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Cost Effectiveness of Paliperidone Versus Risperidone Long-Acting Injectable in Treating Schizophrenia: A Review

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A B S T R A C T

Introduction: Schizophrenia is a debilitating psychiatric condition with a significant social and economic burden. In 2021, the WHO added paliperidone 1-month formulation long-acting injectable (PP1M) to the essential medication list. At present, the currently listed therapeutic alternative to this medication is the risperidone injection (RLAI). This review assesses the existing literature to compare the cost efficacy of paliperidone 1-month versus risperidone injection in the treatment of schizophrenia.

Methods: A narrative literature review was conducted to find articles comparing cost efficacy of PP1M and RLAI. Each item was assessed for relevance based on specified inclusion and exclusion criteria. Search included articles published January 2000 through March 2025.

Results: All studies reviewed demonstrated PP1M to be superior to RLAI in clinical outcomes for treating schizophrenia. In terms of cost efficacy, most studies suggest PP1M to be a more cost-effective treatment when compared to RLAI.

Conclusion: The existing literature suggests PP1M is superior in both clinical outcomes as well as cost-efficacy in treating schizophrenia when compared to RLAI. Future studies comparing these medications should be carried out in other continents and lower resource nations. Given that the most significant treatment gaps in treating schizophrenia are in low- and middle-income countries, PP1M could be a viable method to close this gap while treating patients in a cost-conscious manner.

Keywords: PP1M, Cost Efficacy, Psychiatry, Psychosis

Introduction

Schizophrenia is a debilitating psychiatric condition which affects approximately 1% of the global population while ranking among the top 10 causes of global disability (Marder & Cannon, 2019). Despite the relatively low prevalence of schizophrenia, the WHO has estimated the direct costs of the disease to range from 1.6-2.6% of total health care expenditures in Western countries (Chong et al., 2016). The disease typically begins in early adulthood and is chronic in nature, often affecting adults through the most productive years of their lives. In fact, schizophrenia patients who are frequently admitted and discharged due to relapse are often referred to as “revolving door” patients (Weiden & Glazer, 1997). This leads to immense social dysfunction as well as numerous additional indirect costs. Various national studies have estimated indirect costs to contribute to 50 to 85% of the overall cost associated with schizophrenia (Chong et al., 2016). Schizophrenia has a significant social and economic burden globally and unfortunately significant treatment gaps exist in low- and middle-income countries, with about two thirds of individuals not receiving adequate treatment (Lora et al., 2012).

A diverse selection of treatments exists for schizophrenia. Medication choices range from pills to long-acting injectable (LAI) forms, with LAIs being commonly prescribed for patients with persistent symptoms or difficulties with compliance (Kane et al., 2021). In 2021, the WHO added paliperidone 1-month formulation long-acting injectable (PP1M) to the essential medication list. At present, the currently listed therapeutic alternative to this medication is the risperidone injection ("WHO Electronic Essential Medicines List (eEML)," 2023). Risperidone LAI, or RLAI, is classically administered every two weeks in its injectable form (Harrison & Goa, 2004). Meanwhile, paliperidone can be administered in 1, 3, 6-month formulations (Turkoz et al., 2024). Currently only the 1-month formulation is on the WHO essential medication list and thus will be the focus of this review. The purpose of this review is to assess the existing literature to compare the cost efficacy of paliperidone 1-month versus risperidone injection in the treatment of schizophrenia.

Methods

A traditional literature review using PubMed and Google Scholar was conducted to explore original, peer-reviewed research studies from 2000-2025 comparing the cost efficacy of paliperidone versus risperidone LAI in treatment of schizophrenia. Keywords used were: paliperidone, risperidone, and cost - all in the title and/or abstract. Inclusion criteria were: published 2000-2025, written in English, assessed PP1M formulation, assessed treatment of schizophrenia, original research articles published to peer review journals. Exclusion criteria were: not in English, full text unavailable, abstract only, poster presentation, reviews, case reports. Initial search produced 79 results which were assessed. A total of 12 articles that met the above inclusion/exclusion criteria were reviewed

Results

Key findings of each study reviewed are organized by country and summarized below. Additionally, details and results of each study are included in Table 1.

Croatia

In this 1-year decision analytic framework, PP1M had the fewest relapse days, ER visits, hospitalizations, and lowest overall cost compared to RLAI and OLAI. Furthermore, PP1M had the highest Quality-Adjusted Life Years (QALY) compared to the other two injectables. PP1M was found to be the most cost-effective LAI for treating chronic schizophrenia and Croatia (Jukic et al., 2013).

Of note, Quality-Adjusted Life Years are a number between 0-1 where 1 represents a year of perfect health and 0 represents death (Aleem et al., 2008).

Czech Republic

In this 1-year decision tree model, PP1M had the lowest overall cost and best clinical outcomes (lowest ER visits, lowest number of hospitalizations, highest QALY) compared to RLAI in treating chronic schizophrenia suggesting it as a cost-effective strategy in treating chronic schizophrenia in the Czech Republic (Thomas R. Einarson et al., 2013).

France

In this 5-year Markov decision model, PP1M was found to have the lowest 5-year cost compared to other LAIs assessed. Compared to PP1M, RALI had a slightly higher incremental cost effectiveness ratio (i.e. €4,770,018 per QALY gained) compared to PP1M. PP1M appears to be a cost-effective option in the treatment of schizophrenia in France (Druais et al., 2016).

Finland

In this 1-year decision tree model assessing patient with chronic stable schizophrenia, PP1M had the lowest overall cost and best clinical outcomes (lowest ER visits, lowest number of hospitalizations, lowest rates of relapse days highest QALY) compared to RLAI in treating chronic schizophrenia suggesting it as a cost-effective strategy in treating chronic stable schizophrenia in Finland (T. R. Einarson et al., 2013).

In a separate study, a 1-year decision tree model assessing chronic relapsing schizophrenia patients demonstrated PP1M had the lowest overall cost and best clinical outcomes (lowest ER visits, lowest number of hospitalizations, lowest rates of rehospitalization and relapse, highest QALY, most days with stable disease) compared to RLAI in treating chronic schizophrenia suggesting it as a cost-effective strategy in treating chronic relapsing schizophrenia in Finland (Einarson, Pudas, et al., 2016).

Germany

In this 5-year Markov decision model, PP1M was found to have the best clinical outcomes (most QALY, most avoided relapses), but had higher cost in base-case scenario. However, if cost-effectiveness threshold of €30,000 is assumed, for example, PP1M can be cost effective compared with RLAI in about 92.5 % of cases regarding gained QALYs, and in 78.6 % of cases regarding avoided relapse. (Zeidler et al., 2013)

Authors suggest that PP1M was not found to be economically dominant as compared to the Mehnert Sweden studies (included below in this review) because of differing hospital charges. For calculations, the values of Germany's per diem hospital charge were lower and average length of inpatient stay was shorter compared to Sweden (Zeidler et al., 2013).

Greece

In a 1-year decision tree model assessing chronic relapsing schizophrenia patients in Greece, PP1M is associated with a lower cost and better clinical outcomes (less ER visits & hospitalization, higher QALYS and days in remission) compared to RLAI suggesting it as a cost-effective strategy in treating chronic relapsing schizophrenia in Greece (Einarson et al., 2012)

Portugal

In a 1-year decision tree model assessing chronic relapsing schizophrenia patients in Portugal, PP1M dominated HLAI and RLAI and was cost-effective over oral-OLZ with respect to QALYs gained, relapses avoided, and hospitalizations avoided for patient with chronic relapsing schizophrenia in Portugal. This suggests cost-effective strategy in treating chronic relapsing schizophrenia in Portugal (Einarson, Maia-Lopes, et al., 2016).

Spain

In a cost minimization analysis study of schizophrenia patients in Spain, cost savings related to PP1M were €470 and €689 for years 1 and 2, respectively compared to RLAI suggesting it as a cost-effective treatment strategy for schizophrenia patients in Spain (Quintero et al., 2016).

Sweden

In this 5-year Markov decision model, PP1M was found to have the lowest 5-year cost compared to RLAI, OLAI. It had better clinical outcomes (less relapses, more QALYs) and lower cost suggesting it as a cost-effective strategy in treating multi-episodic schizophrenia in Sweden (Mehnert et al., 2012).

United States of America

In this 1-year retrospective cohort study comparing patients taking PP1M to RLAI, better healthcare outcomes were demonstrated in the PP1M group (lower discontinuation rate, more days of coverage, fewer ER visits, reduced length of inpatient stay, and lower monthly mean differences in total and pharmacy costs). The study found RLAI was cheaper, but that PP1M patients had lower healthcare resource utilization (HRU) outcomes which suggest the clinical and economic value of PP1M relative to its higher cost. Furthermore, authors acknowledged PP1M medication costs may be higher secondary to increased med compliance/taking more doses overall compared to RLAI patients in the study (Joshi et al., 2016).

Although the retrospective cohort study by Pilon et al. was aimed at comparing HRU in LAI versus oral antipsychotic patients, results did show significant findings suggesting PP1M is a cost-effective method at managing schizophrenia in the United States compared to RLAI- among other options. Specifically, out of the LAIs, PP1M in particular was responsible for higher adherence and persistence in taking medication. Furthermore, cost savings relative to OAAs were highest in those taking PP1M compared to other the LAIs (Pilon et al., 2017).

Table 1 - Summary of Articles Reviewed Comparing Cost efficacy of Paliperidone 1-month Versus Risperidone Injection in the Treatment of Schizophrenia

Author	Country	Study Design	Relevant Findings	Conclusion
Jukic et. al 2013	Croatia	-1-year decision analytic framework assessing stable chronic schizophrenia patients with of relapse and hospitalization in Croatia -compared PP1M to RLAI, olanzapine LAI (OLAI), and oral olanzapine	-PP1M had fewest relapse days, ER visits, hospitalizations -lowest overall cost to treat patient for 1 year -PP1M had the highest QALYs (0.817 vs. 0.807, 0.812)	-Compared with RLAI, OLAI, and oral olanzapine, PP1M was the most cost-effective atypical LAI for treating chronic schizophrenia in Croatia.
Einarson et. al, 2013	Czech Republic	-1-year decision tree assessing patients with chronic stable schizophrenia in the Czech Republic -compared PP1M to RLAI, olanzapine LAI (OLAI)	-PP1M demonstrated the lowest average expected cost per patient, lowest ER visits, lowest hospitalizations -PP1M demonstrated the highest QALYs (0.817 vs. 0.809 for RLAI and 0.811 for OLAI)	-PP1M had the lowest overall cost and best clinical outcomes compared to RLAI in treating chronic schizophrenia. -Using PP 1M instead of RLAI could reduce overall costs of care in Czech Republic.
Druais et. al, 2016	France	-5-year Markov decision model (using 3-month cycles) for patients with schizophrenia in France -compared PP1M to RLAI, OLAI, ariprazole LAI (ALAI), haloperidol LAI (HLAI), and oral olanzapine	-All LAI antipsychotics were found to have similar costs over 5 years: approximatively €55,000, except for PP1M which had a discounted cost of €50,880. - PP1M dominated ALAI, OLAI and HLAI in terms of costs per QALY -PP1M was associated with slightly fewer QALYs when compared with RLAI which resulted in a high incremental cost-effectiveness ratio	- Paliperidone LAI appeared to be a cost-effective option in the treatment of schizophrenia from the French health insurance perspective.

			(ICER) (i.e. €4,770,018 per QALY gained) for risperidone LAI compared with paliperidone LAI. - Oral olanzapine was less costly than LAIs (i.e. €50,379 after 5 years) but was associated with fewer QALYs gained and relapses avoided.	
			-PP1M had the lowest estimated annual avg cost -PP1M and highest QALY (0.817 vs. 0.809, 0.810) -PLAI had lowest rates of hospitalizations, ER visits, and relapse days	
Einarson et. al, 2013	Finland	-1-year decision tree assessing patients with chronic stable schizophrenia in Finland -compared PP1M to RLAI, OLAI	-PP1M had the lowest estimated annual avg cost -PP1M and highest QALY (0.817 vs. 0.809, 0.810) -PLAI had lowest rates of hospitalizations, ER visits, and relapse days	-PP1M is associated with a lower cost and better clinical outcomes compared to other atypical LAIS (RLAI, OLAI)
Einarson et. al, 2016	Finland	-1-year decision tree assessing patients with chronic relapsing schizophrenia in Finland -compared PP1M to RLAI, OLAI, ALAI	-PP1M had lowest expected costs -PP1M had highest QALYs (0.683 vs. 0.671 for ALAI, 0.666 for RLAI and 0.672 for OLAI) and most days w/ stable disease -PP1M had lowest rehospitalization and non-admitted relapses	- PP1M is associated with a lower cost and better clinical outcomes compared to other atypical LAIS (RLAI, OLAI, ALAI) For treating chronic relapsing schizophrenia
Zeidler et. al, 2013	Germany	-5-year Markov decision model (using 1-month cycles) for patients with schizophrenia in Germany -compared PP1M vs. RLAI, OLAI olanzapine, oral risperidone, and zuclopenthixol decanoate	-Relative to all other treatment strategies, PP1M is more effective with regard to gained QALYs and avoided relapses but results in higher treatment costs over a 5-year horizon in base-case scenario - If a cost-effectiveness threshold of €30,000 is assumed, for example, PP1M can be considered to be cost effective compared with RLAI in about 92.5 % of cases regarding gained QALYs, and in 78.6 % of cases regarding avoided relapse	-PP1M dominates RLAI and compared with the other treatment strategies PP1M has shown to be more effective but results in higher costs in base-case scenario.
Einarson et. al, 2012	Greece	-1-year decision tree assessing patients with chronic relapsing schizophrenia in Greece -compared PP1M to RLAI	-PP1M demonstrated the lowest average expected cost per patient, more days in remission (325 vs. 318.6), lowest ER visits, lowest hospitalizations	-PP1M I is associated with a lower cost and better clinical outcomes (less ER visits & hospitalization, higher QALYS and days

			-PP1M and highest QALY (0.840 vs. 0.815)	in remission) compared to RLAI in Greece
Einarson et. al, 2016	Portugal	-1-year decision tree assessing patients with chronic relapsing schizophrenia in Portugal - compared PP1M vs. RLAI, HLAI olanzapine, oral olanzapine	-PP1M resulted in higher QALYs and lower hospitalizations and ER compared to other medications -oral olanzapine lowest cost, but PP1M was cost effective over olanzapine in 99% of simulations	- In Portugal, PP1M dominated HLAI and RLAI and was cost-effective over oral-OLZ with respect to QALYs gained, relapses avoided, and hospitalizations avoided for patient with chronic relapsing schizophrenia
Quintero et. al, 2016	Spain	-1- and 2-year cost minimization analysis of a hypothetical cohort of Spanish patients with schizophrenia -compared PP1M vs. RLAI	-Cost savings related to PP1M were €470 and €689 for years 1 and 2, respectively compared to RLAI	-PLAI instead of RLAI could be a cost-saving strategy for the Spanish NHS
Mehnert et. Al, 2012	Sweden	-5-year Markov decision model (using 1 month cycles) for patients with multiepisodic schizophrenia (2+ relapses) in Sweden - compared PP1M vs. RLAI	-Relative to RLAI and OLAI, PP1M is economically dominant: more effective (additional QALYs, less relapses) and less costly treatment	-PP1M can be cost saving from a Swedish payer perspective compared with RLAI and OLAI in the long-term treatment of multi-episode (two or more relapses) schizophrenia patients
Pilon et. al, 2017	USA	-1-year Retrospective longitudinal cohort Study of patients with schizophrenia taking atypical LAI or oral atypical antipsychotic (OAA)	-PP1M was mainly responsible for increased adherence -consistently higher PP1M patients were persistent with treatment compared to OAAs vs other LAIS. -LAIs were associated with lower medical costs. Cost savings relative to OAAs was highest in PP1M users relative to other LAIs	-patients taking LAIs had better adherence and persistence to therapy compared to OAAs. - Particularly PP1M was associated with higher adherence, and with lower medical costs that successfully offset more than one half of the higher pharmacy costs relative to OAA.
Joshi et. al, 2016	USA	-1-year retrospective longitudinal cohort study of patients with schizophrenia taking either RLAI or PP1M	-PP1M patients showed lower discontinuation rate, more days of coverage, fewer ER visits, reduced length of inpatient stay, and lower monthly mean differences in total and pharmacy costs	-RLAI was cheaper, but PP1M patients have lower HRU outcomes which suggest the clinical and economic value of PP1M relative to its higher cost

Key:

QALY: Quality-Adjusted Life Years are a number between 0-1 where 1 represents a year of perfect health and 0 represents death

OAA: oral atypical antipsychotic

LAI: long acting injectable

PP1M: Paliperidone long acting injectable 1-month formulation

RLAI: risperidone long acting injectable

OLAI: olanzapine long acting injectable

ALAI: ariprazole long acting injectable

HLAI: haldoperidol long acting injectable

Discussion

Summary of Findings

All studies reviewed demonstrated PP1M to be superior to RLAI in clinical outcomes for treating schizophrenia. These positive outcomes include, but are not limited to reduced hospitalizations, reduced ER visits, reduced relapse, increased medication adherence, and increased QALYs. This was the case for patient populations with both chronic stable and chronic relapsing schizophrenia. In terms of cost efficacy, most studies did suggest PP1M to be a more cost-effective treatment when compared to RLAI, with exception of the Zeidler and Joshi studies. When balancing the clinical outcomes and cost, it appears that from the findings included in this review that PP1M overall is a more cost-effective medication compared to RLAI in the treatment of schizophrenia.

The observed differences in cost-efficacy and clinical outcomes could be due to a variety of factors. The reduced number of inpatient hospitalizations and ER visits are likely responsible for the reduced direct cost associated with PP1M in most of the studies. In fact, it was suggested in the Zeidler study that differences in associated hospital costs could be responsible for PP1M not being cheaper than RLAI in Germany (hospital costs and length of inpatient stays are less in Germany compared to other countries studied). Increased compliance with PP1M could be attributed to its convenient one-month formulation versus the two-week formulation of RLAI. It is even suggested that this increased compliance could result in higher average pharmacy costs in PP1M patients (Joshi). It is thus possible that there may be an even greater cost differential between the two medications given equal frequency of use.

Limitations

A limitation of this review is that all the studies included Western nations- primarily from Europe. No similar studies comparing cost-efficacy of PP1M to RLAI were found from other regions of the world (aside from the United States). Furthermore, the nations in this study are relatively high-income nations. This is important to acknowledge, as the most significant treatment gaps in treating schizophrenia occur in low- and middle-income nations.

It is also important to acknowledge that all studies included in this review were funding to some extent by Janssen (the drug company that develops and markets paliperidone) which could present a conflict of interest as the majority of these studies supported PP1M as the superior alternative compared to other drugs.

It should be acknowledged that of the studies included in this review, none were randomized control trials (RCTs) or case control studies specifically comparing cost efficacy between PP1M and RLAI. Most studies included in this review used decision analysis models to compare cost efficacy between PP1M and RLAI. Decision analysis is an objective method to apply evidence-based medicine to clinical scenarios (Aleem et al., 2008). A good way of understanding the difference between decision analytic models and RCTs or case control studies is that RCTs and case control studies gather evidence, while decision analytic models process evidence (Kuntz K, 2013). However, decision models are more feasible than RTCs and a standardly used method of cost-efficacy comparison. Furthermore, the variants of the decision tree used in many of the Einarson studies are supported by subsequent cross validation with other models (Einarson & Hemels, 2013).

Future Directions

In addition to PP1M, 3- and 6-month formulations also exist, which could be useful in further increasing adherence and accessibility in low resource nations. Furthermore, paliperidone should be strongly considered for use in low resource nations and remote locations, as it does not require refrigeration- unlike the risperidone injection (Ostuzzi et al., 2022). Current neither the 3-month or 6-month formulations are available in generic form or are approved for the WHO Essential Medicine List. As these formulations become more widely available and less costly, their outcomes and cost-efficacy can be compared to other LAIs. PP1M had a generic form approved in 2015, and RLAI generic became approved 2023. Many of these studies were conducted before both drugs were available in generic forms. Future studies could compare the cost efficacy between generic forms to analyze if the differences in cost-efficacy still exist.

Lastly, it would be helpful if the cost-efficacy comparison between PP1M and RLAI was studied in low and middle-income nations that would benefit immensely from closing existing gaps in schizophrenia treatment. In the meantime, we recommend that PPIM be strongly considered for use in communities of all income levels for treating schizophrenia given its convenience, effectiveness, and cost-efficacy.

Conclusion

This review studied the difference in cost-efficacy between paliperidone 1-month injectable (PP1M) and risperidone long acting injectable (RLAI) in treating schizophrenia. From this review, most of the evidence suggests PP1M is superior in both clinical outcomes as well as cost-efficacy in treating

schizophrenia when compared to RLAI. Given PPIM's convenience, effectiveness, and cost-efficacy seen in European countries and the United States, we recommend that it be used to treat schizophrenia in high-income countries. PPIM now has a generic formulation which is likely to make it even more cost-effective than when the studies were done. More research needs to be done, but we speculate that PPIM will be helpful in closing the treatment gap if it is also used in low and middle-income countries.

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