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Long Acting Injectable Antipsychotics in the Treatment of Schizophrenia and Bipolar Disorder

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ABSTRACT

Schizophrenia and bipolar disorder (BD) are psychiatric disorders with economic and social effects that cause disability. Treatment non-compliance is one of the major problems faced by clinicians in both schizophrenia and BD. Treatment non-compliance is associated with recurrence and impaired functionality. Treatment compliance increases with long-acting injectable antipsychotics (LAIAs) and recurrence times are prolonged, hospitalization rates decrease compared to those who use an equivalent oral form of the same drug. The use of LAIAs in the maintenance treatment of schizophrenia has also been associated with a low mortality rate, decrease in caregiver burden, and increase in patient satisfaction. Studies show that LAIAs are cost-effective compared to their oral forms. Data on the use of LAIAs in first-episode schizophrenia and BD are relatively limited. The results of studies on the use of LAIAs in patients with first-episode schizophrenia indicate that LAIAs have advantageous in preventing relapse and re-hospitalization compared to oral antipsychotics. In BD, with the use of LAIAs, the rate of hospitalization due to mood episodes and the frequency of manic episodes have been decreased. LAIAs have not been found to be as effective in preventing depressive episodes in BD as manic episodes. Although there are many studies supporting the use of LAIAs in maintenance treatment of schizophrenia and BD, more studies are needed on this issue. In this article, studies on the use of LAIAs in schizophrenia, first episode schizophrenia and BD are reviewed and the place of LAIAs in treatment was discussed.

Keywords: Bipolar disorder, first episode schizophrenia, schizophrenia, long acting injectable antipsychotics, depot antipsychotics

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HISTORY OF LONG-ACTING INJECTABLE ANTIPSYCHOTICS

The history of antipsychotics begins with the discovery of chlorpromazine in 1952. Although the use of chlorpromazine and later developed antipsychotics is an important turning point in the treatment of psychotic disorders, these disorders, especially schizophrenia, remains a major health problem for patients, caregivers and society. Time without treatment and relapses in schizophrenia are associated with a poor prognosis (1, 2). As a matter of fact, the study of Mullins et al. indicates that 90.4% of the patients discontinue oral antipsychotic treatment during the one-year treatment period (3). The use of long-acting injectable antipsychotics (LAIAs) has come to the fore in terms of preventing relapses in schizophrenia and increasing treatment compliance. It is also aimed to achieve more stable plasma levels with these drugs. One of the important causes of psychotic relapses is non-adherence to treatment.

The first LAIA was fluphenazine enanthate produced in 1966. About eighteen months later, fluphenazine decanoate was put on the market (4). The first data on the use of these drugs in schizophrenia patients came from England. Denham and Adamson reported that when switching from oral fluphenazine to fluphenazine enanthate and fluphenazine decanoate in patients with schizophrenia, the rate of admission to hospital and the duration of hospitalization decreased (5). Later, flupenthixol decanoate was developed and the results of the study conducted with it were similar (6). First generation (FG) antipsychotics (FGAPs) in the LAIAs form contributed to the evacuation of psychiatric hospitals, and the use of these forms facilitated the outpatient treatment of patients.

The widespread use of second generation (SG) antipsychotics (SGAPs) in the 2000 s has reduced the interest in FG-LAIAs (7). Occurrence of less extrapyramidal side effects and the view that clozapine and other second-generation antipsychotics are effective on cognitive deficits observed in schizophrenia have been effective in the prominence of SGAPs (8). Although treatment compliance is better in oral SGAPs compared to oral FGAPs, non-compliance with treatment has continued to be an important problem (9).

Risperidone was the first agent to produce a long acting injectable (LAI) form among SGAPs. Intramuscular forms of risperidone (25 mg, 37.5 mg and 50 mg) are licensed for use in the maintenance treatment of patients whose symptoms are controlled with oral antipsychotics (10). Subsequently, six more SG-LAIAs was approved for use: olanzapine pamoate, paliperidone palmitate 1 month (PP1M), aripiprazole monohydrate, paliperidone palmitate 3 months (PP3M) and aripiprazole lauroxyl.

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USE OF LONG ACTING INJECTABLE ANTIPSYCHOTICS IN SCHIZOPHRENIA

Schizophrenia is a significant burden on the patients and the caregivers. It is a disease that has social and economic effects (11). Relapses in schizophrenia are associated with suicide, aggressive behavior, neurotoxicity, frequent hospitalizations, and low quality of life (12). The risk of recurrence increases with discontinuation of treatment in schizophrenia. While Alvarez-Jimenez et al. stated that the risk of relapse increased 4-fold with discontinuation of treatment (13), Morken et al. reported a risk increase of 10.3 times (14). The results of the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study indicate that 74% of the patients discontinue treatment within the 18-month period (15). However, there is a great deal of consistent evidence that continuing antipsychotic treatment has a positive effect on the outcome of schizophrenia (16–18). The 20-year follow-up study of Tiihonen et al. indicates that the rates of rehospitalization and death in patients who regularly use antipsychotics are lower than those who do not continue treatment. The risk of death in schizophrenia patients who do not continue treatment was found 174% -214% higher than patients using regular antipsychotics (17). In patients with schizophrenia, not only discontinuation of treatment but also use of medications at a lower dose than the recommended dose or intermittent medication use is also very common. Weiden et al., in their study on 4325 patients, showed that intervals in the treatment process also increased the risk of relapse and related hospitalization. According to the results of this study, an interval of 1–10 days in a year increases the risk of hospitalization by 1.98 times, an interval of 11–30 days 2.86 times, and an interval of more than 30 days 3.96 times (19).

In many studies, the risk of recurrence in LAIAs have been found to be lower than oral antipsychotics. In a study that compared oral risperidone and LAI-risperidone for 2 years in 50 patients who had their first attack, treatment compliance was found to be higher and relapse rates lower in LAI-risperidone at the end of the 1st and 2nd year (20). In a cohort study conducted in Finland, it was found that hospitalization rates were lower in 1182 schizophrenia patients who continued treatment for 30 days or more after discharge compared to those using the equivalent oral form of the same drug (21). In a prospective study conducted on 29823 patients, it has been shown that clozapine and LAIAs have higher success in preventing relapses in schizophrenia, and the rate of rehospitalization is 20–30% lower in LAIAs compared to equivalent oral doses (22). In a meta-analysis consisting of 42 studies, Kishimoto et al. reported that LAIAs are superior to oral antipsychotics in reducing the number of hospitalizations per unit time, but they do not reduce the risk of hospitalization (23). The longer the half-life of the antipsychotic used in the treatment, the longer the patient's relapse time after stopping the drug. In a study comparing oral paliperidone with PP1M and PP3M; recurrence was observed on average 58 days after oral paliperidone discontinuation, on average 172 days after PP1M discontinuation, and 395 days after PP3M discontinuation (24). In this study, the researchers emphasize that LAIAs can provide significant delay in the time of relapse compared to oral equivalents when patients stop treatment. Considering that interruptions in maintenance antipsychotic treatment are unpredictable in schizophrenia, attention is drawn to the use of LAIAs in reducing the risk of relapse. Therefore, LAIAs seem to be advantageous in delaying relapses when it comes to treatment non-compliance.

In different cohort studies in schizophrenia, it has been revealed that regular antipsychotic use is associated with a lower risk of mortality and suicide (25–27). In a cohort study conducted with 29823 schizophrenia patients, the mortality rates, causes of death and antipsychotic use of the patients were examined between 2006 and 2013 (28). During a mean follow-up of 5.7 years, 2515 patients (8.4%) died. Compared to controls (N=21492), the highest overall mortality was observed in patients not using antipsychotics. The lowest mortality rate was found in patients using SG-LAIAs, followed by patients using FG-LAIAs. Mortality was reported to be 33% lower in the use of SG-LAIAs compared to the oral equivalent dose of the same drug. The lowest mortality rate was observed in PP1M users. In a study evaluating the effect of antipsychotic doses on mortality, it was found that annual regular antipsychotic use was associated with a decrease in mortality risk in patients with schizophrenia. However, it has been reported that the use of FGAPs at doses equivalent to 1500 mg/day and above chlorpromazine causes increase in mortality risk (29). The results of a large-based cohort study conducted in Sweden emphasize that schizophrenia patients have a higher mortality rate compared to the general population, this rate is higher in first-episode patients who do not receive treatment, and draw attention to the increased risk of cardiovascular-related mortality using high-dose antipsychotics (30).

The transition from oral therapy to SG-LAIAs in schizophrenia patients seems to reduce the burden of caregivers. Han et al. reported that with the transition from oral therapy to LAI-risperidone, patient compliance to treatment and patient and caregiver satisfaction increased (31). Gopal et al. showed that with the transition from oral paliperidone to PP1M and PP3M, the time spent by the caregiver on care decreased and leisure time increased (32). In addition to reducing the burden of caregivers, SG-LAIAs have also been associated with higher patient satisfaction and an increase in quality of life (33).

The effects of LAIAs on clinical symptoms, functionality and quality of life were mostly investigated through SGAPs. In a study by Pietrini et al. comparing SG-LAIAs with their oral formulations, SG-LAIAs were associated with lower PANSS scores, better scores in health-related quality of life scales, and better functionality in almost all areas of daily life (34). In a study evaluating 182 schizophrenia patients who switched from oral therapy to LAI-risperidone, significant improvements were observed after 6 months in parameters related to disease severity, patient functionality, health-related quality of life and patient satisfaction after switching to LAI-risperidone treatment (35). It is emphasized that the use of LAI-risperidone improves PANSS total and subscale scores and increases the quality of life in observational studies (36–38). The PALMFlexS (Paliperidone Palmitate Flexible Dosage in Schizophrenia) study is a prospective, multi-center, open-label, 6-month Phase IIIb interventional study in which 231 patients with schizophrenia who were not in the acute phase of the disease but were symptomatic were evaluated for transition to PP1M due to failure of previous treatment. The results of the study showed that after the transition to PP1M, two-thirds of the patients had an improvement of 30% or more in the PANSS total score (39). In addition, decrease in symptom severity, increase in subjective well-being improvement in treatment satisfaction and functionality have been reported.

Less data are available on LAI-olanzapine. In a multi-center, randomized, 2-year follow-up study in which oral and LAI-olanzapine were compared, it was emphasized that both forms of olanzapine improved their functionality according to the basal status of the patients and that no significant difference was observed between oral and LAI-olanzapine (40). The results of a multi-center study conducted with LAI-olanzapine reported that there was no significant change in PANSS total and subscale scores. But, patient satisfaction with LAI-olanzapine increased in patients who had previously used LAIAs (41).

The results of the study conducted with LAI-aripiprazole point to an improvement in clinical symptoms, an increase in health-related quality of life and functionality as in other SG-LAIAs (42). The results of a pharmaceutical industry-sponsored study report that LAI-aripiprazole provides significant improvement in health-related quality of life and better clinical outcomes especially in patients under 35 years of age according to paliperidone palmitate (43).

LAIAs are more expensive than oral equivalences. However, the decrease in hospitalization and admission to health services with the use of LAIAs significantly reduce the cost compared to oral antipsychotics (44). Wu et al. drew attention to the fact that a significant decrease in the indirect costs of schizophrenia can be achieved by decreasing the frequency of relapse, improving the patients socially and increasing in working days with using LAIAs (45). Offord et al. report that with the use of LAIAs in the treatment of schizophrenia at an earlier stage, a significant decrease has been achieved in the cost of inpatient health care (46). Achilla and McCrone shared the following results in their study evaluating the results of 28 studies on the cost of using LAIAs: LAI-risperidone is more cost-effective than oral antipsychotics and other LAIAs. However, the results of a Slovenian and an American study indicate that oral or LAI-olanzapine is more cost-effective than LAI-risperidone. PP1M is the most cost-effective treatment compared to oral SGAPs or FG-LAIAs (47). In a study conducted on the basis of Finnish national health data, PP1M treatment was found to be cost-effective in schizophrenia compared to LAI-olanzapine and LAI-risperidone treatments, with a lower hospitalization rate, fewer emergency room admissions and less relapse (48). PP3M provided advantages in both cost-effectiveness and cost-benefit analyzes, with lower relapses, fewer hospitalizations and fewer emergency room admissions compared to PP1M, LAI-haloperidol, LAI-risperidone and oral olanzapine (49). The hospitalization costs in our country are lower compared to the USA and European countries, but still, hospitalization costs are not the only thing that constitutes the cost of hospitalization, and hospitalization of a patient is never desired or preferred.

In addition to the advantages mentioned above, the use of LAIAs also has some disadvantages. Dose titration is adjusted slowly in LAIAs and plasma steady-state concentration is reached in a longer time. This disadvantage is most pronounced in the acute period, where rapid dose titration may be required (50). The use of LAIAs requires oral replacement until the plasma reaches steady-state concentration, which can make dose titration more complicated. This problem was solved with a loading dose in LAI-paliperidone palmitate (51). In addition, side effects that occur with LAIAs may be more disturbing and risky due to the long stay of the drug in the body. In addition, the inability to make flexible dose adjustment with LAIAs as often as in oral forms is another disadvantage of them.

USE OF LONG ACTING INJECTABLE ANTIPSYCHOTICS IN FIRST ATTACK SCHIZOPHRENIA

Approximately 80% of patients with first-episode schizophrenia enter symptomatic remission after antipsychotic treatment, but recurrence is observed in most patients within two years due to low insight into the disease and non-compliance with treatment (52). A five-year observational study indicates that the risk of relapse after discontinuation of treatment is approximately five times higher in patients with first-episode schizophrenia compared to continuous drug therapy (53). In a systematic review evaluating the results of 4 randomized controlled and 2 non-randomized controlled trials that addressed the effects of drug withdrawal, treatment interruption is not recommended (54). However, the results of the EUFEST (the European First Episode Schizophrenia Trial) study show that 42% of first-episode schizophrenia patients discontinue treatment within one year after the onset of the disease (55).

A study conducted by Herres et al. showed that only one out of every four schizophrenia patients who had their first episode was offered the LAIAs option by their psychiatrist, and half of those recommended agreed to use LAIAs (56). Psychiatrists attribute underprescription of LAIAs in the early stages of schizophrenia to patients' reluctance to intramuscular injections as well as a general negative attitude towards LAIAs. In a study investigating the attitudes of clinicians towards LAIAs in England, 38% of the participants stated that LAIAs cannot be used in first-episode schizophrenia (57). However, studies indicate that LAIAs are an effective and acceptable treatment option for first-episode schizophrenia patients.

In a study in which 50 first-episode schizophrenia patients were followed for two years, drug compliance and relapse rates of 22 patients using LAI-risperidone and 28 patients using oral risperidone were compared, and a lower relapse rate and higher drug compliance were observed in the group receiving LAI-risperidone treatment (20). Emsley et al. reported in their study in which they followed first-episode schizophrenia patients with LAI-risperidone for 2 years, 64% of the patients went into remission according to the criteria of the Schizophrenia Study Group (58). Schreiner et al. showed that PP1M is superior to oral antipsychotics in preventing relapses in the early stages of schizophrenia and improving PANSS total score (59). The results of a 20-year follow-up study in which 8719 first-episode schizophrenia patients showed that LAIAs are the most effective treatment method in preventing psychiatric hospitalizations. The study indicates that LAI-flupentixol, LAI-olanzapine and LAI-perphenazine were prominent in preventing re-hospitalizations (60). In a study in Canada where 375 first-episode schizophrenia patients were followed for 3 years, it was reported that 26.7% of the patients were initiated LAIAs. Although the severity of the disease was higher at the beginning and the functionality levels were lower who were started LAIAs, there was a significant improvement in functionality at follow-up (61).

The results of studies on the use of LAIAs in first-episode schizophrenia patients consistently show that LAIAs have an advantage over oral antipsychotics in preventing relapses and re-hospitalizations; however, longer follow-up studies are needed (62).

USE OF LONG-ACTING INJECTABLE ANTIPSYCHOTICS IN BIPOLAR DISORDER

Bipolar disorder (BD) is a recurrent, chronic disease characterized by mood swings. BB is one of the leading causes of disability in young people. Recurrent mood episodes are associated with poorer cognitive functions and higher hospitalization rates. Death rates have increased in BD due to suicide and cardiovascular diseases (63). Due to the nature of the disease, recurrent mood seizures lead to negative consequences and the main goal in treatment should be to prevent the emergence of new mood episodes after the acute seizure is treated (64).

Mood stabilizing agents are frequently used in the treatment and prevention of mood seizures, but antipsychotics are also effective in the treatment and prevention of acute attacks. The use of antipsychotics is also included in the treatment guidelines (65, 66).

Treatment non-compliance in bipolar disorder can reach up to 40% and this is the most important reason for relapses. Studies indicate that LAIAs can be used to prevent relapses in maintenance treatment in BD (67, 68). Results of a cohort study conducted on 18018 BD patients in Finland showed that lithium and LAIAs are the most effective treatments in preventing re-hospitalizations in BD. When the oral form of the same drug is compared with LAIAs, a lower hospital stay rate has been reported in BBs using LAIAs (69).

In BD, although FGAPs are effective on manic episodes, they can increase the risk of worsening of depression (67). For this reason, oral SGAPs and SG-LAIAs are emphasized in the use of antipsychotics in the treatment of BD. Wu et al. compared 752 patients using LAI-risperidone and 3164 patients using FG-LAIAs in terms of relapse of mood episodes and hospitalization rates. In FG-LAIAs users, the rate of hospitalization due to any mood seizures was higher than in the LAI-risperidone. There was no significant difference between the rates of discontinuation of treatment between the two groups (70).

In a six-month, open-label pilot study, 49 BD patients using mood stabilizer and one SGAP were randomized to either continuation of the current oral SGAP or switch to LAI-risperidone while continuing with mood stabilizer. In the group that switched to LAI-risperidone, it was found that there was a significant decrease in the Clinical Global Impression-Severity Scale (CGI-SS) and Young-Mania Rating Scale (YMRS) scores compared to the baseline. In the group using oral SGAPs, it was found that there was decreasing in the total score of the Hamilton Depression Scale (71). In a study by Macfadden et al., It was reported that relapses occur significantly later in patients with a diagnosis of BD– I in whom LAI-risperidone is added to their treatment (72). Again, Macfadden et al. stated that, with the addition of LAI-risperidone to the current treatment of patients with more than four mood episodes in the last year, remission was achieved in 53.3% of the patients. Improvement was observed in CGI-SS, Montgomery-Asberg Depression Scale (MADRS) and YMRS scores. LAI-risperidone has been found effective in preventing recurrence as well as improving symptoms in BD (73). The study of Quiroz et al. revealed that LAI-risperidone monotherapy is effective in preventing manic episodes (74). Similarly, the study of Vieta et al. indicates that although LAI-risperidone is superior to placebo in preventing manic episodes, this difference is not observed in depressive episodes (75). In a retrospective cohort study evaluating the effect of LAI-risperidone treatment on patients with BD, patients were treated with LAI-risperidone or oral SGAPs, divided into four groups as treatment-compliant and non-compliant, and re-evaluated at the end of one year. It has been shown that hospitalization rates and emergency room admissions decreased in the group that under the treatment of LAI-risperidone and complied with treatment (76). LAI-risperidone is recommended as a second line agent in BD maintenance treatment in CANMAT (Canadian Network for Mood and Anxiety Treatments) treatment guidelines, although there is sufficient evidence to prevent manic relapses, it is stated that there is not enough evidence to prevent depressive relapses (77).

The data on the use of LAI-aripiprazole in the treatment of BD is based on studies conducted in BD-I patients. In a double-blind, placebo-controlled 52-week follow-up study comparing LAI-aripiprazole monohydrate and placebo in BD-I patients, less manic relapse was reported in the LAI-aripiprazole monohydrate 400 mg group compared to placebo, and no difference was found in terms of depressive relapse (78). In a study evaluating the effect of 400 mg aripiprazole monthly maintenance treatment on symptoms and functionality after a manic episode in BD-I patients, it was suggested that there was a small change in YMRS scores with LAI-aripiprazole monohydrate compared to placebo and no significant difference was found between the groups in terms of the total MADRS score. In the evaluation of functionality, a significant improvement was found in the group under LAI-aripiprazole treatment. (79). In a study comparing the hospitalization risks in patients with a diagnosis of BD-I who started LAIAs, LAI-aripiprazole monohydrate was found to be superior to LAI-haloperidol and LAI-risperidone in terms of hospitalization rate, and similar to patients using LAI-flufenazine and PP1M (80).

Data on the place of SG-LAIAs other than risperidone in BD treatment is limited. SG-LAIAs other than FG-LAIAs and risperidone are not included in maintenance treatment in treatment guidelines.

CONCLUSION

In the maintenance treatment of schizophrenia, LAIAs provide an advantage over oral antipsychotics in terms of reducing symptoms, treatment compliance, preventing relapses, and decreasing the rate of hospitalization. In schizophrenia, any antipsychotic treatment reduces the mortality rate. In this respect, the lowest mortality rate was found in patients using SG-LAIAs. LAIAs eliminate the burden of patients taking one or more oral medications every day, and are a good option for patients and clinicians. They also enable a reduction in caregiver burden, increase in patient satisfaction and they are cost-effective. However, more studies are needed on the use of LAIAs in first-episode schizophrenia and bipolar disorder.

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