Long-Acting Injection for Psychotic Disorder

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Abstract

We present the case of a patient (27 years old) with a diagnosis of psychotic disorder who started a long-acting therapy after unsuccessful antipsychotic oral treatment. After the first admission, he was treated with haloperidol, but a few months later, he discontinued therapies due to extrapyramidal side effects. A new hospitalization was necessary for reacutization of his psychotic symptoms characterized by severe incongruous laughter, agitation, hostility, and delusions of persecution. In the psychiatric unit, olanzapine was started. By the second day, his psychotic presentation cleared with exception of mild residual perplexity and social isolation. By the fourth day of olanzapine treatment, patient agreed to start long-acting injectable olanzapine with the goal to eventually discontinue the oral olanzapine to provide a safeguard for nonadherence, and he was successfully discharged home.

In the presented case, we modified the dosage and the frequency of the injections on the basis of clinical picture, adapting the long-acting therapy to patient's symptomatology with a good clinical response. Given the complex nature of symptoms presentation and medication regimens, some patients may benefit from personalized treatments. The new long-acting injectable options provide additional flexibility in terms of increasing the time interval between injections.

Keywords

Long-acting injections · Antipsychotic · Depot · Psychotic disorder · Olanzapine

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14.1 Introduction

The management of patients with psychotic disorders should extend beyond acute psychotic symptoms control to include prevention of relapse, amelioration of negative and cognitive symptoms, and improvement in the patient's overall functional capacity and quality of life [1]. Maintained antipsychotic therapy is a key element in relapse prevention because of covert noncompliance to treatment [2]. Poor compliance is the most predictive factor of rehospitalization. Depot preparations of the conventional neuroleptics are recognized for the important role they play in the management of patients with psychotic disorders; they reduce the daily fluctuations in plasma drug concentrations and thus can maximize both the efficacy and tolerability of treatment [3].

This is reflected in reduced rates of relapse and rehospitalization in patients receiving depot neuroleptics compared to those treated with oral formulations [3].

Usually, the use of long-acting injections (LAIs) has been reserved for patients suspected to be poorly adherent and uncooperative or those with refractory illness. Individuals in the early stages of their disorder may be ideal candidates for treatment with an antipsychotic LAI. In psychotic disorders, the initial treatment period represents a critical window which might determine the illness trajectory [4]. These individuals are sensitive to medication side effects and often have limited insight or acceptance of their illness, which in turn contributes to the poor adherence, high-treatment discontinuation rates, and relapse rates. Also, many individuals in the early stages of the disease pathway do not accept the gravity of their illness, and there can be a false sense of treatment being unnecessary or an unwanted imposition. Additionally, many clinicians may have the preconceived view that patients are unwilling to accept injections in the early stages of their disease. This presumption of rejection could be viewed as physician prejudice, in an era when fully informed patient choice is advocated [5].

Recently, many authors have demonstrated the effectiveness and the clinical advantages of LAI even in early schizophrenia [5, 6]. Usually, medication-naïve individuals are acutely sensitive to antipsychotics in terms of responsiveness as well as of side effects, including extrapyramidal symptoms and weight gain [7]. However, it is generally thought that LAIs have a more acceptable side-effect profile in comparison with their oral counterparts due to their differences in pharmacokinetics, and any concerns over debilitating side effects may be due to dosing errors; peaks and troughs in drug concentrations can be minimized via the dose averaging of LAIs, reducing the risk of some adverse effects of these medications [8].

Heres et al. [9] found that the three main factors influencing their choice not to prescribe a LAI for subjects with a psychotic episode were: (a) limited availability of different second-generation antipsychotic depot drugs, (b) the frequent rejection of the depot offer by patients, and (c) the patient's skepticism based on an inexperience of relapse, demonstrating the importance of a patient-centered approach when discussing LAI as a treatment option. The prescription of a LAI should also involve a collaborative psychosocial approach concentrating on the individual's needs and

involving the multidisciplinary team in order to optimize outcomes. This approach would be consistent with first-episode or early intervention services [10].

14.2 Emerging Long-Acting Antipsychotics: What's New, What's Different, and What's Next?

Since the introduction of risperidone long-acting injection in 2003, three additional second-generation antipsychotics have become available in a long-acting injectable formulation: paliperidone, olanzapine, and aripiprazole. Although these different depot options can help with adherence and thus encourage better treatment outcomes, they differ in terms of specific indications, approved injection sites, needle gauge, injection volume, injection interval, requirements for oral supplementation, availability of prefilled syringes, storage needs, and postinjection observation period, as well as potential drug-drug interactions and commonly encountered adverse reactions [11].

There are several new and emerging medication interventions for both the acute and maintenance treatment phases of schizophrenia. Recently approved are two new dopamine-receptor partial agonists, brexpiprazole and cariprazine, as well as two new long-acting injectable antipsychotic formulations, aripiprazole lauroxil and 3-month paliperidone palmitate. The new long-acting injectable options provide additional flexibility in terms of increasing the time interval between injections.

Risperidone microspheres require a period of overlap of 3 weeks with oral risperidone. It has a 2-week dosing interval.

Olanzapine pamoate does not need to overlap with oral olanzapine. It has a small risk of postinjection syndrome (0.07% of injections): symptoms include sedation, confusion, agitation, anxiety, aggressiveness, dizziness, ataxia, and extrapyramidal symptoms. This risk limits olanzapine pamoate use. After injection, the patient must be monitored for 3 h by a health-care professional.

Paliperidone palmitate does not need overlap with oral paliperidone and requires two separate loading dose injections during the first week.

The 3-month paliperidone palmitate (PPM-3) formulation can only be used if the patient has been receiving 1-month paliperidone palmitate injections for at least 4 months. It is administered four times a year, providing the longest interval of any approved LAI.

Aripiprazole monohydrate requires a period of overlap of 2 weeks with oral aripiprazole. Available as a lyophilized powder which needs to be reconstituted.

Aripiprazole lauroxil requires a period of overlap of 3 weeks with oral aripiprazole, available as a prefilled syringe that does not require reconstitution. Aripiprazole lauroxil is not available in Italy.

The first aripiprazole LAI formulation, Abilify Maintena®, was approved in early 2013 at the recommended dose of 400 mg IM injection every 4 weeks. Aripiprazole lauroxil (Aristada®) is a newer LAI aripiprazole formulation, which was FDA approved in October 2015. Aripiprazole lauroxil is an *N*-acyloxymethyl prodrug that undergoes a two-step bioconversion in the plasma from the lauroxil to an

intermediate *N*-hydroxymethyl-aripiprazole via enzyme-mediated hydrolysis. The *N*-hydroxymethyl-aripiprazole then undergoes a hydrolysis reaction to aripiprazole. Aripiprazole lauroxil is available at a dose of 441 mg (deltoid or gluteal), 662 mg, and 882 mg (only gluteal) corresponding to aripiprazole LAI 300 mg, 450 mg, and 600 mg (corresponding to oral aripiprazole 10 mg/day, 15 mg/day, and 20 mg/day), respectively. While these two formulations are similar with respect to dosing/administration intervals, they are different with regard to their formulations which influence some of their pharmacokinetic parameters including $T_{1/2}$ and T_{max} [12].

Considering the prevention of relapses, the effectiveness of newer LAIs (aripiprazole, olanzapine, paliperidone, and risperidone) and older LAIs (haloperidol, fluphenazine, flupenthixol) is similar [13, 14] (Boxes 14.1 and 14.2).

Box 14.1 First-generation antipsychotics available as long-acting injectable medications

Drug	Starting dose (mg)	Maintenance dose (mg)
Haloperidol decanoate	50	50–200 every 3–4 weeks
Fluphenazine decanoate	12.5	12.5–50 every 2–3 weeks
Flupenthixol decanoate	20	50–300 every 2–4 weeks
Zuclopenthixol decanoate	100	200–500 every 1–4 weeks

Second-generation antipsychotics available as long-acting injectable medications

Drug (Brand name)	Manufacturer	Available formulations	Injection interval	Comments
Aripiprazole monohydrate (Abilify Mantenna)	Otsuka/ Lundbeck	300, 400 mg vials, prefilled syringes	400 mg once/ month	Requires a period of 2 weeks of overlap with oral aripiprazole.
Aripiprazole lauroxil (Aristada)	Alkermes	441, 662, 882 mg prefilled syringes	441–882 mg once/month 882 mg q 6 weeks	The 882 mg dose can be administered every 6 weeks. Requires a period of 3 weeks of overlap with oral aripiprazole.
Olanzapine pamoate (Zyprexa Relprew)	Lilly	210, 300, 405 mg vials	150–300 mg q2 weeks 300–405 mg once/month	Requires monitoring post injection (3 h)
Paliperidone palmitate (Invega Sustenna, Xeplion)	Janssen	39, 78, 117, 156 or 234 mg prefilled syringes	117 mg once/ month	Oral supplementation not necessary.

(continued)

Box 14.1 (continued)

Paliperidone palmitate (Invega Trinza)	Janssen	273, 410, 546, 819 mg prefilled syringes	410 mg q3 months	Use in patients already treated with Invega Sustenna
Risperidone microspheres (Risperdal Consta)	Janssen	12.5, 25, 37.5 or 50 mg vials	25 mg q2 weeks	Requires a period of 3 weeks of overlap with oral risperidone

Box 14.2 Potential advantages and disadvantages of long-acting drugs

Potential advantages	Potential disadvantages
• Early identification of nonadherence • Providing a mechanism for monitoring adherence with injections • No need to remember to take medication every day • Regular interactions between patient and medical staff • Reduced relapse frequency and rehospitalization rates • Clear attribution of the cause of relapse or non-response, discriminating between nonadherence or lack of response • Reduce the risk of accidental or deliberated overdose • Treating patients with more stable plasma concentrations than oral medications • Avoidance of first-pass metabolism—better relationship between dose and blood level of drug • Lower and less frequent peak plasma level—reduced side effects	• Slow-dose titration • Longer time to achieve steady-state levels • Less flexibility of dose adjustment • Delayed disappearance of distressing and/or severe side effects • Pain at the injection site can occur, and leakage into the subcutaneous tissue and/or the skin may cause irritation and lesions (especially for oily long-acting injectable) • Burden of frequent travel to outpatient clinics or home visits by community nurses for their administration • Risperidone long-acting injectable needs refrigeration, which may be cumbersome in some latitudes • Perception of stigma

Box 14.3 Recommended dosage scheme between oral olanzapine and olanzapine LAI

Oral dose	Starting dose	Maintenance dose
10 mg	210 mg/2 weeks; 405 mg/4 weeks	150 mg/2 weeks; 300 mg/4 weeks
15 mg	300 mg/2 weeks	210 mg/2 weeks; 405 mg/4 weeks
20 mg	300 mg/2 weeks	300 mg/2 weeks

14.3 Case Presentation

A.S., a 27-year-old Italian male (height 185.0 cm, weight 80 kg) with diagnosis of psychotic disorder not otherwise specified, was referred to our inpatient clinic for the first time in October 2015 for a psychotic episode with aggressiveness and psychomotor agitation.

No previous psychiatric history had been reported before this episode. He had a family history for unipolar major depressive disorder (maternal grandmother). He interrupted studies before college. He works in a mechanical workshop with his father. He had a normal childhood and upbringing. He was shy and reserved, but he had friends during childhood/adolescence.

Substance abuse was reported by the patient: he had used cannabis daily since he was 15 years old and sporadically since he was 17 years old; he had drunk alcohol occasionally since he was 15 years old. His medical history includes previous varicocele, appendectomy, and bacterial pneumonia. The subpsychotic symptoms appeared gradually, and the time frame was not clear. After the first admission (October 2015), he was treated with haloperidol (titrated up to 6 mg/day); after few months he discontinued therapies due to extrapyramidal side effects.

In September 2016 a new hospitalization was necessary: the patient was brought to the emergency room by his father for psychotic reacutization, exhibiting severe incongruous laughter, agitation, hostility, and delusions of persecution.

His family said that he became irritable, sleepless, and aggressive toward his ex-girlfriend, and he presented a delusional jealousy. Furthermore, in the last months, the family referred reduced social drive, loss of motivation, lack of interest, and difficulties in work activities (he missed several days of work), with a decrease in quality of life.

During hospital stay, the patient was disorganized, paranoid, and believed that he was being judged by the public. He was socially isolative with flat affect and neglecting his personal hygiene. He denied any perceptual disturbances. There was no history of mood symptoms or medical illness. The patient's physical examination, laboratory values, revealed no abnormalities. His toxicology screen was negative.

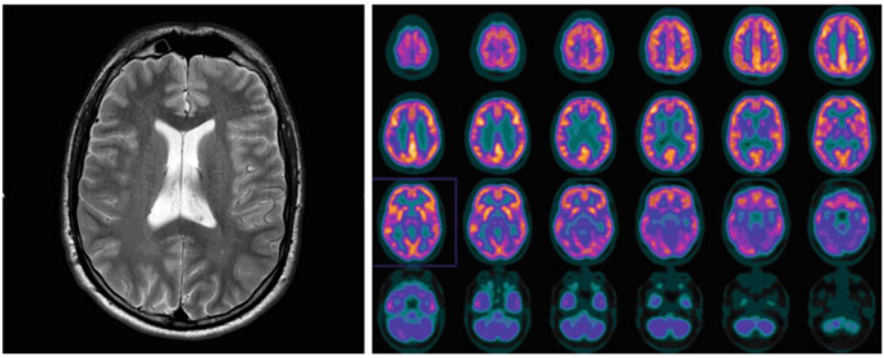

Fig. 14.1 MRI (left) and FDG-PET (right) images

Table 14.1 Neurocognitive evaluation

Test	Normal Score	Score	Comment
Language			
Verbal fluency	v.n. ≥ 31.68	40.50	Normal
Memory			
Verbal memory	v.n. ≥ 33.01	41.00	Normal
Motor proficiency			
Token task	v.n. ≥ 68.77	57.25	**Deficit**
Symbol-coding task	v.n. ≥ 40.49	35.25	**Deficit**
Frontal proficiency			
Working memory	v.n. ≥ 14.93	22.75	Normal
Tower of London	v.n. ≥ 12.37	15.00	Normal

The magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) showed no significant modification in the normal and symmetric brain metabolism (Fig. 14.1). The brief assessment of cognition in schizophrenia (BACS) was assessed, showing a deficient motor proficiency (Table 14.1). Wechsler Adult Intelligence Scale (WAIS) intelligence quotient (IQ) was 88. In the psychiatric unit, treatment with olanzapine was initiated. The patient responded well. By the second day, his psychotic presentation cleared with an exception of mild residual perplexity and social isolation. By the fourth day of olanzapine treatment, A.S. agreed to start long-acting injectable olanzapine with the goal of eventually discontinuing the oral olanzapine to provide a safeguard for nonadherence, and he was successfully discharged home with a diagnosis of schizoaffective disorder.

Subsequently, olanzapine LAI, 300 mg intramuscularly (IM), was administered into the gluteal muscle every 2 weeks in day hospital. At every injection olanzapine plasma levels (PL) were determined (Fig. 14.2). Some weeks after initiating olanzapine LAI, a marked improvement in psychiatric symptoms was noted.

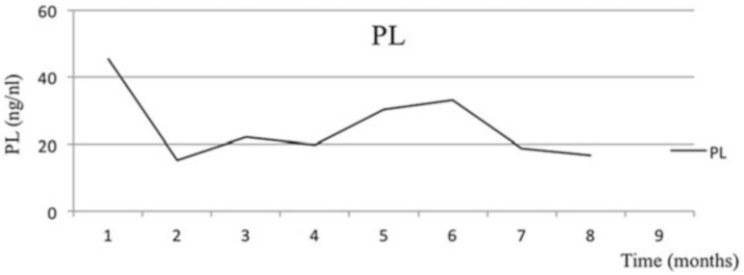

Fig. 14.2 Patient's olanzapine plasma levels during olanzapine LAI treatment

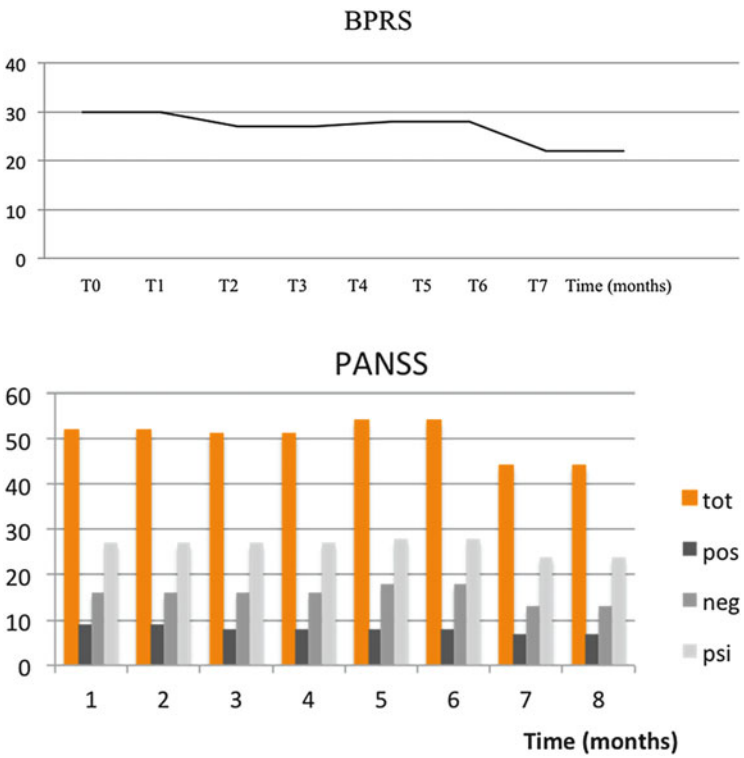

Fig. 14.3 BPRS and PANSS total score (mean values ± SD) time course

Between September and March 2017, A.S. showed a good adherence and clinical stabilization as demonstrated by clinical rating scales BPRS (the Brief Psychiatric Rating Scale) and PANSS (Positive and Negative Syndrome Scale) (Fig. 14.3). A.S. revealed perception disturbance during his stay in the inpatient unit.

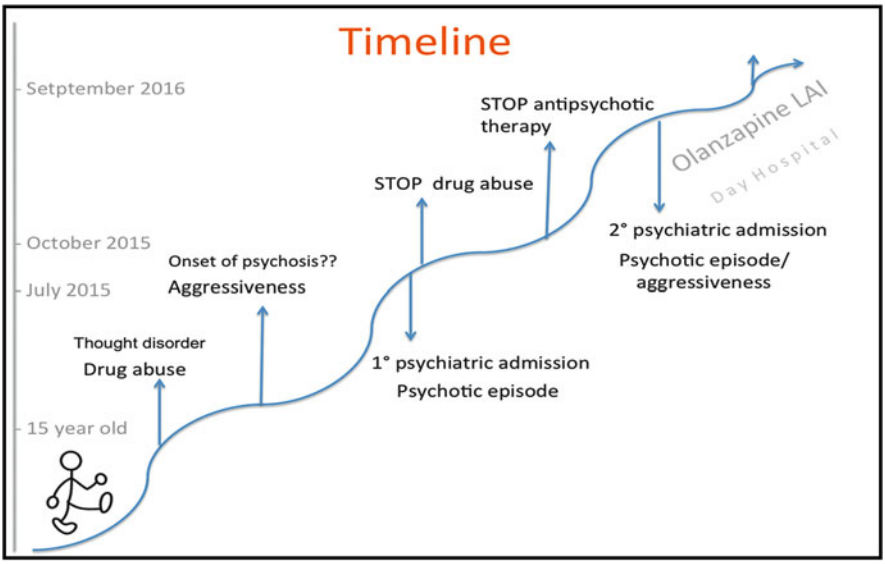

Fig. 14.4 Timeline of course of illness

In April 2017 at follow-up appointment, A.S. presented acute worsening of apathy, social isolation, loss of interest in activities, and hypersomnia. The plan was to reduce the olanzapine LAI frequency from 300 mg IM every 2 weeks to 405 mg every 4 weeks.

In June 2017, since patient complained of worsening irritability and suspiciousness, approximately 5 days prior to his next injection, his current regimen (olanzapine LAI 405 mg every 4 weeks) was modified (olanzapine LAI 405 mg every 3 weeks) for this wearing off of symptoms. These pharmacological changes resulted in a good stabilization of clinical symptomatology (Fig. 14.4). As of July 2017, he continues to tolerate the olanzapine LAI and reports not needing to use oral additional therapies.

14.4 Literature Review

We presented a clinical case of a young patient with a diagnosis of psychotic disorder who started a long-acting therapy after unsuccessful antipsychotic oral treatment.

The guidelines for depot antipsychotic treatment that were developed by a European neuropsychopharmacology consensus conference recommend that: "any patient for whom long-term antipsychotic treatment is indicated should be considered for depot drugs" [15].

Many physicians are still reluctant to use long-acting antipsychotics initially. According to literature, there are several studies in support of depot antipsychotic

use as first-line treatment for patients with schizophrenia, which may improve adherence and thereby lower risk of relapse, suicide, and rehospitalization [16].

In the presented case, we modified the dosage and the frequency of the injections on the basis of the clinical picture, adapting the long-acting therapy to patient's symptomatology with a good clinical response. Given the complex nature of symptoms presentation and medication regimens, some patients may benefit from personalized treatments.

The dosing strategies for LAI antipsychotics include relatively standardized conversions from oral formulations to recommended administration intervals. The injection intervals for LAIs depend on the specific agent and are based on extensive pharmacokinetic studies of patients. Although not extensively reported in the literature, there are clinical reports of some patients requiring shorter dosing intervals or higher than approved doses of LAI antipsychotics with unclear reasons [12].

Regarding olanzapine LAI, there is a broad range in time between injections. Most patients continue to receive the same initial dose instead of switching to a maintenance dose. This may suggest that some clinicians are not reassessing the dose after the initial starting dose because the patient was stabilized on olanzapine oral before beginning olanzapine LAI [17]. Mauri et al. [18] demonstrated efficacy of olanzapine LAI in maintenance treatment of schizophrenia also at lower dosage. The recommended initial and maintenance doses equivalent to those for oral olanzapine are given in Boxes 14.3 and 14.4.

Our case report suggests further investigations of dosing and frequency strategies during a long-acting treatment.

Furthermore, there are multiple studies showing the efficacy of oral atypical antipsychotics in the treatment of bipolar I disorder (BP-I); however, literature data on the use of LAIs in BP-I are lacking. Adherence remains a significant challenge in the treatment of patients with BP-I. Available data on atypical LAI antipsychotics in BP-I are largely derived from controlled studies of risperidone LAI; thus, additional studies on the potential benefits of LAIs in bipolar disorder are needed, including comparisons with oral formulations. Recently aripiprazole LAI has demonstrated efficacy as maintenance treatment for BP-I by reducing the risk of recurrence of mood episodes [19].

Box 14.4 *Olanzapine pamoate:* recommendations

Patients should remain under the supervision of properly qualified staff at a health-care center for at least 3 h after each injection so that signs and symptoms of an olanzapine overdose may be detected.

Before olanzapine-LA therapy is initiated, patients should first be treated with oral olanzapine to determine its tolerability and their response.

There is no need to supplement with oral olanzapine.

Olanzapine-LA should not be used in patients who are elderly or have renal insufficiency unless an effective and well-tolerated dosing regimen for oral

(continued)

Box 14.4 (continued)
olanzapine has been established. For these patients, a lower initial dose (150 mg every 4 weeks) should be considered.

A dosage reduction should be considered when more than one factor is present that could trigger a slowing of the metabolism (female sex, geriatric age, no tobacco habit). Increasing the dosage, if indicated, should be done with caution in these patients.

Because the pamoate salt of olanzapine dissolves slowly to facilitate its steady slow release, which is not complete until approximately 6–8 months after the last injection, a doctor's supervision is required when switching to another antipsychotic drug considered medically appropriate—especially during the first 2 months after interrupting the olanzapine-LA therapy.

Key Points

- Depot neuroleptics were seen to reduce relapse rate and rehospitalization in comparison to oral formulations.
- Long-acting injections (LAIs) had been reserved for patients suspected to be poorly adherent and uncooperative or those with refractory illness: actually, individuals in the early stages of their disease may be ideal candidates for treatment with an antipsychotic LAI.
- The new long-acting injectable options provide additional flexibility in terms of increasing the time interval between injections.
- The effectiveness of newer LAIs, aripiprazole, olanzapine, paliperidone, and risperidone, and older LAIs haloperidol, fluphenazine, flupenthixol, is similar.

Self-Assessment Questionnaire

1. Who should receive LAIs?
   (A) **Consider LAIs for patients with recent-onset schizophrenia and those with risk factors for medication nonadherence**
   (B) Patients with poor insight
   (C) Patients with severe symptoms
   (D) Only patients with chronic schizophrenia
2. Are the newer LAIs more effective than the older LAIs in terms of prevention of relapses?
   (A) **The effectiveness of newer LAIs (aripiprazole, olanzapine, paliperidone, and risperidone) and older LAIs (haloperidol, fluphenazine, flupenthixol) is similar.**
   (B) The newer LAIs are more effective
   (C) The older LAIs are more effective
   (D) Aripiprazole LAI is less effective

3. Which of the following statements is true?
   (A) **Any patient for whom long-term antipsychotic treatment is indicated should be considered for depot drugs**
   (B) The presence of hallucinations is necessary for receiving long-acting therapy
   (C) Risperidone long acting has a small risk of postinjection sedation syndrome
   (D) Olanzapine long acting must overlap with oral supplementation
4. The factors influencing the choice not to prescribe a LAI for first-episode psychosis were:
   (A) **Limited availability of different second-generation long-acting antipsychotics**
   (B) Rejection of the depot by patient's family
   (C) The inexperience of the clinicians with long-acting treatment
   (D) The necessity to receive depot by a health-care professional in a community setting
5. Which of the following antipsychotic medications does not come in a long-acting injectable formulation?
   (A) Risperidone
   (B) Olanzapine
   (C) Haloperidol
   (D) **Quetiapine**

References

1. Buoli M, Caldiroli A, Panza G, Altamura AC. Prominent clinical dimension, duration of illness and treatment response in schizophrenia: a naturalistic study. Psychiatry Investig. 2012;9(4):354–60. https://doi.org/10.4306/pi.2012.9.4.354.
2. Buoli M, Kahn RS, Serati M, Altamura AC, Cahn W. Haloperidol versus second-generation antipsychotics in the long-term treatment of schizophrenia. Hum Psychopharmacol. 2016;31(4):325–31. https://doi.org/10.1002/hup.2542.
3. Altamura AC, Colacurcio F, Mauri MC, Moro AR, De Novellis F. Haloperidol decanoate in chronic schizophrenia: a study of 12 months with plasma levels. Prog Neuro-Psychopharmacol Biol Psychiatry. 1990;14(1):25–35.
4. Altamura AC, Serati M, Buoli M. Is duration of illness really influencing outcome in major psychoses? Nord J Psychiatry. 2015;69(6):403–17. https://doi.org/10.3109/08039488.2014.990919.
5. Taylor M, Ng KY. Should long-acting (depot) antipsychotics be used in early schizophrenia? A systematic review. Aust N Z J Psychiatry. 2013;47(7):624–30.
6. Correll CU, Citrome L, Haddad PM, Lauriello J, Olfson M, Calloway SM, Kane JM. The use of long acting injectable antipsychotics in schizophrenia: evaluating the evidence. J Clin Psychiatry. 2016;77(Suppl 3):1–24.
7. Strassnig M, Miewald J, Keshavan M. Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: one-year analysis. Schizophr Res. 2007;93:90–8.
8. Taylor D. Psychopharmacology and adverse effects of antipsychotic long-acting injections: a review. Br J Psychiatry. 2009;195(Suppl 52):S13–9.
9. Heres S, Reichhart T, Hamann J. Psychiatrists' attitude to antipsychotic depot treatment in patients with first-episode schizophrenia. Eur Psychiatry. 2011;26:297–301.
10. Weiden PJ, Buckley PF, Grody M. Understanding and treating 'first-episode' schizophrenia. Psychiatr Clin North Am. 2007;30:481–510.

11. Citrome L. New second-generation long-acting injectable antipsychotics for the treatment of schizophrenia. Expert Rev Neurother. 2013;13(7):767–83. https://doi.org/10.1586/14737175.2013.811984.
12. Eum S, Schneiderhan ME, Brown JT, Lee AM, Bishop JR. Pharmacogenetic evaluation to assess breakthrough psychosis with aripiprazole long-acting injection: a case report. BMC Psychiatry. 2017;17(1):238.
13. Castillo EG, Stroup TS. Effectiveness of long-acting injectable antipsychotics: a clinical perspective. Evid Based Ment Health. 2015 May;18(2):36–9. https://doi.org/10.1136/eb-2015-102086.
14. McEvoy JP, Byerly M, Hamer RM, et al. Effectiveness of paliperidone palmitate vs. haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. JAMA. 2014;311:1978–87.
15. Kane JM, Aguglia E, Altamura AC, Ayuso Gutierrez JL, Brunello N, Fleischhacker WW, Gaebel W, Gerlach J, Guelfi JD, Kissling W, Lapierre YD, Lindström E, Mendlewicz J, Racagni G, Carulla LS, Schooler NR. Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. Eur Neuropsychopharmacol. 1998;8(1):55–66.
16. Khan AY, Salaria S, Ovais M, Ide GD. Depot antipsychotics: where do we stand? Ann Clin Psychiatry. 2016;28(4):289–98.
17. Case MG, Karagianis JL, Schuh KJ, Hoffmann VP. Real-world use patterns of olanzapine long-acting injection in the United States: comparison to the recommended dosing strategy. Curr Med Res Opin. 2013;29(11):1533–7.
18. Mauri MC, Maffini M, Di Pace C, Reggiori A, Paletta S, Moliterno D, Rovera C, Altamura AC. "Long-acting" olanzapine in maintenance therapy of schizophrenia: a study with plasma levels. Int J Psychiatry Clin Pract. 2015;19:99–105.
19. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, Johnson B, Perry P, Hertel P, Such P, Salzman PM, McQuade RD, Nyilas M, Carson WH. Efficacy and safety of Aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. J Clin Psychiatry. 2017;78(3):324–31.