REVIEW ARTICLE

Drug Safety 2007; 30 (2): 107-121
0114-5916/07/0002-0107/$44.95/0

Use of Contemporary Antidepressants during Breastfeeding

A Proposal for a Specific Safety Index

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Abstract

Despite the well known severe repercussions of maternal depression on infants' well being, women are often reluctant to seek pharmacological treatment for postnatal depression. The fear of adverse events for the suckling infant plays an important role in such maternal considerations. However, the pharmacological approach to mood disorders at postpartum onset often represents one of the most realistic options in a number of clinical conditions. Therefore, the necessity exists to establish the safety of antidepressant treatment in the breastfed infant. For this reason, the aim of this article is to propose a specific safety index that assesses the frequency and degree of severity of adverse events in infants associated with maternal treatment with second-generation antidepressants during puerperium.

The index is derived from a simple formula that uses the number of reports of adverse events in infants exposed to antidepressants as the numerator and the

combined total of reports of healthy outcomes and reports of adverse events as the denominator. The sum is then multiplied by 100. A value of ≤2 indicates that the drug should be relatively safe for use during breastfeeding, a value of 2.1–10 indicates that the drug should be used with great caution and a value >10 indicates that the drug should be contraindicated in breastfeeding mothers. In addition to the figure created by this calculation, each drug will also be assigned a letter or the combination of a letter and a subscripted number to symbolise, respectively, the type and clinical management of the most serious recorded event.

At this early developmental stage of the index, a complete classification of contemporary antidepressants regarding their safety in infants nursed to the breast is unfeasible. Indeed, because of the lack of suitable published data, so far the index has been limited to the evaluation of four antidepressants. In accordance with the index classification for these four antidepressants, sertraline and paroxetine should be considered as first-line medications in women who need to start antidepressant treatment during the postpartum period and wish to continue breastfeeding. The utilisation of fluoxetine and citalopram seems conversely to be associated with a relatively higher risk of adverse events (with a low degree of severity, however). For the other newer antidepressant drugs, the index is still of no assistance to the patient or physician in deciding on the safety of their use in lactation.

A WHO report has named depression as the condition with greatest disease burden for women worldwide.[1] In particular, the childbearing years are a time of increased vulnerability to the onset of major depression for women. During puerperium, the percentage of new mothers who may show symptoms suggestive of major depressive episode ranges from 12% to 16%;[2,3] this figure has been reported to be as high as 26% in adolescent mothers.[4] However, this range may not be representative of the global magnitude of the problem.[5]

Nonetheless, despite the well known severe repercussions of maternal depression on the infants' well being, women are often reluctant to seek treatment for postnatal depression. Indeed, 75% of American women believe their postpartum mood symptoms are normal.[6] British women are also hesitant to accept pharmacological interventions for mood disorders during breastfeeding.[7] Research conducted on Australian women reveal similar findings: such women prefer psychological and social management rather than drugs for depression postnatally.[8] Without a doubt, the fear of adverse events for the suckling infant plays a central role in such maternal considerations.

However, the mother represents the prime environment for her baby. During the first few months of life, the infant has a particular psychological vulnerability, as he/she has a restricted range of capacities tuned specifically to participation in the social world;[9,10] as a consequence, the pattern of interaction with a depressed mother may negatively influence the baby's other relationships and compromise later cognitive outcome.[11-13] Children of depressed parents are also more vulnerable to psychiatric illness.[14] Furthermore, mothers affected by depressive symptoms early in the postpartum period are less likely to breastfeed their infants.[15]

Therefore, it may be essential to achieve a rapid symptomatic remission in the new mother with severe psychiatric impairment.[16] Hence, the pharmacological approach to postpartum major depressive episodes frequently represents one of the most realistic options.

On the other hand, the benefits of breastfeeding for the mother-infant dyad are well known.[17] In the infant, breastfeeding is protective against a number

of infectious and inflammatory diseases: respiratory, urinary and gastrointestinal infections as well as otitis media are less frequent in exclusively breastfed infants, especially if the breastfeeding duration is extended by at least the first 4 months of life.[18,19] The risks of asthma and other atopic diseases, such as gastrointestinal manifestation of food allergies, are also reduced by the consumption of maternal milk as well as the risks of some forms of leukaemia.[20-23] Moreover, breastfeeding facilitates the normal progression of neurocognitive development and plays a protective role against sudden infant death syndrome.[24,25] In addition, the incidence of chronic metabolic diseases are decreased in childhood and later life.[26] Finally, breastfeeding contributes in activating specific immune-defensive capacities and also provides an unique opportunity for bonding between infant and mother.[27,28]

In nursing mothers, suckling induces oxytocin release, which promotes the uterine contractions involved in the postnatal uterine involution.[29] Furthermore, a longer duration of breastfeeding protects women against the development of ovarian and breast cancer.[30,31]

Unfortunately, information on the safety of tricyclic antidepressants for breastfed infants is still anecdotal.[32] Studies evaluating this specific safety-facet of the last generation of antidepressant drugs for suckling infants also provide too few data to make definitive conclusions.[32] This situation is not surprising given that women and children have largely been left out of pharmacological research. As a result, medications that are frequently needed during puerperium are insufficiently studied in this population.[33] The elegant term of 'therapeutic orphans' actually describes the reluctance to include women of reproductive age in studies to determine the effectiveness of drugs.[34]

However, despite this unfavourable background, the necessity exists to establish the safety of antidepressant treatment for breastfed infants.

Therefore, the aim of this paper concerns formulating a specific safety index reassuming frequency and the degree of severity of adverse events in infants associated with maternal treatment with last-generation antidepressants (i.e. the selective serotonin reuptake inhibitors [SSRIs]: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram; the serotonin noradrenaline reuptake inhibitors [SNRIs]: venlafaxine and duloxetine; and other antidepressants: bupropion, mirtazapine, nefazodone and reboxetine) during postnatal period.

In accordance with the general guidelines by Council for International Organizations of Medical Sciences,[35] a characterised index must be based mainly on the frequency of the adverse events. The frequency of adverse events has been calculated on the basis of published trials evaluating the safety of second-generation antidepressants in breastfeeding, as briefly but comprehensively summarised in section 1.

The main source of material for this review came from articles already selected from two literature searches conducted in December 2004 and May 2005, respectively. For the first search, the following search terms were used: 'antidepressants in pregnancy' and/or 'breastfeeding' and/or 'lactation'. No language restrictions were placed on the electronic search on different databases. A separate search was also run to complete the safety profile of each contemporary antidepressant. In addition, the following terms were utilised for the second search: 'human milk', 'child/infant development/neurodevelopment' and 'mood disorders'. Both sets of search terms were utilised to update the article to November 2006 via the TOXNET, EMBASE and MEDLINE/PubMed databases. Resultant articles were cross-referenced for other relevant articles not identified in the initial search. Extensive manual review of pertinent journals and textbooks was also performed. Supplementary data sources were represented by institutions active in the field and manufacturers' information.

Table I. Fluoxetine and breastfeeding

Study	Year	Sample size (mother-infant pairs)	Adverse events	Placental exposure
Moretti et al.[36]	1989	51	Eight (two of such cases, all spontaneously resolved, were suggestive for withdrawal)	40% of mothers
Isenberg[37]	1990	1	Transient irritability (correlation with maternal treatment unclear)	No
Burch and Wells[38]	1992	1	No	No
Lester et al.[39]	1993	1	Colic, increased crying, decreased sleep, increased vomiting and watery stools. All resolved after switching to formula	No
Taddio et al.[40]	1996	11	No	No
Kim et al.[41]	1997	6	No	No
Chambers et al.[42]	1999	26 infants	Reduced infants' growth curve; high frequency of admission to special care nursery in exposed infants (n = 5/26)	Yes
Heikkinen et al.[43]	2003	11	No	Yes
Hendrick et al.[44]	2001	20	No	18/20
Epperson et al.[45]	2003	11	One infant had a substantial variation in platelet serotonin level, which decreased from 133 ng/mL to 54 ng/mL, a 60% change from baseline. However, the infant showed no neurobehavioural adverse reactions	No
Yoshida et al.[46]	1998	4	No	No
Berle et al.[47]	2004	1	The rate of adverse events was not reported. However, at birth there were no differences in the severity of the symptoms between exposed and non exposed infants	Yes
Weissman et al.[48]	2004	1	No	No
Hale et al.[49]	2001	1	Somnolence, lethargy, fever, and unresponsiveness. All resolved after switching to formula	Yes
Brent and Wisner[50]	1998	1	Three seizure-like episodes[a]	Yes
Kristensen et al.[51]	1999	14	One case of colic; one case of colic plus hyperactivity	4/14
Oberlander et al.[52]	2005	6	Altered acute-pain response	Yes
Suri et al.[53]	2002	10	No	No
Kim et al.[54]	2006	23	No	5/23

a The mother also took carbamazepine 600 mg/day and buspirone 45 mg/day during pregnancy and breastfeeding.

1. Contemporary Antidepressants during Puerperium

1.1 Selective Serotonin Reuptake Inhibitors

1.1.1 Fluoxetine

Since launch of the drug in 1989, a relatively large amount of information on the utilisation of fluoxetine in breastfeeding mothers has become available (see table I).[36-52]

The concentration of fluoxetine in breast milk represents a significant predictor of the total infant serum concentration of the drug.[53] Moreover, it has been demonstrated that the amount of drug transferred to an infant depends largely on the maternal drug concentration.[53] In addition, there is a stereoselective disposition of both fluoxetine and its metabolite, resulting in increased concentrations of the biologically active enantiomers in the infant compared with the mother.[54]

Table II. Citalopram/escitalopram and breastfeeding

Study	Year	Sample size (mother-infant pairs)	Adverse events	Placental exposure
Citalopram				
Berle et al.[47]	2004	9	The rate of adverse events was not reported. However, at birth there were no differences in the severity of the symptoms between exposed and non exposed infants	4/9
	2004	2		
Spigset et al.[55]	1997	2	No	No
Jensen et al.[56]	1997	1	No	No
Öhman et al.[57]	1997	2	No	No
Heikkinen et al.[58]	2002	21	One child did not walk at the age of 1 year; however, the neurological status of this child was normal 6 months later	11/21
Rampono et al.[59]	2000	7	No	No
Schmidt et al.[60]	2000	1	Uneasy sleep	No
Lee et al.[61]	2004	31	One case each of colic, decreased feeding and irritability/restlessness	No
Franssen et al.[62]	2004	1		
Escitalopram				
Rampono et al.[63]	2006	8	No	No
Gentile[64]	2006	1	No	Yes

1.1.2 Citalopram/Escitalopram

Citalopram

A significant amount of data regarding the utilisation of antidepressants by breastfeeding women are also available for citalopram (see table II).[47,48,55-62]

Escitalopram

Very recently, it was confirmed that escitalopram is excreted into breast milk.[63] The total relative infant dose for escitalopram plus its demethyl metabolite was calculated at 5.3%. All the infants exhibited normal behavioural and developmental milestones for their age. In addition, the escitalopram absolute infant dose seemed to be lower than that for the equivalent antidepressant citalopram. Hence, escitalopram should be preferred over citalopram for the treatment of depression in breastfeeding women.[63] A recent report also failed to demonstrate any adverse reactions in one infant whose mother took escitalopram during breastfeeding (see table II).[64]

1.1.3 Paroxetine

Exposure to paroxetine appears to be minimal for nursing infants with respect to the resulting maternal serum drug concentrations (see table III).[47,52,65] Öhman et al.[66] concluded that 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.

Studies and single case reports have evaluated the clinical effects of infant's exposure to paroxetine.[48,67-73] The majority of such studies showed reassuring results, whereas the minority showed mild unwanted reactions.

1.1.4 Sertraline

In one of the first studies evaluating the amount of sertraline in the infants breastfed by mothers taking the drug, most breastfed infants had low-serum concentrations of both sertraline and its metabolite, and only one infant showed a relatively high-drug concentration (see table IV).[74] With the exception of anecdotal reports of neonatal complications,[75] data about the safety of sertraline in breastfeeding seem to be quite reassuring.[76]

Table III. Paroxetine and breastfeeding

Study	Year	Sample size (mother-infant pairs)	Adverse events	Placental exposure
Berle et al.[47]	2004	6	The rate of adverse events was not reported. However, at birth there were no differences in the severity of the symptoms between exposed and non exposed infants	3/6
Weissman et al.[48]	2004	3	No	No
Oberlander et al.[52]	2005	20	Altered acute pain response	Yes
Spigset et al.[65]	1996	1	No	No
Öhman et al.[66]	1999	6 lactating women	No	No
Hendrick et al.[67]	2000	1	No	No
Misri et al.[68]	2000	25	No	No
Stowe et al.[69]	2000	16	No	No
Nordeng et al.[70]	2001	NA	Lethargy, poor weight gain and hypotonia	Yes
Hendrick et al.[71]	2001	16	No	6/16
Merlob et al.[72]	2004	27	One case of irritability	No
Begg et al.[73]	1999	10	No	No

NA = not available.

Indeed, more than a few studies confirmed that sertraline concentration is very low in infant serum, although it may vary substantially over the 24-hour day in breast milk.[47,48,52,71,77-86]

However, an extemporaneous and not-replicated observation suggested that maternal sertraline treatment during puerperium may induce a temporary reduction in breast milk supply.[87]

1.1.5 Fluvoxamine

Available published data on fluvoxamine use during puerperium are scarce, although quite reassuring (see table V).[48,71,88-93]

Table IV. Sertraline and breastfeeding

Study	Year	Sample size (mother-infant pairs)	Adverse events	Placental exposure
Berle et al.[47]	2004	6	The rate of adverse events was not reported. However, at birth there were no differences in the severity of the symptoms between exposed and non exposed infants	2/6
Weissman et al.[48]	2004	18	No	No
Oberlander et al.[52]	2005	4	Altered acute pain response	Yes
Hendrick et al.[71]	2001	30	No	9/30
Wisner at al.[74]	1998	9	No	No
Kent and Laidlaw[75]	1995	1	Agitation, restlessness, poor feeding, constant crying, insomnia, enhanced startle reaction	Yes
Epperson et al.[76]	2001	11	No	No
Altshuler et al.[77]	1995	1	No	No
Mammen et al.[78]	1997	3	One case of benign neonatal sleep myoclonus	No
Epperson et al.[79]	1997	4	No	No
Stowe et al.[80]	1997	12	No	3/12
Stowe et al.[81]	2003	26	No	13/26
Dodd et al.[82]	2000	10	No	No
Kristensen et al.[83]	1998	8	No	No

Table V. Fluvoxamine and breastfeeding

Study	Year	Sample size (mother-infant pairs)	Adverse events	Placental exposure
Weissman et al.[48]	2004	1	No	Yes
Hendrick et al.[71]	2001	5	No	2/5
Piontek et al.[88]	2001	2	One case of neonatal jaundice, spontaneously resolved	No
Kristensen et al.[89]	2002	2	No	1/2
Yoshida et al.[90]	1997	1	No	No
Hägg et al.[91]	2000	1	No	Yes
Wright et al.[92]	1991	1	No	No
Gentile[93]	2006	1[a]	No	Yes

a The mother also took quetiapine 400 mg/day.

1.2 Serotonin Noradrenaline Reuptake Inhibitors

1.2.1 Venlafaxine

A low number of cases have been reported on venlafaxine. Preliminary findings suggest no associations between venlafaxine exposure via maternal milk and unwanted repercussions for the infants (see table VI).[47,94-97] It was also suggested that venlafaxine in breast milk could attenuate the noradrenergic-serotoninergic neonatal withdrawal symptoms in infants also exposed to the drug during the fetal life.[98]

1.2.2 Duloxetine

Duloxetine and its metabolites are excreted into the milk of lactating rats.[99] So far, it is unknown whether or not the compounds are also excreted into human milk.[99]

1.3 Other Antidepressants

1.3.1 Bupropion

Four studies (including a total of 14 mothers and only 4 infants) examined the excretion of bupropion in breast milk and the effects of the exposure to the compound on infants or toddlers (see table VII).[100-104] The results indicated that the daily dose of bupropion and its metabolites that would be delivered to an infant from a woman taking a therapeutic dose of bupropion is relatively small. However, the possibility that bupropion might induce serious adverse events in the suckling infants must be taken into consideration.[103]

1.3.2 Nefazodone

Very limited and conflicting published data are available on nefazodone (see table VII).[105,106]

1.3.3 Mirtazapine

One case report evaluated the utilisation of mirtazapine by a breastfeeding mother (see table

Table VI. Venlafaxine and breastfeeding

Study	Year	Sample size (mother-infant pairs)	Adverse events	Placental exposure
Berle et al.[47]	2004	3	The rate of adverse events was not reported. However, at birth, there were no differences in the severity of the symptoms between exposed and non-exposed infants	2/3
Ilett et al.[94]	2002	6	No	No
Ilett et al.[95]	1998	3	No	No
Hendrick et al.[96]	2001	2	No	1/2
Koren et al.[98]	2006	1	Venlafaxine seemed to attenuate neonatal withdrawal syndrome in a neonate exposed to the drug during fetal life	Yes

Table VII. Bupropion, nefazodone and breastfeeding

Study	Year	Sample size (mother-infant pairs)	Adverse events	Placental exposure
Bupropion				
Briggs et al.[100]	1993	1	No	No
Baab et al.[101]	2002	2	No	No
Haas et al.[102]	2004	10 healthy postpartum volunteers	NA	No
Chaudron and Schoenecker[103]	2004	1	One episode of seizure	No
Nefazodone				
Dodd et al.[105]	2000	2	No	No
Yapp et al.[106]	2000	1	Drowsiness, lethargy and body temperature instability[a]	No

a These events occurred in a premature infant (born at week 27 of gestation).

NA = not available.

VIII).[107] The baby showed no adverse events. Very recently, the transference of mirtazapine and its active metabolite into human milk and the dose to the infant via milk were calculated in a small sample size of mother-infant dyads. Mirtazapine was detected in only one of tested infants.[108]

1.3.4 Reboxetine

Only one study was available at the time this article was written (see table VIII). No reboxetine-associated adverse events have been reported to date.[109]

2. Need for an International Case Register

The decision to start treatment with an antidepressant during the postnatal period must always be taken on an individual basis: a pharmacological approach should be considered in all cases of severe maternal disorder and/or when the psychiatric impairment is judged to be likely to adversely impact the infant's neuropsychological development.

Unfortunately, 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 milk-to-plasma [M/P] ratios, are characterised by wide ranges of inter-individual variability among mothers and infants. With regards to M/P ratio, this inter-individual variability also depends on the protein binding, drug-lipophilicity, portion of breast milk, timing of maternal-serum sampling and the aliquot of breast milk assayed.[48,69] This so-called 'measure' of

Table VIII. Mirtazapine, reboxetine and breastfeeding

Study	Year	Sample size (mother-infant pairs)	Adverse events	Placental exposure
Mirtazapine				
Aichhorn et al.[107]	2004	1	No	No
Kristensen et al.[108]	2006	8	No	Mothers with perinatal and/or postnatal depression; no further details available
Reboxetine				
Hackett et al.[109]	2006	4[a]	No	No

a Two mothers also received concomitant antidepressant medications (escitalopram 20 mg/day and sertraline 300 mg/day, respectively).

breastfeeding safety has no reliability because it merely reflects a transfer ratio and provides no information about safety.

Moreover, the percentage of babies showing detectable serum concentrations and, consequently, the magnitude of such concentrations are also correlated both to the individual timing of an infant's hepatic maturation (usually occurring after the third month of life) and eventual cytochrome P450 (CYP) 2D6 polymorphisms.[110] Also, fat-soluble medications can reach concentrations in the cerebral fluid that are 10- to 30-fold higher than those in serum.[111]

Thus, it is not surprising that all these parameters have shown no clear correlations with the clinical outcome.

For all these reasons, despite the limited availability of published data, the choice of the drug should primarily be derived from the number of its safe and unsafe reports. However, although there is a relatively large amount of available data for citalopram, fluoxetine, paroxetine and sertraline, data on bupropion, duloxetine, escitalopram, fluvoxamine, nefazodone, mirtazapine, reboxetine and venlafaxine are either scarce or completely lacking.

In light of these considerations, the institution of an international case register recording the outcome of infants exposed to antidepressive agents through maternal milk might represent an indispensable instrument for collecting additional data, specifically regarding the safety of the most widely used psychotropic medications. The register should include information on maternal psychiatric diagnosis, daily dose of the drug and the duration of both treatment and breastfeeding. The cases of positive outcome should constantly be recorded in the main section of the register, even if characterised by concomitant placental drug exposure and/or maternal polypharmacotherapy. The same section should also include all the cases of adverse events that occurred in infants exposed to antidepressant monotherapy during breastfeeding.

Conversely, the reports describing negative outcomes but characterised by placental exposure and/or by concomitant maternal treatment with other drugs should be recorded in a different section; thus, it may be possible to reduce the risk of including misleading data for events that are due to the interference of two potentially relevant confounding factors. Indeed, the vast majority of adverse events were recorded in infants also exposed to antidepressants during their fetal life; it is possible that such events may not be related to the exposure to the drug via maternal milk, but to toxic events due to placental exposure, which was prolonged during the first days after parturition.

Also, the register must record the clinical outcome and management of any complications.

3. The Breastfed Infant-Antidepressant Safety Index (BI-ASI)

In spite of the limitations of any international case register, such as the tendency to record cases with unhealthy outcome more often and with greater accuracy than cases with a healthy outcome, it might contribute to establishing a new clinical index to assess the safety of newer antidepressive agents for breastfed infants – the Breastfed Infant-Antidepressant Safety Index (BI-ASI). The index has been derived from the formula in equation 1.

$$\frac{\text{No. of reports describing adverse events in infants exposed to antidepressant-(monotherapy solely via maternal milk)}}{\text{No. of infant cases with healthy outcome (even if characterised by placental exposure and/or maternal polypharmacotherapy)} + \text{No. of reports describing adverse events in infants exposed to antidepressant-monotherapy solely via maternal milk}} \times 100$$

(Eq. 1)

The following can be shown from the BI-ASI:

- a cautious theoretical estimation could consider the drugs associated with a BI-ASI of ≤2 as relatively safe;
- BI-ASI = 0 indicates drugs associated with no recorded cases of adverse events;

- in case of BI-ASI values ranging between 2.1 and 10, the utilisation of the drug during breastfeeding should be considered with great caution;
- the drug should be considered as contraindicated in breastfeeding when its BI-ASI is >10; and
- if the overall number of reports describing the outcome of infants exposed to antidepressant monotherapy solely via maternal milk is lower than the theoretical threshold of 50; [1] however, the safety should be considered unknown (the letter 'X' symbolises such a specific situation).

Subsequently, a letter or the combination of a letter and a subscripted number will symbolise, respectively, the type and clinical management of the most serious recorded event for documenting further relevant information (when available).[112] Such symbols follow the number specifying the BI-ASI value (see table IX).

3.1 BI-ASI Limitations

The BI-ASI shows some limitations. The main limitation is represented by the small number of cases reported in the literature to date; thus, the index will reach a higher level of clinical significance when more data become available. Indeed, all cases with positive outcomes that presumably happen in the real world cannot be added to the index denominator until the international case register is instituted. It has actually been estimated that more than a quarter of a million women may want to breastfeed while taking antidepressants.[82]

Table IX. The Breastfed Infant-Antidepressant Safety Index

Letter	Definition
A	Death or permanent handicap
B	Severe event
B_1	Severe event requiring admission to an intensive care unit
B_2	Severe event requiring specific pharmacological treatment and/or a switch to formula
B_3	Severe event requiring supportive treatment
B_4	Severe event that is spontaneously resolved
B_x	Severe event for which no other specific information is available
C	Moderate event
C_1	Moderate event requiring specific treatment and/or a switch to formula
C_2	Moderate event requiring supportive treatment
C_3	Moderate event that is spontaneously resolved
C_x	Moderate event for which no other specific information is available
D	Minor event requiring supportive treatment or that is spontaneously resolved
O	Adverse event of unknown degree of severity

A second limitation is that it estimates the safety of antidepressive agents during only a short period of the infants' life (throughout the breastfeeding period). Thus, possible detrimental repercussions of postnatal exposure to newer antidepressants on the infants' later neurocognitive development cannot be excluded. Animal studies recently suggested that exposure to SSRIs at an early age disrupts the physiological maturation of the serotoninergic pathway and also modifies serotonin-dependent neuronal processes.[113] Even though it is unknown if SSRIs and other antidepressants replicate the same effects in humans, this is the first reproducible data to suggest that intrauterine exposure to such agents may have long-term neurobehavioural consequences. Hence, further studies and specific instruments are needed to fully answer the question about the impact of newer antidepressants on long-term neurocognitive development of infants and toddlers.[114]

Moreover, the possibility that some infants may experience problems in metabolising drugs and/or their metabolites should carefully be taken into consideration.[115]

In addition, the BI-ASI is unable to evaluate the quality (and hence reliability) of the adverse event reports that feature critically in the denominator of the index. Such events should be subjected to a reproducible evaluation (such as the Naranjo Score[116]). Unfortunately the majority of such reports did not provide the use of specific assessment tools.

Furthermore, in the real world, many women could need antidepressant treatment during the last trimesters of pregnancy as well as in the postpartum

1 The choice of the value is imposed by the small amount of existing data about infants exposed to antidepressant monotherapy solely during breastfeeding to date.

Table X. Breastfed Infant-Antidepressant Safety Index (BI-ASI) for each second-generation antidepressant

Drug	BI-ASI	Notes
Fluoxetine	$3.5C_1$	Colic, increased crying, decreased sleep, increased vomiting and watery stools. All resolved after switching to formula
Citalopram	$5.3C_3$	Colic, decreased feeding and irritability/restlessness
Escitalopram	X	
Paroxetine	0.95/D	One case of irritability
Sertraline	0.68/D	Benign neonatal sleep myoclonus
Fluvoxamine	X/C_3	Neonatal jaundice, spontaneously resolved
Venlafaxine	X	
Duloxetine	X	
Bupropion	X/B_4	Seizures
Nefazodone	X/C_1	Drowsiness, lethargy and body temperature instability occurring in a premature infant and resolved after breastfeeding suspension
Mirtazapine	X	
Reboxetine	X	

period. Excluding the reports that describe the outcomes in infants exposed to contemporary antidepressants both via placenta and maternal milk makes the index pure. On the other hand, the possibility exists to neglect relevant information that could assist with risk assessment; hence, any additional information should be taken into consideration in the benefit-risk analysis for all contemporary antidepressants.

Also, an 'X' listing for the majority of these newer drugs is of no assistance to the patient or physician in deciding on the safety of its use in lactation.

Nonetheless, despite such limitations, the index may overcome some limitations shown by the only existing rating system for drug safety during lactation;[117] specifically, some generic definitions (such as "large/limited number of breastfeeding mothers") included in the 'lactation risk categories' may be exactly quantified by using the BI-ASI.

However, the development of such an index is still in an early stage; thus, its clinical validity should be confirmed in the context of a consensus of interested and informed researchers in the field. Ideally, the full development of the BI-ASI should include members of a multidisciplinary group, including gynaecologists, obstetricians, paediatricians, psychiatrists, maternal-fetal medicine specialists, experts active in the women's mental health field, pharmacologists and statisticians.

4. Conclusions

Although the limitations of BI-ASI must not be underestimated, the index could represent an additional useful aid for clinicians to preliminarily classify such medications for safety in infants nursed to the breast. An analogue index might also be extended to all the other psychotropic medications.

At present, in accordance with the index, sertraline and paroxetine should be considered as first-line medications in women who need to start antidepressant treatment during the postnatal period and wish to continue to breastfeed their infants (see table X). The utilisation of citalopram and fluoxetine seems conversely to be associated with a relatively higher risk of adverse events (with a low degree of severity, however). So far, the available data do not support the utilisation of the other newer antidepressants during breastfeeding.

Such results are analogous to those reported by Weissman et al.[48] and Eberhard-Gran et al.;[118] these authors recently suggested that, if SSRI treatment must be started in the postpartum period, fluoxetine and citalopram should not be considered as drugs of first choice because both agents produce relatively high proportions of infant drug concentrations that are elevated >10% of average maternal concentration.

Hence, these results seem to represent the first, albeit preliminary, clinical confirmation that a corre-

lation may exist between the amount of drug in the infant serum and increased risk of adverse events.

Such a concordance between these results and the findings of Weissman et al.[48] and Ebherard-Gran et al.[118] could also represent the first confirmation that BI-ASI could really have an its own intrinsic validity.

However, if antidepressant treatment is deemed appropriate and no clear contraindication toward breastfeeding is appreciable, a careful surveillance of the infants must be provided in order to promptly diagnose any adverse events. Although anecdotal reports have suggested that the prolongation of antidepressant exposure during breastfeeding may attenuate the degree of severity of the neonatal withdrawal syndrome, this caution is still needed in case of concomitant prenatal exposure to the medication.[98] Because of the risk of prenatal drug loading, when an infant exposed to a newer antidepressant agent through placenta shows adverse events during the first hours after birth, the prolongation of exposure to the drug through maternal milk must strongly be avoided. Thus, despite being recently reported that the breastfeeding population should learn to fear the illness more than the antidepressant,[119] in such a situation clinicians should choose between two options: to advise the mother to continue breastfeeding the infant but stop antidepressant treatment or to maintain the maternal psychopharmacological regimen but advise her to discontinue breastfeeding.

Acknowledgements

The author would like to acknowledge Anna Maria Desiati (Educational Sci.D., Information Specialist, Eli Lilly Italia SpA, Scientific Information Division), her colleague Leonardo Pavese, and Raffaella Santero (Pharm.D., Information Specialist, Medical Information Service, Novartis SpA, Italy): their support in obtaining the full-text articles evaluating the outcome of infants exposed to new antidepressant agents via maternal milk was invaluable and professional.

The author wishes also to acknowledge Andrea Rossi (Medical writer, Eli Lilly Italia SpA), for a single but very precious suggestion in the early phase of manuscript preparation.

A very special thank you is due to another person who would prefer to remain anonymous.

Last but not least, a special thank you is also due to the Editor of *Drug Safety*, the whole editorial staff and the anonymous reviewers of *Drug Safety*. Their valuable comments made completion of this article and previously published articles possible.

The author is in the speaker-bureau for Eli Lilly Italia SpA. In the last 5 years, he has also received travel funds from Astra Zeneca, Eli Lilly, Janssen-Cilag, Lundbeck, Novartis, Pzifer and Recordati. No sources of funding were used for the preparation of this review. The author has no potential conflicts of interest that are directly relevant to the contents of this article.

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