Continuing Education

Schizophrenia and Long-Acting Injectibles

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Universal Activity #: 0178-0000-16-104-H01-P | 1.25 contact hours (.125 CEUs)

Initial Release Date: July 20, 2016 | Expires: April 20, 2019

EDUCATIONAL OBJECTIVES

Describe schizophrenia and its prevalence in the US.
List symptoms of schizophrenia.
Discuss treatment options for schizophrenia.
Compare oral antipsychotics to long-acting injectable antipsychotics.

INTRODUCTION

Schizophrenia is a complex and challenging psychiatric disorder that is characterized by disorganized and bizarre thoughts, delusions, hallucinations, and inappropriate affects that lead to impaired psychosocial functioning.[1] The lifetime prevalence of schizophrenia ranges from 2% to 3%, with equal frequency between males and females. Schizophrenia onset typically occurs during late adolescence or early adulthood with male onset being in the early to late twenties and female onset typically in the early thirties.[1]

Schizophrenia is one of the leading causes of disability with about 3.2 million people in the United States diagnosed with schizophrenia in 2014.[2] This mental disability usually requires multiple hospital admissions and social assistance.[3] Treatment and other direct and indirect economic costs due to schizophrenia are estimated to be approximately $65 billion annually.[4] Direct costs include, but are not limited to: hospitalization, rehabilitation, professional services, medication and office visits; while indirect costs are the result of reduction in income due to loss of productivity, disability, premature death, and economic burden to families.[3]

Due to modern scientific advances knowledge about this mental illness has evolved tremendously; however, there is no single theory that can fully explain the etiology of schizophrenia.[1] Various abnormalities in brain structure and function have been demonstrated in research; however, this finding is not consistent among individuals with schizophrenia.[1]

The neurodevelopmental model has suggested that schizophrenia originates from utero disturbances occurring during the second trimester of pregnancy.[3] There is evidence of similarities between abnormal neuronal migration observed in schizophrenia brains and cell migration abnormality during the second trimester of pregnancy. Other maternal stresses during pregnancy have shown a small correlation with schizophrenia development. In addition, upper respiratory tract infections developed during the second trimester of pregnancy is another risk factor for developing schizophrenia. Malnutrition and substance abuse may also lead to schizophrenia by increasing maternal levels of cortisol. Low birth weight, defined as less than 2.5 kg or 5.5 lbs, obstetrical complications, and neonatal hypoxia are also associated with schizophrenia.[1]

Schizophrenic brains have shown decreased cortical thickness and increased ventricular size. In order to explain this phenomenon, it is hypothesized that genetic predisposition, in combination with obstetrical complications, could activate a glutamatergic cascade which in turn results in increased neuronal pruning. Neuronal pruning is a part of normal neurodevelopmental process; however, it is demonstrated that there is a higher percentage of neuronal pruning in the brains of individuals with schizophrenia.[1]

All of the above hypotheses indicate that brain functions and structural abnormalities occur long before the onset of schizophrenia symptoms; which often manifest during late adolescence; therefore, schizophrenia can be a neurodevelopmental disorder. Since this mental illness also manifests as progressive clinical deterioration, it suggests that schizophrenia may also be a neurodegenerative disorder.[5]

Schizophrenia involves alterations of two neurotransmitters in the central nervous system: dopamine and serotonin. There are five dopamine receptors: $D_1 - D_5$, with D_2 being the predominant dopamine receptor responsible for the pathophysiology of schizophrenia.[3] Antipsychotics, whose mechanism of action is to inhibit central nervous system dopamine, decrease the positive symptoms of schizophrenia; however, excessive amounts of dopamine in the central nervous system is not the sole and only cause of schizophrenic symptoms. Apart from positive symptoms, there

are cases of schizophrenia in which residual or negative symptoms are dominant. Table 1 summarizes the positive and negative symptoms associated with schizophrenia. The "hypofrontality theory" states that reduced or dysfunctional dopaminergic neurotransmission within the prefrontal cortex or mesocortical area of schizophrenic brains might be responsible for schizophrenic negative symptoms.[3] Chronically low levels of dopamine ultimately lead to upregulation of dopamine receptors, which in turn, causes supersensitivity of dopamine release when an individual is exposed to environmental stressors. This theory explains why antipsychotics primarily improve positive symptoms, and have minimal effects on negative symptoms.[3]

Serotonin indirectly plays a role in schizophrenia pathophysiology. Agonism of serotonin receptors results in an inhibitory effect on central nervous system dopamine release which is the cause of schizophrenic negative symptoms. Another potential etiology is utero exposure to excitotoxins or viruses, which results in damage of N-methyl-D-aspartic acid (NMDA). The clinical effect of NMDA damage is primarily seen later in adolescence or early adulthood, which is when schizophrenia symptoms usually surface.[3]

DIAGNOSIS OF SCHIZOPHRENIA

In order to have a diagnosis, schizophrenic symptoms must be present for six months, with at least one month of active symptoms, using the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V).[6] Characteristic symptoms of schizophrenia are delusions, hallucinations, grossly disorganized speech and behavior, and all of these symptoms result in social and occupational disability. DSM-IV was the previous diagnostic tool, and one of the main differences between DSM-V and DSM-IV is that DSM-V raises the diagnostic threshold from one to two specified symptoms: delusions, hallucinations, disorganized speech, catatonic behavior, and negative symptoms.[7] Also, DSM-V eliminates the subtype identification since it is not helpful to clinicians since patients often change from one subtype to another. One of the diagnostic criteria for schizophrenia is a significant decrease in social/occupational function, such as work or psychosocial functions, compared to the pre-onset level.[1,6,7] Other rating scales besides the DSM-V are available to monitor clinical status in schizophrenia, which include the Abnormal Involuntary Movement Scale for monitoring tardive dyskinesia, and the Brief Psychiatric Rating Scales (BPRS) and Positive and Negative Syndrome Scale (PANSS) for monitoring psychopathology.[8] These rating scales are important to record patient response to treatment and to allow the patient to be educated about their illness and learn how to observe themselves better. After assessing the patient's diagnosis, an appropriate treatment plan must be communicated and implemented.[8]

Table 1. Schizophrenia Symptom Clusters[3]

Schizophrenia Symptom Clusters		
Positive	**Negative**	**Cognitive**
• Suspiciousness • Unusual thought content (delusions) • Hallucinations • Conceptual disorganization	• Affective flattening • Alogia: difficulty of speech • Anhedonia: inability to feel pleasure • Avolition: lack of goal-directed behavior	• Impaired attention • Impaired working memory • Impaired executive function: (i.e. time management, ability to focus and pay attention, remembering details)

TREATMENT

Treatment of schizophrenia is still a challenge for clinicians despite advancing pharmacotherapy, diagnostic tools, and rehabilitation. Pharmacotherapy has been shown to strengthen psychosocial rehabilitation programs.[1] Antipsychotic therapy is the mainstay in the treatment of schizophrenia. When assessing symptoms, diagnosis and developing a plan of treatment, it is important to realize that diagnosis is a process.[8] The patient should be reevaluated continuously and if needed, treatment should be changed based on evaluation. It is also important to note that a diagnosis of schizophrenia alone does not guide treatment. Treatment depends on manifestations of symptoms along with other resulting conditions, such as depression, suicide, homelessness, substance abuse, etc.[8]

Laboratory work-up is important prior to initiation of therapy, not only because it can exclude other pathologies, but also serve as baseline monitoring parameters.[1] It should include vital signs, complete blood count, electrolytes, hepatic function, renal function, electrocardiogram, fasting plasma glucose, plasma lipids, thyroid function, and urine drug screening.

To be successful in appropriately treating a patient suffering from schizophrenia, the plan should be based on accurate diagnostic and clinical assessments and must consider all key issues that arise in managing this illness.[8] This process should begin with establishing a supportive therapeutic alliance between the psychiatrist and the patient. This allows the patient to build trust and rapport in the psychiatrist and in return, the psychiatrist will gain the essential information needed to better treat the patient. It is recommended that the same psychiatrist be used throughout the treatment process in order to maintain and strengthen this relationship, which is vital for positive results. Relating the treatment outcomes to the patient's goal promotes that therapeutic alliance as well as treatment adherence. Although patients have a designated psychiatrist, which is the main influence throughout the treatment process, most patients with schizophrenia require a variety of treatments that involve multiple clinicians. It is vital that these clinicians develop a treatment team and meet periodically to review the patient's progress and identify any obstacles that may arise.[8]

All too often patients with schizophrenia discontinue their medications, miss appointments, or fail to disclose important information, which decreases the chance of a successful response to treatment.[8] It is essential to address contributing factors to nonadherence, which is based on the patient's belief about the actual need for treatment or barriers to treatment, such as medication adverse reactions. Another component that is essential to a successful outcome is an adequate support system, including family and friends. It is critical for the clinician to identify practical barriers to adherence and implement strategies to overcome these barriers for the patient. The use of a pillbox to assist with medication adherence may be another option for some patients. Family members or significant others may be involved in assisting with filling and monitoring pillbox use. Medications with longer half-lives or long-acting injectable medications may also be an option for forgetful patients to improve adherence. Patients having difficulty paying for their medications should be aided in applying for patient assistance programs, which are available through some pharmaceutical companies. Other patients may not have transportation, which can interrupt their ability to keep medical appointments. Patients with children may lack childcare options which may be another barrier to attending appointments.[8]

If nonadherence becomes a frequent and serious matter, assertive outreach may be appropriate, such as telephone calls and home visits to reengage the patient in treatment.[8] Many states now offer programs available for mandatory outpatient treatment for those patients that pose a threat to themselves or others due to medication nonadherence. Such programs in Alabama can be found in the Mental Illness Provider Directory from the Alabama Department of Mental Health. Another important area to remember is many patients with schizophrenia are likely to have other medical conditions that should be addressed when managing this illness. Some common comorbid conditions are major depressive disorder, substance abuse, post-traumatic stress disorder, diabetes, or cardiovascular diseases. If

these conditions are not treated appropriately, it can increase the mortality rate in these patients.[8]

Another key factor in the patient's treatment success lies in their social circumstances. It has been shown that a patient's social environment extensively correlates with adherence. Examples would include the patient's living situation, their family involvement or relationships, and the patient's income.[8]

NON-PHARMACOLOGIC THERAPY

Comprehensive care, which is the coordination of services across psychiatric, addiction, medical, social, and rehabilitative services, is essential for a successful therapy.[9] Psychosocial rehabilitation programs target basic living skills, education, cognitive therapy, and also financial support. Decreased hospitalization rates have been seen in programs that involve the patient's family. For very low functioning patients, assertive community treatment (ACT) is recommended. ACT is a 24-hour basis program that provides comprehensive care as mentioned above. ACT is designed to assist patients who have been transferred out of an inpatient setting, but would benefit from the similar levels of care. ACT teams consist of mental health professionals, nurses, social workers, employment specialists, and substance abuse counselors. Access to this program is available through social work personnel.[9]

PHARMACOLOGICAL THERAPY

An appropriate treatment plan includes three goals: (1) reduce or eliminate symptoms, (2) maximize quality of life and adaptive functioning, and (3) enable recovery by assisting patients in attaining personal life goals.[3,8] The course of treatment is divided into three phases: the acute phase, the stabilization phase, and the stable phase. The acute phase focuses on new onset or acute exacerbation of symptoms and treats until these symptoms are reduced back to the patient's baseline level and continues into the stabilization phase. These two treatment phases combined usually last around 6 months. The stable phase is an extended treatment and rehabilitation plan where the patient's symptoms are controlled and emphasis is placed on recovery and improving function.[3,8]

Antipsychotics are classified into two groups: first-generation (typical) antipsychotics and second-generation (atypical) antipsychotics. Table 2 below shows the two different classes of antipsychotics and their dose ranges.[3,8] The first-generation antipsychotics are the older agents and work by blocking dopamine receptors centrally. These agents are known to cause neurologic side effects, predominantly extrapyramidal symptoms (EPS) and tardive dyskinesia, and other common adverse effects such as sedation, anticholinergic and cardiovascular effects. Second-generation antipsychotics are newer agents that work by blocking dopamine and serotonin receptors centrally. These agents are more favorable due to the absence or decreased incidence of EPS and tardive dyskinesia and lack of effect on serum prolactin levels. Second-generation antipsychotics are generally more effective against refractory schizophrenia and have a greater activity against negative symptoms. Even though all antipsychotic agents have been shown to be equally effective, second generation antipsychotics are preferred treatments due to their improved side effect profile. Table 3 demonstrates the side effect profile for each antipsychotic agent.[3,8]

Table 2. Commonly Used Antipsychotic Medications[1,10]

First-Generation Antipsychotic Medication	Initial Dose	Usual Dose Range
Chlorpromazine (Thorazine)	50mg po daily to TID	300 to 1000mg/day
Fluphenazine (Prolixin)	5mg po daily	5 to 20mg/day
Mesoridazine (Serentil)	50mg po TID	100 to 400mg/day
Perphenazine (Trilafon)	4 to 8mg po TID	4 to 8mg po TID

First-Generation Antipsychotic Medication (cont)	Initial Dose	Usual Dose Range
Thioridazine (Mellaril)	50 to100mg po TID	300 to 800mg/day
Trifluoperazine (Stelazine)	2 to 5mg BID	15 to 50mg/day
Haloperidol (Haldol)	0.5 to 5mg BID-TID	50 to 20mg/day
Loxapine (Loxitane)	10mg po BID	60 to 100mg/day
Thiothixene (Navane)	2mg po TID	15 to 30mg/day
Second-Generation Antipsychotic Medication	**Initial Dose**	**Usual Dose Range**
Aripiprazole (Abilify)	10 to 15mg po daily	30mg/day
Clozapine (Clozaril)	12.5mg po daily to BID	300 to 450mg/day
Olanzapine (Zyprexa)	5 to 10mg po daily	10 to 20mg/day
Quetiapine (Seroquel)	25mg po BID	150 to 750mg/day
Risperidone (Risperdal)	1 to 2mg po daily	4 to 8mg/day
Ziprasidone (Geodon)	20mg po BID	40 to 100mg BID

Table 3. Antipsychotics and Their Most-Associated Adverse Events[8]

Adverse Event	Drugs
EPS/Tardive dyskinesia	• Thioridazine • Perphanzaine • Haloperidol • Risperidone
Weight Gain/ Glucose Abnormalitites	• Clozapine • Risperidone • Olanzapine • Quietapine
Prolactin Elevation	• Thioridazine • Perphanzaine • Haloperidol • Risperidone
Anticholinergic Effects	• Thioridazine • Clozapine • Olanzapine
QTc Prolongation	• Thioridazine • Ziprasidone
Sedation	• Thioridazine • Perphanzaine • Haloperidol • Quietapine
Hypotension	• Thioridazine • Clozapine • Quietapine

American Psychiatric Association. Practice Guideline for the Treatment of Patients with Schizophrenia, 2nd ed.

When selecting an antipsychotic agent, therapy should be individualized to the patient at hand. The decision should be based on past experience, efficacy and side effects, available dosage forms, adherence history, other medical An antipsychotic should be administered as soon as possible due to the fact that prolonged psychotic episodes without treatment are often accompanied by a worsened course of illness. Dosage forms play a critical role in the acute phase of treatment. Antipsychotics available in oral disintegrating tablets (ODT) or short-acting injectables may be considered depending on how willing the patient is to take the medication. Risperidone, olanzapine, and aripiprazole are available as ODT. Short-acting injectables include options such as haloperidol, olanzapine, ziprasidone and aripiprazole.[3]

Second-generation antipsychotics are the first-line treatment for acute phase comorbidities, and cost considerations.[3] During the acute phase, patients suffer from positive and negative symptoms and the initial treatment is designed to calm agitated patients who could physically harm themselves or others. schizophrenia due to decreased risk of extrapyramidal symptoms and tardive dyskinesia.[8] Clozapine should be used if the patient experiences persistent suicidal ideation, hostility or aggression, or tardive dyskinesia. If a patient struggles with adherence, long-acting injectables should be considered. Table 4 below demonstrates how to choose an antipsychotic agent in the acute phase of schizophrenia.[8] It is important to note that an initial response to antipsychotic therapy will take up to 2 to 4 weeks and clinicians should wait to dose adjust until the patient has reached an adequate time period to see a clinical response. A full response may take up to 6 months or longer .[8]

Table 4. First-Choice Options for Acute Phase of Schizophrenia[8]

Patient Profile	Drug Choice Options
First Episode	Risperidone Olanzapine Quetiapine Ziprasidone Aripiprazole
Persistent suicidal ideation or behavior	Clozapine
Persistent hostility and aggressive behavior	Clozapine
Tardive dyskinesia	Risperidone Olanzapine Quetiapine Ziprasidone Aripiprazole Clozapine
History of sensitivity to extrapyramidal side effects	Low-dose Risperidone Olanzapine Quetiapine Ziprasidone Aripiprazole
History of sensitivity to prolactin elevation	Olanzapine Quetiapine Ziprasidone Aripiprazole
History of sensitivity to weight gain, hyperglycemia, or hyperlipidemia	Ziprasidone Aripiprazole
Repeated nonadherence to pharmacological treatment	Long-acting injectable antipsychotics

During the stabilization phase, guidelines recommend that patients should continue the same therapy they have received benefit from during the acute phase and continued for at least 6 months.[3,8] It is important to note that during the stabilization phase, patients are most vulnerable to relapse. If antipsychotic symptoms continue, some patients and clinicians may wrongly determine that the antipsychotic medication quit working; however, it is crucial to know that antipsychotic medications are shown to provide gradual improvement and the current regimen should be continued.[3,8]

All schizophrenic patients should continue treatment through the stable phase for at least one year.[3,8] Without medication, 60%-70% of schizophrenic patients relapse within one year, and 90% of patients will relapse within two years.[8] Discontinuation of antipsychotic medication can be considered if the patient has only a single episode with predominantly positive symptoms and is symptom free for 1 year after an acute episode. Some patients will not be candidates to discontinue treatment until 5 years or longer if they have a history of multiple episodes. If a patient presents a risk to themselves or others when unmedicated, lifelong treatment will be necessary.[3,8]

Use of adjunctive medications in schizophrenia is usually added to treat comorbid conditions or antipsychotic side effects. Common antidepressants used for depressive symptoms are selective-serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Benzodiazepines can be used to help manage anxiety and agitation with lorazepam being the recommended choice. Drugs that can be used to treat EPS are benztropine mesylate, trihexyphenidyl hydrochloride, amantadine, propranolol, lorazepam or diphenhydramine.[8]

LONG-ACTING INJECTABLE ANTIPSYCHOTICS

Long-acting injectable antipsychotics have been developed to help improve medication adherence and quality of life in patients with schizophrenia. It is estimated that 42% of schizophrenic patients taking oral antipsychotics are not adherent to their medication regimen.[11] With non-adherence, psychosis symptoms, such as delusions and hallucinations, can re-emerge.[12] Long-acting injectable antipsychotics are depot formulations, and are designed to release the antipsychotic drug slowly over time. This slow-release design was formulated so that levels of the drug would remain in the body for an extended period of time, and patients would only need to receive injections every two to four weeks; however, the question still remains if long-acting injectable antipsychotics actually do improve adherence and sustain efficacy in schizophrenia patients.[12]

ORAL VS. LONG-ACTING INJECTABLE ANTIPSYCHOTICS: ADHERENCE

When compared to oral antipsychotics, it is unclear if long-acting injectable antipsychotics improve adherence and relapse.[13] Even though long-acting injectable antipsychotics decrease the number of times a patient has to take their medication, adherence issues can still be found. Patients may just as easily choose to skip their injections as they would a tablet.[13] A systematic review and meta-analysis by *Leucht, et. al.* looked at several different studies, which compared various long-acting injectable formulations with oral antipsychotic medications.[11] For adherence comparisons, 1,141 patients in five different randomized controlled trials reported some adherence information. The total results found non-adherence with 7.8% of patients using long-acting injectables and 9.6% of patients using oral antipsychotics; however, there was no significant difference found between the two groups. It is important to note that adherence was not measured thoroughly in most studies. Because most of the studies included in this meta-analysis were designed as double-blind, double-dummy studies, they theorized the majority of patients included were relatively adherent anyhow. Therefore, patients that would need long acting injectables due to adherence problems may not have been included in the trials.[11,13]

ORAL VS. LONG-ACTING INJECTABLE ANTIPSYCHOTICS: EFFECTIVENESS

The overall effectiveness of long-acting injectables compared to oral antipsychotics is also controversial. In the same meta-analysis by

Leucht, et al., 1,672 total patients, who participated in ten randomized controlled trials assessing relapse rates in patients, were analyzed.[11] In this meta-analysis, patients taking long-acting injectables had significantly fewer relapse events (21.6%) when compared to the oral antipsychotic group (33.3%).[11]

For rehospitalization rates, 1,476 patients in seven studies reported their results in the *Leucht, et. al.* meta-analysis. The results showed no significant difference between the long-acting injectable group (13.7%) and oral antipsychotic group (18.6%). [RR 0.78; 95% CI, 0.57 to 1.05][11] Another trial compared the total psychiatric hospitalization rates of patients taking oral aripiprazole with long-acting injectable aripiprazole.[14] This trial looked at 121 patients over a three-month period. After three months of oral aripiprazole, 28.1% of patients had been re-hospitalized, compared with 6.6% of re-hospitalizations in the long-acting injectable aripiprazole group. The differences found between the two groups were statistically significant.[14]

Table 5. Long-Acting Injectable Antipsychotics[15]

Drug	Class	Half-life Elimination
Prolixin Decanoate (fluphenazine)	First-Generation (Typical)	14 days
Haldol Decanoate (haloperidol)	First-Generation (Typical)	21 days
Abilify Maintena (aripiprazole)	Second-Generation (Atypical)	30-47 days (dose-dependent)
Zyprexa Relprevv (olanzapine)	Second-Generation (Atypical)	30 days
Invega Sustenna (paliperidone, monthly)	Second-Generation (Atypical)	25-49 days
Invega Trinza (paliperidone, 3-month)	Second-Generation (Atypical)	84-139 days
Risperdal Consta (Risperidone)	Second-Generation (Atypical)	3-6 days
Aristada (aripiprazole lauroxil)	Second-Generation (Atypical)	29 to 35 days

LONG-ACTING INJECTABLE ANTIPSYCHOTICS COMPARISONS

Both first-and-second generation antipsychotics have long-acting injectable formulations. Table 5 contains the different injectable antipsychotics available in the United States and displays their class and half-life information.[15] It should be noted that the second-generation injectable antipsychotics, or atypicals, have longer durations of action than the first-generation antipsychotics, or the typicals.

The ACCLAIMS trial was the first randomized trial to compare first- generation long-acting injectable antipsychotics to second-generation injectables.[12,16] In this study, 310 patients who were diagnosed with schizophrenia or schizoaffective disorder and who were at high-risk for relapse due to prior substance abuse or non-adherence, were randomized to receive either haloperidol decanoate or paliperidone palmitate.[12,16] Haloperidol decanoate is classified as a first-generation antipsychotic, whereas, paliperidone palmitate falls into the second-generation classification. Between the two long-acting injectables, there was no statistically significant difference in efficacy found. Efficacy failure was seen in 33.8% of the paliperidone palmitate group and 32.4% of the haloperidol decanoate group.[12,16] On average, the paliperidone palmitate group saw an increase in weight, whereas the haloperidol decanoate group demonstrated weight loss. Paliperidone palmitate patients also saw a significant increase in prolactin and the haloperidol decanoate group saw significant increases in akathisia. These results are presented in Table 6.[16]

In conclusion of the ACCLAIMS trial, the efficacy was similar between both haloperidol decanoate and paliperidone palmitate; however, paliperidone palmitate was associated with more weight gain and serum prolactin increase, whereas haloperidol decanoate increased akathisia rates.[12,16]

Table 6. Adverse Event Comparisons Between Paliperidone Palmitate and Haloperidol Decanoate[16]

Adverse Event	Paliperidone Palmitate (95% CI)	Haloperidol Decanoate (95% CI)	P-value
Weight Change (kg)	2.17 (1.25 to 3.09)	-0.96 (-1.88 to -0.04)	
Hyperprolactinemia Men (ug/mL)	34.56 (29.75 to 39.37)	15.41 (10.73 to 20.08)	<0.001
Hyperprolactinemia Women (ug/mL)	75.19 (63.03 to 87.36)	26.84 (13.29 to 40.40)	<0.001
Akathisia	0.45 (0.31 to 0.59)	0.73 (0.59 to 0.87)	0.006

LONG-ACTING INJECTABLE ANTIPSYCHOTIC DOSING

There are seven long-acting injectable antipsychotics approved for use in the United States: Prolixin Decanoate, Haldol Decanoate, Abilify Maintena, Zyprexa Relprevv, Invega Sustenna, Invega Trinza, Risperdal Consta, and recently approved, Aristada.[15] Doses for various long-acting injectable psychotics differ, but all formulations can be administered intramuscularly. Frequency of injections is drug specific, and typically range from every two to four weeks. Invega Trinza is a newer, long-acting injectable and is approved for three-month injections. Table 7 summarizes the dosing interval between the different long-acting antipsychotics.[15]

Tapering oral medications is important for the use of long-acting injectable antipsychotics. Since the goal of injectable antipsychotic therapy is to allow the drug to stay in the body longer, there are delayed effects seen. In most long-acting injectable formulations, it will take two to seven days to see a benefit with these medications and up to three to four weeks before maximum benefit is seen. Due to this delayed onset, it is necessary with some drugs to bridge with oral medication therapy. This oral overlap is needed to establish the drug levels in the body and keep them consistent until the long-acting injectable formulation can reach steady-state. Table 7 also summarizes the needed oral overlap for specific long-acting injectable antipsychotics.[15]

Table 7. Long-Acting Injectable Antipsychotics Dosing[15]

Drug	Starting dose	Usual dose	Dose interval	Oral Overlap (Titration)
Prolixin Decanoate (fluphenazine)	12.5-25 mg IM/SC	12.5-50mg IM/SC	2-4 weeks	Decrease oral dose by half after first injection; consider d/c after second injection
Haldol Decanoate (haloperidol)	10-20 times oral daily dose IM	10-15 times oral daily dose IM; or 50-200mg IM	4 weeks	Taper oral dose and d/c after the first 2 or 3 injections. Oral overlap not required if using a loading dose regimen
Abilify Maintena (aripiprazole)	400mg IM	400mg IM	Monthly; separate by at least 26 days	Oral overlap for 14 days
Zyprexa Relprevv (olanzapine)	210-405mg IM	150-405mg IM	2-4 weeks	Not required

Drug (cont)	Starting dose	Usual dose	Dose interval	Oral Overlap (Titration)
Invega Sustenna (paliperidone, monthly)	234mg IM on day 1, then 156mg IM 1 week later	Schizoaffective disorder: 78-234mg IM monthly Schizophrenia: 39-234mg IM monthly	4 weeks	Discontinue oral after the second dose
Invega Trinza (paliperidone, 3-month)	Based on previous paliperidone monthly dose	273-819mg IM	Every 3 weeks	Not applicable
Risperdal Consta (Risperidone)	12.5-25mg IM	25-50mg every 2 weeks IM	2 weeks	Continue oral dose for 3 weeks after initiation of therapy

NEW LONG-ACTING INJECTABLE ANTIPSYCHOTICS

Aristada (aripiprazole lauroxil) is the prodrug form of aripiprazole and has recently been approved by the FDA as a long-acting injectable therapy for schizophrenia. Aristada and Abilify Maintena are both long-acting injectable formulations of aripiprazole, but they differ in a few ways. Abilify Maintena (aripiprazole) is not the pro-drug form, which should be administered every 3 to 4 weeks and requires 14-days of overlap with oral aripiprazole to initate therapy. Aristada (aripiprazole lauroxil) can be given every four to six weeks and does not require overlap with aripiprazole oral tablets.[17,18,19]

In a study by *Meltzer et al*, the efficacy, safety, and tolerability of aripiprazole lauroxil was compared to oral aripiprazole in patients exhibiting acute schizophrenia exacerbations. In this study, 163 patients underwent testing using 441mg or 882 mg of aripiprazole lauroxil or placebo. This trial concluded that aripiprazole lauroxil produced statistically and clinically significant improvements in acute exacerbations of schizophrenia. Both the 441mg and 882mg formulations of aripiprazole lauroxil were well tolerated and beneficial.[17]

Currently, there are more studies being done comparing the compliance and efficacy with long-acting injectables and oral antipsychotics. A randomized, multi-site, parallel-group trial comparing the efficacy of aripiprazole once-monthly injections to standard-of-care oral antipsychotics in nonadherent patients is currently ongoing.[20] Another trial assessing the effects of oral and long-acting injectable antipsychotics on the schizophrenia disease progression is also being studied.[20]

CONCLUSION

Schizophrenia is a chronic, complex mental illness requiring pharmacotherapy to manage symptoms and improve quality of life. Treatment is individualized to the patient, and is based on past experiences and the side effect profiles of the medications. In the past, oral antipsychotics have been the preferred treatment options. With oral antipsychotics, adherence continues to be a major concern. New long-acting injectable antipsychotics may provide an advantage over previous oral medications by decreasing relapse and rehospitalization rates. Long-acting injectable antipsychotics enable the patient to have less frequent dosing, which may improve adherence, side effects, and quality of life. With current and future research being done, long-acting injectable antipsychotics may have an important impact on the treatment and management of schizophrenia.

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