PRÓ-REITORIA E PESQUISA E PÓS-GRADUAÇÃO
MESTRADO EM CIÊNCIA ANIMAL

CAROLINA GALANTE SILVA

IMPACTOS DA VENLAFAXINA NA ESPERMATOGÊNESE E FERTILIDADE MASCULINA: REVISÃO SISTEMÁTICA

Presidente Prudente - SP
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Dissertação apresentada a Pró- Reitoria de Pesquisa e Pós-Graduação, Universidade do Oeste Paulista, como parte dos requisitos para a obtenção do título de Mestre em Ciência animal – área de concentração: Fisiopatologia Animal.

Orientador:
Dr. Anthony César de Souza Castilho

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Presidente Prudente, 04 de agosto de 2023.

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DEDICATÓRIA

Dedico este trabalho à minha família, que são o motivo do meu viver.

AGRADECIMENTOS

Aos meus pais, Daniela e Julio Cesar, pois vocês me ensinaram o valor da busca pelo conhecimento e ao crescimento pessoal e profissional.

Ao meu marido Francisco e meu filho Loreto, o qual ainda carrego em meu ventre, por serem minha força nos momentos mais difíceis.

Ao meu orientador, Prof. Dr. Anthony César de Souza Castilho, que teve a compreensão e paciência para me guiar nessa jornada acadêmica.

“O sábio envergonha-se dos seus defeitos,
mas não se envergonha de os corrigir.”

(Confúcio)

ABSTRACT

Impactos da venlafaxina na espermatogênese e fertilidade masculina: revisão sistemática em modelo expeimental

Medicamentos antidepressivos são comumente usados em homens em idade reprodutiva para o tratamento a longo prazo da depressão, bem como de outros distúrbios. Embora os antidepressivos estejam associados a efeitos sexuais negativos, como redução da libido, impotência sexual, anorgasmia ou retardo ejaculatório, a literatura carece de evidências claras sobre o papel dessa terapêutica sobre a fertilidade masculina. A venlafaxina é um antidepressivo inibidor da recaptação da serotonina e noradrenalina com alta eficácia e tolerabilidade, sendo muito utilizado na prática clínica. Assim, nosso objetivo foi revisar e analisar o impacto da venlafaxina sobre aspectos da fertilidade masculina usando os modelos experimentais murinos machos por meio de uma revisão sistemática. Para tanto, fizemos a pesquisa em três bases de dados de literatura. Inicialmente, encontramos 84 artigos em buscas por título e resumo nas plataformas PubMed (n = 6), Embase (n = 47) e Scopus (n = 31). Como critérios de inclusão consideramos estudos controlados e randomizados em murinos machos, submetidos ao uso de venlafaxina, abrangendo todas as línguas e um período aberto. Nos critérios de exclusão consideramos presença de doenças comórbidas e estudos em fêmeas. Após remoção de duplicatas e análise minuciosa e completa, 9 artigos foram incluídos nessa revisão. Os resultados implicados mostraram impacto negativo na concetração de espermatozoides, desregulação hormonal, alteração da histoarquitetura do aparelho reprodutivo, e amplo aumento do estresse oxidativo. Como conclusão observamos que a venlafaxina afeta negativamente a fertilidade de murinos machos.

Palavras-chaves: antidepressivos, infertilidade, depressão, ratos, espermatogênese, masculino.

ABSTRACT

Impacts of venlafaxine on spermatogenesis and male fertility: systematic review

Antidepressant medications are commonly used in men of reproductive age for the long-term treatment of depression, as well as other disorders. Although antidepressants are associated with negative sexual effects, such as reduced libido, sexual impotence, anorgasmia or ejaculatory delay, the literature lacks clear evidence on the role of this therapy on male fertility. Venlafaxine is a serotonin and noradrenaline reuptake inhibitor antidepressant with high efficacy and tolerability, being widely used in clinical practice. Thus, our aim was to review and analyze the impact of venlafaxine on aspects of male fertility using experimental male murine models through a systematic review. To do so, we conducted a survey in three literature databases. Initially, we found 84 articles in searches by title and abstract on PubMed (n = 6), Embase (n = 47) and Scopus (n = 31) platforms. As inclusion criteria, we considered controlled and randomized studies in male mice, submitted to the use of venlafaxine, covering all languages and an open period. In the exclusion criteria, we considered the presence of comorbid diseases and studies in females. After removal of duplicates and thorough and complete analysis, 9 articles were included in this review. The implied results showed a negative impact on sperm concentration, hormonal dysregulation, changes in the histoarchitecture of the reproductive system, and a large increase in oxidative stress. In conclusion, we observed that venlafaxine negatively affects the fertility of male mice.

Keywords: antidepressants, infertility, depression, rats, spermatogenesis, male.

SUMÁRIO

1 ARTIGO CIENTÍFICO

NEGATIVE IMPACT OF VENLAFAXINE ON THE FERTILITY OF MALE MURINES: SYSTEMATIC REVIEW#

Carolina Galante Silva[1]; Anthony César de Souza Castilho[1]*; Raquel Galante Silva[1]; Giovana De Santi Phelippe Nunes[1]; SarahGomes Nunes[2].

Short title: Venlafaxina e infertlidade masculina

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#This article is written in the guidelines of the Brazilian Journal of Psychiaty.

SUMMARY

Objective: To evaluate the impact of venlafaxine on aspects of fertility in male murine experimental models through a systematic review.

Methods: The search was carried out in three literature databases, resulting in a total of 84 articles in searches by title and abstract, being in PubMed (n = 6), Em-base (n = 47) and Scopus (n = 31). A specific clinical question was framed: What impact might venlafaxine have on fertility in male rats? This article was registered on the CAMARADES platform.

Results: After removing duplicates, 10 articles were selected for evaluation by all authors. In a thorough and complete analysis, only 9 articles were included. The implied results showed a negative impact on sperm concentration, hormonal dysregulation, changes in the histoarchitecture of the reproductive system, and a large increase in oxidative stress.

Conclusion: We showed that venlafaxine, awidely used antidepressant, negatively affects sperm parameters, proving to be deleterious to male fertility in experimental murine models.

Keywords: antidepressants, infertility, depression, spermatogenesis, male.

INTRODUCTION

Mental disorders are among the main public health problems in the world, with depressive and anxiety disorders being the most disabling. This high prevalence has occurred for years, for both sexes and in many locations. Both major depressive disorder and anxiety disorders increase the risk of other illnesses and suicide. With the arrival of the COVID-19 pandemic, the increase in the prevalence of these disorders was substantial, including younger populations (COVID-19 Mental Disorders Collaborators; 2021).

In recent years, infertility has become a global public health problem, affecting 15% ofall couples of reproductive age. Among these, male factors are responsible for approximately 25% of cases of infertility, especially related to abnormal semen quality (Salas-Huetos et al., 2017). Oligospermia, defined as a reduced sperm count of less than 15 million/mL in semen, or azoospermia, the complete absence of sperm, are usually the first abnormalities detected in an infertile man in semen analysis (Cooper et al., 2010).

Mental disorders such as stress, depression, sleep disorders, eating disorders and addictions are among the causes of negative effects on reproduction (Corona et al., 2016). Indeed, semen quality may be linked to stress and depression, decreasing luteinizing hormone (LH) release and testosterone pulsation, leading to impaired spermatogenesis and semen quality (Corona et al., 2016). Part of these effects are associated with higher levels of cortisol and apoptosis of germ and Leydig cells (Gao et al., 2020).

Depression is a disease that affects a significant amount of the population, leading to an increase in the use of antidepressant medications. Certain medications, including antipsychotics, antidepressants and anticonvulsants of different classes, have a negative influence on male fertility (Dubovicky et al., 2017; Fenli et al., 2013). Studies have already shown that abnormal sperm morphology, motility and reduced concentration are related to the use of different classes of antidepressants in male patients (Gao et al., 2020; Safarinejad, 2008; Wong et al., 1983). In the last two decades, several epidemiological studies have shown an increase in the prevalence of prescriptions for antidepressants (Lunghi et al.) Total sales of antidepressants in Brazil increased significantly from 2014 to 2019, with selective serotonin reuptake inhibitors being the main category of antidepressants sold in total over the last five years and “other” antidepressants represented a growth rate of 104.7% (Hoefler et al., 2020).

Venlafaxine is a non-tricyclic phenylethylamine derivative that inhibits 5-HT and norepinephrine transporters and is progressively used as an alternative to selective serotonin reuptake inhibitors (SSRIs) (Dubovicky et al., 2017; Fenli et al., 2013). Used as the drug of first

choice in the treatment of moderate to severe depression, since it is more effective in terms of the rate of remission achieved and more extensive remissions (Montgomery et al., 2004), it is also used in the trans- around generalized anxiety, attention deficit, hyperactivity disorder, autism spectrum disorder and agoraphobia in a child, adolescent and adult patient (Stahl, 2014). Although treatment with venlafaxine is well tolerated, common side effects (≥ 1/100 to < 1/10 patients) include sexual dysfunction, abnormal ejaculation, disturbance of serum testosterone and increased estrogen levels in men (Bell et al., 2000; Tanrikut et al., 2010; Stahl, 2014; Gao et al., 2020; Safarinejad, 2008; Wong et al., 1983).

In this context, studies such as the one proposed here warn about the a postei-ori effects that such therapies can have. It is noteworthy the fact that few studies and with immense variability in experimental methodologies show this deleterious effect on male reproduction. Thus, through a systematic review of the literature, our study demonstrates for the first time the impact of venlafaxine on aspects of male fertility using experimental male murine models, which help in the concatenation of ideas and possible explanations for the reproductive effects found together to male infertility.

METHODOLOGY

The protocol of this systematic review was prospectively registered. The review is reported following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Page MJ; et al. 2020).

In order to encompass a holistic view of the current literature on the impact of venlafaxine on fertility using the experimental male murine model, a first exhaustive search was performed on three literature databases, including PubMed, Embase and Scopus, up to 26 /02/2023. A specific clinical question was structured according to the PICO framework (Population - Intervention - Comparison - Outcome): What impact can venlafaxine have on fertility in male rats. Search strategies and descriptors are available in ANNEX 1. This article was registered on the CAMARADES platform.

92 Table 1. Inclusion and exclusion criteria used in the selection of studies.

Inclusion criteria	
Outline	● Pre-clinical controlled and randomized trials
Population	● Male murines
Intervention	● Animals submitted to treatment with venlafaxine
Language	● All
Period	● Open
Exclusion Criteria	
Bias	● Presence of comorbid diseases
Population	● Females
Main Clinical Outcomes	
● Potential risk of male infertility with the use of venlafaxine	

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Selection of studies

96 Abstracts from scientific meetings and conference proceedings were not considered. Two authors, C.G.S. and R.G.S., performed an initial independent screening of title and abstract of all articles and clinical studies to exclude citations considered irrelevant or duplicated by both observers. Fulltexts of potentially relevant articles were retrieved and evaluated for inclusion by three independent reviewers, C.G.S., R.G.S. and AC.S.C.. Any disagreement or uncertainty was resolved by discussion amongreviewers to reach consensus. After evaluating all included articles, nine studies were included in this review.

104 **Data extraction**

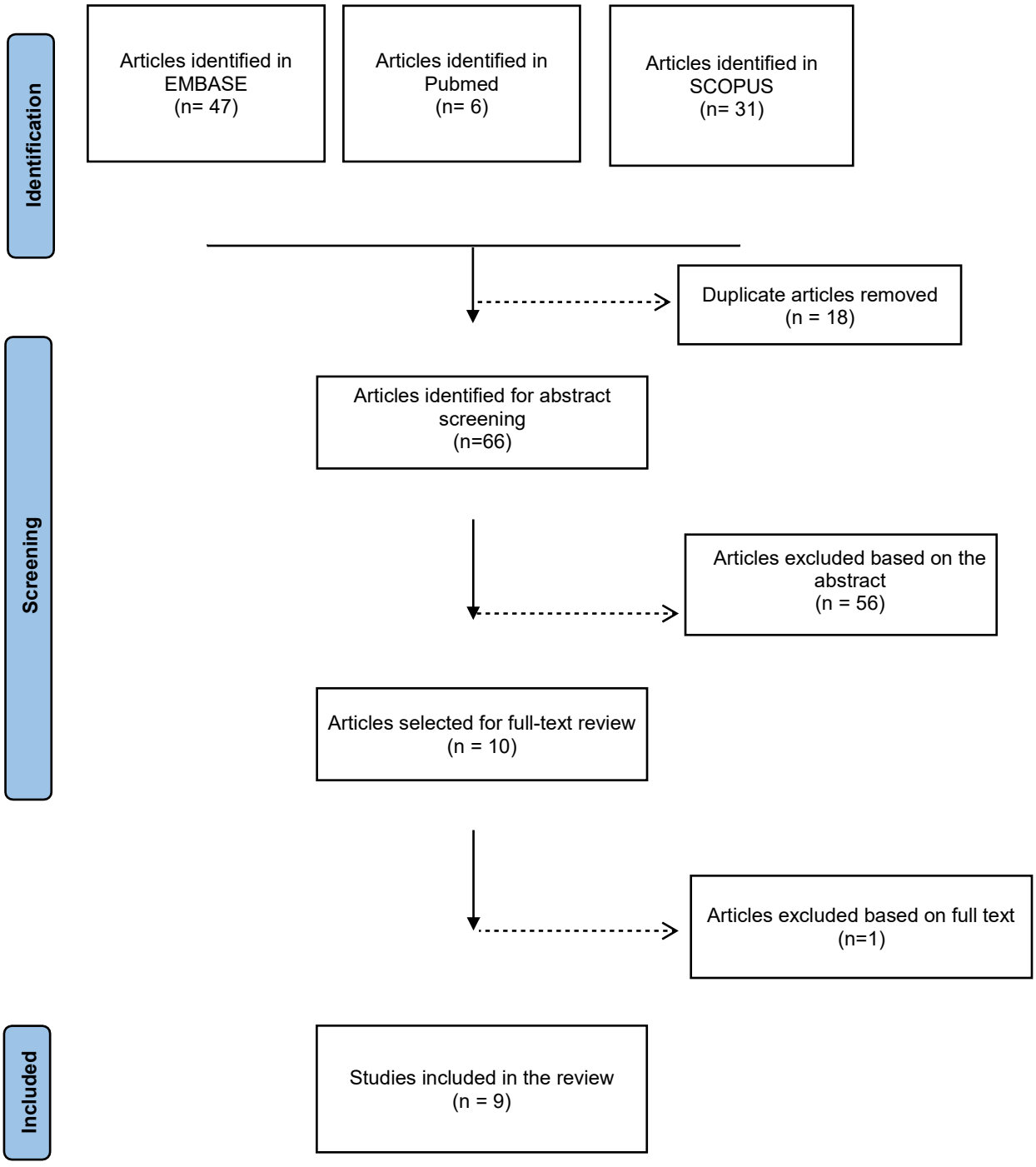
Data were extracted from articles included by all reviewers. No investigator was
106 contacted in case of disappearance or obscure data. The following data were extracted: authors, year of publication, title, study design, inclusion criteria, animal species and weight, drug
108 administration route and dose used, study time, biological targets, adjuvant treatment, number of individuals in each group, main result, secondary results, results in each group, discussion
110 and conclusion.

RESULTS

Study selection and characteristics

A total of 84 articles were found in searches by title and abstract in PubMed (n = 6), Embase (n = 47) and Scopus (n = 31). After removing duplicates, 10 articles were selected for evaluation by all authors. The details of the selection process and the flowchart are detailed in Figure 1 and the general findings are summarized in Table 2.

Figure 1. Flowchart of experimental evidence of venlafaxine use and impact on male murine fertility.



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150 Table 2. Characteristics of studies evaluating fertility in male mice using venlafaxine.

Study	Sample	Experimental model	Dose (mg/Kg) / Route of administration	Time (days or hours)	Biological targets	Main findings
(Saleem et al., 2020)	80	Albino rat	40 e 150 / Oral	70 days	Spermatogenesis	Reduction in sperm count
(Bandegi et al., 2018)	40	Mouse BALB	2 / Oral	35 days	Spermatogenesis	Improvement of sperm parameters (morphology, non-progressive motility and viability)
(Göçmez et al., 2010)	30	Wistar	20 / Injectable	14 days	Reproductive system	Inhibition of contractions in the prostatic and epididymal portions of the vas deferens
(Solek et al., 2021)		Cultured mouse cells	Uninformed	48-96 hours	Genetic material and oxidative stress	Modification in gene expression and increased oxidative stress
(Kaur et al., 2021)	24	Balb/C	60 / Oral	14 days	Spermatogenesis, genetic material, reproductive system and oxidative stress	Decreased concentration and motility of spermatozoa; increased apoptosis of reproductive cells; by causing extensive vacuolization in the germinal epithelium, abnormal basement membrane and reduced number of germ cells and increased oxidative stress
(Sołek et al., 2021)		Cultured mouse cells	Uninformed	48-96 hours	Genetic material, oxidative stress	Modification in gene expression and increased oxidative stress
(de Santi et al., 2021) 1 adrenergic	40	Rat	30 / Oral	35-65 days	Hormones	Increased estrogen levels
(da Silva Moreira et al., 2023)	50	Wistar	3,85, 7,7 e 15.4 / Oral	22 days	Spermatogenesis and hormones	Decrease in type A sperm and increase in type B; changes in androgen receptors

(de Santi et al., 2021) 2	18	Rat	30 / Oral	35 days	Spermatogenesis, reproductive system	Head and tail abnormalities and sperm failure; damage to the seminiferous epithelium, Leydig cell hypertrophy inhibition of Leydig cell steroidogenesis

Impact on spermatogenesis

According to Kaur, et al; 2021, the concentration and motility of rat sperm are negatively impacted by the use of venlafaxine after 10 weeks of treatment. Similarly, Saleem, et al; 2020 described a reduction in sperm count using low doses of venlafaxine S). However, the use of higher dosages did not demonstrate a deleterious effect. In an analysis comparing the time of use of venlafaxine, abnormalities in the head and tail of sperm were observed, in addition to a reduction in the number of spermatozoa with normal morphology after 35 days of treatment. However, after 65 days, normal morphological parameters were recovered, maintaining the same dose of medication (de Santi et al., 2021). Recently, da Silva Moreira et al., 2023, demonstrated that the use of venlafaxine in mothers did not impact the sperm count or morphology of the offspring, but the percentage of type A spermatozoa (mobile with progressive movement) was reduced, on the other hand, type B (mobile without movement progression) increased with the use of medication. Paradoxically, in a randomized study with 40 rats, venlafaxine improved sperm parameters, both in morphology, non-progressive motility and viability 0.019 in mice. However, the study by Bandegi et al. (2018) was anisolated case.

It has also been described, in a longitudinal study, failure of spermiation induced after 35 days of venlafaxine in the seminiferous tubules, with resumption of normalization after 65 days (de Santi et al., 2021). In contrast, Sal-lem et al. (2020) showed the dose-dependent effect, as previously reported.

Hormonal approach

Data evaluated by de Santi, et al. (2021) showed that venlafaxine reduces StAR and testosterone levels, also reducing the aromatization of this androgen. However,after 65 days there was total recovery of testosterone and partial recovery of estrogen (de Santi

et al., 2021). Furthermore, in an intergenerational approach, the presence of venlafaxine in breast milk triggered, in the offspring, alterations in androgen receptors that could indicate an incomplete masculinization of the brain of male rats, but without impact on sexualbehavior of rats in adult life (da Silva Moreira et al., 2023). In an endocrine bias, in general, rats that received venlafaxine showed increased levels of estrogen and increased levels of testosterone in seminiferous tubule cells (de Santi et al., 2022).

Evaluation of genetic material

Venlafaxine is able to increase the apoptosis of male reproductive cells by regulating the expression levels of Bcl-2, Bax, Cas-pase-9 and Caspase-3 proteins (Kaur et al., 2021). It also promotes modifications in the gene expression of the reproductive cells of male rats submitted to the use of venla-faxine (Solek et al., 2021).

Histoarchitecture of the reproductive system

Venlafaxine damages the seminiferous epithelium, induces Leydig cell hypertrophy and inhibits Leydig cell steroidogenesis (de Santi et al., 2022). It is also responsible for causing extensive vacuolization in the germinal epithelium, abnormal basement membrane and reduction in the number of germ cells (Kaur et al., 2021). Further evaluation described alterations in the seminiferous epithelium, where Sertoli cell nuclei with irregular outline, intense basophilia by chromatin condensation and/or clusters of condensed chromatin in the nuclear periphery were found. Some Sertoli cell nuclei were also found among the detached germ cells in the tubular lumen. The number of Sertoli cell nuclei with typical morphology decreased with the use of venlafaxine. In the testicular sections submitted to the TUNEL assay, scarce TUNEL marking was observed in the control group, while several TUNEL-positive germ cells were found in the group treated with venlafaxine, mainly after 65 days of use (de Santi et al., 2021).

Functional alteration of the reproductive system

Treatment with venlafaxine also significantly inhibited contractions in the prostatic and epididymal portions of the vas deferens in rats (Göçmez et al., 2010).

Oxidative stress

According to two studies, there was an increase in oxidative stress in the reproductive system of male rats treated with venlafaxine, causing worsening of fertility, for Kauret al., 2021 and for Solek et al., 2021.

DISCUSSION

The present review systematizes the negative impact of venlafaxine on male fertilityusing an experimental approach in murines. In short, it demonstrates that venlafaxine impairs spermatogenesis, hormone levels, genetic material, histoarchitecture, reproductive system functionality and oxidative stress control. In addition, it establishes that the resumption of fertility and therapeutic strategies for reversing or mitigating the effects are not yet efficient and/or proven, because the few experimental studies described still lack standardization and validation of an adequate in vivo and in vitro model to in order to elucidate the mechanisms and outcomes of this therapeutic approach. The scarcity of studies with uniformityin the number of animals, age, weight and dose of medications evaluating the impact of antidepressants on fertility in preclinical studies was an obstacle to the evaluation of the presented outcomes.

Despite the existence of clinical studies demonstrating evidence of a negative impact on male fertility, much remains to be explored in animal experimentation, since the range of alterations that occur in the reproductive system is complex. In fact, one of the factors that may have interfered with the evaluation refers to the dosage of venlafaxine used in each study, with a variation from 2mg/kg (Bandegi et al., 2018) to 150mg/kg (Saleem et al., 2020). A longitudinal study with a follow-up of more than 65 days would also be feasible, because the duration of the research also suffers from divergences, and there were evaluations in 48 hours (Solek et al., 2021) reaching up to 70 days in duration (Saleem et al., 2020). The age of the rats also needs to be addressed in more depth, comparing the parameters in younger or more adult rats, since changes in androgen levels caused by antidepressants during the perinatal period can alter the testicular descent, onset of puberty, as well as the development of youthful social skills and playful behavior (Schwartz et al., 2019). In addition, the immense amplitude of sample size also makes it difficult to validate some findings, since there have been studies with samples from 18 (de Santi et al., 2021) to 80 rats (Saleem et al., 2020), showing that a discrepant number of animals can impact the qualification of the evidence generated. However, even though such variability requires greater experimental standardization, the evidence highlighted here leaves no doubt as to the deleterious effects and, therefore, warns of the damage that antidepressants can bring to male fertility, especially in relation to their prolonged use.

The greatest concern with male fertility with the use of venlafaxine is related to the prolonged use of this medication, since its therapeutic effects occur in the medium/long term (Sołek et al., 2021). Prolonged ingestion of other antidepressant drugs has also shown a substantial decrease in germ cell count and loss of germinal epithelium in testes of male rats (Sołek et al., 2021). Also worrying is the non-reversal of deleterious effects when therapy is discontinued. In fact, de Santi et al., 2021, described that alterations, such as sperm motility and mitochondrial activity, in animals treated with venlafaxine and with a 65-day break from its ingestion, were unable to recover their full functionality. This study also showed that interruption of treatment for 30 days is insufficient for complete testicular recovery, probably due to a long-term impact of high estrogen levels on the seminiferous epithelium, which culminated in the incomplete restoration of the seminiferous epithelium.

According to the systematic review by Jovana et al., (2021), selective serotonin reuptake inhibitors may impair fertility due to the potential of delaying ejaculation and causing erectile dysfunction. testosterone, as well as an increased incidence of abnormal DNA integrity in sperm cells in healthy men after five weeks of paroxetine therapy. Thus, the negative impact on male fertility may be initially due to the increase in serotonin, which leads to a decrease in libido by acting on 5-HT2 receptors in the brain (Ferguso 2001). Furthermore, peripheral serotonin inhibits nitric oxide leading to erectile dysfunction (Kennedy et al. 2000). As with venlafaxine, Bezerra et.al., 2019, showed that negative changes in epididymal motor activity after the use of fluoxetine and a decrease in sperm count and an acceleration of transit time through the epididymal tubes with the use of sertraline. However, it appears that some dual antidepressants, most notably mirtazapine and bupropion, may be significantly safer than SSRIs in terms of adverse effects on sexual function. Indeed, et al. (2015) showed that bupropion did not alter the reproductive system and fertility potential in male Wistar rats during one month of use. Although buproprion belongs to the venlafaxine class, it has noradrenergic and dopaminergic action, with a lower release of serotonin, unlike what occurs with venlafaxine, and this aspect is a possible explanation for the non-interference in fertility with use of bupropion (Cavariani et al., 2015; Stahl, 2014). Although adverse effects are evident on male fertility, there are possible hypothesized strategies that could alleviate them. The first suggested amelioration comes from the fact that there is an increase in intratesticular levels of testosterone and estrogen, in association with impaired sperm parameters and germ cell death, in rats treated with venlafaxine (de Santi et al., 2022). Thus, in order to ensure that patients can benefit from the potential antidepressant effects of venlafaxine, new therapeutic strategies to prevent testicular disorders need to be developed with the aim of mitigating the effects on increased aromatase activity and the spermatogenic failure. It is known that expression of the aromatase gene in breast cancer cells is regulated by calcitriol, an active form of vitamin D, and that in testes of

mice null for the vitamin D receptor, aromatase activity is impaired, causing a drop in estrogen production. Therefore, it is proposed that vitamin D may be an interesting therapeutic agent to restore spermatogenic alterations induced by estrogen during or after treatment with venlafaxine. Another proposed strategy would be the selenium supplementation in animals treated with venlafaxine, since such an approach is responsible for the repopulation of all germ cells along with the normalization of the germinal epithelium, improvement of motility and sperm concentration in mice treated with venlafaxine (Kaur et al., 2021).

Psychiatric disorders are increasingly prevalent and their consequences are intense, due to mental suffering, disruption of social standards, family disorganization, loss of work functionality, generating economic impacts, hospitalizations and even, in more severe cases, risk of death. suicide. In this context, the increasing use of antidepressants is a reality that must be studied with great attention and urgency. Venlafaxine is one of the widely used antidepressants due to its high efficacy and tolerability, however, evidence points to its negative effect on male fertility. Finally, for clinical practice, we observed the need for a sincere and technical approach by the health professional to the patient who is of reproductive age, with the aim of clarifying the risks-benefits that the use of venlafaxine will cause in their treatment and the scarcity more robust data in the literature on how to mitigate such effects on fertility. The few studies that have shown the use of vitamins and antioxidants to improve the sperm profile and fertility could be a mitigation strategy to be guided by clinicians as a possible safer approach until further studies are carried out. Despite the scarcity of studies addressing the subject, when evaluating the severity of psychiatric disorders and their consequences, this supposed impasse in the use of venlafaxine in fertile patients may not refute it, as it is a highly effective medication for clinical practice.

CONCLUSION

In this review, we compiled, for the first time, the outcomes on the negative impact of venlafaxine on the fertility of male murines, demonstrating the deleterious effects on sperm concentration, motility, testosterone hormone production, reproductive system architecture, germinal seminiferous epithelium and oxidative stress.

316

Conflict of interest

The authors declare that they have no conflicts of interest and that this research was self-funded.

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ANNEX A- SEARCH STRATEGY

For the first search, using PubMed, a combination of Medical Subject Headings (MeSH) and text words were used to generate two subsets of citations, one including studies involving venlafaxine ("Venlafaxine Hydrochloride" OR "1-(2-(dimethylamino)-1-(4-methoxyphenyl)ethyl)cyclohexanol HClCyclohexanol, 1-(2-(dimethylamino)-1-(4-methoxyphenyl)ethyl)-, hydrochloride" OR Dobupal OR Efexor OR Effexor OR

"Hydrochloride, Venlafaxine" OR "Sila Venlafaxine" OR "Sila-Venlafaxine" OR Trevilor OR Vandral OR Venlafaxine OR "Wy 45,030" OR "Wy 45030" OR "Wy-45,030" OR Wy-45030 OR "Wy45,030" OR Wy45030), the second including studies in rats (Rats OR "Laboratory Rat*" OR Rat OR "Rat*, Laboratory" OR "Rats, Norway" OR Rattus OR "Rattus norvegicus" OR "Male rat"), the third including fertility (Fertility OR "Below Replacement Fertility" OR "Determinant*, Fertility" OR "Differential Fertility" OR Fecundability OR Fecundity OR "Fertility Determinant*" OR "Fertility Incentive*" OR "Fertility Preference*" OR "Fertility Survey*, World" OR "Fertility, Below Replacement" OR "Fertility, Differential" OR "Fertility, Marital" OR "Fertility, Natural" OR "Marital Fertility" OR "Natural Fertility" OR "Preference*, Fertility" OR Subfecundity OR "Survey*, World Fertility" OR "World Fertility Survey*"), the fourth sperm (Spermatozoa OR Sperm OR "Sperm, X-Bearing" OR "Sperm, X-Chromosome-Bearing" OR "Sperm, Y-Bea9ring" OR "Sperm, Y-Chromosome-Bearing" OR Spermatozoon) and the fifth infertility (Infertility OR "Reproductive Sterility" OR Sterility OR "Sterility, Reproductive" OR "Sub-Fertility" OR Subfertility).

In the Embase data platform, the search strategy used based on MeSH terms was: venlafaxine/exp AND ('rat'/exp OR 'rodent'/exp) AND ('fertility'/exp OR 'infertility'/exp OR 'reproduction'/exp OR 'testis'/exp OR 'sperm'/exp OR 'spermatogenesis'/exp).

Finally, accessing the Scopus platform, the following search strategies were used: (TITLE-ABS-KEY (venlafaxine) AND TITLE-ABS-KEY (rat*) AND TITLE-ABS-KEY (infertility)), (TITLE-ABS-KEY (venlafaxine) AND TITLE-ABS-KEY (mice*) AND TITLE-ABS-KEY (infertility)), (TITLE-ABS-KEY (venlafaxine) AND TITLE-ABS-KEY (rat*) AND TITLE-ABS-KEY (testis)) e (TITLE-ABS-KEY (venlafaxine) AND TITLE-ABS-KEY (rat*) AND TITLE-ABS-KEY (sperm)).

ANNEX B- NORMS OF THE BRAZILIAN JOURNAL OF PSYCHIATRY

Aims and editorial policy

The Brazilian Journal of Psychiatry is a bimonthly publication that aims to publish original manuscripts in all areas of psychiatry, e.g., basic and clinical neuroscience, translational psychiatry, clinical studies (including clinical trials) and epidemiological studies. The journal is fully open access, and there are no article processing or publication fees. Submitted articles must be written in English.

These instructions are based on the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals, edited by the International Committee of Medical Journal Editors(ICMJE)/.

Manuscript preparation

Manuscripts are accepted for consideration by the Brazilian Journal of Psychiatry based on the understanding that they are original, are not being considered for publication elsewhere, and have not been published previously. The final version of the submitted manuscript should have been approved by all authors.

Manuscript types and word limits

The table below shows the types of manuscript accepted for evaluation and the maximum number of words (from Introduction to end of Discussion), references and tables/figures allowed for each category.

Original articles: These should describe fully, but as concisely as possible, the results of original research, containing all the relevant information for those who wish to reproduce the research or assess the results and conclusions. Original articles should have the following sections: Introduction, Methods, Results, and Discussion. The last paragraph(s) of the Discussion section should address study limitations and concluding remarks, but without separate subtitles.

Review articles: These should be systematic reviews and should include critical assessments of literature and data sources, critically reviewing and evaluating existing knowledge on a designated topic, in addition to commenting on studies by other authors. The search strategy and selection process should be described in detail, according to PRISMA or other appropriate guidelines. The main text may follow a structure similar to that of an original article, or may be adapted to better reflect the presentation of findings. Non-systematic reviews should be submitted in the Special Articles category.

Brief communications: Original but shorter manuscripts addressing topics of interest in the field of psychiatry, with preliminary results or results of immediate relevance. The main text should use the same subtitles described for original articles above.

Special articles: Articles that address specific current topics relevant to clinical practice and are less comprehensive than review articles. These include non-systematic reviews and critical assessments of the literature, reviewing and evaluating existing knowledge on a designated topic. In this category, authors are free to decide upon the article's structure and to use the subtitles that better reflect the contents of their contribution.

Letters to the Editors: Letters can contain reports of unusual cases, comments on relevant scientific topics, critiques of editorial policy, or opinions on the contents of the journal (maximum of four authors).

Editorials: Critical and in-depth commentary invited by the editors or written by a person with known expertise in the topic.

Title page

Page 1 should contain a full title (max. 150 characters, specific, informative, attractive, no abbreviations), authors' names in the form that is wished for publication, their departments and institutions, including city and country. Please also include a running title with a maximum of 50 characters (letters and spaces) and inform of any previous presentations of the manuscript, if applicable (e.g., in abstract or preprint form). The full name, telephone number, e-mail address and full postal address of the corresponding author should be stated.

Abstract

Page 2 should present a structured abstract (where applicable; check table above with abstract requirements for each manuscript type), in English only, with the following sections: Objective, Methods, Results, and Conclusions. Please indicate three to five keywords in strict accordance with MeSH, and avoid repeating words from the title. If submitting a randomized clinical trial, inform the clinical trial registration number at the end of the abstract (see below).

Clinical Trial Registration: The Brazilian Journal of Psychiatry will only accept clinical trials that have been registered in a public registry that meets the World Health Organization (WHO) and ICMJE requirements.

Main text

The manuscript file (Main Document) must be written in English, double-spaced throughout, and should contain the following sections in this order: title page, abstract, manuscript text, acknowledgments (individuals, non-commercial funding agencies, etc.), disclosure (potential conflicts of interest covering the last 3 years, commercial funding sources), references, figure legends, and tables. Use 10-, 11-, or 12-point font size. Abbreviations should be avoided and limited to those considered "standard." All abbreviations should be spelled out at first mention in the text and also in table/figure legends. All units should be metric. Avoid Roman numerals. Generic names of drugs should be used.

The Methods section must include information on ethics committee approval. Studies involving humans must provide details about informed consent procedures, and studies involving animals must describe compliance with institutional and national standards for the care and use of laboratory animals. Patient anonymity should be guaranteed.

References

Authors are responsible for the accuracy and completeness of their references and for correct in-text citation. An EndNote style file can be downloaded here. Number references consecutively in the order they appear in the text using superscript Arabic numerals; do not alphabetize. References cited only in tables or figure legends should be numbered in accordance with the first citation of the tables/figures in the text, i.e., as though they were part of the text.

Please observe the style of the examples below. To include manuscripts accepted, but not published, inform the abbreviated title of the journal followed by "Forthcoming" and the expected year of publication. Journal titles should be abbreviated in accordance with Index Medicus. Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not be cited; if absolutely essential, bibliographic details should be described in the text in parentheses.

Examples:

Journal article: Coelho FM, Pinheiro RT, Silva RA, Quevedo LA, Souza LD, Castelli RD, et al. Major depressive disorder during teenage pregnancy: socio-demographic, obstetric and psychosocial correlates. Braz J Psychiatry. 2013;35:51-6.

List all authors when six or fewer. When there are seven or more, list only the first six authors and add "et al."

Book: Gabbard GO. Gabbard's treatment of psychiatric disorders. 4th ed. Arlington: American Psychiatric Publishing; 2007.

Book chapter: Kennedy SH, Rizvi SJ, Giacobbe P. The nature and treatment of therapy-resistant depression. In: Cryan JF, Leonard BE, editors. Depression: from psychopathology to pharmacotherapy. Basel: Karger; 2010. p. 243-53.

Theses and dissertations: Trigeiro A. Central nervous system corticotropin releasing factor (CRF) systems contribute to increased anxiety-like behavior during opioid withdrawal: an analysis of neuroanatomical substrates [dissertation]. San Diego: University of California; 2011.

Electronic articles and web pages: World Health Organization. Depression and other common mental disorders: global health estimates [Internet]. 2017 [cited 2020 May 11]. https://www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/

Illustrations (figures, tables, boxes)

Illustrations (figures, tables, or boxes) should clarify/complement rather than repeat the text; their number should be kept to a minimum. All illustrations should be submitted on separate pages at the end of the manuscript, following the order in which they appear in the text and numbered consecutively using Arabic numerals. Descriptive legends should be included for each illustration in the main text file, and any abbreviations or symbols used should be explained using these footnotes: ┼ ╬ § ‖ ¶ ┼┼ ╬╬ etc. Asterisks should be reserved for the expression of significance levels: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Illustrations extracted from previously published works should be accompanied by written permission for reproduction from the current copyright holder at the time of submission.

Tables and boxes should preferably be submitted in Word format, appended to the end of the manuscript text file (after any figure legends), rather than uploaded as separate files. However, Excel files are also accepted. If using Excel, do not place tables on individual spreadsheets within the same file because only the first sheet will be visible in the converted

PDF. In tables, each cell should contain only one item of data; subcategories should be in separate rows and cells (i.e., do not use Enter or spaces inside a cell). Tables containing data that could be given succinctly in 1-2 sentences should be converted to text. Large or detailed tables may be submitted separately as online-only supplementary material (see details below).

Figures should be submitted in one of the following acceptable file formats: AI, BMP, DOC, EMF, EPS, JPG, PDF, PPT, PSD, TIF, WMF, and XLS. Figures can be included in the manuscript, but preferably should be uploaded as separate files. If your manuscript is accepted, you may be asked to provide high-resolution, uncompressed TIF files for images, as well as open/editable versions of figures containing text, to facilitate copyediting (e.g., flowcharts made in Word or PowerPoint). Supporting figures may be submitted separately as online-only supplementary material.

Online-only supplementary material

Supporting materials (text, tables, figures) for online-only publication should be submitted as a single Word document with pages numbered consecutively. Each element included in the online-only material should be cited in the main text and numbered in order of citation (e.g., Supplementary Methods, Table S1, Table S2, Figure S1, Figure S2, etc.). The first page of the online-only document should list the number and title of each element included in the document. The editors may select material submitted for publication in the print version to be posted online only.

Submitting your manuscript

The first time you use the manuscript submission site of the Brazilian Journal of Psychiatry, you will be asked to create an account. You will use the same username and password for author and reviewer functions. You may log into the system at any time to submit a manuscript or to check the status of previously submitted manuscripts. To submit a manuscript, select Author and click on Start New Submission/Begin Submission.

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