

# The use of psychotropic medication during pregnancy: how about the newborn?

Noera Kieviet<sup>1</sup>  
Koert M Dolman<sup>1</sup>  
Adriaan Honig<sup>2</sup>

<sup>1</sup>Department of Paediatrics,

<sup>2</sup>Department of Psychiatry, Psychiatry  
Obstetrics Paediatrics Expert  
Center, Sint Lucas Andreas Hospital,  
Amsterdam, The Netherlands

**Abstract:** Infants are at risk of developing symptoms of Poor Neonatal Adaptation (PNA) after exposure to psychotropic drugs in utero. Such symptoms are largely similar after exposure to antidepressants, antipsychotics and benzodiazepines and consist of mostly mild neurologic, autonomic, respirator and gastro-intestinal abnormalities. Most symptoms develop within 48 hours after birth and last for 2–6 days. After exposure to Selective Serotonin Reuptake Inhibitors (SSRIs), mirtazapine or venlafaxine in utero, breastfeeding is presumably protective for development of PNA. The dosage of antidepressants does not seem to be related to the risk of PNA. In order to objectify possible symptoms of PNA, observation of mother and child at the maternity ward is advisable. If PNA symptoms do not occur, an observation period of 48–72 hours is sufficient. This applies to all types of psychotropic drugs. When PNA symptoms are present it is advisable to observe the infant until the symptoms are fully resolved. Observation can be performed by trained nurses using the Finnegan scoring list. This observation list should be administered every 8 hours. Interpretation of the scores should be carried out by a paediatrician. In most cases symptoms are non-specific. Therefore other diagnoses, such as infection or neurologic problems, have to be excluded. When there is any doubt on possible intoxications during pregnancy, toxicological urine screening is indicated. Most cases of PNA are mild, of short duration and self-limiting without need for treatment. Supporting measures such as frequent small feedings, swaddling and increase of skin to skin contact with the mother is usually sufficient. In case of severe PNA it is advised to admit the infant to the Neonatal Care Unit (NCU). Phenobarbital is a safe therapeutic option. There seem to be no major long term effects; however, additional studies are necessary in order to draw definite conclusions.

**Keywords:** withdrawal, neonatal abstinence, psychiatric disorders, SSRI, antidepressants

## Introduction

For women with a known psychiatric disorder, pregnancy and the first six months after delivery are a vulnerable period, in which psychiatric disorders may relapse or worsen. Of all pregnant women, approximately 15% have psychiatric problems, in particular depression and anxiety.<sup>1,2</sup>

The possible negative effects of untreated psychiatric symptoms to mother and child have to be weighed against the possible negative effects of psychotropic medication use during pregnancy, in order to diminish maternal and neonatal complications both during and after pregnancy.

Untreated psychiatric disorders during pregnancy may lead to three major complications. Firstly, it can lead to pregnancy complications, such as low birth weight and prematurity, which is partly due to maternal stress related elevated cortisol levels.<sup>3–6</sup>

Correspondence: Noera Kieviet  
Sint Lucas Andreas Hospital, Psychiatry  
Obstetrics Paediatrics Expert Center,  
Jan Tooropstraat 164, 1061 AE  
Amsterdam, The Netherlands  
Tel +31 0205 108 790  
Fax +31 0206 853 059  
Email n.kieviet@slaz.nl

Secondly, maternal symptoms of depression and anxiety may lead to irritation, agitation, lethargy, and less alertness, as well as poverty of facial expressions in infants.<sup>6-8</sup> Lastly, maternal psychiatric symptoms can lead to attachment problems between mother and child, which are a risk factor for learning and behavioural problems later in life.<sup>9-11</sup>

The possible risks of psychotropic drug use during pregnancy, such as malformations, pregnancy complications, Poor Neonatal Adaptation (PNA), and long term effects should be carefully weighed against the benefits. In daily practice the use of psychotropic drugs during pregnancy increases gradually. Approximately 3.5% of all pregnant women in the Western world use psychotropic drugs during pregnancy.<sup>12</sup>

To assist the decision process regarding the treatment of psychiatric disorders during pregnancy many guidelines have been developed and reviews have been written.<sup>13-15</sup> However, these writings mainly focus on the risk of malformations and do not provide recommendations regarding observation and treatment of PNA. Therefore, this article focuses on PNA in infants exposed to the most commonly used psychotropic drugs in utero; antidepressants, antipsychotics, mood stabilisers and benzodiazepines, and can serve as a guideline for observation of infants exposed to these psychotropic drugs in utero.

## Etiology

Symptoms of PNA are caused by exposure to psychotropic drugs. However, the exact etiology is not fully understood. There are three possible explanations. First of all, symptoms may be caused by withdrawal of psychotropic drugs. In adults, psychotropic drugs, including antidepressants, antipsychotics and benzodiazepines, may result in withdrawal symptoms when not gradually tapered.<sup>16,17</sup> Since all psychotropic drugs pass the placenta,<sup>18-20</sup> abrupt discontinuation of drug exposure after birth can lead to symptoms of withdrawal in infants resembling symptoms of withdrawal in adults. Symptoms include feeding difficulties, irritability and tremors.<sup>21,22</sup> Most symptoms do not develop until eight hours after birth<sup>23-25</sup> and proceed even though medication exposure has ceased, which is a typical symptom of withdrawal.<sup>23,24,26</sup> In most cases of withdrawal, plasma concentrations of psychotropic drugs are low.<sup>20,22,23,25,27</sup>

Another cause of the symptoms is drug toxicity<sup>28,29</sup> which is a known, although rare, phenomenon in adults. Symptoms of drug toxicity are partly similar to symptoms of withdrawal, such as jitteriness and hyperreflexia. However, symptoms of toxicity develop directly after birth.<sup>21,22,29</sup> In most cases of toxicity, plasma concentrations of psychotropic drugs are high.<sup>29-31</sup>

It can be difficult to distinguish withdrawal of toxicity, since symptoms of withdrawal and toxicity are largely similar. Therefore many investigators postulate that a combination of withdrawal and toxicity is possible.<sup>23,24,32-35</sup> Since there is no consensus, multiple terms are used, such as poor neonatal adaptation, neonatal behavioural syndrome, postnatal adaptation syndrome/symptoms, transient neonatal symptoms, neonatal effects, neonatal complications, and neonatal abstinence syndrome.<sup>22,23,35,36</sup> Table 1 presents characteristics of toxicity and withdrawal after exposure to psychotropic drugs in utero.

Furthermore, it has been hypothesized that psychotropic drugs may act as intrauterine stressors. This stress can initiate alterations in fetal programming and development that might produce alterations in the child's behaviour at any age, a phenomenon known in cocaine exposed infants.<sup>37</sup>

Apart from exposure to psychotropic medication in utero, other factors, such as depression and anxiety of the mother,<sup>7,8,36-39</sup> genetic, epigenetic and environmental factors can also lead to symptoms of restlessness in infants.<sup>6,33,35,37,40</sup> This multifactorial origin can also explain the variability of PNA symptoms in infants.<sup>36,37</sup> Thereafter, infants have a limited repertoire of nonspecific activities. This can make it difficult to distinguish PNA from other syndromes such as infection.

**Table 1** Characteristics of toxicity versus withdrawal in infants exposed to psychotropic drugs in utero

	Toxicity	Withdrawal
Onset of symptoms	Immediately post partum	8-48 hours after birth
Medication level of the infant	High	Low
Medication half life time	Long	Short
Type of psychotropic drug	Antidepressants Benzodiazepines Antipsychotics Lithium Lamotrigine <sup>a</sup>	Antidepressants Benzodiazepines Antipsychotics Lamotrigine <sup>a</sup>
Common symptoms		Agitation/irritability Tremors Jitteriness Myoclonia Respiratory distress Hyperthermia and sweating Hyperreflexia Diarrhea Rigidity Feeding difficulties Vomiting Sleeping difficulties Hypo-and hypertonia

**Note:** <sup>a</sup>There is insufficient literature to draw conclusions on the etiology of PNA symptoms after exposure to lamotrigine in utero.

## Symptoms

PNA consists of neurological, autonomic, respirator, and gastro-intestinal symptoms, which are largely similar after exposure to antidepressants, antipsychotics and benzodiazepines (Table 2).<sup>5,13,16,17,19,21–28,33,35,36,40–64</sup>

In most infants symptoms are mild, such as sleep disturbances. Severe symptoms, such as convulsions, are rare.<sup>23,24</sup>

This review presents a resume of the most recent literature on PNA after exposure to the most commonly used psychotropic drugs in utero.

## Selective Serotonin Reuptake Inhibitors

The use of SSRIs during pregnancy has increased during the last few years, as knowledge has grown of the consequences of such use. Nowadays, 1.8%–2.8% of all pregnant women use an SSRI during pregnancy.<sup>24,65–67</sup>

Of all infants exposed to an SSRI in utero, 20%–77% develop symptoms of PNA, although most studies reported percentages around 30%.<sup>24,26,27,35,36,42,45,68</sup> Some studies described an increased incidence of PNA after exposure to paroxetine and fluoxetine compared to other SSRIs,<sup>16,23,34,53,69</sup> though other studies did not find this association.<sup>17,70</sup>

The half-life of the SSRI seems to influence the risk of withdrawal and toxicity; SSRIs with a short half-life, such as paroxetine, cause more withdrawal, however less toxicity, compared to SSRIs with a long half-life, such as fluoxetine.<sup>16,22,23,69,71</sup> However, after exposure to SSRIs with a long half-life, withdrawal is more common than toxicity.

Most symptoms develop within 48 hours after birth and last for 2–6 days.<sup>24,27,42</sup> If PNA symptoms do not occur in the first 48 hours after birth, development of PNA is unlikely.<sup>26,45</sup>

**Table 2** Symptoms of PNA in infants exposed to antidepressants, antipsychotics or benzodiazepines in utero

Common symptom	Less common symptom
<b>Neurological</b>	<b>Neurological</b>
Jitteriness	Convulsions
Muscle tone regulation disorders	Hyperreflexia
Tremors	Lethargia
Sleeping difficulties	<b>Gastro-intestinal</b>
High pitched or frequent crying	Diarrhea
Agitation/irritability	Uncoordinated/weak sucking
Myoclonia	Vomiting/regurgitation
<b>Gastro-intestinal</b>	<b>Autonomus</b>
Feeding difficulties	Temperature instability
<b>Respiratory</b>	Mottling
Respirator distress	Excessive sweating
	Nasal stuffiness

**Abbreviation:** PNA, poor neonatal adaptation.

Some studies<sup>5,42,72,77</sup> showed an increased risk of hypoglycemia and hyperbilirubinemia. However, evidence is limited and there are no published recommendations on whether routine glucose measurements are indicated.<sup>5,22,24,42,48,72,73</sup> There is conflicting clinical evidence regarding an elevated risk of Persistent Pulmonary Hypertension of the Newborn (PPHN) after exposure to SSRIs. The absolute risk cannot be determined, but is very small, probably less than 1%.<sup>74</sup> The FDA advises to treat depression during pregnancy as clinically appropriate since there is not sufficient evidence to conclude that SSRI use in pregnancy cause PPHN. Therefore discontinuation, lowering the dose or switching to another type of antidepressant is not recommended.<sup>75</sup>

## Tricyclic Antidepressants

Of all infants exposed to Tricyclic Antidepressants (TCAs) in utero, 20%–50% develops PNA.<sup>76</sup>

Symptoms of PNA after exposure to TCAs are similar to symptoms after exposure to SSRIs (Table 2).<sup>13,19,72,77</sup> Most symptoms develop within 48 hours of birth and last for 2–6 days.<sup>61</sup>

Apart from PNA, anticholinergic symptoms such as urine retention and obstipation have been described in two case reports. However, these symptoms are rare.<sup>19,77,78</sup>

## Other types of antidepressants

Other allowed and frequently used antidepressants during pregnancy are venlafaxine, a Serotonin Norepinephrine Reuptake Inhibitor (SNRI), bupropion, an atypical antidepressant, and mirtazapine, a Noradrenergic and Specific Serotonergic Antidepressant (NaSSA). After exposure to venlafaxine the risk of PNA seems to be comparable to the risk after exposure to SSRIs.<sup>79,80</sup> After exposure to mirtazapine PNA is described in one case report.<sup>46</sup> There are no reports describing PNA after exposure to bupropion. Data on infants exposed to mirtazapine or bupropion without symptoms of PNA are not published.

## Antipsychotics

Antipsychotics are defined as first generation antipsychotics, also called typical antipsychotics and second generation antipsychotics, also called atypical antipsychotics.

Literature on PNA after exposure to first and second generation antipsychotics is limited. However, there is evidence that exposure to both generation antipsychotics can lead to symptoms of PNA (Table 2).<sup>19,37,50,58,81,82</sup> Numbers on the incidence of PNA after exposure to antipsychotics are lacking.

Extrapyramidal symptoms, such as increased muscle tone, tremors, hyperactivity, agitation, dystonia, decreased sucking reflex, motor restlessness, abnormal movements and primitive reflexes, can also occur.<sup>44,50,58–61,82</sup> Most symptoms develop within 48 hours of birth and last for 2–6 days.<sup>19,50</sup>

## Mood stabilisers

Lithium is the most commonly prescribed mood stabiliser during pregnancy.<sup>83</sup> The most often described syndrome after intrauterine exposure to lithium is the floppy infant syndrome, which develops directly after birth. This syndrome consists of symptoms such as hypotonia, hypothermia, respiratory depression, cyanosis, arrhythmias and decrease sucking reflex.<sup>19,57,58,60–62,83–86</sup> Although exact figures on incidence are lacking, the incidence is suggested to be low.<sup>83</sup> Other described lithium related symptoms are neonatal thyroid toxicity, nephrogenic diabetes insipidus, cardiovascular and renal dysfunctions, hyperbilirubinemia, hepatotoxicity and PPHN. These symptoms are generally self-limiting.<sup>57,59,60,62,83,86</sup> Most symptoms develop within one day and disappear in 2–10 days after birth.<sup>62,87</sup> However, based on literature and our clinical experience, most infants do not show any symptoms.<sup>83,86</sup> Some authors advise to monitor lithium serum levels, thyroid levels, urea and electrolytes in the infant.<sup>84</sup> Since symptoms are rare and self-limiting we do not advise routine additional testing.

A higher serum lithium concentration ( $>0.64$  meq/liter) leads to an increased risk of obstetric and neonatal complications.<sup>18</sup> Therefore, it is advised to discontinue lithium when the pregnancy is in the state of regular contractions (in partu), and re-instate lithium directly post-delivery.<sup>18,82</sup> Since the floppy infant syndrome develops directly after birth and is dose related, it is clearly related to lithium toxicity (Table 1). However, symptoms can also occur in combination with low maternal or neonatal serum levels of lithium,<sup>62,83,86</sup> suggesting that some infants are more vulnerable to develop symptoms of toxicity compared to others. Unfortunately, evidence is too limited to draw conclusions on the exact etiology.<sup>83</sup>

Since lithium is the mood stabiliser most prescribed during pregnancy,<sup>83</sup> other mood stabilisers are less frequently used and therefore also less frequently studied. After exposure to lamotrigine, PNA symptoms, such as decreased muscle tone and sedation, are described.<sup>58</sup> The moment of onset and duration are not described.

Other commonly used mood stabilisers are valproic acid and carbamazepine. However, these drugs are not

recommended during pregnancy since there is an elevated risk of malformations and long term complications after exposure to these drugs in utero.

## Benzodiazepines

Benzodiazepines are frequently prescribed during pregnancy. Approximately 3% of all pregnant women uses this type of medication.<sup>12</sup> After exposure to benzodiazepines during the last trimester of pregnancy, infants may develop symptoms of the floppy infant syndrome, as well as PNA, which can also merge into each other.<sup>19,43,54,58,60–62,88</sup> Figures on the incidence of both syndromes are not available.

Factors which influence the development of neonatal symptoms include the pharmacokinetic properties of the benzodiazepine, degree of placental passage, duration of drug ingestion, dose, moment of last drug ingestion and metabolism and excretion by the infant.<sup>58,89</sup> The floppy infant syndrome is most likely due to benzodiazepine toxicity. High medication dosages (equivalent of diazepam  $>30$  mg) in combination with benzodiazepines with a long half-life, such as nitrazepam and diazepam, give the highest risk, since this leads to accumulation in infants (Table 1).<sup>54,58,61,89</sup> Benzodiazepines with a short half-life, such as oxazepam and temazepam, do not lead to toxicity in most cases. However, the risk of withdrawal is increased compared to benzodiazepines with a long half-life (Table 1).<sup>54,89</sup> Symptoms of the floppy infant syndrome develop directly after birth and can persist for hours to days. Symptoms of PNA mostly develop within hours after birth and can persist for months.<sup>54,62,89</sup> Since the floppy infant syndrome can cause severe morbidity, prescription of benzodiazepines in the last trimester of pregnancy is not recommended.

## Influential factors

Some infants develop symptoms of PNA while others do not. There is limited evidence on factors that create vulnerability to develop PNA. In the next section we will discuss existing literature on possible influencing factors of PNA.

## Prematurity

One study described an increased risk of PNA in premature infants, arguing that these infants show more lung and central nervous system immaturity.<sup>42</sup> Another study did not find this relationship.<sup>70</sup> Some authors hypothesised that prematurity can also be protective for PNA, since this has also been observed in infants exposed to illicit drugs.<sup>23,32</sup>

## Intoxications

Use of alcohol, nicotine and illicit drugs during pregnancy can also cause PNA.<sup>32,90</sup> Based on our experience there is an increased risk of PNA after exposure to these substances in combination with psychotropic drugs. However, literature on the combination of respectively alcohol and illicit drugs with psychotropic drugs is lacking. Although smoking can lead to withdrawal symptoms,<sup>90</sup> studies which examined the effect of smoking on PNA after exposure to psychotropic drugs concluded that smoking did not elevate the risk of PNA.<sup>42,70,91,92</sup>

## Exposure to multiple psychotropic drugs

Only one study examined whether the risk of PNA increased after exposure to multiple psychotropic drugs. Infants exposed to paroxetine combined with clonazepam revealed more PNA symptoms compared to infants exposed to monotherapy of SSRIs during the last trimester of pregnancy.<sup>27</sup> In conclusion, an association between the use of multiple psychotropic drugs and PNA is plausible. However, additional research is necessary in order to investigate this possible association.

## Dosage

After exposure to lithium and benzodiazepines, a relation between maternal dosage and PNA symptoms has been described.<sup>18,27,93</sup> Literature is inconclusive regarding SSRIs.<sup>17,26,27,39</sup> However, an observational study in 247 infants exposed to SSRIs, mirtazapine or venlafaxine, performed by our research group, concluded that there was no relation between the risk of PNA and dosage.

One study investigated the relation between the plasma concentration of clomipramine and symptoms of PNA and showed a weak correlation.<sup>41</sup> The relation between PNA and the dosage of other psychotropic drugs has not been published.

## Timing and duration of exposure

One study described that infants exposed to SSRIs during the last two weeks of pregnancy have the same incidence of PNA compared to infants not exposed to SSRIs during this period. The authors postulate that some adverse neonatal outcomes may not be the result of an acute pharmacological condition such as toxicity or withdrawal.<sup>94</sup> A second study by the same study group showed that in contrast to timing, duration of SSRI exposure was significantly correlated with poor neonatal outcomes.<sup>39</sup>

With regard to lithium, the timing of the last dosage does influence the perinatal outcome (as described earlier).

## Type of feeding

A study of infants exposed to clomipramine did not reveal a relation between PNA and type of feeding.<sup>41</sup> However, two studies in infants exposed to opioids in utero showed that breastfed infants developed less PNA compared to formula fed infants.<sup>95,96</sup> The previously mentioned observational study of our research group concluded that breastfeeding is protective for PNA in 247 infants exposed to SSRIs, mirtazapine or venlafaxine in utero. This finding can be explained by the excretion of small amounts of psychotropic drugs into the breast milk, which might lead to a slower decrease and therefore to less symptoms of PNA.<sup>17,97</sup> Another possible explanation is the increase of skin to skin contact during breastfeeding.

## Maternal psychiatric symptoms

Depression or anxiety during and after pregnancy may lead to irritation, inconsolable crying and decreased activity in infants.<sup>7,8,36–39</sup> Two studies examined the relation between the amount of depressive symptoms and PNA, though results were conflicting.<sup>70,91</sup>

## Genetic factors

Regarding SSRIs, an interaction between genetic factors and environment probably influences the occurrence of PNA.<sup>27,48,52,98</sup>

Fluoxetine, paroxetine and sertraline are metabolised by CYP450 2D6.<sup>27</sup> Therefore, in mothers with a deficiency of this cytochrome (also called poor metabolizers), plasma concentrations of these SSRIs are elevated which can increase the risk of toxicity in the infant.<sup>27,48</sup>

Furthermore, polymorphism in the promoter region of the serotonin transporter gene, SLC6A4, leads to differential gene expression, and consequent differences in clinical effects of SSRIs in adults and infants.<sup>48,98</sup>

## Observation of PNA

In order to objectify possible symptoms of PNA, standardised observation of mother and child at the maternity ward is preferred. Admission at the Neonatal Care Unit (NCU) is not necessary since PNA is mostly mild and admission at the maternity ward enhances attachment between mother and child. Only when PNA symptoms are severe, such as severe tremors or convulsions, admittance to the NCU is warranted.<sup>23</sup>

If PNA symptoms do not occur, an observation period of 48–72 hours is sufficient.<sup>23,24,26,55,99</sup> This applies to all types of psychotropic drugs. When PNA symptoms are present it

is advisable to observe the infant until the PNA symptoms are fully resolved.<sup>100</sup> A shorter observation period entails the risk of development of symptoms at home. Since the symptoms are nonspecific it is difficult to instruct parents. In addition, an infant with symptoms of restlessness with unknown origin can possibly provoke psychiatric symptoms, such as anxiety or depression in mothers with an existing psychiatric disorder.

## Scoring system

To recognise, observe and objectify the development and progression of PNA, a scoring system is essential.<sup>37,101</sup> At present there is no validated scoring system for observation of PNA in infants exposed to psychotropic drugs in utero. However, the Finnegan scoring list is widely used as an observation tool for PNA, although this list was originally designed to assess PNA after exposure to opiates.<sup>23,24,26,32,37,55,76,102</sup> The list consists of 21 symptoms with a point scale ranging from 0 to 5 for each item. A score of 4–7 is indicative for mild symptoms of PNA and a score of 8 and above is considered to illustrate severe symptoms of PNA. Trained nurses administer the score every 8 hours. In case of a score of 8 or higher observation is increased to every 2 hours.<sup>24</sup> To enhance reliability it is important that nurses and doctors are trained in administering the Finnegan scoring list. Since some symptoms, such as loose stools, are not specific for PNA, the score can be elevated in absence of PNA. For this reason interpretation of the score has to be carried out by the pediatrician on daily basis. In cases where the Finnegan score is 8 or higher, the pediatrician should be consulted.

## Differential diagnosis and additional testing

Since infants have a limited repertoire of nonspecific activities, it can be difficult to distinguish between PNA and other neonatal syndromes. The differential diagnosis of PNA consists of infection, metabolic or neurologic problems, hyper viscosity, and excitation syndromes, such as small for gestational age.<sup>32,37,41</sup> In case of debate on the origin of the presenting symptoms, these diagnoses have to be excluded. However, to prevent overmuch additional testing, it is important to observe infants by specialized caregivers in order to recognise PNA.<sup>17,22,24,32,37,42,69</sup> The pediatrician evaluates the moment of onset of symptoms, the course and type of symptoms and examines the infant. When symptoms are present which are not typical for PNA, such as fever, or a nonspecific course of symptoms, such as symptoms that develop >48 hours postpartum, other diagnoses have to be excluded.

Alcohol or illicit drug use during pregnancy can also cause PNA.<sup>32</sup> When there is any doubt on possible intoxications during pregnancy, toxicological urine screening is indicated.<sup>55</sup>

## Treatment

Most cases of PNA are mild, of short duration and self-limiting, without need for treatment.<sup>5,19,22,24,26,42,46,69</sup> Supporting measures, such as frequent small feedings on demand, swaddling and increase of skin to skin contact with mother, leading to an improved temperature regulation, and more regular breathing, is mostly sufficient.<sup>5,19,24,26,37,42,46,69</sup> When there is severe PNA and supporting measures are not sufficient, phenobarital is a safe, therapeutic option.<sup>22–24</sup> This symptomatic treatment is also used in cases of opiate withdrawal.<sup>22–24</sup> Although there are no studies on

**Table 3** Recommendations regarding observation and treatment of Poor Neonatal Adaptation (PNA)

### General recommendations

In otherwise healthy infants routine additional laboratory tests in order to exclude possible neonatal complications are not required. Observation at the maternity ward is preferred. Only when PNA symptoms are severe, admittance to the Neonatal Care Unit is necessary.

Discourage the use of illicit drugs and alcohol since these substances also cause PNA.

An observation period of 48–72 hours is sufficient when no PNA symptoms occur.

When PNA symptoms are present observe the infant until the PNA symptoms are fully resolved.

The Finnegan scoring list has to be administered every 8 hours by trained nurses.

In case of a score of 8 or higher this has to be intensified to every 2 hours. Interpretation of the score has to be carried out by the pediatrician.

In case of debate on the origin of presenting symptoms other diagnoses such as infection, metabolic or neurologic problems, hyper viscosity, and excitation syndromes like small for gestational age have to be excluded.

In case of any doubt on possible intoxications during pregnancy toxicological urine screening is indicated.

Supporting measures such as frequent small feedings on demand, swaddling and increase of skin to skin contact with mother is mostly sufficient.

When there is severe PNA and supporting measures are not sufficient, phenobarital is a safe therapeutic option. When using the Finnegan scoring list  $\geq 2$  scores of 8 or higher in between 2 hours is an indication of pharmacotherapy.

### Drug specific recommendations

After exposure to lithium during pregnancy, discontinue when the patient is in partu and re-instate directly post delivery.

The dosage of antidepressants seems not related to the risk of development of PNA. Therefore, lowering the dosage is not useful in order to prevent PNA.

Encourage breastfeeding after exposure to SSRIs, mirtazapine or venlafaxine, since this probably reduces the risk of PNA.

the efficacy of phenobarbital in this application, efficacy in infants with irritation or convulsions is established and safe.<sup>103</sup> When the Finnegan scoring list is used  $\geq 2$  scores of 8 or higher within a 2 hour period is an indication of pharmacotherapy at the NCU.<sup>24</sup>

Many parents have feelings of guilt when symptoms of PNA are present.<sup>37</sup> It is important to be clear about the diagnosis on one hand, and explain the transitory, self-limiting course of the symptoms on the other.<sup>26,27</sup> Table 3 presents recommendations regarding the observation and treatment of PNA.

## Long term effects of PNA

The effect of PNA on the neurological development in children of 2–6 years is studied by Klinger.<sup>104</sup> In this study 30 infants with PNA, and 52 infants without PNA, all exposed to SSRIs, were followed. There was no significant difference in IQ, findings during neurological examination and total development score<sup>104</sup> (measured by the Denver development test). The subscale ‘social behaviour’ was significantly lower in infants with PNA postpartum.<sup>104</sup> Oberlander assessed the development in children of 2 and 8 months exposed to SSRI and clonazepam and noted no significant differences between infants with and without PNA.<sup>27</sup> Additional research is necessary to examine the long terms effects of PNA.

## Conclusion

After exposure to psychotropic drugs in utero infants are at risk to develop symptoms of PNA. Although there is debate on the exact etiology of PNA the most plausible explanation is withdrawal, toxicity, or a combination of both. Distinguishing PNA of toxicity is difficult since symptoms of PNA and toxicity are largely similar.

PNA consists of neurologic, autonomic, respirator and gastro-intestinal symptoms, which are largely similar after exposure of antidepressants, antipsychotics and benzodiazepines. In most infants symptoms are mild, such as sleep disturbances. Severe symptoms, such as convulsions, are rare. Of all infants exposed to antidepressants in utero, around 20%–50% develop symptoms of PNA. Figures on the incidence of PNA after exposure to antipsychotic drugs, mood stabilizers or benzodiazepines are lacking. Most symptoms of PNA develop within 48 hours and last for 2–6 days. However, after exposure to benzodiazepines, symptoms can persist for months. If symptoms do not occur in the first 48 hours, development of PNA is unlikely.

Influential factors of PNA are scarcely studied. There is conflicting evidence regarding the effect of prematurity and maternal psychiatric symptoms on PNA. After exposure to SSRIs, mirtazapine or venlafaxine in utero, breastfeeding is presumed to be protective for development of PNA. Furthermore, the dosage of antidepressants seems not to be related to the risk of PNA. Therefore, lowering the dosage of antidepressants is not useful in order to prevent PNA. This does not apply for benzodiazepines and lithium.

Observation on the maternity ward is preferred, since PNA is mostly mild and admission at the maternity ward enhances attachment between mother and child. Only when PNA symptoms are severe is admittance to the NCU necessary. If PNA symptoms do not occur, an observation period of 48–72 hours is sufficient. This applies to all types of psychotropic drugs. When PNA symptoms are present it is advisable to observe the infant until the PNA symptoms are fully resolved.

To observe and objectify the development and progression of PNA a scoring system is essential. The Finnegan scoring list has to be administered every 8 hours by trained nurses. In case of a score of 8 or higher this has to be intensified to every 2 hours. Since the Finnegan scoring list lacks specificity, interpretation of the score should be carried out by a pediatrician.

Since infants have a limited repertoire of nonspecific activities, it can be difficult to differentiate between PNA and other neonatal syndromes. The differential diagnosis of PNA consists of infection, metabolic or neurologic problems, hyper viscosity, and excitation syndromes such as small for gestational age. In case of debate on the origin of presenting symptoms these diagnoses have to be excluded. When there is any doubt on possible intoxications during pregnancy, toxicological urine screening is indicated.

Most cases of PNA are mild, of short duration and self-limiting without need for treatment. Supporting measures such as frequent, small feedings on demand, swaddling and increased skin to skin contact with mother, leading to an improved temperature regulation and a more regular breathing, is usually sufficient. When there is severe PNA and supporting measures are not sufficient, phenobarbital is a safe therapeutic option. When using the Finnegan scoring list  $\geq 2$  scores of 8 or higher within 2 hours is an indication of pharmacotherapy.

Long term effects of PNA are examined in two studies.<sup>27,104</sup> There seem to be no major effects; however, additional

studies are necessary in order to draw any conclusions on this matter.

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