Use of Long-Acting Injectables Versus Oral Antipsychotics Among Indigent Populations:

A Systematic Review

An EBP Capstone Project submitted to the St. David's School of Nursing at Texas State University in partial fulfillment of the requirements for the degree of Master of Science in Nursing

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Abstract

Introduction: Schizophrenia affects approximately 3,810,000 people in the United States and is estimated to cost $155.7 billion. It increases unemployment and poverty, and it is estimated that as much as 25% of the homeless population has schizophrenia. The first line of treatment for schizophrenia is an antipsychotic medication which comes in two available formulations, long-acting injectable antipsychotics (LAIAs) or oral antipsychotics (OAs). Long-acting injectable antipsychotics in the treatment of schizophrenia have been shown to improve adherence to treatment, psychosocial outcomes, criminal behavior, and relapse prevention, compared to oral medication. Long acting injectables are rarely offered by providers or considered as treatment options after a patient's first episode. This conflict between scientific evidence and clinical practice prompted this systematic review which examines the cost and effectiveness of the use of long-acting injectable antipsychotics compared to oral antipsychotic medication in indigent populations. *Methods:* Search dates were between 2012 and 2022. Search terms were "long-acting injectables," "schizophrenia," "homeless," "oral medication," and "cost." Databases used were PubMed, CINAHL, and Medline. *Results:* Themes found across the studies were that LAIAs improved adherence to medication, reduced ER visits, decreased cost, improved housing stability, and were under prescribed. *Discussion:* More research needs to be done on using LAIAs, especially among indigent populations. Providers should get involved in local and statewide politics to advocate for indigent patients. Clinical practice guidelines should be updated more regularly and should include patient's needs on a social services level.

Keywords: schizophrenia, long acting injectables, oral antipsychotics, homeless, cost

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Populations: A Systematic Review

It is estimated that 3,810,000 people are being treated for schizophrenia in the United States alone. This estimation is likely quite conservative because the data is collected through Medicare and Medicaid records, which do not include subgroups such as those who are incarcerated and therefore lose their Medicaid (Mojtabai, 2021). Schizophrenia is a debilitating mental illness which has a significant societal impact. It is a severe psychiatric disorder which effects perception, behavior, daily functioning, and disturbances in thought (Citrome et al., 2020). The primary diagnostic criteria are the presence of delusions, hallucinations, or disorganized speech. Some social consequences of schizophrenia are increased unemployment and poverty, and it is estimated that as much as 25% of the homeless population has schizophrenia (Freudenreich, 2019). Treatment for schizophrenia is expensive, and often unsuccessful due to common medication non-adherence among patients. A treatment option that has been shown to be both cost-effective and to increase medication adherence in the general population is long-acting injectable antipsychotics (Okoli et al., 2021). For indigent populations, however, such as the homeless veterans, despite their disparate needs, this treatment is not routinely prescribed (Tsai et al., 2020) This review will examine the evidence surrounding the efficacy and cost to the use of long-acting antipsychotics for the indigent population.

Background and Significance

The estimated cost of schizophrenia in the United States is $155.7 billion is (Lin et al., 2021). Due to the high rate of patients not adhering to their medication, and the nature of this illness, schizophrenia patients often find themselves homeless, visiting emergency rooms, or incarcerated. Greater than 50% of adults who are incarcerated in the United States are diagnosed

with a mental illness (Tadros, 2021). Among the homeless population, it is estimated that as much as 25% suffer from schizophrenia (Freudenreich, 2019). A subgroup of this population is homeless and unstably housed (HUH) veterans. The largest provider of homeless services in the United States is the US Department of Veterans Affairs (VA) and 17.6% of HUH veterans had a prescription for an antipsychotic medication within a year of becoming homeless or unstably housed. In comparison to other veterans, the HUH population is more than three times as likely to be prescribed antipsychotic medication than veterans with stable housing (Tsai et al., 2020).

The first line of treatment for schizophrenia is an antipsychotic medication. This class of medication comes in two available options, long-acting injectable antipsychotics (LAIAs) or oral antipsychotics (OAs). Treatment with LAIAs has been shown to increase medication adherence and decrease visits to the ER (Latorre et al., 2020; Shah et al., 2018). The cost of LAIAs per person per year (PPPY) is greater than that of OAs, but PPPY medical costs are lower, balancing out the initial pharmaceutical costs (Lin et al., 2021). Despite the evidence that cost is equal or reduced, and treatment outcomes are improved, LAIAs are under prescribed for many indigent people with schizophrenia (Tsai et al., 2020).

Review of the Literature

A systematic review and meta-analysis compared the cost and utilization of LAIAs and OAs to assess how they affected medication adherence rate in schizophrenia patients (Lin et al., 2021). They found patients started on LAIAs were less likely to be hospitalized and to visit the ER than patients on OAs (Lin et al., 2021). They also found the overall cost of PPPY was not significantly greater with LAIAs compared with OAs and that patients put on LAIAs were 89% more likely to be medication adherent. This study did not include homeless individuals. Tsai et al. (2021) compared the use of antipsychotic medication among HUH veterans versus non-HUH

veterans and found that 82% of the HUH veterans with a psychotic disorder had at least one prescription for an antipsychotic medication; however, less than 2% of HUH veterans had been prescribed a LAIA. Although this study is very specific to a particular subgroup of homeless individuals, it is stated that the VA is the largest provider of homeless services, so it is a strong representation of the underuse of LAIAs which has been proven effective in the treatment of psychotic disorders.

Yoshimatsu et al. (2019) conducted an exploratory, retrospective, pre-post observational study in outpatient mental health clinics, jails, and inpatient psychiatric facilities in San Francisco County to assess if psychosocial outcomes improved with LAIA treatment. They found criminal behavior, spirituality, medication adherence and housing stability improved when switched from OAs to LAIAs (Yoshimatsu et al., 2019). In the last few years, several systematic reviews have been conducted examining the cost and effectiveness of LAIAs compared to OAs, but not specifically for indigent populations (Lin et al., 2021; Okoli et al., 2021). There have been some small studies showing the correlation between LAIA treatment and reduced criminality (Yoshimatsu et al., 2019) and improved functioning among homeless veterans (Tsai et al., 2020). Showing a strong correlation between using LAIAs, compared to OAs, to treat schizophrenia in indigent populations, at no increased financial cost to the patient or society, could change the standard of care for these indigent populations.

Clinical practice guidelines (CPG) are useful for mental health professionals, but unfortunately, CPGs are not updated as regularly in mental health as they are in other fields of medicine. Schizophrenia is treated based on acuity, past treatment response, patient preference and treatment adherence. Treatment algorithms are not common and LAIAs are not consistently incorporated in them, but often treated as a separate category of medicine. However, The

American Association of Community Psychiatrists (AACP) have recommended using LAIAs for more than just nonadherence due to their convenience and potentially addressing social challenges (Correll et al., 2022).

Purpose and Clinical Question

Long-acting injectable antipsychotics in the treatment of schizophrenia have been shown to result in improved adherence to treatment, psychosocial outcomes, criminal behavior, and relapse prevention, compared to oral medication (Correll & Lauriello, 2020; Yoshimatsu et al., 2019). Despite these findings, patients rarely even receive information about the injectable option from their provider (Correll & Lauriello, 2020). This conflict between scientific evidence and clinical practice illuminated clinical questions prompting this systematic review. In indigent populations with schizophrenia, how do long-acting injectable antipsychotics compare to oral antipsychotics regarding cost, housing, and treatment outcomes?

Conceptual Framework

Nancy Milio, a registered nurse, authored the Framework of Prevention, with a healthcare model asserting six propositions involving primarily community health and indigent populations (Utley et al., 2017, p. 247). Her first proposition asserted that the level of health among a population was based on the resources available. Her second proposition was that communities have limited options for health choices, whether actual or perceived. Thirdly, the perceived options are influenced by the organizations within that community and local governments or policies influence the choices. Fourth, resources available greatly affect a population's choices. Her fifth proposition was that when a population, or a high percentage of a population, changes then social change can occur. And lastly, education alone will not affect individuals' or a population's health, but rather the population must be aware that they have access to and can

afford the health options (Utley et al., 2017, p. 247). This framework guided my project because a population's overall health cannot improve without the patient having both the knowledge of resources available, as well as access to those resources. These principles directly correlated to my study of whether LAIAs are more effective long-term in treating severe mental health issues among indigent populations, in relation to making sure they have the knowledge of and access to this treatment option.

Methods

Project Design

This systematic review of the literature, guided by the Framework of Prevention, examines the cost and effectiveness of the use of long-acting injectable antipsychotics compared to oral antipsychotic medication in indigent populations. The review was undertaken to inform clinical practice regarding the prescription of LAIAs for the indigent population. The proposition of the Framework of Prevention focuses on the importance of providing indigent populations with current knowledge regarding treatment options and access to those options, supporting the rationale for this study.

Search Strategy

When conducting a search for research articles, key terms used were "long-acting injectables," "schizophrenia," "homeless," "oral medication," and "cost." Databases used to extract articles were PubMed, CINAHL, and Medline. To be included in the study, articles were published between 2012 and 2022 (see Figure 1), involved indigent populations with schizophrenia, and addressed cost and efficacy associated with the use of long-acting injectable antipsychotics compared to oral medication.

Selection Process

Articles were reviewed first by the title. If the title appeared to be regarding LAIAs and OAs the abstract was reviewed to see if the study was pertinent and if the population studied was an indigent population. Articles regarding the cost and effectiveness of LAIAs compared to OAs were also pulled. The Flow Diagram (see Figure 1) was used to screen articles using inclusion criteria. Only one person conducted searches, and screened articles, but assistance was provided by a university librarian. The quality appraisal tools used to assess articles were the Joanna Briggs Institute Critical Appraisal Checklists. The checklists help determine the quality of each article being reviewed, and the articles needed a score of greater than 50% to be included in the study.

Results

Search Results

The CINAHL database returned 20 articles, Pubmed 74 articles, and Medline 46 articles. After the initial search, articles were excluded if they weren't in English, or if the title had no clear relevance to the PICO question. After placing the remaining studies in Zotero all duplicates were removed and 49 studies remained. After evaluating titles and abstracts, 21 articles were excluded leaving 28 to be screened. Five of the 28 were not able to be retrieved due to accessibility issues and not being able to get access in time, leaving 23 to be assessed for eligibility using the Joanna Briggs Institute Quality Assessment tools. Of the 23 assessed for eligibility, six studies were discarded due to low quality assessment scores, three for not being primary research, and seven for not applying fully to the PICO question.

Characteristics of Studies

Seven studies had quality assessment scores above 50% and were included in the systematic review (see Table 1). Three of the studies were case series'(Latorre et al., 2020;

Sajatovic et al., 2013; Sajatovic et al., 2017), one was an analytical cross-sectional study (Tsai et al., 2020), and three were cohort studies (Abdel-Baki et al., 2022; Marcus et al., 2015; Shah et al., 2018). Four of the studies addressed homelessness or housing stability directly (Abdel-Baki et al., 2022; Sajatovic et al., 2013; Sajatovic et al., 2017; Tsai et al., 2020), and the other three addressed the effectiveness and cost of the treatment options (Latorre et al., 2020; Marcus et al., 2015; Shah et al., 2018). The studies' sample sizes ranged from 30 (Sajatovic et al., 2013; Sajatovic et al., 2017) to 2,882,993 (Tsai et al., 2020), and all the studies involved patients with schizophrenia or a schizophrenia spectrum disorder. A few of the studies had patients actively receiving treatment who were followed over a specific length of time (Abdel-Baki et al., 2022; Sajatovic et al., 2013; Sajatovic et al., 2017). The other four studies used data from insurance claims and prescription history over a certain time period to collect data (Latorre et al., 2020; Marcus et al., 2015; Shah et al., 2018; Tsai et al., 2020).

Synthesis Across Studies

Some of the themes found among the articles evaluated were improved medication adherence, reduced hospital visits, decreased cost and improved housing stability.

Medication Adherence

In five of the seven studies was that LAIAs improved medication adherence in schizophrenia patients compared to oral antipsychotics (Marcus et al., 2015; Sajatovic et al., 2013; Sajatovic et al., 2017; Shah et al., 2018; Tsai et al., 2020).

Reduced Hospitalizations

Not only did patients' medication compliance improve, but three of the studies showed that they LAIAs reduced hospital and ER visits compared to OAs (Latorre et al., 2020; Marcus et al., 2015; Shah et al., 2018).

Decreased Cost

Three of the studies showed how using LAIAs, both directly and indirectly, decreased cost and economic burden due to decreased ER visits, hospitalizations, and relapse (Latorre et al., 2020; Marcus et al., 2015; Shah et al., 2018).

Improved Housing Stability

The four studies that addressed homeless patients with schizophrenia, were similar in that they all showed an improvement in their level of functioning after using LAIAs compared to OAs, and two showed significant improvement in housing stability after using LAIAs comparted to OAs (Abdel-Baki et al., 2022; Sajatovic et al., 2013).

Nancy Milio's Framework of Prevention asserts that resources affect a population's choices, and when a large portion of a population changes, social change can occur (Utley et al., 2017, p. 247). All the studies showed that with access to the right resources, schizophrenic patients can improve their symptoms and psychosocial functioning. All studies showed that LAIAs improved the functioning of patients with schizophrenia at some level, by either reducing their hospital visits, improving symptoms, or increasing housing stability.

Discussion

The findings in the studies analyzed in this systematic review show that long-acting injectable antipsychotics are cost-effective, improve housing stability, and medication adherence. They improve medication adherence and housing stability in schizophrenia patients without increasing healthcare costs. As stated in the first proposition of Nancy Milio's Framework of Prevention, a population can only be as healthy as its resources (Utley et al., 2017, p. 247).

Recommendations from Findings

Based on the findings, homeless patients diagnosed with schizophrenia should be offered LAIAs sooner, and possibly as a first-line option for patients who are at the highest risk for not complying with their medications or who have unstable housing. Quite often this is offered after they show poor medication adherence, but the studies have shown it to be more effective and it should be considered a first-line treatment option for those patients most likely to have low psychosocial functioning and poor medication compliance. Clinical practice guidelines for schizophrenia patients may need to be adjusted to include not only a patient's diagnosis and symptoms but also their psychosocial risk factors. There are many factors at play when choosing treatment options, and when it comes to indigent populations, it is not just the disease that is being treated, but the person's ability to function in society both safely and successfully.

Another recommendation would be to make sure providers working with the indigent population are well-educated on the long-acting injectable options. If providers are educated and knowledgeable on the LAIA options and their benefits, they can help provide the treatment with the best success rate for adherence and social functioning. More studies will likely need to be done to learn more about how the treatment option for schizophrenia that is chosen affects both the symptoms and social functioning, relative to the cost of treatment.

Limitations

This review had several limitations, the first being that two of the studies were not conducted in the United States (Abdel-Baki et al., 2022; Latorre et al., 2020). This was a limitation because, symptomatically, schizophrenia patients are going to present with similar symptoms and struggles, however, resources and treatment options may vary from country to country, affecting their success rate with medications. Conducting similar long-term studies in the United States would be a useful way to compare the findings. A second limitation was that

more than half of the studies had very small sample sizes, less than 420 patients, some as low as 30. (Abdel-Baki et al., 2022; Latorre et al., 2020; Sajatovic et al., 2013; Sajatovic et al., 2017). Many of the studies lost patients during the study for various reasons, so a small starting sample size may make it hard to achieve reliable findings that can be extrapolated to include all schizophrenia patients. Although it would be more difficult, doing studies with a broader geographic range might improve the sample size. A statewide study versus a local study in one city might be one way to accommodate this.

Lastly, due likely to ethical considerations, another limitation is that there are no high-level, studies comparing the LAIAs to OAs. It would potentially be unethical for a RCT to blindly assign patients with schizophrenia to the oral versus injectable antipsychotics when those with especially poor medication adherence would likely decompensate if they were in the OA group. The best solution to this ethical dilemma is to perform retrospective and longitudinal studies as many researchers have done.

Conclusions and Implications

After conducting this review of studies and the findings it produced, long-acting injectable antipsychotics are beneficial in numerous areas of functioning for people diagnosed with schizophrenia. It improves medication adherence, reduces hospitalizations, improves housing stability, and manages to do this at no extra overall healthcare costs, despite the increased pharmaceutical costs. Clinical practice among providers can be improved by using this data. Nancy Milio's Framework of Prevention asserts that a population will not improve with education alone, they also need to be actively aware of their affordable and accessible resources. We as providers need to make sure we are aware of all options ourselves, and then relay that

information to our patients, providing them with the knowledge to make informed choices regarding their care.

Although this review showed great success in treating the most at-risk schizophrenia patients with LAIAs, there are still many areas that need to be studied, researched, and improved. This systematic review showed that LAIAs are very effective in improving housing stability and decreasing hospital visits, all at no extra healthcare expense in comparison with oral antipsychotics, however, more research needs to be done on the barriers to using LAIAs and especially among indigent populations. This may be a bigger issue in states such as Texas which has limited mental health options. Getting involved in local and statewide politics to advocate for these patients is needed as well. The initial cost of supplying LAIAs is more expensive, but long-term healthcare savings will be equal or reduced due to their effectiveness and this information could be useful in lobbying for change with local and state representatives. As we learn more about schizophrenia, treatment options and psychosocial assistance will continue to improve, but until then we must make sure to get the treatment with the highest evidence-based success rate to as many patients as possible.

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Table 1

Evidence Synthesis Table

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
Abdel-Baki, 2022	Study functional outcomes in patients with first episode of psychosis prescribed LAI vs OA	Cohort study; prospective longitudinal naturalistic 3-year study	416; 1st episode psychosis; 3 yrs; 2 urban early intervention services in Montreal; recruited 2005-2012, final f/u 2015	4 cohorts; LAI only; OA only; LAI switched to OA during 3 yrs; OA switched to LAI during 3 yrs; housing stability measured	LAI only group had highest level of homelessness at baseline, but least residential instability at 36 months; only statistically significant association	QA 7.5/11; Study done in Canada; LAI only group started with lower functioning and OA only had better baseline fx; not randomized; small cohort size	Supports using LAI to improve housing stability, especially in those with lower baseline fx	Abdel-Baki, 2022
Latorre, 2020	Compare hospitalizations and ER visits on OA versus LAI	Observational, retrospective study (case series)	207 pts / Community mental health center; LAI after prior OA	10 year period; pts from 5 mental health clinics; pts had recent switch from OA to LAI; Generalize	Emergency visits significantly reduced; SGA LAI significantly more effective than FGA LAI, economic burden reduced	QA 7.5/10; No control group; not in US; did not study psychiatric sx's or functionality; consecutive/complete inclusion unclear	ER visits significantly reduced after starting LAI; supports LAI use over OA for community health pts	Latorre, 2020

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
Marcus, 2015	Measure nonadherence, discontinuation, &rehospitalization in pts receiving OA vs LAI 6 mos after schizophrenia related hospitalization	Retrospective Cohort	3768 total, 3248 OA, 340 LAI; Indv w/schizophrenia related hospitalization w/hx of nonadherence to OA	d Estimating Equations; Truven Health Analytics MarketScan Medicaid research claims database 2010-2013; discontinuation, hospitalization, adherence; FGA LAI vs FGA OA; SGA LAI vs SGA OA; logistic regressions	LAI had less nonadherence and less rehospitalization, decreased healthcare cost	QA 8.5/10; possible confounding variables unable to be accounted for; only 6 months	LAI = less hospitalization and improved adherence; supports LAI use over OA	Marcus, 2015
Sajatovic, 2013	To assess recovery outcomes in homeless indv	Prospective, uncontrolled trial (case series)	30 recently homeless indv with schizophrenia or	Received Haldol Dec every 4 weeks along with CAE	Time in suboptimal housing went from 56% to 14%; medication adherence improved	QA 6.5/10; low validity of results due to only 4 people left 6 months post study; no	Med adherence and housing stability improved; supports using LAI over OA in	Sajatovic, 2013

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
	w/schizophrenia using CAE approach		schizoaffective d/o; homeless shelters, community mental health clinics, community	session tailored to schizophrenia pts; 6 months of data		control; Haldol Dec only LAI used	homeless populations	
Sajatovic, 2017	To assess recovery outcomes in homeless indv w/schizophrenia using CAE approach	Prospective, uncontrolled trial (case series)	30 recently homeless indv with SMI	LAI and CAE delivered by social worker over 6 months. Adherence measured by TRQ	Symptom improvement, missed medication decreased, 57.7% vs 22% at 6 mo f/u	QA 5.5/10; Only Invega Sustenna used as LAI, small sample size, no control group, non-blind; low reliability and validity	Med adherence improved on Invega Sustenna, supports LAI use for homeless pts	Sajatovic, 2017
Shah, 2018	Compare tx outcome; schizophrenia pts; LAI vs OA	Cohort study	2302 in LAI cohort; 2302 OA cohort	Retrospective claims data 2010-2015; 2 cohorts; LAI vs OA; 12 months	LAI lower discontinuation rates; LAI lower hospital/ER visits; LAI higher med cost, lower healthcare cost;20-30% lower rehospitalization w/LAI	QA 8/10; Diagnoses made on healthcare claims alone; observational study; rx claim does not = proper adherence	LAI had no increased overall costs; improved med adherence and fewer ER visits; supports LAI being cost effective w/improved fx	Shah, 2018

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
Tsai, 2020	to gather information on AP Rx patterns among homeless adults with severe MI	analytical cross-sectional study	veterans who responded to VA screen for housing instability (2,882,993)	compared veterans w and wo AP Rx. Then compared HUH to non-HUH, logistic regression analyses	HUH veterans 3x as likely to have AP Rx. Psychotic and BP d/o strongest link to AP Rx. <2% HUH had LAI Rx, LAI= improved adherence and fx	QA 6/8; Only included veterans; information from data recorded by VA providers only, not clinical interviews; rx hx uncertain outside of VA database	LAI=improved fx. HUH more likely to have AP Rx, yet few have LAI Rx. Supports need for more LAI for HUH	Tsai, 2020

Abbreviations: MI=mental illness; BP=bipolar; d/o=disorder; AP=antipsychotic; OA=oral antipsychotic; Rx=prescription; LAI=long acting injectable; fx-=functioning; Indv=individual; CAE=customized adherence enhancement approach; SMI=serious mental illness; Hx=history; TRQ=tablets routine questionnaire; HUH=homeless and unstably housed; FGA=first generation antipsychotic; SGA=second generation; antipsychotic

Figure 1

Flow Diagram

Identification of studies via databases and registers	
Identification	Records identified from*: Databases Cinahl (n=20) Medline (n=46) Pubmed (n= 74)	Records removed *before screening*: 91 duplicate records removed (n =49)
Screening	Records screened (n=49)	Records excluded based on title and abstract (n = 21)
	Records sought for retrieval (n = 28)	Records not retrieved due to availability and time constraints (n = 5)
	Reports assessed for eligibility (n = 23)	Reports excluded: Reason 1 (n = 3 not primary research) Reason 2 (n = 6 low QA score) Reason 3 (n= 7 did not apply to PICO quite as well)
Included	Studies included in review (n =7)	