**Clinical relevance of drug interactions in psychiatry: antidepressants and antipsychotics.**

Gustavo Modesto Espindola¹, Maria Eugênia Ruas Carvalho¹, Vinicius Barreto da Silva¹.

¹Escola de Ciências Médicas e da Vida. Pontifícia Universidade Católica de Goiás, Goiânia, Goiás, Brasil.

**ABSTRACT**

**OBJECTIVES:** The study aims to analyze drug interactions between antidepressants and antipsychotics, with a focus on their potential adverse effects and clinical relevance. The objective is to provide criteria for minimizing avoidable harm and improving treatment outcomes. **METHODS:** The "Interactions Checker" module of Drugs.com was used to screen for interactions between 14 antidepressants and 11 antipsychotics. Data were collected based on two meta-analyses and interactions were evaluated for their mechanism, clinical outcomes, and management strategies. **RESULTS:** Interactions were categorized into cardiovascular effects (QT interval prolongation and orthostatic hypotension) and central nervous system (CNS) effects (CNS depression, parasympatholytic effects, risk of seizures, and akathisia). Antidepressants such as citalopram, escitalopram, venlafaxine, and paroxetine were associated with QT interval prolongation, while haloperidol, risperidone, and quetiapine were highlighted among antipsychotics. Orthostatic hypotension was notable with quetiapine, clozapine, tricyclic, and tetracyclic antidepressants. CNS effects included depression (SSRIs, ADT, Ziprasidone, Perphenazine), seizures (Bupropion, antipsychotics), akathisia (Pimozide, Paroxetine), and parasympatholytic effects (SSRIs, Ziprasidone, Haloperidol). **CONCLUSION:** This study provides a comprehensive analysis of drug interactions between antidepressants and antipsychotics, emphasizing their clinical implications. The findings offer guidance for healthcare professionals to ensure safer and more effective treatment approaches for patients with psychiatric disorders.

**INTRODUCTION**

The problems generated by adverse effects caused by drug interactions in psychiatry are highly relevant, especially in disorders with epidemiological overlap, such as depressive and psychotic disorders. According to Upthegrove et al., 40% of patients with schizophrenia also present depressive disorders, with a higher percentage in acute episodes and lower in chronic episodes.¹ The combination of both disorders is usually associated with a worse prognosis. In addition, adverse effects attributed to pharmacotherapy have a negative impact on treatment adherence, as pointed out by Solmi et al., which, when associated with symptoms such as anhedonia, mood changes, demotivation, and delusional changes, can make treatment more challenging.² Therefore, analyzing the expected adverse effects of drug interactions between antidepressants and antipsychotics is crucial to mitigate potential complications and improve adherence, and consequently, treatment response.

The use of antidepressant drugs is the primary form of treatment for depressive disorders.² Selective serotonin reuptake inhibitors (SSRIs) are considered the first-line drugs for depressive disorders, with fluoxetine, sertraline, and citalopram being the main representatives. On the other hand, serotonin and norepinephrine reuptake inhibitors (SNRIs) are considered second or third-line treatments, represented by venlafaxine, desvenlafaxine, and duloxetine. When it comes to efficacy, studies suggest that amitriptyline, venlafaxine, and duloxetine are the most effective antidepressants. However, when it comes to acceptability, i.e., the patient's ability to tolerate the medication without interruption, mirtazapine, fluoxetine, and escitalopram are the agents that stand out the most.³

Regarding antipsychotics, they can be divided into typical and atypical. Both have similarities, such as dopamine antagonism, but also present differences, such as the magnitude with which this action is performed. However, there is still no established relationship between the intensity of antagonism and therapeutic efficacy. A meta-analysis conducted by Schneider-Thoma and colleagues evaluated the efficacy of these drugs in preventing relapse in patients with psychotic disorders. The results showed that olanzapine performed better in reducing relapses compared to placebo, confirming its therapeutic efficacy.⁴

Considering that depressive and psychotic disorders often coexist and that, consequently, patients may be concurrently treated with antidepressant and antipsychotic drugs, it is essential that the clinical team recognize the clinical relevance of drug interactions between these two types of drugs. The objective of this study is to describe and characterize the potential severity of these drug interactions in order to contribute to establishing criteria to minimize the risk of avoidable harm to the individual's health. It is important to emphasize that the early identification of possible drug interactions can have a significant impact on the safety and efficacy of treatment, resulting in better clinical outcomes and preservation of the patient's quality of life.

**METHODS**

The screening for drug interactions between antipsychotics and antidepressants was conducted using the "Interactions Checker" module of the pharmacological information repository Drugs.com (https://www.drugs.com/drug\_interactions.html). The drugs selected for the study were collected based on two meta-analyses published by Cipriani et al. and Schneider-Thoma et al. A total of 21 antidepressants and 34 antipsychotics were gathered for the study, with those not available on the Drugs.com platform or those without clinically relevant interactions being excluded. Thus, of the drugs identified, only 14 antidepressants (Amitriptyline, Clomipramine, Mirtazapine, Sertraline, Trazodone, Venlafaxine, Fluoxetine, Citalopram, Escitalopram, Bupropion, Nefazodone, Fluvoxamine, Paroxetine, and Duloxetine) and 11 antipsychotics (Amisulpride, Clozapine, Pimozide, Ziprasidone, Haloperidol, Olanzapine, Chlorpromazine, Fluphenazine, Perphenazine, Quetiapine, and Risperidone) were used in the study.³⁻⁴

The searches were performed in a combined manner, crossing the information between the drugs belonging to each of the two studied groups. The potential for interactions of each drug combination was described based on three levels, including the probable mechanism of interaction, the expected clinical outcome, and the clinical management. Interactions were grouped based on the expected clinical outcome, and only interactions with clinical relevance and potential harm to patients were included in order to synthesize the interactions most detrimental to population health.

**RESULTS**

During data collection, the found alterations were divided into two groups: cardiovascular effects and central nervous system (CNS) effects. The outcomes with potential impact on the cardiovascular system include prolongation of the QT interval and orthostatic hypotension, with the former being the most relevant due to its great impact on health and the larger number of drugs associated with such effect. In the CNS, interactions could be classified according to the following implications: CNS depression, parasympatholytic effects, risk of seizures, and akathisia.

Regarding cardiovascular effects, the antidepressants that have more described studies regarding QT interval prolongation are SSRIs, especially citalopram, escitalopram, venlafaxine, and paroxetine. As for antipsychotics, haloperidol, risperidone, and quetiapine can be highlighted, as they are also the most prescribed worldwide (Table 01). Considering orthostatic hypotension, antipsychotics such as quetiapine and clozapine, and tricyclic (TCA) and tetracyclic (TeCA) antidepressants are the most relevant agents (Table 02).

For outcomes related to the CNS, the depressive effect is the most relevant, with ISRS, ADT, and antipsychotics Ziprasidone and Perphenazine standing out (Table 03). Other significant neurological complications include seizures caused by Bupropion and antipsychotics (Table 04); akathisia (uncontrollable psychomotor agitation) caused by Pimozide and Paroxetine (Table 05); and parasympatholytic effects generated by ISRS, Ziprasidone, and Haloperidol (Table 06).

**DISCUSSION**

1. **Cardiovascular Effects:**
2. **Prolongation of the QT interval:**

The QT interval is a period in the electrocardiogram that represents the time from the start of ventricular depolarization to the end of ventricular repolarization. Its normal limit varies with heart rate. Prolongations of this interval are associated with an increased risk of torsades de pointes (TdP), a polymorphic ventricular tachycardia, and atrial fibrillation. The main causes include cardiomyopathies, myocardial ischemia, severe intracranial injuries, electrolyte abnormalities, and medications such as antipsychotics and antidepressants.⁵

This interval is affected by the movement of sodium, potassium, and calcium ions through specific receptors in the cell membrane and endoplasmic reticulum of the cells. Fast sodium channels are responsible for depolarization, slow channels for repolarization, calcium channels maintain the plateau in the action potential, and potassium channels (Ikr) are important in repolarization. Abnormalities in these receptors, such as those caused by some drugs, can affect the cardiac action potential, prolonging the QTc interval. Haloperidol, for example, acts on the Ikr channel and can dose-dependently prolong the QTc interval. Tricyclic antidepressants can enhance the effects of sodium channel blockade when used with a drug that blocks Ikr, such as haloperidol and amitriptyline (Table 1).⁶

Interactions between certain drugs, as mentioned above, can prolong the QT interval. This effect can be explained through two mechanisms: pharmacodynamic interactions, when two or more drugs that prolong the QT interval are combined, leading to a synergistic effect; or pharmacokinetic interactions, when a drug that does not prolong the QT interval, such as paroxetine, reduces the hepatic metabolism, through CYP450 inhibition, of another drug that prolongs it, such as pimozide (Table 01).⁷

The QTc interval is considered normal when it is less than 450ms for men and 460ms for women. Values above 500ms are associated with a significant increase in the risk of TdP. In a study by Trinkley et al., for every 10ms increase in the QTc interval, there is a 5-7% increase in the risk of developing TdP.⁸ Prolongation of the QT interval can lead to various symptoms and serious complications, such as syncope, palpitations, dizziness, cardiac arrest, TdP, and sudden death.⁶

SSRIs can affect the QT interval, with citalopram being the most described as having an impact on this prolongation, although the clinical relevance is not well defined. In an analysis by Castro et al., a review of 38,397 ECGs showed a dose-dependent relationship between this drug, along with escitalopram and amitriptyline, and prolongation of the QT interval, which was even more pronounced in individuals over 60 years old. However, SSRIs generally have a lower number of adverse events, including arrhythmias, compared to tricyclic antidepressants, with sertraline considered the agent with the greatest cardiac safety and paroxetine the only SSRI that has never been reported as having an association with prolongation of the QT interval or TdP.⁹

Among SNRIs, venlafaxine remains the only drug with a significant association with QT prolongation, although this risk remains low at lower doses. Duloxetine did not have a clinically significant association with this effect, although caution should be employed when associated with other agents capable of prolonging the QT interval, as it has the potential to cause plasma increases of these via CYP450 inhibition (table 01).⁵

Among antipsychotics, typical ones present a greater risk of prolongation of the QT interval (less than 5ms) and can increase the risk of AV or sudden death compared to olanzapine, risperidone, or quetiapine, as demonstrated by Leonard et al. in adults aged 30-75 receiving haloperidol.¹⁰ Atypical antipsychotics, although having the potential for QT interval prolongation, have less intensity than typical ones, as demonstrated by Isbister et al. in a study of ECGs from 2,356 individuals who overdosed on antipsychotics. Quetiapine, olanzapine, and risperidone demonstrated QT interval prolongation in 5%, 3%, and 12% of patients, respectively.¹¹

Therefore, it is important to consider the risk of prolonging the QT interval with medications when prescribing antidepressants and antipsychotics. Patients with more than one risk factor, such as smoking, systemic hypertension, and dyslipidemia, are more likely (greater than 85%) to experience this adverse effect. Therefore, it is recommended to avoid prescribing citalopram in patients with a history of heart disease or risk factors for QT interval prolongation and prefer sertraline as the first-choice drug. A baseline ECG is indicated, and if there is no QT interval alteration, monitoring ECGs are not necessary unless there are symptoms such as palpitations, dizziness, and syncope. It is advisable to avoid combining more than one antipsychotic in patients with risk factors for QT interval prolongation, but if the combination is made, monitoring ECG is essential. Therefore, analyzing related QT risk factors and other medications that may interfere with this interval is the best clinical intervention to avoid adverse effects during prescription.⁵

1. **Orthostatic Hypotension (OH):**

OH, characterized by a drop in systolic blood pressure (SBP) of at least 20mmHg or in blood pressure (BP) of at least 10mmHg within the first 3 minutes of assuming the orthostatic position, is a common problem in the elderly, affecting 30 to 70% of them. This condition can cause various complications such as dizziness, syncope, falls, fractures, ischemic events, cognitive impairment, and even death. This occurs due to the intravascular volume redistribution mechanisms involved in the transition from the supine to the orthostatic position, which leads to a decrease in venous return, stroke volume, and total cardiac output. To compensate for the drop in blood pressure, the sympathetic system is activated, increasing heart rate, venous return, and cardiac contractility, restoring BP to normal values in seconds. However, the use of certain medications can interfere with this process, such as the release of norepinephrine from post-ganglionic sympathetic nerves, which can prolong the time required for BP to return.¹²

Some drugs may have hypotensive side effects, such as TCA, with amitriptyline (reduction of up to 10mmHg in SBP) and clomipramine being an example, which are related to the blockade of α-1-adrenergic receptors influential in the vasoconstriction process. Hypotension, in addition to OH, can also be explained by a postsynaptic dysregulation of β-adrenergic receptors and decreased responsiveness to catecholamines in chronic TCA users.¹³ In cases of overdose with these drugs, hypotension is a cause for significant clinical concern (table 02).

Mirtazapine, an antidepressant, can also lead to hypotensive side effects as it inhibits α-2-adrenergic receptors and acts as an antagonist to H1 and 5-HT receptors.¹⁴ In a study conducted by Khawaja et al., mirtazapine was reported to cause hypotension in 7% of treated patients.¹⁵ However, this effect is still being investigated, and it is currently considered a safe drug for patients with cardiovascular diseases.

Furthermore, antidepressants that modulate 5-HT receptors, such as nefazodone and trazodone, have a higher number of reports of hypotensive effects. A reduction of up to 7mmHg in patients treated with high doses of nefazodone was observed, and this effect is a consequence of the mediated inhibition of serotonin in the cardiac sympathetic system, as well as vascular tone.¹⁶ Trazodone mainly acts by inhibiting 5-HT receptors and blocking H1 and α-1-adrenergic receptors, which can lead to hypotension in elderly patients with pre-existing cardiac conditions. Cases of severe hypotension due to overdose, even unresponsive to volume replacement, have been described for trazodone.¹⁷

Among antipsychotics, atypical ones have the highest incidence of hypotension, with clozapine being the drug with the highest reported effect, followed by quetiapine. Clozapine blocks α-1-adrenergic receptors, while quetiapine acts as an antagonist to 5-HT and dopaminergic D2 receptors. In a study conducted by the US National Institute of Mental Health (NIMH) in 2009, 24% of patients treated with clozapine and 12% of patients treated with quetiapine reported hypotension. Therefore, hypotension should be analyzed at the time of prescription, especially in elderly patients and those with pre-existing cardiac conditions. SSRIs are the preferred choice due to their neutral effect on blood pressure, while ADTs and ADTCs should be avoided. The prescription of antipsychotics should be carefully evaluated, especially for clozapine and quetiapine, due to their higher incidence of hypotension, particularly in high-risk patients, such as those with systemic diseases associated with autonomic instability, dehydration, age, and patients using drugs that interact with each other. Clinical management involves changing the drug, reducing the dose, or altering the administration schedule, as well as adequate volume replacement. It is important to monitor high-risk patients with regular analysis of blood pressure and symptoms of hypotension. When prescribing antidepressants and antipsychotics together, synergistic interactions should be analyzed, and combination should be avoided if possible (Table 02).¹⁸

1. **Effects of the Central Nervous System**
2. **Depressant effects on the CNS:**

The side effects on the CNS, although not having a well-defined mechanism of action, may be the result of the affinity of some antidepressants and antipsychotics (table 03) for histamine H1 receptors. The central H1 is expressed in presynaptic histaminergic receptors in the tuberomamillary nucleus of the hypothalamus and plays a role in controlling circadian rhythms and wakefulness.¹⁹ Therefore, when drugs from both classes are used together, they can result in a synergistic effect, leading to sedation of the patient and depression of the CNS.

Mirtazapine is an example of tetracyclics that works by increasing neurotransmitter activity in the CNS. Although it has good tolerability, mirtazapine is often associated with excessive sedation as a side effect due to its affinity with H1 receptors. In addition, mirtazapine can cause other CNS side effects such as dizziness, vertigo, and drowsiness, which can affect the ability to perform activities that require attention and coordination.¹⁹

Some antidepressants have been associated with changes in sleep behavior, such as excess muscle tone and/or muscle spasms, enactment of dreams, and, in more severe cases, violent behavior, a condition known as REM sleep behavior disorder.²⁰ In addition, some drugs that are antagonists of serotonin receptors have been associated with amnesia in a study conducted by Nikitin and colleagues in 2018, which may contribute to memory loss during the use of these drugs.²¹

The adopted management is to monitor the patients' breathing when using the combination of these drugs and to make a dose adjustment if necessary. According to Dauvillers et al., an alternative to consider is the use of bupropion, which does not have the aforementioned side effects.²⁰ In addition, some antipsychotics such as clozapine and quetiapine can be used as therapy for narcolepsy. Patients who use antipsychotics and antidepressants (table 03) should be advised to avoid dangerous activities that require motor coordination and mental alertness.²²

1. **Increased risk of seizures:**

Epileptic seizures are common side effects among compounds that act on the central nervous system, with drug-induced seizures classified as "conditions with epileptic seizures that do not require a diagnosis of epilepsy". Therefore, the effects are caused by transient actions of drugs in the CNS.²³

The risk of seizures has been associated with various antipsychotics when used in conjunction with bupropion (Table 04). The high risk associated with the use of bupropion, which was withdrawn from the market due to its high side effect profile at high doses, is already known. Therefore, bupropion is contraindicated in patients at increased risk of seizures and, upon reintroduction to the market, a maximum dose of 450mg/day was established, since its effects are dose-dependent.²⁴ According to Steinert et al., bupropion is classified as a substance with low to moderate risk, but the effect can increase by up to 37% in patients with intoxication, emphasizing the need not to exceed its therapeutic range.²³ Although the mechanism has not been fully elucidated, the drug and its metabolites have a weak inhibitory effect on the reuptake of norepinephrine and dopamine. The sympathomimetic amine structure of bupropion suggests that it may act via the release of catecholamines in the CNS and possibly lead to hypothalamic stimulation. This mechanism may be partially responsible for the seizures observed in cases of bupropion overdose.²⁵

In the use of antipsychotics, a study by Górska et al. compared a control group with another group of patients using these drugs and found a 4% increase in the number of seizure episodes. This risk is related to increased plasma levels of the medications. Among first-generation antipsychotics, the risk was relatively low, except for chlorpromazine, which had a risk of 9% for patients treated with high doses (equivalent to 1,000 mg/day), 0.7% in patients with moderate doses, and 0.3% in patients with low doses. Haloperidol, fluphenazine, and perphenazine had lower potential epileptogenic activity due to their low therapeutic doses. Regarding second-generation antipsychotics, olanzapine and quetiapine appear to be safer than chlorpromazine, although they are selective for mesolimbic dopamine receptors, which have more intense pro-convulsive effects. Quetiapine and olanzapine showed seizure rates of 0.9%.²⁶

The study by Steinert et al. found that the use of extended-release formulations of bupropion presented a significantly lower seizure rate than immediate-release formulations, becoming an option to be considered in patients at risk of seizures. Other safe drugs include sertraline and venlafaxine, which are preferred to avoid drug interactions in patients with epilepsy. In case of seizures due to drug interactions with bupropion, the first-line therapy is diazepam and other benzodiazepines, while phenytoin can be used in cases non-responsive to benzodiazepines.²³ Furthermore, it is important to note that antipsychotics should not be combined with bupropion, as this may decrease the seizure threshold.²⁴

1. **Akathisia:**

Akathisia is a movement disorder characterized by subjective feelings of restlessness and excessive movements, almost exclusively induced by medication. Diagnosis can be difficult due to its subjectivity, which can compromise treatment by leading to decreased adherence as patients relate the disorder to medication use, or by causing patients to autonomously increase their medication dose, associating the disorder with the disease. Dopaminergic blockade is the most well-known mechanism, but research also indicates a relationship with anticholinergic antipsychotics and β-adrenergic blockers, as well as an association of these with SSRIs (Table 05).²⁷

This disorder is more common in SSRIs such as paroxetine, and its mechanism is not fully understood, but research suggests that it may be related to an increase in serum serotonin and the consequent inhibition of dopamine release. Among antipsychotics, akathisia is linked to dopaminergic blockade and usually occurs after the initiation of pharmacotherapy or dose increase.²⁸ Research points to a low risk of akathisia attributed to olanzapine, which is actually a drug that can cause sedation. Quetiapine also has a low risk of causing akathisia due to its lower affinity for dopaminergic receptors compared to other antipsychotics. Finally, pimozide has a higher risk among the described antipsychotics (Table 05) and is recommended only for severely affected patients or those resistant to other treatments.²⁹

Therefore, due to the impact that akathisia can have on treatment adherence, it is important to conduct a thorough analysis of the prescription. Combining antipsychotics or combining some antipsychotics with SSRIs should be avoided. If a reduction in dose or medication discontinuation is not possible, the combination with other classes of drugs may help control this effect. Low-dose beta-blockers and benzodiazepines are used to decrease restlessness, but their efficacy is not clearly described in the current literature. In addition, switching antidepressants may be useful in patients who do not tolerate beta-blockers, as mirtazapine has been shown to be effective in treating akathisia in a study by Miller and colleagues.³⁰ Since the diagnosis of akathisia is complex and there is low consensus on treatment, it is advisable to adequately monitor patients using antipsychotics, especially in combination with SSRIs. If dose reduction is not possible, the use of the mentioned drugs may help treat this syndrome.²⁷

1. **Parasympatholytic effects:**

Anticholinergic effects, such as constipation, mydriasis, blurred vision, tachycardia, and urinary retention, have been associated with the simultaneous use of some medications (Table 06). A 2021 meta-analysis by Oliva et al. reported that patients using antipsychotics and antidepressants experienced abdominal pain, dry mouth, dizziness, and constipation.³¹ Connections between the CNS and the enteric nervous system occur at various levels, including the gut, which contains most of the body's serotonin and is responsible for regulating gastrointestinal development and functionality. Serotonin, or 5-HT, also plays an important role in intestinal inflammation and physiological gastrointestinal motility. There is evidence linking the microbiome-gut-brain axis, meaning that emotional disturbances can cause gastrointestinal disorders and vice versa.³² Therefore, drugs that act on serotonin receptors can also affect the gastrointestinal tract, such as antidepressants that are associated with serotoninergic neurons. According to the CANMAT guidelines, escitalopram and mirtazapine showed a prevalence of constipation between 4% and 13%. Furthermore, venlafaxine and sertraline were also associated with constipation in a study by Oliva et al.³¹

Constipation associated with antipsychotics is a frequent and severe adverse effect, particularly in individuals who are taking clozapine. Clozapine has been found to impede gastrointestinal motility, resulting in constipation, and has been reported in up to 60% of patients receiving this medication. In rare instances, complications can even be life-threatening. It is crucial to prescribe appropriate laxatives for managing constipation in individuals on antipsychotic treatment, yet there is a lack of guidance regarding the comparative effectiveness and potential harm of different agents within this specific population. The exact cause of antipsychotic-induced constipation is not clear, but it is believed to be due to anticholinergic action, 5-HT receptor antagonism, and H1 receptor antagonism. These effects can impair intestinal autonomic regulation, inhibit smooth muscle contraction, and prolong intestinal transit time, leading to constipation.³³

Another common adverse effect related to antidepressants and antipsychotics is dry mouth, which can cause difficulties in eating, speaking, and dental complications. Salivary secretion is regulated by the Autonomic Nervous System, with parasympathetic stimulation responsible for increasing salivary secretion through cholinergic transmission and muscarinic receptor action. SNRIs produce a central accumulation of norepinephrine and activation of α-2 receptors, inhibiting salivary neurons and resulting in dry mouth. In the meta-analysis by Oliva et al., venlafaxine, sertraline, and escitalopram differed from placebo, causing dry mouth.³¹ Additionally, citalopram, trazodone, and mirtazapine were also identified as potential causes of this effect. Regarding antipsychotics, dry mouth was reported as an adverse effect in the treatment of alcohol dependence with the cited drugs, being one of the reasons for treatment discontinuation.³⁴

Mydriasis is an important adverse effect characterized by dilation of the pupil, which may occur as a result of the use of antidepressants and antipsychotics. The diameter of the pupil is regulated by the sympathetic and parasympathetic autonomic nervous system, and SNRIs may influence the dilation mechanism. In a study conducted by Howell and colleagues, mydriasis was reported in 36.6% of cases of venlafaxine overdose, an SNRI.³⁵ In addition, blurred vision is a common effect related to the use of antidepressants, especially SSRIs and SNRIs. The theories about the mechanism of this effect include the anticholinergic effect and rapid fluctuations in intraocular pressure. A study with 124 patients reported that sertraline, venlafaxine, fluoxetine, escitalopram, and citalopram were the most prevalent antidepressants associated with blurred vision, reported by 63.7% of patients.³⁶

Furthermore, urinary retention is a side effect that may occur in patients using antipsychotics and antidepressants, even without any underlying urological cause. The meta-analysis by Faure Walker and colleagues showed that the effect occurred in 5% of patients using haloperidol. This may be related to the fact that first-generation antipsychotics, which act predominantly on dopamine D2 receptors, are not selective and may cause anticholinergic effects. These effects may influence the capacity and residual volume of the bladder, the intervals between contractions of the smooth bladder musculature, the function of the external urethral sphincter, and the volume of urine during micturition, through inhibition of spinolobular reflexes.³⁷

Finally, tachycardia is an important but rare effect. At therapeutic doses, it has been shown to be almost insignificant in the use of atypical and typical antipsychotics, although it is more prevalent among the latter. On the other hand, at extreme doses, such effect may arise, associated or not with others, such as hypotension, prolongation of the QT interval, and cardiovascular toxicity. In the case of antidepressants, SNRIs and SSRIs are moderately safer in relation to this effect, and SSRIs may even decrease heart rate, with paroxetine being the most cardioprotective reported in the current literature. Conversely, SNRIs may increase heart rate, with venlafaxine being the least tolerated and therefore avoided in patients with cardiovascular history.³⁸

Parasympatholytic effects should be considered when prescribing these medications. It is important to avoid concomitant use of the drugs presented (Table 06) due to the risk of interaction. If discontinuation of treatment is not possible, the possibility of changing medications should be evaluated, such as avoiding the use of SNRIs and SSRIs in patients with vision-related effects. Monitoring the patient for the onset of effects is essential if drugs with potential interactions are maintained. Dose reduction may be an option to consider, as many effects are dose-dependent. Additionally, symptoms such as tachycardia can be controlled with the addition of other drugs, such as beta blockers. The recommended management includes adopting a healthy lifestyle, controlling the underlying disease, and adjusting the prescription of antipsychotics and antidepressants. This may involve physical exercise, defecation training, dietary adjustments (with increased intake of fiber and water) and avoiding the prescription of medications with interactions (Table 06).³⁹

In summary, this article analyzed the main drug interactions between antidepressants and antipsychotics, described the most important clinical effects according to prevalence and impact on the patient, and stratified them according to the affected system. Thus, it provided a schematization to allow easy access to the clinical team, which should be aware of these issues to offer a more effective and safe treatment to patients with psychiatric disorders.

**REFERENCES**

1. Upthegrove R, Marwaha S, Birchwood M. Depression and Schizophrenia: Cause, Consequence or Trans-diagnostic Issue? SCHBUL. 2016:sbw097.
2. Solmi M, Miola A, Croatto G, Pigato G, Favaro A, Fornaro M, et al. How can we improve antidepressant adherence in the management of depression? A targeted review and 10 clinical recommendations. Braz J Psychiatry. 2021;43:189–202.
3. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet. 2018;391:1357–66.
4. Schneider-Thoma J, Chalkou K, Dörries C, Bighelli I, Ceraso A, Huhn M, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. The Lancet. 2022;399:824–36.
5. Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT Prolongation, Torsades de Pointes, and Psychotropic Medications: A 5-Year Update. Psychosomatics. 2018;59:105–22.
6. Khatib R, Sabir FRN, Omari C, Pepper C, Tayebjee MH. Managing drug-induced QT prolongation in clinical practice. Postgraduate Medical Journal. 2021;97:452–8.
7. Wiśniowska B, Tylutki Z, Wyszogrodzka G, Polak S. Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect - comprehensive overview of clinical trials. BMC Pharmacol Toxicol. 2016;17:12.
8. Trinkley KE, Lee Page R, Lien H, Yamanouye K, Tisdale JE. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. Current Medical Research and Opinion. 2013;29:1719–26.
9. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ. 2013;346:f288–f288.
10. E Leonard C. Antipsychotics and the Risks of Sudden Cardiac Death and All-Cause Death: Cohort Studies in Medicaid and Dually Eligible Medicaid-Medicare Beneficiaries of Five States. J Clin Exp Cardiolog. 2012;01.
11. Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice: Clinical assessment of drug-induced QT prolongation. Br J Clin Pharmacol. 2013;76:48–57.
12. Frith J, Parry SW. New Horizons in orthostatic hypotension. Age Ageing. 2016:168–74.
13. Zhang W, Wang Y, Wang L, Gu J, Song Z, Liu Y. Clomipramine-induced vasoconstriction in the rat aorta is mediated via inhibition of calcium-activated potassium channels. Cardiovasc Toxicol. 2018;18:139-147.
14. Jilani TN, Gibbons JR, Faizy RM, Saadabadi A. Mirtazapine. StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
15. Khawaja IS, Feinstein RE. Cardiovascular Effects of Selective Serotonin Reuptake Inhibitors and Other Novel Antidepressants: Heart Disease. 2003;5:153–60.
16. Agelink M. Autonomic neurocardiac function in patients with major depression and effects of antidepressive treatment with nefazodone. Journal of Affective Disorders. 2001;62:187–98.
17. Camacho LD, Stearns J, Amini R. Management of Trazodone Overdose with Severe Hypotension. Case Reports in Emergency Medicine. 2019;2019:1–3.
18. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018;17:341–56.
19. Tono K, Nango E, Sugahara M, Song C, Park J, Tanaka T, et al. Diverse application platform for hard X-ray diffraction in SACLA (DAPHNIS): application to serial protein crystallography using an X-ray free-electron laser. J Synchrotron Rad. 2015;22:532–7.
20. Dauvilliers Y, Schenck CH, Postuma RB, Iranzo A, Luppi P-H, Plazzi G, et al. REM sleep behaviour disorder. Nat Rev Dis Primers. 2018;4:1–16.
21. Nikitin VP, Solntseva SV, Kozyrev SA, Nikitin PV, Shevelkin AV. NMDA or 5-HT receptor antagonists impair memory reconsolidation and induce various types of amnesia. Behavioural Brain Research. 2018;345:72–82.
22. Das B, Ramasubbu SK, Agnihotri A, Kumar B, Rawat VS. Leading 20 drug–drug interactions, polypharmacy, and analysis of the nature of risk factors due to QT interval prolonging drug use and potentially inappropriate psychotropic use in elderly psychiatry outpatients. Therapeutic Advances in Cardiovascular Disease. 2021;15:175394472110588.
23. Steinert T, Fröscher W. Epileptic Seizures Under Antidepressive Drug Treatment: Systematic Review. Pharmacopsychiatry. 2018;51:121–35.
24. Costa R, Oliveira NG, Dinis-Oliveira RJ. Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects. Drug Metabolism Reviews. 2019;51:293–313.
25. Kara H, Ak A, Bayir A, Acar D, Istanbulluoglu R, Degirmenci S. Seizures After Overdoses of Bupropion Intake. Balkan Med J. 2013;30:248–9.
26. Górska N, Słupski J, Cubała WJ. Antipsychotic drugs in epilepsy. Neurol Neurochir Pol. 2019;53:408–12.
27. Sienaert P, Van Harten P, Rhebergen D. The psychopharmacology of catatonia, neuroleptic malignant syndrome, akathisia, tardive dyskinesia, and dystonia. Handbook of Clinical Neurology, vol. 165. Elsevier; 2019. p. 415–28.
28. Ohno Y, Kunisawa N, Shimizu S. Antipsychotic Treatment of Behavioral and Psychological Symptoms of Dementia (BPSD): Management of Extrapyramidal Side Effects. Front Pharmacol. 2019;10:1045.
29. Zareifopoulos N, Panayiotakopoulos G. Treatment Options for Acute Agitation in Psychiatric Patients: Theoretical and Empirical Evidence. Cureus. 2019.
30. Miller CH, Fleischhacker WW. Managing Antipsychotic-Induced Acute and Chronic Akathisia: Drug Safety. 2000;22:73–81.
31. Oliva V, Lippi M, Paci R, Del Fabro L, Delvecchio G, Brambilla P, et al. Gastrointestinal side effects associated with antidepressant treatments in patients with major depressive disorder: A systematic review and meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2021;109:110266.
32. Generoso JS, Giridharan VV, Lee J, Macedo D, Barichello T. The role of the microbiota-gut-brain axis in neuropsychiatric disorders. Braz J Psychiatry. 2021;43:293–305.
33. Every-Palmer S, Newton-Howes G, Clarke MJ. Pharmacological treatment for antipsychotic-related constipation. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2014. p. CD011128.
34. Kishi T, Sevy S, Chekuri R, Correll CU. Antipsychotics for Primary Alcohol Dependence: A Systematic Review and Meta-Analysis of Placebo-Controlled Trials. J Clin Psychiatry. 2013;74:e642–54.
35. Howell C, Wilson AD, Waring WS. Cardiovascular toxicity due to venlafaxine poisoning in adults: a review of 235 consecutive cases. Br J Clin Pharmacol. 2007;64:192–7.
36. Healy D, Mangin D, Lochhead J. Development and persistence of patient-reported visual problems associated with serotonin reuptake inhibiting antidepressants. JRS. 2022;33:37–47.
37. Faure Walker N, Brinchmann K, Batura D. Linking the evidence between urinary retention and antipsychotic or antidepressant drugs: A systematic review: Urinary Retention and Antipsychotics or Antidepressants. Neurourol Urodynam. 2016;35:866–74.
38. Manolis TA, Manolis AA, Manolis AS. Cardiovascular Safety of Psychiatric Agents: A Cautionary Tale. Angiology. 2019;70:103–29.
39. Xu Y, Amdanee N, Zhang X. Antipsychotic-Induced Constipation: A Review of the Pathogenesis, Clinical Diagnosis, and Treatment. CNS Drugs. 2021;35:1265–74.

**TABLES**

Table 01: Drug interactions associated with QT interval prolongation.

|  |  |  |
| --- | --- | --- |
| **Antipsychotics** | **Antidepressants** | **Mechanisms** |
| Amisulpride | Amitriptyline | Synergistic effect of drugs |
| Clozapine | Clomipramine |  |
| Pimozide | Mirtazapine |  |
| Ziprasidone | Sertraline |  |
| Haloperidol | Trazodone | Haloperidol may increase serum concentrations of tricyclic antidepressants by inhibiting their metabolism via CYP450. |
|  | Venlafaxine |
|  |  |  |
| Amisulpride | Fluoxetine | Synergistic effect of drugs |
| Ziprasidone |  |  |
| Pimozide |  | Pimozide plasma increase by co-administration with CYP450 inhibitors. |
|  |  |  |
| Amisulpride | Citalopram | Synergistic effect of drugs |
| Chlorpromazine | Escitalopram |  |
| Fluphenazine |  |  |
| Haloperidol |  |  |
| Perphenazine |  |  |
| Pimozide |  |  |
| Quetiapine |  |  |
| Risperidone |  |  |
| Ziprasidone |  |  |
| Clozapine |  | Clozapine plasma increase by co-administration with CYP450 inhibitors. |
|  |  |  |
| Pimozide | Bupropion | Plasma increase of Pimozide and Risperidone by co-administration with CYP450 inhibitors. |
| Risperidone |  |
|  |  |  |
| Clozapine | Nefazodone | Plasma increase of Pimozide and Clozapine by co-administration with CYP450 inhibitors. |
| Pimozide |  |
|  |  |  |
| Olanzapine | Fluvoxamine | Plasma increase of Pimozide and Olanzapine by co-administration with CYP450 inhibitors |
| Pimozide |  |
|  |  |  |
| Pimozide | Paroxetine | Pimozide plasma increase by co-administration with CYP450 inhibitors. |
|  | Duloxetine |

Table 02: Drug interactions associated with orthostatic hypotension.

|  |  |  |
| --- | --- | --- |
| **Antipsychotics** | **Antidepressants** | **Mechanisms** |
| Clozapine | Nefazodone | Synergistic effect of drugs |
| Quetiapine |   |   |
|   |   |   |
| Clozapine | Amitriptyline | Synergistic effect of drugs |
|   | Trazodone |   |
|   | Mirtazapine |   |

Table 03: Drug interactions associated with CNS depression.

|  |  |  |
| --- | --- | --- |
| **Antipsychotics** | **Antidepressants** | **Mechanisms** |
| Amisulpride | Citalopram | Synergistic effect of drugs |
| Chlorpromazine | Escitalopram |   |
| Fluphenazine |   |   |
| Haloperidol |   |   |
| Perphenazine |   |   |
| Ziprasidone |   |   |
|   |   |   |
| Ziprasidone | Clomipramine | Synergistic effect of drugs |
|   | Fluoxetine |   |
|   | Venlafaxine |   |
|   |   |   |
| Haloperidol | Mirtazapine | Synergistic effect of drugs |
| Ziprasidone | Sertraline |   |
|   | Trazodone |   |

Table 04: Drug interactions associated with seizures.

|  |  |  |
| --- | --- | --- |
| **Antipsychotics** | **Antidepressants** | **Mechanisms** |
| Chlorpromazine | Bupropion | Synergistic effect of drugs |
| Fluphenazine |   |
| Haloperidol  |   |
| Olanzapine |   |   |
| Perphenazine |   |
| Quetiapine |   |   |
| Ziprasidone |   |   |

Table 05: Drug interactions associated with akathisia.

|  |  |  |
| --- | --- | --- |
| **Antipsychotics** | **Antidepressants** | **Mechanisms** |
| Ziprasidone | Clomipramine | Synergistic effect of drugs |
|   | Fluoxetine |   |
|   | Venlafaxine |   |
|  |  |  |
| Haloperidol | Mirtazapine | Synergistic effect of drugs |
| Ziprasidone | Sertraline |   |
|   | Trazodone |   |
|  |  |  |
| Flufenazine | Citalopram | Synergistic effect of drugs |
| Haloperidol | Escitalopram |   |
| Ziprasidone |   |   |

Table 06: Drug interactions associated with parasympatholytic effects.

|  |  |  |
| --- | --- | --- |
| **Antipsychotics** | **Antidepressants** | **Mechanisms** |
| Ziprasidone | Clomipramine | Synergistic effect of drugs |
|   | Fluoxetine |   |
|   | Venlafaxine |   |
|  |  |  |
| Haloperidol | Mirtazapine | Synergistic effect of drugs |
| Ziprasidone | Sertraline |   |
|   | Trazodone |   |
|  |  |  |
| Fluphenazine | Citalopram | Synergistic effect of drugs |
| Haloperidol | Escitalopram |   |
| Ziprasidone |   |   |