Disciplinarum Scientia. Série: Ciências da Saúde, Santa Maria, v. 23, n. 3, p. 35-54, 2022.
Recebido em: 13.07.2022. Aprovado em: 25.02.2023.
ISSN 2177-3335
DOI: doi.org/10.37777/dscs.v23n3-003

TREATMENT OF DEPRESSION IN ELDERLIES WITH VORTIOXETIN: A REVIEW BASED ON CLINICAL STUDIES

TRATAMENTO DA DEPRESSÃO DE IDOSOS COM VORTIOXETINA: REVISÃO BASEADA EM ESTUDOS CLÍNICOS[1]

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ABSTRACT

Depression is a health problem that is increasing in the world population, affecting 300 million people, mainly among the elderly, and is treated with traditional psychotropic drugs, which generate adverse effects and delays in resolution, besides relapses. Vortioxetine is a new psychotropic drug prescribed for young adults and the elderly. The aim of this study was to perform a literature review on the efficiency and safety of vortioxetine for the treatment of the elderly with depression, also addressing the occurrence of interactions with hypoglycemic and hypotensive agents, aiming at knowledge diffusion. This study was developed by searching for scientific articles that address clinical trials, published in the last 10 years by means of descriptors in Health Science: "depression, vortioxetine, elderly, vortioxetine-hypoglycemic interaction and vortioxetine-hypotensors interaction, efficacy and safety", in English, Spanish and Portuguese. Based on this survey, it was demonstrated that the use of vortioxetine is safe because it presented light to moderate adverse effects and no serious effects when used alone, and presented efficacy in the treatment for depression in the elderly people, reported in 42% of the clinic trials evaluated. It was not possible to define interactions between vortioxetine and anti-hypertensives or hypoglicaemic agents due to the scarcity of clinical studies that approached subject, yet, it is recommended to monitor the therapy and, if necessary, adjust the dosage or substitute the drug according to the patient's clinical case. There is no evidence of use in children, under 18s and pregnant women.

Keywords: Efficacy, Safety, Psychotropics, Interactions.

RESUMO

A depressão é um problema de saúde que está aumentando na população mundial, atingindo 300 milhões de pessoas, principalmente entre idosos, sendo tratada com psicofármacos tradicionais, os quais geram efeitos adversos e demora de resolutividade, além de reincidivas. A vortioxetina é um novo psicofármaco prescrito para jovens adultos e idosos. O objetivo deste estudo foi realizar uma revisão da literatura sobre eficácia e segurança da vortioxetina para o tratamento do idoso com depressão, abordando também a ocorrência de interações com hipoglicemiantes e hipotensores, visando a difusão do conhecimento. Esse estudo foi desenvolvido por meio da busca de artigos científicos que abordem ensaios clínicos, publicados nos últimos 10 anos por meio de descritores em Ciência em Saúde: "depressão, vortioxetina, idoso, interação vortioxetina-hipoglicemiantes, interação vortioxetina-hipotensores arteriais, eficácia e segurança", em inglês, espanhol e português. Com base nesse levantamento, demonstrou-se que o uso da vortioxetina é seguro pois apresentou efeitos adversos leves a moderados e nenhum efeito grave quando utilizada de forma isolada e, apresenta eficácia de tratamento da depressão do idoso, relatado em 42% dos ensaios clínicos avaliados. Não

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foi possível definir interações entre a vortioxetina e anti-hipertensivos ou hipoglicemiantes devido escassez de estudos clínicos que abordassem esse enfoque, logo, recomenda-se monitorar a terapia e, se necessário ajuste de dosagens ou substituição de medicamentos conforme o caso clínico do paciente. Não há evidências do uso com crianças, menores de 18 anos e gestantes.

***Palavras-chave**: Eficácia, Segurança, Psicofármacos, Interações.*

INTRODUCTION

Depression is a type of affective disorder that manifests itself in any age group (being predominant among adolescents and the elderly), by means of psychological suffering, affecting more than 300 million people worldwide. In Brazil, according to data from the Brazilian Institute of Geography and Statistics, depression affects 16.3 million Brazilians over the age of 18 (SOUZA *et al.*, 2021).

According to the World Health Organization (WHO), depression is a mood disorder that involves much more than a state of melancholy, it includes permanent sadness and a loss of interest or inability to perform daily activities, for at least two weeks or longer. It alters the body's behavior, thinking and emotional responses, and fatigue after minimal effort is common (FONSECA, COUTINHO and AZEVEDO, 2008). The symptoms are related to changes in sleep, appetite, fatigue, difficulty of concentrating, slowness, feeling of guilt, recurrent thoughts of death and suicide attempts (around 800 thousand people/year) and, can last for months and years, interfering in the personal, professional and social life of the individual (CARDOSO *et al.*, 2019; ARAÚJO, 2005).

The incidence of depression in the population has increased even more due to the pandemic caused by the coronavirus, experienced from the 2020, which imposed the seclusion of the population in their homes, social distancing and quarantine for social reinsertion after contagion. However, the elderly become more and more vulnerable, since dementias are more common over the age of 60 and, furthermore, many have underlying pathologies, such as hypertension and diabetes, which can worsen the health condition (SANTOS and BARBOSA, 2017; RIBEIRO *et al.*, 2020). The elderly is more susceptible to depression due to the fact that they go through several physiological, psychological, social and/or financial changes (CARDOSO *et al.*, 2019).

The clinical diagnosis is made through anamnesis, evaluation of symptoms, frequency, duration, and examination based on medical references such as Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association, considering the occurrence of one or two associated symptoms or three or four other symptoms described in chart 1, persistent for at least two weeks (SILVA, 2010). Depending on the number and severity of these symptoms, a depressive episode can be categorized as mild, moderate or severe (SANTOS and BARBOSA, 2017).

Chart 1 - Symptoms of major depression, according to DSM-IV.

	Symptoms of Depression
1	Depressed mood most of the day, almost every day.
2	Markedly decreased interest/enjoyment in all of most activities.
3	Significant weight loss or weight gain, or decreased or increased appetite.
4	Insomnia or hypersomnia almost every day.
5	Agitation or psychomotor retardation almost every day
6	Fatigue or loss of energy almost every day.
7	Feeling of inappropriate self-worth or excessive guilt.
8	Decreased ability to think or concentrate, or indecisiveness.
9	Recurrent thoughts of death, or suicidal ideation or attempts.
10	Feeling of hopelessness.

Source: Adapted from SANTOS and BARBOSA (2017) and SILVA (2010).

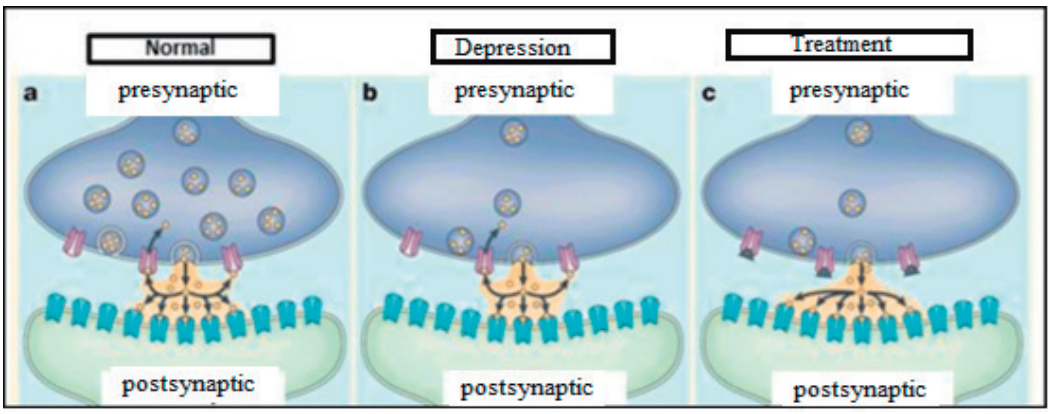
Some instruments help in the diagnostic evaluation by estimating the symptoms of depression, such as: Beck Depression Inventory (BDI) which contains 21 items that address cognitive, affective, behavioral and depression components and presents a score of 0-63 (GIAVONI *et al.*, 2008), the Montgomery and Åsberg Depression Scale (MADRS) contains 10 items ranging from 0-60; Hamilton Depression Scale (HAM-D) with 21 items, later changed to HAM-17, which ranges from 0-50; California Psychological Inventory Depression Scale (CPI-D), with 27 items applied to elderly and children with a score of 0-47, among other scales. The MADRS scale has greater sensitivity in distinguishing between mild (7-17), moderate (18-24) and severe depression (above 25 or 28) compared to the Hamilton Depression Scale (HAM-17), being more frequently applied to diagnosis (GIAVONI *et al.*, 2008).

However, for the diagnosis of depression in the elderly, the levels detected by the scales may not be reliable, since items related to somatic symptoms serve both to diagnose depression and symptoms resulting from aging. In addition, common diseases in the elderly, such as Alzheimer's and Parkinson's, may overestimate the diagnosis, while the use of medication may mask the symptoms (GIAVONI *et al.*, 2008).

There are several causes of depression: genetic manifestations (such as dysfunctions in neurotransmitters), developmental problems (include personality problems or specific event in childhood), physiological changes (age, hormones, pathologies), and psychosocial stress (such as an unemployment situation, divorce, or loss of loved ones) (DINIZ *et al.*, 2020; SANTOS and BARBOSA, 2017).

Depression develops from the reduction of noradrenergic and serotoninergic neurotransmitters in the synaptic cleft due to genetic dysfunction or intracellular alterations of postsynaptic neurons due to chemical exposure (SILVA, 2010; SCHILDKRAUT, 1965). This chemical imbalance requires the institution of a therapy with psychotropic drugs, either to alleviate symptoms, reduce disability, shorten the course of the disease or prevent recurrences. Psychopharmaceuticals can alter the state of consciousness, cognitive processes, or mood, as shown in Figure 1 (SOUZA *et al.*, 2021; CARDOSO *et al.*, 2019; BRATS, 2012; MORENO, MORENO and SOARES, 1999).

Figure 1 - Physiology of normal nerve transmission under depressive state and effects of treatment with usual antidepressants.



Source: CASTRÉN, 2005.

In the normal brain (Fig.1A), monoaminergic neurotransmitters (serotonin (SE), noradrenaline (NA) and dopamine (DA)) are released and activate postsynaptic receptors. The neurotransmission is terminated by reuptake of the neurotransmitter in the presynaptic neuron. In depression (Fig.1B), patients have lower concentrations of monoamines in the synaptic cleft and treatment with the usual psychotropic drugs (Fig.1C) causes increased concentrations of the neurotransmitters in the cleft, the blockade of monoamine reuptake to the presynaptic neuron and/or inhibition of their metabolism, increasing by all these routes their concentrations and bioavailability in the synaptic cleft and thus restoring the mood of depressed patients (CASTRÉN, 2005; SCHILDKRAUT, 1965).

Treatment of depression involves psychotherapy (minimum 6 months), the use of psychopharmaceuticals (minimum 2-4 weeks for clinical response) and/or a combination of both (BRATS, 2012).

Vortioxetine (VORTIOXETINE, 2014), a serotoninergic modulator, approved by the National Health Surveillance Agency (ANVISA) in 2015 in Brazil, emerged; however, it is not available in generic form. It is indicated for depression in adults, showing better tolerability of side effects, less deleterious effects on cognition, and significant improvement of depressive symptoms at doses of 5 to 20 mg/day (JORNADA CIENTÍFICA DO INTERNATO MÉDICO, 2019; CHRISTENSEN *et al.*, 2018).

The present study aimed to investigate scientific evidence based on clinical case studies about the efficacy and safety of vortioxetine for the treatment of depression in the elderly and is justified by the increase in cases of depression nowadays, especially among the elderly, who constitute a vulnerable population group and who still use polytherapies due to associated diseases such as hypertension and diabetes, requiring greater health care. Also, for the need of further studies of new active ingredients for depression, as the case of vortioxetine, mainly due its differential, which acts on multiple receptors, improving cognition and reducing adverse effects in relation to traditional psychotropic drugs and, is able to inhibit the occurrence of refractory depression.

METHODOLOGY

This study comprises a literature review on specialized health websites (Google academic, Science direct, Pubmed, among others available) using scientific evidence from clinical case studies involving the treatment of depression with vortioxetine in the elderly. Publications from the last 10 years, in English, Spanish and Portuguese were considered using as descriptors in Health Science (DeCS) the terms: "depression, vortioxetine, elderly, vortioxetine-hypoglycemic agents' interaction and vortioxetine- arterial hypotensor interaction, efficacy and safety". Inclusion criteria were clinical studies with adult and elderly groups, and exclusion criteria were those that did not contain a complete description of the sampling or descriptors chosen. The results collected were exposed and discussed in the text.

One of the methods used to calculate the effectiveness of antidepressant therapy is by calculating the number needed to harm (NNH) and the number needed to treat (NNT). NNT is the number of people who need to be treated during a specific period to promote an additional good outcome or avoid an additional bad outcome, while NNH is the number of people who need to be treated during a specific period before a negative disease outcome occurs. Both are used as comparative parameters in clinical trials, with NNH expected to be greater than NNT (SCHATZBERG *et al.*, 2014).

TREATMENT OF DEPRESSION WITH TRADITIONAL PSYCHOTROPIC DRUGS

From the literature review, 52 articles were evaluated, addressing depression and its treatments. The emergence of antipsychotics for the treatment of mental disorders revolutionized the history of psychiatry, with tricyclic antidepressants being the first to appear, followed by the classic MAOIs (1950-1970). Between the 1970s-1990s, atypical antipsychotics emerged (SOUZA *et al.*, 2021; MORENO, MORENO, and SOARES, 1999). Traditional psychotropic drugs are classified into the following groups, as shown in Table 1:

Table 1 - Classification of antidepressants according to mechanisms of action.

Class	Subclass	Mecanism of action	Adverse effects/side effects	Examples
Tricyclic Antidepressants (ADTs)	Tertiary amines (NA and SE) and secondary amines (NA)	They block the non-selective reuptake of NA, SE, and DA; block muscarinic (cholinergic), histaminergic type 1, -2, and -adrenergic, serotoninergic (5-HT), and, dopaminergic receptors.	There is low tolerability and risk of toxicity, blocks the effects of antihypertensives	Amitriptyline, Clomipramine, Imipramine and doxepin (tertiary) and, Nortriptyline, Desipramine and Protriptyline, (secondary)
Monoamine oxidase inhibitors (IMAO)	Non-selective and Irreversible	Reduces action of MAO-A and MAO-B enzymes, results in increased concentration of SE, NA, and DA in the CNS and SNAS. There is subsensitization of 2- or -adrenergic and 5-HT receptors.	"cheese" reaction, orthostatic hypotension and syncope, anticholinergic effects, tachycardia, sexual dysfunction and peripheral edema	Phenelzine, Isocarboxazid, Iproniazid, Tranylcypramine
	Selective and Irreversible	MAO-A metabolizes DA, NA and SE, while MAO-B metabolizes DA	severe orthostatic hypotension, diarrhea, edema in the feet and ankles	Clorgiline (MAO-A) Selegiline (MAO-B)
	Selective and Reversible	They deaminate 5-HT and NA receptors.	Severe orthostatic hypotension, diarrhea, edema in the feet and ankles	Moclobemide (MAO-A)
Atypical or New Antidepressants	Selective Serotonin Reuptake Inhibitors (SSRIs)	They block the reuptake of NA, SE, and DA; bind strongly to plasma proteins, affecting cytochrome P450 enzymes, and potently and selectively inhibit SE reuptake.	Headache, gastrointestinal effects (nausea, diarrhea), lack of coordination, changes in sleep and energy level, sexual dysfunction and hyponatremia prolongation of the QT depolarization and repolarization ventricular interval, dose dependent with the use of citalopram, leads to premature births in the 3rd trimester of gestation and withdrawal symptoms in neonates, such as tremors, irritability, restlessness, and nervousness	Fluoxetine Sertraline, Citalopram, Paroxetine, Fluvoxamine, Escitalopram
	Selective SE/NA reuptake inhibitors (SSRIs)	They downregulate cAMP-coupled -adrenergic receptors and prevent SE and NA reuptake.	nausea, vomiting, insomnia, dizziness and headache, transient dose-dependent elevation of blood pressure, constipation, risk of gastrointestinal bleeding and ejaculation disorders	Venlafaxine Duloxetine
	Serotonin reuptake inhibitors/antagonists (IRSA)	Inhibit neuronal uptake of SE and NA, antagonize serotonergic receptors and α-1 adrenergic and histamine receptors.	sedation, orthostatic hypotension, dizziness, headache, nausea, dry mouth. Allergic reactions and gastric irritation may appear.	Nefazodone, Trazodone

	SE reuptake stimulants (ERS)	Decreases SE in the brain, modulates glutamatergic receptor activity and affects the release of brain-derived neurotrophic factor, which decreases neural plasticity and reduces available SE.	anorexia, nightmares, insomnia, sleepiness, headache, tachycardia, heat waves, dyspnea, dry mouth, nausea, and others.	Tianeptine
	Selective NA reuptake inhibitors (SNRIs)	Displays selective activity on the reuptake of NA reuptake, with α-2 antagonist activity.	tachycardia, impotence, urinary hesitancy or retention, insomnia, excessive sweating, constipation, dry mouth.	Reboxetine, Viloxazine
	Selective inhibitors of DA reuptake (ISRDN)	It acts on DA, inhibits NA, DA and furthermore considerably increases the presynaptic availability of NA.	agitation, skin rash, anxiety, decreased appetite, dry mouth, induction of convulsions.	Amineptine Bupropion Minaprine
	Specific noradrenergic and serotoninergic antidepressant (ANASE)	Blocks the α-2-adrenergic receptor and 5-HT2. Increases central AN and SE. Also has sedative effect, due to its affinity for histamine H1 receptors.	Excessive sedation, tachycardia, weight gain, dry mouth, dizziness, edema, constipation, dyspnea.	Mirtazapine, Mianserine

Source: Author's construction, based on sources: BRATS (2012); CIPRIANI *et al.* (2010); MORENO, MORENO and SOARES (1999). 5-HT: serotonin receptor; SE: serotonin; NA: noradrenaline; DA: dopamine, SNC: central nervous system, SNAS: sympathetic nervous system, AMPc: cyclic adenosine monophosphate.

Considering the sales in pharmaceutical establishments, in 2001, 26.74 billion daily doses of psychotropic drugs were consumed worldwide (ANDRADE, ANDRADE e SANTOS, 2004). The psychotropic drugs used as 1st line of treatment include SSRIs, NSAIDs, IRNDs IRSA, ANASE and multimodal agents, leaving in 2nd line ADTs and MAOIs due to trigger more adverse effects and drug and/or food interactions, which can even be fatal to the elderly patient (CIPRIANI *et al*., 2010).

Fluoxetine (SSRI) stands out as the most prescribed psychotropic drug, followed by amitriptyline (ADT), paroxetine (SSRI), sertraline (SSRI) and nortriptyline (ADT). The use of psychotropic drugs (antidepressants, mainly tricyclics, and short-acting benzodiazepines) has been associated with an increased risk of falls for the elderly due to adverse reactions and interactions between ingested medications, treatment abandonment or delay of clinical responses with tricyclic medications and clinical delay with the use of MAOIs that increases the risk of suicide have also been reported (MARTINS, MAIA and PEREIRA, 2007).

Traditional psychotropic drugs require at least two weeks of administration (latency period) for pharmacodynamic adaptations and the beginning of pharmacological effects, and at least four weeks of use to observe improvement of the clinical picture (BRATS, 2012). The American Psychiatric Association - APA suggests maintaining use for at least 16 to 20 weeks with full doses after improvement or remission of symptoms and the World Health Organization suggests 24 weeks or more

of use after symptom improvement (SOUZA, 1999). For vortioxetine, similarly, a minimum treatment of 6 months is recommended (VORTIOXETINA, 2016).

The treatment of depression is divided into three phases: acute (symptom remission, 6-12 weeks), continuation (relapse prevention, 4-9 months), and maintenance (chronic depression, drug resistant, with suicide attempts) (BRATS, 2012; SOUZA *et al*., 2021).

The response to treatment is measured by the patient's clinical improvement and can be partial or total, considering the remission of symptoms and the recovery of normal levels of functioning and well-being. In the case of a partial response, the first course of action is to increase the dose; if there is no remission, the medication is changed to another class of psychotropic drugs. If there is no response again, the possibility of treatment resistant depression (TRD) must be considered (SOUZA, 1999).

The choice of antidepressant should be based on evidence of efficacy and observing the clinical characteristics of the depressive episode, possible adverse effects, and personal or family history of previous response to medication. For good clinical practice, it is recommended to use the antidepressant gradually until the therapeutic dose is reached (maximum dose indicated by the posology) and reevaluate its continuity after 3 weeks. In case of withdrawal of medication, this should be gradual to avoid the appearance of abrupt discontinuation symptoms (BRATS, 2012; SOUZA, 1999).

Elderly patients have high rates of therapeutic transgression due to neglect or lack of memory. Their depression comes from a high prevalence of affective disorders (mixture of depression and anxiety), and they are patients more susceptible to interactions due to reduced hepatic and renal function. It is more often recommended the indication, within the group of ADTs, of secondary amines because they generate fewer adverse effects, especially to the elderly (SILVA, 2010; MORENO, MORENO and SOARES, 1999).

The use of IMAOS can generate undesirable adverse effects, besides toxicity, being potentially lethal in cases of overdose (SILVA, 2010; MORENO, MORENO e SOARES, 1999).

Some ADTs, in particular amitriptyline and doxapine, can cause excessive drowsiness and sedation (SILVA, 2010). The sedative effect seems to be related to the potency of the blockade of histaminergic H1 receptors. Mental confusion is often caused by excessive doses in the elderly, requiring dosage adjustment. Other ADTs may produce agitation, with the appearance of fine tremors, which may disturb writing and precise gestures, and in those more sensitive, seizures may occur (1-4%) (REZENDE, 2012; SILVA, 2010).

And, atypical antidepressants (SSRIs) are the least toxic, although they can potentiate the serotonin syndrome when associated along with MAOIs, ADTs, and tryptophans, represent the main class for the treatment of depression (NETO, 2018).

The drugs that increase the risk of falling (antipsychotics, sedative hypnotics, psychotropic drugs and cardiovascular drugs) by causing effects such as orthostatic hypotension, muscle weakness, arrhythmia, cognitive dysfunction, balance disorders, dizziness, somnolence, motor dysfunction,

visual changes and parkinsonism are considered dangerous for the elderly and should be prescribed and monitored with caution (REZENDE, 2012).

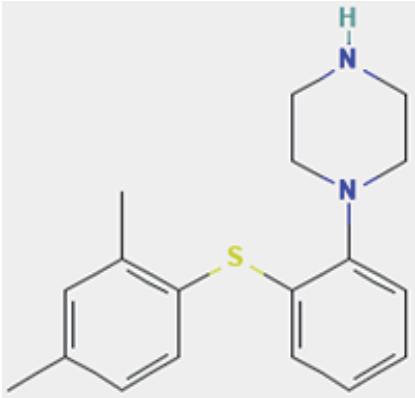
Besides the use of isolated medications, there is also polypharmacy that can bring risks to the health of the elderly, given the possibility of occurrence of iatrogenic and adverse reactions (REZENDE, 2012) and, it is important to study new antidepressant molecules, of fast action, safe and effective for the treatment of depression, especially for use in the elderly.

VORTIOXETINE

Of the 52 articles reserarched, 12 articles (20%) were used, which refer to clinical case studies with vortioxetine in the treatment of depression in the elderly, and their drug interactions.

Vortioxetine, whose chemical formula is $C_{18}H_{22}N_2S$ (Figure 2), was developed with the indication for acute and chronic treatment of depression in young adults to the elderly, demonstrating efficacy and safety. It is recommended to start therapy at 5 mg and gradually increase up to 20 mg, being observed the control of symptoms and that the patient feels well, and should be used for at least six (6) months (VORTIOXETINA, 2016). Vortioxetine can be abruptly discontinued. However, it is recommended that doses of 15-20 mg/day be reduced to 10 mg/day for one week before total discontinuation, if possible, to minimize the likelihood of withdrawal symptoms occurring (CHEN *et al.*, 2017; MORENO, MORENO and SOARES, 1999).

Figure 2 - Structural formula of vortioxetine (chemical name:
(hidrobrometo de 1-[2-(2,4- dimethyl-phenylsulfanyl)-phenyl]-piperizine hydrobromide)



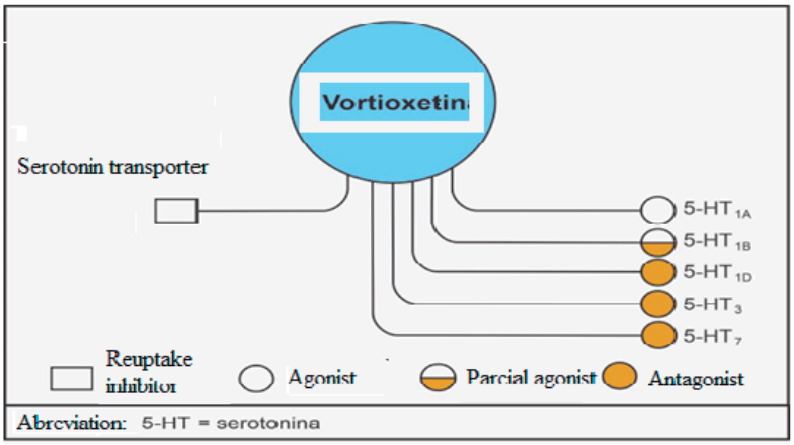
Source: VORTIOXETINE (2021).

Once ingested it binds strongly to plasma proteins (98-99%), having an absolute bioavailability of 75%, and is extensively metabolized by cytochrome P450 isoenzymes (mainly CYP2D6) in the liver. The maximum plasma vortioxetine concentration (C_{max}) after a single dose is reached within 7-11 h. It has a half-life of 66 hours and a clearance of 33 L/h, with 2/3 of its inactive metabolites being excreted in urine and 1/3 in feces (CHEN *et al.*, 2017).

Vortioxetine is in the class of atypical antidepressant psychotropic drugs, called bisarylfulfanil amine, being a modulator of several neurotransmitters, such as serotonin, DA, NA, histamine, glutamate and gamma-aminobutyric acid (GABA) (SANCHEZ, ASIN and ARTIGAS, 2015; VORTIOXETIN, 2016). It presents a multimodal mechanism of action, acting on different receptors and generating specific properties, such as the regulation of cognitive function, this being its main advantage (SANCHEZ, ASIN and ARTIGAS, 2015).

The mechanism of action of vortioxetine is not fully understood. It acts as an inhibitor of serotonin transporters, causing inhibition of its reuptake, and, acts as an agonist of the 5HT1A receptors (promoting neuroplasticity), partial agonist of the 5HT1B receptor (autoreceptor for serotoninergic neurotransmission) and antagonist of 5HT1D (increases serotoninergic flux), 5HT3 (activates prefrontal cortex, related to attention, motivation, pleasure and release of DA, NA, acetylcholine (Ach)) and 5HT7 (improves circadian cycle, memory and cognitive abilities), having the highest affinity for the 5HT1D receptor (Figure 3) (SALAGRE *et al.* , 2018; D'AGOSTINO, ENGLISH, and REY, 2015; SCHATZBERG *et al.*, 2014).

Figure 3 - Neurotransmitters and mechanism of action of vortioxetine



Source: adapted from Schatzberg *et al.* (2014).

The most significant adverse effects of vortioxetine are reported with concomitant use of MAOIs, due to the occurrence of symptoms related to Serotonin Syndrome and Neuroleptic Malignant Syndrome, which can be fatal and require discontinuation of use at the first detectable sign. It can also rarely lead to bleeding disorders (VORTIOXETINA, 2016).

As the most common adverse effects, in a clinical study of 3000 patients aged 18-75 years segregated into groups treated with vortioxetine at concentrations of 5, 10, 15 and 20 mg/day for periods 2, 4, 6 and 8 weeks, the therapy was found to be generally well tolerated. The most frequent adverse effects were found to be mild to moderate and transient including nausea, vomiting, constipation, diarrhea, dry mouth, dizziness, and headache. Only nausea occurred in 2 patients, leading to discontinuation of use and being considered statistically relevant compared to placebo. There is the

observation that nausea lasts 1 to 2 weeks, being more frequent in women and is the most common cause of treatment abandonment (CHEN *et al*., 2017; DIEGO, 2016; VORTIOXETINE, 2014).

In the clinical study by Baldwin et al (2016), 1,817 patients treated with placebo and 3018 patients treated with vortioxetine 5-20 mg/day for 52 weeks were observed for the presence of the adverse effects already described above as mild to moderate (SALAGRE *et al*., 2018; BALDWIN *et al*., 2016; VORTIOXETINE, 2014), and also included nasopharyngitis, weight gain, insomnia, sexual dysfunction (BALDWIN *et al*., 2016). The incidence of serious adverse effects occurred in 4.6% of the placebo group, 2.9% of patients on vortioxetine 5-10 mg/day and 5.8% of those on 15-20 mg/day and, included hypertensive crisis, increased risk of suicide and pancreatitis (SALAGRE *et al*., 2018; BALDWIN *et al*., 2016).

Clinical case studies of vortioxetine use are still scarce addressing efficacy and safety, of those researched to date follow:

The efficacy of vortioxetine (5-20 mg/day) based on 11 short-term (6-8 weeks) clinical trials was compared with placebo involving 400 adults (age range not cited) with moderate or severe depression classified according to DSM-IV Diagnostic Manual criteria. Efficacy was assessed as improvement in symptomatology based on change in scores on the MADRS and/or HAM-D scales, and a 50% improvement in scores on these scales and clinical symptomatology was observed in patients with moderate to severe depression compared to placebo (DIEGO, 2016).

A meta-analysis with 11 studies and 6,145 patients (age range not cited) showed sometimes contradictory results regarding dose, administered over 8 weeks. Compared to placebo, response rates regarding treatment efficacy were significantly higher with vortioxetine at 10 mg and 20 mg, than with vortioxetine at 5 and 15 mg (DIEGO, 2016).

The efficacy and tolerability of vortioxetine were evaluated with 560 patients aged 18 to 75 years, with a diagnosis of major depressive disorder (MDD), under the MADRS Scale, whose score was at least 26 and, demonstrated that all doses of vortioxetine (10 and 20 mg/day vs. placebo, administered once daily for 8 weeks) reduced Hamilton Scale (HAM-24) scores, with results with the 10 mg dose shown to be the dose of potential effect (D'AGOSTINO, ENGLISH and REY, 2015).

Also, a randomized trial with 1824 elderly patients were treated with placebo and 3304 (over 65 years old) using vortioxetine at 5 to 20 mg/day for 8 weeks and confirmed a reduction in 10 items of depression by the MADRS scale with doses of 10 and 20 mg significantly compared to placebo (THASE *et al*., 2016).

The effects of age on vortioxetine pharmacokinetics were evaluated in a two-phase study, the first comprising 24 young volunteers aged 18-45 years and the second phase 24 elderly volunteers aged 65-85 years. After a single dose of vortioxetine at 10 mg daily for 14 days demonstrated superior responses in the elderly than in the young regarding maximum concentration and area under the curve which were 23 and 27% higher, respectively (CHEN *et al*., 2017).

Vortioxetine has also demonstrated positive effects on cognition through clinical trials being evaluated at concentrations of 10 and 20 mg/day vs. placebo, for 8 weeks of treatment with 602 patients (18-65 years old) who had moderate depressive episode disorders. The vortioxetine treated group, regardless of dose, scored significantly higher on the Digit Symbol Substitution Test (DSST), which assesses processing speed, executive functions and attention and; on the Rey's Auditory Verbal Learning Test (RAVLT), which assesses learning and memory (SALAGRE *et al*., 2018; McINTYRE *et al*., 2014).

Thus, it is concluded that vortioxetine improves learning disabilities and prevents stress-induced learning deficits, having a positive effect on memory and favoring neuroplasticity (SALAGRE *et al*., 2018). Also, these positive effects on cognition are confirmed by magnetic resonance imaging, modulating and reversing abnormalities of neural pattern networks (CHEN *et al*., 2017).

VORTIOXETINE INTERACTIONS WITH OTHER PSYCHOTROPIC DRUGS, WITH HYPOGLYCEMIC AGENTS AND WITH HYPOTENSIVES

A Vortioxetine therapy is reported to be affected by other drugs such as irreversible and non-selective MAOIs due to the risk of Serotonin Syndrome and is contraindicated. It can only be started after 14 days of discontinuation of MAOIs and vice versa, and should be discontinued 14 days before starting treatment with MAOIs (CHEN *et al*., 2017; MORENO, MORENO and SOARES, 1999). Likewise, it should not be combined with reversible and selective MAOI-A such as moclobemide and reversible and non-selective MAOIs and; if these associations are necessary, it should be used at the lowest dosage and with careful monitoring of the Serotonin Syndrome. With irreversible and selective MAOI-B and serotonergic drugs (including St. John's Wort, Hypericum perforatum) the joint administration should be cautious and monitored. Interactions are also observed with linezolid and methylene blue (VORTIOXETINE, 2014).

Care should be taken when associating with drugs that reduce seizure threshold such as ADTs, SSRIs, NRIs, neuroleptics, bupropion, tramadol, and mefloquine (CHEN *et al*., 2017; VORTIOXETINE, 2014; MORENO, MORENO and SOARES, 1999).

Different drug interaction studies have evaluated the effect of other drugs, including bupropion, fluoxetine, quinidine, and paroxetine on vortioxetine concentration. Bupropion used concomitantly with vortioxetine is well tolerated, does not interfere with safety, however, dosage adjustments may be required (VORTIOXETINE, 2014).

A sample of 44 patients who received bupropion at 150 mg/day, 2 (two) times/day (75 mg each administration) for 14 days and, received from days 15 to 28, together with vortioxetine 10 mg/day. Upon exposure of vortioxetine approximately increased the area under the curve (AUC) (0-24) h by 2.3 times and by 2.1 times the maximum concentration (C_{max}), thus, they showed synergistic effect

(SALAGRE *et al.*, 2018; CHEN *et al.*, 2017). In this study there was an increase in adverse effects with a threefold increase in probability of occurrence, so it is recommended to reduce the dose of vortioxetine by half when combined with bupropion or other CYP2D6 inhibitors such as fluoxetine, quinidine or paroxetine and a dose adjustment of vortioxetine if a cytochrome P450 inducer such as rifampicin, carbamazepine, phenytoin is added (SALAGRE *et al.*, 2018; CHEN *et al.*, 2017; VORTIOXETINE, 2014).

In general, caution is advised when combining vortioxetine with an anticoagulant or antiplatelet agent due to a significant increase in bleeding risk (SALAGRE *et al.*, 2018; BALDWIN *et al.*, 2016).

Caution of joint prescribing with lithium or tryptophan is also reported due to possible potentiation of effects, but no clinically relevant effects are observed. However, tryptophan may affect serotonin metabolism, so caution and caution should be used concomitantly with vortioxetine (VORTIOXETINE, 2014).

Regarding cardiac and vascular profiles, vortioxetine and vilazodone (SSRIs) are considered safe, with non-relevant effects on blood pressure and a cardiovascular profile comparable to placebo (CALVI, 2021).

No evidence has been found in the literature on vortioxetine interactions with hypoglycemic and antihypertensive drugs to date, and clinical studies that could be performed for this observation are lacking.

DISCUSSION

After surveying the literature regarding the use of traditional psychotropic drugs, it was found that fluoxetine is the most prescribed. There is evidence that fluoxetine may act to promote weight loss for several months after initiation of therapy, which may contribute to high consumption. Following fluoxetine, there are significant rates of amitriptyline and nortriptyline prescriptions, despite possible toxic and side effects (ANDRADE, ANDRADE and SANTOS, 2004).

Lack of adherence to treatment and discontinuation of psychotropic drug therapy is one of the concerns of health professionals, because adherence is relatively low, ranging from 40 to 90% in different studies. Interruption rates are higher during the first month of treatment due to the side effects of traditional antidepressants (Table 1), which contributes to the recurrence of the disorder and increased risk of suicide. Based on the difficulty of patient adherence to therapy, it is necessary to provide adequate support, teach about the disease and possible treatments, and encourage patients to maintain treatment, especially during the first weeks (BRATS, 2012).

The elderly constitutes a vulnerable population group due to their age and associated comorbidities, which makes therapy and follow-up more delicate. Hypertensive elderly people have a 45% higher risk of developing depression compared to normotensive people (SCUTERI et al, 2010) and

60% of Brazilian elderly people have hypertension (PLAVNIK *et al*., 2016). As for diabetic patients, there was a worldwide increase of 16% between the years 2019 and 2021, and in Brazil, an estimated 16.8 million people with diabetes, about 7% of the population (BARRETO, 2021).

Care is needed for drug associations between psychotropic drugs and antihypertensives in order to avoid serious interactions such as those that occur in:

- ADTs or MAOIs with propranolol,

- paroxetine or fluoxetine (SSRIs) with metoprolol (antagonist 1),

- venlafaxine (SSRIs) with captopril, angiotensin-converting enzyme inhibitors (ACEIs) or with calcium channel blockers,

- MAOIs with tyramine-containing foods (cheese, wine or beer) or with adrenergic stimulants e.g. decongestants which can lead to increased blood pressure, hypertensive crisis and death (ORLANDI, MEDEIROS and FERREIRA, 2021; BRATS, 2012; MORENO, MORENO and SOARES, 1999).

Also, it is reported that the use of bupropion or mirtazapine used alone can increase blood pressure in cardiac patients (MORREALE and WAKE, 2020).

When it comes to interactions between psychotropic drugs and hypoglycemic agents, we can mention:

- ADTs or MAOIs should be avoided by elderly diabetics because they inhibit insulin release by the pancreas and cause increased glucose levels, yet ADTs cause postural hypotension and cardiovascular symptoms, which makes it possible to amplify diabetes symptoms (FRÁGUAS, SOARES and BRONSTEIN, 2009).

- ADTs antagonize hypotensive agonists 2;

- Fluoxetine (SSRI) with glibenclamide causes an antagonistic effect since fluoxetine generates hyperglycemia and cancels the hypoglycemic effect of glibenclamide, suggesting that fluoxetine may exert its glycemic effects by altering insulin secretion (OLIVEIRA *et al*., 2008).

- Methyldopa may potentiate the toxicity of digoxin and/or lithium and antagonize the effects of oral hypoglycemia (ELLIOTT, 2006).

It is also reported that, on average, 35% of patients do not respond to drug therapy, with relapse of symptoms, so there is an urgent need for the development of new psychopharmaceuticals of fast action, effective and safe (JORNADA CIENTÍFICA DO INTERNATO MÉDICO, 2019).

Thus, vortioxetine emerged in 2015 in Brazil, being a drug little publicized among patients, with few clinical studies still available and, mainly, with distinct protocols, which makes it difficult to obtain a comparative and representative statistical evidence. In the studies that evaluated the adverse effects of vortioxetine, it was found to have only mild to moderate effects that last up to 2 weeks and are the most common cause of treatment abandonment.

When evaluating efficacy, none of the clinical studies with vortioxetine cited in this research involved the evaluation of efficacy through the calculation of NNT and NNH, but all were based on

the reduction of scores of the depression scales that consider the symptomatology of the patient. It was possible to observe that several studies demonstrate the efficacy of vortioxetine treatment at doses of 10 and 20 mg for moderate to severe depression in adult and elderly patients. And, analyzing the work of Diego (2016), who cites that doses of 5 and 15 mg of vortioxetine did not show significant results, it is found that this response is due to the fact that the dose of 5 mg is probably low to observe improvement of symptoms while the dose of 15 mg does not bring significant results compared to the doses of 10 and 20 mg (MEEKER, 2015).

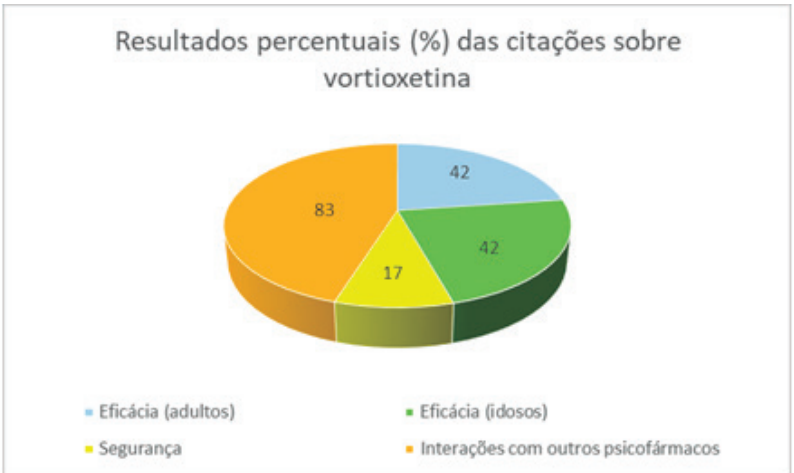
Safety and tolerability were evaluated in all randomized trial studies and vortioxetine was statistically superior to placebo. Safety and tolerability assessments included vital signs and weight, physical examination, clinical safety laboratory tests, electrocardiogram (ECGs), and reported adverse events (MAHABLESHWARKAR *et al*., 2015).

Vortioxetine is contraindicated in children and pregnant women due to risk-benefit considerations, as the safety of vortioxetine use in human pregnancy has not yet been established. Also, vortioxetine is not indicated for use in patients under 18 years of age, as it has not demonstrated efficacy or this has not been established (VORTIOXETINE, 2014). For patients over 65 years of age it is recommended to start treatment with vortioxetine at 5 mg/day, being careful about doses higher than 10 mg (which require monitoring) and, in cases of patients who have severe renal or hepatic insufficiency or, even if they have a history of seizures (BALDWIN *et al*., 2016; VORTIOXETINE, 2014).

Double care should be taken when polytherapies are used, and even greater caution should be taken with patients at risk, such as elderly patients with liver cirrhosis or those treated concomitantly with medications that cause hyponatremia. In these cases, it is suggested to discontinue the use of vortioxetine and institute appropriate intervention (D'AGOSTINO, ENGLISH e REY, 2015).

Below is Figure 4, which demonstrates the percentage results of the literature citations addressed in this research.

Figure 4 - Percentage results (%) of citations about vortioxetine



Source: Prepared by the author.

Through this survey it was possible to confirm the efficacy of vortioxetine with adult patients (5 articles, 42%) and elderly patients (5 articles, 42%) proven in different clinical trials, especially in doses of 10 and 20 mg/day, as well as its safety by causing mild to moderate adverse effects (2 articles, 17%). However, we emphasize that vortioxetine is contraindicated to be used concomitantly with MAOIs, and also the importance of monitoring the elderly patient, especially those with liver and kidney disorders, and that greater caution should be taken with doses higher than 10 mg/day. It is also noteworthy that the use of polypharmacy by the elderly becomes an aggravating factor for the triggering of possible adverse effects and that, so far, there are no reports of vortioxetine interactions with antihypertensives or oral hypoglycemic agents. In view of this study, it was observed that the pharmaceutical and/or medical follow-up is necessary to provide some care to elderly patients.

CONCLUSION

The present research contributes to the clarification of the population affected by major depressive disorder and users of psychotropic drugs, in order to clarify doubts about the usual therapeutic classes and present the new psychotropic drug, vortioxetine.

The advantages of vortioxetine are that it has a multimodal action mechanism, acting on different neurotransmitter receptors and reducing depressive symptoms, including improving cognition. Although it requires the same treatment time as traditional drugs, vortioxetine has mild to moderate adverse effects when used alone, and no serious effects have been reported. Therefore, the use of vortioxetine has proven effective in reducing symptoms of depression at doses of 10 and 20 mg/day, being well tolerated and safe.

However, vortioxetine is not recommended for the treatment of depression in children 7 to 11 years of age, as the safety and efficacy of vortioxetine in this age group have not been established. Similarly in pregnancy and infants, in which there are limited data on the use of vortioxetine. Animal studies show the excretion of vortioxetine metabolites in milk so vortioxetine is expected to be excreted in breast milk (VORTIOXETINE, 2014).

Use for pregnant women should make the decision about discontinuing breastfeeding or discontinuing/abstaining vortioxetine therapy after considering the benefit of breastfeeding to the child and the benefit of therapy to the mother.

Among the interactions with other psychotropic drugs, it is recommended not to use it together with MAOIs to avoid the Serotoninergic and Neuroleptic Syndromes and to observe the patient when associated with ADTs, SSRIs or NRSRIs. Regarding the possible interactions of the use of vortioxetine for hypertensive and/or diabetic elderly people, no evidence was found in clinical studies so far, however, caution and monitoring of patients is recommended, especially in doses higher than 10 mg/day.

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