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Review on Antipsychotics: Long Injectable Antipsychotics For Treatment of Schizophrenia

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ABSTRACT:-
Bipolar disorder (BD) and schizophrenia are mental illnesses that lead to impairment and have social and economic repercussions. One of the main issues that physicians deal with in both schizophrenia and BD is treatment noncompliance. Recurrence and decreased functionality are linked to treatment non-compliance. Compared to patients using an equivalent oral form of the same medication, treatment compliance is higher with long-acting injectable antipsychotics (LAIAs), recurrence times are delayed, and hospitalization rates are lower. A low death rate, less caregiver stress, and higher patient satisfaction have all been linked to the use of LAIAs in the maintenance treatment of schizophrenia. Research indicates that LAIAs are more affordable than their oral counterparts. There is a dearth of information regarding the use of LAIAs in first-episode schizophrenia and bipolar disorder, but studies on the use of LAIAs in first-episode schizophrenia patients show that they are more effective at preventing relapse and re-hospitalization than oral antipsychotics, and in BD, using LAIAs has reduced the rate of hospitalization for mood episodes and the frequency of manic episodes. It has been discovered that LAIAs are less successful than manic episodes at preventing depressive episodes in BD. More research is required on this topic even though there are numerous studies that support the use of LAIAs in the maintenance treatment of BD and schizophrenia. This article reviews research on the use of LAIAs in treating BD, schizophrenia, and first episode schizophrenia. It also discusses the use of LAIAs in treatment.
Keywords: Bipolar Symptoms, Schizophrenia, BD, LAIA

I. INTRODUCTION:

A prevalent and incapacitating psychotic chronic illness, schizophrenia places a significant burden on its victims, their families, and society at large [1- 2]About 1% of people worldwide will experience schizophrenia at some point in their lives. The debilitating illness can strike at any age, although it usually begins in young adulthood with prodromal signs of psychosis that lead to a first psychotic episode. [2, 3]. Schizophrenia patients have a lower life expectancy than the normal population, are more likely to suffer from physical illnesses, particularly cardiovascular disease, and are more likely to commit suicide or sustain an accident. [2, 4–6]. Schizophrenia's long-term course is characterized by periods of partial or complete remission interspersed with relapses; social and occupational functioning, quality of life, and the capacity to lead an independent life are all limited; and there is a higher risk of substance abuse, suicide, and violent behavior, particularly during the relapse period. [2, 7].

While the prevention of relapse, accompanied by delusions, which may potentially cause harm to the patient and their societal contacts, hallucinations, and disorganized speech and behavior, is a major challenge in schizophrenia, the disease is also characterized by poor adherence to antipsychotic medication leading to a need for multiple rehospitalizations and a substantial direct and indirect cost burden [2, 8–12].

With an emphasis on the second-generation antipsychotic LAI aripiprazole, we review the evidence supporting the comparative effectiveness of oral versus long-acting antipsychotics in the management of schizophrenia. In this narrative review, we look at published clinical data from the development of long-acting injectable (LAI) formulations of antipsychotic drugs and present evidence from studies with explanatory and naturalistic/pragmatic trial designs, which is bolstered by the authors' clinical experience.

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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USE OF LONG ACTING INJECTABLE ANTIPSYCHOTICS IN SCHIZOPHRENIA:-

Both patients and caregivers are greatly burdened by schizophrenia.

This illness has an impact on society and the economy (11). Suicide, aggressive conduct, neurotoxicity, repeated hospital stays, and a poor quality of life are all linked to relapses in schizophrenia (12). When schizophrenia therapy is stopped, the chance of re-occuring rises.

Alvarez-Jimenez et al. claimed that stopping therapy raised the chance of relapse four times (13), however Morken et al. found that the risk increased 10.3 times (14) instead.). 74% of patients cease therapy within the 18-month term, according to the findings of the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) research (15). Nonetheless, there is a wealth of reliable data showing that ongoing antipsychotic therapy improves schizophrenia outcomes(16–18). According to Tiihonen et al.'s 20-year follow-up study, patients who consistently take antipsychotics had lower rates of re-hospitalization and death than those who stop using them. Patients with schizophrenia who stop receiving medication had a 174%–214% increased chance of dying compared to those who take regular antipsychotics (19). In addition to stopping therapy, it's usual for patients with schizophrenia to take their drugs intermittently or at a dose lower than what is advised. In their analysis of 4325 patients, Weiden et al. demonstrated that breaks in the course of treatment also raised the chance of recurrence and the associated hospitalization. The study's findings indicate that the risk of hospitalization increases 1.98 times for intervals between 1 and 10 days in a year, 2.86 times for intervals between 11 and 30 days, and 3.96 times for intervals more than 30 days (20). Compared to oral antipsychotics, the likelihood of recurrence in LAIAs has been demonstrated to be decreased in numerous trials. Treatment compliance was higher and relapse rates were lower in LAI-risperidone at the end of the first and second years, according to a study that compared oral risperidone with LAI-risperidone for two years in 50 patients who experienced their first attack (21). According to a Finnish cohort research, 1182 schizophrenia patients who continued treatment for at least 30 days after being discharged had lower hospitalization rates than those who took the same medication orally (22). Clozapine and LAIAs have been demonstrated to be more effective at preventing relapses in a prospective analysis involving 29823 participants. Clozapine and LAIAs are more effective at preventing relapses in schizophrenia, and the rate of rehospitalization is 20–30% lower with LAIAs than with equal oral doses, according to a prospective research involving 29823 patients (23). According to Kishimoto et al.'s meta-analysis of 42 studies, LAIAs are better than oral antipsychotics at lowering hospitalization rates per unit of time, but they don't lower hospitalization risk (24) The patient's time to relapse after stopping the medication increases with the length of the antipsychotic's half-life. A research comparing oral paliperidone with PP1M and PP3M found that recurrence occurred on average 58 days after stopping oral paliperidone, 172 days after stopping PP1M, and 395 days after stopping PP3M (25) The authors of this study stress that, in comparison to oral equivalents, LAIAs can significantly postpone the time at which patients relapse after stopping treatment.

The use of LAIAs in lowering the likelihood of relapse is of interest because maintenance antipsychotic treatment interruptions are unexpected in schizophrenia. Thus, in terms of treatment non-compliance, LAIAs appear to be helpful in postponing relapses.

In patients with schizophrenia, switching from oral treatment to SG-LAIAs appears to lessen the strain on caretakers. According to Han et al., patient and caregiver satisfaction as well as treatment compliance rose when oral therapy was replaced with LAI-risperidone (26). According to Gopal et al., the caregiver's time spent providing care decreased and their free time increased when oral paliperidone was switched to PP1M and PP3M (27). SG-LAIAs have been linked to improved patient satisfaction and quality of life in addition to lessening the strain on caregivers (28). SGAPs were primarily used to examine how LAIAs affected clinical symptoms, functionality, and quality of life. When SG-LAIAs were compared to their oral formulations in a study by Pietrini et al., they were linked to improved functionality in nearly every aspect of daily living, reduced PANSS scores, and higher scores on health-related quality of life measurements (29) . Significant improvements were noted after six months in parameters pertaining to disease severity, patient functionality, health-related quality of life, and patient satisfaction following the switch to LAI-risperidone treatment in a study assessing 182 schizophrenia patients who had previously received oral therapy (30). In observational studies, it is highlighted that using LAI-risperidone raises

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quality of life and improves PANSS total and subscale scores (36–38). 231 patients with schizophrenia who were symptomatic but not in the acute phase of the illness were assessed for transition to PP1M because of the failure of prior treatment in the prospective, multi-center, open-label, 6-month Phase IIIb interventional study known as PALMFlexS (Paliperidone Palmitate Flexible Dosage in Schizophrenia). According to the study's findings, two-thirds of the patients experienced a 30% or greater improvement in their PANSS total score following the switch to PP1M (31). Furthermore, there have been reports of improvements in treatment satisfaction and functionality, a decrease in the severity of symptoms, and a rise in subjective well-being.

LAI-olanzapine has fewer data available. It was highlighted that both oral and LAI-olanzapine enhanced their functionality based on the patients' baseline status and that there was no discernible difference between the two types of olanzapine in a multi-center, randomized, 2-year follow-up study (32). The PANSS total and subscale ratings did not significantly change, according to the findings of a multi-center study using LAI-olanzapine. However, patients who had previously used LAIAs reported higher levels of satisfaction with LAI-olanzapine (33).

Similar to previous SG-LAIAs, the study's findings for LAI-aripiprazole indicate a reduction in clinical symptoms as well as an improvement in health-related quality of life and functionality (34). According to the findings of a study funded by the pharmaceutical business, LAI-aripiprazole significantly improves clinical outcomes and health-related quality of life, particularly in patients under the age of 35 who are using paliperidone palmitate (35).

Compared to oral equivalencies, LAIAs are more costly. When compared to oral antipsychotics, the cost of using LAIAs is much lower due to the decrease in hospitalization and admission to health services (36). Wu et al. highlighted how employing LAIAs can significantly reduce the indirect costs of schizophrenia by reducing the incidence of relapses, enhancing social functioning, and lengthening working days (37).

According to Offord et al., the cost of inpatient medical care has been decreased when LAIAs are used to treat schizophrenia at an earlier stage (38). In their analysis of 28 studies on the expense of employing LAIAs, Achilla and McCrone reported the following findings: Compared to other LAIAs and oral antipsychotics, LAI-risperidone is more affordable. Nonetheless, oral or LAI-olanzapine is more economical than LAI-risperidone, according to the findings of a Slovenian and an American investigation. When compared to oral SGAPs or FG-LAIAs, PP1M is the most economical course of treatment (39). PP1M treatment was shown to be more cost-effective for treating schizophrenia than LAI-olanzapine and LAI-risperidone treatments, with a lower hospitalization rate, fewer ER visits, and less relapse, according to a study based on Finnish national health data (40). When compared to PP1M, LAI-haloperidol, LAI-risperidone, and oral olanzapine, PP3M shown benefits in both cost-effectiveness and cost-benefit analyses, as evidenced by decreased relapses, hospitalizations, and ER visits (41). Although our nation's hospitalization expenses are less than those of the United States and Europe, hospitalization is never wanted or preferred, and there are other factors that contribute to hospitalization expenditures.

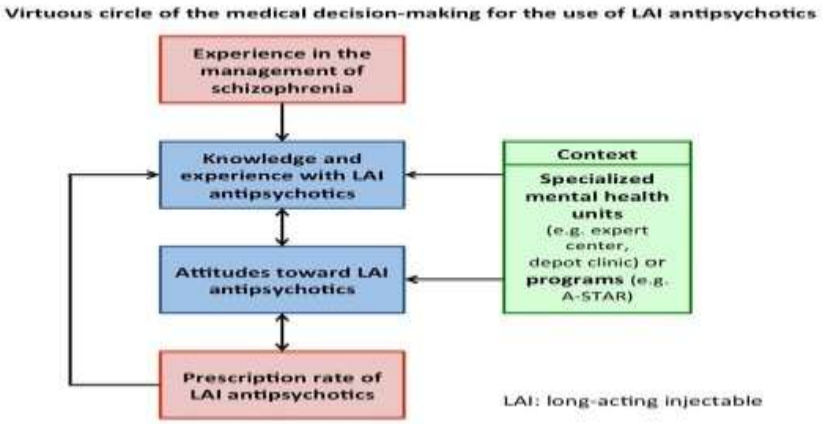

Figure 1 Aripiprazole Long-Acting Injectable in Schizophrenia

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Aripiprazole is an antipsychotic of the second generation. Aripiprazole's antipsychotic effectiveness, in contrast to that of other first- and second-generation antipsychotics now on the market, has mostly been ascribed to a mixture of partial antagonism at human dopamine D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A receptors [42–45]. Aripiprazole has a moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, a1-adrenergic and histamine H1 receptors, dopamine D2 and D3 receptors, serotonin 5-HT1A and 5-HT2A receptors, and a moderate affinity for the serotonin reuptake site [46]. As such, there is little chance of aripiprazole causing drowsiness, weight gain, or metabolic side effects that are clinically significant [47-49].

The body distributes aripiprazole extensively and absorbs it well [50]. The geometric mean highest concentration (mean 19%) of aripiprazole 5 mg administered short-acting intramuscularly (IM) is higher than the Cmax of the tablet formulation [51]. It is not anticipated that the IM route of administration will change the metabolic pathways of aripiprazole, and systemic exposure following oral tablet administration and aripiprazole IM injection is typically comparable during a 24-hour period [52]. When strong CYP3A4 or CYP2D6 inhibitors are administered concurrently with aripiprazole, the dosage should be decreased; conversely, if aripiprazole is administered concurrently with strong CYP3A4 inducers, the dose should be raised [53].

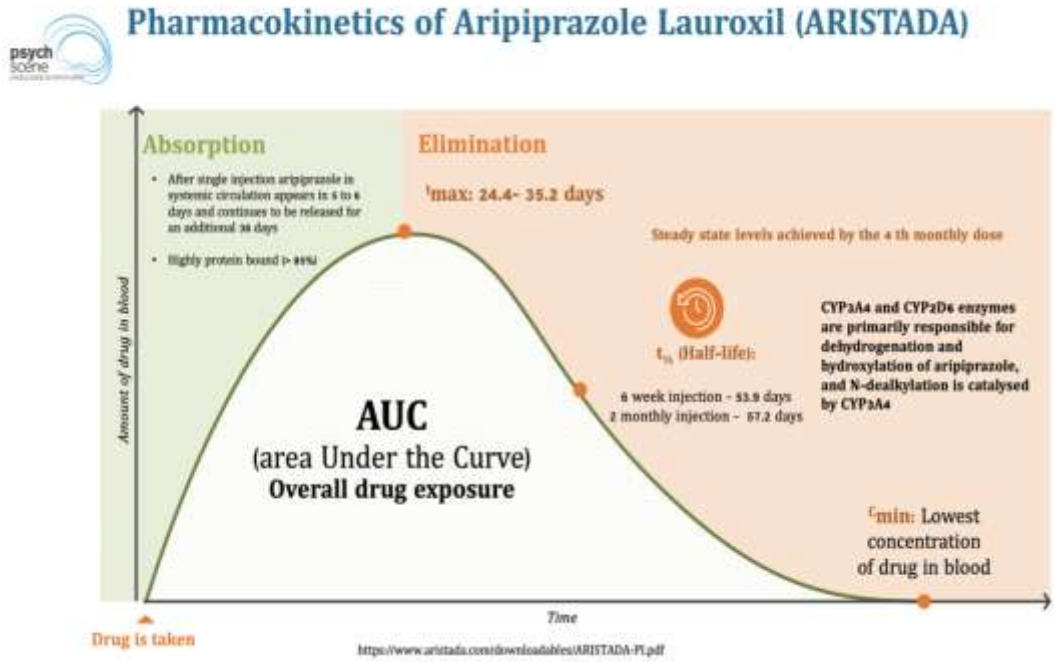

Figure 2 Pharmacokinetics of Aripiprazole Lauroxil [87]

Abilify Maintena; aripiprazole 400 mg once-monthly (AOM 400) is an extended release version of aripiprazole that has been created [54]. In Europe, AOM 400 and 300 are both authorized for use as maintenance treatments for adult patients with schizophrenia who have been stabilized with oral aripiprazole. For intramuscular injection into the gluteal or deltoid muscles, the formulation consists of a powder that must be reconstituted in sterile water [55]. A 24-week, open-label, parallel arm pharmacokinetic research examined the pharmacokinetics, safety, and tolerability of taking aripiprazole once a month. The study determined that 400 mg is the recommended initial and maintenance dose [56]. Without producing any clinically significant alterations in adverse events, laboratory results, vital signs, or electrocardiogram readings, AOM 400 produced sustained mean plasma concentrations of aripiprazole that were equivalent to those obtained with several consecutive daily doses of oral aripiprazole 10–30 mg/day at steady state [57]. In patients who are known to be cytochrome P450 (CYP) 2D6 poor metabolizers or in the case of adverse effects, the 400 mg recommended maintenance dose of AOM may be lowered to 300 mg. A dose reduction to 300 mg is also necessary for patients taking AOM 400 concurrently with strong CYP3A4 (such as

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ketoconazole or itraconazole) or strong CYP2D6 inhibitors (such as fluoxetine, paroxetine, or quinidine) for longer than 14 days [58]. It is prohibited to administer AOM concurrently to patients who have been using CYP3A4 inducers (such as carbamazepine, rifampicin, or phenobarbital) for longer than 14 days.

USE OF LONG ACTING INJECTABLE ANTIPSYCHOTICS IN FIRST ATTACK SCHIZOPHRENIA

Antipsychotic treatment results in symptomatic remission for around 80% of patients with first-episode schizophrenia; however, most patients experience return within two years because of a lack of understanding of the illness and treatment noncompliance (59). According to a five-year observational research, patients with first-episode schizophrenia who stop treatment have a roughly five-fold increased risk of relapsing when compared to those who continue taking medication (60). Treatment interruption is not advised, according to a comprehensive analysis analyzing the findings of four randomized controlled and two non-randomized controlled trials that examined the effects of medication withdrawal (61). But according to the findings of the European First Episode Schizophrenia Trial, or EUFEST, 42% of patients with first-episode schizophrenia stop taking their medication within a year of the illness starting (62)

According to a research by Herres et al., half of those who were advised to utilize LAIAs agreed to do so, and only one in four patients with schizophrenia who experienced their first episode had their psychiatrist offer the LAIAs option (63). Psychiatrists blame patients' resistance to intramuscular injections and a general distaste for LAIAs for the underprescription of these medications in the early stages of schizophrenia. 38% of participants in a research examining doctors' perceptions of LAIAs in England said that they couldn't be utilized for first-episode schizophrenia (64). Nonetheless, research suggests that LAIAs are a viable and efficient therapy choice for individuals with first-episode schizophrenia.

The drug compliance and relapse rates of 22 patients taking LAIrisperidone and 28 patients taking oral risperidone were compared in a study that followed 50 patients with first-episode schizophrenia for two years. The group receiving LAI-risperidone treatment showed a lower relapse rate and higher drug compliance (20). According to the Schizophrenia research Group's criteria, 64% of the patients in Emsley et al.'s research, which followed first-episode schizophrenia patients on LAI-risperidone for two years, experienced remission (65). According to Schreiner et al., PP1M improves the PANSS total score and prevents relapses in the early stages of schizophrenia better than oral antipsychotics (66). The most successful treatment strategy for avoiding mental hospitalizations is LAIAs, according to the findings of a 20-year follow-up research involving 8719 individuals with first-episode schizophrenia. According to the study, LAI-perphenazine, LAI-olanzapine, and LAI-flupentixol were important in reducing the need for readmissions (67). According to a Canadian study that tracked 375 individuals with first-episode schizophrenia for three years, 26.7% of them started LAIAs. There was a notable improvement in functionality at follow-up, despite the fact that the illness severity was higher and the functional levels were lower in those who began LAIAs (68).

Longer follow-up studies are necessary, although the results of trials on the use of LAIAs in patients with first-episode schizophrenia consistently demonstrate that LAIAs are superior than oral antipsychotics in preventing relapses and re-hospitalizations (69).

USE OF LONG-ACTING INJECTABLE ANTIPSYCHOTICS IN BIPOLAR DISORDER

Mood swings are a recurring, persistent feature of bipolar disorder (BD). One of the main reasons why young people get disabilities is BB. Higher hospitalization rates and worse cognitive abilities are linked to recurrent mood episodes. Cardiovascular illnesses and suicide have led to higher death rates in Bangladesh (70). Recurrent mood seizures have detrimental effects due to the nature of the illness, hence the primary objective of treatment should be to stop additional mood episodes from occurring once the acute seizure has been treated (71).

Although antipsychotics are also useful in treating and preventing acute episodes, mood stabilizing drugs are commonly used to treat and prevent mood seizures. The treatment guidelines also cover the use of antipsychotics (72, 73).

The primary cause of relapses in bipolar disorder is treatment non-compliance, which can amount to as much as 40%. Research suggests that LAIAs can be utilized to keep BD patients from relapsing during maintenance treatment (74, 75). The best therapy for reducing re-hospitalizations in BD are lithium and LAIAs, according to the

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findings of a cohort research that involved 18018 BD patients in Finland. BBs employing LAIAs have been found to have a decreased hospital stay rate when compared to the oral form of the same medication (76).

While FGAPs are useful for manic episodes in BD, they may also raise the chance that depression may worsen (77). Because of this, oral SGAPs and SG-LAIAs are prioritized when using antipsychotics to treat BD. Wu et al. examined the relapse of mood episodes and hospitalization rates of 3164 patients taking FG-LAIAs and 752 patients on LAI-risperidone. Hospitalization for mood seizures was more common among FG-LAIA users than among LAI-risperidone users. The rates of treatment discontinuation did not differ significantly between the two groups (78).

49 BD patients on mood stabilizer and one SGAP were randomly assigned to either continue taking the oral SGAP or switch to LAI-risperidone while still taking mood stabilizer in a six-month open-label pilot research. The Clinical Global Impression-Severity Scale (CGI-SS) and Young-Mania Rating Scale (YMRS) scores significantly decreased in the group that switched to LAI-risperidone when compared to the baseline. It was discovered that the Hamilton Depression Scale's overall score decreased in the group using oral SGAPs (79). According to a study by Macfadden et al., patients with a diagnosis of BD-I who get LAI-risperidone as part of their treatment experience relapses much later (80). . Once more, Macfadden et al. reported that 53.3% of patients who had more than four mood episodes in the previous year experienced remission when LAI-risperidone was added to their existing medication. Scores on the Montgomery-Asberg Depression Scale (MADRS), YMRS, and CGI-SS all showed improvement. LAI-risperidone has been shown to be useful in both BD symptom improvement and recurrence prevention (81). Manic episodes can be avoided with LAI-risperidone monotherapy, according to a research by Quiroz et al. (82). Similarly, Vieta et al.'s study shows that while LAI-risperidone is better than a placebo at preventing manic episodes, this difference is not shown in depressive episodes (83). Patients with BD were treated with LAI-risperidone or oral SGAPs, split into four groups (treatment-compliant and noncompliant), and reassessed after a year as part of a retrospective cohort research assessing the impact of treatment. It has been demonstrated that the group receiving LAI-risperidone and adhering to treatment experienced a drop in hospitalization rates and ER visits (84). According to CANMAT (Canadian Network for Mood and Anxiety Treatments) treatment guidelines, LAI-risperidone is advised as a second line agent in BD maintenance treatment. While there is enough evidence to prevent manic relapses, it is stated that there is insufficient evidence to prevent depressive relapses (81).

Studies on BD-I patients provide the data on the usage of LAI-aripiprazole in the treatment of BD. In BD-I patients, a 52-week follow-up trial that was double-blind and placebo-controlled revealed that the 400 mg group with LAIaripiprazole monohydrate experienced fewer manic relapses than the placebo group, while there was no difference in depressed relapses (83). It was proposed that there was a slight change in YMRS scores with LAI-aripiprazole monohydrate compared to placebo in a study assessing the impact of 400 mg aripiprazole monthly maintenance treatment on symptoms and functionality following a manic episode in BD-I patients, and that there was no discernible difference between the groups in terms of the total MADRS score. A notable improvement in functionality was observed in the group receiving LAI-aripiprazole medication. (83) In a study evaluating the hospitalization risks of patients diagnosed with BD-I who began taking LAIAs, it was discovered that LAI-aripiprazole monohydrate had a higher hospitalization rate than LAI-haloperidol and LAI-risperidone, and was comparable to individuals on PP1M and LAI-flufenazine (85).

There is little information on the role of SG-LAIAs other than risperidone in the treatment of BD. Treatment guidelines do not include risperidone or SG-LAIAs other than FG-LAIAs in maintenance treatment.

II. CONCLUSION

When it comes to symptom reduction, medication compliance, relapse prevention, and hospitalization rates, LAIAs are superior to oral antipsychotics in the maintenance treatment of schizophrenia. Any antipsychotic medication lowers the death rate in schizophrenia. In this regard, patients who used SG-LAIAs had the lowest mortality rate. LAIAs are a wonderful choice for both patients and clinicians since they relieve the burden of people taking one or more oral drugs daily. They also make it possible to lessen the strain on caregivers, improve patient satisfaction, and save money. The use of LAIAs in

bipolar disorder and first-episode schizophrenia, however, requires further research.

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