs may have a significant effect on the overall economics of the disease and it is essential to consider their effect to analyse the costs accounted by the disease from a broader perspective.

The main aim of the cost-of-illness studies is to evaluate the direct costs of treatment as they are of considerable importance to the policy makers, insurance companies and health care service providers. Estimates to cost-of-illness studies acknowledge the relevance of choosing the most effective treatment in reducing costs and predicting a better long-term prognosis of the disorder. Various studies have reported that the primary factor that accounts for the augmented cost in the treatment of schizophrenia is the rate of hospitalisation. Davies and Drummond[51], 1994 used the prevalence approach to estimate the total cost of treatment per year. Results indicated that hospital and residential care cost account for approximately 74% of total direct costs and are the contributory factors in the treatment expenditure.[59] Various other studies demonstrated results in agreement with the association of increased hospitalisation rates and augmented treatment cost.

Briefly, Weiden & Olfson[61], 1995, in their meta-analysis of relapse studies in schizophrenia estimated that while the cost of treatment for first-episode in-patient service were approximately $ 2.3 Billion, the direct cost of rehospitalisation following relapse were also approximately $2 Billion, 63% of which was attributed to loss of medication response and 37% to non-adherence to treatment. In a retrospective study[20] (Almond et al, 2004) patients with schizophrenia who had experienced relapse in the preceding 6 months from the study time point and patients who did not experience relapse in the same time point were identified. Results indicated that the cost for relapse cases were higher as compared to the non-relapse group, the in-patient days as the major cost driver in the relapse group.

Weiden & Glazer[60], in order to determine the pattern of relapse, identified schizophrenia patients with frequent relapse and hospitalisation referred to as "revolving door phenomenon". The average hospitalisation rate reported in the sample was 1.3 hospitalisations/ year in the preceding 3 years, additionally, these patients had a median of 5 months between recurrent hospitalisation. The results from this study indicated that the most common reason for relapse was non-adherence to medical treatment followed by non-response to antipsychotic treatment. Thus, it has been advised that increasing compliance to antipsychotic medicines should be a primary aim in treatment of schizophrenia, supported by National Institute of Clinical Excellence.

The total rate of non-adherence in schizophrenia is nearly 40-60%. Studies show that around 35% of patients have issues with complying to the treatment in initial 4-6 weeks. This number rises up to 75% in about 2 years of initiating treatment.[3]

Non-adherence can be a consequence of various factors such as negative and positive symptoms, lack of insight, cognitive impairment, complexity of dose schedule, extra pyramidal effects and the refusal to undergo treatment.[7] Irregularity in the antipsychotic treatment is a strong predictor of increased severity of symptoms, relapses and hospitalizations. Consequently, this implies that compliance to antipsychotics is associated with lower relapse, decrease in number of hospitalizations and reduced overall cost of treatment.[7]

In an attempt to enhance compliance to treatment and reduce relapse, Squibb and sons in the year 1966 formulated Fluphenazine enanthate, the foremost Long Acting Injection (LAI/Depot) antipsychotic.[3] Chemically, depot antipsychotics are formed by the esterification of the classical antipsychotic agent by a fatty acid. LAI treatment eliminates the need for everyday oral medication administration as patients are required to visit the hospital once in 1-6 weeks for LAI administration.[11]

When compared to oral antipsychotics, long acting injections have been reported to have few advantages:[3,9]

LAI antipsychotics are administered by the clinical staff; thus, the use of LAI eliminates the covert non-adherence due to forgetfulness. The administration by staff allows the clinicians to contact the patient immediately in case of a missed appointment.

LAI are also advantageous in increasing the pharmacokinetic coverage of the antipsychotic, thus reducing the change of withdrawal symptoms accounted by partial compliance.

LAIs are directly injected into the body. Hence, they are not influenced by the first pass mechanism. Thus, reducing the potential harm induced by drug-drug interaction.
LAI also seem to be advantageous than oral antipsychotics in terms of side effects as the slow rate of LAI absorption curbs the drastic change between maximum and minimum plasma level.

It is also important to consider the potential disadvantages of using long acting injections in order to select the appropriate treatment approach.[3,64]

The depot antipsychotic is directly injected into the body and is slowly released in to the blood. The rate of depot absorbed is regulated in the body to prevent the side effects of free drug release. Thus, depot antipsychotics take longer time to reach their full potential.

Additionally, once the drug is released into the body, it is difficult to make any changes in the prescribed dose. Thus, consequently it may be difficult to control for the side effects of the drug.

Rare side effects have also been reported with the use of depot such as, tardive dystonia, neuroleptic malignant syndrome and dyskinesia.
Another disadvantage of depot use is that not lack of availability of depot equivalent for all oral antipsychotic formulations

Finally, pain related to injection administration and fear of injections may also limit the use of depot antipsychotics.

Considering these potential advantages and disadvantaged of depot antipsychotics, it is important to further evaluate the effectiveness of Long Acting injections with other antipsychotic mode of administration in improving disease outcome and reducing overall cost of treatment.

Long Acting injections versus placebo
Typically, Depot antipsychotics formulation were introduced for the prevention of relapse by increase compliance to treatment. Randomised Controlled Trials, with placebo-controlled group have indicated the superiority of depot antipsychotics in reducing symptom severity and relapses.

In a double-blind RCT conducted by Pandina et al[68], 652 patients diagnosed with schizophrenia were randomised (1:1:1:1) to different doses of Paliperdione Palmiate or placebo (1:1:1:1) for 13-weeks. Significant (<= 0.034) change was observed in the Positive and Negative Syndrome Scale scores (PANSS) evaluated from baseline to endpoint in all patients randomised to Paliperidone Palmiate dose group as compared to Placebo group.

Kane et al[67], also conducted at double blind multi centre randomised control trial to evaluate the effective of first atypical long acting injection, Risperidone. The study population comprised of hospital inpatients and outpatients diagnosed with schizophrenia. The patients were randomised into two groups, one group was treated with placebo while the other group was administered risperidone LAI. Within the Risperdione group, patients were treated with different doses of risperidone (25mg, 50mg, 75mg). The endpoint of the study was 12 months and the measure of effectiveness was described as reduction in PANSS score by minimum 20% from the baseline score. A dose of 5mg risperidone was administered in the

LAI arm for one week. The results from the study demonstrated that patients treated with Rispersione LAI had significant change in the PANSS score. Additionally, risperidone was well tolerated and the severity of extrapyramidal effects had minimum change at baseline and endpoint measurement for both placebo and risperidone. Spontaneously reported adverse effects were also comparable in both trial arms. The patients treated with Long acting injections reported mild pain at the site of injection administration. Thus, the pain associated with LAIR can be regarded as an unlikely factor affecting the acceptance of depot formulation. Results from Multicentre, Multiphase, double-blind RCT conducted by Berwaerts et al[66] were also in agreement with other studies demonstrating significant reduction in relapses with Long-acting injections as compared to Placebo.

From the above studies, it can be implicated that treatment depot antipsychotics is a good predictor of better outcome and are well tolerated in patients with schizophrenia.[65] However, use of antipsychotics in the treatment of schizophrenia have often been regarded as more effective than placebo. Thus, the effects of LAI observed in the previous studies may partially be explained by the use of antipsychotic in general rather than the effectiveness of using LAI in particular.

LAI versus Oral Antipsychotics

The treatment with depot antipsychotic have shown superiority in predicting better outcome as compared to placebo. However, treatment with antipsychotics has generally been considered favourable than placebo. Thus, limiting the assumption regarding the superiority of Long Acting Injection in particular.

The comparison of depot with oral antipsychotics provides a more accurate picture of treatment in the real world. Early meta-analysis by Davis et al,[33] demonstrated the superiority of depot in comparison to oral antipsychotics in reducing relapse rate in schizophrenia. Yet, inconsistency between studies persists regarding the comparative effectiveness of Long acting injections in the treatment of schizophrenia. A randomised control trial[69] in the veteran schizophrenia population was conducted to evaluate the duration before medicine discontinuation between the patients prescribed LAIR and the patients treated with other antipsychotics. The results indicated that the patients treated with LAIR were more likely to discontinue their treatment before the 2-year end-point, with only 54% on LAIR continuing their treatment over 18 months. LAIR and oral trial arms displayed distinctive characteristics such that patients treated with LAIR were more likely to have a dual diagnosis of schizophrenia and drug/ alcohol abuse, were older and were possibly have had a psychiatric hospitalisation. The study indicated that patients treated with LAI had augmented severity of symptoms. Furthermore, the rates of discontinuation reflected that patient's perception of Long acting injections as burdensome and coercive limited the use of LAI.

Majority of the RCTs found no difference between the two modes of administration. For example: Kishimoto et al[24], found similar rates of relapse and treatment discontinuation for all causes for oral and depot formulation in the systematic review of 21 Randomised Control Trials (n=5,176) analysed over different time points. Adams et al, 2001[78] observed no major difference between LAI and Oral antipsychotics in preventing relapse, extrapyramidal symptoms and need for anticholinergic drugs in his meta-analysis of RCTs randomising both, in-patients and out-patients diagnosed with schizophrenia. One exception to this was the meta-analysis of RCTs conducted by Leutch et al.[24] The meta-analysis addressed various methodological limitations (Discussed in the critical review section) included RCTs

conducted for a longer duration (More than 1 year) and exclusively conducted on samples of outpatients diagnosed with schizophrenia. A significant reduction in the rate of relapse was observed in depot group (21.6%) as compared to the oral group (33.3%). Despite the significant effect of depot reported in the study, factors such as no information of the blinding status used the studies, publication bias, inclusion of studies conducted over 30 years of time duration may have impacted the study results.

Contrary to the results of Randomized Control Trials, observational studies such as prospective, retrospective and mirror studies are more likely to report the superiority of depot antipsychotics.

In a mirror study, Peng et al[38], aimed to assess the change in the level of adherence, hospitalisation and cost of care in patients (n=147) with schizophrenia, 6 months pre-and 6 months post depot initiation. The results from the study favoured the superiority of LAI in increasing compliance to treatment. Patients showed significant improvement in medication adherence with only 36.8% adhering to treatment preceding LAI initiation to 60% patients adhering to treatment in the post initiation of depot analysis ($p<0.001$). The rate of hospitalisation for any reason, psychiatric reason and hospitalisation for schizophrenia also significantly decreased after initiating depot. A significant decrease in the inpatient cost pre-and-post depot was also observed but no change in the outpatient cost was significant. The study is a good example reflecting the mechanism of depot antipsychotics in reducing overall cost of treatment by improving adherence to antipsychotic therapy.

The potential clinical consequences of non-compliance to treatment can be drastic as it may include unnecessary medication change, addition use of concomitant medication, false diagnosis of inefficacy of existing treatment and also labelling the patient as resistant to treatment. However, Measuring adherence to treatment is a challenge often faced by the researchers as the qualitative adherence reported is often a count of medication availability and can vary from the true estimate of adherence measured by physical biomarkers or patient's self-report.

A three-year prospective study[74] testing the clinical consequences of non-adherence in schizophrenia patients reported that nonadherence to treatment in patients was a high indicator of increase in psychiatric rehospitalisation (26.8% in adherent v/s 14.1% in non-adherent), emergency care (10% v/s 6%), increase in violent behaviour in non-adherent patients and augmented substance abuse. Typically, the use of depot antipsychotics is restricted to patients non-compliant to oral antipsychotic treatment of patients with stabilized schizophrenia as a maintenance treatment. Even though higher non-compliance and lack of insight are observed in patients with first episode of psychosis use of depot in first episode of psychosis patients is debatable, the difficulty to sensibly and quickly adjust for LAI drugs in case of side effect, uncertainty of diagnosis and the aim to gradually reduce the antipsychotic dosage are few factors that limit LAI use in FEP70. A large nationwide cohort[37] in Finland, extracted data from the Finnish National Discharge Register for patients who were discharged after their first hospitalisation for psychosis. The effect of depot and oral antipsychotics were compared in respect to their effectiveness in reduce relapses after the discharge. Depot formulation were compared to their oral equivalent, results from the study indicated depot reduced the rate of relapse by 50%-65%. The cohort study had the methodological advantage over systematic reviews and RCTs comparing addressing question as the results were not attributed the selection bias. Also, the results of the study showed substantial superiority of depot antipsychotics even when the temporality sequence

(switch from depot to oral or switch from oral to depot) of the medication was adjusted for. The results from this study can be inferred to improve treatment outcome of the patients by improving adherence as the same formulation was compared for depot and oral antipsychotics.

Healthcare cost studies

Various studies have indicated the potential for LAI to reduce the total cost of treatment by reducing relapses and hospitalisation by improving adherence in patients diagnosed with schizophrenia. Researches addressing the question of costs in LAI use have found inconsistency in their results[39]. In a longitudinal retrospective[72] cohort study comparing the health care utilization and related costs in the veteran population, extracting the data from the veteran outpatient and inpatient data set patients were compared for the difference in their health care costs on the basis of their treatment with either Paliperidone Palmiate Long acting injections or other antipsychotics. Results from the study indicated that the patients treated with paliperidone were more likely to have more severe symptoms than patients administered oral antipsychotics but had significantly low inpatients and hospitalisation costs at 12 months follow-up. The PP cohort also had fewer hospital admissions and inpatient days as compared to the oral cohort. Despite the reduction in hospitalisation and admission cost, there was no significant difference in the two cohorts for the total healthcare cost at 12 months follow-up. LAI antipsychotics are administered by the trained healthcare provider and have a higher drug cost. Hence, the increased outpatient cost may have limited the effects of LAI in reducing the overall cost of treatment.

Another study[71]in the veteran health administered patients compared the health care utilization and costs of patients randomized to LAIR and patients treated with oral antipsychotics. Significant difference was observed in the medication cost and LAI group incurred a higher medical cost than the oral group. No significant difference was observed in the inpatient and outpatient cost. Moreover, the researchers claimed that the reduction in costs reported for LAI administration may be overestimated.

On the contrary, Several Mirror-studies have demonstrated the effectiveness of reducing overall cost of treatment with LAI use. Niaz and Haddad[46], 2007 in their 35-week retrospective study recruited patients (n=74) examined the effect of Risperidone LAI (LAIR). The results indicated significant reduction in total admissions, compulsory admissions and total inpatient days with the use of LAIR. The financial saving from reduction in hospitalisation costs also exceeded the acquisition and administration cost associated with LAIR. Edward et al[4], also found significant reduction in the study comparing cost effectiveness of LAI-R and alternative oral antipsychotic agents in patients diagnosed with schizophrenia in USA. Patients prescribed to LAIR saved up to $161 per year of health cost as compared to patients on oral risperidone. When compared to patients on other oral antipsychotic compositions, LAIR cohort predicted to save up to $724 of healthcare cost per year.

Lin and Colleagues[11] comparing the health care cost reduction in patients with schizophrenia, prescribed to LAI (n=394) versus those prescribed to oral (n=2,610) found a substantial difference between the two cohorts group of patients who were commercially insured. Schizophrenia-related hospitalisation costs decreased by a mean $ 5,981 in the group administered depot and increased by a mean value of $ 758 in the oral antipsychotic cohort ($p<0.001$). Similar outcomes were observed in Medicare insured patients. Difference in the patient characteristic between Commercially insured and Medicare insured patients.

The commercially insured patient initiated depot comparatively later in the treatment as compared to Medicare insured patients, in which the use of LAI could have been related to presence or absence of comorbid factors. The research also concluded that the two different insurance groups may require different incentive for LAI use as only 13% commercially insured patients were prescribed depot as compared to 22% in Medicare insured patients.

Several international studies have also examined the use of LAI on healthcare costs for the treatment of schizophrenia. A mirror study examining the treatment cost for 1 year pre-and post-depot formulation, conducted in Hong Kong[73] found that the cost significantly decreased for few outcomes (Non-medication services and in-patient service utilisation) but there was an increase in costs in depot use in outcomes like outpatient psychiatry and medication costs. Similar findings were demonstrated by another mirror-study conducted in Taiwan. Depot use was associated with reduction is costs in hospitalisation costs and in-patient services but a rise in cost related medication and out-patient services were observed.

Drawing conclusions from the past research, a pattern of reduction in inpatient cost but, an increase in out-patient cost and medication cost can be associated with expensiveness of LAI administration and drug cost. Since, the pharmacy costs contribute to a relatively small percentage of the total treatment cost, LAI can be considered cost effective by reducing the cost of hospitalisation and in-patient treatment which are the major contributors on the economic burden associated with the treatment of schizophrenia.

Critical Analysis

Studies addressing the effectiveness of Long Acting injections in the treatment of schizophrenia have indicated inconsistency in their outcome. While few studies argue the superiority of LAI as compared to oral antipsychotics, others show no evidence for the same.

The inconsistency in results can be explained by the difference in study designs adapted to answer the question of comparative effectiveness of Long acting injections and oral antipsychotics in treatment of schizophrenia. The selection of the most accurate study design for any particular research is based on its ability to correctly address the primary objective.

Moreover, study design selected to address one particular objective may not always be the most accurate design in addressing other objectives, despite the interrelatedness between the study objectives. (American Psychological Association, 2010). Explanatory studies, often also referred to as efficacy studies aim to explore the suitability of treatment in a constrained environment. The explanatory studies display the advantages of having high internal validity. Explanatory Randomised Controlled Trials are often regarded as the gold standard of evaluation in clinical research but they may not always be appropriate in addressing questions associated with high degree of real world phenomenon such as Adherence. RCTs are conducted in highly controlled and well treatment conditions in order to reduce ambiguity in addressing the primary objective.[30,75]

RCTs often aim to reduce bias and thus have a strict selection criteria. This often leads to selection of the study population; this may often lead to selection of participants that may not accurately represent the target population in which the intervention will be used. This may be particularly true in studies addressing the issue of non-compliance.[30] As for an example: In the comparison of oral versus depot antipsychotics, explanatory RCT may overestimate adherence to the treatment as patients are being observed (Hawthorne effect), Frequent use of other factors such as exceptionally close follow up with patients, financial

incentives to participants, burdensome healthcare assessments may also contribute to obscure the real-world conditions. For example: Leutch et al, in his meta-analysis addressed the limitations of previous RCTs as the RCTs tended to include both inpatients and outpatients and were usually short term. The inclusion of both inpatients and outpatients could have led to an overestimated adherence as antipsychotics were administered by the nursing staff. Furthermore, RCTs may recruit participants who have more insight into their treatment, less comorbid factors and more adherence to prescribed treatment, conclusion drawn from these studies may not be generalizable.[75]

In Contrast, Effectiveness or Pragmatic study designs aims to answer the study question from a more real-world perspective. Mirror-studies adapting a more pragmatic approach have often been considered as more suitable than RCTs in addressing the issue of effectiveness of depot versus oral antipsychotics. Additionally, mirror studies adapt a longitudinal study design. The longitudinal design is more appropriate in addressing relapse as the progression of relapse in uneven in schizophrenia. Furthermore, the results of mirror studies are not limited by Hawthorne effect or other incentives that can affect the rate of adherence leading to bias in results.

With higher external validity, pragmatic studies are often more generalizable in the target population. Though, it has its own limitations, mirror studies in case of depot versus oral have been often observed unidirectional, i.e., patients switching from oral to depot. As depot is often used in patients with high level of non-compliance, it may not report the accurate effectiveness of treatment. In addition to the lack of 'depot to oral' mirror studies, mirror studies also lack blinding to treatment which may account for an inherent bias towards improvement.[31,75]

Furthermore, the use of systematic reviews in addressing the comparative effectiveness of the two modes of administration, has been frequently observed in the literature. Though systematic reviews may indicate a more accurate picture, its generalizability can be limited due to factors such as publication bias, difference in measures used to analyse the outcome variable, heterogeneity in population, different definitions for factors directly influencing the outcomes, such as relapse, adherence, etc.[24]

Prospective and Retrospective studies offer an advantage over RCTs and Mirror studies as the prospective studies adapt a more realistic view, while also having the advantage of longitudinal design, larger sample size and results more generalizable in the target population. However, the choice of depot and oral antipsychotics in patients is dependent on the psychiatrist's choice. Prospective and retrospective studies may fail to take into account the reasons of treatment with one particular mode of administration, Example: Depot use is less frequently reported than the use oral antipsychotics. Furthermore, the use of depot is likely to depend on the attitude of the psychiatrist and patient towards the acceptance of depot medication. In a survey evaluating the practitioner's perception regarding LAI, majority of psychiatrists felt that oral and depot antipsychotics were equal in their efficacy (91%) and depot is likely to improve to patient's adherence (81%) and consequently reduce relapse (94%); however, regardless of the positive findings, 48% felt depot antipsychotics were comparatively more stigmatising as compared to oral antipsychotics. 69% believed that patients were less likely to accept depot antipsychotics as they were perceived to be more coercive and compromise the patient's autonomy. However, favourable attitude towards depot antipsychotics was positive associated with practitioner's knowledge of depot antipsychotics.[29] Thus, the use of depot antipsychotics is likely to be restricted to patients

with more severe symptoms or non-adherence to oral antipsychotic. This may lead to bias in the study result.[37]

CONCLUSION

Cost of illness studies are especially beneficial for the policy makers evaluating the Pharmacoeconomics of different antipsychotics or overall cost of treatment if, evaluated from a broader perspective.[77] Thus, majority of studies addressing the question of cost effectiveness, extract data for individual costs from clinical medical records or big medical database. Even though it may provide an accurate measure for the direct costs involved with the treatment of schizophrenia, this may not be appropriate to evaluate the treatment costs from a societal perspective. Hence, it is necessary to consider both medical and non-medical cost data to address the true comparativeness of any treatment. The exclusion of indirect costs in the evaluating the overall cost of treatment may not give an accurate measure of the real cost accounted by schizophrenia.[63] The use of self-report questionnaires such as cost diary or Client Service Receipt inventory can be one measure to address this problem. Studies comparing GP records and Client Service Receipt inventory have shown good agreement in costs evaluated from the two perspectives. Thus, the use of self-report questionnaire may provide an additional advantage of including relevant measure of indirect cost and evaluating the overall cost of treatment from a broader perspective.[77]

REFERENCES

1. David, A. S., Gibbs, A., & Patel, M. X. (2009). Long-Acting Antipsychotic Medication and the Outcome of Schizophrenia. Advances in Schizophrenia Research 2009,403-415. doi:10.1007/978-1-4419-0913-8_23
2. Yang, L., Li, M., Tao, L., Zhang, M., Nicholl, M. D., & Dong, P. (2009). Cost-Effectiveness of Long-Acting Risperidone Injection versus Alternative Atypical Antipsychotic Agents in Patients with Schizophrenia in China. Value in Health,12. doi:10.1111/j.1524-4733.2009. 00630.x
3. Olivares, J. M., Pinal, B., & Cinos, C. (2011). Comparison of long-acting antipsychotic injection and oral antipsychotics in schizophrenia. Neuropsychiatry,1(3), 275-289. doi:10.2217/npy.11.24
4. Patel, M., Zoysa, N. D., Bernadt, M., & David, A. (2008). Depot and oral antipsychotics: Patient preferences and attitudes are not the same thing. Journal of Psychopharmacology,23(7), 789-796. doi:10.1177/0269881108092124
5. Kirson, N. Y., Weiden, P. J., Yermakov, S., Huang, W., Samuelson, T., Offord, S. J., . Wong, B. J. (2013). Efficacy and Effectiveness of Depot Versus Oral Antipsychotics in Schizophrenia. The Journal of Clinical Psychiatry,74(06), 568-575. doi:10.4088/jcp.12r08167
6. Lachaine, J., Lapierre, M.-E., Abdalla, N., Rouleau, A., & Stip, E. (2015). Impact of Switching to Long-Acting Injectable Antipsychotics on Health Services Use in the Treatment of Schizophrenia. Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie, 60(3 Suppl 2), S40–S47.
7. Mahadun, P. N., & Marshall, M. (2008). Insight and treatment attitude in schizophrenia: Comparison of patients on depot and atypical antipsychotics. Psychiatric Bulletin,32(02), 53-56. doi:10.1192/pb.bp.107.015875
8. Ascher-Svanum, H., Peng, X., Faries, D., Conley, R., & Schuh, K. (2011). Decline in hospitalization risk and health care cost after initiation of depot antipsychotics in the treatment of schizophrenia. ClinicoEconomics and Outcomes Research,9. doi:10.2147/ceor.s16061

9. Zhornitsky, S., & Stip, E. (2012). Oral versus Long-Acting Injectable Antipsychotics in the Treatment of Schizophrenia and Special Populations at Risk for Treatment Nonadherence: A Systematic Review. Schizophrenia Research and Treatment,2012, 1-12. doi:10.1155/2012/407171
10. González, G. P., Moscoso, N. S., & Lago, F. P. (2017). A Review of Clinical and Economic Evaluations Applied to Psychotropic Therapies Used in the Treatment of Schizophrenia in Argentina. PharmacoEconomics - Open. doi:10.1007/s41669-017-0058-8
11. Lin, J., Wong, B., Offord, S., & Mirski, D. (2013). Healthcare Cost Reductions Associated with the Use of LAI Formulations of Antipsychotic Medications Versus Oral Among Patients with Schizophrenia. The Journal of Behavioral Health Services & Research,40(3), 355-366. doi:10.1007/s11414-013-9329-z
12. Laux, G., Heeg, B. M., Hout, B. A., & Mehnert, A. (2005). Costs and effects of long-acting risperidone compared with oral atypical and conventional depot formulations in Germany. PharmacoEconomics,23(S1), 49-61. doi:10.2165/00019053-200523001-00005
13. Haycox, A. (2005). Pharmacoeconomics of long-acting risperidone: Results and validity of cost-effectiveness models. PharmacoEconomics,23(S1), 3-16. doi:10.2165/00019053-200523001-00002
14. Graeve, D. D., Smet, A., Mehnert, A., Caleo, S., Miadi-Fargier, H., Mosqueda, G. J., . Peuskens, J. (2005). Long-acting risperidone compared with oral olanzapine and haloperidol depot in schizophrenia: A Belgian cost-effectiveness analysis. PharmacoEconomics,23(S1), 35-47. doi:10.2165/00019053-200523001-00004
15. Leal, A., Rosillon, D., Mehnert, A., Jarema, M., & Remington, G. (2004). Healthcare resource utilization during 1-year treatment with long-acting, injectable risperidone. Pharmacoepidemiology and Drug Safety,13(11), 811-816. doi:10.1002/pds.978
16. Almond, S., & Odonnell, O. (1998). Cost Analysis of the Treatment of Schizophrenia in the UK. PharmacoEconomics,13(5), 575-588. doi:10.2165/00019053-199813050-00010
17. Thieda, P., Beard, S., Richter, A., & Kane, J. (2003). An Economic Review of Compliance with Medication Therapy in the Treatment of Schizophrenia. Psychiatric Services,54(4), 508-516. doi: 10.1176/appi.ps.54.4.508
18. Test, M. A. (1980). Alternative to Mental Hospital Treatment. Archives of General Psychiatry,37(4), 409. doi:10.1001/archpsyc.1980.01780170051005
19. Knapp, M. (2000). Schizophrenia costs and treatment cost-effectiveness. Acta Psychiatrica Scandinavica,102, 15-18. doi:10.1046/j.1467-0658.2001. 00137.x-i1
20. Almond, S., Knapp, M., Francois, C., Toumi, M., & Brugha, T. (2004). Relapse in schizophrenia: Costs, clinical outcomes and quality of life. British Journal of Psychiatry,184(04), 346-351. doi:10.1192/bjp.184.4.346
21. Rössler, W., Salize, H. J., Os, J. V., & Riecher-Rössler, A. (2005). Size of burden of schizophrenia and psychotic disorders. European Neuropsychopharmacology,15(4), 399-409. doi: 10.1016/j.euroneuro.2005.04.009
22. Whyte, A., & Parker, C. (2016). A review of the efficacy and tolerability of antipsychotic long-acting injections. Progress in Neurology and Psychiatry,20(4), 22-28. doi:10.1002/pnp.436
23. Correll, C. U., Citrome, L., Haddad, P. M., Lauriello, J., Olfson, M., Calloway, S. M., & Kane, J. M. (2016). The Use of Long-Acting Injectable Antipsychotics in Schizophrenia. The Journal of Clinical Psychiatry,1-24. doi: 10.4088/jcp.15032su1
24. Leucht, C., Heres, S., Kane, J. M., Kissling, W., Davis, J. M., & Leucht, S. (2011). Oral versus depot antipsychotic drugs for schizophrenia—A critical systematic review

and meta-analysis of randomised long-term trials. Schizophrenia Research,127(1-3), 83-92. doi: 10.1016/j.schres.2010.11.020

25. Wilson, M., Guttierez, B., Offord, S., Blanchette, C., Eramo, A., Earnshaw, S., & Kamat, S. (2016). Inpatient resource use and costs associated with switching from oral antipsychotics to aripiprazole once-monthly for the treatment of schizophrenia. Drugs in Context,5, 1-10. doi:10.7573/dic.212273
26. Misawa, F., Kishimoto, T., Hagi, K., Kane, J. M., & Correll, C. U. (2016). Safety and tolerability of long-acting injectable versus oral antipsychotics: A meta-analysis of randomized controlled studies comparing the same antipsychotics. Schizophrenia Research,176(2-3), 220-230. doi: 10.1016/j.schres.2016.07.018
27. Jukic, V., Jakovljevic, M., Filipcic, I., Herceg, M., Silic, A., Tomljanovic, T., & Jensen, R. (2012). PMH22 Cost-Utility Analysis of Depot Atypical Antipsychotics for Chronic Schizophrenia in Croatia. Value in Health,15(7). doi: 10.1016/j.jval.2012.08.812
28. Kane, J. M., Kishimoto, T., & Correll, C. U. (2013). Assessing the comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry. Journal of Clinical Epidemiology,66(8). doi: 10.1016/j.jclinepi.2013.01.012
29. Hamann, J., Mendel, R., Heres, S., Leucht, S., & Kissling, W. (2010). How much more effective do depot antipsychotics have to be compared to oral antipsychotics before they are prescribed? European Neuropsychopharmacology,20(4), 276-279. doi: 10.1016/j.euroneuro.2010.01.001
30. Bossie, C. A., Alphs, L. D., & Correll, C. U. (2015). Long-acting injectable versus daily oral antipsychotic treatment trials in schizophrenia: Pragmatic versus explanatory study designs. International Clinical Psychopharmacology,1. doi:10.1097/yic.0000000000000082
31. Rosenheck, R. A., Leslie, D. L., Sint, K. J., Lin, H., Li, Y., Mcevoy, J. P., . . . Stroup, T. S. (2016). Cost-Effectiveness of Long-Acting Injectable Paliperidone Palmitate Versus Haloperidol Decanoate in Maintenance Treatment of Schizophrenia. Psychiatric Services,67(10), 1124-1130. doi: 10.1176/appi.ps.201500447
32. Rosenheck, R. A., Krystal, J. H., Lew, R., Barnett, P. G., Fiore, L., Valley, D., . . . Liang, M. H. (2011). Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia. New England Journal of Medicine,364(9), 842-851. doi:10.1056/nejmoa1005987
33. Davis, J. M., Metalon, L., Watanabe, M. D., & Blake, L. (1994). Depot Antipsychotic Drugs. Drugs,47(5), 741-773. doi:10.2165/00003495-199447050-00004
34. Kishimoto, T., Robenzadeh, A., Leucht, C., Leucht, S., Watanabe, K., Mimura, M., . . . Correll, C. U. (2012). Long-Acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials. Schizophrenia Bulletin,40(1), 192-213. doi:10.1093/schbul/sbs150
35. Davis, J. M., Schaffer, C. B., Killian, G. A., Kinard, C., & Chan, C. (1980). Important Issues in the Drug Treatment of Schizophrenia. Schizophrenia Bulletin,6(1), 70-87. doi:10.1093/schbul/6.1.70
36. Lasser, R. A., Bossie, C. A., Gharabawi, G. M., & Baldessarini, R. J. (2005). Clinical improvement in 336 stable chronically psychotic patients changed from oral to long-acting risperidone: A 12-month open trial. The International Journal of Neuropsychopharmacology,8(3), 427-438. doi:10.1017/s1461145705005225
37. Tiihonen, J., Haukka, J., Taylor, M., Haddad, P. M., Patel, M. X., & Korhonen, P. (2011). A Nationwide Cohort Study of Oral and Depot Antipsychotics After First

Hospitalization for Schizophrenia. American Journal of Psychiatry,168(6), 603-609. doi: 10.1176/appi.ajp.2011.10081224

38. Peng, X., Ascher-Svanum, H., Faries, D., & Conley, R. (2011). Decline in the rate and cost of psychiatric hospitalization following initiation of depot antipsychotics in the treatment of schizophrenia. International Clinical Psychopharmacology,26. doi: 10.1097/01.yic.0000405809. 66498.a6
39. Kaplan, G., Casoy, J., & Zummo, J. (2013). Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. Patient Preference and Adherence,1171. doi:10.2147/ppa. s53795
40. Biagi, E., Capuzzi, E., Colmegna, F., Mascarini, A., Brambilla, G., Ornaghi, A., . . . Clerici, M. (2017). Long-Acting Injectable Antipsychotics in Schizophrenia: Literature Review and Practical Perspective, with a Focus on Aripiprazole Once-Monthly. Advances in Therapy,34(5), 1036-1048. doi:10.1007/s12325-017-0507-x
41. Dilla, T., Ciudad, A., & Á. (2013). Systematic review of the economic aspects of nonadherence to antipsychotic medication in patients with schizophrenia. Patient Preference and Adherence,275. doi:10.2147/ppa. s41609
42. Edwards, N. C., Locklear, J. C., Rupnow, M. F., & Diamond, R. J. (2005). Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA. PharmacoEconomics,23(S1), 75-89. doi:10.2165/00019053-200523001-00007
43. Fuller, M., Shermock, K., Russo, P., Secic, M., Dirani, R., Vallow, S., & Flanders, S. (2009). Hospitalisation and resource utilisation in patients with schizophrenia following initiation of risperidone long-acting therapy in the Veterans Affairs Healthcare System. Journal of Medical Economics,12(4), 317-324. doi:10.3111/13696990903303902
44. Gilmer, T. P., Dolder, C. R., Lacro, J. P., Folsom, D. P., Lindamer, L., Garcia, P., & Jeste, D. V. (2004). Adherence to Treatment with Antipsychotic Medication and Health Care Costs Among Medicaid Beneficiaries with Schizophrenia. American Journal of Psychiatry,161(4), 692-699. doi: 10.1176/appi.ajp.161.4.692
45. Mccrone, P., Craig, T. K., Power, P., & Garety, P. A. (2010). Cost-effectiveness of an early intervention service for people with psychosis. British Journal of Psychiatry,196(05), 377-382. doi:10.1192/bjp.bp.109.065896
46. Niaz, O. S., & Haddad, P. M. (2007). Thirty-five months experience of risperidone long-acting injection in a UK psychiatric service including a mirror-image analysis of in-patient care. Acta Psychiatrica Scandinavica,116(1), 36-46. doi:10.1111/j.1600-0447.2006. 00980.x
47. Taylor, M., Currie, A., Lloyd, K., Price, M., & Peperell, K. (2008). Impact of risperidone long-acting injection on resource utilization in psychiatric secondary care. Journal of Psychopharmacology,22(2), 128-131. doi:10.1177/0269881107084068
48. Patel, M. X., & David, A. S. (2005). Why arent depot antipsychotics prescribed more often and what can be done about it? Advances in Psychiatric Treatment,11(3), 203-211. doi:10.1192/apt.11.3.203
49. Taylor, D. (2009). Psychopharmacology and adverse effects of antipsychotic long-acting injections: A review. British Journal of Psychiatry,195(S52). doi:10.1192/bjp.195.52. s13
50. Stevens, G. L., Dawson, G., & Zummo, J. (2015). Clinical benefits and impact of early use of long-acting injectable antipsychotics for schizophrenia. Early Intervention in Psychiatry,10(5), 365-377. doi:10.1111/eip.12278

51. Davies, L., & Drummond, M. (1990). The economic burden of schizophrenia. Psychiatric Bulletin, 14(9), 522-525. doi:10.1192/pb.14.9.522
52. Mcgrath, J., Saha, S., Welham, J., Saadi, O. E., Maccauley, C., & Chant, D. (2004). A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Medicine, 2(1). doi:10.1186/1741-7015-2-13
53. Tajima-Pozo, K., de Castro Oller, M. J., Lewczuk, A., & Montañes-Rada, F. (2015). Understanding the direct and indirect costs of patients with schizophrenia. F1000Research, 4, 182. http://doi.org/10.12688/f1000research.6699.2
54. https://www.nice.org.uk/guidance/cg178/chapter/1-Recommendations
55. Kavanagh, S., Opit, L., Knapp, M. et al. Soc Psychiatry Psychiatr Epidemiol (1995) 30: 206. https://doi.org/10.1007/BF00789055
56. Knapp M. Schizophrenia costs and treatment cost-effectiveness. Acta Psychiatr Scand 2000: 102 (Suppl. 407): 15±18
57. Knapp, M., Chisholm, D., Leese, M., Amaddeo, F., Tansella, M., Schene, A., . . . Becker, T. (2002). Comparing patterns and costs of schizophrenia care in five European countries: The EPSILON study. Acta Psychiatrica Scandinavica, 105(1), 42-54. doi:10.1034/j.1600-0447.2002. 10310.x
58. Dasgupta, R., & Dasgupta, C. (2009). CATIE and CUtLASS (UK): Is it time psychiatrists start changing their practice? - The debate goes on! Indian Journal of Psychiatry, 51(2), 161. doi:10.4103/0019-5545.49464
59. Davies, L. M., & Drummond, M. F. (1990). The economic burden of schizophrenia. Psychiatric Bulletin, 14(09), 522-525. doi:10.1192/pb.14.9.522
60. Weiden, Peter & Glazer, William. (1997). Assessment and Treatment Selection for "Revolving Door" Inpatients with Schizophrenia. The Psychiatric quarterly. 68. 377-92. 10.1023/A:1025499131905.
61. Weiden, P., & Olfsen, M. (1993). Measuring direct costs of relapse in schizophrenia. Schizophrenia Research, 9(2-3), 142. doi:10.1016/0920-9964(93)90247-g
62. Drummond, M., Knapp, M., Burns, T., Miller, K., & Shadwell, P. (1998). Issues in the design of studies for the economic evaluation of new atypical antipsychotics: The ESTO study. The Journal of Mental Health Policy and Economics, 1(1), 15-22. doi:10.1002/(sici)1099-176x(199803)1:13.3.co;2-f
63. Zhornitsky, S., & Stip, E. (2012). Oral versus Long-Acting Injectable Antipsychotics in the Treatment of Schizophrenia and Special Populations at Risk for Treatment Nonadherence: A Systematic Review. Schizophrenia Research and Treatment, 2012, 1-12. doi:10.1155/2012/407171
64. Brissos, S., Veguilla, M. R., Taylor, D., & Balanzá-Martinez, V. (2014). The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. Therapeutic Advances in Psychopharmacology, 4(5), 198–219. http://doi.org/10.1177/2045125314540297
65. Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., & Davis, J. M. (2012). Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: A systematic review and meta-analysis. The Lancet, 379(9831), 2063-2071. doi:10.1016/s0140-6736(12)60239-6
66. Berwaerts, J., Liu, Y., Gopal, S., Nuamah, I., Xu, H., Savitz, A., . . . Hough, D. W. (2015). Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia. JAMA Psychiatry, 72(8), 830. doi:10.1001/jamapsychiatry.2015.0241

67. Kane, J., Eerdekens, M., Keith, S., Lesem, M., Karcher, K., & Lindenmayer, J. (2002). Long-acting injectable risperidone: Efficacy and safety. European Neuropsychopharmacology, 12, 325. doi:10.1016/s0924-977x(02)80495-3
68. Pandina, Gahan & Lindenmayer, Jean-Pierre & Lull, Julia & Lim, Pilar & Gopal, Srihari & Herben, Virginie & Kusumakar, Vivek & Yuen, Eric & Palumbo, Joseph Michael. (2010). A Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of 3 Doses of Paliperidone Palmitate in Adults with Acutely Exacerbated Schizophrenia. Journal of clinical psychopharmacology. 30. 235-44. 10.1097/JCP.0b013e3181dd3103.
69. Mohamed, S., Rosenheck, R., Harpaz-Rotem, I., Leslie, D., & Sernyak, M. J. (2009). Duration of Pharmacotherapy with Long-Acting Injectable Risperidone in the Treatment of Schizophrenia. Psychiatric Quarterly, 80(4), 241-249. doi:10.1007/s11126-009-9111-9
70. Kim, B., Lee, S., Yang, Y. K., Park, J., & Chung, Y. (2012). Long-Acting Injectable Antipsychotics for First-Episode Schizophrenia: The Pros and Cons. Schizophrenia Research and Treatment, 2012, 1-8. doi:10.1155/2012/560836
71. Barnett PG, Scott JY, Krystal JH, et al; CSP 555 Research Group. Cost and cost-effectiveness in a randomized trial of long-acting risperidone for schizophrenia. J Clin Psychiatry. 2012;73(5):696–702. PubMed doi:10.4088/JCP.11m07070
72. Baser O, Xie L, Pesa J, et al. Healthcare utilization and costs of Veterans Health Administration patients with schizophrenia treated with paliperidone palmitate long-acting injection or oral atypical antipsychotics. J Med Econ. 2015;18(5):357–365. PubMed doi:10.3111/13696998.2014.1001514
73. Bin-Chia D, Le EHM, Chung WS, et al. Cost analysis of risperidone long-acting injection in the treatment of schizophrenia and schizoaffective disorder in Hong Kong: an approach using generalized estimating equations. Psychol Res. 2013; 210:745–750
74. Ascher-Svanum H, Faries DE, Zhu B, et al. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry. 2006;67(3):453–460. PubMed doi:10.4088/JCP.v67n0317
75. Alphs, L., Schooler, N., & Lauriello, J. (2014). How study designs influence comparative effectiveness outcomes: The case of oral versus long-acting injectable antipsychotic treatments for schizophrenia. Schizophrenia Research, 156(2-3), 228-232. doi: 10.1016/j.schres.2014.04.024
76. Goossens, M. E., Mölken, M. P., Vlaeyen, J. W., & Linden, S. M. (2000). The cost diary. Journal of Clinical Epidemiology, 53(7), 688-695. doi:10.1016/s0895-4356(99)00177-8
77. A comparison of two methods of collecting economic data in primary care
Anita Patel-Alison Rendu-Paul Moran-Morven Leese-Anthony Mann-Martin Knapp - Family Practice – 2005
78. Adams, C., Fenton, M., Quraishi, S., & David, A. (2001). Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *British Journal of Psychiatry, 179*(4), 290-299. doi:10.1192/bjp.179.4.290

Acknowledgement

The author appreciates all those who participated in the study and helped to facilitate the research process.

Conflict of Interest

The author declared no conflict of interest.

How to cite this article: Rana A. (2020). Role of long acting injection in treatment of schizophrenia: literature review. *International Journal of Indian Psychology*, *8*(4), 921-937. DIP:18.01.110/20200804, DOI:10.25215/0804.110