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A Literature Review on the Efficacy of Injectable Neuroleptics in the Treatment of Schizophrenia

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Abstract

Introduction: Schizophrenia is a chronic brain disorder of which the cause is unknown. This disorder affects less than one percent of the population and involves symptoms such as hallucinations, delusions, disorganization, and negative symptoms. Treatment for schizophrenia is mainly used to alleviate symptoms of schizophrenia, therefore improving their quality of life. Injectable neuroleptics are frequently used in patients with schizophrenia to prevent relapses attributed to nonadherence. This literature review will examine the current and potential future uses of injectable neuroleptics as a treatment for individuals with schizophrenia.

Methods: This literature review was assembled using the PubMed, Google Scholar, and Science Direct databases to evaluate the efficacy of injectable neuroleptics for individuals with schizophrenia. Keywords for the search include: "neuroleptics", "schizophrenia", "risperidone", "aripiprazole," "clozapine", "long-acting injections", "treatment", "clinical trial" as well as additional related keywords.

Results: In all of the RCTs identified in the reviewed studies, clozapine was considered the most effective in alleviating symptoms associated with schizophrenia although it did not affect the progression of the disorder.

Discussion: The literature discussing various injection neuroleptics has been shown to be safe and effective in treating symptoms of schizophrenia but has not been proven to be effective in the slowing of the progression of schizophrenia. As such, future research in this area would be beneficial to the scientific community. Given the limited number of studies, additional research is needed to assess the efficacy of long-acting injectable antipsychotics in slowing the progression of the disorder. One possible research avenue would involve the examination of a combination therapy of both injectable and oral neuroleptic treatments.

Conclusion: Long-acting injectable antipsychotics have been shown to be effective in alleviating many of the debilitating symptoms for individuals with schizophrenia. Further studies are needed to evaluate the most effective method of treating the progression of this disorder, such as combination therapy using both injectable as well as oral antipsychotics.

Keywords: injectable neuroleptics; schizophrenia; risperidone; aripiprazole; clozapine; long-acting injections; treatment

Introduction

Schizophrenia is a chronic and complex mental health disorder that manifests in a variety of different ways [1]. The most recognized signs and symptoms include hallucinations, delusional beliefs, and neurotic disturbances. [2]. Symptoms are divided into two categories, negative which involve "restricted emotional expression and avolition" [3] and positive which are changes in behavior or thoughts [4]. The "*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition *(DSM-5)"* is what physicians use to assess and diagnose schizophrenia [1]*."* Due to the plethora of symptoms that accompany individuals diagnosed with schizophrenia, worsened quality of life (QoL) is often observed. Objective, subjective, and biological measures have been used to assess the QoL in schizophrenic individuals. Although the main predictors for low QoL are depression and negative symptoms, there is a lack of clarity in the measurement and definition [5]. The relationship between depression and QoL seems to be the most significant and this may be due to factors such as self-esteem issues, nonoptimal living conditions and negative views of their overall condition [5]. Some aspects of QoL that are most affected in individuals with schizophrenia are physical and psychiatric health, social relations, and living conditions [5]. As such, the primary goal of treatments for schizophrenia involves the improvements in QoL and social functioning, as well as decreasing the risk of mortality.

Treatments

The primary objective in treating schizophrenia involves increasing adaptive functioning (how well they handle typical demands of life, level of independence, etc.). Although normal adaptive functioning is the aim of treatment, patients often fail to return to their baseline of adaptive functioning and as such, treatments are used to reduce symptoms to manage both short-term and long-term outcomes of the disease [6]. The American Psychiatric Association classifies second-generation antipsychotics (SGAs) as the first-line treatment for schizophrenia except for clozapine, as there is a risk of agranulocytosis, a severe condition causing low white blood cell counts [7]. SGAs are the first-line treatment over first-generation antipsychotics (FGAs) as there are fewer extrapyramidal side effects, although metabolic side effects such as weight gain and increased risk of diabetes are often observed [8].

Treatment of schizophrenia follows a six-stage pharmacotherapeutic guideline provided by the Texas Medication Algorithm Project (TMAP). Treatment begins with monotherapy of an SGA and if there is no response, stage 2 involves combination therapy of two SGAs. If there is little or no response at this point, clozapine monotherapy is administered while monitoring for agranulocytosis. Stage 4 involves combination therapy using clozapine with an FGA or SGA followed by stage 5 which involves monotherapy with an FGA or SGA that has not been used yet. If these 5 stages are unsuccessful, stage 6 involves combination therapy with SGA, FGA, and electroconvulsive therapy [7]. Individuals who are noncompliant with oral antipsychotics often benefit from treatment with long-acting injectable antipsychotic medications (LAI APs).

LAI APs have been found to have significant benefits regarding symptom reduction compared to oral antipsychotics. This is attributable to the fact that they are associated with lower rates of relapse and rehospitalization [9]. LAI APs are also linked to improved adaptive functioning and quality of life and are used in patients who are typically non-compliant with oral antipsychotics [9]. As such, they are considered an effective treatment in both improving adherence to treatment as well as reducing symptoms, despite their low rate of use among individuals with schizophrenia. LAI APs are administered once or twice a month and work by delaying the release of medication into the body [10]. Specifically, these injectables work to bypass first-pass metabolism in the liver to allow for a more potent action, therefore allowing for a smaller initial dose [10].

One of the biggest concerns when medicating individuals with schizophrenia involves a lack of compliance. Injectable neuroleptics are administered by healthcare professionals, as compared to oral pills administered by individuals with schizophrenia. As individuals with schizophrenia may experience symptoms that prevent them from remembering to take their medication, lack of compliance is observed frequently in individuals taking oral APs. Increased compliance can be associated with these LAI APs due to their assistive administration, and thus decreased risk for instances of relapse [11]. Although injectables are very beneficial for improving compliance and relapse prevention, they still can result in side effects similar to oral AP's, such as weight gain [8]. Examples of these LAI APs include olanzapine, clozapine, risperidone, and aripiprazole [11]. This literature review will examine the current and potential future uses of injectable neuroleptics as a treatment for individuals with schizophrenia, as well as their efficacy compared to oral antipsychotic medications.

Methods

A literature review was conducted using PubMed, Google Scholar, and Science Direct databases to assess the efficacy of injectable neuroleptics in the treatment of schizophrenia. Papers published between 2005-2022 were considered for the literature review. Throughout the database search, 120 articles fit the inclusion criteria. Following further review to remove duplicate articles as well as reviewing the titles, 70 articles were selected. When the more specific exclusion criteria were applied during review of the abstracts, 40 articles remained. Finally, as the full text was reviewed, 7 studies were used for the data analysis and discussion of this review. The language was restricted to English.

Criteria for inclusion included patients between the ages of 16-65 years old that had been diagnosed with schizophrenia or schizoaffective disorder according to the DSM-IV-TR criteria. Studies included randomized controlled clinical trials, observational studies and mirror-image studies and had the outcomes of symptom reduction, decreased rates of re-hospitalization or relapse and improvement of quality of life. Measures of efficacy used in the studies included the positive and negative syndrome scale (PANSS), clinical global impression severity (CGI-S), Global Assessment of Functioning (GAF), Extrapyramidal symptoms rating scale (ESRS) as well as rates of re-hospitalization. Quality of life was measured via various tools such as the Heinrichs–Carpenter Quality of Life Scale, the Personal and Social Performance scale, and the Quality of Well-Being scale.

Results

Efficacy

Compared to oral medications, long acting-injectable antipsychotics have been demonstrated to reduce the rate of treatment failure, relapse, and re-hospitalization in individuals with schizophrenia [12, 13, 14, 15]. The risk of rehospitalization was shown to be between 20% to 30% lower in individuals who were administered LAI APs compared to oral medications [12]. Kim et al. found similar results which included a reduction of the rate of readmission by 29% compared to oral medications, and

43% in patients who were not on any medications [13]. A lower relapse rate, greater rate of remission and symptom alleviation was seen after injectable neuroleptic treatment as well [14, 15].

Quality of Life

Although there is evidence that LAI neuroleptics are beneficial in improving the rehospitalization rates, remission rates, and treatment success, impacts on symptom reduction and improvements of overall QoL are less conclusive. One of the most prominent negative side effects with the use of LAI APs involves pain at the injection site [16]. Although adverse effects regarding the injection site are common, individuals receiving LAI APs had favorable attitudes regarding pain, side effects, efficacy, relapse prevention, and cost [17]. This study by Sugawara et al., further suggested that there were no significant differences between overall treatment satisfaction between individuals taking oral or LAI APs [17]. A study conducted by Kaplan et al., suggested that there were significant improvements in QoL scores and symptom control in individuals that switched from oral APs to LAI APs [18]. Conversely, a review conducted by Rosenheck et al., concluded that there were no significant differences between those specifically taking oral risperidone versus LAI risperidone in terms of symptom reduction and QoL measures [16]. Financially, LAI have been suggested to be more expensive forms of treatment administration, however, they reduce the costs of rehospitalizations, therefore generating a net positive effect in this avenue [12].

Discussion

Efficacy of Injectable APs Versus Oral APs

The management of schizophrenic disorders is difficult due to the high risk of relapse given that the treatment required is often lifelong. Antipsychotics are typically the first line of treatment for patients prone to relapse due to a history of non-adherence and for these patients, the use of long-acting injectable medications (LAI's) is the most common form of treatment. Despite extensive research surrounding the efficacy of LAIs, there are still controversial opinions on whether their efficacy compared to oral medications. Since non-compliant patients are at the highest risk of relapse, one of the primary goals of injectable neuroleptic therapy is to treat patients who have the poorest adherence and would benefit the most from it. Studies carried out by Tiihonen et al. and Kim et al. both support findings that LAI's decrease the readmission rate by 20-30% compared to oral antipsychotics [12, 13]. Psychiatric hospitalization was the main outcome measured in these studies, alongside treatment failure [12, 13]. Patients who were administered paliperidone once a month were observed to have the lowest risk of rehospitalization (HR=0.51, CI=95%, 0.52-0.65) [12]. When examining the within-subject analysis, there was a 22% lower risk of rehospitalization in individuals with LAI treatment, comparative to the oral medications [12]. In patients who have not received medications, the risk of readmission was lowered by 43% [13]. These results are indicative that LAI's are the provide greater long-term benefits for early onset psychosis, however, studies suggest that participating patients are more adherent and tolerable to these specific treatments [12, 13].

A randomized clinical trial done by Gaebel et al. indicates time to relapse was longer when patients were administered RLAI [14]. 16.5% of patients undergoing RLAI treatment relapsed, while 31.3% of patients relapsed with the oral medication quetiapine [14]. This study addresses nonadherence as a result of poor tolerability to antipsychotics, which coincides with our findings that neuroleptic injections may be a new and effective way of treating non-compliant individuals. It is difficult to establish the effectiveness of LAI's for non-adherent patients because the findings are based on RCTs, which are not indicative of real-world settings. Therefore, further research should be done over the long term.

Moreover, in a study that compared open label to a randomized control trial, results showed a significant decrease in all-cause withdrawals with the RLAI group, exhibiting an overall efficacy of injectable neuroleptic treatment in early-stage psychosis [15]. Emsley et al. findings exhibit a great reduction in the PANSS score of the RLAI group and a lower relapse rate (42.1% in the oral medication group compared to 9.1% in the LAI group, P=0,001) [15]. A greater remission rate was also found (40.4% (oral group) vs 64% (LAI group), P= 0.028) [15]. Results are indicative of efficacy advantages of RLAI vs oral antipsychotics when treating individuals diagnosed with psychosis. The results of these studies indicate that more research must be done to look at effectiveness and tolerability in non-adherent patients diagnosed with a schizophrenic disorder.

Implications on Quality of Life

The general findings from this literature search suggest that taking LAI APs have been attributed with both significant and insignificant changes in QoL improvements and symptom reduction. As mentioned, injection site pain and discomfort are one disadvantage to LAI APs compared to oral APs [16, 17]. The study conducted by Rosenheck et al., compared the effects of LAI risperidone against oral risperidone [16]. Injection related pain, hardening of the skin around the injection site, and extrapyramidal symptoms were all adverse effects shown to be significantly greater in the LAI group versus the oral group [16]. This same study also concluded no significant difference in symptom reduction or QoL improvements between groups [16].

Sugawara et al. conducted an analysis of anonymous questionnaire responses from individuals with schizophrenia [17]. The results of these responses suggested individuals taking LAIs had favourable attitudes

towards categories such as side effects, relapse prevention, efficacy, pain, and cost [17]. Interestingly, there were discrepancies between patient and physician attitudes towards treatment with injectables where patients believed LAIs had lower appropriateness regarding how well the treatment prevents relapse rates and the pain associated with these injections [17]. These discrepancies between patient and physician opinions could be a potential factor that contributes to the underuse of LAI APs as treatment for individuals with schizophrenia.

In addition to the study by Rosenheck et al., an analysis performed by Kaplan et al., concluded that individuals switching from oral to injectable treatment or just beginning injectable treatments had significant improvements in QoL, symptom control, treatment satisfaction, and functioning [18]. These results are very promising and in support of the argument to increase the frequency of LAI APs as treatments for schizophrenia; however, the stigma behind these injectables and their negative effects on QoL for individuals with schizophrenia is still ever-present. Kaplan et al., further suggest that physicians often ignore the beneficial effects of these injectables on reducing rehospitalization and remission rates in fear of having negative implications, specifically painful administration, on the individuals taking these medications [18].

One additional factor that has been considered when discussing treatment via LAI APs as opposed to oral APs is the financial aspect. As mentioned, Tiihonen et al. found that although administration of LAI APs is typically more costly than the administration of oral APs, the decreased prevalence of rehospitalization and therefore hospitalization costs result in an overall less expensive treatment option favouring LAI APs [12]. This is yet another reason to consider LAI APs as a treatment option for individuals with schizophrenia.

The aim of this literature review was to compile information on whether LAI APs are efficacious treatment options within both pharmacological and social measures. The discrepancies in the findings of current literature can potentially be attributed to numerous limitations and lack of research in this field of study.

Limitations

There are several limitations to consider as a result of the inclusion criteria for the literature search. During the process of selecting the studies, there were limited studies that fit the 2005–2022-time restriction. This indicates that there is insufficient research available on this specific topic that has been done within the last 20 years. As such, additional research is needed to further assess the efficacy of injectable neuroleptics on the treatment of schizophrenia. Another limitation was that the studies included had an average of approximately 30% participants who did not complete participation in the study primarily due to treatment failure, which is defined as rehospitalization, discontinuation of medication or death (Tiihonen et al., 2017). This indicates that the issue of poor adherence to treatment continues to be a limitation in both acquiring sufficient data as well as indicating that further research is necessary to continue to improve rates of adherence. Further, there was a low yield of longitudinal studies included in this review as most studies were conducted over a 3–5-year period. This limits the possible observations on the progression of the treatment over an extended period.

Future Directions

Due to the complexity of schizophrenia as well as the treatment plans required, future research is required to broaden the situations in which injectable neuroleptics are used. There is evidence that these treatments are appropriate for use in young/pre-schizophrenic individuals as well as not just in situations of poor adherence or when oral antipsychotics have failed. This emphasizes the possible further uses of this method of treating schizophrenia and the need for further research in this direction. Additionally, there are several studies on new and possibly more effective types of injectable neuroleptics that have been done using animal models such as the effect of ketamine injections on symptom reduction in rats. Overall, further research is needed to investigate the long-term impact of treatment on the progression of the disease as well as the possible broader scope of appropriate uses.

Conclusion

This literature review concludes that the use of LAI APs can be beneficial for the treatment of schizophrenia, specifically due to their increased efficacy as compared to oral APs. In addition to the improved efficacy of LAI APs, numerous studies have concluded that equal or superior improvements in symptom reduction. The main disadvantages surrounding the use of these drugs are negative patient and physician opinions and fear of painful injection sites. Future areas of research should be conducted surrounding LAI APs to solidify the results of this literature review, as well as studying the benefits of these drugs in newly diagnosed and pre-schizophrenia patients. This future research will hopefully alleviate the stigma surrounding the use of these injectable neuroleptics and allow for more efficacious and reliable treatment for individuals with schizophrenia.

List of Abbreviations

RCT: randomized control trial
QoL: quality of life
SGA: second generation antipsychotics
TMAP: Texas Medication Algorithm Project
AP: antipsychotics
LAI AP: long-acting injectable antipsychotics
LAI: long-acting injectables
RLAI: risperidone long-acting injectables

Conflicts of Interest
The authors Erika Coward, Madison Clancy, and Olivia Pashkja declare that they have no conflict of interests.

Authors' Contributions
EC: made contributions to the design of the study, collected, and analyzed data, drafted the manuscript, and gave final approval of the version to be published.
MC: made contributions to the design of the study, collected, and analyzed data, drafted the manuscript, and gave final approval of the version to be published.
OP: made contributions to the design of the study, collected, and analyzed data, drafted the manuscript, and gave final approval of the version to be published.

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References
[1] Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. Pharmacy and Therapeutics. 2014 Sep;39(9):638.
[2] Hany M, Rehman B, Azhar Y. Schizophrenia. [Updated 2020 Dec 8]. StatPearls Publishing. 2021.
[3] Mitra S, Mahintamani T, Kavoor AR, Nizamie SH. Negative symptoms in schizophrenia. Industrial psychiatry journal. 2016 Jul;25(2):135. https://doi.org/10.4103%2Fipj.ipj_30_15
[4] Rahman T, Lauriello J. Schizophrenia: An Overview. Focus. 2016 Jul;14(3):300-7. https://doi.org/10.1176/appi.focus.20160006
[5] Suttajit S, Pilakanta S. Predictors of quality of life among individuals with schizophrenia. Neuropsychiatric disease and treatment. 2015;11:1371. https://doi.org/10.2147%2FNDT.S81024
[6] Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: A Pathophysiologic Approach, ed. Connecticut: Appleton and Lange. 2014;4:141-2. https://doi.org/10.1345/aph.1l477
[7] Moore TA, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML, Essock SM, Finnerty M, Marder SR, Miller DD, McEvoy JP. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. The Journal of clinical psychiatry. 2007 Nov 15;68(11):20823. https://doi.org/10.4088/jcp.v68n1115
[8] Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J, McIntyre JS, Charles SC, Altshuler K, Cook I. Practice guideline for the treatment of patients with schizophrenia. American Journal of psychiatry. 2004 Feb;161(2 SUPPL.).
[9] Stevens GL, Dawson G, Zummo J. Clinical benefits and impact of early use of long-acting injectable antipsychotics for schizophrenia. Early intervention in psychiatry. 2016 Oct;10(5):365-77. https://doi.org/10.1111/eip.12278
[10] Brissos, S., Veguilla, M.R., Taylor, D. and Balanzá-Martinez, V., 2014. The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. *Therapeutic advances in psychopharmacology*, *4*(5), pp.198-219. https://doi.org/10.1177/2045125314540297
[11] Kishimoto T, Hagi K, Nitta M, Leucht S, Olfson M, Kane JM, Correll CU. Effectiveness of long-acting injectable vs oral antipsychotics in patients with schizophrenia: a meta-analysis of prospective and retrospective cohort studies. Schizophrenia Bulletin. 2018 Apr 6;44(3):603-19. https://doi.org/10.1093/schbul/sbx090
[12] Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E et al. Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia. JAMA Psychiatry. 2017;74(7):686. https://doi.org/10.1001/jamapsychiatry.2017.1322
[13] Kim H, Seo G, Lee B. Real-world effectiveness of long-acting injections for reducing recurrent hospitalizations in patients with schizophrenia. Annals of General Psychiatry. 2020 Jan 14;19(1). https://doi.org/10.1186/s12991-019-0254-2
[14] Gaebel W, Schreiner A, Bergmans P, de Arce R, Rouillon F, Cordes J et al. Relapse Prevention in Schizophrenia and Schizoaffective Disorder with Risperidone Long-Acting Injectable vs Quetiapine: Results of a Long-Term, Open-Label, Randomized Clinical Trial. Neuropsychopharmacology. 2010;35(12):2367-2377. https://doi.org/10.1038/npp.2010.111
[15] Emsley R, Oosthuizen P, Koen L, Niehaus D, Medori R, Rabinowitz J. Oral versus injectable antipsychotic treatment in early psychosis: Post hoc comparison of two studies. Clinical Therapeutics. 2008;30(12):2378-2386. https://doi.org/10.1186/s12991-019-0254-2
[16] Rosenheck RA, Krystal JH, Lew R, Barnett PG, Fiore L, Valley D, Thwin SS, Vertrees JE, Liang MH. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. New England Journal of Medicine. 2011 Mar 3;364(9):842-51. https://doi.org/10.1056/nejmoa1005987

[17] Sugawara N, Kudo S, Ishioka M, Sato Y, Kubo K, Yasui-Furukori N. Attitudes toward long-acting injectable antipsychotics among patients with schizophrenia in Japan. Neuropsychiatric Disease and Treatment. 2019;15:205. https://doi.org/10.2147%2FNDT.S188337

[18] Kaplan G, Casoy J, Zummo J. Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. Patient preference and adherence. 2013;7:1171. https://doi.org/10.2147%2FPPA.S53795

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