Perinatal Selective Serotonin Reuptake Inhibitor (SSRI) and Other Antidepressant Exposure
Effects on Anxiety and Depressive Behaviors in Offspring: A Review of Findings in Humans
and Rodent Models

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1. Introduction

Up to 20% of pregnant mothers experience depressed mood (Pawluski, Lonstein, & Fleming, 2017) and are commonly treated with selective serotonin reuptake inhibitor antidepressant medications (SSRIs) (i.e. fluoxetine, paroxetine, sertraline, citalopram) (Charlton et al., 2015; Oberlander, Warburton, Misri, Aghajanian, & Hertzman, 2006). SSRI use by pregnant women ranges between 5 and 13% in Australia and the USA, and between 2 and 7% in Canada and Western European countries (Charlton et al., 2015; Cooper et al., 2007; Hayes et al., 2012; Lupattelli et al., 2014; Oberlander et al., 2006; Zoega et al., 2015). These medications readily cross the placenta and have been reported in breast milk (Kim et al., 2006a;b; Rampono et al., 2009). SSRIs inhibit the reuptake of serotonin (5-HT), via 5-HT transporter blockade at presynaptic neurons, thereby increasing synaptic 5-HT concentrations (Whitaker-Azmitia, Druse, Walker, & Lauder, 1995). 5-HT is a key neurotransmitter (Hellendall, Schambra, Liu, & Lauder, 1993) widely distributed throughout key brain regions that influence cognition, attention, stress, and emotion regulation (Lesch, 2007; Lucki, 1998).

Serotonergic neurons appear as early as 5 weeks gestation (Lira et al., 2003) and setting appropriate 5-HT levels during early brain growth is central to the regulation of social/emotional and cognitive development (i.e. amygdala, prefrontal cortex) (Martín-Ruiz et al., 2001; Miller, & Friedhoff, 1986). 5-HT is implicated in the pathophysiology of numerous psychiatric and developmental disorders (Azmitia, 1999; Curtius et al., 1981; Nielsen, Lou, & Andresen, 1990) and is a target of numerous pharmacological therapies. Long before 5-HT becomes a neurotransmitter in the mature brain, it plays a role as a neurodevelopmental signal and regulates cell growth (Di Pino et al., 2004; Huether, Thömke, & Adler, 1992; Whitaker-Azmitia, Druse, Walker, & Lauder, 1995). In the fetal brain, 5-HT and its receptors are over-expressed and

widespread in regions where they are absent in adults (Miller, & Friedhoff, 1986; Seeman et al., 1987) pointing to a time-dependent specificity to 5-HT expression during development. Thus, early alterations of 5-HT, either via environmental or genetic manipulations, can change neural development (Oberlander, Gingrich, & Ansorge, 2009). Manipulating prenatal¹ 5-HT levels in animal models using genetic variations, 5-HT agonists, or SSRI exposure, alters brain morphology and may constrain 5-HT maturation in ways that result in increased risk of anxiety- and depressive-like behaviors (Homberg, Schubert, & Gaspar, 2010).

In humans, there have been reports that prenatal SSRI exposure is associated with increased internalizing and anxiety behaviors during early childhood (Brandlistuen et al., 2015; Hanley, Brain, & Oberlander, 2015; Hermansen, Røysamb, Augusti, & Melinder, 2016) and higher rates of depression diagnoses (Malm et al., 2016), but this is not always the case (Grzeskowiak et al., 2015; Lupattelli et al., 2018; Misri et al., 2006; Nulman et al., 2012; 2015; Pedersen et al., 2013). In rodent models there are also reports that pre- and post-natal² SSRI exposure impacts affective behaviors in offspring, but these effects vary based on methodological factors (Gemmell et al., 2017; Popa, Léna, Alexandre, & Adrien, 2008; Rayen et al., 2013; Boule et al., 2016). In addition, while there is a possible direct impact of perinatal (i.e. pre- and post-natal) exposure to SSRIs on affective behaviors, anxiety, and depressive behaviors, these behaviors can also be influenced by indirect mechanisms that include maternal depressive symptoms, maternal stress, maternal-offspring interactions, and gene x environment variations. For example, maternal stress influences the developing serotonergic system (St-Pierre, Laurent, King, & Vaillancourt, 2016) and there is a large literature on maternal stress effects on offspring outcomes (Glover, 2015; Maccari et al., 2003; Weinstock 2005).

¹ Occurring before birth

² During gestation and throughout lactation in rodent models. For simplicity these time pre- and post-natal time periods will be considered as ‘perinatal’ throughout the review unless otherwise specified.

Recent reviews have reported the effects of perinatal SSRI exposure on offspring social behaviors, neurodevelopmental disorders, anxious behavior, and cognition (Gemmell et al., 2018; Grieb & Ragan, 2019; Millard et al., 2017; Ramsteijn et al., 2020). This review focuses on the effects of perinatal SSRI exposure on both anxiety and depression in offspring as there is considerable overlap between these two affective behaviors, possibly reflecting a common stress-related origin (Smoller, 2016). We also review the effects of other common antidepressant treatments for perinatal depression and/or anxiety on offspring behavioral outcomes in rodents as this has not been done before. We will focus on associations between perinatal SSRI exposure and offspring affective behaviors that include anxiety, depression, and maternal/offspring interactions using evidence from human and rodent studies (see Fig. 1).³ We will also review the limited literature investigating the effects of perinatal exposure to other antidepressant medications on offspring affective outcomes.

When reviewing findings from studies in humans and rodent models we will consider: 1) how to distinguish effects of maternal mood symptoms from perinatal SSRI (and other antidepressant medications) effects on offspring outcomes, 2) how rodent development during the postnatal period may be similar to brain development during the third trimester in humans, and 3) how models of maternal stress in rodents may compare with the human experience of depression.

In humans, separating the impact of perinatal maternal affective disturbances and/or mood symptoms from the impact of antidepressant medication exposure raises critical methodological challenges (Grzeskowiak, Gilbert, & Morrison, 2012) as randomizing prenatal SSRI exposures is not feasible and ethical. Animal models provide a valuable resource in this

³ Computerized literature and manual search was conducted to identify relevant English-language studies from first available year to July 2020

1 regard as one can control for SSRI exposures and maternal stress factors. In addition, it is
2 important to consider environmental factors and offspring characteristics (age and sex/gender)
3 when investigating the risks and benefits of SSRI medication use to treat maternal mood
4 disorders. Thus, understanding of the longitudinal developmental impact of perinatal SSRI
5 exposure in the context of a variety of factors will allow us to illustrate why some children may
6 be vulnerable to prenatal SSRI exposure effects while others remain resilient or even show a
7 developmental benefit.

8 **2. Perinatal SSRIs, Anxiety, and Depressive Behavior in Children**

9 There is a growing body of clinical research investigating how perinatal SSRI exposure
10 affects childhood anxiety and depression risk (see Table 1). Recent findings have shown that
11 prenatal SSRI exposure was linked with higher levels of internalizing (anxious and depressive)
12 behavior in young children (Hermansen et al., 2016), increased risk of psychiatric disorders (e.g.,
13 mood; behavioural and emotional) in children up to 16 years of age (Liu et al., 2017), and higher
14 rates of depression diagnoses, but not anxiety diagnoses, in children and youth up to 14 years of
15 age (Malm et al., 2016). It is important to note that these three studies were limited as they did
16 not account for the impact of maternal mood, namely confounding by indication: whereby,
17 women with higher levels of depression symptoms are more likely to be treated with SSRIs and
18 it could be that the higher levels of depression symptoms, rather than the medication itself that
19 could be contributing to group differences.

20 As randomizing parental exposures is not possible for ethical and logistical reasons,
21 stringent analytic approaches have been used to address potential differences that exist between
22 depressed mothers treated and not treated with an antidepressant during pregnancy. These
23 approaches include high-dimensional propensity scores (Schneeweiss et al., 2009), discordant

1 sibling matches (an extension of matched case-control design, see Sujan et al., 2017) or
2 comparison groups of mothers with a psychiatric history and discontinued SSRIs before
3 pregnancy (Brown et al., 2016; Malm et al., 2016). Interestingly, even while these approaches
4 attenuated some of the associations between SSRI exposure and child behavior (Brown et al.,
5 2017; Malm et al 2016; Sujan et al., 2017), confounding continued to contribute to
6 developmental outcomes, suggesting that even with such optimal methodological approaches,
7 unaccounted maternal and environmental factors continue to play a role and illustrate the limits
8 to how successfully residual confounding can be eliminated.

9 Clinical studies have generally reported that maternal depression symptoms and not SSRI
10 exposure are related to childhood anxiety and depression outcomes. Cross-sectional and
11 population-based studies showed that maternal depressive symptoms, and not prenatal SSRI
12 exposure, were related to higher levels of internalizing behavior (Grzeskowiak et al., 2015; Misri
13 et al., 2006; Nulman et al., 2012; 2015) or higher levels of conduct and prosocial problems in
14 children (Pedersen et al., 2013). In a similar vein, another population-base study found that
15 maternal depressive symptoms, not SSRI exposure, were associated with more maternal reported
16 affective problems during early childhood (age 1.5- 6 years), and these results were also
17 observed using paternal reported affective problems (El Marroun et al., 2014). Other smaller
18 clinical studies have shown that in a longitudinal cohort, prenatal SSRI exposure was associated
19 with increased anxiety behaviors at three years, but did not persist to 6 years (Hanley et al., 2015;
20 Oberlander et al., 2010). In the same cohort, higher levels of depressive symptoms at 3 years
21 were also reported (Hanley et al., 2015). Another study found increased risk of prenatal SSRIs
22 exposure affecting childhood anxiety (at 5 years) has been suggested to be due to SSRI exposure
23 during late pregnancy (28 weeks or more), and not at other time points in the pregnancy

(Lupattelli et al., 2018). Besides population-based and cohort based clinical studies, one study compared children exposed prenatally to SSRIs with those siblings not exposed to SSRIs and reported that prenatal antidepressant exposure was associated with increased anxiety behaviors in three year olds compared to non-exposed siblings (Brandlistuen et al., 2015), regardless of maternal mood symptoms.

In summary, the majority of studies in humans suggest that prenatal SSRI exposure does not increase risk for internalizing and anxious behaviors in young children when maternal mood is taken into account. However, as risk for internalizing or anxious behavior may emerge later in life. Thus, additional research involving adolescents with prenatal SSRI exposure is urgently needed. It should also be noted that only one population based study investigated depressive symptoms in children after prenatal SSRI exposure. They found that prenatal SSRI exposure was related to increased rate of diagnosed depression in children less than 14 years of age (Malm et al., 2016). Taken together, the majority of research on how prenatal SSRI exposure affects childhood affective behaviors has examined internalizing and anxious behaviors and further research on prenatal SSRI exposure effects on depressive behavior in children is urgently needed. Given the impact that maternal mood symptoms can have on both the mother and child, it is also clear that effectively treating maternal mental illness should be a priority.

3. Perinatal SSRIs, Anxiety, and Depressive Behavior Research in Rodent Offspring

Rodent models investigating perinatal SSRI exposure have examined the impact on internalizing-like behaviors in offspring (i.e., anxiety, anhedonia) using a variety of SSRIs including: fluoxetine, fluvoxamine, citalopram, paroxetine, zimelidine, escitalopram, Lu10–134-C, reboxetine, and sertraline (see Table 2). Other studies have examined the impact of other antidepressant medications that also alter 5-HT signaling (though not exclusively) . These

include: clomipramine, desipramine, clorgyline, imipramine, bupropion, and buspirone (Table 3). For simplicity, we will categorize the rodent lifespan with pre-weaning at postnatal day (P) P0- P21, juvenile at P21- P50, and adult at P50 and beyond (Sengupta, 2013). It is generally agreed that P0 to P14 is similar to human fetal brain development during the third trimester (Romijn, Hofman, & Gramsbergen, 1991). In the sections below, we will first briefly describe the typical tasks used to measure anxiety and depression in rodent models (3.1), then compare possible patterns of results between: pre- versus post-natal SSRI exposure (3.2), male versus female offspring (3.3), studies that include models of maternal stress (3.4), studies that use non-SSRI medications (3.5), and then conclude with a summary of findings (3.6).

3.1 Measures of Anxiety and Depressive Behavior

There are six tasks typically used to measure anxiety-like behavior in rodents: Elevated Plus Maze (EPM), Elevated Zero Maze (EZM), Open Field Test (OFT), Novelty-Suppressed Feeding (NSF), Light-dark Choice test, and Marble Burying. In brief, EPM, EZM, and OFT assess rodents' conflict between withdrawal and approach tendencies in novel, potentially threatening environments (Rodgers & Dalvi, 1997). Rodents that are more anxious spend less time exploring potentially threatening parts of the test apparatus (e.g., open arms of the EPM or EZM, central regions of the OFT,) and spend more time in safer areas (e.g., enclosed arms of the EPM or EZM, corners of the OFT).⁴ The NSF (also known as the novelty-induced hypophagia test) is a task with a 12–24 hour food-deprived rodent who is placed in a novel environment with food to measure how long the rodent takes to obtain the food (Lee, & Lee, 2012). Rodents that

⁴ While some researchers report other aspects related to the OFT as indicators of anxiety, such as differences in the number of times of a rodent rears or “stands” up on its hind legs (e.g., Grim & Frieder, 1987; Popa et al., 2008), dips its head (e.g., Butkevich et al., 2018), distance traveled (e.g., Lee et al., 2012), or ambulation (e.g., Hilakivi et al., 1984; Hilakivi 1988a; Lisboa et al., 2007), we will focus on the clear indicator of time in the centre of the OFT. For the EPM, some researchers may report differences in the number of entries in the closed or open arms (e.g., Forcelli et al., 2008), however, again, we focused on the most definitive measure of anxiety and that is time spent on the open arms.

1 are more anxious take more time to start feeding. In the light-dark choice test, rodents are placed
2 in a box divided equally into bright and dark compartments for five minutes (Holmes et al.,
3 2003). Rodents that are more anxious spend less time in the light compartment. The marble
4 burying task places rodents in a standard rat cage filled with clean bedding and 18 marbles
5 (Borsini et al., 2002; Njung'e and Handley, 1991). After 20 minutes, the number of marbles that
6 are at least two-thirds buried is recorded. Rodents that are more anxious will bury more marbles
7 as this task tests defensive anxiety and repetitive behavior.⁵ There are two other tasks: Fear to
8 Novel Tone task (Khatri et al., 2014; Rodriguez-Porcel et., 2011; Simpson et al., 2011) and the
9 Defensive Withdrawal Test (Capello et al., 2011), which will not be included in this review, as
10 they are not standard measures of anxiety.

11 In general, three tasks are frequently used to indicate depressive- or despair-like behavior
12 in rodents. These are the forced swim test (FST), tail suspension test (TST), and the sucrose
13 preference test (SPT). The FST (Porsolt, Le Pichon, & Jalfre, 1977) requires rodents to swim in
14 an inescapable cylinder of water. After a period of vigorous activity (e.g., climbing, swimming),
15 the rodent eventually becomes immobile (e.g., moving just enough to keep its head above water).
16 The amount of time spent immobile in the FST is interpreted as a rodent's level of despair or
17 helplessness, whereby the rodent 'gives up' struggling to escape. The TST requires mice to be
18 suspended by the tail with adhesive tape to a hook connected to a strain gauge that computes the
19 total duration of immobility during a brief period of time (El Yacoubi et al., 2003; Alexandre et
20 al., 2006). As the loss of pleasure (anhedonia) is a core feature of depression, this can be
21 measured in rodent models by using the SPT (Kalueff et al., 2006). To do this, rodents are given
22 a choice between water or sucrose solution (typically 1% or 2% in water) and the preference for

⁵ Some have suggested that this task is a better test of repetitive behavior, others have argued that it should be included as a comprehensive battery of tasks rather than relying only on the Elevated Plus Maze or the Elevated Zero Maze to measure anxiety (Sprowles et al., 2017).

sucrose over water is calculated as the volume of sucrose solution consumed relative to the total volume of liquid consumed. Reduced sucrose consumption is thought to indicate more anhedonia and increased depressive-like behavior. There is an urgent need for more tests of depressive-like behaviors in rodent models such as working memory and motivation that would provide greater insight into depressive phenotypes, particularly when looking at research on prenatal SSRI exposure on development.

3.2 Anxiety and depressive-like behaviors after Pre- and/or Post-natal SSRI exposure

There is a growing body of research in rodent models examining perinatal SSRI effects on anxiety-like behavior and results are mixed (see Table 2). We have organized this information based on the time point of behavioral testing (pre-weaning, juvenile, or adult) as it is possible that the impact of SSRI exposure may emerge at different time points depending on various factors (e.g., timing of SSRI exposure, SSRI dose etc). It should be noted that the majority of this early research did not consider maternal stress or ‘mood’ as a factor on offspring outcomes and thus SSRIs were given to healthy rodents. Although interesting, translation of these findings to the clinic should be done with caution.

There have been two studies conducted during the pre-weaning period. One study found that lower doses of prenatal fluoxetine exposure increased anxiety-like behavior in mice offspring (Noorlander et al., 2008). However, another study failed to find significant differences in offspring anxiety behaviors (Bairy et al., 2007).

There have been many studies conducted with rodents during the juvenile period. Prenatal and/or postnatal SSRI exposure has been associated with increased anxiety during adolescence (Bairy et al., 2007; Butkevich & Mikhailenko, 2018; Francis-Oliveira et al., 2013;

1 Millard et al., 2019; Lee et al., 2009; 2012). Conversely, other studies have failed to find
2 significant differences between groups (prenatal and/or postnatal SSRI exposure) in adolescent
3 offspring (Avitsur et al., 2016; Coleman et al., 1999; Ehrlich et al., 2015; Forcelli et al., 2008;
4 Lisboa et al., 2007; Mikhailenko & Butkevich, 2019; Toffoli et al., 2014; Lee et al., 2012; Popa
5 et al., 2008; Rayen et al., 2011).

6 There has also been substantial research on perinatal SSRI exposure effects in adult
7 offspring using rodent models. Many studies that examined prenatal and/or postnatal SSRI
8 exposure reported increased anxiety in adult offspring (Bairry et al., 2007; Cagiano et al., 2008;
9 Noorlander et al., 2008; Olivier et al., 2011b; Smit-Rigter et al., 2012; Sprowles et al., 2016;
10 2017). (Ko et al., 2014; Soga et al., 2012; Gobinath et al., 2016; Sarkar et al., 2014; Karpova et
11 al., 2009; Rebello et al., 2014; Yu et al., 2014; Boulle et al., 2016a). Conversely, others have
12 reported that perinatal SSRI exposure decreased anxiety during adulthood (Kiryanova et al.,
13 2014; 2016; McAllister et al., 2012). Still yet other studies report no effect of pre- or post-natal
14 SSRI exposure on anxiety-like behaviors in adult offspring (Ansorge et al. 2008; Avitsur et al.,
15 2016; Boulle et al., 2016b; Bourke et al., 2013b; Coleman et al., 1999; Ehrlich et al., 2015;
16 Francis-Oliveira et al., 2013; Glover et al., 2015; Hansen et al., 1997; Harris et al., 2012;
17 Kiryanova et al., 2014; 2016; Ko et al., 2014; Lisboa et al., 2007; Meyer et al., 2018; Olivier et
18 al., 2011b; Salari et al., 2016; Sprowles et al., 2016; 2017; Zohar et al., 2016). Thus, there are a
19 number of studies with varied outcomes related to whether or not perinatal SSRI exposure affects
20 anxiety-like behaviors in offspring, as measured in these rodent models.

21 Despite the lack of research in humans on perinatal SSRI effects on the development of
22 depression, there is a rather large body of research investigating how early life exposure to SSRI
23 medications may impact depressive-like behaviors in rodent models with a focus on juvenile and

adult offspring (Table 2). One study conducted with rodents during the juvenile period have reported associations between prenatal SSRIs and increased depressive-like behavior (Millard et al., 2019). Conversely, other studies have reported that prenatal SSRI exposure decreased depressive-like behavior during adolescence (Butkevich & Mikhailenko, 2019; Mikhailenko & Butkevich, 2019), while other studies have failed to find significant effects of perinatal SSRIs on depressive-like behaviors in adolescent offspring (Avitsur et al., 2016; Butkevich & Mikhailenko, 2018; Francis-Oliveira et al., 2013; Lisboa et al., 2007, males only). For postnatal SSRI exposure, one study failed to find significant effects of SSRIs exposure (Rayen et al., 2011).

In terms of perinatal SSRI effects on depressive-like behavior in adult offspring, some studies have shown associations between prenatal SSRIs and higher levels of depressive-like behavior (Bhagya et al., 2015; Glover et al., 2015; Lisboa et al., 2007; Sprowles et al., 2016; Zohar et al., 2016). Yet, other studies have reported that prenatal SSRI exposure decreased depressive-like behavior during adulthood (Avitsur et al., 2016; McAllister et al., 2012). Finally, other studies have failed to find significant effects of perinatal SSRIs on depressive-like behaviors in adult offspring (Coleman et al., 1999; Francis-Oliveira et al., 2013; Olivier et al., 2011b; Salari et al., 2016; Sprowles et al., 2017).

Regarding postnatal SSRI exposure in rodent models, the results are more consistent with postnatal SSRI exposure being associated with increased immobility in adult rat offspring (Bhagya et al., 2015; Glover et al., 2015; Hilakivi et al., 1987; Ko et al., 2014; Rebello et al., 2014; Sarkar et al., 2014; Boulle et al 2016, Females). Conversely, two studies have reported that postnatal SSRI exposure decreased depressive-like behavior in adult offspring (Karpova et al., 2009; Mendes-da-Silva et al., 2002), while another study failed to find significant differences

1 between groups during adulthood (Boulle et al., 2016a). In sum, it is evident the perinatal
2 exposure to SSRIs does not consistently alter anxiety or depressive-like behaviors in offspring.
3 These inconsistencies may be due to a number of methodological factors and further research is
4 needed to fully determine the impact of perinatal SSRIs and maternal mood symptoms on
5 offspring outcomes.

6 **3.3 Sex Differences**

7 There are marked sex differences in affective disorders such as anxiety and depression
8 and thus it is always important to consider sex as a biological variable. Although a majority of
9 studies in rodent models have been carried out in male offspring, five perinatal SSRI studies
10 have revealed sex differences in adult offspring (Boulle et al., 2016a,b; Gobinath et al., 2016;
11 Rayen et al., 2011; Sprowles et al., 2016). Sprowles and colleagues (2016) found that female (not
12 male) rats with prenatal SSRI exposure had increased anxiety-like behavior in the OFT
13 compared to controls; however, both sexes were more anxious on the marble burying task and no
14 differences were found on the EPM compared to controls. This study illustrates how results can
15 vary within one study depending on sex and types of tasks used to measure anxiety. Another
16 study with rats reported that only males (not females) with postnatal SSRI exposure were more
17 anxious during the EPM (less time in open arms) than controls, yet, both sexes were more
18 anxious on the NSF task (increased latency to feed) compared to controls (Gobinath et al., 2016).
19 Boulle et al (2016a, b) also performed similar studies in male and female offspring and showed
20 that exposure to fluoxetine after birth via administration to the rat dam resulted in increased
21 anxiety-like behavior in adult male, but not female, offspring. Taken together, these sex
22 differences in the long-term effects of perinatal exposure to SSRIs indicate the importance of
23 future researchers to include sex specific analyses.

Although limited, perinatal SSRIs have been reported to have sexually differentiated effects on depressive-like behavior in rodent offspring. As mentioned previously, Lisboa et al. (2007) found that prenatal fluoxetine was associated with increased depressive-like behavior in adolescent female, not male, mice. Boulle et al (2016a,b) also showed that early postnatal SSRIs, regardless of maternal stress, increased depressive-like behavior in adult female, but not male, rat offspring. Postnatal SSRI exposure via lactation, as performed in Boulle et al (2016a,b), had no effect on depressive-like behavior in adolescent male or female rat offspring (Rayen et al 2011) suggesting a possible post-pubertal effect of SSRIs on depression. Future research considering sex of the offspring is vital to determine how early life exposures alter developmental trajectories.

3.4 Models of Maternal Stress

Maternal mood is an important factor to consider when looking at perinatal SSRI effects on development. In rodent models, maternal stress has been used to model aspects of maternal depression and maternal stress itself can also affect anxiety and depressive outcomes in offspring. When taking maternal gestational stress exposure into account, recent studies have found that perinatal SSRI exposure protected against the effects of maternal stress by reducing anxiety-like behaviors induced by maternal stress (Boulle et al., 2016a; Butkevich & Mikhailenko, 2019; Kiryanova et al., 2016; Mikhailenko & Butkevich, 2019; Rayen et al., 2011; Salari et al., 2016; Zohar et al., 2016), while others found that perinatal SSRIs did not protect against the effects of prenatal stress on anxiety outcomes in offspring (Avitsur et al., 2016; Boulle et al., 2016b; Bourke et al., 2013b; Ehrlich et al., 2015; Zohar et al., 2016). One study has reported that prenatal SSRI exposure exacerbated the effects of exposure to maternal depression in a rodent model of endogenous high levels of depression (Millard et al., 2019). The

differences in results from these studies may be due to sex of the offspring tested, stress paradigm used, SSRI dose, offspring age and testing paradigms.

Interestingly, the effects of perinatal SSRIs on offspring anxiety and depressive-like behaviors are not always in the same direction. For example, Zohar and colleagues (2016) found that prenatal SSRI exposure protected against prenatal stress effects on anxiety (EPM), but not on depressive-like behavior; whereas, Boulle et al. (2016b) showed that regardless of maternal stress exposure adult female offspring exposed via lactation to SSRIs did not differ in levels of anxiety-like behaviors but did show increases in immobility. Taken together, the majority of this limited number of studies suggest that prenatal SSRI exposure may buffer against the negative impact of maternal stress during pregnancy on rodent offspring anxious behavior, but sex-specific effects are evident.

3.5 Perinatal exposure to other antidepressant medications

When looking at the effects of other pharmacotherapies to treat perinatal anxiety and depression symptoms and their effects on anxious behavior in rodent offspring (Table 3), mixed results are also evident. One study reported that only male rats with prenatal venlafaxine exposure (7.5mg/kg) were less anxious during the Light Dark task (more time in light) compared to controls, while female rats with prenatal venlafaxine exposure at a higher dosage (37.5mg/kg) were less anxious on this same task compared to controls (Bogi et al., 2018). This study illustrates how results can vary within one study by both sex and dosage of medication exposure. However, other studies with buspirone or buspirone combined with fluoxetine administered perinatally reported no significant differences in anxiety in juvenile offspring (Mikhailenko & Butkevich, 2019; Sprowles et al., 2017). Postnatal clorgyline, an anti-anxiety or antidepressant medication, administration after birth resulted in increased anxiety in adult offspring (Yu et al.,

2014). As there only a few studies examining the relation between other anti-depressant or anti-anxiety medications (administered pre- or post-natal) more research is needed before stronger conclusion can be drawn.

In terms of perinatal antidepressant medication effects on offspring depressive-like behavior (Table 3), some researchers have reported that perinatal exposure to non-SSRIs reduced depressive-like behaviors in juvenile offspring (Mikhailenko & Butevich, 2019; Butkevich & Mikhailenko, 2019) while others failed to find significant effects of perinatal antidepressant medication exposure on depressive-like behavior (Sprowles et al., 2017). Other researchers have reported the perinatal non-SSRI exposure increased depressive-like behaviors in adult offspring (Bhagya et al., 2015; Hilakivi et al., 1987b; Limón-Morales et al., 2014; Vázquez-Palacios et al., 2005; Velazquez-Moctezuma et al., 1992; Yang et al., 2008). Conversely, adult female rat offspring with prenatal venlafaxine (37.5mg/kg) exposure were less depressed (reduced immobility) than male offspring (Bogi et al., 2018). Interestingly, Bhagya and colleagues (2015) found that prenatal exposure to clomipramine was associated with increased depressive-like behaviors, which was reversed in offspring with a combination of clomipramine and reboxetine treatment during adulthood, suggesting that reboxetine may be beneficial to treat those with prenatal exposure to antidepressants, but this needs to be supported with additional research before firmer conclusions can be drawn. To date, no studies with non-SSRIs have examined possible sex differences or included models of maternal stress in relation to depressive-like behavioral outcomes in offspring. These factors need to be addressed by future research.

3.6 Summary of Findings

Rodent studies suggest that perinatal SSRIs, and other types of antidepressant medications to treat maternal stress-related disorders, are not consistently associated with

changes in offspring anxiety as the majority of tasks administered report null results ($n = 75$, 56%, see Figure 2). These conclusions are consistent with a recent meta-analysis that found no significant differences between animals with and without perinatal SSRI exposure in relation to anxiety behaviors ($p = .06$; Ramsteijn et al., 2020). However, our conclusion diverges from Grieb and Ragan (2019) who suggest that perinatal SSRI treatment modifies anxiety behaviors as our count of null results ($n = 75$) exceed the count of tasks demonstrating increased and decreased anxiety behaviors (total $n = 45$, 14, respectively). One possibility to explain this discrepancy is that we chose to count all tasks within a study indicating outcomes in anxiety behaviors, while Grieb and Ragan (2019) provided only a summary outcome of each study when two or more tasks were in the same direction. Their type of global summary underestimates the total number of anxiety behavior outcomes. Our review also includes more recent studies (e.g., Millard et al., 2019), which would not have been available to Grieb and Ragan (2019).

In terms of depressive-like behavior, the majority of rodent studies suggest that perinatal SSRIs, and other antidepressant medications to treat maternal mental illnesses, may increase depressive-like behavior in offspring ($n = 30$, 47%, see Figure 2). As this is the first review of these outcomes in animal models, no cross-review comparisons can be made. While there are more instances of increased depressive-like behavior associated with perinatal SSRI and non-SSRI exposure, there are also a substantial number of null results ($n = 16$; 25%). It is also possible that the number of null results may be underestimated as it is typically more challenging to publish non-significant findings. A similar number of studies reported that perinatal SSRIs, and other antidepressant medications to treat maternal mental illnesses, may decrease depressive-like behavior in offspring ($n = 18$; 28%). Discrepancies between study results may be due to a number of factors but clearly more research is needed that considers maternal mood/stress,

1 medication type and dose, timing of exposure and sex of the offspring before stronger
2 conclusions about perinatal SSRI exposure effects on anxiety and depressive-like behavior in
3 offspring can be made.

4 **4. Perinatal SSRIs, Maternal Depressive Symptoms, and Mother-Child Interactions**

5 Mother-child interactions, as well as father-child interactions, are important as they
6 contribute to the security of children's attachment (e.g., Bowlby, 1982) and insecure attachment
7 has been linked with higher rates of specific anxiety symptoms in children, including: separation
8 anxiety (Moss, Smolla, Cyr, Dubois-Comtois, Mazzarello, & Berthiaume, 2006), school phobia
9 (Bar-Heim, Dan, Eshel, & Sagi-Schwartzl, 2007), and social anxiety (Bar-Heim et al., 2007;
10 Bohlin, Hagekull, & Rydell, 2000; Brumariu & Kerns, 2008). As 5-HT modulates maternal mood
11 and several socially motivated behaviors, it is not surprising that it plays a role in the transition to
12 motherhood and the regulation of mother-child interactions thereafter (Pawluski, Li, & Lonstein,
13 2019). In addition, mothers with anxiety, depression, and stress frequently demonstrate changes
14 in their offspring caregiving behaviors (Pawluski et al., 2017; Hillerer et al., 2012; Talge et al.,
15 2007). Specifically, anxious and depressed mothers often respond more negatively, and less
16 sensitively, to their infants compared to non-depressed mothers (Field, 1995; Field et al., 1990;
17 Fleming et al., 1988). In terms of interactions, depressed mother-infant dyads often have reduced
18 mutual attention, vocal and visual communications, touching, and smiling when compared to
19 healthy controls (Field, 1995; Field et al., 1990).

20 While clinical studies are scarce, it has been reported that during free-play and feeding,
21 mothers treated with SSRIs do not differ in negative or positive interaction compared to mothers
22 not treated with SSRIs, yet, mothers treated with SSRIs and Rivotal (a benzodiazepine
23 derivative) show more inconsistent negative and positive messages towards their infants (Reebye

et al., 2002). Another study which controlled for maternal depressive symptoms found that SSRI treated mothers interrupted their infants more than control dyads (Weikum et al., 2013). Further, maternal depression was related to poorer infant readiness to play in both control and SSRI treated dyads (Weikum et al., 2013), suggesting a complex relationship between SSRIs, maternal mood, and mother-child interactions.

There is growing evidence that gestational stress is associated with postpartum depression-like behavior and altered maternal interactions in rodent models. For example, daily restraint stress during pregnancy affects nursing, nest building, and other aspects of caring for offspring (Belnoue et al., 2016; Champagne & Meaney, 2006; Hillerer et al., 2012; Smith, Seckl, Evans, Costall, & Smythe, 2004). These maternal care-giving behaviors can have long-term effects on offspring neurobehavioral development including disorganized attachment patterns (Meaney, 2001; O'Donnell et al., 2014; Rifkin-Graboi et al., 2015; Wazana et al., 2015).

SSRI treatment to rodent dams during pregnancy has also been associated with increased nesting, licking and touching offspring (high doses only) and maternal aggression (Johns et al., 2005). Others have reported that gestational SSRI treatment to dams reduces time nursing (Kott et al., 2018). When SSRIs are administered during the postpartum, increased active nursing behaviors (i.e. arched-back nursing) and decreased passive nursing behavior have been reported (Pawluski et al., 2012b; Workman et al., 2016). Interestingly, one study in adult female offspring exposed to SSRIs prenatally, found delayed maternal behavior particularly in pup retrieval in the early postpartum period (Svirsky, Levy, & Avitsur, 2016). This suggests a potential long-term effect of SSRIs on maternal behavior across generations.

Although sparse, there is evidence from rodent research that SSRIs combined with maternal stress can affect maternal offspring-directed caregiving behaviors (for review see

Pawluski et al 2019) but much more research is needed in this area. Regardless, differences in maternal care-giving behaviors in rodent models during the first week of life may mediate and moderate the effects of perinatal exposures on developmental outcomes.

5. Perinatal SSRIs, Maternal Depressive Symptoms, and Gene/ Environment Variation

While alterations in 5-HT signaling associated with developmental exposure to SSRIs may shape vulnerability for anxiety and depressive disturbances in childhood or across the life span, such exposures alone do not explain why some children are at risk and others remain resilient. Thus, incorporating information about interactions between genetic variations and the perinatal environment may offer a window into explaining heterogeneity in developmental outcomes (Boyce & Ellis, 2005; Moffitt et al., 2005). Allelic variations influence susceptibility to environmental context (i.e. Gene Environment (G x E) interactions) (Belsky & Pluess, 2009; Caspi & Moffitt, 2006; Moffitt et al., 2005) and allelic variations in SLC6A4 (serotonin transporter gene) in particular have been widely studied as a key moderator of early life environmental influences. Caspi et al. (2003) reported that childhood maltreatment predicts adult depression among individuals with at least one copy of the short allele. Building on this seminal paper, the short allele has been widely studied as a crucial moderator of mental illness risk in adulthood (Karg et al., 2011; Kendler, 2005; Kendler et al., 2005; Lesch, 2011; Schinka et al., 2004). However, not all outcomes associated with having the short allele are negative (Risch et al., 2009) and not all studies have replicated these relationships (Willis-Owen et al., 2005), raising questions about the role of other factors that may underlie G x E interactions (Duncan, 2013), such as maternal mood disturbances and/ or perinatal SSRI exposure.

In line with this, higher levels of prenatal maternal anxiety predicted higher levels of negative emotionality in 6 month old infants with two short alleles than those with long alleles

(Pluess et al., 2011). However, when there was low maternal stress, genotype failed to have an impact, suggesting that infant genotype only mattered in the context of prenatal maternal mood. Similarly, Weikum et al. (2013) showed that 6 years olds with the short allele of SLC6A4 (reflecting reduced levels of 5-HT reuptake) showed resilience to increased maternal depressive symptoms in mothers, as they did not exhibit compromised executive function. In contrast, children with two long alleles (reflecting greater availability of serotonin transporter) who were exposed to mothers with fewer depressive symptoms had higher scores on executive function tasks, while exposure to greater depressive symptoms correlated with the lowest executive function scores, suggesting higher sensitivity of the L allele to maternal depressive symptoms.

Beyond genetic factors, everyday context also matters. For example, a recent study examined associations between day-to-day home environment and child self-regulation skills in 6 year olds (Dhaliwal et al., 2017; Dhaliwal et al., in press). Interestingly, children of mothers with higher prenatal depressive symptoms (regardless of SSRI treatment) were less susceptible to the everyday chaos at home (e.g., household noise, disorganization, etc). In contrast, children of mothers with lower levels of prenatal mood symptoms were much more susceptible to the household environment and in this setting this effect was moderated by prenatal exposure to SSRIs. This suggests that prenatal SSRI exposure with lower depressive symptoms serves as a risk factor for greater sensitivity to house chaotic environment, while prenatal maternal mood regardless to SSRI exposure may “buffer” the child’s outcomes from the current house environment. Taken together, both variation in genetics and environment (maternal depressive symptoms and/ or SSRI exposure) can influence children’s outcomes and this needs to be the focus of future research in order to determine risk and reliance.

6. Limitations and Strengths

Our aim was to provide a review of human and animal literature that reports effects of perinatal SSRIs on anxiety and depression in offspring. In doing so we chose the most significant measures of anxiety and depression in animal models and summarized these in Tables 2 and 3. Other reviews on this topic have used only one behavioral test per study (e.g., Ramsteijn et al., 2020 only use data from the first time a behavioral test was administered, unless there was a learning component, to provide a “snap shot” of each study) or the overall results of a study (Grieb & Ragan, 2019); whereas, we chose to treat each assessment within a study as a separate task as it occurred at a different developmental time point. For example, Bairy et al., (2007) measured anxiety during pre-weaning (P18) using one task and the juvenile stage (P30) using two tasks. Thus, we counted all three tasks as only counting the first assessment point would underestimate our knowledge of anxiety behaviors in rodents throughout their lifespan. We also chose to focus on summarizing the research results and we chose not to weigh results according to sample size as this was beyond the scope of the review; however, future researchers should consider this option.

It remains difficult to generalize rodent literature to wide variations of symptoms and environmental factors inherent to human clinical setting. We acknowledge that while preclinical research is incredibly valuable for further investigation in the clinic, these are models that provide insight into the human condition but may be fraught with limitations due to testing paradigms, physiological differences, and the difficulty of measuring human affective states in animals.

7. Future Directions and Conclusion

Our review of rodent studies suggests that results from perinatal exposure to both SSRIs and other common antidepressants may more consistently increase depressive-like, but not

1 anxious behaviors, in offspring. Among studies of outcomes in humans, the majority of studies
2 suggest that prenatal SSRI exposure does not increase risk for internalizing and anxious
3 behaviors in young children, especially when maternal mood is controlled for using stringent
4 analytic approaches (Rommel et al., 2020). Moreover, to date research studying SSRI exposure
5 and depressive behaviors remains limited and needs increased attention.

6 Emotional and behavioral dysregulation in early childhood has been linked to poor social
7 adjustment and psychiatric diagnoses later in life (Cicchetti, Rogosch, & Toth, 1998; Nilsen,
8 Gustavson, Røysamb, Kjeldsen, & Karevold, 2013; Rutter, Kim-Cohen, & Maughan, 2006).
9 Thus, understanding how perinatal maternal mental health and antidepressant treatment
10 contributes to anxiety and depression behaviors in childhood should remain a critical research
11 focus. Identifying factors that shape the development of anxiety and depression patterns across
12 the early life span could lead to earlier mental health detection and prevention. Whether
13 developmental exposure to SSRIs program processes that reflect that disruption of 5-HT
14 homeostasis results in alterations in anxiety and depressive symptoms remains to be conclusively
15 demonstrated in humans.

16 It remains a significant challenge to identify a main or direct effect of SSRI exposure in
17 the context of such a complex phenomenon as maternal mood disorders during pregnancy.
18 Clarifying developmental risk in this setting requires continued studies that consider long-term
19 behavioral outcomes in the context of stress, role of genetic variations, positive care-giving, and
20 other possible factors that account for vulnerability and resiliency in this context. With this in
21 mind, it may be less important to distinguish the component of behavior that is more susceptible
22 to maternal mood or perinatal SSRI exposure, but instead focus on the context of the child's
23 environment. Regardless of how perinatal SSRIs and perinatal maternal depressive symptoms

1 contribute to the development of anxiety and depression symptoms in children, it remains an
2 urgent undertaking to identify and treat maternal mood disorders during pregnancy (Pawluski &
3 Dickens, 2019). Beyond SSRI exposure, poorly or undertreated depression during the peripartum
4 and beyond has adverse consequences for mothers and their children. Finding ways to best
5 promote optimal maternal and child health in the context of maternal perinatal mood
6 disturbances remains essential.

References

- American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th edn.). Arlington, VA: American Psychiatric Publishing.
- Alexandre, C., Popa, D., Fabre, V., Bouali, S., Venault, P., Lesch, K. P., ... & Adrien, J. (2006). Early life blockade of 5-hydroxytryptamine 1A receptors normalizes sleep and depression-like behavior in adult knock-out mice lacking the serotonin transporter. *Journal of Neuroscience*, 26(20), 5554-5564.
- Altieri, S. C., Yang, H., O'brien, H. J., Redwine, H. M., Senturk, D., Hensler, J. G., & Andrews, A. M. (2015). Perinatal vs genetic programming of serotonin states associated with anxiety. *Neuropsychopharmacology*, 40(6), 1456-1470.
- Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry*, 40(01), 57–87. doi:10.1111/1469-7610.00424.
- Ansorge, M. S., Morelli, E., & Gingrich, J. A. (2008). Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice. *Journal of Neuroscience*, 28(1), 199-207.
- Ansorge, M. S., Zhou, M., Lira, A., Hen, R., & Gingrich, J. A. (2004). Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science*, 306(5697), 879-881.
- Avitsur, R., Grinshpahet, R., Goren, N., Weinstein, I., Kirshenboim, O., & Chlebowsky, N. (2016). Prenatal SSRI alters the hormonal and behavioral responses to stress in female mice: Possible role for glucocorticoid resistance. *Hormones and Behavior*, 84, 41-49.
- Azmitia, E. C. (1999). Serotonin neurons, neuroplasticity, and homeostasis of neural tissue. *Neuropsychopharmacology*, 21(1), 33-45.
- Bairy, K. L., Madhyastha, S., Ashok, K. P., Bairy, I., & Malini, S. (2007). Developmental and behavioral consequences of prenatal fluoxetine. *Pharmacology*, 79(1), 1-11.
- Bar-Haim, Y., Dan, O., Eshel, Y., & Sagi-Schwartz, A. (2007). Predicting children's anxiety from early attachment relationships. *Journal of Anxiety Disorders*, 21, 1061–1068.
- Belnoue, L., Malvaut, S., Ladevèze, E., Abrous, D. N., & Koehl, M. (2016). Plasticity in the olfactory bulb of the maternal mouse is prevented by gestational stress. *Scientific Reports*, 6, 37615.
- Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: differential susceptibility to environmental influences. *Psychological Bulletin*, 135(6), 885.
- Bhagya, V., Srikumar, B. N., Raju, T. R., & Shankaranarayana Rao, B. S. (2015). The selective noradrenergic reuptake inhibitor reboxetine restores spatial learning deficits, biochemical changes, and hippocampal synaptic plasticity in an animal model of depression. *Journal of Neuroscience Research*, 93(1), 104-120.
- Bogi, E., Belovicová, K., Ujhazy, E., Mach, M., Koprdoval, R., Zilava, L., ... & Dubovicky, M. (2018). Perinatal exposure to venlafaxine leads to lower anxiety and depression-like behavior in the adult rat offspring. *Behavioural pharmacology*, 29(5), 445-452.
- Bohlin, G., Hagekull, B., & Rydell, A. M. (2000). Attachment and social functioning: A longitudinal study from infancy to middle childhood. *Social Development*, 9, 24–39.
- Borsini, F., Podhorna, J., & Marazziti, D. (2002). Do animal models of anxiety predict anxiolytic-like effects of antidepressants?. *Psychopharmacology*, 163(2), 121-141.
- Boulle, F., Pawluski, J. L., Homberg, J. R., Machiels, B., Kroeze, Y., Kumar, N., ... & Van den

- 1 Hove, D. L. (2016a). Prenatal stress and early-life exposure to fluoxetine have enduring
2 effects on anxiety and hippocampal BDNF gene expression in adult male offspring.
3 *Developmental Psychobiology*, 58(4), 427-438.
- 4 Boulle, F., Pawluski, J. L., Homberg, J. R., Machiels, B., Kroeze, Y., Kumar, N., ... & van den
5 Hove, D. L. (2016b). Developmental fluoxetine exposure increases behavioral despair
6 and alters epigenetic regulation of the hippocampal BDNF gene in adult female offspring.
7 *Hormones and Behavior*, 80, 47-57.
- 8 Bourke, C. H., Capello, C. F., Rogers, S. M., Megan, L. Y., Boss-Williams, K. A., Weiss, J. M.,
9 ... & Owens, M. J. (2013a). Prenatal exposure to escitalopram and/or stress in rats.
10 *Psychopharmacology*, 228(2), 231-241.
- 11 Bourke, C. H., Stowe, Z. N., Neigh, G. N., Olson, D. E., & Owens, M. J. (2013b). Prenatal
12 exposure to escitalopram and/or stress in rats produces limited effects on endocrine,
13 behavioral, or gene expression measures in adult male rats. *Neurotoxicology and*
14 *Teratology*, 39, 100-109.
- 15 Bourke, C. H., Stowe, Z. N., & Owens, M. J. (2014). Prenatal antidepressant exposure: clinical
16 and preclinical findings. *Pharmacological Reviews*, 66(2), 435-465.
- 17 Bowlby, J. (1982). *Attachment and loss: Vol. 1. Attachment* (2nd ed.). New York: Basic Books.
- 18 Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary–
19 developmental theory of the origins and functions of stress reactivity. *Development and*
20 *Psychopathology*, 17(2), 271-301.
- 21 Brandlistuen, R. E., Ystrom, E., Eberhard-Gran, M., Nulman, I., Koren, G., & Nordeng, H.
22 (2015). Behavioural effects of fetal antidepressant exposure in a Norwegian cohort of
23 discordant siblings. *International Journal of Epidemiology*, 44(4), 1397-1407.
24 doi:10.1093/ije/dyv030
- 25 Brown, H. K., Ray, J. G., Wilton, A. S., Lunsby, Y., Gomes, T., & Vigod, S. N. (2017).
26 Association between serotonergic antidepressant use during pregnancy and autism
27 spectrum disorder in children. *JAMA*, 317(15), 1544-1552.
- 28 Brummelte, S., & Galea, L. A. (2010). Chronic corticosterone during pregnancy and postpartum
29 affects maternal care, cell proliferation and depressive-like behavior in the dam.
30 *Hormones and Behavior*, 58(5), 769-779.
- 31 Brummelte, S., & Galea, L. A. (2016). Postpartum depression: Etiology, treatment and
32 consequences for maternal care. *Hormones and Behavior*, 77, 153-166.
- 33 Brummelte, S., Pawluski, J. L., & Galea, L. A. (2006). High post-partum levels of corticosterone
34 given to dams influence postnatal hippocampal cell proliferation and behavior of
35 offspring: A model of post-partum stress and possible depression. *Hormones and*
36 *Behavior*, 50(3), 370-382.
- 37 Brumariu, L., & Kerns, K. A. (2010). Parent–child attachment in internalizing symptomatology
38 in childhood and adolescence: A review of empirical findings and future directions.
39 *Development and Psychopathology*, 22, 177–203.
- 40 Butkevich, I. P., & Mikhailenko, V. A. (2018). Effect of fluoxetine in prenatal period on
41 nociceptive system reactivity and psychoemotional behavior in young female rats.
42 *Bulletin of Experimental Biology and Medicine*, 165(2), 209-212.
- 43 Butkevich, I. P., Mikhailenko, V. A., Vershinina, E. A., & Barr, G. A. (2019). Differences
44 Between the Prenatal Effects of Fluoxetine or Buspirone Alone or in Combination on
45 Pain and Affective Behaviors in Prenatally Stressed Male and Female Rats. *Frontiers in*
46 *Behavioral Neuroscience*, 13, 125.

- 1 Cagiano, R., Flace, P., Bera, I., Maries, L., Cioca, G., Sabatini, R., ... & Stefanelli, R. (2008).
2 Neurofunctional effects in rats prenatally exposed to fluoxetine. *European review for*
3 *medical and pharmacological sciences*, 12(3), 137.
- 4 Capello, C. F., Bourke, C. H., Ritchie, J. C., Stowe, Z. N., Newport, D. J., Nemeroff, A., &
5 Owens, M. J. (2011). Serotonin transporter occupancy in rats exposed to serotonin
6 reuptake inhibitors in utero or via breast milk. *Journal of Pharmacology and*
7 *Experimental Therapeutics*, 339(1), 275-285.
- 8 Caspi, A., & Moffitt, T. E. (2006). Gene–environment interactions in psychiatry: joining forces
9 with neuroscience. *Nature Reviews Neuroscience*, 7(7), 583.
- 10 Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., ... & Poulton, R.
11 (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-
12 HTT gene. *Science*, 301(5631), 386-389.
- 13 Champagne, F. A., & Meaney, M. J. (2006). Stress during gestation alters postpartum maternal
14 care and the development of the offspring in a rodent model. *Biological Psychiatry*,
15 59(12), 1227-1235.
- 16 Charlton, R. A., Jordan, S., Pierini, A., Garne, E., Neville, A. J., Hansen, A. V., ... & Bos, H. J.
17 (2015). Selective serotonin reuptake inhibitor prescribing before, during and after
18 pregnancy: A population-based study in six European regions. *BJOG: An International*
19 *Journal of Obstetrics & Gynaecology*, 122(7), 1010-1020.
- 20 Cicchetti, D., Rogosch, F. A., & Toth, S. L. (1998). Maternal depressive disorder and contextual
21 risk: Contributions to the development of attachment insecurity and behavior problems in
22 toddlerhood. *Development and Psychopathology*, 10(2), 283-300.
- 23 Cipriani, A., Brambilla, P., Furukawa, T. A., Geddes, J., Gregis, M., Hotopf, M., ... & Barbui, C.
24 (2005). Fluoxetine versus other types of pharmacotherapy for depression. *Cochrane*
25 *Database of Systematic Reviews*, (4).
- 26 Coleman, F. H., Christensen, H. D., Gonzalez, C. L., & Rayburn, W. F. (1999). Behavioral
27 changes in developing mice after prenatal exposure to paroxetine (Paxil). *American*
28 *Journal of Obstetrics and Gynecology*, 181(5), 1166-1171.
- 29 Curtius, H. C., Niederwieser, A., Viscontini, M., Leimbacher, W., Wegmann, H., Blehova, B., ...
30 & Schmidt, H. (1981). Serotonin and dopamine synthesis in phenylketonuria. In
31 Serotonin (pp. 277-291). Springer, Boston, MA.
- 32 Dalley, M. B., Bolocofsky, D. N., & Karlin, N. J. (1994). Teacher ratings and self-ratings of
33 social competency in adolescents with low- and high-depressive symptoms. *Journal of*
34 *Abnormal Child Psychology*, 22(4), 477–485. doi:10.1007/BF02168086.
- 35 Dhaliwal, G., Weikum, W., Jolicoeur-Martineau, A., Brain, U., Grunau, R., & Oberlander, T.
36 (2017). Household chaos, maternal depression and prenatal ssri exposure interact to
37 affect executive function of 6 year old children. *Paediatrics & Child Health*, 22(suppl_1),
38 e8-e9.
- 39 Da-Silva, V. A., Altenburg, S. P., Malheiros, L. R., Thomaz, T. G., & Lindsey, C. J. (1999).
40 Postnatal development of rats exposed to fluoxetine or venlafaxine during the third week
41 of pregnancy. *Brazilian Journal of Medical and Biological Research*, 32(1), 93-98.
- 42 da Silva, A. I., Monteiro Galindo, L. C., Nascimento, L., Moura Freitas, C., Manhaes-de-Castro,
43 R., Lagranha, C. J., & Lopes de Souza, S. (2014). Fluoxetine treatment of rat neonates
44 significantly reduces oxidative stress in the hippocampus and in behavioral indicators of
45 anxiety later in postnatal life. *Canadian Journal of Physiology and Pharmacology*, 92(4),
46 330-337.

- 1 Di Pino, G., Moessner, R., Lesch, K. P., Lauder, J. M., & Persico, A. M. (2004). Roles for
2 serotonin in neurodevelopment: more than just neural transmission. *Current*
3 *Neuropharmacology*, 2(4), 403-417.
- 4 Duncan, L. E. (2013). Paying attention to all results, positive and negative. *Journal of the*
5 *American Academy of Child & Adolescent Psychiatry*, 52(5), 462-465.
- 6 Ehrlich, D. E., Neigh, G. N., Bourke, C. H., Nemeth, C. L., Hazra, R., Ryan, S. J., ... & Stowe, Z.
7 N. (2015). Prenatal stress, regardless of concurrent escitalopram treatment, alters
8 behavior and amygdala gene expression of adolescent female rats. *Neuropharmacology*,
9 97, 251-258.
- 10 Ellfolk, M., & Malm, H. (2010). Risks associated with in utero and lactation exposure to
11 selective serotonin reuptake inhibitors (SSRIs). *Reproductive Toxicology*, 30(2), 249-260.
- 12 El Marroun, H., et al. (2014). Prenatal exposure to selective serotonin reuptake inhibitors and
13 social responsiveness symptoms of autism: population-based study of young children.
14 *British Journal of Psychiatry*, 205(2): 95-102.
- 15 El Yacoubi, M., Bouali, S., Popa, D., Naudon, L., Leroux-Nicollet, I., Hamon, M., ... &
16 Vaugeois, J. M. (2003). Behavioral, neurochemical, and electrophysiological
17 characterization of a genetic mouse model of depression. *Proceedings of the National*
18 *Academy of Sciences*, 100(10), 6227-6232.
- 19 Feldman, R., Granat, A., Pariente, C., Kanety, H., Kuint, J., Gilboa-Schechtman, E., 2009.
20 Maternal depression and anxiety across the postpartum year and infant social
21 engagement, fear regulation, and stress reactivity. *Journal of American Academy of Child*
22 *Adolescent Psychiatry*, 48, 919-927. Doi:10.1097/CHI.0b013e3181b21651.
- 23 Fichter, M. M., Quadflieg, N., Fischer, U. C., & Kohlboeck, G. (2010). Twenty-five-year course
24 and outcome in anxiety and depression in the upper Bavarian longitudinal community
25 study. *Acta Psychiatrica Scandinavica*, 122(1), 75-85.
26 doi:10.1111/j.160-0447.2009.01512.x.
- 27 Field, T., 1995. Psychologically depressed parents. In: Bornstein, M. (Ed.), Handbook of
28 Parenting. L. Erlbaum Associates, New Jersey.
- 29 Field, T., Healy, B., Goldstein, M., Guthertz, M., 1990. Behavior-state matching and synchrony
30 in mother-infant interactions of nondepressed versus depressed dyads. *Developmental*
31 *Psychobiology*, 26, 7-14.
- 32 Fleming, A.S., Ruble, D.N., Flett, G.L., Shaul, D., 1988. Postpartum adjustment in first time
33 mothers: relations between mood, maternal attitudes and mother-infant interactions'.
34 *Developmental Psychobiology*, 24, 71-81.
- 35 Forcelli, P. A. and S. C. Heinrichs (2008). Teratogenic effects of maternal antidepressant
36 exposure on neural substrates of drug-seeking behavior in offspring. *Addiction Biology*
37 13(1): 52-62.
- 38 Fritz, C. O., Morris, P. E., & Richler, J. J. (2012). Effect size estimates: current use, calculations,
39 and interpretation. *Journal of Experimental Psychology: General*, 141(1), 2.
- 40 Gemmel, M., Bögi, E., Ragan, C., Hazlett, M., Dubovicky, M., van den Hove, D. L., ... &
41 Pawluski, J. L. (2018). Perinatal selective serotonin reuptake inhibitor medication (SSRI)
42 effects on social behaviors, neurodevelopment and the epigenome. *Neuroscience &*
43 *Biobehavioral Reviews*, 29, 1169-1184.
- 44 Gentile, S. (2017). Untreated depression during pregnancy: Short- and long-term effects in
45 offspring. A systematic review. *Neuroscience*, 342, 154-166.
- 46 Glover, V. (2015). Prenatal stress and its effects on the fetus and the child: possible underlying

- biological mechanisms. In *Perinatal programming of neurodevelopment* (pp. 269-283). Springer, New York, NY.
- Glover, M. E., Pugh, P. C., Jackson, N. L., Cohen, J. L., Fant, A. D., Akil, H., & Clinton, S. M. (2015). Early-life exposure to the SSRI paroxetine exacerbates depression-like behavior in anxiety/depression-prone rats. *Neuroscience*, 284, 775-797.
- Gobinath, A. R., Workman, J. L., Chow, C., Lieblich, S. E., & Galea, L. A. (2016). Maternal postpartum corticosterone and fluoxetine differentially affect adult male and female offspring on anxiety-like behavior, stress reactivity, and hippocampal neurogenesis. *Neuropharmacology*, 101, 165-178.
- Goodman, S. H., Rouse, M. H., Connell, A. M., Broth, M. R., Hall, C. M., & Heyward, D. (2011). Maternal depression and child psychopathology: A meta-analytic review. *Clinical Child and Family Psychology Review*, 14(1), 1-27. doi:10.1007/s10567-010-0080-1
- Grieb, Z. A., & Ragan, C. M. (2019). The effects of perinatal SSRI exposure on anxious behavior and neurobiology in rodent and human offspring. *European Neuropsychopharmacology*.
- Grimm, V. E., & Frieder, B. (1987). Prenatal and early postnatal exposure to zimelidine: behavioral, neurochemical and histological findings in rats. *International Journal of Neuroscience*, 33(3-4), 225-235.
- Grzeskowiak, M. L. E., Gilbert, A. L., & Morrison, J. L. (2011). Investigating outcomes following the use of selective serotonin reuptake inhibitors for treating depression in pregnancy. *Drug Safety*, 34(11), 1027-1048.
- Grzeskowiak, L. E., Gilbert, A. L., & Morrison, J. L. (2012). Long term impact of prenatal exposure to SSRIs on growth and body weight in childhood: Evidence from animal and human studies. *Reproductive Toxicology*, 34(1), 101-109.
- Grzeskowiak, L. E., Morrison, J. L., Henriksen, T. B., Bech, B. H., Obel, C., Olsen, J., & Pedersen, L. H. (2015). Prenatal antidepressant exposure and child behavioural outcomes at 7 years of age: A study within the Danish National Birth Cohort. *BJOG: An International Journal of Obstetrics & Gynaecology*, 123(12), 1919-1928.
- Handley, S. L. (1991). Evaluation of marble-burying behavior as a model of anxiety. *Pharmacology Biochemistry and Behavior*, 38(1), 63-67.
- Hanley, G. E., Brain, U., & Oberlander, T. F. (2015). Prenatal exposure to serotonin reuptake inhibitor antidepressants and childhood behavior. *Pediatric Research*, 78(2), 174. doi:10.1038/pr.2015.77
- Hansen, H. H., Sanchez, C., & Meier, E. (1997). Neonatal administration of the selective serotonin reuptake inhibitor Lu 10-134-C increases forced swimming-induced immobility in adult rats: a putative animal model of depression?. *Journal of Pharmacology and Experimental Therapeutics*, 283(3), 1333-1341.
- Harris, S. S., Maciag, D., Simpson, K. L., Lin, R. C., & Paul, I. A. (2012). Dose-dependent effects of neonatal SSRI exposure on adult behavior in the rat. *Brain research*, 1429, 52-60.
- Hellendall, R. P., Schambra, U. B., Liu, J. P., & Lauder, J. M. (1993). Prenatal expression of 5-HT1C and 5-HT2 receptors in the rat central nervous system. *Experimental Neurology*, 120(2), 186-201.
- Hermansen, T. K., Røysamb, E., Augusti, E. M., & Melinder, A. (2016). Behavior and inhibitory control in children with prenatal exposure to antidepressants and medically untreated depression. *Psychopharmacology*, 233(8), 1523-1535.

- 1 Hilakivi, L. A., Sinclair, J. D., & Hilakivi, I. T. (1984). Effects of neonatal treatment with
2 clomipramine on adult ethanol related behavior in the rat. *Developmental Brain*
3 *Research*, 15(1), 129-132.
- 4 Hilakivi, L. A., Stenberg, D., Sinclair, J. D., & Kiianmaa, K. (1987a). Neonatal desipramine or
5 zimeldine treatment causes long-lasting changes in brain monoaminergic systems and
6 alcohol related behavior in rats. *Psychopharmacology*, 91(4), 403-409.
- 7 Hilakivi, L. A., & Hilakivi, I. (1987b). Increased adult behavioral 'despair' in rats neonatally
8 exposed to desipramine or zimeldine: an animal model of depression?. *Pharmacology*
9 *Biochemistry and Behavior*, 28(3), 367-369.
- 10 Hilakivi, L. A., Taira, T., & Hilakivi, I. (1988a). Early postnatal deprivation of active sleep with
11 desipramine or zimeldine impairs later behavioural reactivity to auditory stimuli in rats.
12 *Acta physiologica scandinavica*, 132(2), 191-198.
- 13 Hilakivi, L. A., Taira, T., Hilakivi, I., & Loikas, P. (1988b). Neonatal Treatment with
14 Monoamine Uptake Inhibitors Alters Later Response in Behavioural 'Despair' Test to β
15 and GABA-B Receptor Agonists. *Pharmacology & Toxicology*, 63(1), 57-61.
- 16 Hill, M.A. (2020, September 2) **Embryology Rat Development Stages**. Retrieved from
17 https://embryology.med.unsw.edu.au/embryology/index.php/Rat_Development_Stages
- 18 Hiller, K. M., Neumann, I. D., & Slattery, D. A. (2012). From stress to postpartum mood and
19 anxiety disorders: how chronic peripartum stress can impair maternal adaptations.
20 *Neuroendocrinology*, 95(1), 22-38.
- 21 Holmes, A., Li, Q., Murphy, D. L., Gold, E., & Crawley, J. N. (2003). Abnormal anxiety-related
22 behavior in serotonin transporter null mutant mice: the influence of genetic background.
23 *Genes, Brain and Behavior*, 2(6), 365-380.
- 24 Huether, G., Thömke, F., & Adler, L. (1992). Administration of tryptophan-enriched diets to
25 pregnant rats retards the development of the serotonergic system in their offspring.
26 *Developmental Brain Research*, 68(2), 175-181.
- 27 Hutchison, S. M., Masse, L. C., Pawluski, J. L., & Oberlander, T. F. (2018). Perinatal selective
28 serotonin reuptake inhibitor (SSRI) effects on body weight at birth and beyond: A review
29 of animal and human studies. *Reproductive Toxicology*, 77, 109-121.
- 30 Ishikawa, C., & Shiga, T. (2017). The postnatal 5-HT_{1A} receptor regulates adult anxiety and
31 depression differently via multiple molecules. *Progress in Neuro-Psychopharmacology*
32 *and Biological Psychiatry*, 78, 66-74.
- 33 Johns, J. M., Joyner, P. W., McMurray, M. S., Elliott, D. L., Hofler, V. E., Middleton, C. L., ...
34 & Walker, C. H. (2005). The effects of dopaminergic/serotonergic reuptake inhibition on
35 maternal behavior, maternal aggression, and oxytocin in the rat. *Pharmacology*
36 *Biochemistry and Behavior*, 81(4), 769-785.
- 37 Kalueff, A. V., Gallagher, P. S., & Murphy, D. L. (2006). Are serotonin transporter knockout
38 mice 'depressed'? Hypoactivity but no anhedonia. *Neuroreport*, 17(12), 1347-1351.
- 39 Karpova, N. N., Lindholm, J., Pruunsild, P., Timmusk, T., & Castrén, E. (2009). Long-lasting
40 behavioural and molecular alterations induced by early postnatal fluoxetine exposure are
41 restored by chronic fluoxetine treatment in adult mice. *European*
42 *neuropsychopharmacology*, 19(2), 97-108.
- 43 Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter
44 variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic
45 moderation. *Archives of General Psychiatry*, 68(5), 444-454.
- 46 Kendler, K. S. (2005). Toward a philosophical structure for psychiatry. *American Journal of*

- 1 *Psychiatry*, 162(3), 433-440.
- 2 Kendler, K. S., Kuhn, J. W., Vittum, J., Prescott, C. A., & Riley, B. (2005). The interaction of
3 stressful life events and a serotonin transporter polymorphism in the prediction of
4 episodes of major depression: a replication. *Archives of General Psychiatry*, 62(5), 529-
5 535.
- 6 Khatri, N., Simpson, K. L., Lin, R. C., & Paul, I. A. (2014). Lasting neurobehavioral
7 abnormalities in rats after neonatal activation of serotonin 1A and 1B receptors: possible
8 mechanisms for serotonin dysfunction in autistic spectrum disorders.
9 *Psychopharmacology*, 231(6), 1191-1200.
- 10 Kim, J., Riggs, K. W., Misri, S., Kent, N., Oberlander, T. F., Grunau, R. E., ... & Rurak, D. W.
11 (2006a). Stereoselective disposition of fluoxetine and norfluoxetine during pregnancy and
12 breast-feeding. *British Journal of Clinical Pharmacology*, 61(2), 155-163.
- 13 Kim, J., Riggs, K. W., Misri, S., Kent, N., Oberlander, T. F., Grunau, R. E., ... & Rurak, D. W.
14 Oberlander, T. F., Warburton, W., Misri, S., Aghajanian, J., & Hertzman, C. (2006b).
15 Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor
16 antidepressants and maternal depression using population-based linked health data.
17 *Archives of general psychiatry*, 63(8), 898-906.
- 18 Kiryanova, V., & Dyck, R. H. (2014). Increased aggression, improved spatial memory, and
19 reduced anxiety-like behaviour in adult male mice exposed to fluoxetine early in life.
20 *Developmental Neuroscience*, 36(5), 396-408.
- 21 Kiryanova, V., Meunier, S. J., Vecchiarelli, H. A., Hill, M. N., & Dyck, R. H. (2016). Effects of
22 maternal stress and perinatal fluoxetine exposure on behavioral outcomes of adult male
23 offspring. *Neuroscience*, 320, 281-296.
- 24 Ko, M. C., Lee, L. J. H., Li, Y., & Lee, L. J. (2014). Long-term consequences of neonatal
25 fluoxetine exposure in adult rats. *Developmental Neurobiology*, 74(10), 1038-1051.
- 26 Lesch, K. P. (2011). When the serotonin transporter gene meets adversity: the contribution of
27 animal models to understanding epigenetic mechanisms in affective disorders and
28 resilience. In *Molecular and Functional Models in Neuropsychiatry* (pp. 251-280).
29 Springer, Berlin, Heidelberg.
- 30 Lee, L. J. (2009). Neonatal fluoxetine exposure affects the neuronal structure in the
31 somatosensory cortex and somatosensory-related behaviors in adolescent rats.
32 *Neurotoxicity research*, 15(3), 212-223.
- 33 Lee, L. J., & Lee, L. J. H. (2012). Neonatal fluoxetine exposure alters motor performances of
34 adolescent rats. *Developmental Neurobiology*, 72(8), 1122-1132.
- 35 Lesch, K. P. (2007). Linking emotion to the social brain. *EMBO reports*, 8(S1), S24-S29.
- 36 Lewinsohn, P. M., Zinbarg, R., Seeley, J. R., Lewinsohn, M., & Sack, W. H. (1997). Lifetime
37 comorbidity among anxiety disorders and between anxiety disorders and other mental
38 disorders in adolescents. *Journal of Anxiety Disorders*, 11(4), 377-394.
39 doi:10.1016/S0887-6185(97)00017-0.
- 40 Limón-Morales, O., Soria-Fregozo, C., Arteaga-Silva, M., Vázquez-Palacios, G., & Bonilla-
41 Jaime, H. (2014). Altered expression of 5-HT1A receptors in adult rats induced by
42 neonatal treatment with clomipramine. *Physiology & Behavior*, 124, 37-44.
- 43 Lisboa, S. F., Oliveira, P. E., Costa, L. C., Venâncio, E. J., & Moreira, E. G. (2007). Behavioral
44 evaluation of male and female mice pups exposed to fluoxetine during pregnancy and
45 lactation. *Pharmacology*, 80(1), 49-56.
- 46 Lira, A., Zhou, M., Castanon, N., Ansorge, M. S., Gordon, J. A., Francis, J. H., ... & Kung, H. F.

- (2003). Altered depression-related behaviors and functional changes in the dorsal raphe nucleus of serotonin transporter-deficient mice. *Biological Psychiatry*, 54(10), 960-971.
- Liu, X., Agerbo, E., Ingstrup, K. G., Musliner, K., Meltzer-Brody, S., Bergink, V., & Munk-Olsen, T. (2017). Antidepressant use during pregnancy and psychiatric disorders in offspring: Danish nationwide register based cohort study. *bmj*, 358, j3668.
- Lucki, I. (1998). The spectrum of behaviors influenced by serotonin. *Biological Psychiatry*, 44, 151-162.
- Lupattelli, A., Wood, M., Ystrom, E., Skurtveit, S., Handal, M., & Nordeng, H. (2018). Effect of time-dependent selective serotonin reuptake inhibitor antidepressants during pregnancy on behavioral, emotional, and social development in preschool-aged children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 57(3), 200-208. doi:10.1016/j.jaac.2017.12.010
- Maccari, S., Darnaudery, M., Morley-Fletcher, S., Zuena, A. R., Cinque, C., & Van Reeth, O. (2003). Prenatal stress and long-term consequences: Implications of glucocorticoid hormones. *Neuroscience & Biobehavioral Reviews*, 27(1-2), 119-127.
- Malm, H., Brown, A. S., Gissler, M., Gyllenberg, D., Hinkka-Yli-Salomäki, S., McKeague, I. W., ... & Sourander, A. (2016). Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: a national register-based study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(5), 359-366. doi:10.1016/j.jaac.2016.02.013
- Martín-Ruiz, R., Puig, M. V., Celada, P., Shapiro, D. A., Roth, B. L., Mengod, G., & Artigas, F. (2001). Control of serotonergic function in medial prefrontal cortex by serotonin-2A receptors through a glutamate-dependent mechanism. *Journal of Neuroscience*, 21(24), 9856-9866.
- Matsumoto, A. K., Higashi, C. M., Bonifácio, K. L., Barbosa, M. A., Klein, R. M., Filgueiras, G. B., ... & Moreira, E. G. (2016). Co-exposure to fish oil or folic acid does not reverse effects in the progeny induced by maternal exposure to fluoxetine. *Neurotoxicology and Teratology*, 56, 1-8.
- McAllister, B. B., Kiryanova, V., & Dyck, R. H. (2012). Behavioural outcomes of perinatal maternal fluoxetine treatment. *Neuroscience*, 226, 356-366.
- Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience*, 24(1), 1161-1192.
- Mendes-da-Silva, C., Souza, S. L. D., Barreto-Medeiros, J. M., Freitas-Silva, S. R. D., Antunes, D. E. C., Cunha, A. D. U., ... & Manhães-de-Castro, R. (2002). Neonatal treatment with fluoxetine reduces depressive behavior induced by forced swim in adult rats. *Arquivos de neuro-psiquiatria*, 60(4), 928-931.
- Meyer, L. R., Dexter, B., Lo, C., Kenkel, E., Hirai, T., Roghair, R. D., & Haskell, S. E. (2018). Perinatal SSRI exposure permanently alters cerebral serotonin receptor mRNA in mice but does not impact adult behaviors. *The Journal of Maternal-Fetal & Neonatal Medicine*, 31(11), 1393-1401.
- Mikhailenko, V. A., & Butkevich, I. P. (2019). Prenatal stimulation of 5-HT 1A receptors improves adaptive behavior in prenatally stressed rats. *Bulletin of experimental biology and medicine*, 166(3), 306-309.
- Millard, S. J., Weston-Green, K., & Newell, K. A. (2017). The effects of maternal antidepressant

- use on offspring behaviour and brain development: Implications for risk of neurodevelopmental disorders. *Neuroscience & Biobehavioral Reviews*, 80, 743-765.
- Millard, S. J., Lum, J. S., Fernandez, F., Weston-Green, K., & Newell, K. A. (2019). Perinatal exposure to fluoxetine increases anxiety-and depressive-like behaviours and alters glutamatergic markers in the prefrontal cortex and hippocampus of male adolescent rats: A comparison between Sprague-Dawley rats and the Wistar-Kyoto rat model of depression. *Journal of Psychopharmacology*, 33(2), 230-243.
- Miller, J. C., & Friedhoff, A. J. (1986). Development of specificity and stereoselectivity of rat brain dopamine receptors. *International Journal of Developmental Neuroscience*, 4(1), 21- 26.
- Misri, S., & Kostaras, X. (2002). Benefits and risks to mother and infant of drug treatment for postnatal depression. *Drug Safety*, 25(13), 903-911.
- Misri, S., Reebye, P., Kendrick, K., Carter, D., Ryan, D., Grunau, R. E., & Oberlander, T. F. (2006). Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. *American Journal of Psychiatry*, 163(6), 1026-1032.
- Mnie-Filali, O., Faure, C., Lambás-Señas, L., El Mansari, M., Belblidia, H., Gondard, E., ... & Blier, P. (2011). Pharmacological blockade of 5-HT 7 receptors as a putative fast acting antidepressant strategy. *Neuropsychopharmacology*, 36(6), 1275-1288.
- Moffitt, T. E., Caspi, A., & Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry*, 62(5), 473-481.
- Moss, E., Smolla, N., Cyr, C., Dubois-Comtois Mazzarello, T., & Berthiaume, C. (2006). Attachment and behavior problems in middle childhood as reported by adults and child informants. *Development and Psychopathology*, 18, 425-444.
- Nielsen, J. B., Lou, H. C., & Andresen, J. (1990). Biochemical and clinical effects of tyrosine and tryptophan in the Rett syndrome. *Brain and Development*, 12(1), 143-147.
- Nilsen, W., Gustavson, K., Røysamb, E., Kjeldsen, A., & Karevold, E. (2013). Pathways from maternal distress and child problem behavior to adolescent depressive symptoms: a prospective examination from early childhood to adolescence. *Journal of Developmental & Behavioral Pediatrics*, 34(5), 303-313.
- Noorlander, C. W., Ververs, F. F., Nikkels, P. G., van Echteld, C. J., Visser, G. H., & Smidt, M. P. (2008). Modulation of serotonin transporter function during fetal development causes dilated heart cardiomyopathy and lifelong behavioral abnormalities. *PloS one*, 3(7), e2782.
- Nulman, I., Koren, G., Rovet, J., Barrera, M., Pulver, A., Streiner, D., & Feldman, B. (2012). Neurodevelopment of children following prenatal exposure to venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression. *American Journal of Psychiatry*, 169(11), 1165-1174. doi:10.1176/appi.ajp.2012.11111721
- Nulman, I., Koren, G., Rovet, J., Barrera, M., Streiner, D. L., & Feldman, B. M. (2015). Neurodevelopment of children prenatally exposed to selective reuptake inhibitor antidepressants: Toronto sibling study. *The Journal of Clinical Psychiatry*, 76(7), e842-7.
- Oberlander, T., Gingrich, J. A., & Ansorge, M. S. (2009). Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: molecular to clinical evidence. *Clinical Pharmacology & Therapeutics*, 86(6), 672-677.
- Oberlander, T. F., Papsdorf, M., Brain, U. M., Misri, S., Ross, C., & Grunau, R. E. (2010).

- Prenatal effects of selective serotonin reuptake inhibitor antidepressants, serotonin transporter promoter genotype (SLC6A4), and maternal mood on child behavior at 3 years of age. *Archives of Pediatrics & Adolescent Medicine*, 164(5), 444-451. doi:10.1001/archpediatrics.2010.51
- Oberlander, T. F., Reebye, P., Misri, S., Papsdorf, M., Kim, J., & Grunau, R. E. (2007). Externalizing and attentional behaviors in children of depressed mothers treated with a selective serotonin reuptake inhibitor antidepressant during pregnancy. *Archives of Pediatrics & Adolescent Medicine*, 161(1), 22-29.
- O'Donnell, K. A., Gaudreau, H., Colalillo, S., Steiner, M., Atkinson, L., Moss, E., ... & Silveira, P. P. (2014). The maternal adversity, vulnerability and neurodevelopment project: theory and methodology. *The Canadian Journal of Psychiatry*, 59(9), 497-508.
- Olivier, J. D. A., Blom, T., Arentsen, T., & Homberg, J. R. (2011a). The age-dependent effects \ of selective serotonin reuptake inhibitors in humans and rodents: A review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 35(6), 1400-1408.
- Olivier, J. D., Valles, A., van Heesch, F., Afrasiab-Middelmann, A., Roelofs, J. J., Jonkers, M., ... & Martens, G. J. (2011b). Fluoxetine administration to pregnant rats increases anxiety-related behavior in the offspring. *Psychopharmacology*, 217(3), 419.
- Pawluski, J. L., Charlier, T. D., Fillet, M., Houbart, V., Crispin, H. T., Steinbusch, H. W., & van den Hove, D. L. (2012b). Chronic fluoxetine treatment and maternal adversity differentially alter neurobehavioral outcomes in the rat dam. *Behavioural Brain Research*, 228(1), 159-168.
- Pawluski, J., & Dickens, M. (2019). Pregnancy: A final frontier in mental health research. *Archives of Women's Mental Health*, 22(6), 831-832.
- Pawluski, J. L., Li, M., & Lonstein, J. S. (2019). Serotonin and motherhood: From molecules to mood. *Frontiers in Neuroendocrinology*.
- Pawluski, J. L., Lonstein, J. S., & Fleming, A. S. (2017). The neurobiology of postpartum anxiety and depression. *Trends in Neurosciences*, 40(2), 106-120.
- Pawluski, J. L., Rayen, I., Niessen, N. A., Kristensen, S., van Donkelaar, E. L., Balthazart, J., ... & Charlier, T. D. (2012). Developmental fluoxetine exposure differentially alters central and peripheral measures of the HPA system in adolescent male and female offspring. *Neuroscience*, 220, 131-141.
- Petersen, I., Gilbert, R. E., Evans, S. J., Man, S. L., & Nazareth, I. (2011). Pregnancy as a major determinant for discontinuation of antidepressants: An analysis of data from The Health Improvement Network. *The Journal of Clinical Psychiatry*, 72(7), 979-985.
- Pluess, M., Velders, F. P., Belsky, J., Van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., Jaddoe, V. W., ... & Tiemeier, H. (2011). Serotonin transporter polymorphism moderates effects of prenatal maternal anxiety on infant negative emotionality. *Biological Psychiatry*, 69(6), 520-525.
- Popa, D., Léna, C., Alexandre, C., & Adrien, J. (2008). Lasting syndrome of depression produced by reduction in serotonin uptake during postnatal development: Evidence from sleep, stress, and behavior. *Journal of Neuroscience*, 28(14), 3546-3554.
- Porsolt, R. D., Le Pichon, M., & Jalfre, M. L. (1977). Depression: a new animal model sensitive to antidepressant treatments. *Nature*, 266(5604), 730.
- Rampono, J., Simmer, K., Ilett, K. F., Hackett, L. P., Doherty, D. A., Elliot, R., ... & Forman, T. (2009). Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry*, 42(03), 95-100.

- 1 Ramsteijn, A. S., Van de Wijer, L., Rando, J., van Luijk, J., Homberg, J. R., & Olivier, J. D.
2 (2020). Perinatal selective serotonin reuptake inhibitor exposure and behavioral
3 outcomes: a systematic review and meta-analyses of animal studies. *Neuroscience &*
4 *Biobehavioral Reviews*.
- 5 Rayen, I., Van Den Hove, D. L., Prickaerts, J., Steinbusch, H. W., & Pawluski, J. L. (2011).
6 Fluoxetine during development reverses the effects of prenatal stress on depressive-like
7 behavior and hippocampal neurogenesis in adolescence. *PloS one*, 6(9), e24003.
- 8 Rebello, T. J., Yu, Q., Goodfellow, N. M., Cagliostro, M. K. C., Teissier, A., Morelli, E., ... &
9 Lambe, E. K. (2014). Postnatal day 2 to 11 constitutes a 5-HT-sensitive period impacting
10 adult mPFC function. *Journal of Neuroscience*, 34(37), 12379-12393.
- 11 Reebye, P.N., Morison, S.J., Panikkar, H., Misri, S., Grunau, R.E., 2002. Affect expression in
12 prenatally psychotropic exposed and non exposed mother–infant dyads. *Infant Mental*
13 *Health Journal* 23, 403–416.
- 14 Rifkin-Graboi, A., Kong, L., Sim, L. W., Sanmugam, S., Broekman, B. F. P., Chen, H., ... &
15 Gluckman, P. D. (2015). Maternal sensitivity, infant limbic structure volume and
16 functional connectivity: a preliminary study. *Translational Psychiatry*, 5(10), e668.
- 17 Risch, N., Herrell, R., Lehner, T., Liang, K. Y., Eaves, L., Hoh, J., ... & Merikangas, K. R.
18 (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life
19 events, and risk of depression: A meta-analysis. *Jama*, 301(23), 2462-2471.
- 20 Rodgers, R. J., & Dalvi, A. (1997). Anxiety, defence and the elevated plus-maze. *Neuroscience*
21 *& Biobehavioral Reviews*, 21(6), 801-810.
- 22 Rodriguez-Porcel, F., Green, D., Khatri, N., Harris, S. S., May, W. L., Lin, R. C., & Paul, I. A.
23 (2011). Neonatal exposure of rats to antidepressants affects behavioral reactions to
24 novelty and social interactions in a manner analogous to autistic spectrum disorders. *The*
25 *Anatomical Record*, 294(10), 1726-1735.
- 26 Romijn, H. J., Hofman, M. A., & Gramsbergen, A. (1991). At what age is the developing
27 cerebral cortex of the rat comparable to that of the full-term newborn human baby?. *Early*
28 *Human Development*, 26(1), 61-67.
- 29 Rommel, A. S., Bergink, V., Liu, X., Munk-Olsen, T., & Molenaar, N. M. (2020). Long-Term
30 Effects of Intrauterine Exposure to Antidepressants on Physical, Neurodevelopmental,
31 and Psychiatric Outcomes: A Systematic Review. *The Journal of Clinical Psychiatry*,
32 81(3).
- 33 Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities in
34 psychopathology between childhood and adult life. *Journal of Child Psychology and*
35 *Psychiatry*, 47(3-4), 276-295.
- 36 Salari, A. A., Fatehi-Gharehlar, L., Motayagheni, N., & Homberg, J. R. (2016). Fluoxetine
37 normalizes the effects of prenatal maternal stress on depression-and anxiety-like
38 behaviors in mouse dams and male offspring. *Behavioural brain research*, 311, 354-367.
- 39 Sarkar, A., Chachra, P., & Vaidya, V. A. (2014). Postnatal fluoxetine-evoked anxiety is
40 prevented by concomitant 5-HT2A/C receptor blockade and mimicked by postnatal 5-
41 HT2A/C receptor stimulation. *Biological psychiatry*, 76(11), 858-868.
- 42 Seeman, P., Bzowej, N. H., Guan, H. C., Bergeron, C., Becker, L. E., Reynolds, G. P., ... &
43 Tourtellotte, W. W. (1987). Human brain dopamine receptors in children and aging
44 adults. *Synapse*, 1(5), 399-404.
- 45 Sengupta, P. (2013). The laboratory rat: relating its age with human's. *International Journal of*
46 *Preventive medicine*, 4(6), 624.

- 1 Schaefer, T. L., Grace, C. E., Braun, A. A., Amos-Kroohs, R. M., Graham, D. L., Skelton, M. R.,
2 ... & Vorhees, C. V. (2013). Cognitive impairments from developmental exposure to
3 serotonergic drugs: citalopram and MDMA. *International Journal o*
4 *Neuropsychopharmacology*, 16(6), 1383-1394.
- 5 Scharfstein, L., Alfano, C., Beidel, D., & Wong, N. (2011). Children with generalized anxiety
6 disorder do not have peer problems, just fewer friends. *Child Psychiatry and Human*
7 *Development*, 42(6), 712–723. doi:10.1007/s10578-011-0245-2.
- 8 Scharfstein, L. A., & Beidel, D. C. (2015). Social skills and social acceptance in children with
9 anxiety disorders. *Journal of Clinical Child & Adolescent Psychology*, 44(5), 826–838.
10 doi:10.1080/15374416.2014.895938.
- 11 Schinka, J. A., Busch, R. M., & Robichaux-Keene, N. (2004). A meta-analysis of the association
12 between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety.
13 *Molecular Psychiatry*, 9(2), 197.
- 14 Schneeweiss, S., Rassen, J. A., Glynn, R. J., Avorn, J., Mogun, H., & Brookhart, M. A. (2009).
15 High-dimensional propensity score adjustment in studies of treatment effects using health
16 care claims data. *Epidemiology*, 20(4), 512- 522.
- 17 Shah, F., & Morgan, S. B. (1996). Teacher's ratings of social competence of children with high
18 versus low levels of depressive symptoms. *Journal of School Psychology*, 34(4), 337–
19 349. doi:10.1016/S0022-4405(96)00019-2.
- 20 Shaw, D. S., Connell, A., Dishion, T. J., Wilson, M. N., & Gardner, F. (2009). Improvements in
21 maternal depression as a mediator of intervention effects on early childhood problem
22 behavior. *Development and Psychopathology*, 21(2), 417-439.
- 23 Simpson, K. L., Weaver, K. J., de Villers-Sidani, E., Lu, J. Y. F., Cai, Z., Pang, Y., ... & Lin, R.
24 C. (2011). Perinatal antidepressant exposure alters cortical network function in rodents.
25 *Proceedings of the National Academy of Sciences*, 108(45), 18465-18470.
- 26 Smit-Rigter, L. A., Noorlander, C. W., von Oerthel, L., Chameau, P., Smidt, M. P., & van Hooft,
27 J. A. (2012). Prenatal fluoxetine exposure induces life-long serotonin 5-HT₃ receptor-
28 dependent cortical abnormalities and anxiety-like behaviour. *Neuropharmacology*, 62(2),
29 865-870.
- 30 Smith, J. W., Seckl, J. R., Evans, A. T., Costall, B., & Smythe, J. W. (2004). Gestational stress
31 induces post-partum depression-like behaviour and alters maternal care in rats.
32 *Psychoneuroendocrinology*, 29(2), 227-244.
- 33 Smoller, J. W. (2016). The genetics of stress-related disorders: PTSD, depression, and anxiety
34 disorders. *Neuropsychopharmacology*, 41(1), 297-319.
- 35 Soga, T., Wong, D. W., Putteeraj, M., Song, K. P., & Parhar, I. S. (2012). Early-life citalopram-
36 induced impairments in sexual behavior and the role of androgen receptor. *Neuroscience*,
37 225, 172-184.
- 38 Sprowles, J. L., Hufgard, J. R., Gutierrez, A., Bailey, R. A., Jablonski, S. A., Williams, M. T., &
39 Vorhees, C. V. (2016). Perinatal exposure to the selective serotonin reuptake inhibitor
40 citalopram alters spatial learning and memory, anxiety, depression, and startle in
41 Sprague-Dawley rats. *International Journal of Developmental Neuroscience*, 54, 39-52.
- 42 Sprowles, J. L., Hufgard, J. R., Gutierrez, A., Bailey, R. A., Jablonski, S. A., Williams, M. T., &
43 Vorhees, C. V. (2017). Differential effects of perinatal exposure to antidepressants on
44 learning and memory, acoustic startle, anxiety, and open-field activity in Sprague-
45 Dawley rats. *International Journal of Developmental Neuroscience*, 61, 92-111.
- 46 St-Pierre, J., Laurent, L., King, S., & Vaillancourt, C. (2016). Effects of prenatal maternal stress

- on serotonin and fetal development. *Placenta*, 48, S66-S71.
- Sujan, A. C., Rickert, M. E., Öberg, A. S., Quinn, P. D., Hernández-Díaz, S., Almqvist, C., ... & D'Onofrio, B. M. (2017). Associations of maternal antidepressant use during the first trimester of pregnancy with preterm birth, small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder in offspring. *JAMA*, 317(15), 1553-1562.
- Svirsky, N., Levy, S., & Avitsur, R. (2016). Prenatal exposure to selective serotonin reuptake inhibitors (SSRI) increases aggression and modulates maternal behavior in offspring mice. *Developmental Psychobiology*, 58(1), 71-82.
- Talge, N. M., Neal, C., Glover, V., & Early Stress, Translational Research and Prevention Science Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health. (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: how and why?. *Journal of Child Psychology and Psychiatry*, 48(3-4), 245-261.
- Toffoli, L. V., Rodrigues Jr, G. M., Oliveira, J. F., Silva, A. S., Moreira, E. G., Pelosi, G. G., & Gomes, M. V. (2014). Maternal exposure to fluoxetine during gestation and lactation affects the DNA methylation programming of rat's offspring: modulation by folic acid supplementation. *Behavioural Brain Research*, 265, 142-147.
- Vázquez-Palacios, G., Bonilla-Jaime, H., & Velázquez-Moctezuma, J. (2005). Antidepressant effects of nicotine and fluoxetine in an animal model of depression induced by neonatal treatment with clomipramine. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 29(1), 39-46.
- Velazquez-Moctezuma, J., & Ruiz, O. D. (1992). Neonatal treatment with clomipramine increased immobility in the forced swim test: an attribute of animal models of depression. *Pharmacology Biochemistry and Behavior*, 42(4), 737-739.
- Vesselinovitch, S. D., & Mihailovich, N. (1967). The neonatal and infant age periods as biologic factors which modify multicarcinogenesis by urethan. *Cancer Research*, 27(8 Part 1), 1422-1429.
- Wazana, A., Moss, E., Jolicoeur-Martineau, A., Graffi, J., Tsabari, G., Lecompte, V., ... & Atkinson, L. (2015). The interplay of birth weight, dopamine receptor D4 gene (DRD4), and early maternal care in the prediction of disorganized attachment at 36 months of age. *Development and Psychopathology*, 27(4pt1), 1145-1161.
- Weikum, W. M., Mayes, L. C., Grunau, R. E., Brain, U., & Oberlander, T. F. (2013). The impact of prenatal serotonin reuptake inhibitor (SRI) antidepressant exposure and maternal mood on mother–infant interactions at 3 months of age. *Infant Behavior and Development*, 36(4), 485-493.
- Weinstock, M. (2005). The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain, Behavior, and Immunity*, 19(4), 296-308.
- Whitaker-Azmitia, P. M., Druse, M., Walker, P., & Lauder, J. M. (1995). Serotonin as a developmental signal. *Behavioural Brain Research*, 73(1), 19-29.
- Willis-Owen, S. A., Turri, M. G., Munafò, M. R., Surtees, P. G., Wainwright, N. W., Brixey, R. D., & Flint, J. (2005). The serotonin transporter length polymorphism, neuroticism, and depression: A comprehensive assessment of association. *Biological Psychiatry*, 58(6), 451-456.
- Workman, J. L., Gobinath, A. R., Kitay, N. F., Chow, C., Brummelte, S., & Galea, L. A. (2016).

- 1 Parity modifies the effects of fluoxetine and corticosterone on behavior, stress reactivity,
2 and hippocampal neurogenesis. *Neuropharmacology*, 105, 443-453.
- 3 World Health Organizatio (WHO) (n.d.). Retreved from:
4 https://www.who.int/maternal_child_adolescent/topics/maternal/maternal_perinatal/en/
- 5 Yang, L. M., Hu, B., Xia, Y. H., Zhang, B. L., & Zhao, H. (2008). Lateral habenula lesions
6 improve the behavioral response in depressed rats via increasing the serotonin level in
7 dorsal raphe nucleus. *Behavioural brain research*, 188(1), 84-90.
- 8 Yu, Q., Teixeira, C. M., Mahadevia, D., Huang, Y., Balsam, D., Mann, J. J., ... & Ansorge, M. S.
9 (2014). Dopamine and serotonin signaling during two sensitive developmental periods
10 differentially impact adult aggressive and affective behaviors in mice. *Molecular*
11 *psychiatry*, 19(6), 688-698.
- 12 Zheng, J., Xu, D. F., Li, K., Wang, H. T., Shen, P. C., Lin, M., ... & Wang, R. (2011). Neonatal
13 exposure to fluoxetine and fluvoxamine alteres spine density in mouse hippocampal CA1
14 pyramidal neurons. *InternationalJjournal of Clinical and Experimental Pathology*, 4(2),
15 162.
- 16 Zohar, I., Shoham, S., & Weinstock, M. (2016). Perinatal citalopram does not prevent the effect
17 of prenatal stress on anxiety, depressive-like behaviour and serotonergic transmission in
18 adult rat offspring. *European Journal of Neuroscience*, 43(4), 590-600.
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Table 1

Summary of human research investigating perinatal SSRI exposure and internalizing behavior in children

Reference	# of Pt.	Group	Time	Design	Age	Measures	Results	Maternal Mood
Grzeskowiak et al., 2015	210 231 48,737	AD D-No AD No AD	Prenatal	Retro	0-7	DSDQ	AD $\neq$ internalizing (emotional symptoms, peer problems) D-No AD $\uparrow$ internalizing	Controlled for prenatal mental disturbances
Malm et. al., 2016	15,729 9,651 7,980 31,394	SSRI PD P.SSRI Control	Prenatal or before pregnancy	Retro	0-14	Diagnosis of depression, anxiety	SSRI $\uparrow$ Depression, $\neq$ anxiety	-
Liu et al., 2017	854,241 30,079 17,560 3,503	No AD AD Dis AD AD NU	Prenatal and new users during pregnancy	Retro	0-16	Psychiatric diagnosis codes in children	AD $\uparrow$ psychiatric disorder (e.g., mood; neurotic, stress related, and somatoform disorder; behavioural and emotional) compared to no AD use	-
Lupattelli et al., 2018	290 3,775	SSRI No SSRI	Early, Mid, Late (28+ weeks)	Prosp	1.5, 3, 5	CBCL	Late-pregnancy SSRI only $\uparrow$ Anxiety, Depression at 5 years	Controlled for prenatal anxiety and depression symptoms
Brandlistuen et al., 2015	112 14,323	AD No AD siblings	Prenatal	Retro	1.5, 3	CBCCL/2-3	AD $\uparrow$ Anxiety at 3 years than siblings	Controlled for prenatal and postpartum anxiety/depression symptoms, and lifetime depression
El Marroun et al., 2014	69 376 5531	SSRI D-No SSRI Control	Prenatal	Retro	1.5, 3, 6	Dutch version of CBCL	SSRI $\neq$ affective problems MDS $\uparrow$ affective problems	Controlled for prenatal and postpartum depressive symptoms
Oberlander et	33	SSRI	Prenatal	Prosp	3	CBCL	SSRI $\uparrow$ internalizing behavior	Controlled for

al., 2010	42	No SSRI						prenatal and postpartum depressive symptoms
Hanley et al., 2015	44 66	SSRI No SSRI	Prenatal	Prosp	3, 6	CBCL at 3 years, HBQ at 6 years	SSRI ↑ internalizing behavior, anxiety, depression at 3 years SSRI ↑ internalizing behavior, ≠ anxiety at 6 years	Controlled for prenatal and postpartum depression/anxiety
Hermansen et al., 2016	28 42 33	SSRI D-No AD Control	Prenatal	Prosp	5-6	CBCL	SSRI ↑ internalizing behavior	-
Misri et al., 2006	22 14	SSRI No SSRI	Prenatal	Prosp	4-5	CBCL, CBCL teacher report, Clinician rated mother-child interactions	SSRI ≠ internalizing behavior (parent, teacher, clinician rating) MDS ↑ internalizing behavior (parent rating only)	Controlled for concurrent depression and anxiety symptoms
Nulman et al., 2012	62 62 54 62	VEN SSRI D-No AD Control	Prenatal	Prosp	3-6	CBCL, CPRS	SSRI & VEN ≠ internalizing behavior MDS ↑ internalizing behavior	Controlled for depressive symptoms at 4-5 years and recall measure prenatal depressive symptoms
Nulman et al., 2015	45 45	SSRI No SSRI Sibling	Prenatal	Prosp	3-6	CBCL, CPRS	SSRI ≠ internalizing behavior MDS ↑ internalizing behavior	Controlled for depressive symptoms at 4-5 years and recall measure prenatal depressive symptoms
Pedersen et al., 2013	127 98 723	AD D-No AD Control	Prenatal	Retro	4-5	DSDQ	AD ≠ internalizing (emotional symptoms, peer problems) D-No AD ↑ conduct and prosocial problems	Controlled for concurrent depressive symptoms

Note. Arrows indicate significant differences (increases/ decreases) between SSRI exposed and controls, $\neq$ = no differences. SSRI = selective serotonin reuptake inhibitors; # of Pt. = number of participants; Time = timing of SSRI treatment; Age = age of assessment in years; Maternal mood = Study controlled for perinatal maternal mood (e.g., depression symptoms); AD = antidepressant prenatal exposure; Retro = retrospective; Prosp = prospective; IB = internalizing behavior; A = anxiety; D = depression; CBCCL = Child Behavior Checklist; HBQ = MacArthur Health and Behavior Questionnaire; MDS = maternal depressive symptoms; PD = exposed to psychiatric disorder, no antidepressant exposure; P.SSRI = exposed to SSRI only before pregnancy, Control = no exposure to AD or PD; ASD = autism spectrum disorder; ADHD = attention deficit/ hyperactivity disorder; AD Dis = AD discontinued during pregnancy; AD NU = AD new user (use only during pregnancy); D-No AD = depressed but no AD; D-No SSRI, depressed but no SSRI; DSDQ = Danish Strengths and Difficulties Questionnaire for internalizing and externalizing problems; CPRS = Conner's Parent Rating Scale; VEN = Venlafaxine, a type of serotonin-norepinephrine reuptake inhibitor.

Table 2

Summary of rodent research investigating how perinatal SSRI exposure affects anxiety and depressive behavior

Test Dates	SSRI Time	SSRI dose/day	Method admin	Sex	Strain	Maternal Stress	Results	Reference
							Pre-weaning Testing (P0-21)	
P18	G6-20	FLX 8 & 12 mg/kg	OA	F/M	Wistar	-	FLX ↓ Anxiety (OFT: more central crossing, more time in center)	Bairy et al., 2007
P20	G8-18	FLUX .3, .6, .8mg/kg, FLUV 4.2mg/kg	IP	F/M	C57BL/6-Jlco	-	FLX ↑ Anxiety (EPM: less time in open arms) FLUV ↑ Anxiety (EPM: less time in open arms)	Noorlander et al., 2008
							Juvenile Testing (P21-50)	
P22	G0-P21	FLX 5mg/kg	OA	M	Wistar	-	FLX ≠ Anxiety (OFT, EPM)	Toffoli et al., 2014
P25	G9-21	FLX 10mg/kg	PI	M	Wistar	Prenatal Stress	FLX ≠ Anxiety (EPM) FLX ↓ Depression (FST: reduced immobility) *FLX protected against the effects of prenatal stress on the EPM and FST	Mikhailenko & Butkevich, 2019
P29	G9-20	FLX 10mg/kg	IP	F	Wistar	-	FLX ↑ Anxiety (EPM: less time in open arms) FLX ≠ Depression (FST)	Butkevich & Mikhailenko, 2018
P30	G0-G16.5	PAR 30mg/kg	FB	F/M	CD1	-	PAR ≠ Anxiety (EPM)	Coleman et al., 1999
P30	G1-P0	FLX 1mg/ml/kg	IPI	F	ICR (CD1)	Prenatal stress	FLX ≠ Anxiety (EPM, OFT) FLX ≠ Depression (FST) *FLX did not protect against effects of prenatal stress	Avitsur et al., 2016
P30	G14-28	FLX 10mg/kg	SC pump	F/M	Wistar	-	FLX ≠ Anxiety (EPM)	Forcelli et al., 2008
P30-31	P0-4	FLX 20mg/kg	SC	M	Wistar	-	FLX ↑ ≠ Anxiety (OFT: fewer counts into central region, less time in center; EPM: ≠)	Lee et al., 2012
P30	P0-6	FLX 10mg/kg	SC	F/M	Wistar	-	FLX ↑ Anxiety (OFT: less time in center)	Lee et al., 2009
P30-35	G6-20	FLX 8 & 12 mg/kg	OA	F/M	Wistar	-	FLX ↑ ≠ Anxiety (OFT: less central crossing, less time in center; EPM: ≠)	Bairy et al., 2007
P32-39	P1-21	FLX 5mg/kg	SC	F/M	Sprague-Dawley	Prenatal stress	FLX ≠ Anxiety (OFT) FLX ≠ Depression (FST) * FLX protected against effects of prenatal stress on FST	Rayen et al., 2011
P35	G1-21	FLX 5mg/kg	OA	F/M	Wistar	-	FLX ↑ ≠ Anxiety (EPM: less time in open arms; NSF: ≠)	Matsumoto et al., 2016
~P42+	P5-19	ESC 10mg/kg	SC	F	CD1 mice	-	ESC ≠ Anxiety (EPM, LD) ESC ↑↑↑ Depression (FST: increased immobility; TST:	Popa et al., 2008

							reduced mobility; SPT: reduced consumption)	
P28-35	G7-P2	ESC 12.2mg/kg	SC pump	F	Sprague-Dawley	Prenatal stress	ESC $\neq$ Anxiety (EPM, OFT) *ESC did not protect against effects of prenatal stress	Ehrlich et al., 2015
P30, P40	G0-P21	FLX 7.5mg/kg	OA	F/M	Swiss	-	FLX $\neq$ Anxiety (EPM, OFT) FLX $\uparrow$ Depression (FST: increased immobility; F only) FLX $\neq$ Depression (FST: M only)	Lisboa et al., 2007
P35	G0-P21	FLX 5mg/kg	OA	F/M	Wistar	-	FLX $\uparrow$ Anxiety (NSF: increased latency to feed) FLX $\neq$ Depression (SPT)	Francis-Oliveira et al., 2013
P35-39	G0-P14	FLX 10mg/kg	OA	M	Sprague-Dawley, Wistar-Kyoto	Wistar-Kyoto (model of depression)	FLX $\uparrow \uparrow$ Anxiety (OFT: less time in open arms- Sprague-Dawley only, EPM: less time in open arms-both strains) FLX $\uparrow$ Depression (FST: increased immobility- both strains) *FLX did not protect against effects of innate model of depression, actually exacerbates effects	Millard et al., 2019
							Adult Testing (P50+)	
P50	P5-21	ESC 10mg/kg	SC	F/M	CD-1 x 129SvEv 5-HTT+/+	-	ESC $\downarrow \downarrow$ Anxiety (OFT: more time in center, EPM: more time in open arms) ESC $\neq$ Depression (FST)	Altieri et al., 2015
P54	P7-21	ZIM 25mg/kg	IP	M	Wistar	-	ZIM $\uparrow$ Depression (FST: increased immobility)	Hilakivi et al., 1988b
P55	P1-21	FLX 10mg/kg	SC	M	Wistar	-	FLX $\downarrow$ Anxiety (EPM: more time in open arms)	da Silva et al., 2014
P56	G6-20	FLX 8 & 12 mg/kg	OA	F/M	Wistar	-	FLX $\uparrow$ Anxiety (OFT: reduced central crossings, less time in center)	Bairy et al., 2007
P56	P0- 4	FLX 20mg/kg	SC	F/M	Wistar	-	FLX $\uparrow \neq$ Anxiety (OFT: less time in center; EPM: $\neq$) FLX $\uparrow$ Depression (FST: increased immobility)	Ko et al., 2014
P56	G12-P12	FLX 25mg/kg	DW	M	C57BL/6	Prenatal stress	FLX $\downarrow \neq$ Anxiety (EPM: more time in open arms; OFT: $\neq$) *FLX protected against effects of prenatal stress	Kiryanova et al., 2016
P56, P140	P7-18	ZIM 25mg/kg	IP	M	Wistar, Long-Evans	-	ZIM $\uparrow \uparrow$ Depression (FST: increased immobility at both time points)	Hilakivi et al., 1987a
P60	P8-21	FLX 10mg/kg	IP	M	Sprague-Dawley	-	FLX $\uparrow$ Anxiety (OFT: less time in center)	Mnie-Filali et al., 2011
P60	G6-P20	CIT 10mg/kg	SC	F/M	Sprague-Dawley	-	CIT $\uparrow \uparrow$ (F only) $\neq$ Anxiety (MB: increased marbles buried; OFT: less time in center (F only); EPM $\neq$) CIT $\uparrow$ Depression (FST: increased mobility)	Sprowles et al., 2016
P60	G6-P20	CIT 5mg/kg, FLX 5mg/kg,	SC	F/M	Sprague-Dawley	-	CIT $\uparrow \neq \neq$ Anxiety (MB: increased marbles buried; EZM: $\neq$; OFT: $\neq$) CIT $\neq$ Depression (FST) FLX $\uparrow \neq \neq$ Anxiety (MB: increased marbles buried; EZM: $\neq$; OFT: $\neq$)	Sprowles et al., 2017

							FLX ≠ Depression (FST)	
P60	G7-P21	CIT 10mg/kg	OA	F/ M	Wistar	Prenatal stress	CIT ≠ Anxiety (EPM) CIT ↑ Depression (FST: increased immobility) *CIT did protect against effects of prenatal stress in EPM, but not FST	Zohar et al., 2016
P60	G15-P12	FLX 25mg/kg	DW	M	C57BL/6	-	FLX ↓ ≠ Anxiety (EPM: more time in open arms; OFT: ≠)	Kiryanova et al., 2014
P60	G13-20	FLX 5mg/kg, 10mg/kg	SC	M	Wistar	-	FLX ↑ Anxiety (PAT: increased approach latency)	Cagiano et al., 2008
P60	G1-P0	FLX 1mg/ml/kg	IP	F	ICR (CD1)	Postnatal Stress	FLX ≠ ≠ Anxiety (EPM, OFT) FLX ↓ Depression (FST: decreased immobility) *FLX did not protect against effects of prenatal stress	Avitsur et al., 2016
P60	P1-21	FLX 10mg/kg	SC	F/M	Wistar	-	FLX ↓ Depression (FST: decreased immobility)	Mendes-da-Silva et al., 2002
P60-90	G0-G16.5	PAR 30mg/kg	FB	F/M	CD1	-	PAR ≠ Anxiety (EPM) PAR ≠ Depression (FST)	Coleman et al., 1999
P60, P150	P7-18	ZIM 25mg/kg	IP	M	Wistar	-	ZIM ↑ ↑ Depression (FST: increased immobility at both time points)	Hilakivi et al., 1987b
P63	P8-21	CIT 10mg/kg	SC	M	C57BL/6N	-	CIT ↑ Anxiety (OFT: less time center)	Soga et al., 2012
P63+	P1-21	FLX 5mg/kg	OA	M	BALB/c	-	FLX ↓ Anxiety (EPM: more time in open arms) FLX ≠ ≠ Depression (FST; SPT)	Ishikawa & Shiga, 2017
P65	G11-P0	FLX 12mg/kg	OA	M	Wistar	-	FLX ↑ ≠ Anxiety (NSF: increased latency to feed) FLX ≠ Depression (FST)	Olivier et al., 2011b
P67	P2-23	FLX 10mg/kg	SC	F/M	Sprague-Dawley	-	FLX ↑ ↑ Anxiety (NSF: increased latency to feed; EPM: less time in open arms- males only)	Gobinath et al., 2016
P70	G0-P21	FLX 7.5mg/kg	OA	F/M	Swiss	-	FLX ≠ ≠ Anxiety (EPM, OFT) FLX ↑ Depression (FST: increase immobility- female only)	Lisboa et al., 2007
P70-80	G10-P20	FLX 8mg/kg	DW	M	NMRI	Prenatal stress	FLX ≠ ≠ ≠ Anxiety (OFT, EZM, LD) FLX ≠ ≠ Depression (FST, SPT) *FLX protected against effects of prenatal stress	Salari et al., 2016
P:73-83	G15-P12	FLX 25mg/kg	OA	F	C57BL/6J	-	FLX ↓ ≠ Anxiety (EPM: more time in open arms, OFT: ≠) FLX ↓ Depression (FST: reduced immobility)	McAllister et al., 2012
P75	G0-P21	PAR 10mg/kg	OA	M	HR/LR Sprague-Dawley	-	PAR ≠ Anxiety (EPM) PAR ↑ Depression (FST: increased immobility)	Glover et al., 2015; Experiment 2
P75	G0-P21	FLX 5mg/kg	OA	F/M	Wistar	-	FLX ≠ Anxiety (NSF) FLX ≠ Depression (SPT)	Francis-Oliveira et al., 2013
P84	P4-21	FLX 10mg/kg	IP	F/ M	129S6/SvE	-	FLX ↑ ↑ ↑ Anxiety (EPM: less time in open arms, OFT: ↑)	Ansorge et al., 2008

					v		less time in center area, NSF: increased latency to feed)	
P90	G8-18	FLUX .3, .6, or .8mg/kg FLUV 4.2mg/kg	IP	F/M	C57BL/6-Jlco	-	FLUX $\uparrow \neq$ Anxiety (NSF: increased latency to feed, EPM: $\neq$) FLUV $\neq \neq$ Anxiety (NSF, EPM)	Noorlander et al., 2008
P90	P4-21	FLX 10mg/kg FLU 10mg/kg	IP	M	C57BL/6	-	FLX $\neq$ Anxiety (PFT) FLU $\neq$ Anxiety (PFT)	Zheng et al. 2011
P90	P8-21	CIT 5, 10, 20mg/kg	SC	M	Long	-	CIT $\neq$ Anxiety (EPM)	Harris et al., 2012
P90-100	P2-21	FLX 10mg/kg	OA	M	Sprague-Dawley	-	FLX $\uparrow \uparrow$ Anxiety (EPM: less time in open arms, OFT: less time in center) FLX $\uparrow$ Depression (FST: increased immobility)	Sarkar et al., 2014
P90+	P2-11	FLX 10mg/kg	IP	F/M	129S6SvEv Tac	-	FLX $\uparrow \uparrow$ Anxiety (OFT: less time in center, NSF: increased latency to feed) FLX $\uparrow$ Depression (FST: increased immobility)	Rebello et al., 2014
P90+	P2-21,	FLX 10mg/kg, CLOL 20mg/kg	IP	F/M	129S6/SvEv	-	FLX $\uparrow \uparrow$ Anxiety (OFT: less time in center, NSF: increased latency to feed- only for P2-21 group) CLOL $\uparrow \uparrow$ Anxiety (OFT: less time in center, NSF: increased latency to feed- only for P2-21 group)	Yu et al., 2014
P90+	G7-P2	ESC 12.2mg/kg	SC pump	F	Sprague-Dawley	Prenatal stress	ESC $\neq \neq$ Anxiety (EPM, OFT) *ESC did not protect against effects of prenatal stress	Ehrlich et al., 2015
P90-120	G-7 - P2	ESC 12.2mg/kg	SC pump	M	Sprague-Dawley	Prenatal stress	ESC $\neq \neq \neq$ Anxiety (EPM, OFT, SPT, MB) *ESC did not protect against effects of prenatal stress **FST results not reported due to heavy mass of rodents	Bourke et al., 2013b
P90	G8-18	FLX .6mg/kg	IP	F/M	C57BL/6	-	FLX $\uparrow$ Anxiety (NSF: increased latency to feed)	Smit-Rigter et al., 2012
P110 +	P4-21	FLX 10mg/kg	IP	M	C57BL/6J	-	FLX $\uparrow \uparrow$ Anxiety (OFT: less time in center, LD: less time in dark) FLX $\downarrow$ Depression (FST: decreased immobility)	Karpova et al., 2009
P119-P126	P8-21	LU 2.5, 5,10, 15 mg/kg	IP	M	Wistar	-	LU $\neq$ Anxiety (OFT) LU $\uparrow$ Depression (FST: increased immobility)	Hansen et al., 1997
P140	G0-P14	SER 5mg/kg	IP	F/M	C57BL/6	-	SER $\neq$ Anxiety (EPM)	Meyer et al., 2018
P140	P1-21	FLX 5mg/kg	SC	M	Sprague-Dawley	Prenatal stress	FLX $\uparrow \neq$ Anxiety (OFT: less time in center, EZM: $\neq$) FLX $\neq$ Depression (FST) *FLX protected against effects of prenatal stress	Boulle et al., 2016a
P140	P1-21	FLX 5mg/kg	SC	F	Sprague-Dawley	Prenatal stress	FLX $\neq \neq$ Anxiety (EZM, OFT) FLX $\uparrow$ Depression (FST: increased immobility, regardless of prenatal stress) *FLX did not protect against effects of prenatal stress	Boulle et al., 2016b

Note. Arrows indicate significant differences (increases/ decreases) between SSRI exposed and controls on **one task**, $\neq$ = no differences, results were the same across all dose levels. SSRI = selective serotonin reuptake inhibitors, also includes serotonin norepinephrine reuptake inhibitors (SNRIs); Time = Timing of administration; Method admin = method of administration to mother unless otherwise indicated; Test Dates = Date of assessments; P = postnatal day; G = gestational day; M = male; F = female; FB = food bars; OA = oral administration; IP = intraperitoneal injection; SC = subcutaneous injection; ? = Timing not specified; DW = Drinking water; FLX = Fluoxetine; FLUV = Fluvoxamine; CIT = Citalopram; PAR = Paroxetine; ZIM = Zimelidine; ESC = Escitalopram; Lu = Lu10–134-C; SER = Sertraline; EPM = Elevated Plus Maze (measure of anxiety); EZM = Elevated zero maze (measure of anxiety); OFT = Open Field Test (measure of anxiety); LD – Light/ dark test (measure of anxiety); PAT = Passive avoidance test (measure emotionality, anxiety); MB = Marble Burying test (measure of anxiety-like behavior); NSFT = Novelty Suppressed Feeding (measure of anxiety/ depressive-like behavior); FST = Forced Swim Test (measure of depression-like behavior); TST = Tail suspension test (measure of depression-like behavior); SPT = Sucrose preference test (measure of depression-like behavior); High Novelty Responder/Low Novelty Responder (HR/LR) rat lines.

Table 3

Summary of rodent research investigating other antidepressant medications to treat perinatal depression or anxiety and offspring anxiety and depressive behavior

Test Dates	Time	Drug dose/day	Method admin	Sex	Strain	Maternal Stress	Results	Reference
							Juvenile Testing (P21-50)	
~P21+	P8-21	CLO 40mg/kg	IP	M	Wistar	Prenatal Stress	CLO ↑ Depression (FST: increased immobility)	Yang et al., 2008
P25	G9-21	BUS 3.5mg/kg or FLX 10mg/kg & BUS 3.5mg/kg	PI	M	Wistar	Prenatal Stress	BUS ≠ Anxiety (EPM) FLX & BUS ≠ Anxiety (EPM) BUS ↓ Depression (FST: decreased immobility) FLX & BUS ↓ Depression (FST: decreased immobility) *BUS protected against the effects of prenatal stress on the EPM *BU, FLX & BUS protected against the effects of prenatal stress on the FST	Mikhailenko & Butkevich, 2019
P25	G9-21	BUS 3.5mg/kg or FLX 10mg/kg & BUS 3.5mg/kg	PI	F/M	Wistar	Prenatal Stress	BUS ↓ Depression (FST: decreased immobility) FLX & BUS ↓ Depression (FST: decreased immobility) *BU, FLX & BUS protected against the effects of prenatal stress on the FST	Butkevich & Mikhailenko, 2019
							Adult Testing (P50+)	
P54	P7-21	DES 5mg/kg, NOM 10mg/kg	IP	M	Wistar	-	DES ↑ Depression (FST: increased immobility) NOM ↑ Depression (FST: increased immobility)	Hilakivi et al., 1988b
P60	G6- P20	BU 15mg/kg	SC	F/M	Sprague-Dawley	-	BU ≠ ≠ Anxiety (EZM, OFT, MB) BU ≠ Depression (FST)	Sprowles et al., 2017
P60, P150	P7-18	DES 5mg/kg	IP	M	Wistar	-	DES ↑ ↑ Depression (FST: increased immobility at both time points)	Hilakivi et al., 1987b
P60-85	G15- P20	VEN 7.5, 37.5, 75mg/kg	OA	F/M	Wistar	-	VEN 7.5mg ↓ ↓ Anxiety (EPM: more time in open arms, LD: more time in light- males only), ↓ Depression (FST: decreased immobility) VEN 37.5mg ↓ ≠ Anxiety (LD: more time in light-females only; EPM: ≠), ↓ Depression (FST: decreased immobility- females only) VEN 75mg ≠ ≠ Anxiety (EPM, LD), ≠ Depression (FST)	Bogi et al., 2018
P84	P8-21	CLO 15mg/kg	SC	M	Wistar	-	CLO ↑ Depression (FST: increased immobility)	Limón-Morales et al.,

								2014
P84	P4-21	DES10mg/kg, CLO 20mg/kg	IP	F/ M	129S6/SvEv	-	DES $\neq \neq \neq$ Anxiety (EPM, OFT, NSF) CLO $\uparrow \uparrow \neq$ Anxiety (EPM: less time in open arms, OFT: less time in center area, NSF: $\neq$)	Ansorge et al., 2008
P90	P8-21	CLO 15mg/kg	SC	M	Wistar	-	CLO $\uparrow \uparrow$ Depression (FST: increased immobility, SPT: reduced consumption)	Bhagya et al., 2015
P90	P8-21	CLO 15mg/kg + RB 5 (P76- 89), 10 mg/kg	SC	M	Wistar	-	CLO + RB $\downarrow \downarrow$ Depression (FST: reduced immobility, SPT: increased consumption, for both dosages)	Bhagya et al., 2015
P90+	P2-21,	CLOL 20mg/kg	IP	F/M	129S6/SvEv	-	CLOL $\uparrow \uparrow$ Anxiety (OFT: more time in center, NSF: increased latency (only for P2-21 group))	Yu et al., 2014
P112	P8-21	CLO 15mg/kg	SC	M	Wistar	-	CLO $\uparrow$ Depression (FST: increased immobility)	Vázquez-Palacios et al., 2005
P168	P8-21	CLO 15mg/kg	SC,	M	Wistar	-	CLO $\uparrow$ Depression (FST: increased immobility)	Velazquez-Moctezuma et al., 1992

Note. Arrows indicate significant differences (increases/ decreases) between medication exposed and controls on one task, $\neq$ = no differences. Results were the same across all dose levels unless specifically indicated (e.g., Bogi et al., 2018). Time = Timing of administration; Method admin = method of administration to mother unless otherwise indicated; Test Dates = Date of assessments; P = postnatal day; G = gestational day; M = male; F = female; FB = food bars; OA = oral administration; IP = intraperitoneal injection; SC = subcutaneous injection; ? = Timing not specified; DW = Drinking water; VEN = Venlafaxine, a serotonin-norepinephrine reuptake inhibitor; CLO = Clomipramine, a non-SRI used to treat depression; DES = Desipramine, a non-SRI used to treat depression; CLOL = Clorgyline, a non-SRI used to treat depression; IMI = Imipramine, a non-SRI used to treat depression; BU = Bupropion, non-SRI used to treat depression; BUS = buspirone, an non-SRI used to treat anxiety; NOM = Nomifensine, a non-SRI used to treat depression; RB = Reboxetine, an norepinephrine reuptake inhibitor that was used with Clorgyline; EPM = Elevated Plus Maze (measure of anxiety); EZM = Elevated zero maze (measure of anxiety); OFT = Open Field Test (measure of anxiety); MB = Marble Burying test (measure anxiety-like behavior; FST = Forced Swim Test (measure depression-like behavior).

Figure 2. Schema summarizing rodent research on perinatal SSRI and other antidepressant medication exposure and offspring anxious or depressive like behavior

Note: Arrows indicate significant differences (increases/ decreases) between SSRI and other antidepressant medications exposed and controls on one task to measure anxiety or depressive like behavior, ≠ = no differences between groups the one task, n = number of times a task intended to measure anxiety or depressive behavior has been reported in a peer reviewed study with those results. See Table 2 and 3 for details. Tasks that had different results depending on sex of rodent were included in the count (e.g., Elevated Plus

Maze, Gobinath et al., 2016) or if the tasks was only administered to females or males, see Table 2 for details. SSRI = selective serotonin reuptake inhibitors.