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Placental Transfer of Antidepressant Medications: Implications for Postnatal Adaptation Syndrome

Grace Ewing¹, Yekaterina Tatarchuk, M.D.¹, Dina Appleby, M.S.¹, and Deborah Kim, M.D.¹

¹ Penn Center for Women's Behavioral Wellness, Dept. of Psychiatry, Perelman School of Medicine at the University of Pennsylvania. 3535 Market St., 3rd Floor, Philadelphia, PA 19104.

Abstract

Seven to thirteen percent of women are either prescribed or taking (depending on the study) an antidepressant during pregnancy [1]. Although generally low risk, antidepressants have been associated with postnatal adaptation syndrome [2]. Because antidepressants freely cross into the intrauterine environment, it is our aim to summarize the current findings on placental transfer of antidepressants. The antidepressants reviewed are limited to those that are commonly prescribed to the pregnant patient suffering from depression or anxiety. The biological mechanisms regulating placental transport are both complex and multi-determined. Placental anatomy and pharmacokinetics are reviewed along with the latest advances in the understanding of active cellular molecular transport and placental metabolism. In addition, we consider how non-placental and fetal factors contribute to the distribution of drugs across the placenta. The data on placental passage of antidepressants is discussed in the context of the three commonly used research methodologies: animal models, ex vivo perfusion models, and in vivo models. The goal of this review is to inform clinical decision-making by improving understanding of how placental and pharmacokinetic factors relate to the data on antidepressant drug transfer and postnatal adaptation syndrome (PNAS). Incorporating maternal and fetal genetics will be the next step in assisting clinicians to make more informed choices regarding which antidepressants are the least likely to have extensive fetal exposure.

1. Introduction

Depressive symptoms during pregnancy are common, affecting up to 20% of pregnant women with 7-13% meeting diagnostic criteria for a major depressive episode [3, 4]. It has been suggested that 7-13% of pregnancies are exposed to an antidepressant [1, 5], with the majority of pregnant women taking a selective serotonin reuptake inhibitor (SSRI) [6]. Because antidepressants cross the placental barrier, research over the past decade has sought to determine how maternal antidepressant use can affect the development of the neonate [7]. The most robust and consistent finding is a constellation of neurobehavioral symptoms in the neonate collectively called postnatal adaptation syndrome (PNAS). This has been found to occur in up to 30% of infants exposed to SSRIs or selective norepinephrine reuptake

Corresponding Author Complete Contact Information: Grace Ewing 3535 Market Street, 3rd Floor, Philadelphia, PA 19104. grewing@mail.med.upenn.edu, Phone: (215) 746-1158.

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inhibitors (SNRIs) during the third trimester of pregnancy [8]. Symptoms associated with PNAS include: infant irritability, hypertonia, jitteriness, and trouble feeding. These symptoms occur at birth or within a few days after and resolve within days or weeks [9]. Fluoxetine, paroxetine and venlafaxine are the drugs that have been most strongly associated with antenatal SSRI/SNRI exposure and PNAS [8]

The selection of a particular antidepressant during pregnancy should be based on a variety of factors including potential fetal exposure and toxicity, past maternal response, as well as clinician and patient comfort [10]. Although there are many considerations involved, it would be helpful for clinicians to know whether there are specific patterns of placental passage of these drugs into the fetal compartment and how this may relate to PNAS. For instance, it is possible that antidepressants with higher transfer percentages are also the antidepressants most closely linked to PNAS. However, the biological mechanisms regulating placental transport are both complex and multi-determined. The clinician who has an understanding of placental anatomy, antidepressant pharmacokinetics and the non-placental maternal and fetal factors that contribute to the distribution of drugs across the placenta will be better able to counsel her patients. This review aims to examine the factors associated with antidepressant transplacental passage and their relationship to PNAS. Such knowledge could guide clinical decision-making and improve the understanding of the relationship between exposure and outcomes.

2. Placental Anatomy and Pharmacokinetics

The placenta is a lipid-soluble barrier that plays a crucial role in monitoring and controlling nutrient absorption, waste elimination and gas exchange between the mother and the fetus. By the 10th week of pregnancy, the placenta has established the maternal and fetal circulation systems, which consist of functional units called cotyledons, composed of the fetal syncytiotrophoblast and maternal decidua basalis tissue [11]. Cotyledons are the primary area of exchange between the maternal and fetal systems. Like other biological lipid-soluble membranes, the placenta is selectively permeable. Biological molecules and xenobiotic compounds, such as antidepressants, that are small (molecular size ~500 Daltons), non-ionized, and lipophilic can freely cross the placenta via passive diffusion [12]. Therefore, placenta structure and function determine the rate of drug transfer. Passive diffusion is greatest at term when the microvilli increase in surface area and become thinner allowing greater exchange between fetal capillaries and maternal blood [13]. While passive diffusion is the primary mechanism of antidepressant transfer, other factors such as active cellular transport and placental metabolism contribute to transfer differences seen among antidepressants (Table 2).

2.1 Active Transport

Active efflux proteins, which are expressed in many tissues throughout the human body, can transport drugs against the concentration gradient and therefore act to decrease fetal exposure to xenobiotics, such as drugs. Three active efflux proteins from the ATP-binding cassette (ABC) superfamily are involved in the passage of drugs across the placenta: P-glycoproteins (P-gp), breast cancer-resistance proteins and the multi-drug resistance-associated proteins [12]. Only P-gp has been identified as being involved in the transport of

antidepressants [14]. Protein expression of P-gp decreases throughout pregnancy affecting the efflux of drugs with advancing gestational age (Table 1) [13, 15]. However, there is little data on the activity of placental P-gp throughout gestation [13].

P-gp is a product of the ABCB1 gene and is located on the microvillus border of the syncytiotrophoblast, on the fetal side of the placenta. Antidepressants can be substrates, inhibitors and/or inducers of P-gp. Inducers and inhibitors can impact the transfer of other drugs and potentially cause drug-drug interactions, while substrates will be actively transported out. Studies that have identified the relationship of particular antidepressants to P-gp in brain and renal tissue found, for example, sertraline and paroxetine are strong P-gp inhibitors [14]. However, a recent study found that this relationship is tissue specific. Sertraline causes greater P-gp efflux in the placenta and less across the blood brain barrier resulting in increased efflux of sertraline across the placenta, but less across the blood brain barrier [16]. Also, studies have demonstrated that there are single nucleotide polymorphisms (SNPs) of P-gp that can either increase or decrease efflux activity thereby influencing fetal drug exposure [13]. Because studies measure the fetal to maternal (F:M) drug percent when P-gp activity is decreased at term and rarely report maternal or fetal genetic information, it is currently difficult to apply this information clinically [17]

2.2 Placental Metabolism

The metabolic breakdown of drugs by the placenta can limit fetal drug exposure. Metabolic enzymes are categorized as either Phase I or Phase II enzymes depending on how they interact with the parent compound. In the placenta, the only phase I enzymes that have been identified are cytochrome P450s (CYPs) found in the trophoblastic tissue. However, in comparison to the liver, the activity of these enzymes in the placenta is relatively low and thought to have a minor role in affecting drug levels [18]. Of the CYPs involved in the metabolism of antidepressant medications (Table 2), only CYP3A4, CYP1A2, CYP2B6 have been identified in the human placenta [19-23]. CYP3A4 has been identified at both the mRNA and protein level [13, 22], while only mRNA expression has been identified for CYP1A2 [19-21]. There is a general trend for increased expression of mRNA and protein as well as activity of CYPs to decrease as pregnancy progresses potentially leading to greater drug exposure towards the end of pregnancy (Table 1) [13, 18]. However, there is no research aside for CYP2B6 for bupropion [23, 24], to confirm CYP activity leads to placental metabolism of antidepressants during pregnancy. Therefore, conclusions about the extent to which this mechanism relates to fetal exposure are not possible.

Phase II enzymes are also present at low levels in the placenta. These enzymes include uridine diphosphate glucuronosyltransferases, glutathione S-transferases, epoxide hydrolase, sulfotransferase, and catechol-O-methyltransferase. These enzymes are expressed in the placenta at low levels. Their relationship to antidepressant placental transfer has not been studied [14].

2.3 Bioavailability and Half-Life of Antidepressant Medications

Both the bioavailability and the half-life of a drug are important pharmacokinetic factors that can influence fetal exposure to drugs. Bioavailability, or the fraction of the active drug that

reaches the circulation system, is determined using an area under the plasma drug concentration time curve (AUC) analysis. AUC is typically used to estimate total drug exposure [25]. Drugs that have lower bioavailability will be present in lower concentrations in the circulation system and therefore could suggest lower fetal exposure. The half-life of a drug or the amount of time it takes the original concentration to decrease by 50%, can influence the AUC curve. For instance, larger AUC values may be associated with drugs with longer half-lives like fluoxetine [26, 27]. This could lead to prolonged drug concentrations in the fetal circulation systems potentially resulting in toxicity [28]. Table 2 contains the oral bioavailability percentages and half-lives for antidepressant medications.

3. Non-placental Maternal and Fetal Factors

Non-placental maternal and fetal factors determine the amount of the free form of a drug present and available for transport across the placenta.

3.1 Maternal and Fetal Drug Metabolism

Several studies have demonstrated that from 20 weeks to delivery, the metabolism of antidepressants increases, resulting in lower plasma levels of the active form of the drug and decreased effectiveness [29]. The changes in metabolism are likely due to changes in activity of CYPs in the human liver. Particular CYPs with the corresponding antidepressant substrates are summarized in Table 2 [30-36]. In addition to these gestational changes, maternal genetic polymorphisms in CYPs can determine how well a drug is metabolized and subsequently how much may pass into the fetal compartment. For instance, despite an increase in plasma cord blood concentrations with higher maternal dosage, the increase in an individual infant's plasma levels is quite variable, in part, because of these maternal differences in metabolism [7]. A mother who is a poor metabolizer (PM) of a drug may increase fetal exposure, as a greater amount of the drug would be available to cross the placenta. The opposite would be true for an ultrametabolizer (UM), which could lead to decreased fetal exposure. While an individual's ability to metabolize an antidepressant is now available to clinicians [37], this information has not been studied in large clinical samples to see if this is helpful to predict fetal exposure.

3.2 Protein Binding

Plasma protein binding, involving albumin and alpha-1-acid glycoprotein (AAG), also determine the amount of free drug in the maternal circulation. The unbound or free form of the drug will cross the placenta and equilibrate between the maternal and fetal circuits. During the 1st-3rd trimester, the F:M percentage of albumin increases from 28% to 120% and AAG increases from 9% to 37% [38]. A threefold increase of free fatty acids, which competitively bind to albumin and displace drugs from the binding site, occurs only in the mother. These factors lead to lower fetal free form of the drug compared to the mother and may lead to an increase in drug transport to the fetal side (Table 1) [38]. By contrast, lower affinity of drug binding to AAG is observed in the fetal versus the maternal circulation, which could shift drug equilibrium towards the maternal side.

4. Research Methods of Placental Drug Transfer

Five different research methods are used to estimate fetal exposure to drugs during pregnancy. These include animal models, ex vivo human studies, in vivo human studies, assessment of placental tissue cultures for expression of placental efflux protein transporters and metabolic enzymes involved in placental drug transport mechanisms [38]. The first three methods involve comparing fetal cord blood or fetal tissue concentrations to maternal plasma concentrations. This results in a fetal to maternal (F:M) percentage, which serves as an estimate of fetal exposure. The latter two methods focus on drug transport mechanisms rather than measurements of fetal exposure and therefore are not emphasized in this paper. Each method for estimating fetal exposure has advantages and disadvantages in terms of clinical relevance.

Animal models can ensure uniform maternal dosage and report the percentage of transfer at different gestational ages as well as drug accumulation in fetal tissues. While rat and mice models do provide information about transplacental transfer of medications, the placenta is the most species-specific organ and therefore non-human primates models (baboons, rhesus macaques) offer the greatest insight into human transplacental drug transport [39]. Currently, only one study has used a non-human primate to investigate transplacental drug transport of antidepressant medications [23]. Animal models allow researchers to determine the maximum fetal exposure as well as how quickly the exposure occurs after a maternally ingested single dose [28, 40, 41]. This is data that is not available using in vivo human models. For instance, if maternal plasma and fetal cord blood or infant sampling at delivery occurs before or after maximum concentration is reached in the fetal circulation after a mother's daily dose, the F:M percent could be an underestimate [41]. Animal models demonstrate that maximum fetal exposure reaches a peak and then declines [28]. In vivo models assume that the mothers are at steady state at delivery when conducting the study. It is hard to determine whether such peaks in transfer exist or how they would contribute to fetal exposure when the mother is at steady state.

The ex vivo placental perfusion method, which involves perfusing a human placenta with a particular drug, offers a way to control drug dose across human subjects. This ensures steady-state levels as well as a uniform duration of exposure to the drug. However, ex vivo models lack the ecological validity of in vivo models as they do not simulate the changes of AAG or albumin binding during pregnancy and can underestimate placental transfer levels [38]. Conversely, in vivo studies may lack uniformity across participants in terms of the establishment of steady state levels, maternal dose and timing of the last dose versus sample collection at delivery. Both in vivo and ex vivo methods use term placentas, which do not provide information about how placental passage of antidepressants changes throughout pregnancy. In contrast, comparing amniotic fluid concentrations to maternal plasma concentrations allows for an opportunity to assess placental permeability to antidepressants during the 2nd trimester, an important time for fetal growth [42, 43].

Ultimately, none of these methods provide information about the mechanism of transfer or how the mechanism may change throughout pregnancy. For instance, the physiological changes that occur to the placenta during pregnancy, such as increased surface area,

increased blood flow rate, and decreased P-gp activity, culminate to favor the transfer of pharmacological agents later in gestation [15, 38]. With these limitations in mind, a summary of the extant data on transplacental passage of several antidepressant classes follows. Because not all antidepressants have been studied and some are less clinically relevant than others (e.g. monoamine oxidase inhibitors), the information below is limited to those classes that have been studied and are used in the pregnant population.

5. Selective Serotonin Reuptake Inhibitors (SSRI's)

SSRIs are the most commonly prescribed antidepressants during pregnancy [6].

Accordingly, the greatest amount of data exists on the transplacental transfer of SSRIs, with evidence from all three types of research methodologies (Tables 2, 3 & 4).

5.1 Animal Models

With the exception of one study that examines the transplacental transfer of fluvoxamine (N=4), the four other animal model studies have exclusively focused on fluoxetine. Animal studies have found that the F:M percentage of fluoxetine ranges from 59% in sheep [44] to 83% in rats [45], with similar ranges reported for norfluoxetine, its metabolite [46, 47]. Compared to fluoxetine, a lower mean F:M percentage (30%) has been found for fluvoxamine in mice [47].

Studies using animal models have demonstrated that fluoxetine not only crosses the placenta, but also accumulates within fetal brain tissue within 5 hours after drug administration [45, 46]. Fetal concentrations of radioactive labeled fluoxetine and norfluoxetine at 4, 8 and 24 hours after administration of 12.5 mg/kg to the mother were higher on gestation day 18 (5.45 ug/mL) compared to day 12 (3.60 ug/mL) [46]. This is in accordance with the finding that placental permeability to drugs increases throughout pregnancy. A different study, which administered 12 mg/kg of fluoxetine to rats throughout gestation (gestational day 11 to birth), reported even higher fetal brain tissue concentrations for fluoxetine (13 ug/mL) and its metabolite (22 ug/mL). This suggests drug accumulation within the fetal system increases with prolonged exposure [45] (Table 3). A 12.5 mg/kg rodent dose is approximately 1.5 the maximum human dose of 80 mg.

Only one study has examined the effects of transplacental transfer of fluoxetine on offspring development in mice. They found that after a 0.8 mg/kg dose, 81% died before post-natal day 20. This finding has unclear clinical relevance as 0.8 mg/kg is equivalent to a 0.065 mg/kg dose in humans, which is about a 4 mg dose for a 60 kg person [48]. Given the lack of toxicity in humans, this is an example of animal data that does not reflect clinical experience in humans.

5.2 Ex vivo

Fluoxetine and citalopram are the only SSRIs that have been investigated using an ex vivo perfusion model. F:M percentages for fluoxetine (8.7%, SD=3.5%), norfluoxetine (9.1%, SD=3.6%), citalopram (9.1%, SD=2.7%) and desmethylcitalopram (5.6%, SD=2.5%) are considerably lower than in vivo reports (Table 4) [49]. In addition, the F:M percentage was significantly higher for citalopram than its metabolite ($p=.017$). These data are likely

underestimates because initial maternal rather than steady state concentrations are used to calculate the F:M percentage.

5.3 In vivo

Infant concentrations of SSRIs were first documented by case reports of infant toxicity from mother's taking SSRIs during pregnancy. Two case reports from mothers taking fluoxetine documented drug (25 and 129 ng/mL) and metabolite (55 and 227 ng/mL) levels in the infant to be within the therapeutic range for adults [50, 51]. However, these cases are likely outliers, as most infants do not show signs of toxicity [8]. In addition, because maternal plasma levels of the drug were not reported, it is unclear how much of the drug was transferred to the fetus.

5.3.1 Fetal Cord Blood and Maternal Plasma Concentrations—Studies that record the fetal cord blood and maternal plasma concentrations at delivery to calculate the F:M percentage provide the best estimate of drug transfer across the placenta compared to ex vivo perfusion model and animal studies. Although this data on SSRIs is generally limited, it has been investigated for the following drugs: fluoxetine, citalopram, sertraline, paroxetine, escitalopram and fluvoxamine. The F:M percentage has been documented in the greatest number of women for fluoxetine, citalopram and sertraline, with less data on paroxetine, escitalopram, and fluvoxamine (Table 2). All studies examining SSRIs report mean or median F:M percentages of greater than 50% for most drugs and their metabolites [7, 26, 52-54]. In addition, large interindividual variation has been found within each drug. For instance, paroxetine was not detected in fetal cord blood in three out of eight women on the drug throughout pregnancy [7]. Interindividual variation is further corroborated by large standard deviations between 25-30%. Genetic polymorphisms for CYPs likely contribute to these interindividual differences across drugs [55].

For sertraline and paroxetine, reported percentages are small to moderate. Studies that report mean F:M percentages for sertraline suggest reduced placental drug transfer, although not all findings have been consistent. The majority of studies (N=3) found sertraline and its metabolite to have mean F:M percentages less than 45% [7, 54, 56], while one study reported a mean F:M percentage of 78% [53]. The latter percentage is similar to that of other SSRIs [53]. Data from paroxetine suggests moderate mean F:M percentage of approximately 50% [53, 56].

5.3.2 Amniotic Fluid to Maternal Plasma Concentrations—When compared to the mean percentages of F:M concentrations documented at term, fetal amniotic fluid to maternal plasma concentrations are consistently lower for all SSRIs that have been investigated [42, 43]. This is consistent with data on placental physiology, which suggests the placenta is less permeable to drugs prior to the 3rd trimester. In every woman studied, amniotic fluid concentrations have been less than 25% of maternal plasma concentration, except for citalopram which was documented as 35% in one individual, with undetected amounts of desmethylcitalopram [42].

6. SNRIs

Currently, there are no animal models or ex vivo experiments investigating SNRI passage across the placenta and the data in humans is very limited. There are two case reports and one study examining venlafaxine and two case reports of women taking duloxetine during pregnancy. With values over 100% in some cases, SNRIs may accumulate more readily in the fetal compartment than SSRIs.

6.1 In vivo

6.1.1 Fetal Cord Blood and Maternal Plasma Concentrations—Very high F:M percentages have been reported for venlafaxine and its metabolite. For instance, two case reports documented F:M percentages for venlafaxine and desvenlafaxine of 110% and 100% and 170% and 313%, respectively [43, 53]. Another study of two women on venlafaxine was consistent with these percentages for the parent drug, but found lower F:M percentages for the metabolite [54]. Additionally, a larger study reported an F:M percentage median of 72% (IQR=41-111%) for venlafaxine and 108% (IQR=68-117%) for its metabolite [56]. Similar to SSRIs large interquartile ranges indicate large interindividual variability across women.

Even less data exists for duloxetine, with one case report documenting a F:M of 122%. However, this estimate compares fetal cord blood concentrations (65 ug/L) taken at delivery with a maternal plasma sample (53 ug/L) obtained at 32 days post-partum, which makes the data hard to interpret [57]. Another case reported an F:M of 12%, suggesting minimal fetal exposure. However, the accuracy of this estimate is uncertain because information on when the samples were obtained was not available [58]. More data must be collected to fully assess patterns of fetal exposure to duloxetine during pregnancy.

6.1.2 Amniotic Fluid and Maternal Plasma Concentrations—The transfer of SNRIs across the placenta during pregnancy has only been investigated for venlafaxine. One case report at 17 weeks gestation documented identical concentrations of venlafaxine in the amniotic fluid (16 ng/mL) and the mother (16 ng/mL), which suggests the placenta is not a barrier for fetal venlafaxine exposure at all [43]. A study of four women on venlafaxine confirmed this high transfer rate with mean percentages of 173% (SD=91%) for venlafaxine and 300% (SD=230%) for its metabolite [42]. This suggests unimpeded transfer of venlafaxine during pregnancy and accumulation in the fetus that may be higher compared to transfer at term.

7. Atypical Antidepressants

No in vivo data exists for atypical antidepressants. Two animal models and an ex vivo model have been used to study this drug class.

7.1 Animal Model

One study documented concentrations of trazodone in placental and fetal tissue of rats to be <25 ng/g. In this study the mothers were on 30 mg/kg per day, which is a human equivalent

dose of 4.8 mg/kg or about a 288 mg dose for a 60 kg person. Unfortunately, estimates of placental transfer were not calculated [40].

Additionally, one animal model using three baboons (*Papio cynocephalus*) investigated the transplacental transport of bupropion at term. They were administered a single dose of 4.32 mg/kg which was determined to be equivalent to a 150 mg dose in humans. The mean F:M percent was 89% (SD=18%) for bupropion and 24% (SD=10%) for hydroxybupropion, its primary metabolite [23].

7.2 Ex vivo

An ex vivo model of the human placenta was used to examine the placental transfer of bupropion. The term placenta was perfused with two different doses (150 ng/mL and 450 ng/mL) of bupropion. The mean F:M percentages were 24% (SD=3%) for a 150 ng/mL dose and 23% (SD=2%) for a 450 ng/mL dose [59]. Although, the ex vivo data suggest lower transplacental transfer of bupropion compared to other antidepressants, the animal data for bupropion suggests transfer percentages that are higher (Table 3 & Table 4). No in vivo human studies have been conducted to clarify this.

8. Tricyclic Antidepressants

Of the tricyclic antidepressants, imipramine (IMP), nortriptyline (NOR), amitriptyline (AMI) and clomipramine (CMI) have been studied using a variety of models.

8.1 Animal Model

IMP and its metabolite, desmethylimipramine (DMI) is the only tricyclic to be studied in an animal model. Rats were given a 10 mg/kg of IMP [60] or DMI [61], then sacrificed at 5 different time points between baseline and 20 minutes after drug administration. The human equivalent is 1.6 mg/kg or a 96 mg dose for a 60 kg person, which is about half the recommended maximum dose (200 mg) [48]. Both IMP and DMI rapidly accumulated in the fetal circulation with a maximum F:M percent of 170% for IMP [60] and a lower maximum F:M percent of 50% for DMI [61] (Table 3). A higher F:M percentage may be observed for IMP than DMI due to the fact that DMI, but not IMI becomes ionized at a physiological pH. Because the placenta is less permeable to ionized or charged particle, transfer of DMI may be reduced. No conclusions about interindividual differences in drug metabolism can be inferred.

A later animal model examined the transplacental passage of IMP and DMI by comparing concentrations from AUC analysis. Five rats were administered a 30 mg/kg dose on GD 18 to 19. Ratios comparing the AUC for maternal plasma concentration to whole fetus, to fetal liver and to fetal brain were computed. For IMI the respective ratios were 7.52, 16.6, and 16.9, with similar values for DMI 7.44, 15.1, and 16.4 [28]. This suggests much greater concentrations of IMI and DMI within fetal tissue compared to maternal plasma.

8.2 Ex vivo

The placental transfer of tricyclic antidepressants using an ex vivo model is limited to a study with NOR and AMI. The study found low mean F:M percentages for both drugs. For

instance, the mean F:M percentage for NOR was 6.5% (SD=2%) and was 8% (SD=2%) for AMI [62]. The mean F:M percentage for AMI was slightly, but significantly higher than NOR ($p=0.037$). Yet, both values are very low and may be underestimates. Because this is the only data on the placental transfer of AMI, in vivo studies are needed to clarify this.

8.3 In vivo

In vivo studies of the placental transfer of tricyclic antidepressants have only been studied for NOR and CMI. One case report in a mother taking NOR during the last 12 days of her pregnancy preceded by an overdose of 1.75 g prior to delivery, reported fetal cord blood concentrations to be 20% of maternal plasma levels [63]. This data is not generalizable as steady state levels of the drug may not have been established. Another case reported an F:M percentage of 47% for NOR and 65% for its metabolite [54]. An in vivo study found the mean F:M percentage to be 68% (SD=40%) for NOR and 140% (SD=240%) for its primary metabolite, cis-10-hydroxy-nortriptyline and mean F:M percentages of 60% (SD=50%) for CMI and 80% (SD=60%) for desmethyldimipramine [64]. Compared to the ex vivo data for NOR, these data suggest there is high transfer of NOR and its primary metabolite across the placenta, with a large range of variability.

10. Conclusion

In summary, antidepressants have been demonstrated to cross the placenta and enter the intrauterine environment with a wide range of variability for each drug. Given the importance of the human placenta in drug transfer, it would be helpful to understand if estimates of fetal exposure for the antidepressant medications associated with PNAS. This discussion focuses on in vivo human data because it the only research method that has been used to study the three antidepressants associated with PNAS. After examining the data on the transplacental transfer of antidepressant medications, it does not seem that drugs with the highest transfer percentages are necessarily those most likely to be associated with PNAS. Fluoxetine, paroxetine and venlafaxine are all associated with PNAS more often than other antidepressants [8], but tend to vary in transfer percentages. According to in vivo human studies, paroxetine has one of the lowest transfer percentages, while the percentages for fluoxetine and venlafaxine tend to be higher (Table 2). In addition, antidepressants such as citalopram and NOR, which have transfer percentages similar to fluoxetine and venlafaxine, have not been linked to PNAS [8]. Although all three drugs linked to PNAS have high (>80%) bioavailability, many other antidepressants not linked to PNAS have this characteristic as well (Table 2). Therefore, it is likely that pharmacokinetic factors other than placental permeability and bioavailability inform the pattern of which antidepressants are associated with the neurobehavioral symptoms of PNAS.

The pharmacokinetic factors that may lead to PNAS are likely related to the half-life of drugs (Table 2) and receptor affinity. These factors may contribute to concentration levels over time without impacting placental transfer from the mother to fetus. It has been suggested that a drug like paroxetine, with a short half-life (22 hours) and high cholinergic receptor affinity may be more likely to induce symptoms of withdrawal [9, 27]. Conversely, drugs with longer half-lives like fluoxetine (2-4 days) and its primary metabolite

norfluoxetine (7-15 days), may lead to toxicity, as the drug is more likely to accumulate within the fetal system [9, 26]. The contrasting drug profiles of paroxetine and fluoxetine may be a reason why antidepressant transfer percentages alone do not explain the phenomenon of PNAS. Therefore, placental passage percentages are not necessarily the most informative or indicative of a drug's likelihood to cause adverse outcomes.

However, it is important to consider the limitations of the data from which this conclusion is drawn. While pharmacokinetic factors contribute to the interindividual variation for a given antidepressant, differences in research methodology are another significant factor. One source of variation is the number of hours between the dose of the drug and the collection of maternal plasma samples at delivery. If the samples were not collected at a uniform time across participants, it is hard to compare ratios and accurately assess variability among women. Timing in collection is especially important, as the measured values are dependent on when the sample was taken compared to how quickly after maternal ingestion the drug enters and reaches a maximum level within the fetal system. For instance, if a drug reaches a maximum level six minutes after ingestion, any sampling before or after this window may underestimate exposure [41]. This parameter of timing is uncertain in human studies and may contribute to the variability in the data.

Interindividual variability for each drug is one of the strongest trends in this data. In addition to the methodological problems that contribute to variability, these differences may be related to polymorphisms that have been shown to affect maternal metabolism (CYP P450), placental metabolism (CYP P450) and placental efflux transport (ABC transporters) (Table 1) [15, 30]. To account for these potential differences, personal pharmacogenomics could be used to tailor a drug choice to a mother's genetic make-up. However, no studies have investigated how these genetic polymorphisms relate to antidepressant placental drug transfer and fetal exposure or whether this would impact maternal or infant outcomes. For instance, one could hypothesize that women who are ultrametabolizers (UM) for a particular drug may protect their fetus from in utero antidepressant exposure and developing PNAS. In contrast, infants whose mothers' are poor metabolizers (PM) for a particular drug could be at a greater risk for developing PNAS. It is also possible that infants who inherit PM genes for a particular drug are at risk for developing PNAS. Research needed to investigate the relationship between maternal and fetal metabolism and infant outcome.

Ultimately, it should be recognized that the mean transfer percentages for paroxetine, fluoxetine and venlafaxine come from small samples with large variation. Therefore, it is possible that PNAS is still related to high fetal exposure, such that the infants who are exposed to higher levels develop PNAS due to a mother or infant who is a PM for that particular drug. This relationship cannot be discerned given the current data. Antidepressant metabolism is different for every drug in terms of the type CYPs involved and how much a particular CYP contributes to the metabolism (Table 2). Therefore, a woman who is a PM for one drug, could be a UM for another. In order to make the most clinically informed decisions about the use of antidepressants in pregnancy, studies that link maternal, placental and fetal genetic polymorphisms, placental transfer rates and infant outcomes are needed. Ultimately, it is unclear whether higher levels of exposure to particular antidepressants

contribute to adverse fetal/infant outcomes. Therefore, at this time non-clinical data must be interpreted with caution and in context for each particular patient.

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Key Points

- There is no consistent pattern between antidepressants that have higher placental transfer percentages and the antidepressant medications associated with PNAS.
- The data on placental passage of antidepressants has large interindividual variability for each drug.
- Further research is needed to investigate how maternal and fetal genetics may relate to fetal drug exposure and adverse birth outcomes.

Table 1

Observed Maternal Pharmacokinetic Changes as Pregnancy Progresses

Pharmacokinetic activity	Direction of Change in Pharmacokinetic Activity	Potential Effect on Drug Transfer
Expression of P-gp's in Placenta	Decrease	Greater drug transfer to fetus
Expression of CYPs in Placenta	Decrease	Greater drug transfer to fetus
Expression of CYPs in Liver	Increase	Decrease in drug concentration reaching the fetus
F:M albumin ratio	Increase	Greater drug transfer to fetus
F:M AAG alpha-1-acid glycoprotein (AAG) ratio	Increase	Greater drug transfer to fetus
Free Fatty Acids	Increase	Greater drug transfer to fetus

Abbreviations: P-glycoprotein (P-gp), Cytochrome P450 (CYP) Fetal to Maternal Ratio (F:M), Alpha-1-acid-glycoprotein (AAG)

Table 2
Pharmacokinetic Variables and Estimates of Fetal Exposure for Antidepressants Medications from In Vivo Human Studies

Drug	Half Life	Cytochrome P450 (CYP) responsible for metabolism	Oral Bioavailability[65, 66]	Estimate of Exposure to Parent Drug	Estimate of Exposure to Metabolite
<i>SSRI</i>					
Citalopram	36 hrs [27]	CYP2C19, CYP2D6, <u>CYP3A4</u> ^[30]	80%	64-71% (54%) ^[7, 26, 53, 54, 56]	51-69% (27%) ^[753, 54, 56]
Fluoxetine	1-4 days [27]	CYP2C9, CYP2C19, CYP2D6 ^[30]	100%	58-73% (7-25%) ^[7, 52, 54, 56]	63-71% (9-34%) ^[7, 52, 54, 56]
Sertraline	26 hrs [27]	CYP2B6, CYP2C9, CYP2C19, CYP2D6, <u>CYP3A4</u> ^[30]	>80%	29-73% (16-38%) ^[7, 53, 54, 56]	29-63% (11-19%) ^[7, 53, 54, 56]
Paroxetine	20 hrs [27]	CYP2D6, <u>CYP3A4</u> ^[30]	>80%	46 % (31%) ^{B [7, 53, 56]}	n/a
Escitalopram	27-33 hrs [67]	CYP2D6, <u>CYP3A4</u> ^[30]	80%	73% [71-91%] ^{B [54, 56]}	70% [66-80%] ^{B [54, 56]}
Fluvoxamine	15 hrs [27]	<u>CYP1A2</u> , CYP2D6 ^[30]	53%	8-78% ^{A [47, 5456]}	n/a
<i>SNRI</i>					
Venlafaxine	5 hrs [65]	CYP2C9, CYP2C19, CYP2D6, <u>CYP3A4</u> ^[30]	92%	72% [41-111%] ^{B [53, 54, 56]}	56% [68-117%] ^{B [53, 54, 56]}
Duloxetine	10-12 hrs [68]	<u>CYP1A2</u> , CYP2D6 ^[30]	>70%	12% ^{D [57]} , 122% ^{D [56]}	n/a
<i>Atypical Antidepressants</i>					
Trazodone	10-12 hrs [69]	<u>CYP3A4</u> ^[35]	65%	No data	No data
Bupropion	8-24 hrs [65]	CYP2B6, <u>CYP3A4</u> ^[34]	85%	No data	No data
<i>Tricyclic Antidepressants</i>					
Amitriptyline	31-46 hrs [65]	CYP2C19, CYP1A2, <u>CYP3A4</u> , CYP2C9, CYP2D6 ^[31]	>80%	No data	No data
Nortriptyline	16-19 hrs [65]	<u>CYP3A4</u> , CYP2D6 ^[32]	51%	68% (40%) ^[42, 54, 63]	140% (240%) ^[42, 54, 63]
Clomipramine	19-37 hrs [65]	<u>CYP3A4</u> , CYP2C19 ^[36]	>80%	40% (50%) ^[42]	55% (60%) ^[42]

Data that did not provide a SD or TOR are not included in the range reported in the table, with the exception of those listed below. The cytochrome P450 (CYP) enzymes known to be expressed in the placenta are underlined to demonstrate that the placenta may play a role in metabolism for that particular drug. The references are in superscript next to each data point except for values of oral bioavailability.

A=no standard deviation provided

B=data represents median values [IQR] as no mean values were available

C= drug in which all raw data available was combined to reflect a total mean due to small Ns per individual study

D=Individual values reported due to lack of data

Table 3

Animal Model Data on the Placental Transfer of Antidepressants

Parent Drug	Author	Species	N	Dose (mg/kg/day)	Duration of Exposure	Timing of Collection	Type of Fetal Exposure Measurement	Fetal Exposure to Parent Drug	Fetal Exposure to Drug Metabolite	Comments
Fluoxetine	Olivier et al. 2011	Rat	13	12	GD 11-birth	5 hours after daily dose	F:M %	83% ^A	78% ^A	
	Olivier et al. 2011	Rat	13	12	GD 11-birth	5 hours after daily dose	Fetal tissue concentration	13 ug/mL	22 ug/mL	
	Noorlander et al. 2008	Mouse	4	0.3, 0.6, 0.8	GD 8-18	5 hours after daily dose	F:M %	69% ^A	N/A	
	Kim et al. 2004	Sheep	5	50	10 min. (3 rd trimester)	10 min after dose	F:M %	59% ^A	65% ^A	
	Pohland et al. 1989	Rat	12	12.5	One dose	4, 8, 24 hrs on GD 12 or GD 18	Fetal tissue concentration	GD 12: 3.60 ug/mL GD 18: 5.45 ug/mL	N/A	
Fluvoxamine	Noorlander et al. 2008	Mouse	4	4.2	GD 8-18	5 hours after daily dose	F:M %	30% ^A	N/A	
Trazodone	Devane et al., 1998	Rat	5	30	GD 16-20	Unspecified	Fetal tissue Concentration	< 25 ng/mL	N/A	
Bupropion	Rtting et al., 2014	Baboon	3	4.62	One dose (3 rd trimester)	1 hr prior to delivery	F:M %	89% (SD=18%)	24% (SD=10%)	
Imipramine	Hume & Douglas 1967	Rat	20	10	Unspecified	Between baseline to 20 mins.		170% ^A	N/A	
Imipramine	Devane et al., 1985	Rat	5	30	One dose (3 rd trimester)	10 min intervals (baseline to 18 hrs post-dose)	Ratio of area under curve analysis for tissue to maternal plasma	Whole fetus: 7.52 Fetal liver: 16.6 Fetal brain: 16.9	Whole fetus: 7.44 Fetal liver: 15.1 Fetal brain: 16.4	
Desmethy-imipramine	Douglas & Hume 1969	Rat	25	10	Unspecified	Between baseline to 20 mins	F:M %	50% ^A	N/A	
Isocarboxazid	Sato et al., 1972	Rat	4	30	One dose	15 min to 24 hrs	Placental and amniotic fluid concentration	N/A	Amniotic fluid: 5.2 ug/g, placenta: 20.4 ug/g	Values given as Max conc. Over 24 hrs.

GD = Gestation Day

^A no standard deviation given

Table 4

Ex vivo Human Data on the Placental Transfer of Antidepressants

Name of Parent Drug	Total Number of Cases	Estimates of Exposure to Parent Drug (Mean (SD))	Estimates of Exposure of Drug Metabolite (Mean (SD))
Fluoxetine [49]	7	8.7% (3.5%)	9.1% (3.6%)
Citalopram [49]	8	9.1% (3.9%)	5.6% (2.5%)
Bupropion [59]	10	23-24% (2-3%)	n/a
Amitriptyline [62]	9	8% (2%)	n/a
Nortriptyline [62]	9	6.5% (2%)	n/a