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Use of Antidepressants to Treat Postpartum Depression, During Breast Feeding

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Abstract

Postpartum depression affects approximately 14.5% of women and it can affect both mother and infant. Therefore, rapid attention and treatment are imperative. The pharmacological approach often represents one of the most realistic options of treatment. However, women may be reluctant to take antidepressants because of the fear of adverse effects for the infant, since that most drugs pass into breast milk. The use of pharmacotherapy has not been extensively documented in this population. The objective of this review is to evaluate the risk benefit of using antidepressants during breastfeeding to treat postpartum depression.

An electronic search was performed by using PubMed database, from January 2001 through December 2010. The search was limited to articles in the English language and to articles that relate human's research. Manual searches of bibliographies were also conducted to identify additional pertinent studies.

The use of antidepressants that do not appear in infants' plasma, for which use during breastfeeding is better documented and at standard therapeutic doses is recommended, such as sertraline and paroxetine. Fluoxetine has a long half-life which can lead to a long infant exposition through breast milk and citalopram can cause adverse effects in infants exposed through breast milk. Therefore, citalopram and fluoxetine should not be used as first-line treatments. More information is needed about the use of the other antidepressants referred in this study.

This study aims to emphasize the importance of postpartum depression treatment, always considering its repercussions for the breastfed infants. Studies are needed with larger samples to properly evaluate the short and long-term effects of antidepressants on infants exposed through breast milk, so that clinicians can create standard decisions regarding the treatment of postpartum depression, without putting infants at risk.

Keywords: Antidepressants; Antidepressive agents; Breastfeeding; Breast milk; Bupropion; Citalopram; Drug milk level; Duloxetine; Escitalopram; Fluoxetine; Fluvoxamine; Lactation; Mirtazapine; Paroxetine; Postpartum depression; Reboxetine; Sertraline; Venlafaxine

Introduction

Postpartum depression

Postpartum Depression (PPD) is classified as a major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders; Fourth Edition (DSM-IV) criteria [1]. Although classification systems consider onset within four weeks (DSM-IV) or six weeks (the International Statistical Classification of Diseases; 10th Revision) of the birth; clinicians and researchers suggest that onset can occur any time within the first year after birth [1,2]. However; the risk of developing PPD or other psychiatric disorder is higher in the first months [3]. The woman may experience symptoms such as depressed or irritable mood; anxiety;anhedonia; sleep changes like early morning wakening before the baby; weight loss or gain; appetite alterations; loss of energy; feelings of excessive guilt or worthlessness; hopelessness; psychomotor agitation or retardation and; in more severe cases; suicidal ideation [1,2,4].

Diagnosis of PPD

Women should be carefully evaluated after childbirth about depressive or anxiety symptoms with adequate screening tools and methods to avoid diagnostic errors; especially when dealing with women who present risk factors. Additionally; the mother may not recognize that her symptoms can be related to PPD. The obstetrician/gynaecologist follow-up visit provides a good opportunity for screening; as well as it can be helpful to distinguish postpartum blues from PPD or vice versa; when the visit is made at the correct time [1].

The Edinburgh Postnatal Depression Scale (EPDS) is one of the most common self-report screening instruments used for PPD [1]. This 10-item scale has a satisfactory validity; split-half reliability and is also sensitive to changes in the severity of depression over time; as shown in the study where it was developed [5]. The clinical verification of the diagnosis with EPDS is essential because many women without depression might be falsely identified as depressed [6].

Differential diagnosis of PPD

Regarding the differential diagnosis of PPD there are two mood disorders that may arise after delivery including postpartum blues and postpartum psychosis. Postpartum blues is the most common of these disorders affecting 50-80% of new mothers [1]. It is a transitional syndrome during which the mother may exhibit symptoms such as emotional lability; anxiety; fatigue; insomnia; anger; sadness and

irritability generally resolved within 10 to 14 days after birth [1,7]. Nevertheless; 20% of women with maternity blues will develop PPD during the first year after delivery [8]. Postpartum psychosis is themostseriouspsychiatric disorderthat mayoccurafterchildbirth and alsomoredifficulttodefine [2]. It occurs in approximately 0.1% of all deliveries [9] and represents a medical emergency due to the acute onset of manic or depressive psychosis soon after birth; with risk of infanticide or suicide [2,10,11].

Risk factors for PPD

PPD affects approximately 14.5% of women during the first 3 months after birth and this percentage appeared to be higher in adolescent mothers [8,12]. The causes of PPD are not well known; but there are many factors that may increase the risk of developing the disease [1]. The childbearing years seem to be a time of increased risk for depression as well as individual or family history of a depression episode or other psychiatric conditions; depression or anxiety during pregnancy and history of previous PPD. There are other risk factors such as recent stressful life events; lack of supportive partner; experience of abuse or violence; inadequate social support and lower socioeconomic status [1,2,11,13,14]. Reproductive-related hormonal changes may play a role too [9,15]. Nevertheless history of depression appears to be the factor with greatest clinical relevance [11].

Effects of PPD on mother and infant

Mood disorders; such as PPD can affect both mother and infant. Depressed women show interactive and emotional difficulties with their children; which can lead to a disengagement from the baby [11]. The mother tends to reflect her infant's negative feeling states more often than she respond to their smiles or positive social initiatives [1]. The duration of breastfeeding may also be affected; since new mothers with depression may have more difficulties and dissatisfaction with breastfeeding [16]. Indeed breastfeeding is less common among postpartum depressed women [17,18]. However the fact that a mother is depressed alone does not indicate how well she cares for her baby [1].

The mother represents the prime environment for her baby [18]. Therefore the interaction of the newborn with a depressed mother may have detrimental consequences particularly with regard to cognitive emotional and social development since during this early period of baby's life the capacities for emotional regulation and healthy attachment relationships are developing [1,19,20]. These infants tend to show more regulation difficulties less eye contact fewer vocalizations delayed language development and lower activity level than infants of non-depressed mothers [1]. In other words impairment in the mother can lead to impairment in the infant [19]. Therefore rapid attention and treatment are imperative [11].

Treatment options for PPD

Several treatments for PPD have been found to be effective [21]. These include individual psychotherapy antidepressant drug therapy and others that need more research like oestrogen therapy nurse home visits and possibly group therapy [21,22]. The combination of treatments such ascombination of antidepressants and psychotherapy also needs more research. It is possible that a previous depression or previous antidepressant treatment may be associated with pharmacotherapy use while breastfeeding may be associated with psychotherapy as a preferred treatment option [22]. These treatments should be combined with patient education about the illness the specific treatment selected and other mechanisms for promoting health such as social support and a healthy lifestyle [21]. Non-pharmacological treatments such as interpersonal psychotherapy are recommended for mild to moderate depression [2]. Antidepressant therapy should be considered in women who have moderate to severe symptoms who have not responded to non-pharmacological treatments or who are at a risk of suicide or infanticide [13].

Prevention of PPD

In women who are at risk of developing PPD prevention can help to avoid it and since there is a clear marker that is birth there is an opportunity to prevent it. Despite the need for additional randomized clinical trials sertraline can be used to prevent PPD and has shown better results than nortriptyline compared with placebo [23].

Benefits/importance of breastfeeding

Breastfeeding has clear benefits for both mother and infant [4]. Human milk represents the ideal primary source of nutrients immunological defences and growth-promoting factors for the term and preterm newborn and provides the mother-infant dyad with major short and long-term health benefits [10]. Breastfeeding decreases the incidence and/or severity of a wide range of infectious diseases like bacterial meningitis diarrhoea respiratory and urinary infections necrotizing enterocolitis otitis media and sepsis. Some studies suggested decrease risk of haematological cancers asthma diabetes mellitus obesity and hypercholesterolemia in infants and older individuals who were breastfed [10,24]. Additionally human milk feeding has been associated with slightly enhanced performance on tests of cognitive development and decreased rates of sudden infant death syndrome in the first year of life [24,25]. Breast feeding benefits for the mother include decreased postpartum bleeding and more rapid uterine involution decreased risk of breast and ovarian cancer and possibly decreased risk of osteoporosis in the postmenopausal period [24].

The American Academy of Pediatrics Section on Breastfeeding American College of Obstetricians and Gynecologists American Academy of Family Physicians Academy of Breastfeeding Medicine World Health Organization United Nations Children's Fund and many other health organizations recommend exclusive breastfeeding for the first 6 months of life [24].

Methods

An electronic search was performed by using PubMed database from January 2001 through December 2010 using the following keywords: antidepressants; antidepressive agents; breast feeding; breast milk; bupropion; citalopram; drug milk level; duloxetine; escitalopram; fluoxetine; fluvoxamine; lactation; mirtazapine; paroxetine; postpartum depression; reboxetine; sertraline; venlafaxine. The drugs studied were the selective serotonin reuptake inhibitors the serotonin noradrenaline reuptake inhibitors and others that were more studied. The search was limited to articles in the English language and to articles that relate human's research. Manual searches of bibliographies were also conducted to identify additional pertinent studies. All of the references were then organized and analyzed.

Results

Treatment and/or breastfeeding

Women with PPD may be reluctant to take antidepressants because of the fear of adverse effects for the suckling infant [18,26]. Women with more functional impairment and those suffering higher levels of symptoms were more likely to pursue pharmacologic treatment and breastfeeding women who opted for antidepressant treatment were more likely to have had past experiences taking psychotropic medications a likely factor in their current treatment choice [14]. The use of pharmacotherapy for the treatment of PPD has not been extensively documented since women and children have largely been left out of pharmacological research [11,18]. As a result medications that are frequently needed during puerperium are insufficiently studied in this population [18].

Infant exposure to psychotropic medications is greater during pregnancy through placental passage than during the postnatal period through breast milk that is much more selective [13,25]. However most drugs do pass into maternal milk [25]. The United States Food and Drug Administration do not approve any antidepressant medication for use during lactation [8,14,21]. Despite this the pharmacological approach often represents one of the most realistic options [18].

Pharmacological treatment of PPD

Selective serotonin reuptake inhibitors (SSRIs)

Citalopram

Reported milk-to-plasma (M/P) ratios of citalopram ranged from 1.3 to 3.3 which indicate higher concentrations of the drug in milk than in maternal plasma. Despite this infant exposure levels to citalopram in milk are usually small because the maximal dose the infant would ingest (estimated from the drug concentrations in milk) is approximately 5% to 6% of the maternal dose on a weight-adjusted basis. However uneasy sleep colic decreased feeding and irritability/restlessness have been reported in infants of mothers treated with citalopram [27].

Escitalopram

Escitalopram is the therapeutically active enantiomer of the SSRI citalopram and is noted for its highly selective serotonin reuptake inhibition [10]. Escitalopram and its main metabolite demethylescitalopram are excreted in breast milk. One study demonstrated a total relative infant dose for the combination escitalopram and its metabolite of 5.3% of the maternal weight-adjusted dose which is less than 10%. Overall escitalopram contributed some 70% of the oral dose that the breastfed infant is calculated to receive. The recommended dose ranges of escitalopram (10-20 mg) suggest better efficacy for escitalopram if compared with citalopram (20-60 mg) which led the authors to hypothesize that the absolute infant dose of escitalopram would be lower than that for citalopram conferring a higher safety margin when the drug is used to treat depression in breastfeeding women. The assessment of the eight breastfed infants in the study revealed no adverse effects and low or undetectable plasma drug levels in five of the infants where blood sample was taken. These clinical observations suggested that escitalopram has a low potential for causing adverse effects in the breastfed infant. However the fact that the sample was small has to be considered [28].

Although one most account for the fact that animal data cannot accurately reflect human situations very high doses of escitalopram have been associated with decreased foetal body weight and delayed ossification in rats [29].

Fluoxetine

Fluoxetine is the parent drug of the SSRIs and was introduced in the 1980s. The main product of fluoxetine metabolism is the demethylated metabolite norfluoxetine which has a comparable pharmacological activity and a longer half-life contributing significantly to the therapeutic efficacy of fluoxetine. Plasma levels of the drug and/or its metabolite can be high even weeks after the discontinuation of the therapy [30]. This factor has to be considered on breastfeeding mothers taking fluoxetine.

There is a stereoselective disposition of fluoxetine and norfluoxetine resulting in increased concentrations of the biologically active enantiomers in the infant compared with the mother [31]. In a study including eleven infants exposed to fluoxetine through breast milk it was reported a variation in platelet serotonin levels in one infant but no adverse effects were observed [32].

The breast milk fluoxetine dose can be a significant predictor of the total infant serum concentration. Age-related and metabolic factors seem to have a significant role in the relationship between breast milk and infant serum concentrations [33]. In a study with twenty mother-infant pairs fluoxetine was present in 30% of the infants and norfluoxetine was present in 85% of the infants. These results show a high correlation between infants' serum concentrations of norfluoxetine and maternal serum concentrations of fluoxetine and norfluoxetine. The longer half-life of norfluoxetine relative to fluoxetine may explain the greater likelihood of detecting the metabolite in infants' serum. A significant relationship was also observed between the concentrations of fluoxetine and norfluoxetine in breast milk and the concentration of norfluoxetine in infant serum. Fluoxetine and norfluoxetine were typically nondetectable or at very low concentrations in the serum of the breastfed infants if maternal medication dosage was 20 mg/day or lower. A daily maternal dosage of fluoxetine of 30 mg or greater was significantly more likely to produce detectable serum concentrations of medication in an infant. Although most infants had no detectable serum concentration of fluoxetine the infants whose mothers took 30 mg of fluoxetine or more had significantly higher serum concentrations of norfluoxetine. Peak breast milk concentrations of fluoxetine and norfluoxetine correlated highly with serum concentrations of norfluoxetine in the infants and with maternal serum concentrations of these medications. This study did not report any adverse effects [34]. Breastfeeding is not absolutely contraindicated for women who continue to use fluoxetine. Nursing women should take the lowest effective dosage of fluoxetine and their infants should be monitored closely for potential sequel resulting from the medication exposure [34].

Fluvoxamine

Fluvoxamine has no active metabolites and its mean half-life is 15.6 hours the shortest half-life among all SSRIs [10]. In a study included four breastfed infants whose mothers were taking fluvoxamine to treat depression serum concentrations of the drug were undetectable in all

infants exposed. This study's findings suggested that fluvoxamine is a reasonable choice for nursing women requiring treatment for depression [35].

Paroxetine

Paroxetine is excreted in milk in small amounts. Undetectable or low plasma paroxetine concentrations were observed in some studies and no adverse effects have been reported. The short half-life high protein binding difficulty entering milk low M/P ratio and low or undetectable concentrations in infant serum are reasons to consider paroxetine as an acceptable solution for maternal depression during breastfeeding [35,36]. The relative infant dose of paroxetine to a suckling infant is lower than that reported for fluoxetine and citalopram but higher than that reported for sertraline and fluvoxamine [18]. However lowest doses of paroxetine and avoiding combinations of drugs are recommended [37].

Sertraline

Sertraline is excreted in milk with a M/P ratio ranging from 1 to 4 and a weigh-adjusted relative infant dose of 2% has been calculated [36]. The sertraline concentrations in breast milk vary substantially over the course of a 24 hour period with a peak probably occurring between 1 and 9 hours after ingestion [28].

It appears that at typical clinical doses sertraline administered to mothers has a negligible effect on platelet serotonin transport in breastfed infants. The usual absence of a discernible effect on infant platelet serotonin transport is consistent with the relatively low levels of sertraline in infant plasma [38].

In a study included thirty infants exposed to sertraline detectable medication was present in 24% of the serum samples obtained from the infants usually in the form of the metabolite desmethylsertraline. Maternal serum concentrations of sertraline and desmethylsertraline correlated highly with infant serum concentrations of desmethylsertraline. Maternal dosage also presented a high correlation with infant serum concentrations of desmethylsertraline. Doses of 100 mg or above were significantly more likely to produce detectable concentrations in the infant. Despite sertraline was detectable in 24% of the infant serum samples no adverse effects were reported. According to this study there are no reasons to discourage breastfeeding among women taking sertraline at standard therapeutic dosages [34].

Serotonin noradrenaline reuptake inhibitors (SNRIs)

Duloxetine

Duloxetine was approved by the Food and Drug Administration in 2004 [39]. At this time it was unknown if the drug is excreted into human milk it was only known that duloxetine and its metabolites are excreted into the milk of lactating rats [18]. Several properties of duloxetine like its molecular weight a relatively long elimination half-life and high lipid solubility suggest that it is excreted into breast milk. Conversely the high plasma protein binding and extensive metabolism to inactive metabolites suggest limited transfer of active drug into milk. A case report of a woman who used duloxetine during pregnancy and lactation found M/P ratios measured over a 24 hour period at the peak and through 1.21 and 1.29 respectively. The drug was not detected in the infant after exclusive breastfeeding [39].

In an open-label study duloxetine 40 mg was given orally with food at 12-hour intervals for 3 days and once on the morning of the fourth day to six healthy lactating women (who stopped breastfeeding during and after the study) in order to obtain quantitative information on the extent of duloxetine transfer into the breast milk and to obtain an estimate of the duloxetine dose that an infant may consume through breast milk. Duloxetine concentrations in breast milk were consistently lower than in plasma and the exposure in breast milk was approximately one-fourth of the concentration observed in plasma. The mean estimated infant dose was approximately 0.14% of the maternal dose. Thirty of the 35 adverse effects reported during the study were judged by the investigator to be related to duloxetine and the most frequent effects were dizziness nausea and fatigue. Some subjects had notable changes in either their systolic or diastolic blood pressures. Although the mean estimated infant dose was low and considering the adverse effects reported in this study more information is needed to evaluate the benefit/risk of breastfed an infant when the mother is taking duloxetine [40].

Venlafaxine

Venlafaxine and its O-desmethyl metabolite were studied to characterize M/P ratio and infant dose in breastfeeding women taking venlafaxine for the treatment of depression and to determine the plasma concentration and effects of the drug in their infants. The authors found mean M/P ratios of 2.5 for venlafaxine and 2.74 for its metabolite and mean relative infant doses of 3.2% for venlafaxine and 3.2% for the metabolite. The presence of mainly O-desmethylvenlafaxine in the infant's plasma indicates that all had significant capacity to metabolize the venlafaxine. Nevertheless the authors suggested that particular care should be taken with preterm and very young neonates where hepatic drug metabolizing enzyme levels would be expected to be low. The safety of venlafaxine for the infant appears to be satisfactory as no adverse effects were noted. However O-desmethylvenlafaxine was detected in plasma from four of the seven infants. Therefore venlafaxine should be used with cautious in breastfeeding women and occasional monitoring of O-desmethylvenlafaxine in the infant's plasma could be undertaken as a safety measure [41].

Additionally it was suggested that venlafaxine provided in breast milk may moderate the effects of noradrenergic-serotoninergic neonatal withdrawal syndrome in infants exposed to venlafaxine during pregnancy [41].

Other antidepressants

Bupropion

Bupropion and its active metabolites are present in the breast milk of lactating women. The results of a cohort study performed with ten healthy postpartum mothers indicated that the daily dose of buproprion and its metabolites that would be delivered to an infant of a woman taking a therapeutic dose of bupropion is small. Although the results suggest that bupropion during breastfeeding should not present a concern for most infants exposure may be greater for some infants like premature infants for example [42]. Moreover it is necessary to consider that the study does not provide information on the adverse effects that could benotedin infants exposed to bupropion.

Mirtazapine

The transfer of mirtazapine into breast milk was measured by a mean M/P ratio of 1.1 in a study. The calculated mean relative infant dose for mirtazapine plus its metabolite was 1.9% of the weight-adjusted dose which is lower than 10 % and hence mirtazapine is predicted to have a wide margin of safety in breastfeeding. Additionally none of the infants showed any drug related adverse effects. Only very low concentrations of mirtazapine were detected in the plasma of one out of the four infants tested. These findings suggested that short-term mirtazapine use during breastfeeding is safe [43].

Reboxetine

The first study on reboxetine use during breastfeeding suggested that reboxetine use by lactating women is safe for the breastfed infant. The transfer of reboxetine into milk was very low resulting in a very small M/P ratio (mean 0.06). The calculated mean relative infant dose was 2% of the weight-adjusted maternal dose and none of the infants exhibited any drug-related adverse effects. Therefore reboxetine is predictive to have a wide margin of safety in breastfeeding. However it is necessary to consider that the study had only four mother/infant pairs [44] (Table 1).

Antidepressants		Important considerations	Recommendations
SSRI	Citalopram	Higher concentrations in milk than in maternal plasma Maximal dose the infant would ingest is approximately 5% to 6% of the maternal dose Adverse effects reported: uneasy sleep colic decreased feeding and irritability/restlessness.	Escitalopram is preferred to citalopram to treat PPD Should not be used as first choice
	Escitalopram	Relative infant dose for the combination escitalopram and its metabolite of 5.3% of the maternal weight-adjusted dose Absolute infant dose of escitalopram would be lower than that for citalopram Low potential for causing adverse effects.	Escitalopram is preferred to citalopram to treat PPD
	Fluoxetine	Long half-life Stereoselective disposition of fluoxetine and norfluoxetine	Lowest effective dosage Infant monitoring Should not be used as first-choice
	Fluvoxamine	Shortest half-life among all SSRIs	Reasonable choice but more information about its use is needed
	Paroxetine	Excreted in milk in small amounts Short half-life high protein binding difficulty entering milk low M/P ratio low or undetectable concentrations in infant serum Relative infant dose is lower than that reported for fluoxetine and citalopram but higher than that reported for sertraline and fluvoxamine.	Reasonable choice but lowest effective dose is recommended Can be used as first choice
	Sertraline	Prevention of PPD Weigh-adjusted relative infant dose of 2% has been calculated At typical clinical doses sertraline administered to mothers has a negligible effect on platelet serotonin transport in breastfed infants.	There are no reasons to discourage breastfeeding among women taking sertraline at standard therapeutic dosages Can be used as first choice
SNRI	Duloxetine	Recent drug compared with other antidepressants Low mean estimated infant dose There are not many data available.	More information about its use is needed
	Venlafaxine	Mean relative infant doses of 3.2% Safety appears to be satisfactory Its metabolite can be present in infant serum When it is provided in breast milk may moderate the effects of neonatal withdrawal syndrome in infants exposed to the drug during pregnancy.	Venlafaxine should be used with cautious
Others	Bupropion	Daily dose of bupropion and its metabolites that would be delivered to an infant of a woman taking a therapeutic dose of bupropion appear to be small.	More information about its use is needed
	Mirtazapine	Calculated mean relative infant dose for mirtazapine plus its metabolite was 1.9% of the weight-adjusted dose.	Short-term mirtazapine use during breastfeeding is safe

	Reboxetine	Calculated mean relative infant dose was 2% of the weight-adjusted maternal dose.	More information about its use is needed

Table 1: Summary table of the results about the drugs studied

Discussion

Postpartum depression is classified as a major depressive disorder and the causes are not well known. The childbearing years seem to be a time of increased risk for depression and women should be carefully evaluated after childbirth.

Mood disorders such as PPD can affect both mother and infant. Therefore rapid attention and treatment are imperative. Several treatments have been found to be effective and antidepressant therapy should be considered in women who have moderate to severe symptoms who have not responded to non-pharmacological treatments or who are at a risk of suicide or infanticide. The pharmacological approach often represents one of the most realistic options.

Breastfeeding has clear benefits for both mother and infant and it is recommended in exclusivity for the first 6 months of life.

The benefits of antidepressant therapy should be discussed with the patient and her partner in order to help them make an informed decision that will benefit the well-being of both mother and infant.

Perhaps the most important clinical recommendation to psychiatrists treating women with mood disorders during childbearing is to use a team approach. A team approach is likely to improve outcomes and provide more consistent support to the mother as she makes difficult choices about her own health and the health of her baby [18].

Escitalopram is preferred to citalopram to treat postpartum depression because the absolute infant dose for escitalopram has shown to be significantly lower than for citalopram at clinically comparable doses [28]. Fluoxetine has a long half-life which can lead to a long infant exposition through breast milk. However when the drug is used by nursing women they should take the lowest effective dosage and their infants should be monitored. Fluvoxamine has the shortest half-life among all SSRIs. Undetectable or low plasma paroxetine concentrations were observed in some studies and no adverse effects have been reported but lowest doses are recommended. It was suggested that fluvoxamine and paroxetine are reasonable choices for nursing women requiring treatment for depression. Despite sertraline is detectable in some infants' serum it was suggested that there are no reasons to discourage breastfeeding among women taking sertraline at standard therapeutic dosages since no adverse effects were reported in a study.

Duloxetine is a recent drug compared with other antidepressants so there are not many data available on its use during breastfeeding. More information about its use is needed. The safety of venlafaxine for infant appears to be satisfactory and it was suggested that when it is provided in breast milk may moderate the effects of neonatal withdrawal syndrome in infants exposed to the drug during pregnancy. Nevertheless venlafaxine should be used with cautious in breastfeeding women and infant monitoring of its metabolite in the infant's plasma could be used as a safety measure.

Although bupropion and reboxetine seem to be safe during breastfeeding more information is needed about its effects on the infants. Some findings suggested that short-term mirtazapine use during breastfeeding is safe.

In accordance to previous review studies sertraline and paroxetine are safe and could be used as first-line medications in women who need to start antidepressant treatment during the postnatal period and wish to continue to breastfed their infants. Fluoxetine and citalopram should not be the drugs of first choiceespecially in high doses [10,18,20,44]. However if treatment has already started during pregnancy and is effective medication should not be altered [20]. It had been suggested that given the lack of data on the excretion of other antidepressants into breast milk the use of other classes of antidepressants for which use during breastfeeding is better documented is recommended and in addition drugs that do not appear in infants' plasma are preferable [20,45].

In a recent study an author proposed a clinical index to assess the safety of newer antidepressants for breastfed infants the Breastfed Infant-Antidepressant Safety Index. In addition the study has suggested the institution of an international case register recording the outcome of infants exposed to antidepressants through maternal milk [18].

Review studies have suggested that infant levels of antidepressants above 10% of the maternal level would have potential clinical significance [45]. It was also suggested that a M/P ratio of >1.0 does not necessarily mean that the drug is contraindicated during lactation but just that is less desirable than a drug characterized by a M/P ratio <1.0 [46].

There is a disparity in the most accurate method for quantifying infant exposure to antidepressants through breastfeeding [8]. The parameters most frequently evaluated for establishing the safety of antidepressants for the breastfed infant such as the amount of the drug excreted into maternal milk and/or detectable in the infant's serum percentage of infants with detectable serum concentrations and M/P ratios are characterized by wide ranges of inter-individual variability among mothers and infants [18].

The researchers also should consider the factors that affect drug transfer and concentration in breast milk such as maternal plasma drug level adult half-life of the drug drug lipophilicity protein binding and days postpartum [25]. Accurate prediction of daily infant dose via breast feeding requires a model that takes into account: first that the composition of breast milk varies from the initial colostrums (which shows relatively higher protein concentration) to mature milk and thus drug concentrations change after the first 3 to 4 days of lactation and second that the milk composition varies even during a single breastfeeding session with milk expressed towards the end of a feeding having greater fat contents. Therefore a random milk sample may not accurately reflect the infant exposure [8,46,47].

Conclusion

This study aims to emphasize the importance of PPD treatment always considering its repercussions for the breastfed infants such as uneasy sleep colic decreased feeding and irritability/restlessness reported during citalopram treatment. Like in other review studies the

lack of data limited the research principally clinical trials. The antidepressants are one of the most prescribed drugs and its use in certain groups of patients is not extensively documented like during breastfeeding. Studies are needed with larger samples to properly evaluate the short and long-term effects of antidepressants on infants exposed through breast milk so that clinicians can create standard decisions regarding the treatment ofPPD without putting infants at risk.

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