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Review Article

A current approach to the use of antidepressants in the management of postpartum depression

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Objective: this study aimed to characterize the use of antidepressants in the management of postpartum depression. **Method:** an integrative literature review of the PubMed and Virtual Health Library databases was used, with the application of descriptors, aiming to answer the guiding question of the work, between February 25th and March 10th, 2019. Based on the inclusion and exclusion criteria, 23 articles were selected that were later submitted to categorization. **Results:** sertraline should be the drug of choice for the pharmacological treatment of puerperal depression. It was also found that the prophylactic use of antidepressants in susceptible women is controversial and little is known about the possible side effects. In addition, it was found that there is no consensus on the superiority of pharmacological therapy to the detriment of psychotherapies. **Conclusion:** there is evidence supporting the use of sertraline, paroxetine, duloxetine, nortriptyline and imipramine to treat women with postpartum depression, and breastfeeding is always recommended. It is worth noting that the need for studies with representative samples to validate or restrict the use of psychotropic drugs in the prophylaxis of puerperal depression emerges.

Descriptors: Postpartum Depression; Psychotropics; Antidepressant Agents; Sertraline.

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Uma abordagem atual da utilização de antidepressivos no manejo da depressão pós-parto

Objetivo: caracterizar a utilização de antidepressivos no manejo da depressão pós-parto. **Método:** empregou-se uma revisão integrativa de literatura, das bases de dados PubMed e Biblioteca Virtual em Saúde, com aplicação de descritores, visando responder a pergunta norteadora do trabalho, entre os dias 25 de fevereiro e 10 de março de 2019. Com base nos critérios de inclusão e exclusão, foram selecionados 23 artigos que, posteriormente, foram submetidos à categorização. **Resultados:** a sertralina deve ser a droga de escolha para o tratamento farmacológico da depressão puerperal. Constatou-se também, que a utilização profilática de antidepressivos em mulheres susceptíveis é contestável e pouco se sabe sobre os possíveis efeitos colaterais. Ademais, foi encontrado que não há consenso sobre a superioridade da terapia farmacológica em detrimento às psicoterapias. **Conclusão:** há evidencias que fundamentam o uso de sertralina, paroxetina, duloxetina, nortriptilina e imipramina para tratar mulheres com depressão pós-parto, sendo a amamentação sempre recomendada. Ressalta-se que emerge a necessidade de estudos com amostras representativas para validar ou restringir o uso de psicofármacos na profilaxia da depressão puerperal.

Descritores: Depressão Pós-Parto; Psicotrópicos; Agentes Antidepressivos; Sertralina.

Enfoque actual de la utilización de antidepresivos en el manejo de la depresión postparto

Objetivo: el presente estudio tuvo como objetivo caracterizar la utilización de antidepresivos en el manejo de la depresión posparto. **Método:** revisión integradora de literatura, de las bases de datos PubMed y Biblioteca Virtual de Salud, con aplicación de descriptores, para responder a la pregunta orientadora del trabajo, entre el 25 de febrero y el 10 de marzo de 2019. Con base en los criterios de inclusión y exclusión, se seleccionaron 23 artículos que posteriormente se sometieron a categorización. **Resultados:** la sertralina debe ser la droga elegida para el tratamiento farmacológico de la depresión puerperal. Además, se constató que la utilización profiláctica de antidepresivos en mujeres susceptibles es discutible y poco se sabe sobre los posibles efectos colaterales. Asimismo, se encontró que no hay consenso sobre la superioridad de la terapia farmacológica en detrimento de las psicoterapias. **Conclusión:** hay evidencias que fundamentan el uso de sertralina, paroxetina, duloxetina, nortriptilina e imipramina para tratar a mujeres con depresión posparto, siendo la lactancia siempre recomendada. Se destaca que surge la necesidad de realizar estudios con muestras representativas para validar o restringir el uso de psicofármacos en la profilaxis de la depresión puerperal.

Descriptores: Depresión Postparto; Psicotrópicos; Agentes Antidepresivos; Sertralina.

Introduction

Depression is the leading cause of disability worldwide[1]. The psychiatric disorder at issue is more frequent in the postpartum period than at other times in life, affecting nearly 10-15% of the adult mothers, and has the increased risk for suicide and infanticide as main consequences[2-4].

This mental disorder is associated with barriers in the mother-child interaction that occur, at least in part, due to the impact of depression on the negative maternal perception of her baby's facial expression[5]. Although the approach to this pathology includes other therapeutic modalities, antidepressants are still, for the most part, the drugs of choice[1].

The main risk factors are of a social nature, generally resulting from a stressful life, stress in child care, and prenatal anxiety. The symptoms are the same as those of depression at other times of life but, in addition to depressed mood, irritability, sleep disturbances, and changes in appetite, the mothers also feel guilty about their inability to care for their new baby[2]. A plausible hypothesis for the genesis of postpartum depression is that, in the puerperal period, the decline in estradiol and the increase in monoamine oxidase enzymes result in a worse maternal mood[6].

The pharmacological treatment for puerperal depression has received much attention in recent years and, in the current practice, nearly 70% of the cases are treated with antidepressants[1,4]. In addition, the discussion on this topic has shown to be relevant, especially due to the possible teratogenic effects and to the neonatal toxicity of antidepressant drugs[4].

Therefore, in view of the importance of the theme in question, this study has the following guiding question: How have antidepressants been used to manage postpartum depression? Consequently, this article aims to characterize the use of antidepressants in the management of postpartum depression, allowing us to address the view of different authors about the drugs of choice and their adverse effects, as well as the use of alternative therapies, such as psychotherapy.

Method

This study carried out an integrative literature review to characterize the current perspectives on the use of antidepressants in the management of postpartum depression, following the path shown in Figure 1, based on Souza, Silva and Carvalho[7].

The research used the PubMed and BVS (Latin American and Caribbean Center for Health Sciences Information) databases. The following Health Sciences Descriptors and their associations were used: *Depressão Pós-Parto* (*Postpartum Depression*) and *Antidepressivos* (*Antidepressants*); with the assistance of the Boolean operator AND. The databases were searched between February 25th and March 10th, 2019.

The selection of articles was carried out in two stages. Initially, the abstracts were read and, soon afterwards, the articles selected in the first stage were read in full, based on the inclusion and exclusion criteria. The inclusion criteria used were the following: a) studies that identified the drug of choice for managing postpartum depression; b) studies that evaluated the prophylactic use of antidepressants in women susceptible to puerperal depression; c) publications that evaluated the safety and/or adverse effects of antidepressants while breastfeeding; d) articles that compared the effectiveness of psychiatric drugs and psychotherapies in the management of postpartum depression; e) publication period from 2009 to 2018; and f) publications in English, Spanish, and Portuguese.

The following were used as exclusion criteria: a) publication date before 2009; b) studies in a language other than English, Spanish or Portuguese; c) articles that did not answer the guiding question of this research. After applying these criteria, 23 articles relevant to the topic were selected.

The selected articles were grouped, according to their results, into the following themes: *Benefits of using sertraline to treat postpartum depression; Adverse events and/or safety in antidepressant therapy in breastfeeding; Psychotherapy and psychopharmacology in the management of postpartum depression.* Subsequently, they were categorized and discussed in the following topics: *Considerations for using antidepressants; Drug of choice and introduction of pharmacological therapy based on the severity of the disease; Prophylactic use of antidepressants in susceptible women; Antidepressants, breastfeeding, and adverse effects on the infant; Pharmacological treatment vs. Psychological treatment.*

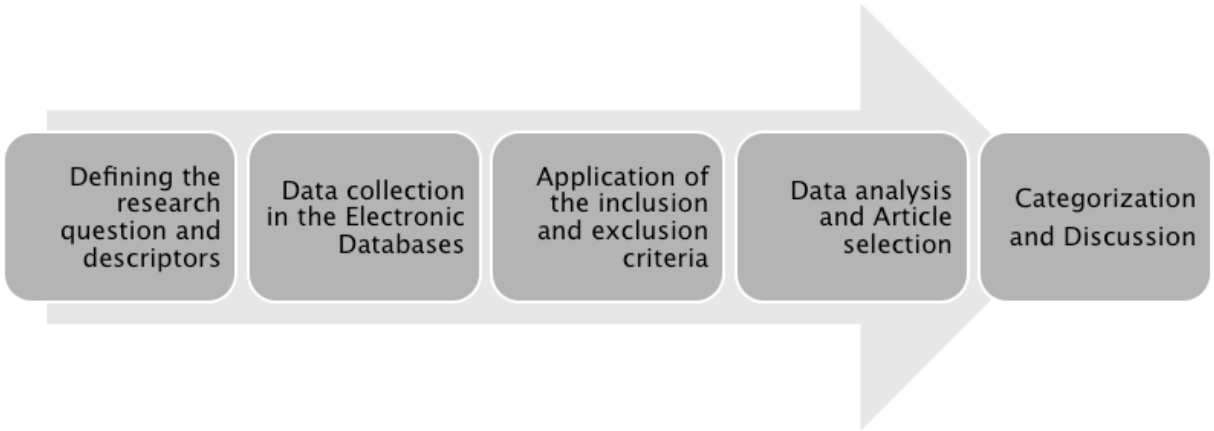

Figure 1 - Methodological path of data collection and analysis in the integrative review to characterize the current perspectives of the use of antidepressants in the management of postpartum depression

Results

The results found in the research demonstrate that women of a reproductive age are susceptible to interferences in the mechanism of action of several antidepressants due to the effects of estrogen, genetic individualities, changes in the volume of distribution, hormonal effects on liver enzymes and a higher concentration of proteins that bind to the drugs[3,8]. It must be highlighted that the use of antidepressants as initial therapy is recommended only in severe postpartum depression, with the remaining cases being treated with psychotherapies[1,9-10].

Several authors agree that, when deciding to initiate the pharmacological therapy, sertraline must be the drug of choice for treating postpartum depression. Figure 2 displays findings from studies that support the preference for this drug.

Regarding the prophylactic use of antidepressants in susceptible women, it was found that the efficacy of these drugs is questionable and little is known about the possible side effects[11-12]. However, if the physician decides to start prophylactic antidepressant therapy, sertraline is the drug indicated by most publications[6,13-14].

AUTHORS/YEAR	RESULTS
Molenaar et al. (2018)	Low concentration in breast milk and in children's serum
Kim et al. (2014)	Effective therapeutic response in up to 67% of the cases
Kim et al. (2014)	Disease recurrence of only 7%
Logsdon et al. (2009)	Improved gratification of the maternal role
Hantsoo et al. (2014)	Response rate significantly higher than placebo (53% vs. 21%)

Figure 2 - Studies that present evidence of the benefits of using sertraline to treat postpartum depression.

Breastfeeding provides several benefits to the mother-baby dyad and, therefore, it must be recommended, regardless of the antidepressant medication used. In addition to influencing the acceptance of pharmacotherapy, its interruption can be involved in the genesis of postpartum depression[1,15-16]. Figure 3 exposes findings from studies that evaluated adverse events and/or safety of antidepressant therapies in breastfeeding.

AUTHORS/YEAR	RESULTS
Di Scalea; Wisner (2009)	Sertraline, paroxetine, nortriptyline, and imipramine are associated with undetectable serum levels in the infant and with no reports of adverse effects in the short term.
Andrade (2014)	Duloxetine can be safely administered while breastfeeding.
Chad et al. (2013)	Irritability, refusal to eat, and sleep problems are adverse events reported in babies exposed to antidepressants.
Sie et al. (2012)	The SSRIs* are associated with mild and self-limited side effects.
Chad et al. (2013)	Adverse events are frequent after exposure to fluoxetine and citalopram.
Di Scalea; Wisner (2009)	Doxepin is associated with respiratory depression, sedation, hypotonia, and vomits.
Sie et al. (2012)	Using SSRIs* in the puerperal period seems to increase the risk of long-term behavioral abnormalities.

*SSRIs = Selective Serotonin Reuptake Inhibitors

Figure 3 - Studies that present the adverse events and/or safety of antidepressant therapy in breastfeeding

Finally, it is emphasized that there is no consensus on the superiority of the pharmacological therapy to the detriment of psychotherapies. Figure 4 shows results from studies that compare these two therapeutic modalities in the management of postpartum depression.

AUTHORS/YEAR	RESULTS
Sharp et al. (2010)	Drugs had significantly higher clinical efficacy than general supportive care.
Milgrom, et al. (2015)	Cognitive behavioral therapy was superior to sertraline and combination therapy after 12 weeks of treatment.
Di Scalea; Wisner (2009)	Fluoxetine and paroxetine, on monotherapy, are equally effective as cognitive behavioral therapy.
Bloch et al. (2012)	The rates for therapeutic response and disease remission are not significantly altered when adding sertraline to psychotherapy.

Figure 4 - Results of studies comparing psychotherapy and psychopharmacology in the management of postpartum depression

Discussion

Considerations for using antidepressants

Estrogen levels in women of a reproductive age are especially associated with interferences in the mechanism of action of several antidepressants[3]. Therefore, psychopharmacotherapy for postpartum depression must be started on monotherapy and in the least amount possible, with subsequent dose adjustment[8,17]. Before starting this antidepressant therapy, it must be considered that the puerperal women can be excessively sensitive to medications due to hormonal effects on the liver enzymes, changes in the volume of distribution, and a higher concentration of proteins that bind to the drugs[8].

The therapeutic response with the use of antidepressants is also marked by variability that can be explained by genetic individualities[3]. Therefore, the choice of antidepressant should, ideally, consider the mother and baby genotypes for best results. After using pharmacotherapy, the patients must be reevaluated within two weeks and treatment must be extended for a minimum of six months[8].

Drug of choice and introduction of pharmacological therapy based on the severity of the disease

Various authors agree that sertraline must be the drug of choice for treating postpartum depression[1,6,9,18]. In addition, the preference for sertraline is justified by its low concentration in breast milk and in children's serum[1].

Sertraline is associated with an effective therapeutic response in up to 67% of the women treated for postpartum depression[6]. In this study, disease recurrence was only 7% for those who used sertraline, and 50% for those treated with placebo. Other effects obtained with the use of sertraline in postpartum depression are the following: response rate significantly higher than placebo (53% vs. 21%) and improved gratification of the maternal role, with no effect on the mother-child interaction[9,18].

Despite some authors[8] advocating the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in the initial treatment of mild to moderate puerperal depression, the researchers[10] found that there is no significant benefit in adding sertraline to psychotherapy in the treatment of mild to moderate postpartum depression, since the rates of therapeutic response and remission of the disease are not significantly altered.

In this perspective, most of the guidelines recommend the use of antidepressants as initial therapy only in severe postpartum depression. Therefore, in mild to moderate depression, psychotherapies are recommended as an initial treatment[1].

It must be highlighted that tricyclic antidepressants can be considered the first-choice treatment, if there is a history of successful previous treatment and there are no contraindications for their use, such as the probability of suicide[13].

Prophylactic use of antidepressants in susceptible women

A very controversial issue in the management of postpartum depression is the prophylactic use of antidepressants in susceptible women[11-12]. Although widely used in the prevention of postpartum depression, the effectiveness of these medications is questionable and little is known about the possible side effects, particularly during breastfeeding. The evidence supporting the use of these drugs is limited to studies with reduced samples due to insufficient data in the literature[11-12].

The impacts of the pathology encourage preventive pharmacological treatment for women with a history of postpartum depression. Therefore, these patients are candidates to start sertraline to prevent new episodes of the disease from occurring[13].

When using these drugs to prevent postpartum depression, the woman's preferences, the severity of the symptoms, and the history of previous depression episodes must be considered[11]. In addition, it must also be considered that the safety of the antidepressants during pregnancy is controversial. The use of these drugs has been associated with deficient neonatal adaptation, risk of cardiovascular malformations, neonatal persistent pulmonary hypertension, premature birth, low birth weight, and psychiatric disorders[1].

Some authors[14] found benefits in using sertraline to prevent postpartum depression. However, this therapy was associated with an increased risk of maternal side effects. Considering nortriptyline, the author showed no benefit in the prevention of depressive episodes.

Therefore, if prophylactic use of antidepressants is indicated, the recommendation is to choose an SSRI, preferably sertraline. It must be highlighted that, if the patient has already been treated for puerperal depression,

it is reasonable to choose the antidepressant with which she obtained the best response[6].

Antidepressants, breastfeeding, and adverse effects on the infant

Human milk is the ideal primary source of nutrients and immune defenses for the newborn, providing several benefits to the mother-baby dyad[13]. Most of the guidelines recommend encouraging breastfeeding, regardless of the antidepressant medication used[1]. However, if the patient's clinical condition leads to the use of high doses of antidepressants or if multiple drugs are prescribed, it is probable that breastfeeding will have to be interrupted[17].

Breastfeeding influences the acceptance of pharmacotherapy by women, since many mothers avoid using medications due to concerns about adverse effects on the infants[15].

The initial negative experiences with breastfeeding would be associated with the occurrence of depressive symptoms, including postpartum depression[16]. Lactogenic hormones, oxytocin, and prolactin have antidepressant and anxiolytics effects; therefore, they can be involved in this process.

The relative infant dose is an important parameter that measures the dose of the drug offered to the infant through milk. Values below 10% of the dose adjusted to maternal weight are considered safe in breastfeeding[19]. Paroxetine and sertraline produce doses between 0.5% and 3%, while fluoxetine, venlafaxine, and citalopram produce levels closer to or even above the 10% limit. Therefore, sertraline and paroxetine are the recommended drugs after delivery[19].

In addition to sertraline and paroxetine, nortriptyline and imipramine are among the four drugs with the most evidence for use during breastfeeding[15]. The drugs at issue are associated with undetectable serum levels in the infant and with no reports of adverse effects in the short term. In this scenario, duloxetine is another drug that can be safely administered to a breastfeeding woman, since the baby's exposure to the drug is less than 1% of the dose that has been adjusted to the maternal weight[20].

It is possible to state that all the antidepressants used in postpartum depression are detectable in breast milk and can culminate in disorders of the central nervous system, as well as of the gastrointestinal and respiratory systems, in infants breastfed by women who used these drugs[17]. Symptoms such as irritability, refusal to eat, and sleep problems are adverse events reported in babies exposed to antidepressants through breast milk. These events are more frequent after exposure to fluoxetine and citalopram[19].

Selective Serotonin Reuptake Inhibitors (SSRIs) are drugs that are increasingly used during pregnancy and in the postpartum period. Despite being excreted in breast milk, their side effects are usually mild and self-limiting, but still require careful observation for at least 48 hours[21].

Despite being considered a safe SSRI during breastfeeding, sertraline is associated with adverse effects for the newborn that include irritability and refusal to feed. It must be emphasized that, if the child was born premature or with low weight, these effects are more evident[21-22].

In contrast, doxepin is an example of a tricyclic antidepressant contraindicated for treating postpartum depression. The drug is associated with respiratory depression, sedation, hypotonia, and vomits[13].

Although there is scarce evidence of serious adverse effects in babies exposed to antidepressants through breast milk, the long-term effect on neurological development has not been adequately studied[19]. From this perspective, when assessing the long-term effects of these drugs, there seems to be no impact on cognitive development, but behavioral abnormalities appear to be more common[21].

Pharmacological treatment vs. Psychological treatment

Much is discussed about what would be the most effective therapeutic strategy in the management of postpartum depression. Therefore, the choice between psychotherapy, pharmacotherapy or a combination of both is not a consensus in the literature.

When comparing the clinical efficacy of antidepressant therapy with general supportive care in mothers with postpartum depression, a study verified that the drugs were significantly superior[23]. In contrast, some authors[(24)] found that monotherapy with Cognitive Behavioral Therapy (CBT) is superior to sertraline and combination therapy after 12 weeks of treatment for postpartum depression. In their turn, fluoxetine and paroxetine, in monotherapy, are equally effective as CBT, and no additional advantage is obtained by combining the therapies[13].

Still on the combination of therapies, other authors[10] found that the rates of therapeutic response and disease remission are not significantly altered when adding sertraline to psychotherapy in the treatment of postpartum depression. In contrast, the combination of psychotherapy and antidepressants must be the treatment of choice for moderate to severe depression[8].

As for the mothers' preferences, one author verified that women with previous episodes of depression prefer antidepressants over psychotherapy[6]. On the other hand, breastfeeding women tend to choose psychotherapy.

In addition, as already mentioned, most of the guidelines recommend the use of antidepressants in severe postpartum depression, with psychotherapies recommended for mild to moderate disease[1].

Conclusion

Severe postpartum depression must be treated with antidepressants and sertraline must be the drug of choice. Low concentration in breast milk, effective therapeutic response, and low disease recurrence are some of the factors that justify the preference for this drug.

It is highlighted that there is no consensus on the superiority of pharmacological therapy to the detriment of psychotherapies in the management of puerperal depression, as well as the association between these therapies.

Breastfeeding must be recommended regardless of the antidepressant medication used. There is diverse evidence that support the use of sertraline, paroxetine, duloxetine, nortriptyline, and imipramine during breastfeeding. In contrast, some authors advocate against the use of fluoxetine, citalopram, and doxepin due to the potential side effects of these drugs.

Regarding the prophylactic use of antidepressants, there is scarcity of data in the literature. Therefore, there is no consensus on the universal use of drugs in women susceptible to the referred psychiatric disorder. Finally, given the controversies regarding the prophylactic use of antidepressants, there is a need for new studies with representative samples that aim to validate or restrict this applicability of psychotropic drugs.

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Study concept and design: Thiago Guimarães Da Silva, Ivan Gilson Silva Moura. Obtaining data: Thiago Guimarães Da Silva, Ivan Gilson Silva Moura. Data analysis and interpretation: Thiago Guimarães Da Silva, Pedro Fonseca De Vasconcelos, Ivan Gilson Silva Moura. Drafting the manuscript: Thiago Guimarães Da Silva, Pedro Fonseca De Vasconcelos. Critical review of the manuscript as to its relevant intellectual content: Pedro Fonseca De Vasconcelos, Ivan Gilson Silva Moura. Formatting: Pedro Fonseca De Vasconcelos.

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