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Duloxetine: An update

Duloxetina: Uma atualização

Duloxetina: Una actualización

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Abstract
Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has established itself as a versatile therapeutic agent across a spectrum of psychiatric and neurological disorders. The objective of this article is to update the pharmacological properties of duloxetine. To this end, a review was carried out on the pharmacology, clinical efficacy, safety and tolerability of duloxetine, focusing on its application in the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), diabetic peripheral neuropathic pain, fibromyalgia and musculoskeletal pain. chronic. Comparative analyzes highlight the relative effectiveness of duloxetine versus other antidepressants and its unique advantage in managing conditions with overlapping mood and pain symptoms. Safety profiles and pharmacological interactions, particularly with NSAIDs and tamoxifen, highlight the importance of personalized treatment plans and vigilant monitoring. The review concludes with an assessment of the clinical utility of duloxetine, emphasizing individual patient assessment to maximize therapeutic outcomes while minimizing risks. Future research directions are suggested to further delineate the role of duloxetine in treatment algorithms and explore potential new indications.
Keywords: Duloxetine hydrochloride; Pharmacology; Mental disorders; Usos Terapêuticos; Drug interactions.

Resumo
A duloxetina, um inibidor da recaptação da serotonina-noradrenalina (IRSN), estabeleceu-se como um agente terapêutico versátil em um espectro de distúrbios psiquiátricos e neurológicos. O objetivo deste artigo é atualizar sobre as propriedades farmacológicas da duloxetina. Para tal foi realizada uma revisão sobre farmacologia, eficácia clínica, segurança e tolerabilidade da duloxetina, com foco em sua aplicação no tratamento de transtorno depressivo maior (TDM), transtorno de ansiedade generalizada (TAG), dor neuropática periférica diabética, fibromialgia e dor musculoesquelética crônica. Análises comparativas destacam a eficácia relativa da duloxetina contra outros antidepressivos e sua vantagem única no manejo de condições com sobreposição de sintomas de humor e dor. Os perfis de segurança e as interações farmacológicas, particularmente com AINEs e tamoxifeno, sublinham a importância de planos de tratamento personalizados e de monitorização vigilante. A revisão conclui com uma avaliação da utilidade clínica da duloxetina, enfatizando a avaliação individual do paciente para maximizar os resultados terapêuticos e, ao mesmo tempo, minimizar os riscos. São sugeridas direções de pesquisas futuras para delinear melhor o papel da duloxetina nos algoritmos de tratamento e explorar novas indicações potenciais.
Palavras-chave: Cloridrato de duloxetina; Farmacologia; Transtornos mentais; Usos terapêuticos; Interações medicamentosas.

Resumen
La duloxetina, un inhibidor de la recaptación de serotonina y norepinefrina (IRSN), se ha establecido como un agente terapéutico versátil en un espectro de trastornos psiquiátricos y neurológicos. El objetivo de este artículo es actualizar las propiedades farmacológicas de la duloxetina. Para ello se realizó una revisión sobre la farmacología, eficacia clínica, seguridad y tolerabilidad de la duloxetina, centrándose en su aplicación en el tratamiento del trastorno depresivo mayor (TDM), trastorno de ansiedad generalizada (TAG), dolor neuropático periférico diabético, fibromialgia. y dolor musculoesquelético crónico. Los análisis comparativos destacan la eficacia relativa de la duloxetina frente a otros antidepresivos y su ventaja única en el tratamiento de afecciones con síntomas de dolor y estado de ánimo superpuestos. Los perfiles de seguridad y las interacciones farmacológicas, particularmente con los AINE y el tamoxifeno, resaltan la importancia de los planes de tratamiento personalizados y la vigilancia atenta. La revisión concluye con una evaluación de la utilidad clínica de la duloxetina, enfatizando la evaluación individual del paciente para maximizar los resultados terapéuticos y minimizar los riesgos. Se sugieren direcciones de investigación futuras para delinear mejor el papel de la duloxetina en los algoritmos de tratamiento y explorar nuevas indicaciones potenciales.
Palabras clave: Clorhidrato de duloxetina; Transtornos mentales; Farmacología; Usos terapéuticos; Interacciones farmacológicas.

1. Introduction

Duloxetine, a medication classified as a serotonin-norepinephrine reuptake inhibitor (SNRI), has become a cornerstone in the pharmacological management of various psychiatric and neurological conditions. Its development marked a significant advancement in the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), fibromyalgia, and diabetic peripheral neuropathic pain (Dhaliwal et al., 2023; Eli Lilly & Company, 2004; Rodrigues-Amorim et al., 2020). By influencing the central nervous system's neurotransmitters, duloxetine offers a multifaceted approach to treating conditions characterized by both emotional and physical symptoms. Its unique action on both serotonin and norepinephrine sets it apart from other antidepressants, providing a broad therapeutic potential (Dhaliwal et al., 2023; Eli Lilly & Company, 2004; Rodrigues-Amorim et al., 2020).

The journey of duloxetine from its inception to clinical use underscores the ongoing quest for more effective and well-tolerated antidepressant medications(Hunziker et al., 2005). Approved by the FDA in 2004 for the treatment of major depressive disorder, its indications have expanded over the years to include a wider range of disorders(Dhaliwal et al., 2023; Eli Lilly & Company, 2004; Rodrigues-Amorim et al., 2020). This expansion reflects the medication's versatile pharmacodynamic properties and its ability to address a spectrum of symptoms beyond traditional antidepressant targets. Duloxetine's approval was based on extensive clinical trials that demonstrated its efficacy in improving mood disorders, anxiety symptoms, and pain related to various conditions (Eli Lilly & Company, 2004; Goldstein, 2007; Hunziker et al., 2005).

Pharmacologically, duloxetine works by inhibiting the reuptake of serotonin and norepinephrine in the brain, enhancing the action of these neurotransmitters(Dhaliwal et al., 2023; Muller et al., 2008; Rodrigues-Amorim et al., 2020). This dual-action mechanism is particularly effective in treating symptoms of depression and anxiety, as well as pain perception, which is often a component of the disorders it treats. By increasing the availability of these neurotransmitters, duloxetine helps to correct the imbalances believed to be underlying factors in these conditions. The drug's efficacy in managing pain, a common comorbidity in depressive and anxiety disorders, highlights its role in treating complex patient presentations (Dhaliwal et al., 2023; Muller et al., 2008; Rodrigues-Amorim et al., 2020).

Despite being a new medication, with several indications and easily accessible, it is still little used in the public system. For this reason, this review aims to update doctors on the potential of duloxetine, as well as its indications and future prospects.

2. Methods

This is a narrative review (Snyder, 2019) in update format that searched for articles in the Pubmed, Scielo, and Google Scholar databases using the following keywords: Cloridrato de Duloxetina; Farmacologia; Transtornos Mentais; Usos Terapêuticos; Interações Medicamentosas. There were no language restrictions. Articles were limited to publication in the last 10 years. Systematic or non-systematic reviews on the topic, as well as meta-analyses, were included. Reports and case series, editorials or conference proceedings were excluded. The review was narrative as the author did not use tools to score the evidence and randomly chose the best information, he deemed necessary for clinical practice (Snyder, 2019).

3. Results and Discussion

Pharmacology

Mechanism of Action

Duloxetine is classified as a serotonin-norepinephrine reuptake inhibitor (SNRI). It exerts its antidepressant and pain-relieving effects primarily through the potent inhibition of serotonin and norepinephrine reuptake in the central nervous system (Dugan & Fuller, 2004; Sansone & Sansone, 2014). By blocking the reuptake transporters for these neurotransmitters, duloxetine increases their availability in the synaptic cleft, enhancing neurotransmission(Dhaliwal et al., 2023; Dugan & Fuller, 2004;

Rodrigues-Amorim et al., 2020). This dual reuptake inhibition is believed to contribute to duloxetine's efficacy in treating mood disorders, anxiety, and pain syndromes associated with fibromyalgia and diabetic neuropathy. Unlike selective serotonin reuptake inhibitors (SSRIs), duloxetine's action on norepinephrine is thought to be crucial for its analgesic properties, particularly in chronic pain conditions (Dugan & Fuller, 2004; Eli Lilly & Company, 2004; Sansone & Sansone, 2014).

Pharmacokinetics

The pharmacokinetic profile of duloxetine is characterized by its absorption, distribution, metabolism, and excretion:

Absorption: Duloxetine is well absorbed after oral administration, with peak plasma concentrations typically occurring 6 hours post-dose. Its bioavailability is approximately 50%, and food does not have a significant impact on its absorption(Eli Lilly and Company, 2004; Rizea-Savu et al., 2020).

Distribution: It is extensively distributed throughout the body and is highly bound to plasma proteins, mainly albumin and α1-acid glycoprotein, which may affect its distribution in various tissues(Eli Lilly and Company, 2004; Rizea-Savu et al., 2020).

Metabolism: Duloxetine undergoes extensive metabolism in the liver. The primary pathway involves cytochrome P450 1A2 (CYP1A2) and cytochrome P450 2D6 (CYP2D6) enzymes, leading to the formation of numerous metabolites, none of which significantly contribute to the drug's therapeutic effects. This extensive metabolism may involve potential interactions with other medications metabolized by the same enzymes(Eli Lilly and Company, 2004; Lobo et al., 2008; Rizea-Savu et al., 2020; Shelton, 2019; Wernicke et al., 2005).

Excretion: The drug and its metabolites are primarily excreted through the urine. The elimination half-life of duloxetine is approximately 12 hours, though this can vary based on individual factors such as genetic polymorphisms affecting CYP450 enzyme activity(Eli Lilly and Company, 2004; Rizea-Savu et al., 2020).

Pharmacodynamics

The pharmacodynamic properties of duloxetine involve its actions beyond the inhibition of serotonin and norepinephrine reuptake. While these are the primary mechanisms contributing to its therapeutic effects, duloxetine also exhibits minor inhibitory effects on dopamine reuptake in the prefrontal cortex(Fasipe, 2018; Trivedi et al., 2008). This action, although less significant, may play a role in its efficacy in certain patient populations and clinical scenarios. Additionally, the modulation of pain signaling pathways, likely through its effects on norepinephrine, contributes to its analgesic properties in conditions like diabetic peripheral neuropathy and fibromyalgia (Fasipe, 2018; Trivedi et al., 2008).

Clinical uses

Major Depressive Disorder (MDD)

Duloxetine is approved for the treatment of major depressive disorder (MDD) (Goldstein, 2007; Ishtiak-Ahmed et al., 2024). It helps alleviate depressive symptoms by increasing the levels of serotonin and norepinephrine in the central nervous system, neurotransmitters that are often imbalanced in individuals with depression (Cipriani et al., 2018; Gautam et al., 2017). Clinical trials have demonstrated its effectiveness in improving mood, cognitive symptoms, and overall functioning in patients with MDD (Cipriani et al., 2018; Gautam et al., 2017; Goldstein, 2007; Ishtiak-Ahmed et al., 2024; Kraus et al., 2019; Rodrigues-

Amorim et al., 2020). However, compared to another antidepressants duloxetine had higher droup-out rates (Cipriani et al., 2018).

For MDD, duloxetine has shown comparable efficacy to SSRIs and other SNRIs in several meta-analyses and head-to-head trials. It's particularly effective in patients with significant physical symptoms or pain, an area where duloxetine may have an edge due to its dual-action mechanism. However, the choice between duloxetine and other antidepressants often depends on individual patient factors, including side effect profiles, patient history, and specific symptomatology (Goldstein, 2007; Ishtiak-Ahmed et al., 2024; Rodrigues-Amorim et al., 2020).

Generalized Anxiety Disorder (GAD)

The medication is also indicated for the treatment of generalized anxiety disorder (GAD), characterized by excessive, uncontrollable worry about various aspects of life. Duloxetine has been shown to reduce anxiety symptoms, improve quality of life, and enhance daily functioning in patients with GAD (Baldacara et al., 2023; Rodrigues-Amorim et al., 2020; Wittchen et al., 2002).

In treating GAD, duloxetine is effective and comparable to SSRIs and other SNRIs. Its advantage lies in its dual mechanism of action, addressing both the psychological and somatic symptoms of anxiety. Some studies suggest duloxetine may offer rapid relief of anxiety symptoms, although long-term outcomes are generally consistent across different classes of antidepressants (Rodrigues-Amorim et al., 2020; Wright & Vandenberg, 2009).

Diabetic Peripheral Neuropathic Pain

Duloxetine is effective in managing pain associated with diabetic peripheral neuropathy, a common complication of diabetes characterized by nerve damage resulting in pain, tingling, and numbness, primarily in the legs and feet. Its action on norepinephrine is believed to be particularly relevant in modulating pain perception and providing relief from neuropathic pain (Birkinshaw et al., 2023; Rodrigues-Amorim et al., 2020).

Duloxetine's efficacy in managing diabetic peripheral neuropathic pain is well-documented and compares favorably with other commonly used medications for neuropathic pain, such as gabapentin and pregabalin. Its unique action on norepinephrine is believed to contribute to its effectiveness in pain management, offering an alternative for patients who may not respond to or tolerate other pain medications (Rodrigues-Amorim et al., 2020).

Fibromyalgia

In patients with fibromyalgia, a chronic condition marked by widespread pain, fatigue, and tenderness in localized areas, duloxetine has been found to alleviate pain and improve physical function. Its effectiveness in treating fibromyalgia symptoms highlights its role in managing pain syndromes beyond its psychiatric indications (Birkinshaw et al., 2023; Li et al., 2017; Rodrigues-Amorim et al., 2020).

For fibromyalgia, duloxetine has been shown to reduce pain and improve quality of life, with comparative studies indicating similar efficacy to other SNRIs, like milnacipran, and better overall tolerance compared to SSRIs. Its ability to target both the mood and pain components of fibromyalgia makes it a valuable option for comprehensive management of this condition (Rodrigues-Amorim et al., 2020).

Chronic Musculoskeletal Pain

Duloxetine has indications for the treatment of chronic musculoskeletal pain, including chronic back pain and osteoarthritis pain. By modulating pain pathways in the brain, it can provide significant pain relief and improve quality of life

for individuals suffering from chronic pain conditions (Birkinshaw et al., 2023; Brown & Boulay, 2013; Li et al., 2017; Smith et al., 2012).

In the context of chronic musculoskeletal pain, including chronic back pain and osteoarthritis, duloxetine demonstrates significant pain reduction and is considered an effective non-opioid alternative. Comparative efficacy studies show duloxetine to be as effective as nonsteroidal anti-inflammatory drugs (NSAIDs) in some patient populations, with the added benefit of a favorable side effect profile, especially concerning gastrointestinal risks associated with long-term NSAID use (Brown & Boulay, 2013).

Dosage

The dosage of duloxetine can vary based on the condition being treated, patient response, and tolerability. It's important to follow a healthcare provider's directions precisely. However, general dosage guidelines for duloxetine are as follows (Baldacara et al., 2023; Eli Lilly & Company, 2004; Rodrigues-Amorim et al., 2020):

For Major Depressive Disorder (MDD):

Adults: The typical starting dose is 40 mg per day (given as 20 mg twice daily) to 60 mg per day (given either once daily or as 30 mg twice daily). Some patients may start at 30 mg once daily for one week, to allow patients to adjust to the medication before increasing to 60 mg once daily. The maximum recommended dose is 120 mg per day.

For Generalized Anxiety Disorder (GAD):

Adults: The recommended starting dose is 60 mg once daily. Some patients may start at 30 mg once daily for one week, to allow adjustment to the medication. The dose can be increased in 30 mg increments to a maximum of 120 mg per day based on response and tolerability.

Elderly: Initiation of treatment often starts at a lower dose to assess tolerability.

Children and Adolescents (7 to 17 years old): The typical starting dose is 30 mg once daily for two weeks before considering an increase to 60 mg. The maximum recommended dose is 120 mg per day.

For Diabetic Peripheral Neuropathic Pain:

Adults: The recommended dose is 60 mg per day, but some patients may start at 30 mg once daily for one week before increasing to 60 mg once daily.

For Fibromyalgia:

Adults: The recommended starting dose is 60 mg once daily. Some patients may benefit from starting at 30 mg once daily for one week before increasing to 60 mg once daily to improve tolerability.

For Chronic Musculoskeletal Pain:

Adults: The recommended dose is 60 mg once daily.

It is important to note that the discontinuation of duloxetine should be done gradually to avoid withdrawal symptoms. Adjustments in dosage should be made based on clinical response and patient tolerability, under the guidance of a healthcare provider. Always refer to the prescribing information or consult a healthcare professional for the most accurate and personalized dosing recommendations.

Safety and Tolerability

The safety and tolerability of duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), are critical considerations for its use in clinical practice. While it offers significant benefits across a range of conditions, understanding its side effect profile and potential risks is essential for optimizing patient outcomes. This overview provides insight into duloxetine's safety, common and serious side effects, and considerations for its use(Dhaliwal et al., 2023; Eli Lilly and Company, 2004; He et al., 2019; Lobo et al., 2008; Rizea-Savu et al., 2020; Rodrigues-Amorim et al., 2020; Shelton, 2019; Wernicke et al., 2005; Westanmo et al., 2005).

Common Side Effects

Duloxetine is generally well-tolerated by most patients, but like all medications, it can cause side effects. The most reported side effects include(Dhaliwal et al., 2023; Eli Lilly and Company, 2004; He et al., 2019; Lobo et al., 2008; Rizea-Savu et al., 2020; Rodrigues-Amorim et al., 2020; Westanmo et al., 2005):

Nausea: This is one of the most frequently reported side effects, often occurring early in the treatment and usually subsiding with time.

Dry mouth: Patients may experience decreased saliva production.

Headache: Some individuals may report headaches, which often decrease in frequency and intensity over time.

Dizziness: This can occur, particularly when standing up quickly, due to blood pressure changes.

Fatigue and Sleepiness: Patients may feel unusually tired or sleepy.

Insomnia: Difficulty falling or staying asleep is reported by some patients.

Constipation: Duloxetine can affect gastrointestinal motility, leading to constipation.

Increased Sweating: This can occur even without physical exertion or high temperatures.

These side effects are generally mild to moderate and tend to diminish as the body adjusts to the medication. Healthcare providers often manage these by adjusting the dosage or recommending supportive treatments.

Serious Side Effects and Risks (Dhaliwal et al., 2023; Eli Lilly & Company, 2004; He et al., 2019; Lobo et al., 2008; Rizea-Savu et al., 2020; Rodrigues-Amorim et al., 2020; Westanmo et al., 2005)*:*

While less common, duloxetine can cause serious side effects in some patients, which require immediate medical attention:

Hepatotoxicity: Duloxetine can impact liver function, leading to increased liver enzymes, and in rare cases, severe liver injury. It is generally not recommended for patients with chronic liver disease or substantial alcohol use.

Suicidal Thoughts and Behaviors: As with other antidepressants, duloxetine may increase the risk of suicidal thinking and behavior in children, adolescents, and young adults. However, this risk is only present in the first days of treatment and the long-term benefits outweigh this situation. Monitoring is recommended at the beginning of treatment (Baldaçara et al., 2021; Baldacara et al., 2021).

Serotonin Syndrome: A potentially life-threatening condition can occur, particularly if duloxetine is taken in conjunction with other medications that affect serotonin levels.

Severe Skin Reactions: Rarely, duloxetine can cause serious skin reactions, necessitating discontinuation of the medication.

Orthostatic Hypotension: Duloxetine may lead to a drop in blood pressure upon standing, increasing the risk of falls, especially in elderly patients.

Other cardiovascular side effects (Park et al., 2020).

Urinary Retention: Difficulty urinating can be a concern, particularly in individuals with pre-existing urinary conditions.

Special Considerations(Dhaliwal et al., 2023; Eli Lilly and Company, 2004; He et al., 2019; Lobo et al., 2008; Rizea-Savu et al., 2020; Rodrigues-Amorim et al., 2020; Westanmo et al., 2005)*:*

Withdrawal Syndrome: Abrupt discontinuation of duloxetine can lead to withdrawal symptoms. Gradual tapering under medical supervision is recommended(Fava et al., 2018).

Pregnancy and Breastfeeding: Duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is excreted in breast milk, so caution is advised.

Pharmacological interactions

Duloxetine, as a serotonin-norepinephrine reuptake inhibitor (SNRI), is subject to various pharmacological interactions with other medications. These interactions can affect the efficacy and safety of duloxetine or the co-administered drug, necessitating careful consideration and management. Here are some key pharmacological interactions associated with duloxetine(Dhaliwal et al., 2023; Eli Lilly and Company, 2004; He et al., 2019; Lobo et al., 2008; Rizea-Savu et al., 2020; Rodrigues-Amorim et al., 2020; Westanmo et al., 2005):

Cytochrome P450 Enzyme System

CYP1A2 and CYP2D6 Inhibitors: Duloxetine is metabolized primarily by these enzymes. Co-administration with inhibitors of CYP1A2 (such as fluvoxamine, ciprofloxacin) or CYP2D6 (such as bupropion, fluoxetine, paroxetine) can lead to increased levels of duloxetine in the blood, potentially heightening the risk of side effects.

CYP1A2 Inducers: Smoking and certain medications (e.g., rifampicin) can induce CYP1A2, potentially reducing duloxetine's efficacy by increasing its metabolism.

Serotonergic Drugs: Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), and Other Serotonergic Agents: Concurrent use with these agents can increase the risk of serotonin syndrome, a potentially life-threatening condition characterized by symptoms such as agitation, hallucinations, rapid heart rate, fluctuations in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea.

Monoamine Oxidase Inhibitors (MAOIs): The use of duloxetine with or within 14 days of discontinuing an MAOI intended to treat psychiatric disorders is contraindicated due to the risk of serotonin syndrome. Similarly, an MAOI should not be started within 5 days of stopping duloxetine.

Antiplatelet Agents and Anticoagulants: NSAIDs, Aspirin, Warfarin, and Other Blood Thinners: Duloxetine can increase the risk of bleeding when taken with these medications, due to its effect on platelet function and serotonin reuptake inhibition, which is involved in platelet aggregation.

CNS-active Drugs: The concomitant use of duloxetine with other centrally acting medications, including benzodiazepines, antipsychotics, and alcohol, can enhance their sedative effects, increasing the risk of CNS depression, impaired motor function, and cognitive deterioration.

Drugs Affecting Gastric Acidity: Duloxetine has an enteric coating that may be sensitive to changes in gastric pH. Medications that alter gastric acidity, such as proton pump inhibitors (PPIs), H2 antagonists, and antacids, could potentially affect the release and absorption of duloxetine, although the clinical significance is likely minimal.

Tamoxifen: The interaction between duloxetine and tamoxifen is an important consideration due to the potential impact on the efficacy of tamoxifen in treating hormone receptor-positive breast cancer. This interaction primarily involves the cytochrome P450 2D6 (CYP2D6) enzyme, which is crucial for the metabolism of both medications.

4. Conclusion

In summary, duloxetine serves as a crucial pharmacological option for treating a variety of conditions, notably major depressive disorder, generalized anxiety disorder, neuropathic pain, and fibromyalgia. Its dual mechanism of action on serotonin and norepinephrine reuptake underpins its efficacy across both mental health and pain management domains. While generally well-tolerated, awareness of potential side effects and drug interactions is essential for optimizing patient outcomes. The careful selection of patients and personalized management strategies enhance its therapeutic benefits. Future research should expand the indications for this antidepressant to other disorders and evaluate factors related to the prediction of patients who will be better responders to its effects.

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