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Atypical Antipsychotics

2.00 Contact Hours

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Outcomes

≥ 92% of participants will be able to identify the uses, forms, and possible adverse effects of atypical antipsychotic medications.

Objectives

After completing this continuing education course, the participant will be able to:

1. Describe the labeled uses of atypical antipsychotics.
2. Analyze the adverse effects that can result from taking atypical antipsychotics.
3. Identify the rationale for utilizing long-acting injectable forms of atypical antipsychotics.
4. Describe the body's reaction to abrupt discontinuation of atypical antipsychotics.
5. Explain the monitoring that must be considered when caring for a patient prescribed atypical antipsychotics.

Introduction

Atypical antipsychotics, also called second-generation antipsychotics, are effective in treating the signs and symptoms of schizophrenia, and they are the first choice for the pharmacologic treatment of schizophrenia (Fabrazzo et al., 2022; Meltzer & Gadaleta, 2021; Radhakrishnan et al., 2019), (Drosos et al., 2022; Radhakrishnan et al., 2019; Reus, 2022).

There are currently 14 different atypical antipsychotics available in the United States. These drugs are similar in their mechanism of action and adverse effect profile, and research suggests that in terms of efficacy, there are no important differences between them (Radhakrishnan et al., 2019). However, there are differences in how the therapeutic effect of each drug is mediated, differences in what adverse effects each drug can cause, and how likely these adverse effects are to occur. These are important considerations, especially for clinicians who will be administering an atypical antidepressant and monitoring for adverse effects.

History of Antipsychotics

The first antipsychotics were phenothiazines like chlorpromazine, and they were used as antiemetics and pre-operative sedatives (Kumar et al., 2019; Owens & Johnstone, 2018; Remington et al., 2021). These drugs were later found to be effective for treating schizophrenia, but they caused serious neurological adverse effects, particularly extrapyramidal symptoms (EPS) (Juurlink, 2019; Nichols et al., 2023).

In the early 1970s, clozapine (Clozaril®), a drug that had been investigated for use as an antidepressant, was found to be effective for treating schizophrenia, *and* it was less likely than the original antipsychotics to cause EPS (Owens & Johnstone, 2018; Juurlink, 2019; Weston-Green, 2022). Extrapyramidal symptoms were a *typical* part of the adverse effect profile of the first antipsychotics, and clozapine and the antipsychotics that were developed after clozapine thus became known as *atypical* or second-generation antipsychotics.

Pharmacology

The mechanism of action of antipsychotics is mediated by complete and partial neurotransmitter receptor site antagonism and/or agonism (de Bartolomeis et al., 2022; Nichols et al., 2023; Radhakrishnan et al., 2019; Weston-Green, 2022). The *primary therapeutic* effect of these medications is thought to be caused by dopamine₂ receptor site antagonism (de Bartolomeis et al., 2022). However, the therapeutic effects, as well as the adverse effects, of the atypical antipsychotics are also mediated by partial or complete antagonism/agonism of other neurotransmitter receptor sites, including (but not limited to) the ones listed in Table 1 below.

Table 1: Neurotransmitter Receptor Sites and Atypical Antipsychotics (de Bartolomeis et al., 2022; Katzung et al., 2021; Nichols et al., 2023; Radhakrishnan et al., 2019; Weston-Green, 2022)

Dopamine ₂₋₄ receptors
Serotonin receptors, multiple sub-types
Alpha ₁ and alpha ₂ receptors
Histamine receptors
Acetylcholine receptors, muscarinic
Glutamate receptors

Each atypical antipsychotic has a neurotransmitter receptor site binding profile that explains its efficacy and its adverse effects and explains, in part, how well a patient responds to that drug.

- Example: Clozapine (Clozaril®), the first atypical antipsychotic, binds weakly to dopamine₂ receptors and it is a strong serotonin receptor (5-HT_{2A} sub-type) antagonist. The weak dopamine₂ receptor effect likely explains the lower risk of EPS, and the serotonin receptor effect is an underpinning of clozapine's therapeutic effects (de Bartolomeis et al., 2022; Radhakrishnan et al., 2019).
- Example: Aripiprazole (Abilify®) is a partial dopamine₂ and dopamine₃ and 5-HT_{1A} *agonist* as well as being a very strong dopamine₂ antagonist, and it has been postulated that the dopamine₂ antagonism/agonism reduces dopamine activity in one part of the brain and increases it in others, and this explains how aripiprazole is effective for treating the positive and negative symptoms of schizophrenia and improving cognitive function (Anam et al., 2022; de Bartolomeis et al., 2022).

The pharmacology of the atypical antipsychotics is very complex, and it is not completely understood. de Bartolomeis et al. (2022) wrote: "Therefore, nearly 70 years after

chlorpromazine was marketed, the mode of action of APs remains in some respects an enigma . . . and despite many years of research, an accurate picture of how APs work is struggling to emerge” (de Bartolomeis et al., 2022, p.2).

Labeled Uses and Available Forms

All the atypical antipsychotics that are marketed in the United States have a labeled use for treating schizophrenia, except pimavanserin: Pimavanserin is used to treat psychosis associated with Parkinson’s disease.

Clozapine has a labeled use for:

1. Treatment-resistant schizophrenia, *i.e.*, patients for whom other atypical antipsychotics were not effective.
2. Reducing the risk of suicidal behavior in patients who have schizophrenia or schizoaffective disorder.

In certain circumstances/conditions, an atypical antipsychotic can be prescribed but only with concurrent/adjunctive use of another psychiatric medication like an antidepressant or lithium. Atypical antipsychotics have other labeled uses, depending on the drug, and some of these are listed below:

1. Bipolar disorder
2. Irritability associated with autistic disorder
3. Major depressive disorder, unipolar, treatment-resistant
4. Tourette's disorder
5. Agitation/aggression associated with psychiatric disorders

Table 2 lists the atypical antipsychotics that are currently available in the US. The generic name is followed by the brand name.

Table 2: Atypical Antipsychotics: Available Forms (WebMD, 2021)

Aripiprazole – Abilify®
Asenapine – Saphris®
Brexipiprazole – Rexulti®
Cariprazine – Vraylar®
Clozapine – Clozaril®
Iloperidone – Fanapt®
Lumateperone – Caplyta®
Lurasidone – Latuda®
Olanzapine – Zyprexa®
Paliperidone – Invega®
Pimavanserin – Nuplazid®

Quetiapine – Seroquel®

Risperidone – Risperdal®

Ziprasidone – Geodon®

Some of these medications are available as long-acting injectables (VandenBerg, 2022).

The long-acting injectable (LAI) formulations can be given, depending on the drug, once every two weeks or even just twice a year (VandenBerg, 2022). This can improve patient adherence to the prescribed regimen, and it may decrease fluctuations in the serum level of the drug, increasing the efficacy of the medication (VandenBerg, 2022). Long-acting injectables will be discussed in more detail shortly.

Adverse Effects

It is helpful to remember that atypical antipsychotics bind to many different neurotransmitter receptor sites and that some of the common adverse effects of these drugs are caused by this natural binding. Examples are listed below:

- Acetylcholine receptors, muscarinic Receptors: Anticholinergic signs, and symptoms
- Alpha₁ Receptors: Orthostatic hypotension
- Alpha₂ Receptors, pre-synaptic: Tachycardia
- Dopamine₂ Receptors: EPS
- Histamine Receptors: Sedation
- Serotonin Receptors: Hyperprolactinemia, weight gain, serotonin syndrome

The adverse effects of atypical antipsychotics are usefully divided into four categories:

1. Cardiac
2. Hematologic
3. Metabolic
4. Neurologic/Psychologic

Cardiovascular

Atypical antipsychotics can cause many different cardiovascular adverse effects: Some of them are common, some are rare, some are minor, and others can be lethal. Determining the level of risk for these adverse effects is challenging because:

1. Compared to the general population, people who have schizophrenia have a higher risk of sudden cardiac death, a higher risk for developing cardiovascular disease, and they are more likely to have risk factors for cardiovascular disease like metabolic syndrome and smoking (Huhn et al., 2020; Peritogiannis et al., 2022).
2. The atypical antipsychotics are a direct and an indirect cause of cardiovascular complications in patients who have schizophrenia (Crawford & Go, 2022; Stoner, 2018).

This section will discuss the cardiovascular adverse effects that are possible, including cardiomyopathy, myocarditis, orthostatic hypotension, QT prolongation and torsades de pointes (TdP), and sinus tachycardia.

Cardiomyopathy

The prescribing information for clozapine has a Boxed Warning that states: *Fatal myocarditis and cardiomyopathy have occurred with treatment*. Discontinue clozapine and obtain a cardiac evaluation upon suspicion of these reactions.

Cardiomyopathy is, fortunately, a rare complication of atypical antipsychotics (Garg et al., 2020; Rohde et al., 2018; Siskind et al., 2020; Sweeney et al., 2020). It happens most often with clozapine (Sweeney et al., 2020), but it can be caused by aripiprazole, olanzapine, quetiapine, and risperidone, as well (Rohde et al., 2018; Stoner, 2018).

It is not clear why atypical antipsychotics cause cardiomyopathy (Garg et al., 2020). It may be a hypersensitivity reaction or a direct toxic effect of the drug, but it does not appear to be dose-related (Garg et al., 2020).

Cardiomyopathy may begin within three weeks of starting therapy with clozapine, but an onset of a year or several years has been reported more commonly (Garg et al., 2020; Patel et al., 2019; Siskind et al., 2020; Stoner, 2018). The signs and symptoms are non-specific, and they include (but are not limited to) cough, fatigue, orthopnea, palpitations, and shortness of breath (Garg et al., 2020; Stoner, 2018). The mortality rate of this adverse effect of clozapine has been estimated to be 7.8% (Garg et al., 2020). The *primary* treatment in this case is to discontinue the use of the drug (Garg et al., 2020; Stoner, 2018).

Myocarditis

Myocarditis is an inflammation of the myocardium that causes necrosis and functional impairment (Sweeney et al., 2020).

Myocarditis is a rare adverse effect of atypical antipsychotics, and it occurs most often with clozapine, but it can be caused by aripiprazole, olanzapine, quetiapine, and risperidone, as well (Adetiloye et al., 2022; Skivakumar et al., 2020; Sweeney et al., 2020; Rohde et al., 2018).

It is not clear why atypical antipsychotics and clozapine, in particular, cause myocarditis. Possible reasons include (Adetiloye et al., 2022; Patel et al., 2019; Shivakumar et al., 2019; Koenig et al., 2022; Hamilton et al., 2022):

- Concurrent use of another atypical antipsychotic
- Delayed hypersensitivity reaction
- A high level of circulating catecholamines caused by the drug
- Inflammation
- Genetic variations that affect the metabolism of the drug or that make a patient more likely to develop myocarditis
- Oxidative stress

The exact incidence of myocarditis caused by clozapine is unknown, and the estimates vary considerably, from 0.01% to 9% (Shivakumar et al., 2020; Sweeney et al., 2020). This wide range may be due to differing diagnostic criteria and differences in awareness and monitoring (Dawson et al., 2018). The onset is usually within four weeks of starting therapy with clozapine, and most cases occur within several months (Sweeney et al., 2020).

The clinical presentation is quite variable. Some patients have mild signs and symptoms, and others present with cardiogenic shock (Patel et al., 2019). The signs and symptoms are non-specific, and they include (but are not limited to) chest pain, fever, palpitations, and shortness of breath (Hamilton et al., 2022; Patel et al., 2019; Sweeney et al., 2020; Shivakumar et al., 2020). The mortality rate of cardiomyopathy caused by atypical antipsychotics has been

estimated to be 10% to 50% (Shivakumar et al., 2020; Sweeney et al., 2020). The *primary treatment* is to stop the use of the offending drug (Adetiloye et al., 2022; Patel et al., 2019).

Orthostatic Hypotension

Orthostatic hypotension is defined as a decrease in systolic blood pressure >20 mmHg or a decrease in diastolic blood pressure of >10 mmHg that occurs within three minutes after moving from a lying to a standing position and the decrease is sustained (Tanzer et al., 2022).

Moving from lying to sitting causes a large amount of blood to pool in the lower extremities, and in response, adrenergic stimulation of the α_1 receptors causes peripheral vasoconstriction. Atypical antipsychotics are antagonists at the α_1 receptors, and when a patient changes position, the peripheral vasoconstriction response may not occur, and orthostatic hypotension happens (Bhanu et al., 2021; Nkemijka et al., 2022; Tanzer et al., 2022).

Bhanu et al. (2021) did a systematic review of the literature, and the authors found that compared to the placebo, the atypical antipsychotics had an odds ratio (OR) of 2.8 for causing orthostatic hypotension. Clozapine has the highest risk of causing orthostatic hypotension, approximately 9%, and for the other atypical antipsychotics, the risk is much less (Bhanu et al., 2021; Tanzer et al., 2022).

QT Prolongation and Torsades de Pointes

The QT interval represents the beginning of ventricular depolarization to the end of ventricular repolarization. The normal QT for men is ≤ 430 msec, and for women, ≤ 450 msec is normal. For men, a QT > 450 msec is prolonged, and for women, a QT > 470 msec is prolonged (Xiong et al., 2020). The QT interval is measured by correcting for the heart rate – the QTc.

Drug-induced QT prolongation is defined as a QTc > 500 msec or a QTc that is > 60 msec of a patient's baseline QTc, and a prolonged QT is a risk factor for lethal ventricular arrhythmias, most Torsades de Pointes (TdP) (Li & Ramos, 2017; Kahlon et al., 2022; Khatib et al., 2021; Xiong et al., 2020). Research has suggested that a QTc > 500 msec is associated with a twofold to threefold increase in risk for TdP and that every 10 msec increase in the QTc may increase the risk of TdP by 5% to 7% (Li & Ramos, 2017; Khatib et al., 2021).

Torsade de Pointes is a ventricular arrhythmia that is characterized by polymorphic ventricular tachycardia and specific ECG findings (Li & Ramos, 2017). Torsades de Pointes can cause ventricular fibrillation, cardiac arrest, and sudden death (Danielsson et al., 2020; Li & Ramos, 2017).

Torsades de Pointes is likely a rare arrhythmia, but an episode of TdP can be brief, *and* it may spontaneously resolve, *or* it can cause sudden death, at times unwitnessed, so the true incidence of drug-acquired TdP is not known (Li & Ramos 2017; Danielsson et al., 2020; Maril et al., 2022; Wu et al., 2022).

The signs and symptoms of TdP include (but are not limited to) (Li & Ramos, 2017; Danielsson et al., 2020):

- Cardiac arrest
- Chest pain
- Dizziness
- Hypotension
- Seizure
- Shortness of breath
- Syncope

QT prolongation is a significant risk factor for TdP, but it is only one of many risk factors that can cause TdP (Diaz et al., 2020; Xiong et al., 2020). Fortunately, most patients with QTc prolongation do not ultimately suffer from TdP (Maril et al., 2022). QT prolongation is a common adverse effect of some antipsychotics, but TdP caused by/associated with these drugs is rare (Xiong et al., 2020).

Table 3 lists factors that increase the risk of developing QT prolongation, TdP, or both. This list is not all-inclusive. Most patients who develop QT prolongation or TdP will have multiple risk factors present (Khatib et al., 2021).

Table 3: Risk Factors for QT Prolongation & TdP (Das et al., 2019; Diaz et al., 2020; Gustafsson et al., 2022; Kahlon et al., 2022; Li & Ramos, 2017; Ramasubbu et al., 2022; Xiong et al., 2020).

Age $\geq$ 65 years
Bradycardia
Cardiovascular disease
Congenital long-QT syndrome
Cirrhosis
Diuretic use
Drug-drug interactions: Concurrent use of two or more drugs that can cause prolonged QT and/or TdP
Concurrent use of a drug that can cause prolonged QT and/or TdP <i>and</i> a drug that increases the serum concentration of that first drug
Electrolyte disturbances: Hypocalcemia, hypomagnesemia, hypokalemia
Female gender
Genetic predisposition
Hypothyroidism
Overdose of an atypical antipsychotic
Rapid IV infusion of an IV antipsychotic
Renal failure
Sepsis

Sinus Tachycardia

Sinus tachycardia has been reported to occur in 1% to 4% of patients who are taking an atypical antipsychotic (Huhn et al., 2022; Sweeney et al., 2020). It is a common adverse effect of

iloperidone, and especially of clozapine, occurring in 3% to 67% of patients taking that drug (Adeyemo et al., 2020; Sweeney et al., 2020; Huhn et al., 2022; Lally et al., 2016).

The primary causes of this adverse effect are (Adeyemo et al., 2020; Sweeney et al., 2020):

1. Antagonism of muscarinic cholinergic receptors, which decreases vagal tone
2. Antagonism of α_1 receptors, which causes peripheral vasodilation and reflex tachycardia

For clozapine, sinus tachycardia is thought to be caused by the antagonism of muscarinic cholinergic receptors and presynaptic α_2 receptors and the indirect activation of beta-adrenergic receptors (Adeyemo et al., 2020).

Most cases of sinus tachycardia caused by an atypical antipsychotic, even by clozapine, are mild and self-limiting; they resolve in several weeks, and the patient does not require treatment (Adeyemo et al., 2020; Sweeney et al., 2020).

There are currently no specific guidelines for treating this adverse effect (Adeyemo et al., 2020; Lally et al., 2016). Beta-blockers, ivabradine, and verapamil have been used in the past (Sweeney et al., 2020). If sinus tachycardia persists, it is prudent to look for other causes. If the patient is taking clozapine, it should be remembered that clozapine can cause cardiomyopathy and myocarditis as well (Sweeney et al., 2020).

Hematologic

Neutropenia is defined as a neutrophil count $< 1500/\text{mm}^3$. Clozapine, paliperidone, quetiapine, and risperidone have been found to cause neutropenia (Atolagbe et al., 2021; Fryer & Billings, 2020; Johannsen et al., 2022; Martos et al., 2021; Oloyede et al., 2022).

Severe neutropenia, defined as an absolute neutrophil count (ANC) $< 500 \text{ mm}^3$, is a potentially life-threatening adverse effect that is almost exclusively caused by clozapine. Severe neutropenia has been estimated to occur in 0.4% of patients taking clozapine, and it can cause life-threatening opportunistic infections, even in patients who are immunocompetent (Johannsen et al., 2022; Atolagbe et al., 2021).

The prescribing information for clozapine has a Boxed Warning about this adverse effect that states: *Before starting treatment with clozapine, a WBC and an absolute neutrophil count must be done, and these tests should be done regularly during treatment* (Clozaril®, n.d.). In addition, because of the risk of severe neutropenia, clozapine must be prescribed through the Clozapine Risk Evaluation and Management Strategy (REMS) program.

Metabolic

The atypical antipsychotics are also known to cause hyperlipidemia, glucose dysregulation, hyperprolactinemia, metabolic syndrome, and weight gain (Bernardo et al., 2021; Carli et al., 2021; Dehelean et al., 2020). Since 2003, pharmaceutical companies have been required to include a warning about these adverse effects in the prescribing information. For example, the prescribing information for Risperdal® (2007) states that atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/ cerebrovascular risk. It instructs providers to monitor patients for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness, monitor glucose regularly in patients with diabetes or at risk for diabetes, and monitor for weight gain (Risperdal®, 2007).

The cause or causes of these metabolic adverse effects appear to be mediated by agonism and antagonism of the atypical antipsychotics at adrenergic, central and peripheral dopaminergic, histaminergic, muscarinic, and serotonergic receptor sites (Horska et al., 2022). However, the exact mechanisms that initiate glucose and lipid changes, metabolic syndrome, and weight gain are not well understood, and determining their pathogenesis is difficult because these metabolic complications are all common comorbidities of severe psychiatric illnesses like schizophrenia (Bernardo et al., 2021; Liao et al., 2021).

Hyperlipidemia

Clozapine, olanzapine, and quetiapine can significantly increase serum triglycerides and total cholesterol (Pillinger et al., 2020; Yuen et al., 2021).

Glucose Dysregulation

Atypical antipsychotics can affect glucose metabolism and decrease insulin sensitivity, which can cause elevated fasting glucose. This can also cause or exacerbate Type 2 diabetes and occasionally, though rarely, can cause serious diabetic complications like Diabetic Ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) (Gao et al., 2022; Tugwell et al., 2020; Yuen et al., 2021).

The risk of glucose dysregulation differs for each drug (Bernardo et al., 2021; Fève & Scheen, 2022; Pillinger et al., 2020). A recent review by Pillinger et al. (2020) concluded that clozapine and olanzapine were associated with a significant elevation of fasting glucose.

Fève & Scheen (2022) found that the risk of developing diabetes varies depending on which medication is taken. A higher risk of diabetes development has been associated with clozapine or olanzapine, an intermediate risk for risperidone and quetiapine, and the lowest risk for aripiprazole (Fève & Scheen, 2022).

The mortality rate of the adverse effect of glucose dysregulation has been estimated to be 26.5%, and the mortality rate for DKA is < 1% (Powers et al., 2022; Polcwiartek et al., 2016).

Hyperprolactinemia

Hyperprolactinemia is a well-known adverse effect of atypical antipsychotics that can occur in men and women (Al Harthi et al., 2022; Dehelean et al., 2020). Hyperprolactinemia caused by antipsychotics has been associated with (Shen et al., 2019):

- Decreased bone mineral density
- Decreased libido
- Galactorrhea
- Gynecomastia
- Infertility
- Menstrual irregularities
- Sexual dysfunction

It has been speculated that decreased bone density associated with atypical antipsychotic use may increase the risk for osteoporotic fracture, but a direct cause-and-effect relationship between one and the other has not been proven (Shen et al., 2019).

Hyperprolactinemia has been associated with an increased risk for breast cancer, and an association between atypical antipsychotics and an increased risk for breast cancer has been reported (Joo et al., 2020; Leung et al., 2022).

While hyperprolactinemia has been reported to be an adverse effect of most atypical antipsychotics, paliperidone and risperidone are the ones that are most likely to cause it (Dehelean et al., 2019; Karslioglu et al., 2022; Stojkovic et al., 2022).

Metabolic Syndrome

Compared to the general population, people who have schizophrenia are more likely to develop metabolic syndrome and atypical antipsychotics are associated with an increased risk of developing the individual components of metabolic syndrome like dyslipidemia, glucose regulation dysfunction, and weight gain, and the metabolic syndrome itself (Gupta et al., 2021; Carli et al., 2021).

Weight Gain

Atypical antipsychotics have been associated with significant weight gain (Gupta et al., 2021).

Neurologic

Anticholinergic Signs and Symptoms/Histaminergic Effects

Most atypical antipsychotics can cause some level of muscarinic receptor antagonism, resulting in anticholinergic effects including (but not limited to) blurred vision, constipation, dry mouth, tachycardia, and urinary retention (Muench & Hamer, 2010; Stroup & Gray, 2018). Clozapine, olanzapine, and quetiapine are more likely than the other atypical antipsychotics to cause anticholinergic effects (Stroup & Gray, 2018).

Atypical antipsychotics, to a lesser or greater degree, are histamine receptor site antagonists, and this effect can cause drowsiness and sedation.

Increased Risk for Death: Dementia-Related Psychosis

Atypical antipsychotics have a Boxed Warning stating that elderly patients who have dementia-related psychosis and who are treated with an antipsychotic are at an increased risk for death. Atypical antipsychotics are often used to treat dementia patients who have behavioral and psychological symptoms (Jalil et al., 2022). This is an unlabeled use of these drugs. Research has shown that atypical antipsychotics are not highly effective for this purpose, and adverse effects of atypical antipsychotics like anticholinergic signs and symptoms, EPS, orthostatic hypotension, and sedation, are especially dangerous for elderly patients (Jalil et al., 2022; Marcinkowska et al., 2020; Calsolaro et al., 2021). Drug therapy for behavioral and psychological symptoms of dementia should be used only when these symptoms are severe or refractory or if other treatments cannot be used (Tampi & Jeste, 2022).

Movement Disorders

Movement disorders caused by atypical antipsychotics include EPS, neuroleptic malignant syndrome (NMS), seizures, and serotonin syndrome (Juurlink, 2019; Khoury & Ghosshoub, 2019; Mostel et al., 2022; Miyamatsu et al., 2021). Neuroleptic malignant syndrome and seizures are discussed separately. Serotonin syndrome is unlikely to occur unless an atypical antipsychotic and a serotonergic drug are used concurrently (Miyamatsu et al., 2021; Mostel et al., 2022).

Atypical antipsychotic-induced EPS includes akathisia, dystonias, parkinsonism, and tardive dyskinesia (Juurlink, 2019). It has been estimated that EPS occurs in up to 30% of patients taking an atypical antipsychotic, and these adverse effects can have a significant negative effect on a patient's emotional, physical, and psychological functioning and well-being (Bjarke et al., 2022; Jouini et al., 2022; Kadakia et al., 2022).

Akathisia is characterized by intense, subjective feelings of restlessness and observable repetitive movements (Jouini et al., 2022; Juurlink, 2019; Pringsheim et al., 2018). The onset of akathisia is usually within days or weeks of starting the drug, and akathisia has been reported to occur in up to 27% of patients taking an atypical antipsychotic (Bjarke et al., 2022; Pringsheim et al., 2018). Akathisia can be treated by stopping the use of the drug, switching to another antipsychotic, lowering the dose, or giving the patient an anticholinergic drug, a beta-blocker, or a benzodiazepine (D'Souza & Hooten, 2022; Juurlink, 2019; Keepers et al., 2020).

Dystonias are involuntary contractions of agonist/antagonist muscles that cause abnormal, rhythmic, and repetitive movements and abnormal postures that are intermittent or sustained (Juurlink, 2019; Olanow & Klein, 2022). Dystonias are often seen in the head, face, neck, tongue, and ocular muscles, but they can affect the extremities, as well (Juurlink, 2019). Examples of dystonia include oromandibular dystonia, which is characterized by abnormal movements of the jaw, lips, lower face, and tongue (Olanow & Klein, 2022).

The onset of dystonia is usually within hours of taking the first dose, but it can be delayed for several days (Juurlink, 2019). Because of individual susceptibility to dystonias, different patient populations, and the number (15) of atypical antipsychotics, it is difficult to determine the incidence of dystonia associated with these drugs. Except for laryngeal dystonia, which can compromise airway integrity, atypical antipsychotic-induced dystonias are uncomfortable and frightening, but they are not dangerous, and they can be effectively treated with an anticholinergic drug like benztropine or diphenhydramine or a benzodiazepine (D'Souza & Hooten, 2022; Juurlink, 2019; Keepers et al., 2020; Stroup & Gray, 2018).

Parkinsonism is characterized by signs and symptoms that mimic Parkinson's disease, including (but not limited to) bradykinesia, postural instability, muscular rigidity, and tremor (Juurlink, 2019; d'Errico et al., 2022). The incidence of Parkinsonism has been estimated to be 20% to 40% (Pieters, 2018). Treatment includes (but is not limited to) discontinuing use, lowering the dose, amantadine, dopamine agonists, or an anticholinergic drug (D'Souza & Hooten, 2022; Juurlink, 2019; Keepers et al., 2020). Most cases of Parkinsonism will resolve if the use of the antipsychotic is discontinued (Feldman et al., 2022).

Tardive dyskinesia (TD) is characterized by involuntary, repetitive, and choreiform movements of the jaw, mouth, and tongue, e.g., rhythmic and repetitive puckering of the lips, rhythmic and repetitive protruding of the tongue (Jain & Correll, 2018; Takeuchi et al., 2022). Occasionally, TD affects the extremities and other body areas (Jain & Correll, 2018). Tardive refers to the delayed onset of this adverse effect; TD usually begins three months after beginning therapy with an antipsychotic, but TD can begin after years of use, and it can begin after a patient has stopped taking an antipsychotic (Jain & Correll, 2018). The prevalence of TD associated with atypical antipsychotics has been estimated to be ~ 20% (Stegmayer et al., 2018). Tardive dyskinesia is difficult to treat, and it can be, and often is, irreversible (Jain & Correll, 2018; Takeuchi et al., 2022; Juurlink, 2019).

Dystonias Versus Tardive Dyskinesia

The definitions of dystonias and TD make them sound similar, and dystonias are a type of dyskinesia – an abnormal muscle movement – as are other abnormal muscle movements like tremors. Key differences between these two adverse effects are the onset, response to treatment, and their characteristic physical presentation (Olanow & Klein, 2022; Ropper et al., 2019; Ford et al., 2019):

1. The onset of drug-induced dystonia typically happens very soon after taking an antipsychotic. The onset of TD is delayed, and it may begin after the use of the drug has

stopped.

2. Drug-induced dystonia typically can be stopped very quickly with the administration of an anticholinergic or a benzodiazepine; TD often does not respond to treatment.
3. Tardive dyskinesia is less likely than dystonias to affect the extremities and the trunk, and orofacial and lingual dyskinesias, the rhythmic and repetitive puckering of the lips and rhythmic and repetitive protruding of the tongue caused by TD are a very common manifestation of TD.
4. Dystonias can be painful, frightening, and uncomfortable, and patients seek help. Many people who have the classic orofacial and lingual dyskinesias of tardive dyskinesia do not know they have them.

Tardive akathisia and tardive dystonias can also occur; a discussion of these pathologies is beyond the scope of this course.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a rare and potentially lethal adverse effect of atypical antipsychotics (Juurlink, 2019). NMS is characterized by an altered mental status, autonomic instability (signs like diaphoresis and tachycardia), intense muscular rigidity (often called lead-pipe rigidity), hyperthermia, and rhabdomyolysis (Chang et al., 2022; Deng et al., 2022; Juurlink, 2019; Sedhai et al., 2021).

The onset of NMS is usually within 30 days of starting therapy with an antipsychotic, but NMS can happen at any time, and it is particularly likely to occur when there has been a rapid increase in the dose (Chang et al., 2022; Juurlink, 2019). The mortality rate of NMS has been reported to be between 10% to 30% (Chang et al., 2022). The incidence of NMS caused by atypical antipsychotics is not known; there are case reports of NMS caused by clozapine, olanzapine, quetiapine, risperidone, and ziprasidone (Sedhai et al., 2021).

Seizures

The prescribing information for atypical antipsychotics advises clinicians that these drugs should be used cautiously in patients who have a seizure disorder or who have a condition that can lower the seizure threshold, *e.g.*, head trauma. The prescribing information for clozapine has a Boxed Warning stating that clozapine has caused dose-related seizures (Clozaril, n.d.). Atypical antipsychotics can lower the seizure threshold, and their use has been associated with a significant increase in the incidence of and the risk for seizures (Jeon et al., 2022; Jeon et al., 2021a; Jeon et al., 2021b; Khoury & Ghosshoub, 2019).

Psychiatric

Suicidal Ideation

Clozapine is the only atypical antipsychotic that has a labeled use for reducing the risk of suicidal behavior in patients who have schizophrenia or schizoaffective disorder, and the research shows that (Forte et al., 2021; Gammon et al., 2021; Taipale et al., 2021):

1. Clozapine is effective for this purpose.
2. The other atypical antipsychotics are not effective for this purpose.

Some atypical antipsychotics like aripiprazole and quetiapine are used as adjunctive therapy for patients who have treatment-resistant unipolar major depression. These patients are taking an antidepressant, as well, and the prescribing information for these atypical antipsychotics has a Boxed Warning that indicates that antidepressants have been associated with an increased risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term

studies (Abilify, 2020). Providers and parents are instructed to closely monitor all antidepressant-treated patients for clinical worsening and the emergence of suicidal thoughts and behaviors (Abilify, 2020).

Long-Acting Injectable Antipsychotics

The first long-acting injectable version of the atypical antipsychotic risperidone was approved in 2003. Aripiprazole, olanzapine, paliperidone, and risperidone are all now available as long-acting injectable preparations.

Adherence

Adherence to treatment with antipsychotics is poor, approximately 40% to 50%, and non-adherence can worsen the illness, significantly increase the risk of relapse, and increase the need for hospitalization (Kane et al., 2021; Youykheang et al., 2023).

The American Psychiatric Association recommends that patients be treated with a long-acting injectable (LAI) antipsychotic if they have a history of poor adherence to antipsychotic treatment (Keepers et al., 2020). Compared to oral antipsychotics, long-acting injectable antipsychotics have been associated with a higher rate of adherence, and unlike self-administered medications, a provider will know if a patient skips a dose or stops taking the drug (Kane et al., 2021; Lin et al., 2021; Romagnoli et al., 2021; VandenBerg, 2022). However, VandenBerg (2022) pointed out that the use of LAIs will still not ensure adherence. Patient preference and the clinical situation must be considered when prescribing and using these medications, and clinicians must be realistic in their expectations in terms of adherence. It is important to note here that there are state restrictions that impact insurance coverage for LAIs resulting in the need for prior authorizations prior to the initiation of LAIs, which can ultimately lead to delays in treatment (Bustamante et al., 2025).

Efficacy

Compared to oral antipsychotics, LAI antipsychotics, including atypical antipsychotics, have been shown to reduce the need for hospitalization, prevent relapses, and reduce the risk of suicide (Kishimoto et al., 2021; Lin et al., 2021; Wei et al., 2022). Initially, the LAI antipsychotics were used after treatment with oral antipsychotics failed, but they can be effective as a first-choice treatment (Kane et al., 2021).

Safety

The LAI atypical antipsychotics do not appear to have an unusually high risk of causing EPS (Misawa et al., 2022; Zhand et al., 2022). The adverse effects of LAI antipsychotics are similar to those of oral antipsychotics (Kane et al., 2021).

Administration

The LAI antipsychotics should be given intramuscularly. Do not give them intravenously (IV) or subcutaneously. See the prescribing information for each specific drug for administration instructions. Some of the LAI atypical antipsychotics should only be administered at a certain site, like the deltoid muscle or ventrogluteal muscle (Zolezzi et al., 2021).

Pain at the injection site is a common adverse effect of LAI antipsychotics, but severe pain appears to be unusual (Zolezzi et al., 2021). Techniques that may help to reduce injection site

pain are increasing the duration between injections, minimizing the volume of the injection, and rotating injection sites (Zolezzi et al., 2021).

Discontinuing Therapy

Continued use of drugs that affect the CNS, like alcohol, benzodiazepines, antidepressants, and illicit substances like heroin, can down-regulate and up-regulate neuroreceptors and change neuroreceptor sensitivity (Chouinard et al., 2017; Horowitz & Taylor, 2019). When the use of the drug/medication is suddenly stopped, adaptive mechanisms that try to restore neurologic homeostasis can cause withdrawal signs and symptoms, otherwise known as discontinuation syndrome (Brandt et al., 2020; Horowitz & Taylor, 2019; Read, 2022).

Abrupt discontinuation of treatment with an atypical antipsychotic can cause withdrawal, but there is relatively little published information about this phenomenon (Brandt et al., 2022; Read, 2022; Larsen-Barr, 2018a). Withdrawal after discontinuing the use of an antipsychotic is common (Brandt et al., 2020; Larsen-Barr, 2018b; Read, 2022). Self-completion of surveys and a systematic review of the literature found that withdrawal after discontinuation occurred in 53% to 72% of patients (Larsen-Barr, 2018b; Read, 2022; Brandt et al., 2020).

Note: The terms “discontinuation syndrome” and “withdrawal” are both used and sometimes used interchangeably to describe the signs and symptoms that are caused by the abrupt discontinuation of psychotropic medication.

There is no universally accepted/used definition of antipsychotic withdrawal; the signs and symptoms are non-specific, and they include (but are not limited to) (Blackman et al., 2022; Brandt et al., 2020; Read, 2022):

- Abdominal pain
- Agitation
- Anxiety
- Confusion
- Diarrhea
- Headache
- Insomnia
- Nausea
- Restlessness
- Tremors
- Vertigo

Withdrawal syndrome can be severe, and it can precipitate a relapse of a patient’s psychiatric illness (Read, 2022; Larsen-Barr et al., 2018b; Larsen-Barr, 2021).

There are recommendations to slowly taper the dose of an antipsychotic, but there is limited available evidence to help guide these practices (Larsen-Barr et al., 2021; Seroquel, 2022). In the case of clozapine, abrupt discontinuation may be necessary if the patient has a cardiac complication, NMS, or severe neutropenia, but there is currently no formal procedure on how to safely discontinue clozapine (Blackman et al., 2022).

Nursing Considerations

The pharmacology of atypical antipsychotics is complex, and they have a lengthy adverse effect profile, but administering these drugs effectively and safely can be simplified by using a systems approach.

Beginning Treatment

Before treatment with an atypical antipsychotic is begun, a detailed history should be done, and this should include a history of the patient's medical conditions, a family health history (cardiac disease, long QT syndrome, history of sudden death), and a medication profile (Diaz et al., 2020). It is prudent to measure serum calcium, magnesium, and potassium and do a 12-lead ECG, and for patients who will be taking clozapine, measuring their absolute neutrophil count (ANC) is mandatory.

Cardiovascular Monitoring

Patients receiving atypical antipsychotics require cardiovascular monitoring. The following are cardiovascular issues to look out for:

- Orthostatic hypotension: Patients can become dizzy and suffer a fall when they move from lying to sitting or from sitting to standing.
- Sinus tachycardia: Persistent sinus tachycardia and sinus tachycardia accompanied by symptoms are not normal; if they occur, the provider should be contacted.
- QT prolongation: Hypocalcemia, hypokalemia, or hypomagnesemia increase the risk for QT prolongation, and/or TdP are increased. Monitor levels of these electrolytes. Also, drug-drug interactions can decrease the metabolism and increase the serum level of medications that prolong the QT. Providers and pharmacists look for these drug-drug interactions when a new medication is prescribed, but nurses should check, as well.
- Patients who have risk factors for QT prolongation should have a 12-lead ECG done before starting treatment with an atypical antipsychotic, and Diaz et al. (2020) advise that after that, an ECG should be done once a month for six months and then once/twice a year.
- Myocarditis, cardiomyopathy: Patients taking clozapine should be monitored for signs and symptoms of myocarditis and cardiomyopathy.

Hematologic Monitoring

Monitor patients for signs and symptoms of opportunistic infections.

To prescribe, dispense, and use clozapine, providers, dispensing pharmacies, and patients must be enrolled in the Clozapine REMS program, and the program has requirements for ANC monitoring (Clozapine REMS, 2023). The ANC must be measured and monitored in patients who are starting treatment with clozapine and in patients who are taking clozapine: the recommended schedule for this is outlined below (Clozapine REMS, 2023):

- First six months of treatment, the ANC must be measured once a week.
- After that, if the ANC count is normal, it can be measured every two weeks.
- After one year of treatment, if the ANC count has been normal, it can be measured once a month.

Detailed information about the hematologic adverse effects of clozapine and ANC monitoring is available on the Clozapine REMS website. Use this link: www.newclozapinerems.com/home.

Metabolic Monitoring

Monitor body weight and glucose levels and monitor patients for signs and symptoms of DKA and hyperosmolar hyperglycemic osmolar state.

Neurologic Monitoring

Patients receiving atypical antipsychotics require neurological monitoring as well. The following are neurological issues to look out for:

- Anticholinergic/histaminergic signs and symptoms: Blurred vision, constipation, dry mouth, sedation, tachycardia, and urinary retention are common adverse effects of atypical antipsychotics, and they are a common reason why patients discontinue use.
- Movement disorders/EPS: The signs and symptoms of EPS are usually quite obvious, but they can be subtle, so knowledge of EPS is an essential part of the nursing care of patients taking an atypical antipsychotic. Also, it is important to remember that the onset of EPS can be delayed.
- Neuroleptic malignant syndrome: Hyperthermia, muscle rigidity, and altered mental status are abnormal for any patient but for a patient taking an atypical antipsychotic, these can be the signs and symptoms of a potentially lethal adverse effect.
- Seizures: Atypical antipsychotics increase the risk of seizures.

Psychiatric Monitoring

Patients who are taking an atypical antipsychotic and an antidepressant should be closely monitored for suicidal behavior and/or ideation.

Patient Education

Patients who are taking an atypical antipsychotic should be instructed to call their provider or to seek medical attention if they have any of the following signs or symptoms:

- Cardiovascular: Chest pain, dyspnea on exertion, signs/symptoms of orthostatic hypotension, palpitations, or shortness of breath.
- Metabolic: Elevated blood sugar (patients who measure their blood sugar), weight gain.
- Neurologic: Abnormal muscle movements and/or difficulty in controlling body movements, anticholinergic signs and symptoms, difficulty swallowing, difficulty passing urine, fever, muscle rigidity, sedation, seizure, signs, and symptoms of an infection, syncope, or suicidal behavior and/or ideation.

Patients should be educated about the adverse effects of abruptly discontinuing the use of atypical antipsychotics. Instruct patients that if they are having difficulty tolerating their medication or if for any reason, they are thinking they will stop taking their antipsychotic, they should not discontinue the use of the drug, they should contact the provider as there are effective treatments for adverse effects and there are ways to make treatment with an antipsychotic more tolerable.

Case Study: Edward

Edward is a 55-year-old male who has a past medical history of schizophrenia and major depression. He has been taking olanzapine 20 mg PO, every day and fluvoxamine 100 mg PO every day for the past 15 months. The patient has complained of blurred vision, dry mouth, and sedation, but these adverse effects have been intermittent, and relatively mild, and they have not caused significant disruptions in activities of daily living. The patient also has a past medical history of hypertension (treated with hydrochlorothiazide and lisinopril) and obesity. He does not smoke, use illicit drugs, or drink alcohol. The provider is aware that concurrent use of an ACE inhibitor and olanzapine may lower blood pressure, but the patient's blood pressure has been normal, and he has never had any signs/symptoms of orthostatic hypotension.

The patient's psychiatrist has had regular contact with Edward and the therapist felt that the patient's schizophrenia and depression are well controlled. In addition, the patient has not gained weight, his blood glucose measurements have been normal, and his lipid profile, although borderline high, does not require pharmacologic intervention. A 12-lead ECG has been done every six months, and the QTc has always been normal.

However, several life events have recently caused a significant relapse. The patient has developed auditory and visual hallucinations, and the patient and his family reported that he has had suicidal ideation, and the ideation has been becoming more frequent. The psychiatrist feels that these symptoms were severe and that the patient's level of depression has worsened, so she decides to taper the dose, discontinue the use of olanzapine and start the patient on clozapine. The psychiatrist, the dispensing pharmacy, and the patient are all enrolled in the Clozapine REMS program. Before beginning therapy with clozapine, a CBC, serum calcium, magnesium, and potassium are measured, and a 12-lead ECG is done. The patient is told about the schedule for measuring the ANC and the reason for this. Serum calcium and magnesium are normal; serum potassium is 3.1 mEq/L, and the QTc is prolonged, 475 msec.

A cardiologist is consulted, and because the patient has only one correctable risk factor for TdP, it is felt that with potassium supplementation to increase the level, decreasing the dose of HCTZ, and monitoring electrolytes and ECGs, continuing use of an atypical antipsychotic is safe. The patient will continue to take fluvoxamine (at a lower dose) as he is not in the risk category for suicide and antipsychotics. He has reliable family members who can monitor his mood and behavior, and he keeps in close contact with the psychiatrist.

Two months after beginning treatment with clozapine, the patient's auditory and visual hallucinations have resolved and although there has been a moderate improvement in his depression, he no longer has suicidal ideation. The ANC measurements have been normal, the QTC measurements have been < 440 msec, the patient's blood pressure and blood glucose have been normal, and the lipid profile is unchanged. The patient has gained 2 kilograms, but he has started an exercise program to work to offset the weight gain.

Implicit Bias Statement

CEUFast, Inc. is committed to furthering diversity, equity, and inclusion (DEI). While reflecting on this course content, CEUFast, Inc. would like you to consider your individual perspective and question your own biases. Remember, implicit bias is a form of bias that impacts our practice as healthcare professionals. Implicit bias occurs when we have automatic prejudices, judgments, and/or a general attitude towards a person or a group of people based on associated stereotypes we have formed over time. These automatic thoughts occur without our conscious knowledge and without our intentional desire to discriminate. The concern with implicit bias is that this can impact our actions and decisions with our workplace leadership, colleagues, and even our patients. While it is our universal goal to treat everyone equally, our implicit biases can influence our interactions, assessments, communication, prioritization, and decision-making concerning patients, which can ultimately adversely impact health outcomes. It is important to keep this in mind in order to intentionally work to self-identify our own risk areas where our implicit biases might influence our behaviors. Together, we can cease perpetuating stereotypes and remind each other to remain mindful to help avoid reacting according to biases that are contrary to our conscious beliefs and values.

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