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Tricyclic antidepressants: An update

Antidepressivos tricíclicos: Uma atualização

Antidepresivos tricíclicos: Una actualización

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Abstract
Tricyclic antidepressants (TCAs) are a class of psychotropic medications primarily used in the treatment of major depressive disorders, although their indications extend to a variety of psychiatric and neurological conditions. This class of medications was one of the first to be developed for the treatment of depression, marking a revolution in the management of this condition in the mid-20th century. The aim of this study is to present a narrative review in the form of an update on the pharmacokinetic properties, pharmacodynamics, indications, and side effects of tricyclic antidepressants. For this purpose, a narrative review in the format of an update was carried out, which analyzed 42 manuscripts. TCAs have various pharmacological and therapeutic properties, low cost, but their major limitation is their side effects. Since the clinical trials for this class were conducted well before the launch of new antidepressants, new research is needed to allow comparison of these groups within the same methodology and with more up-to-date statistics.
Keywords: Tricyclic antidepressive agents; Mental disorders; Psychotropic drugs; Therapeutic uses; Drug-related side effects and adverse reactions.

Resumo
Os antidepressivos tricíclicos (ADTs) são uma classe de medicamentos psicotrópicos utilizados principalmente no tratamento de transtornos depressivos maiores, embora suas indicações se estendam a uma variedade de condições psiquiátricas e neurológicas. Esta classe de medicamentos foi uma das primeiras a ser desenvolvida para o tratamento da depressão, marcando uma revolução no manejo desta condição na metade do século XX. O objetivo deste estudo é apresentar uma revisão narrativa na forma de atualização sobre as propriedades farmacocinéticas, farmacodinâmicas, indicações e efeitos colaterais dos antidepressivos tricíclicos. Para tal foi realizada uma revisão narrativa no formato de atualização que analisou 42 manuscritos. Os ADTs apresentam diversas propriedades farmacológicas e terapêuticas, custo baixo, porém sua maior limitação são seus efeitos colaterais. Como os ensaios clínicos dessa classe foram realizadas em período bem anterior ao lançamento dos novos antidepressivos são necessárias novas pesquisas que permitam a comparação desses grupos dentro da mesma metodologia e com estatística mais atualizada.
Palavras-chave: Antidepressivos tricíclicos; Transtornos mentais; Psicotrópicos; Usos terapêuticos; Efeitos colaterais e reações adversas relacionados a medicamentos.

Resumen
Los antidepresivos tricíclicos (ATC) son una clase de medicamentos psicotrópicos utilizados principalmente para el tratamiento de trastornos depresivos mayores, aunque sus indicaciones se extienden a una variedad de condiciones psiquiátricas y neurológicas. Esta clase de medicamentos fue una de las primeras en ser desarrollada para el tratamiento de la depresión, marcando una revolución en el manejo de esta condición en la mitad del siglo XX. El objetivo de este estudio es presentar una revisión narrativa en forma de actualización sobre las propiedades farmacocinéticas, farmacodinámicas, indicaciones y efectos secundarios de los antidepresivos tricíclicos. Para ello se realizó una revisión narrativa en formato de actualización que analizó 42 manuscitos. Los ATC presentan diversas propiedades farmacológicas y terapéuticas, bajo costo, sin embargo, su mayor limitación son sus efectos secundarios. Como los ensayos clínicos de esta clase fueron realizados en un período mucho anterior al lanzamiento de los nuevos

antidepresivos, son necesarias nuevas investigaciones que permitan la comparación de estos grupos dentro de la misma metodología y con estadísticas más actualizadas.
Palabras clave: Antidepresivos tricíclicos; Transtornos mentales; Psicotrópicos; Usos terapéuticos; Efectos colaterales y reacciones adversas relacionados con medicamentos.

1. Introduction

The advent of tricyclic antidepressants (TCAs) in the 1950s heralded a new epoch in the treatment of depression, establishing themselves as a promising alternative (Gillman, 2007; Moraczewski et al., 2024). With mechanisms of action that involve the inhibition of neurotransmitter reuptake, such as serotonin and norepinephrine, they have demonstrated significant efficacy in ameliorating depressive symptoms. However, their usage has been accompanied by a side effect profile that often limited their applicability (Gillman, 2007; Moraczewski et al., 2024; Schneider et al., 2019).

As time progressed and new classes of antidepressants emerged, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), the clinical use of TCAs has seen a decline. These newer medications offer more tolerable side effect profiles, leading many healthcare providers to favor them as first-line treatments for depression (J. Moraczewski et al., 2024). Despite this, TCAs retain an important role in the therapeutic arsenal, particularly in cases of treatment-resistant depression and various chronic pain conditions (Moraczewski et al., 2024; Schneider et al., 2019).

Beyond their use in depression, TCAs have been applied to a surprisingly broad range of medical conditions, reflecting their unique pharmacological properties (Gillman, 2007; Moraczewski et al., 2024). These include, but are not limited to, neuropathic pain disorders, irritable bowel syndrome, migraines, and insomnia. The effectiveness of TCAs in these conditions, often at lower doses than those used for treating depression, underscores their versatility as therapeutic agents. This expanded use underlines the importance of fully understanding their action mechanisms, side effect profiles, and appropriate management strategies to maximize therapeutic benefits while minimizing risks (Gillman, 2007; Moraczewski et al., 2024; Schneider et al., 2019).

Depression stands out for its high prevalence and morbidity, being one of the leading causes of global disease burden. Furthermore, depression is a major cause of absenteeism and presenteeism in the workplace, being the third leading cause of work disability in Brazil. The country leads the ranking of depression prevalence among developing nations, with a frequency of 10 to 18% over a twelve-month period, representing 20 to 36 million people affected – equivalent to 10% of the global depression population (Calvi et al., 2021). Depression and anxiety are estimated to account for an annual productivity loss of over one trillion dollars. In light of the needs presented by society, the investment gap in the treatment of mental disorders remains disproportionate, especially in low- and middle-income countries: mental health investment is less than 1% of the health budget, and only 20 to 40% of people receive treatment (Calvi et al., 2021).

The costs of depressive disorders and other mental and neurological disorders stem from their high prevalence, excess mortality, and loss of productivity, coupled with externalities in various sectors of society. The benefits of treatment are reflected in the improvement of clinical status and individual functionality, quality of life, productivity at work, and the reduction of externalities. Treatment of mental disorders benefits others: for example, mental health care for a mother with postpartum depression positively impacts the motor, cognitive, and emotional development of the child. Although there is no definitive cure for mental disorders, the treatment of depression is effective, low-cost, and cost-effective.

Faced with the challenges associated with the management of depression and other complex medical conditions, TCAs remain a valuable tool. Their role in current medical practice, despite the existence of new pharmacological therapies, reflects the ongoing need for diverse and low-cost treatment options (Gillman, 2007; Moraczewski et al., 2024; Schneider et al., 2019). As we move forward, it is crucial for healthcare professionals to maintain a comprehensive understanding of TCAs, recognizing both their limitations and therapeutic potential (Schneider et al., 2019). The future of TCA utilization will depend on our ability

to integrate new research with established clinical practices, optimizing outcomes for patients across an increasingly broad spectrum of conditions. Thus, the objective of this review is to provide an update on the pharmacology and clinical applications of TCAs.

2. Methodology

This is a narrative review in an updated format, following the structure proposed by Snyder (2019) (Snyder, 2019), which conducted a search for articles in the PubMed, Scielo, and Google Scholar databases using the following keywords: "Tricyclic Antidepressants, Pharmacology, Mental Disorders, Therapeutic Uses, Drug Interactions." There were no restrictions based on language. The search was limited to articles published in the last 10 years. Included in the review were systematic or non-systematic reviews on the topic, as well as meta-analyses. Reports and case series, editorials, or conference proceedings were excluded. This review was narrative, as the author did not employ tools to score the evidence but rather selectively curated the most relevant information deemed essential for clinical practice (Snyder, 2019).

3. Results and Discussion

Mechanism of action

Tricyclic antidepressants (TCAs) primarily function through the inhibition of neurotransmitter reuptake, specifically targeting serotonin (5-HT) and norepinephrine (NE), in neuronal synaptic clefts. This inhibition elevates the concentration of these neurotransmitters within the synaptic space, amplifying their effect on postsynaptic receptors, and subsequently improving symptoms of depression. The antidepressant effect is, therefore, linked to the sustained increase of 5-HT and NE levels in the synaptic cleft, enhancing neural communication and modulating the brain pathways that govern mood and emotional regulation (Calvi et al., 2021; Gillman, 2007; J. Moraczewski et al., 2024; Schneider et al., 2019; Shaha, 2023).

Beyond the reuptake inhibition of 5-HT and NE, TCAs interact with a range of other receptors, which contributes to their therapeutic effects and side effect profile. They act as antagonists at alpha-1 adrenergic receptors, histamine H1 receptors, and muscarinic cholinergic receptors. These receptor interactions explain some of the common side effects of TCAs, such as sedation (from H1 receptor antagonism), anticholinergic effects (like dry mouth, blurred vision, and constipation from muscarinic receptor antagonism), and orthostatic hypotension (from alpha-1 adrenergic receptor antagonism) (Calvi et al., 2021; Gillman, 2007; Moraczewski et al., 2024; Schneider et al., 2019; Shaha, 2023).

TCAs' extensive action across various neurotransmitter systems is responsible for their efficacy in diverse psychiatric and neurological conditions but also contributes to the complexity of their clinical management due to the necessity of balancing therapeutic benefits against the potential for adverse effects (Calvi et al., 2021; Gillman, 2007; J. Moraczewski et al., 2024; Schneider et al., 2019; Shaha, 2023).

Pharmacokinetics (Baldaçara et al., 2019; Baldaçara & Tung, 2020; J. Moraczewski et al., 2024; Schneider et al., 2019)

The pharmacokinetics of tricyclic antidepressants (TCAs) involves the absorption, distribution, metabolism, and elimination of these drugs in the body. Although there are specific differences among the various TCAs, many share common pharmacokinetic characteristics, which play an important role in the efficacy and side effect profile of these medications (Moraczewski et al., 2024; Schneider et al., 2019).

Absorption**:** TCAs are well absorbed by the gastrointestinal tract after oral administration. The presence of food may delay the absorption of some TCAs, but it does not significantly affect the total amount of drug absorbed (Moraczewski et al., 2024; Schneider et al., 2019).

Onset of action**:** Although absorption occurs rapidly, with peak plasma concentrations reached within a few hours after dosing, the clinical onset of antidepressant action usually takes several weeks (Moraczewski et al., 2024; Schneider et al., 2019).

Distribution**:** Plasma Protein Binding: TCAs have a high affinity for plasma proteins, mainly albumin and alpha-1-acid glycoprotein, which means that a large proportion of the drug in plasma is bound to proteins, with only a small fraction free to exert pharmacological effects (Moraczewski et al., 2024; Schneider et al., 2019).

Volume of distribution**:** They have a large volume of distribution, penetrating well into body tissues, including the brain, which is essential for their antidepressant activity (Moraczewski et al., 2024; Schneider et al., 2019).

Metabolism**:** TCAs are extensively metabolized in the liver, primarily through the cytochrome P450 system. The metabolism results in metabolites that can be active or inactive. In some cases, the active metabolites contribute to the therapeutic action or to the side effects of the medications. A significant first-pass hepatic effect reduces the oral bioavailability of some TCAs, which means that a portion of the administered dose is metabolized before reaching the systemic circulation (Moraczewski et al., 2024; Schneider et al., 2019).

Half-life**:** The TCAs have a variable half-life, which can range from about 10 hours to over 24 hours, depending on the specific drug and the metabolic characteristics of the patient. This influences the dosing frequency of the medications (Moraczewski et al., 2024; Schneider et al., 2019).

Excretion**:** The metabolites of TCAs are primarily excreted by the kidneys in urine, although a small amount may also be excreted in feces. The complete elimination of the drug and its metabolites can take several days. The pharmacokinetics of TCAs can be affected by various factors, including age, liver and kidney function, drug interactions, and genetic variations in drug metabolism. For example, elderly patients or those with impaired liver function may have reduced clearance of TCAs, leading to higher plasma concentrations and an increased risk of side effects. Therefore, dosage adjustments and careful monitoring are often necessary to optimize TCA therapy and minimize risks (Moraczewski et al., 2024; Schneider et al., 2019).

Pharmacodynamics

The pharmacodynamics of tricyclic antidepressants (TCAs) involves their mode of action in the central and peripheral nervous system, influencing various neurotransmitters and receptors. These underlying mechanisms contribute both to their therapeutic effects and to the profile of side effects. Here is a summary of the main aspects of the pharmacodynamics of TCAs (Moraczewski et al., 2024; Schneider et al., 2019).

Serotonin and norepinephrine: The primary mechanism by which TCAs exert their antidepressant effects is the inhibition of the reuptake of serotonin (5-HT) and norepinephrine (NE) at the presynaptic terminals. This increases the availability of these neurotransmitters in the synaptic cleft, enhancing serotonergic and noradrenergic neurotransmission and improving communication between neurons. This increased availability of 5-HT and NE is associated with the improvement of depressive symptoms (Moraczewski et al., 2024; Schneider et al., 2019).

Activity at adrenergic receptors: Alpha-1 Receptor Blockade: TCAs can block alpha-1 adrenergic receptors, which contributes to some of their side effects, such as orthostatic hypotension (a drop in blood pressure upon standing) and sedation (Calvi et al., 2021).

Activity at histaminergic receptors: H1 Receptor Blockade: Many TCAs have a strong affinity for histaminergic H1 receptors, resulting in antihistaminic effects that can cause sedation and weight gain (Shaha, 2023).

Anticholinergic effects: TCAs block muscarinic cholinergic receptors (M1), resulting in anticholinergic effects such as dry mouth, constipation, urinary retention, blurred vision, and in some cases, confusion or delirium, especially in elderly patients (J. Moraczewski et al., 2024; Schneider et al., 2019).

Cardiac effects: TCAs can affect cardiac conduction by acting as sodium channel blockers, which can prolong the QT interval and increase the risk of cardiac arrhythmias, especially at high doses or in patients with pre-existing cardiac conditions (Moraczewski et al., 2024; Schneider et al., 2019).

Neuromodulatory effects: With prolonged use, TCAs can promote the regulation of various receptor systems in the brain, including the downregulation of beta-adrenergic receptors and the sensitization of certain serotonin receptor subtypes, contributing to the long-term therapeutic effects and to the normalization of brain function in depressive states (Moraczewski et al., 2024; Schneider et al., 2019).

The complexity of the pharmacodynamics of TCAs explains their wide range of therapeutic applications, but also their significant side effect profile. This understanding aids in the careful choice of treatment for patients, considering the potential benefits against the risks and adverse effects.

Indications

Tricyclic antidepressants (TCAs) were initially developed for the treatment of depression, but their clinical indications have expanded significantly over the years. Although their use has decreased with the introduction of medications with more favorable side effect profiles, such as selective serotonin reuptake inhibitors (SSRIs), TCAs are still used for a variety of conditions due to their efficacy in various clinical contexts. The main indications for TCAs include (J. Moraczewski et al., 2024; Schneider et al., 2019):

Depressive disorder

The original indication of TCAs is that they are effective in the treatment of major depression, especially in cases considered resistant to treatment with other antidepressants (Arroll et al., 2005; J. Moraczewski et al., 2024; Schneider et al., 2019). They can be used in monotherapy or for augmentation (Arroll et al., 2005; Lenze et al., 2023). In 89 head-to-head trials, there was no detectable overall difference in responder rates or percent-improvement between TCAs and SSRIs (Undurraga & Baldessarini, 2017). In addition to non-difference between drug-types, outcomes were unrelated to reporting-year, trial-size or nominal duration, proportion of women participants, initial depression ratings, rating scales, subjects/arm, imipramine-equivalent mg/day drug dose, or dropout rate (Undurraga & Baldessarini, 2017). Trial size and duration increased significantly over the years 1980-2016 (Undurraga & Baldessarini, 2017).

A metanalysis compared Tranylcypromine and TCAs and observed that both have an antidepressant effect in a mean sample of depressed patients with mixed psychomotor symptoms. However, Tranylcypromine might be superior to TCAs in depression with predominant psychomotor retardation (Ulrich et al., 2020). Combined antidepressant plus benzodiazepine therapy may help than antidepressants alone in improving depression severity, response in depression and remission in depression in the early phase (Ogawa et al., 2019). However, these effects were not maintained in the acute or the continuous phase. Combined therapy resulted in fewer dropouts due to adverse events than antidepressants alone, but combined therapy was associated with a greater proportion of participants reporting at least one adverse effect (Ogawa et al., 2019).

Anxiety disorders

Incluindo transtorno de ansiedade generalizada (TAG), transtorno do pânico, agorafobia e fobia social (Bakker et al., 2002; Bandelow et al., 2015; Guaiana et al., 2023; Royal et al., 2003; Zohar & Westenberg, 2000). Entretanto, a eficácia para a fobia social é duvidosa, enquanto as melhores evidências são observadas para o transtorno do pânico. Os ADTs podem ser particularmente úteis em pacientes com sintomas depressivos concomitantes (Moraczewski et al., 2024; Schneider et al., 2019).

Neuropathic pain

Os ADTs são amplamente reconhecidos por sua eficácia no tratamento da dor neuropática, incluindo a dor diabética periférica e a neuralgia pós-herpética (J. Moraczewski et al., 2024; Schneider et al., 2019). For TCAs, the Number-Needed-To-Treat (NNTs) is 3.6 to achieve at least moderate pain relief compared to placebo, the Number-Needed-To-Harm (NNH) for major adverse effects leading to withdrawal is 28 and for minor adverse effects (sedation, dizziness, dry mouth, constipation, urinary retention and headaches) is 6 (Saarto & Wiffen, 2007; Thouaye & Yalcin, 2023).

Fibromyalgia

Evidence suggests that TCAs can reduce pain and improve sleep quality in patients with fibromyalgia (FM) (Chinn et al., 2016; Moraczewski et al., 2024; Schneider et al., 2019). Medications with the best efficacy in the treatment of FM include the tricyclic antidepressants amitriptyline and nortriptyline (Skaer, 2014).

Obsessive-compulsive disorder (OCD)

Clomipramine, a TCA, is one of the most effective medications for OCD, having been the first drug approved by the FDA specifically for this disorder (Marazziti et al., 2017; Moraczewski et al., 2024; Schneider et al., 2019). Tricyclic antidepressants are equally effective as SSRIs, but are less well tolerated (Bandelow, 2008).

Nocturnal enuresis

TCAs, especially imipramine, are used in the treatment of nocturnal enuresis in children, acting through mechanisms that are not yet fully understood (Moraczewski et al., 2024; Schneider et al., 2019). There is evidence that tricyclics are effective at reducing the number of wet nights during treatment, but do not have a sustained effect after treatment stops, with most children relapsing (Caldwell et al., 2016).

Eating disorders

TCAs may be useful in treating certain aspects of eating disorders, although the evidence is limited and mixed (J. Moraczewski et al., 2024; Schneider et al., 2019). For bulimia nervosa evidence exists with a moderate-risk-benefit ratio for tricyclic antidepressants (Aigner et al., 2011).

Irritable Bowel Syndrome (IBS)

Although the mechanisms are not completely understood, TCAs have shown efficacy in managing abdominal pain and other symptoms related to IBS (Barbara et al., 2023; Chang et al., 2022; Moraczewski et al., 2024; Schneider et al., 2019).

Chronic headache

TCAs can be prescribed as preventative therapy for several types of chronic headaches, including migraines and tension headaches (Chan et al., 2009). It is important to note that although TCAs can be effective for these conditions, they are not always the first line of treatment, primarily due to their side effect profile and risk of toxicity in overdose (Chan et al., 2009; Moraczewski et al., 2024; Schneider et al., 2019). The choice to use an ADT should be based on a careful assessment of the benefit and risk profile for the individual patient, considering factors such as the severity of the condition, the presence of comorbidities and the response to previous treatments (Chan et al., 2009; Moraczewski et al., 2024; Schneider et al., 2019).

Insomnia

Doxepin is a tricyclic antidepressant that received an indication for insomnia in 2010 at low doses based on several phase 3 trials that demonstrated improvements in total sleep time, sleep efficiency, wake time after sleep onset, and patient reported sleep quality compared to placebo (Everitt et al., 2018; Shaha, 2023). Doxepin did not decrease sleep-onset latency significantly, and its benefit in younger adults was not as pronounced as in older adults. Other tricyclic antidepressants are for off-label use in treatment resistant insomnia and insomnia related to depression or anxiety (Everitt et al., 2018; Shaha, 2023).

Chronic urticaria

Doxepin seems to be a reasonable, efficient, and affordable alternative for the treatment of chronic urticaria in patients who respond poorly to antihistamine therapy (Özkaya et al., 2019).

Dosage

Doses of tricyclic antidepressants (TCAs) can vary significantly depending on the specific medication, the condition being treated, the individual patient's response, and the presence of side effects. It is important to start treatment with a low dose and gradually increase until an effective therapeutic dose is reached, thus minimizing side effects. Below (Table 1) are typical starting and maintenance doses for some of the most prescribed TCAs for treating depression, although doses may be adjusted for other conditions such as neuropathic pain and anxiety disorders.

Table 1 - Dosage of tricyclic antidepressants (Baldaçara et al., 2019; Baldaçara & Tung, 2020; J. Moraczewski et al., 2024; Schneider et al., 2019).

Medicação	Dose inicial	Dose de manutenção
Amitriptyline	25-75 mg per day, given in divided doses or as a single dose in the evening	50-150 mg per day, though some patients may need higher doses, up to a maximum of 300 mg per day
Clomipramine	25 mg/day	Increase the dosage gradually to reach a typical daily amount of 100-150 mg for treating depression and 100-250 mg for managing obsessive-compulsive disorder
Desipramina	25-100 mg per day, either in divided doses or as a single evening dose	The usual dosage is 100-200 mg daily, with certain patients needing as much as 300 mg per day
Doxepina	25-75 mg per day, administered in divided doses or as a single dose at night	75-150 mg per day, although some patients may require up to 300 mg per day
Imipramina	25-75 mg per day in divided doses, with a gradual increase as needed	75-200 mg per day, with most patients being well-managed on 150 mg per day
Nortriptilina	10-25 mg/dia	Administer 50-150 mg daily, tailoring the dose according to plasma levels for optimal therapeutic effect and minimal side effects

Source: Baldaçara et al. (2019); Baldaçara & Tung (2020); J. Moraczewski et al. (2024); Schneider et al. (2019).

It is crucial to monitor patients for side effects and make dose adjustments as needed, especially in vulnerable populations such as the elderly, who may be more sensitive to the effects of TCAs (Baldaçara et al., 2019; Baldaçara & Tung, 2020; J. Moraczewski et al., 2024; Schneider et al., 2019). Furthermore, drug interactions must be carefully considered due to the potential to alter plasma levels of TCAs and the increased risk of serious side effects such as serotonin syndrome and cardiotoxicity (Baldaçara et al., 2019; Baldaçara & Tung, 2020; J. Moraczewski et al., 2024; Schneider et al., 2019).

Determination of the exact dose should always be guided by a qualified healthcare professional, who will consider all factors relevant to each individual patient.

Side effects (Kerr, 2001; J. Moraczewski et al., 2024; Schneider et al., 2019)

Tricyclic antidepressants (TCAs) can cause a variety of side effects due to their action on different neurotransmitter systems and receptors in the body. These side effects reflect the broad spectrum of pharmacological action of TCAs, including inhibition of serotonin and norepinephrine reuptake, as well as interaction with adrenergic, muscarinic (cholinergic), and histaminergic receptors. Some of the most common side effects include (Kerr, 2001; J. Moraczewski et al., 2024; Schneider et al., 2019):

Anticholinergic effects: TCAs can block the action of acetylcholine, an important neurotransmitter in the parasympathetic nervous system. This can lead to:

- Dry mouth
- Blurred vision
- Constipation
- Urinary retention
- Difficulty urinating

Sedation: Many TCAs have sedative effects due to their blockade of the H1 histaminergic receptors. This can result in drowsiness and fatigue, particularly in the initial stages of treatment.

Orthostatic hypotension: The blockade of alpha-1 adrenergic receptors can cause a sudden drop in blood pressure upon standing up, which can lead to dizziness or even fainting.

Weight gain: The use of TCAs may be associated with weight gain, partly due to increased appetite (Bezerra et al., 2023).

Cardiovascular effects: TCAs can affect heart rhythm and conduction, leading to cardiac arrhythmias in susceptible patients. They may also prolong the QT interval on an electrocardiogram, increasing the risk of serious arrhythmias.

Neurological effects: Tremors, muscle stiffness, and coordination disorders may occur, especially at high doses. Seizures.

Psychiatric symptoms: In some cases, TCAs may exacerbate symptoms of anxiety, cause agitation, or lead to mood changes. In individuals with bipolar disorder, they may trigger a manic switch.

Serotonin syndrome: Although less common than with other antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), the concurrent use of tricyclic antidepressants (TCAs) with other medications that increase serotonin levels can lead to this potentially fatal condition, characterized by agitation, confusion, increased heart rate, pupil dilation, tremors, and sweating.

Due to these side effects, tricyclic antidepressants (TCAs) are often not the first choice for treating depression, especially in elderly patients or those with pre-existing conditions that may be exacerbated by these effects. However, in certain cases, especially when other treatments have not been effective or when the patient has comorbid conditions that can also be treated by TCAs (such as neuropathic pain), they can be a valuable therapeutic option.

Management in acute intoxication (Baldaçara et al., 2019; Baldaçara & da Silva, 2021; Baldaçara, Pettersen, et al., 2022; Baldaçara & Tung, 2020; Kerr, 2001; Moraczewski et al., 2024; Schneider et al., 2019)

Acute intoxication can occur due to overdose, combination of psychotropic drugs, recreational abuse, suicide attempts, or distraction (ingestion beyond the prescribed amount in patients who have difficulty administering their own medication). Essentially, the approach should begin with support and subsequently specific actions according to the predominant signs and symptoms (see Table 2).

Table 2 - Clinical features and treatment options for tricyclic antidepressant poisoning (Kerr, 2001).

Clinical features	**Treatment**
Respiratory depression	Intubation and mechanical ventilation
Acidosis and prolonged QRS	Administer sodium bicarbonate to promote alkalinization, thereby reducing the affinity of tricyclic antidepressants for sodium channels. Aim for a target blood pH of 7.45 to 7.55, and elevate serum sodium to compete with the sodium channel blockade by administering a hypertonic saline bolus
Hypotension	Vasopressors, intravenous fluid boluses
Torsade de pointe, supraventricular and ventricular arrhythmia	Maintain normal potassium and magnesium levels, consider lidocaine administration, and prepare for electrical cardioversion if necessary
Life-threatening cardiac events and cardiac arrest	Initiate acute life support and resuscitation measures. Evaluate the use of a 20% intralipid emulsion and extracorporeal membrane oxygenation (ECMO) as potential interventions. There are anecdotal reports of plasmapheresis or hemodialysis, though these are not typically recommended
Seizures, hyperthermia	Benzodiazepines, general anesthesia, cooling, consider intralipid 20% emulsion
All adverse reactions	Activated charcoal to decrease further absorption of tricyclic antidepressants

Source: Modified from Kerr (2001) and based on Baldaçara, Pettersen, et al., (2022); Gillman, (2007); Kerr, (2001); J.; Moraczewski et al., (2024).

In addition, patients who enter a state of intoxication under suspicion of a suicide attempt should, in addition to clinical support, receive protection and begin approaches aimed at reducing the risk of suicide and ensuring safety. (Baldaçara, 2021; Baldaçara & da Silva, 2021; Baldaçara et al., 2021; Baldaçara et al., 2021; Baldaçara, Weber, et al., 2022; Nascimento et al., 2023).

4. Final Considerations

Tricyclic antidepressants are old, well-studied medications with many therapeutic indications. Their side effects can be the main limitation for use; however, correct prescription and follow-up can compensate for such eventualities (Gillman, 2007; J. Moraczewski et al., 2024; Schneider et al., 2019). Moreover, they are very low-cost medications when compared to other antidepressants and other psychotropic drugs. For example, an initial treatment with amitriptyline can have a starting price of approximately R$ 13.00 to 46.00 (US$ 2.60 to 9.20) for a box with 30 tablets. While fluoxetine 20mg has an approximate cost of R$ 18.60 to 352.00 (US$ 3.70 to 70.30) for a box with 28 or 30 capsules or tablets and venlafaxine 75mg R$ 52.00 to 430.00 (US$ 10.40 to 86.00) for a box with 28 or 30 capsules (Brasil., 2024). In turn, they are medications of simplified production and can be easily introduced into the public health system. Finally, it is important to highlight that most of the clinical trials for tricyclic antidepressants were conducted 20 to 30 years ago with methodology and statistical models quite different from the more modern options. This situation makes comparison difficult, mainly by meta-analysis and the development of guidelines. Even so, at least one study observed no differences when compared to serotonin-reuptake inhibitor antidepressants (Undurraga & Baldessarini, 2017).

We conclude that although there are various more modern antidepressants and psychotropic drugs with fewer side effects, there is still a place in the health system for tricyclics. Research with this group should not stop, and new studies should be encouraged to assess their safety, efficacy, and cost-benefit for various diseases.

References

Aigner, M., Treasure, J., Kaye, W., Kasper, S., & Disorders, W. T. F. O. E. (2011). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. *World J Biol Psychiatry*, *12* (6), 400-443. https://doi.org/10.3109/15622975.2011.602720

Arroll, B., Macgillivray, S., Ogston, S., Reid, I., Sullivan, F., Williams, B., & Crombie, I. (2005). Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *Ann Fam Med*, *3* (5), 449-456. https://doi.org/10.1370/afm.349

Bakker, A., van Balkom, A. J., & Spinhoven, P. (2002). SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis. *Acta Psychiatr Scand*, *106* (3), 163-167. https://doi.org/10.1034/j.1600-0447.2002.02255.x

Baldaçara, L. (2021). Emergências Psiquiátricas. In A. G. da Silva, A. E. Nardi, & A. P. Diaz (Eds.), *Programa de Educação Continuada em Psiquiatria (PEC-ABP). Temas fundamentais* (1 ed., pp. 267-282). Artmed.

Baldaçara, L., Cordeiro, D. C., Calfat, E. L. B., Cordeiro, D. C., & Chung, T. C. (2019). *Emergências Psiquiátricas* (2, Ed.). Elsevier.

Baldaçara, L., & da Silva, A. G. (2021). *Suporte em Emergências Psiquiátricas (SEP)* (1 ed.). AMPLA.

Baldaçara, L., Grudtner, R. R., Leite, V. S., Porto, D. M., Robis, K. P., Fidalgo, T. M., Rocha, G. A., Díaz, A. P., Meleiro, A., Correa, H., Tung, T. C., Malloy-Diniz, L. F., & da Silva, A. G. (2021). Brazilian guidelines for the management of suicide behavior. Part 2. Screening, intervention, and prevention. *Braz J Psychiatry*, *Forthcoming 2020*.

Baldaçara, L., Pettersen, A. G., Leite, V. D. S., Ismael, F., Motta, C. P., Freitas, R. A., Fasanella, N. A., Pereira, L. A., Barros, M. E. L., Barbosa, L., Teles, A. L. S., Palhano, R., Guimaraes, H. P., Braga, M. A., Castaldelli-Maia, J. M., Bicca, C., Gligliotti, A., Marques, A., & da Silva, A. G. (2022). Brazilian Psychiatric Association Consensus for the Management of Acute Intoxication. General management and specific interventions for drugs of abuse. *Trends Psychiatry Psychother*. https://doi.org/10.47626/2237-6089-2022-0571

Baldaçara, L., Rocha, G. A., Leite, V. D. S., Porto, D. M., Grudtner, R. R., Diaz, A. P., Meleiro, A., Correa, H., Tung, T. C., Quevedo, J., & da Silva, A. G. (2021). Brazilian Psychiatric Association guidelines for the management of suicidal behavior. Part 1. Risk factors, protective factors, and assessment. *Braz J Psychiatry*. https://doi.org/10.1590/1516-4446-2020-0994

Baldaçara, L., & Tung, T. C. (2020). *Condutas em psiquiatria*. Manole.

Baldaçara, L., Weber, C. A. T., Gorender, M., Grudtner, R. R., Peu, S., Teles, A. L. S., Cavalcante, I. P., Quevedo, J., & da Silva, A. G. (2022). Brazilian Psychiatric Association guidelines for the management of suicidal behavior. Part 3. Suicide prevention hotlines. *Braz J Psychiatry*. https://doi.org/10.47626/1516-4446-2022-2536

Bandelow, B. (2008). The medical treatment of obsessive-compulsive disorder and anxiety. *CNS Spectr*, *13* (9 Suppl 14), 37-46. https://doi.org/10.1017/s1092852900026924

Bandelow, B., Reitt, M., Rover, C., Michaelis, S., Gorlich, Y., & Wedekind, D. (2015). Efficacy of treatments for anxiety disorders: a meta-analysis. *Int Clin Psychopharmacol*, *30* (4), 183-192. https://doi.org/10.1097/YIC.0000000000000078

Barbara, G., Cremon, C., Bellini, M., Corsetti, M., Di Nardo, G., Falangone, F., Fuccio, L., Galeazzi, F., Iovino, P., Sarnelli, G., Savarino, E. V., Stanghellini, V., Staiano, A., Stasi, C., Tosetti, C., Turco, R., Ubaldi, E., Zagari, R. M., Zenzeri, L., & Marasco, G. (2023). Italian guidelines for the management of irritable bowel syndrome: Joint Consensus from the Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), General Medicine (SIMG), Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) and Pediatrics (SIP). *Dig Liver Dis*, *55* (2), 187-207. https://doi.org/10.1016/j.dld.2022.11.015

Bezerra, T. P. T., Fabrício, A. I. C. R., Minervino, A. J., & Santos, R. M. d. (2023). Psychoactive drugs and metabolic disorders. *Debates em Psiquiatria*, *13*, 1-20. https://doi.org/10.25118/2763-9037.2023.v13.439

Brasil. (2024). *Listas de preços de medicamentos*. Ministério da Saúde - ANVISA. https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/precos

Caldwell, P. H., Sureshkumar, P., & Wong, W. C. (2016). Tricyclic and related drugs for nocturnal enuresis in children. *Cochrane Database Syst Rev*, *2016* (1), CD002117. https://doi.org/10.1002/14651858.CD002117.pub2

Calvi, A., Fischetti, I., Verzicco, I., Belvederi Murri, M., Zanetidou, S., Volpi, R., Coghi, P., Tedeschi, S., Amore, M., & Cabassi, A. (2021). Antidepressant Drugs Effects on Blood Pressure. *Frontiers in Cardiovascular Medicine*, *8*. https://doi.org/10.3389/fcvm.2021.704281

Chan, H. N., Fam, J., & Ng, B. Y. (2009). Use of antidepressants in the treatment of chronic pain. *Ann Acad Med Singap*, *38* (11), 974-979. https://www.ncbi.nlm.nih.gov/pubmed/19956820

Chang, L., Sultan, S., Lembo, A., Verne, G. N., Smalley, W., & Heidelbaugh, J. J. (2022). AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Constipation. *Gastroenterology*, *163* (1), 118-136. https://doi.org/10.1053/j.gastro.2022.04.016

Chinn, S., Caldwell, W., & Gritsenko, K. (2016). Fibromyalgia Pathogenesis and Treatment Options Update. *Curr Pain Headache Rep*, *20* (4), 25. https://doi.org/10.1007/s11916-016-0556-x

Everitt, H., Baldwin, D. S., Stuart, B., Lipinska, G., Mayers, A., Malizia, A. L., Manson, C. C., & Wilson, S. (2018). Antidepressants for insomnia in adults. *Cochrane Database Syst Rev*, *5* (5), CD010753. https://doi.org/10.1002/14651858.CD010753.pub2

Gillman, P. K. (2007). Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol*, *151* (6), 737-748. https://doi.org/10.1038/sj.bjp.0707253

Guaiana, G., Meader, N., Barbui, C., Davies, S. J., Furukawa, T. A., Imai, H., Dias, S., Caldwell, D. M., Koesters, M., Tajika, A., Bighelli, I., Pompoli, A., Cipriani, A., Dawson, S., & Robertson, L. (2023). Pharmacological treatments in panic disorder in adults: a network meta-analysis. *Cochrane Database Syst Rev*, *11* (11), CD012729. https://doi.org/10.1002/14651858.CD012729.pub3

Kerr, G. W. (2001). Tricyclic antidepressant overdose: a review. *Emergency Medicine Journal*, *18* (4), 236-241. https://doi.org/10.1136/emj.18.4.236

Lenze, E. J., Mulsant, B. H., Roose, S. P., Lavretsky, H., Reynolds, C. F., Blumberger, D. M., Brown, P. J., Cristancho, P., Flint, A. J., Gebara, M. A., Gettinger, T. R., Lenard, E., Miller, J. P., Nicol, G. E., Oughli, H. A., Pham, V. T., Rollman, B. L., Yang, L., & Karp, J. F. (2023). Antidepressant Augmentation versus Switch in Treatment-Resistant Geriatric Depression. *New England Journal of Medicine*, *388* (12), 1067-1079. https://doi.org/10.1056/NEJMoa2204462

Marazziti, D., Albert, U., Dell'Osso, B., Tundo, A., Cuniberti, F., Maina, G., Moroni, I., Benatti, B., Mucci, F., Massimetti, G., Piccinni, A., & Brakoulias, V. (2017). Italian prescribing patterns in obsessive-compulsive disorder. *Hum Psychopharmacol*, *32* (6). https://doi.org/10.1002/hup.2641

Moraczewski, J., Awosika, A. O., & Aedma, K. K. (2024). *Tricyclic Antidepressants*. StatPearls.

Moraczewski, J., Awosika, A. O., & Aedma, K. K. (2024). Tricyclic Antidepressants. In *StatPearls*. https://www.ncbi.nlm.nih.gov/pubmed/32491723

Nascimento, C. d. P., Couto, H. Z., Baldaçara, L., Silva, A. G. d., Mello, M. F. d., & Mello, A. F. d. (2023). Pharmacological treatment of post-traumatic stress disorder: a treatment guide based on a systematic literature review. *Debates em Psiquiatria*, *13*, 1-72. https://doi.org/10.25118/2763-9037.2023.v13.1037

Ogawa, Y., Takeshima, N., Hayasaka, Y., Tajika, A., Watanabe, N., Streiner, D., & Furukawa, T. A. (2019). Antidepressants plus benzodiazepines for adults with major depression. *Cochrane Database Syst Rev*, *6* (6), CD001026. https://doi.org/10.1002/14651858.CD001026.pub2

Özkaya, E., Babuna Kobaner, G., Yılmaz, Z., & Kutlay, A. (2019). Doxepin in difficult-to-treat chronic urticaria: A retrospective, cross-sectional study from Turkey. *Dermatologic Therapy*. https://doi.org/10.1111/dth.12993

Royal, A., New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Panic, D., & Agoraphobia. (2003). Australian and New Zealand clinical practice guidelines for the treatment of panic disorder and agoraphobia. *Aust N Z J Psychiatry*, *37* (6), 641-656. https://doi.org/10.1080/j.1440-1614.2003.01254.x

Saarto, T., & Wiffen, P. J. (2007). Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*, *2007* (4), CD005454. https://doi.org/10.1002/14651858.CD005454.pub2

Schneider, J., Patterson, M., & Jimenez, X. F. (2019). Beyond depression: Other uses for tricyclic antidepressants. *Cleve Clin J Med*, *86* (12), 807-814. https://doi.org/10.3949/ccjm.86a.19005

Shaha, D. (2023). Insomnia Management: A Review and Update. *J Fam Pract*, *72* (06 Supp). https://doi.org/10.12788/jfp.0620

Skaer, T. L. (2014). Fibromyalgia: disease synopsis, medication cost effectiveness and economic burden. *Pharmacoeconomics*, *32* (5), 457-466. https://doi.org/10.1007/s40273-014-0137-y

Snyder, H. (2019). Literature review as a research methodology: An overview and guidelines. *Journal of Business Research*, *104*, 333-339. https://doi.org/10.1016/j.jbusres.2019.07.039

Thouaye, M., & Yalcin, I. (2023). Neuropathic pain: From actual pharmacological treatments to new therapeutic horizons. *Pharmacol Ther*, *251*, 108546. https://doi.org/10.1016/j.pharmthera.2023.108546

Ulrich, S., Ricken, R., Buspavanich, P., Schlattmann, P., & Adli, M. (2020). Efficacy and Adverse Effects of Tranylcypromine and Tricyclic Antidepressants in the Treatment of Depression: A Systematic Review and Comprehensive Meta-analysis. *J Clin Psychopharmacol*, *40* (1), 63-74. https://doi.org/10.1097/JCP.0000000000001153

Undurraga, J., & Baldessarini, R. J. (2017). Direct comparison of tricyclic and serotonin-reuptake inhibitor antidepressants in randomized head-to-head trials in acute major depression: Systematic review and meta-analysis. *J Psychopharmacol*, *31* (9), 1184-1189. https://doi.org/10.1177/0269881117711709

Zohar, J., & Westenberg, H. G. (2000). Anxiety disorders: a review of tricyclic antidepressants and selective serotonin reuptake inhibitors. *Acta Psychiatr Scand 403*, 39-49. https://doi.org/10.1111/j.1600-0447.2000.tb10947.x