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Neonatal adaptation issues after maternal exposure to prescription drugs: withdrawal syndromes and residual pharmacological effects

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Abstract

Exposure to drugs during pregnancy has the potential of harming the offspring. Teratogenic effects are the most feared adverse outcomes in newborns. However, a wide spectrum of less known, usually reversible and often acute, neonatal adverse events can also occur due to drug intake by mothers during pregnancy and particularly in close proximity of the delivery. These effects can be explained by withdrawal syndromes caused by the delivery-related discontinuation of the drug disposition from the mother to the fetus, or by a residual pharmacological effect due to an accumulation of the drug in the blood and tissues of the newborn. Although these adverse reactions have been described mainly for abuse drugs, several prescription drugs have been also involved. These include mainly psychotropic medications such as opioids, antidepressants, antiepileptics and antipsychotics. With few exception, validated protocols for the assessment and management of withdrawal or residual pharmacological effects of these drugs in neonates are often lacking or incomplete. Spontaneous reporting of these adverse reactions seems limited, although it might represent a useful tool for improving our knowledge about drug-induced neonatal syndromes. This narrative review is aimed at the description of drugs and drug classes for which a licit maternal use in the pre-delivery period has been associated with neonatal non-teratogenic disorders. For each drug class, epidemiology, clinical features, biological mechanism and management of these adverse reactions have been discussed in detail.

Key points

- Newborns exposed in pregnancy to psychotropic drugs may experience neonatal syndromes, including neonatal withdrawal symptoms and/or residual pharmacological effect
- Psychotropic drugs most involved in neonatal adaptation issues are opioids, antidepressants, antiepileptics (including barbiturates and benzodiazepines), and antipsychotics

Introduction

It is well known that exposure during pregnancy to compounds endowed with pharmacologic activity has the potential of harming the offspring. Teratogenic effects are definitely the most feared adverse outcomes in newborns.[1] However, a wide spectrum of less known, usually reversible and often acute, adverse events can also occur in newborns due to drug intake by mothers during pregnancy and particularly in close proximity of the delivery. With some exceptions, the majority of these adverse events likely results from withdrawal syndromes. Indeed, the delivery determines a discontinuation of the drug intake that the baby was receiving from the mother. In the traditional Pharmacovigilance classification of adverse drug reactions, these events belong to the "E" (end of use) category.[2] In other settings, these effects may result from "residual" activities of drugs, particularly those endowed with long half-life (type "A" - augmented - adverse drug reactions).[2] In these settings, the immaturity of metabolic functions in newborns are likely to play an important role.[3] Early identification of the origin of symptoms is of primary importance for the appropriate management of newborns. Indeed, in case of withdrawal, the newborn may benefit from a reintroduction of the discontinued drug or its safer alternative within the same drug class; by contrast, in case of residual toxicity, being exposed further to the withdrawn drug may have detrimental effects on the newborn.[4]

Withdrawal symptoms have been extensively investigated since many years in drug-addicted pregnant women exposed to abuse substances. Nevertheless, some prescription drugs have been also reported to be associated with such events in neonates. Their clinical presentation is variable and usually includes several signs and symptoms ranging from behavioral abnormalities to neurological impairments. For this reason, these effects are usually defined as a syndrome, which is sometimes designated as "neonatal abstinence syndrome",[5] "neonatal withdrawal syndrome",[6] "neonatal adaptation syndrome"[7] or even "neonatal behavioral syndrome"[8] depending on the putative mechanism. In this narrative review, we will use the definition "neonatal abstinence syndrome" (NAS), which is the most frequently employed to describe withdrawal symptoms, making a distinction from other kind of events, which can be more likely explained by a residual pharmacological effect of the drug on the fetus or newborn.

Overall, based on the above background, this narrative review is aimed at the description of drugs and drug classes for which a licit maternal use in the pre-delivery period has been associated with neonatal non-teratogenic disorders. These disturbances have been reviewed and described in detail on the basis of currently available evidence.

Methods

English-language literature indexed in MEDLINE was explored without limits of time up to December 31st, 2015, using the terms "neonatal abstinence syndrome", "neonatal withdrawal syndrome", "neonatal behavioral

syndrome" and "neonatal adaptation syndrome". Since there is no standard clinical definition for this syndrome, case reports dealing with neonatal behavioral and neurological alterations after exposure to any drug were used to generate clusters of symptoms suggestive of this syndrome. These clusters were then used as search terms to identify studies reporting the frequency of such neonatal outcomes (including single behavioral signs, poor neonatal adaptation, and admission to neonatal intensive care unit [NICU]). The reference lists of identified articles were examined carefully for additional pertinent publications.

For inclusion in the present review, meta-analyses, clinical trials, observational studies, case series and single case reports had to evaluate neonatal events consistent with the syndrome after exposure to any prescription drug. Studies addressing the neonatal effects of drugs used for recreational purposes during pregnancy were excluded. Articles evaluating only teratogenic effects, congenital malformations, miscarriage, stillbirth and abortion were also excluded. Abstracts presented at national and international meetings were not included.

Results

Drugs associated with neonatal symptoms, consistent with a drug withdrawal or a pharmacological residual effect consequent to pre-birth exposure, belong to several psychotropic drug groups and include opioids, antidepressants, antiepileptic drugs (AEDs) and antipsychotics. Notably, the lipophilic chemical nature of these drugs generally allows their placental disposition and/or excretion into breastmilk, in accordance with the pharmacokinetics of each drug, thus explaining the variability of perinatal exposure and neonatal effects among drugs. Table 1 summarizes the main clinical patterns of these neonatal syndromes. Each drug class has been then discussed in details in the following sections.

Opioids

Opioids represent the most investigated drug class for their involvement in the occurrence of neonatal neuro-behavioral syndromes. This is largely due to the illicit use of these drugs for recreational purposes since immemorial time. Contrarily to other drug classes, there is no discussion about the fact that the mechanism underling these symptoms result from residual pharmacological activity instead of a withdrawal effect, since the entire available literature always describe the symptoms as a NAS (Jansson, 2009). However, we can not excluded that some early symptom can be attributed to a residual opioid activity (see for instance Khan et al, 1997). Opioid-associated NAS has been documented in western countries since 1875, with a first case published in US in 1892.[5] In the USA, it has been estimated that from 2000 to 2009 antepartum opioids use increased from 1.19 to 5.63 per 1,000 live births.[9] Over the same period, the incidence of NAS increased from 7 to 27 cases per 1,000 admissions to NICU,[10] and related hospitalization costs per infant with NAS increased from $39,400 to $53,400.[9] The reason accounting for this epidemic remains unclear, even though most evidence points to prescription opioids, and not to their illicit use. In Canada, from 1992 to 2011, the incidence of opioid-related NAS increased by 15 folds (from 0.28 to 4.29 per 1,000 live births), and from 2006 to 2011 NAS could be ascribed to prescription opioids in 67% of cases.[11] In USA, from 2008 to 2012 about one third of fertile women was prescribed an opioid. In Norway, 6% of pregnant women filled at least one opioid prescription between 2004 and 2006.[12] A study performed in Tennessee estimated that 63% of the cases of NAS occurred in women receiving prescription opioids.[13] A large observational study (n=290,605), performed on the Medicaid database, indicated that the absolute risk of NAS due to prescription opioids, in the absence of other risk factors (history of opioid misuse or dependence, alcohol or other drug misuses, exposure to other psychotropic medications late in the pregnancy and smoking), was low (5.9 per 1,000 deliveries).[14] However, the risk increased with long term use as compared with the short term (relative risk: 2.05; 95% confidence interval [CI] 1.81-2.33), as well as for late pregnancy as use compared with early use (relative risk: 1.24; 95%CI 1.12-1.38), independently of additional risk factors.[14] Overall, 50-80% of opioid-exposed infants required a

pharmacologic treatment for NAS management.[15, 16, 5] Preterm infants have been reported as being at lower risk of opioid withdrawal, with less severe and/or prolonged courses.[17, 18]

Besides analgesic use, opioids are mainly prescribed for maintenance purposes in addicted women during pregnancy. The mainstay of this treatment is represented by the tapering of methadone or buprenorphine.[19] Evidence in favor of the use of buprenorphine over methadone is growing due to more favorable neonatal brain growth patterns with buprenorphine.[19] Although evidence supporting teratogenic effects of opioids is scarce,[20-23] the long term use during pregnancy has been associated with brain development impairments.[24, 25] Furthermore, although the occurrence of NAS has been reported for both methadone and buprenorphine,[26-32] it has been observed that prenatally buprenorphine-exposed neonates required significantly less morphine for NAS management, required a significantly shorter duration of NAS treatment, and had a significantly shorter hospital stay as compared with prenatally methadone-exposed neonates.[15, 33] Higher neurobehavioral score and less severe NAS have been described also in newborns after in utero exposure to buprenorphine, as compared with those exposed to methadone.[34] The relationship between methadone or buprenorphine dose and NAS severity is currently controversial, with some studies indicating an association and some not.[35-41] Other prescription opioids that have been associated with withdrawal syndrome include morphine,[42] codeine,[43-47] tramadol,[48-52] propoxyphene,[53-56] fentanyl,[57, 42] and pentazocine.[58-60] Besides individual genetic factors,[61] the onset of withdrawal signs and the peak of symptom severity likely depend on opioid pharmacokinetics. For instance, prenatal exposure to morphine displays a shorter time-to-onset of newborn withdrawal (average 36 hours), as compared with methadone (average 60 hours).[62] NAS associated with buprenorphine generally starts after approximately 12-48 hours and peaks at approximately 72-96 hours.[63] For tramadol, the onset was described within 35-48 hours, with a peak in 3-7 days.[48-50] For codeine, initial symptoms appears even after 2 hours, with a peak within 24-48 hours.[43, 46] Fentanyl-associated NAS was described to develop within 24 hours with a peak in 72 hours,[57, 42] even when the drug was administered by transdermal devices.[57]

The mechanism of opioid induced NAS is complex and not fully understood. Opioids are small lipophilic molecules that can easily cross the placental barrier.[16] One of the most accepted theories suggests a pivotal role for a second messenger, cyclic adenosine monophosphate (cAMP), responsible for signal transduction in several cellular systems. The activation of opioid receptors strongly inhibits adenyl-cyclase, thus preventing the synthesis of cAMP. After repeated opioid exposure, the cells attempt to compensate for the lack of cAMP by enhancing the expression of adenyl-cyclase. When opioid intake is discontinued, the hyper-expressed adenyl-cyclase is no longer inhibited, with consequent overproduction of cAMP. The latter leads to an excessive release of norepinephrine (NE), which then binds noradrenergic

receptors, causing overactivation of the autonomic nervous system that becomes responsible for the onset of signs and symptoms associated with the withdrawal syndrome.[64-67]

Opioid-related NAS can develop with a range of different symptoms that affect critical regulatory functions of post-natal adaptation, ranging from neurologic hyperexcitability (insomnia, irritability, hypertonia, hyperreflexia, tremors, and seizures), to gastrointestinal (GI) symptoms (vomiting, diarrhea, feeding disturbances), and sympathetic/parasympathetic dysregulation (sweating, hyperthermia, tachypnea, and congestion).[68, 69] Several scales and scores have been developed to assess NAS severity in opioid-exposed infants.[70] These are very heterogeneous and include, amongst the others: Neonatal Abstinence Syndrome Score, known also as Finnegan score, the most used in USA[71] in its modified versions (an example is displayed in table 2);[72] Narcotic Withdrawal Score (Lipsitz Score);[73] the Neonatal Narcotic Withdrawal Index;[74] Neonatal Narcotic Withdrawal Inventory;[75] MOTHER NAS Scale (a modified version of the Finnegan scale).[15] In newborns with NAS, these scores are estimated by caregivers every few hours. Based on their values, standard thresholds have been defined to establish the extent (e.g. dose) and duration (e.g. dose-titration scheduling for maintenance approaches) of pharmacological and non-pharmacological interventions.[9]

The management of opioid-induced NAS is also controversial. The most common approaches include non-pharmacological and pharmacological interventions.[64, 76] Among non-pharmacological interventions, the infant feeding methods are the most explored. In particular, the effect of feeding approach has been investigated in seven observational retrospective studies.[77-83] Although these studies are flawed by significant limitations and their results are not easily comparable,[70] their findings suggest that, in infants with NAS breastfeeding from mothers stable in methadone or buprenorphine maintenance (i.e. not using illicit opioids) is associated with an overall decrease in the need for pharmacological treatment (30% reduction), a decrease in NAS scores as well as a decreased duration of pharmacological therapy and hospitalization (3-19 days shorter).[70] Notably, methadone excreted in the maternal milk may theoretically provide an indirect maintenance treatment for babies with NAS. However, a study showed that methadone concentration in the blood of newborns breastfed by methadone-maintenance mothers is too low to explain a "pharmacological compensation" of the delivery-induced drug withdrawal.[84] Thus, in this setting, the beneficial impact of breastfeeding on NAS symptoms likely results from the positive comfort associated with maternal contact.[84] Other non-pharmacologic approaches, for which lesser evidence of benefit in NAS is available, include rooming-in, bed type, infant position and non-insertive acupuncture.[70]

The pharmacological management of opioid-induced NAS may include a reintroduction of the discontinued drug (or an alternative safer opioid) or the use of symptomatic treatments. Orally administered morphine (morphine chloride or even in the form of opium tincture, 0.3-1.0 mg/kg/day, administered every 3-4 hours, titrated to effect and reduced

every 24-48 hours), or methadone (titrated in the range of 0.3-1.0 mg/kg/day, administered every 4-12 hours and then weaned) are the most commonly used first-line medications, although there is no evidence on what drug is superior.[70, 85] Buprenorphine has been also investigated in recent studies, showing a decrease in treatment duration and reduced hospital stay as compared with methadone[86] or opium solution.[87] Second lines of treatment include phenobarbital, clonidine and clonazepam.[16, 88, 64, 89] Notably, randomized clinical trials (RCTs) investigating the above pharmacological approaches are small, employed different assessment tools and protocols to escalate and wean medications, and adjusted for different covariates, and therefore they are very difficult to compare. In RTCs, morphine was shown to be more beneficial than phenobarbitone (significantly shorter duration of treatment and reduced need for second line treatment and NICU admission),[90] but less effective than opium tincture (n=33, longer length of treatment and length of hospitalization).[91] In another RCT, conducted on 25 infants with NAS, buprenorphine displayed a reduced length of hospital stay as compared with neonatal opium solution.[92] Finally, the benefits of add-on therapies to first line opioids, with clonidine and phenobarbital, have been investigated, showing a decrease in the duration of first line therapy, with phenobarbital showing shorter duration of treatment when directly compared with clonidine.[93, 94, 89]

Antenatal methadone exposure has been reported also to be associated with transient prolongation of QT interval in newborns, usually within the first 2 days of life.[95] This effect may partly explain the high rate of infant sudden death syndrome in newborns from mothers on maintenance with methadone, although the pathophysiology of this adverse outcome is likely to be multifactorial in nature.[96] In particular, this adverse effect has been ascribed to a direct toxicity after placental transfer of methadone and not to a withdrawal syndrome.[95]

Antidepressants

It has been estimated that 13.5% of pregnant women present depressive disorders.[97] Depression may have a negative impact on pregnancy outcomes, including low birth weight and prematurity, irritation, agitation, lethargy, reduced attention, and relationship issues between mother and child, with consequent learning and behavioral problems during childhood.[98, 99] Therefore, treatment with antidepressants is usually recommended.[97] In Europe, 1-3% of pregnant women take antidepressants (mainly selective serotonin reuptake inhibitors [SSRI, including fluoxetine, paroxetine, sertraline, citalopram, escitalopram and fluvoxamine] and serotonin-norepinephrine reuptake inhibitors [SNRI, including venlafaxine and duloxetine] because of their effectiveness and safety), while in the USA the percentage is about 4-13%. Overall, 25% of women treated with antidepressants continues their treatment during pregnancy, and 0.5% of women starts a treatment during pregnancy.[100]

In 2004, the US Food and Drug Administration (FDA) issued a class labeling change for SSRI and SNRI antidepressants, introducing a warning about the association of third trimester exposure to antidepressants and signs and symptoms consistent with NAS.[99] About 20-77% of children exposed in utero to SSRIs has been estimated to develop symptoms of NAS,[98] with paroxetine and fluoxetine having the higher incidence as compared to other SSRIs.[101-104] The incidence of NAS in newborns exposed in utero to tricyclic antidepressants (TCA) is about 20-50%.[98, 105] NAS symptoms associated with SSRIs, SNRIs and TCAs are similar and include a variety of mild to moderate behavioral, autonomic and neurological signs such as irritability, persistent crying, chills, tremors, restlessness, feeding difficulties, jaundice, vomiting, hypotonia, hypertonia and sleep disorders. [98, 106-120] However, NAS may rarely occur also with severe symptoms requiring NICU management, such as respiratory distress syndrome and seizures.[108, 121, 122, 119, 123-125, 109, 110, 126, 127] Motor signs, respiratory, GI and metabolic dysfunctions, usually mild to moderate and self-limiting, occur in the majority of cases shortly after birth, within the first 24-72 hours, and generally disappear within few weeks. Residual pharmacological effects of antidepressants occur immediately after the birth, and symptoms may depend on the specific antidepressant. Following exposure to TCAs, anticholinergic symptoms, such as urinary retention and constipation can be observed.[98] For the SSRIs, symptoms are expected to be similar to those of a serotonergic syndrome in adults.[98]

Several studies have attempted an estimation of the risk of NAS in babies exposed in utero to antidepressants. Late SSRI exposure is estimated to carry an overall risk ratio of 3.0 (95%CI 2.0-4.4) for NAS as compared with non-exposed or earlier exposures.[97] Grigoriadis et al.[128] found a significant increase in the risk of NAS as a result of exposure to antidepressants during pregnancy (odds ratio [OR]: 5.7; 95%CI 3.25-7.90), and its signs such as respiratory distress (OR: 2.20; 95% CI 1.81-2.66) and tremors (OR: 7.89; 95%CI 3.33-18.73).[128] In a study conducted on 997 infants, whose mothers had used antidepressants during the latter part of pregnancy, excess neonatal problems were observed more frequently after the use of TCAs than SSRIs; in particular, an increased risk was detected for respiratory distress (TCAs OR: 2.20; 95%CI 1.44-3.35; SSRIs OR: 1.97; 95%CI 1.38-2.83), neonatal hypoglycemia (TCAs OR: 2.07; 95%CI 1.36-3.13; SSRIs OR: 1.35; 95%CI 0.90-2.03), and neonatal seizures (TCAs OR: 6.8; 95%CI 2.2-16.0; SSRIs OR: 3.6; 95%CI 1.0-9.3), but not for neonatal jaundice (TCAs OR: 1.37; 95%CI 0.88-2.12; SSRIs OR: 0.96; 95%CI 0.63-1.46), after exposure to TCAs as compared to SSRIs.[125] As far as SNRIs are concerned, late-pregnancy exposure to duloxetine can be associated with a poor risk of NAS, but the extent of this risk remains unclear.[129] Notably, the risk of NAS after exposure to venlafaxine seems to be comparable to the risk after exposure to SSRIs.[98]

Antidepressants are known to cross the placental barrier.[130-132] The mechanism of NAS associated with SSRIs is not fully understood and likely reflects a similar condition of withdrawal as observed in adults.[133] Some

authors have speculated about a temporary deficiency of synaptic serotonin occurring after an abrupt withdrawal of an SSRI.[134] Indeed, during treatment serotonin re-uptake is blocked and therefore synaptic serotonin levels remain elevated. This circumstance could induce a down-regulation of post-synaptic serotonin receptors (desensitization), which could remain in their relatively hypoactive condition for days to weeks.[134] At delivery, the blockade of serotonin re-uptake is abruptly interrupted and serotonin synaptic levels are expected to rapidly decrease. This "serotonin shortage" and receptor desensitization are thought to translate into a decrease of serotonin transmission, which can have significant consequences not only on the serotonin system but even on the dopaminergic, noradrenergic and cholinergic neurotransmissions, owing to the modulating control exerted by serotonin on these pathways in the central nervous system (CNS). The alterations resulting from this neurotransmitter interplay may explain the development of NAS symptoms.[135, 101, 136, 134] Withdrawal from TCAs has been brought back to a cholinergic and adrenergic theory.[105] The cholinergic theory is based on the fact that TCAs bind both peripheral and central muscarinic receptors, with blockade of cholinergic activity, and consequent up-regulation of muscarinic receptors (that is an explanation for tolerance to cholinergic adverse effects). When TCAs are discontinued, the upregulation of muscarinic receptors promotes a condition of "cholinergic overdrive" in some patients.[135] Notably, this mechanism has been described for paroxetine too, and this circumstance may provide an explanation for the higher frequency of the NAS associated with paroxetine as compared with other SSRIs.[97]

The adrenergic theory holds that treatment with TCAs causes inhibition of norepinephrine reuptake, with an increase in the synaptic concentration of this mediator. Initially, this condition leads to a decrease in norepinephrine turnover and in a lowering of norepinephrine release mediated by the overactivation of presynaptic α2-adrenoceptors. However, with the prolonged drug intake, a down-regulation of presynaptic α2-adrenoceptors occurs, leading to a further increase in the synaptic accumulation of norepinephrine. Following an abrupt discontinuation of TCA therapy, the synaptic levels of norepinephrine would be expected to decrease rapidly, however owing to the desensitization of presynaptic α2-adrenoceptors, a significant facilitation of norepinephrine release is maintained for a certain period, with a subsequent temporary persistence of the activity of noradrenergic neurotransmission.[135]

The diagnosis of antidepressant-associated NAS is complicated by the lack of standard diagnostic criteria, the difficulty of discriminating between NAS and residual pharmacological effects, the overlapping between the two clinical pictures, and the metabolic immaturity of newborns.[98, 135, 137, 129] For SSRIs/SNRIs, the main differences between NAS and residual pharmacological effects (usually consistent with a picture of serotonergic overstimulation) are likely in the time-to-event onset and the serum concentrations of the drug or serotonin metabolites (i.e. 5-hydroxyindoleacetic acid [5-HIAA]) in the umbilical cord. Indeed, in the case of residual serotonin toxicity, symptoms occur soon after the

delivery and high concentrations of antidepressants can be detected in the umbilical cord serum.[98] By contrast, NAS symptoms occur within 24-72 hours from labor,[118, 138, 139] and 5-HIAA levels are low and the concentration inversely related with symptoms severity.[140] The time-to-onset and duration of withdrawal symptoms or serotonergic overstimulation in exposed infants depend of the pharmacokinetics of the specific antidepressant.[106] The half-life of the antidepressant might influence the risk of NAS and serotonin toxicity, while the drug dose does not seem to be related with the occurrence or severity of NAS.[98]

Commonly used scores for evaluating the severity of NAS (i.e. Finnegan score)[72] have never been validated for this drug class. In most cases, symptoms are non-specific, and the diagnosis is carried out by excluding infectious problems, neurological diseases, intoxications and metabolic dysfunctions (hypoglycemia, hypocalcemia, etc.).[98, 141, 137] Maternal depression is an important confounding factor.[135] Oberlander et al.[142] showed that only the neonatal respiratory distress was a symptom related to antidepressant withdrawal, while other neonatal symptoms, such as feeding problems, jaundice and even convulsions, were found in both exposed and non-exposed infants from depressed mothers.[142] Moreover, pregnant women taking antidepressants are often exposed to other treatments with psychotropic drugs,[109] such as benzodiazepines (BZDs),[127] which might contribute to the occurrence of neonatal adverse effects.[103] Children undergoing a NAS typically display normal cognitive abilities, but they may have a higher risk of developing social and behavioral abnormalities than children without NAS. A follow-up of these infants has been recommended.[143]

Most NAS cases are mild in nature, being characterized by short duration and self-limiting symptoms, and, therefore they do not generally require a treatment.[144] The medical management consists mainly in a close monitoring of the newborn exposed to antidepressants in utero at least in the first hours after the delivery,[145] should the syndrome occur fully, a supportive care must be provided.[102, 146, 147, 97, 98, 137] The evolution of the clinical picture can be monitored using the Finnegan score: a score of 8 on a survey of more than 3 consecutive measurements is considered a serious NAS requiring medication or transfer to NICU.[137, 98, 141, 126] Phenobarbital has shown a good safety profile in newborns and it can be used to control irritability, stiffness and seizures.[141, 148, 108, 98, 137, 147] Breastfeeding has shown to reduce the severity and duration of NAS.[98, 145] Available evidence does not allow to exclude that in mothers receiving SSRIs during lactation this beneficial effect can be partly explained by the excretion of low amounts of these antidepressants into the maternal milk. In this way, drug exposure would not be abruptly interrupted by delivery. Therefore, some authors recommend breastfeeding as a preventive strategy for SSRI-induced NAS.[98, 149-151, 145] In this case, the differential diagnosis between SSRI/SNRI serotonin withdrawal and toxicity is a critical issue for the clinical management.[138, 4] Indeed, in case of withdrawal, the newborn may benefit from being treated with a SSRI through lactation; by contrast, in case of serotonin toxicity, being exposed to an SSRI may have detrimental effects.[4]

Antiepileptic drugs (AEDs)

AEDs include a variety of drugs that are highly heterogeneous both for mechanisms of action and indications. These drugs have been associated with the development of neonatal abnormalities related to drug exposure in utero, described as neonatal withdrawal symptoms or residual toxicities. In this section, neonatal syndromes related to maternal exposure to AEDs have been reviewed with a focus on barbiturates and BZDs, for which specific information are available in the medical literature.

Epilepsy has been estimated to affect 0.3-1% of pregnant women and its treatment with AEDs should be aimed at carefully balancing the risk of seizures for both the mother and the baby[152] with the risk of teratogenic and other adverse effects in the newborn.[153-158] In a recent study, performed on data from the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) database, it was estimated that from 2001 to 2007 the use of AEDs during pregnancy increased, mainly owing to a 5-fold increase in the use of newer AEDs. Older AEDs (i.e. BZDs, valproic acid [VPA], carbamazepine and phenytoin) were the most commonly used drugs, with BZDs being involved in over half of the exposed pregnancies. Among the newer AEDs, the most frequently used drugs were: gabapentin; lamotrigine; topiramate; oxcarbazepine; levetiracetam. The most prevalent indications were psychiatric disorders, pain disorders and epilepsy.[159] Second-generation AEDs (e.g. lamotrigine) are progressively replacing first-generation AEDs (e.g. VPA) both in monotherapy and polytherapy in pregnancy.[160-162] The trend towards an increased use of the newest AEDs in pregnant women is in line with the clinician concerns about the teratogenic risk associated with older compounds, such as VPA, phenytoin, phenobarbital, primidone and carbamazepine. Newer AEDs appear to be safer in pregnancy as compared with older AEDs, even though data are still limited to issue solid recommendations.[163, 164, 159]

NAS has been described in newborns exposed prenatally to AEDs. Several small observational studies have attempted an estimation of the frequency of withdrawal syndrome in babies born from mothers exposed to AEDs during pregnancy. A frequent limitation of investigations attempting a comparison is the selection of non-epileptic mothers as reference group, which does not allow to exclude that epilepsy may have a role in the occurrence and severity of symptoms. A prospective study (n=123) estimated that the frequency of withdrawal-related jitteriness, in babies exposed in utero to phenytoin alone, VPA alone or a combination of other AEDs (VPA, carbamazepine, phenytoin, phenobarbital, sulthiame, and primidone), was 18% vs 0% in non-epileptic women.[165] Another study[166] evaluated the effects of in utero exposure to AEDs using apathy and hyperexcitability scores, and showed higher apathy scores for phenobarbital and phenytoin, and higher hyperexcitability scores for VPA, as compared with a non-epileptic reference group. Dean et al. (2002) observed that 50 (20%) of 255 newborns exposed in utero to AEDs experienced a withdrawal syndrome with

a relative risk of 7.45 (95%CI 1.06-52.37), when compared to 1 case (3%) over 38 non-exposed epileptic pregnancies.[155] Phenobarbital monotherapy was less likely to be associated with neonatal withdrawal symptoms (13%), while polytherapy was most likely to be (30%, p=0.001). Neonatal withdrawal was significantly more frequent in newborns exposed to VPA monotherapy (24%, p=0.006) and phenytoin monotherapy (21%, p=0.018) than in the non-exposed group (3%).[155] A small study described 10 cases of NAS among 22 newborns exposed in utero to VPA as monotherapy or combined with carbamazepine.[167] A case-control study described 4 cases of NAS among 37 newborns exposed to VPA monotherapy or in combination with primidone, carbamazepine or lamotrigine, as compared with no cases in control groups (untreated epileptic women or healthy women).[153]

Symptoms of AED-related NAS are similar to those of opioid withdrawal. They usually occur during the first few hours after birth, up to one week after delivery, and may persist for weeks and months.[168-171] Symptoms may include: irritability; jitteriness; abnormal tone; hypotonia; seizures; feeding disorders; hypoglycaemia; apnoeic episodes and vomiting.[152, 166, 155, 172, 173] Hypotonia and feeding problems may depend on the sedative effect of AEDs.[169] Notably, withdrawal symptoms have been described as a part of the "fetal anticonvulsant syndrome", characterized also by malformations, developmental disorders and facial dysmorphism.[172] VPA in monotherapy or polytherapy (in combination with phenytoin, carbamazepine, ethosuximide, or primidone), oxcarbazepine and lamotrigine, used during pregnancy for the treatment of epilepsy, have been described in case reports as the suspected causative drugs for NAS.[152, 174, 169, 175] Withdrawal symptoms were reported also in infants born from women treated during pregnancy with gabapentin or baclofen for the management of neuropathic pain and paraplegia, respectively.[176, 171, 170] In late preterm infants, withdrawal symptoms developed 1-3 days after birth and were preceded by bradycardia, difficulty in breathing, cyanosis, intercostal retractions, apnea, and hypotonia at birth.[152, 174, 176]

Most AEDs cross the placenta by diffusion in substantial amounts.[166] For VPA and gabapentin an active transportation has been also described.[177, 168, 178-180] Notably, for many new generation AEDs, gestational pharmacokinetic data are still limited.[177] The occurrence of withdrawal symptoms in newborns from epileptic mothers has been correlated positively with the mean dose of VPA given in the third trimester and the concentration of the free fraction of VPA in maternal plasma at the delivery.[167, 169] VPA concentrations at birth have been correlated with hyperexcitability in the newborn, while apathy was associated with high serum concentrations of unbound phenobarbital.[166] Jitteriness was related to phenytoin concentrations in maternal blood and cord blood.[165] Of note, these data are not conclusive, since other studies failed to show any correlation between the drug dose or cord blood serum concentrations and the occurrence of withdrawal syndrome.[155, 165] Furthermore, deficient hepatic and renal elimination capacities in the neonate can result in a longer half-life of AEDs when compared to adults, such as in the case

of VPA. By contrast, in utero exposures to phenytoin, carbamazepine and primidone have shown to induce the fetal hepatic enzyme systems, resulting in drug elimination patterns similar to adults.[168] The presentation of signs and symptoms of NAS may sometimes be delayed, consistently with the elimination time of drug metabolites in the neonate. Alternatively, the delay can be explained by an increase in AED concentrations after the delivery, likely due to their slow disposition from the CNS and lipid stores.[171, 174] Indeed, the fetus can be considered as a 'deep compartment' filled up by these compounds during long-term therapy throughout pregnancy.[168] Accordingly, after delivery, AEDs (phenobarbital, primidone, VPA and BZDs) have been found to persist in neonatal plasma for several days. This mechanism can explain some earlier neonatal events (direct toxicity) such as sedation, hypotonia, weak sucking, feeding problems and later neonatal withdrawal syndrome.[169, 173, 181] Signs of drug withdrawal in neonates can be monitored using the Finnegan scoring system.[176, 170, 174] Other scores have been used occasionally.[166]

The mechanism underlying AED-induced NAS has not been fully understood yet, and it is likely to differ across the various drugs. In adults, the γ-aminobutyric acid (GABA) system is known to play a pivotal role in the pathogenesis of withdrawal symptoms associated with BZDs, barbiturates, gabapentin and baclofen.[182, 183] Prolonged use of baclofen induces also the inhibition of monoamine neurotransmitter systems leading to the upregulation of dopamine and noradrenergic receptors. When baclofen is suddenly withdrawn, a disinhibition of the previously suppressed monoamine pathways occurs, with a consequent release of norepinephrine and dopamine onto upregulated receptors, leading to autonomic arousal (i.e., tachycardia, hypertension, agitation, restlessness) as well as delusions, hallucinations, and delirium.[183] The administration of VPA in rats was related to increased levels of striatal met-encephalin that might participate in the occurrence of VPA-induced abstinence behaviour.[184] Withdrawal symptoms observed with carbamazepine have been suggested to be consistent with those of TCAs, likely due to chemical similarities.[185] Hypoglycaemia belongs also to the symptoms expected for the AED withdrawal syndrome. This condition is often associated with neonatal feeding issues. However, hypoglycaemia may depend on a residual toxicity of in utero exposure to VPA, since this drug has been shown to decrease gluconeogenesis and impair glycogenolysis in newborns.[167, 152]

A standard treatment of AED-induced NAS has not been defined. Symptoms can be mild and transient or severe to such an extent to require transfer to NICU.[176, 152, 174, 169] Infants developing symptoms of withdrawal, after abrupt discontinuation of AEDs (VPA in mono- and poly-therapy), have been treated with phenobarbital and diazepam (in case of repeated seizures),[169, 167] or with the re-administration of the drug responsible for withdrawal (gabapentin, baclofen).[176, 170, 171] Some infants required enteral feeding or breast milk supplemented with formula milk, usually because of feeding problems caused by withdrawal symptoms.[167, 176] Among the preventive strategies, discontinuing AEDs during pregnancy is not usually an option, since a recurrence of seizures in pregnant women is expected.[155]

Monotherapy and the lowest drug dose may limit the risk of neonatal withdrawal.[169] Tapering down slowly the dose of AEDs (i.e. gabapentin) prior to delivery over a period of weeks to months can be useful in the minimization of NAS.[176, 172]

Barbiturates

Barbiturates have been indicated since decades for the treatment of several clinical conditions during pregnancy that, at least initially, included anxiety, sedation, prevention of hyperbilirubinemia in the newborn, preeclampsia and epilepsy.[186, 187] The management of epilepsy with barbiturates during pregnancy remains a controversial issue, since in utero exposure to these drugs may result in newborn behavioral abnormalities, neurological impairments and/or NAS.[187, 188]

Although the abstinence syndrome is well described in adults,[189] barbiturate-related NAS is less documented, and it is often described by case reports and small case series published during the 70s, when these compounds were more frequently prescribed by physicians for the management of epilepsy in pregnant women as well as for preeclampsia.[190, 191, 187, 166, 188] These early cases provide limited information, mainly due to diagnostic uncertainties related to the great variability of symptoms and to the pioneering approach to NAS. In a retrospective study, performed in 15 infants born from mothers receiving barbiturates during pregnancy, Desmond et al.[187] reported that the syndrome develops with an early acute phase, characterized by symptoms such as persistent crying, tremors, sleeplessness, hiccups and mouthing, followed by a subacute phase, with symptoms like hyperphagia, episodes of prolonged crying, irritability, hyperacusia and sweating.[187] Other symptoms reported in literature include hypotonia, feeding accompanied by gagging, vomiting, jitteriness, and seizures.[191, 190, 192]

Although symptoms are similar to those observed in opioid-exposed infants, barbiturate withdrawal symptoms appear to have a later onset (median age: 6 days, range 30 minutes-14 days) than opioid ones (median age: 6 hours, range 10 minutes-2 days).[193, 187, 191] This delay can be explained by the mechanism of tissue accumulation (described above in the section dedicated to AEDs in general) and by the poor conjugating capacity of the neonate, as well as the poor glomerular and tubular function of immature kidneys.[187, 186, 188] The duration of symptoms can vary from 2 to 4 months (with a median of 3 months), although they may persist for up to 6 months.[187] Moreover, newborns receiving barbiturate (as compared with opiates) are less frequently jaundiced, have better Apgar scores, and have no apparent residual injury following withdrawal[191, 187] as well as no autonomic and GI distress.[190]

Barbiturates can easily cross the placental barrier and can be detected at high concentrations in the newborn serum and umbilical cord serum.[193, 188, 194, 195] A lower plasma protein binding (3-43%) in newborns, as compared to adults (51%), could also explain the higher blood levels as compared with the mother.[196] Factors that may affect serum levels of phenobarbital in the offspring include maternal dose, gestational age, neonatal weight and days of life as well as the duration of prenatal exposure.[191, 188] The mechanism of barbiturates-induced NAS is not clear, but it is likely similar to that described in the section of this review dedicated to BZDs, thus involving GABA neurotransmission.[197]

Standard treatments for the management of barbiturate-associated NAS are not available. Phenobarbital has been shown to be effective in the management of the syndrome, even if an elevated rate of tolerance was reported. A daily dosage of 5-7 mg/kg/day of phenobarbital in newborns affected by seizures or drug abstinence syndrome has been considered useful and safe for infants.[196] As far as preventive approaches are concerned, evidence and data obtained from studies conducted on infants from pregnant epileptic women confirmed the need for treating them with the minimum effective dose, in order to reduce the risk of withdrawal in infants, following placental disposition.[188]

Benzodiazepines

BZDs are frequently used by women of reproductive age and by pregnant women for a variety of indications, including anxiety, sleep disturbances, control of seizures and managing of pre-eclampsia or eclampsia in the late phase of pregnancy.[198-200] It has been estimated that approximately 2-3% of pregnant women use BZDs.[201, 98, 202, 203]

Despite the relatively frequent use of BZDs during pregnancy, data on neonatal outcomes are still limited and the safety of these drugs in pregnancy, including their teratogenic potential, remains controversial.[204, 205, 201, 206-208] When BZDs are administrated late in pregnancy, they are easily disposed into the fetus, where they have the potential to accumulate causing two major neonatal syndromes: a NAS designated as ‘Opiate-like withdrawal syndrome’ lasting several days and a ‘Floppy infant syndrome’ (FIS), characterized by signs of poisoning within the first hours or days.[209, 204] At present, the actual prevalence of neonatal issues with BZDs remains unknown, since they can be used also as illicit drugs. Moreover, a small number of studies have examined newborns exposed prenatally to BZD monotherapy, and the pathophysiology of neonatal syndromes associated with BZDs has been poorly described and understood.[5] [206] The neonatal consequences of BZD use at the end of pregnancy have been evaluated in an observational study performed by the Regional Pharmacovigilance Center of Tours (France) on 73 pregnancies recorded from 1998 to 2002.[210] The most commonly used BZDs were oxazepam, bromazepam, alprazolam, clonazepam and clorazepate. The indications included depression, anxiety, epilepsy, insomnia and psychiatric disorders. In this study, exposure to BZDs was associated

with adverse reactions in 51.5% of newborns, comprising an “impregnation syndrome” (characterized by hypotonia and hypoventilation) in 42%, and a withdrawal syndrome in 20% of the cases (tremors as the main symptom).[210] Another study, performed to investigate infant and maternal characteristics of NAS in selected Hospitals in Florida from 2010 to 2011, showed that BZDs were the second most commonly reported drug class associated with NAS (40.5%).[211] Lastly, an analysis of the Swedish Medical Birth Register found that a late exposure to BZDs and receptor agonists (zopiclone, zolpidem, zaleplon) is associated with a higher risk of respiratory problems (OR: 2.21; 95%CI 1.62-3.02) and low Apgar score (OR: 2.20; 95%CI 1.11-4.39). A trend towards an increased risk for signs of CNS disorders (e.g. seizures) was also detected, but it was not statistically significant (OR:1.53; 95%CI 0.42-3.92).[204] Notably, some case series and studies, conducted on specific BZDs (diazepam, clonazepam, lorazepam, oxazepam, chlordiazepoxide, midazolam), did not show any neonatal toxicity or withdrawal syndromes in babies born from mothers who had taken BZDs during pregnancy.[212-219]

Symptoms of NAS and FIS are largely similar and it can be difficult to distinguish them, since the two syndromes may occur in sequence and their symptoms can partly overlap.[98, 202] Signs and symptoms of these syndromes have been described in several case reports and case series of pregnant women exposed to BZDs.[220-226, 216, 227, 209, 228-235, 214, 236-240, 200] Symptoms of both NAS and FIS are documented also in dated observational studies.[241-247]

NAS can be hardly recognized since it may start several days after delivery, up to 21 days in the case of chlordiazepoxide,[233] and symptoms may last for up to 3-6 months.[207, 248] Time-to-onset and duration of symptoms correlates well with the pharmacokinetics and placental disposition of BZDs, and their accumulation in neonatal tissues.[200] NAS symptoms reported in case reports include: tremors; irritability; hyperactivity; hypertonicity; tachypnea; vigorous sucking; poor weight gain; loose stools; vomiting.[220, 222, 225, 227, 230-233, 237, 200] The involved BZDs included diazepam (10-20 mg/day), chlordiazepoxide (20-30 mg/day), lorazepam (1 mg/day), alprazolam (1.5-8 mg/day), oxazepam and clobazam taken for the management of psychiatric disorders and anxiety throughout pregnancy or in the last 3-5 months.[220, 222, 225, 227, 230-233, 237, 200] Concomitant medications may have contributed to the occurrence of symptoms.[222, 227] Notably, in one case the infant died at 6 weeks of age, following a withdrawal syndrome associated with in utero exposure to diazepam treated with phenobarbital for 28 days. Death was attributed to the sudden infant death syndrome.[227]

Usually, FIS occurs when the fetus is exposed to long-acting BZDs on long-term basis, or when BZDs are administered shortly before the delivery, leading to a newborn intoxication of variable severity and duration. FIS symptoms (hypotonia, inactivity, weak cry, lethargy, sucking difficulties, low Apgar score, hypothermia, apnea, cyanosis, hyperbilirubinemia, CNS depression) occurred mainly within the first hours after labor and lasted for up to 14 days.[223,

224, 226, 216, 209, 228, 229, 234, 235, 214, 221, 236, 240] Diazepam (10-30 mg i.v. or 6-25 mg/day) was the mostly reported drug, followed by nitrazepam (5-10 mg/day), lorazepam (7.5 mg/day), chlordiazepoxide (500 mg i.v. or 100 mg/day), clonazepam (0.75 mg/day) and flunitrazepam, taken late in pregnancy for treatment of psychiatric disorders, or during labor in the case of pre-eclampsia or premature labor.[223, 224, 226, 216, 209, 228, 235, 214, 221, 240] Only few reports have described cases of neonatal apnea or mild depression associated with maternal exposure to clonazepam (5.5 mg/day) for treatment of epilepsy.[229, 236] In some reports, we cannot exclude the contribution of other psychotropic medications to the occurrence of neonatal symptoms.[209, 224, 226, 216, 228, 214]

The onset of NAS and FIS, their severity, and duration can be influenced by a number of factors: properties of the specific drug (plasma protein binding, ionization, lipophilicity, molecular weight, half-life, oral bioavailability), maternal treatment (dose, duration of exposure, time of last dose intake, co-medication with other drugs), infant characteristics (fetal absorption and storage, postnatal tissue binding and release, metabolism and excretion), and underlying maternal/fetal conditions.[204, 98, 227] Neonatal complications following in utero exposure to BZDs seem to be related also to the lipophilic nature of these drugs that allows an easy crossing of the placental barrier.[249, 204, 225, 235, 245, 223] Placenta can be considered also as a ‘deep compartment’ where the drug and its metabolites accumulate and are eliminated slowly, in a similar situation to that described generally for AEDs in the previous section.[225] Oxazepam, lorazepam, nitrazepam and, especially, flunitrazepam, appear to penetrate the human placenta more slowly than diazepam, but the clinical significance of this remains undetermined.[249, 212, 213] Long-acting BZDs (i.e. diazepam, chlordiazepoxide, chlorazepate, flurazepam, prazepam, nitrazepam) have sustained actions, that often can produce a ‘hangover’ type of effect with long-term treatments resulting in drug accumulation. Short-acting drugs (i.e. alprazolam, lorazepam, oxazepam, temazepam, lormetazepam) display a relatively little residual effect, but they can induce withdrawal symptoms more commonly.[200] Due to immaturity, less total body fat, and differences in the overall drug exposure, preterm infants may exhibit fewer signs of withdrawal than term infants. However, it is conceivable that the drug metabolism can be delayed in the premature neonate with reduced enzymatic functions in the liver.[213, 247] The long half-life of some BZDs and the immaturity of metabolic pathways in the newborn are not the only factors to be considered for explaining the persistence of neonatal symptoms for weeks after birth. Indeed, BZDs can be relatively easily metabolized by the neonate, and some BZDs (i.e. diazepam and clorazepate) can be converted into active compounds with a longer half-life than those produced by the maternal metabolism.[209, 213, 247, 227]

Infants may develop NAS with the classical mechanism of abrupt BZD discontinuation after a passive addiction acquired during pregnancy.[250] The underlying mechanism seems to be related to the mechanism of action of these drugs, and it likely results from the modulation of GABA-A receptors. Indeed, BZDs enhance the affinity of GABA-A

receptor for GABA, and this results in an increment of chloride conductance, thus promoting a condition of CNS depression.[251, 202]

The mechanism and significance of seizures associated with BZD withdrawal are unclear.[16] In adults, chronic therapy with BZDs may lead to conformational changes in GABA-A receptors, with a decrease in receptor affinity resulting in a decreased GABA activity. When BZDs are withdrawn, the condition of decreased GABA receptor activity leads to a reduced GABA inhibitory control on excitatory neurotransmitters, thus promoting a pro-excitatory status in the CNS.[252] BZDs with a short half-life, such as oxazepam and temazepam, do not usually result in toxicity, but the risk of withdrawal is increased as compared to BZDs with a longer half-life.[98] The mechanism by which BZDs can induce FIS is likely related to an enhancement of GABA effects on GABA-A receptors at limbic, thalamic, and hypothalamic levels, resulting in sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant effects.[199] The fetal BZD effects seem to be mediated by a central depression of cardiac and/or respiratory reflex centers.[253] High medication dosages (i.e. diazepam > 30 mg)[245] and BZDs with a long half-life (i.e. nitrazepam and diazepam) were shown to have the highest risk owing to their accumulation in newborns.[98]

The standard management of BZD-related neonatal syndromes (NAS and FIS) has not yet been defined, as well as a treatment protocol driven by an assessment tool.[5] The Finnegan score, to assess the severity of withdrawal syndrome, can be useful for initiating, monitoring, and terminating treatments in neonates,[225, 202, 246] as well as the Apgar score to evaluate acute neonatal outcomes.[246, 254] The initial treatment option is commonly based on a supportive non-pharmacological intervention, and symptoms resolve spontaneously without sequelae.[224, 221, 199] Mechanical feeding and ventilation have been described for the management of the most severe acute phases.[228] In the most severe situations, a pharmacological treatment can be required.[202] There is general agreement that neonates can benefit from sedative pharmacotherapy.[5] Three cases of severe tremors, occurred in the newborns after diazepam exposure in utero, were treated with phenobarbital.[227] Two case reports showed rapid, complete and sustained reversal of prolonged apnea and hypotonia induced by diazepam following treatment with flumazenil.[223, 209]

Current information is not sufficient to determine whether the potential benefits of BZD treatment in pregnant women overcome the risk for the fetus.[199] Bearing in mind the relative risk of drug exposure versus the potential impact of untreated psychiatric disorders,[214] when necessary, physicians should prescribe BZDs that have more robust safety data, in monotherapy, at the lowest effective dose for the shortest period of time, dividing the daily dosage into at least two doses and avoiding high single doses, multidrug regimes, and repeated and prolonged administration of BZD during pregnancy.[234, 199] If possible, the use of the shorter acting agents should be considered and their discontinuation should be performed with doses well tapered down prior to delivery.[200, 199]

Antipsychotics

The prevalence of pregnancy in women with schizophrenic and other severe and persistent psychiatric disorders (SPPDs) has increased since the deinstitutionalization of mental hospitals and the consequent increased availability of sexual partners.[255-257] Moreover, the progressive reduction of use of first generation antipsychotics (FGAs), endowed with hyperprolactinemic effects that may exert a control on fertility, in favor of second generation antipsychotics (SGAs), often lacking effects on fertility, are further fostering the frequency of pregnancy in patients with SPPD.[258, 259]

Evidence regarding the impact of pregnancy on the course of schizophrenia is inconclusive. Women with a history of psychotic disorders may experience a worsening rather than an improvement of symptoms during pregnancy. [260, 261] As far as the bipolar disorder is concerned, the issue of whether this disease worsens during pregnancy is controversial, with some studies showing a worsening[262, 263] and other studies showing no consequences.[264-268] In this scenario, it is particularly important that the mental health of women with SPPDs is stable if they are about to become parents.

Antipsychotics are effective medications for psychotic and bipolar manic episodes, and their use is rising among pregnant women with bipolar disorder, schizophrenia, and unipolar depression as well as other SPPDs.[269-272] However, reproductive safety data on these drugs are limited. Studies investigating the teratogenic potential of antipsychotic medications have shown a general increase in the risk of malformations associated with the overall drug class. This finding does not allow to exclude that the underlying disease or unidentified confounding factors may explain the increased risk.[273] Overall, the use of both SGAs and FGAs during late pregnancy has been associated with increased rates of neonatal complications (i.e. deficits in neuromotor performance, hypertonicity, tremors) as compared with exposure to antidepressant and non-psychotropic drugs.[274, 275]

In 2011, the US FDA issued a warning about neonatal extrapyramidal symptoms and possible medication withdrawal based on data from the Adverse Event Reporting System (AERS).[276] Indeed, from 2008 to 2011 the AERS database identified 69 cases of neonatal extrapyramidal or withdrawal symptoms associated with several antipsychotic drugs. The reported symptoms included agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder. Blood levels were not provided, making it not possible to determine whether the events resulted from NAS or residual pharmacological effects. The time to event onset ranged from delivery to one month after delivery. Symptoms varied in severity: some neonates recovered within few hours or days without specific treatment, while others required NICU support and prolonged hospitalization.[276]

A study on 142 live births, recorded by the Australian National Register of Antipsychotic Medication in Pregnancy (NRAMP), described medication withdrawal symptoms in 15% of babies. These newborns have displayed at least two of the following symptoms: excessive high pitched crying, pronounced Moro reflex, myoclonic jerks, intermittent bouts of sneezing and/or yawning, excessive drowsiness, tremors, pronounced irritability, difficult feeding, vomiting and loose stools.[277] Babies who experienced withdrawal symptoms had been exposed to higher doses of antipsychotics at 12 weeks of gestation (4.4 mg/ day vs 2.7 mg/day), though this difference did not reach statistical significance (p=0.162). Symptoms were prolonged in several babies, lasting up to 6–8 weeks.[277]

Differences can be highlighted among individual antipsychotic drugs. Neonatal complications ranging from mild withdrawal reactions to seizures have been described for risperidone. [278-281] A case report described a case of hyperbilirubinemia, thermoregulation and feeding problems associated with in utero exposure to risperidone (4 mg/day), requiring hospitalization of the newborn for 6 weeks.[280] Neonatal alterations associated with late in utero exposure to haloperidol may include thermoregulation impairments, decreased muscle tone, tremor on stimulation, vomiting, and poor feeding.[282] In a study, neonatal symptoms were observed in 8 out of 30 (27%) olanzapine-exposed infants versus one out of 51 (2%) non-exposed controls. These symptoms included respiratory distress (2 cases), hypotonia (1 case), poor sucking or feeding difficulty (2 cases), and unspecified withdrawal syndrome (3 cases).[283] For clozapine, reported neonatal complications include retinopathy, transient and severe neonatal hypoxemic encephalopathy and FIS.[284-287, 273, 288, 289, 224, 290-292] Two case reports have described delayed extrapyramidal symptoms in infants following prenatal fluphenazine administration. [293, 294] One developed neurologic symptoms, such as choreoathetoid and dystonic movements of the upper limbs, jitteriness, and hypertonicity that began 3 weeks after birth and lasted for 9 months. The second case had extrapyramidal manifestations that began 4 weeks after delivery. Both infants responded to treatment with diphenhydramine hydrochloride. In these two cases, respiratory effects were not reported. Another case described an infant with severe rhinorrhea and upper respiratory distress after 8 hours from birth.[295] Over the next 48 hours nasal congestion, rhinorrhea, extrapyramidal movements and vomiting improved and the baby was discharged on day 3. Nasal congestion and rhinorrhea persisted for 3 months.

All psychotropic medications can diffuse readily to the fetus across the placenta, due to their relatively small molecular size and lipophilic properties.[296] Fetal exposure to these drugs appears to vary according to the level of placental transfer. To quantify the placental permeability to antipsychotic medications, Newport et al. (2007)[297] conducted a prospective observational study in which maternal and umbilical cord plasma samples were collected at the delivery from 50 women exposed to antipsychotics in pregnancy. The highest placental transfer ratio was observed for olanzapine (mean ratio ± standard deviation: 72.1 ± 42.0%), followed by haloperidol (65.5 ± 40.3%), risperidone (49.2 ±

33.9%) and quetiapine (23.8 ± 11.0%). The mechanism underlying these effects is unclear. Withdrawal symptoms have been suggested to depend on a cholinergic rebound, rather than a dopaminergic-blockade.[298, 299] However, we cannot rule out that at least a part of early symptoms is related to a residual toxicity.

A standard treatment of neonatal complications associated with in utero exposure to antipsychotic medications is not available. In an analysis of 114 babies in the NRAMP database, those who were exclusively breastfed early after delivery were less likely to experience withdrawal symptoms than those receiving exclusively artificial feeding (9 of 74 [12.2%] vs 11 of 40 [27.5%]; OR: 2.74, 95% CI 1.02-7.32).[300] Mild symptoms may resolve spontaneously without treatments. The clinical management of the most severe cases is based on symptom control with sedative drugs, such as phenobarbital and BZDs.[276]

Other drugs

In the medical literature, NAS or residual pharmacological effects due to drug exposure during pregnancy have been anecdotally described for clonidine (hypertension related symptoms),[301] hydroxyzine (neurological symptoms),[302, 303] methyldopa (neonatal jitteriness),[304] pyridoxine (neonatal seizures),[305] and lithium (FIS).[98] However, the evidence for these drugs is very limited and further studies are needed.

Conclusions

Several drugs prescribed during pregnancy can be associated with the development of neonatal abnormalities, resulting from delivery-related withdrawal symptoms or representing a direct harm of the drugs accumulated in the blood and tissues of the newborn during the fetal period. These drugs are substantially used to treat CNS diseases or are able to interfere with neurotransmission both in the brain or in the peripheral nervous system. These effects can be severe and rarely fatal, and their early recognition and management can be helpful in reducing their clinical impact on newborns. Unfortunately, with the potential exception of opioids, validated protocols for the assessment and management of withdrawal or residual toxic effects of these drugs in neonates are often lacking and incomplete. Spontaneous reporting of these adverse reactions seems limited, although it might represent a useful tool for improving our knowledge about drug-induced neonatal syndromes.

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Table 1. Prescription drug classes most frequently associated with drug-induced neonatal syndromes

Drug class	Neonatal abstinence syndrome		Residual pharmacological effects	
	Symptoms	**Onset since delivery**	**Symptoms**	**Onset since delivery**
Opioids	Congestion, diarrhea, feeding disorders, fever, hypertonia, hyperreflexia, insomnia, irritability, seizure, sweating, tachypnea, tremors, vomiting	Methadone: 60 hours Buprenorphine: 12-48 hours Morphine: 36 hours Tramadol: 35-48 hours Codeine: 2 hours Fentanyl: 24 hours	Rarely described (i.e. methadone-induced QT interval prolongation)	Not assessed
Antidepressants	Chills, feeding disorders, hypotonia, hypertonia, irritability, jaundice, persistent crying, respiratory distress, restlessness, seizures, sleep disorders, tachypnea, tremors, vomiting	Within 24-72 hours	Withdrawal-like effects TCAs: Anticholinergic effects (constipation, urinary retention) SSRIs: serotonin-like symptoms (fever, myoclonus, tremors)	First hours
AEDs	Abnormal tone, apnea, feeding disorders, hypoglycemia, hypotonia, irritability, jitteriness, seizures, vomiting	First hours up to one week	Feeding disorders, hypoglycaemia (VPA), hypotonia, sedation	First hours
Barbiturates	Feeding disorders, hiccups and mouthing, hyperacusia, hyperphagia, hypotonia, irritability, jitteriness, persistent crying, sleep disorders, seizures, sweating, tremors, vomiting	6 days (average) (from 30 minutes to 14 days)	Not assessed	Not assessed
BZDs	Feeding disorders, hyperactivity, hypertonicity, irritability, loose stools, poor tachypnea, tremors, vomiting, weight gain	First hours up to three weeks	Apnea, CNS depression, cyanosis, feeding disorders, hyperbilirubinemia, hypothermia, hypotonia, inactivity, low Apgar score, lethargy, weak crying	First hours
Antipsychotics	Agitation, feeding disorders, hypertonia, hypotonia, respiratory distress, somnolence, tremors	First hours to one month	Withdrawal-like effects	Not assessed

AEDs: antiepileptic drugs; BZDs: benzodiazepines; TCAs: tricyclic antidepressants; SSRIs: selective serotonin reuptake inhibitors; VPA: valproic acid; CNS: central nervous system

Table 2. Neonatal abstinence syndrome score. This tool assigns a cumulative score based on interval observation of several items related to signs of neonatal withdrawal.[88]

Group	Signs and symptoms	Description and scores
Neurologic hyperexcitability	Excessive crying	Score 2: infants who cannot stop crying and are difficult to console; score 3: infants who cannot stop crying with comfort measures
	Sleeping	The longest amount of time that the infant sleeps continuously between feeding and scoring periods. Score 0: > 3 hours; score 1: 2-3 hours; score 2: 1-2 hours; score 3: < 1 hour
	Moro reflex	Score 2: hyperactive response with excessive abduction at the shoulder and extension at the elbow; score 3: the above signs occurred with marked adduction flexion at the elbow with arms crossing the midline
	Tremors disturbed (stimulated) Tremors undisturbed (not stimulated)	Score 1: mild tremors, occurring frequently in fussy or crying states and occasionally in quiet alert states; score 2: moderate to severe tremors occurring occasionally in drowsy states, often in quiet alert states and consistently in fussy or crying states
	Increased muscle tone (hypertonia)	Tone is the resistance of parts of the body to passive movements and can be assessed by testing the infant's motor resistance. Score 1: generalized increased resistance to extension and flexion of the limbs and head lag on pull to sit; score 2: exaggerated increased tone, sometimes visible without handling, with difficulty in straightening or bending the arms with or without head lag (or chin tuck) on pull to sit
	Excoriation	Excoriation is redness or a superficial lesion of the skin that results from the rubbing on linen due to excessive and uncontrolled movements of the extremities (tremors) and head (rooting). Score 1: skin is red but intact; score 2: skin is broken
	Generalized seizure	Score 8: presence of seizure activity
Autonomic dysregulation	Sweating	Score 1: dampness of the infant's forehead or upper lip
	Hypertermia	Score 1: body temperature > 37.3°C (99.0°F)
	Yawning	Score 1: yawning > 4 times within 3-4 hours testing period
	Nasal stiffness	Score 1: any nasal noise on breathing
	Sneezing	Score 1: sneezing > 4 times within 3-4 hours testing period
	Tachypnea	Score 2: respiratory rate > 60 breaths/minute
Enteric symptoms	Poor feeding	Score 2: difficulties in feeding for any reason (sucking impairments, positioning, muscle rigidity, etc.)
	Vomiting	Score 2: vomiting the whole feed or >2 times during feeding
	Loose stools	Score 2: liquid or a half solid and a half liquid stools
Other signs	Failure to thrive	Score 2: weight gain is > 10% below birth weight
	Excessive irritability	Score 2: infant that displays 2-3 signs of irritability (i.e. grimacing or being sensitive to touch, light and sound, gaze aversion, pull down) and it is consoled only with intervention after time; score 3: infant in which consoling did not reduce symptoms of irritability