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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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► To cite this version:

Sarah M Hutchison, Louise C Mâsse, Jodi L Pawluski, Tim F Oberlander. 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. *Reproductive Toxicology*, 2021, 99, pp.80-95. 10.1016/j.reprotox.2020.11.013 . hal-03094965

HAL Id: hal-03094965

<https://hal.science/hal-03094965>

Submitted on 21 Jan 2021

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1 Perinatal Selective Serotonin Reuptake Inhibitor (SSRI) and Other Antidepressant Exposure
2 Effects on Anxiety and Depressive Behaviors in Offspring: A Review of Findings in Humans
3 and Rodent Models
4

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19 **Acknowledgements**

20 We are grateful to Colleen Pawliuk, our librarian, and Ursula Brain, our research manager, for
21 their assistance. S.M.H is supported by the BC Children's Hospital Research Institute
22 (University of British Columbia), Brain Canada and Kids Brain Health Network, Developmental
23 Neurosciences Research Training Award.

24 L.C.M. is a professor in the School of Population and Public Health at the University of British
25 Columbia and her work is supported by the BC Children's Hospital Research Institute and the
26 Canadian Institutes for Health Research.

27 J.L.P. is supported with funding from l'Institut des Neurosciences Cliniques de Rennes (INCR).
28 T.F.O is the R. Howard Webster Professor in Brain Imaging and Child Development at the
29 University of British Columbia and his work is supported by the BC Children's Hospital
30 Research Institute and the Canadian Institutes for Health Research. Funding sources had no role
31 in the study.
32

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1 **1. Introduction**

2 Up to 20% of pregnant mothers experience depressed mood (Pawluski, Lonstein, &
3 Fleming, 2017) and are commonly treated with selective serotonin reuptake inhibitor
4 antidepressant medications (SSRIs) (i.e. fluoxetine, paroxetine, sertraline, citalopram) (Charlton
5 et al., 2015; Oberlander, Warburton, Misri, Aghajanian, & Hertzman, 2006). SSRI use by
6 pregnant women ranges between 5 and 13% in Australia and the USA, and between 2 and 7% in
7 Canada and Western European countries (Charlton et al., 2015; Cooper et al., 2007; Hayes et al.,
8 2012; Lupattelli et al., 2014; Oberlander et al., 2006; Zoega et al., 2015). These medications
9 readily cross the placenta and have been reported in breast milk (Kim et al., 2006a;b; Rampono
10 et al., 2009). SSRIs inhibit the reuptake of serotonin (5-HT), via 5-HT transporter blockade at
11 presynaptic neurons, thereby increasing synaptic 5-HT concentrations (Whitaker-Azmitia, Druse,
12 Walker, & Lauder, 1995). 5-HT is a key neurotransmitter (Hellendall, Schambra, Liu, & Lauder,
13 1993) widely distributed throughout key brain regions that influence cognition, attention, stress,
14 and emotion regulation (Lesch, 2007; Lucki, 1998).

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

1 widespread in regions where they are absent in adults (Miller, & Friedhoff, 1986; Seeman et al.,
2 1987) pointing to a time-dependent specificity to 5-HT expression during development. Thus,
3 early alterations of 5-HT, either via environmental or genetic manipulations, can change neural
4 development (Oberlander, Gingrich, & Ansorge, 2009). Manipulating prenatal¹ 5-HT levels in
5 animal models using genetic variations, 5-HT agonists, or SSRI exposure, alters brain
6 morphology and may constrain 5-HT maturation in ways that result in increased risk of anxiety-
7 and depressive-like behaviors (Homberg, Schubert, & Gaspar, 2010).

8 In humans, there have been reports that prenatal SSRI exposure is associated with
9 increased internalizing and anxiety behaviors during early childhood (Brandlistuen et al., 2015;
10 Hanley, Brain, & Oberlander, 2015; Hermansen, Røysamb, Augusti, & Melinder, 2016) and
11 higher rates of depression diagnoses (Malm et. al., 2016), but this is not always the case
12 (Grzeskowiak et al., 2015; Lupattelli et al., 2018; Misri et al., 2006; Nulman et al., 2012; 2015;
13 Pedersen et al., 2013). In rodent models there are also reports that pre- and post-natal² SSRI
14 exposure impacts affective behaviors in offspring, but these effects vary based on
15 methodological factors (Gemmell et al., 2017; Popa, Léna, Alexandre, & Adrien, 2008; Rayen et
16 al., 2013; Boulle et al., 2016). In addition, while there is a possible direct impact of perinatal (i.e.
17 pre- and post-natal) exposure to SSRIs on affective behaviors, anxiety, and depressive behaviors,
18 these behaviors can also be influenced by indirect mechanisms that include maternal depressive
19 symptoms, maternal stress, maternal-offspring interactions, and gene x environment variations.
20 For example, maternal stress influences the developing serotonergic system (St-Pierre, Laurent,
21 King, & Vaillancourt, 2016) and there is a large literature on maternal stress effects on offspring
22 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.

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

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

19 In humans, separating the impact of perinatal maternal affective disturbances and/ or
20 mood symptoms from the impact of antidepressant medication exposure raises critical
21 methodological challenges (Grzeskowiak, Gilbert, & Morrison, 2012) as randomizing prenatal
22 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

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

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

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

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

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

10 **3.1 Measures of Anxiety and Depressive Behavior**

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

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

7 **3.2 Anxiety and depressive-like behaviors after Pre- and/or Post-natal SSRI** 8 **exposure**

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

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

21 There have been many studies conducted with rodents during the juvenile period.
22 Prenatal and/or postnatal SSRI exposure has been associated with increased anxiety during
23 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 (Bairy 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

1 adult offspring (Table 2). One study conducted with rodents during the juvenile period have
2 reported associations between prenatal SSRIs and increased depressive-like behavior (Millard et
3 al., 2019). Conversely, other studies have reported that prenatal SSRI exposure decreased
4 depressive-like behavior during adolescence (Butkevich & Mikhailenko, 2019; Mikhailenko &
5 Butkevich, 2019), while other studies have failed to find significant effects of perinatal SSRIs on
6 depressive-like behaviors in adolescent offspring (Avitsur et al., 2016; Butkevich &
7 Mikhailenko, 2018; Francis-Oliveira et al., 2013; Lisboa et al., 2007, males only). For postnatal
8 SSRI exposure, one study failed to find significant effects of SSRIs exposure (Rayen et al.,
9 2011).

10 In terms of perinatal SSRI effects on depressive-like behavior in adult offspring, some
11 studies have shown associations between prenatal SSRIs and higher levels of depressive-like
12 behavior (Bhagya et al., 2015; Glover et al., 2015; Lisboa et al., 2007; Sprowles et al., 2016;
13 Zohar et al., 2016). Yet, other studies have reported that prenatal SSRI exposure decreased
14 depressive-like behavior during adulthood (Avitsur et al., 2016; McAllister et al., 2012). Finally,
15 other studies have failed to find significant effects of perinatal SSRIs on depressive-like
16 behaviors in adult offspring (Coleman et al., 1999; Francis-Oliveira et al., 2013; Olivier et al.,
17 2011b; Salari et al., 2016; Sprowles et al., 2017).

18 Regarding postnatal SSRI exposure in rodent models, the results are more consistent with
19 postnatal SSRI exposure being associated with increased immobility in adult rat offspring
20 (Bhagya et al., 2015; Glover et al., 2015; Hilakivi et al., 1987; Ko et al., 2014; Rebello et al.,
21 2014; Sarkar et al., 2014; Boulle et al 2016, Females). Conversely, two studies have reported that
22 postnatal SSRI exposure decreased depressive-like behavior in adult offspring (Karpova et al.,
23 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.

1 Although limited, perinatal SSRIs have been reported to have sexually differentiated
2 effects on depressive-like behavior in rodent offspring. As mentioned previously, Lisboa et al.
3 (2007) found that prenatal fluoxetine was associated with increased depressive-like behavior in
4 adolescent female, not male, mice. Boulle et al (2016a,b) also showed that early postnatal SSRIs,
5 regardless of maternal stress, increased depressive-like behavior in adult female, but not male, rat
6 offspring. Postnatal SSRI exposure via lactation, as performed in Boulle et al (2016a,b), had no
7 effect on depressive-like behavior in adolescent male or female rat offspring (Rayen et al 2011)
8 suggesting a possible post-pubertal effect of SSRIs on depression. Future research considering
9 sex of the offspring is vital to determine how early life exposures alter developmental
10 trajectories.

11 **3.4 Models of Maternal Stress**

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

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

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

12 **3.5 Perinatal exposure to other antidepressant medications**

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

1 2014). As there only a few studies examining the relation between other anti-depressant or anti-
2 anxiety medications (administered pre- or post-natal) more research is needed before stronger
3 conclusion can be drawn.

4 In terms of perinatal antidepressant medication effects on offspring depressive-like
5 behavior (Table 3), some researchers have reported that perinatal exposure to non-SSRIs reduced
6 depressive-like behaviors in juvenile offspring (Mikhailenko & Butevich, 2019; Butkevich &
7 Mikhailenko, 2019) while others failed to find significant effects of perinatal antidepressant
8 medication exposure on depressive-like behavior (Sprowles et al., 2017). Other researchers have
9 reported the perinatal non-SSRI exposure increased depressive-like behaviors in adult offspring
10 (Bhagya et al., 2015; Hilakivi et al., 1987b; Limón-Morales et al., 2014; Vázquez-Palacios et al.,
11 2005; Velazquez-Moctezuma et al., 1992; Yang et al., 2008). Conversely, adult female rat
12 offspring with prenatal venlafaxine (37.5mg/kg) exposure were less depressed (reduced
13 immobility) than male offspring (Bogi et al., 2018). Interestingly, Bhagya and colleagues (2015)
14 found that prenatal exposure to clomipramine was associated with increased depressive-like
15 behaviors, which was reversed in offspring with a combination of clomipramine and reboxetine
16 treatment during adulthood, suggesting that reboxetine may be beneficial to treat those with
17 prenatal exposure to antidepressants, but this needs to be supported with additional research
18 before firmer conclusions can be drawn. To date, no studies with non-SSRIs have examined
19 possible sex differences or included models of maternal stress in relation to depressive-like
20 behavioral outcomes in offspring. These factors need to be addressed by future research.

21 **3.6 Summary of Findings**

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

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

13 In terms of depressive-like behavior, the majority of rodent studies suggest that perinatal
14 SSRIs, and other antidepressant medications to treat maternal mental illnesses, may increase
15 depressive-like behavior in offspring ($n = 30$, 47%, see Figure 2). As this is the first review of
16 these outcomes in animal models, no cross-review comparisons can be made. While there are
17 more instances of increased depressive-like behavior associated with perinatal SSRI and non-
18 SSRI exposure, there are also a substantial number of null results ($n = 16$; 25%). It is also
19 possible that the number of null results may be underestimated as it is typically more challenging
20 to publish non-significant findings. A similar number of studies reported that perinatal SSRIs,
21 and other antidepressant medications to treat maternal mental illnesses, may decrease depressive-
22 like behavior in offspring ($n = 18$; 28%). Discrepancies between study results may be due to a
23 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

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

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

13 SSRI treatment to rodent dams during pregnancy has also been associated with increased
14 nesting, licking and touching offspring (high doses only) and maternal aggression (Johns et al.,
15 2005). Others have reported that gestational SSRI treatment to dams reduces time nursing (Kott
16 et al., 2018). When SSRIs are administered during the postpartum, increased active nursing
17 behaviors (i.e. arched-back nursing) and decreased passive nursing behavior have been reported
18 (Pawluski et al., 2012b; Workman et al., 2016). Interestingly, one study in adult female offspring
19 exposed to SSRIs prenatally, found delayed maternal behavior particularly in pup retrieval in the
20 early postpartum period (Svirsky, Levy, & Avitsur, 2016). This suggests a potential long-term
21 effect of SSRIs on maternal behavior across generations.

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

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

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

5 While alterations in 5-HT signaling associated with developmental exposure to SSRIs
6 may shape vulnerability for anxiety and depressive disturbances in childhood or across the life
7 span, such exposures alone do not explain why some children are at risk and others remain
8 resilient. Thus, incorporating information about interactions between genetic variations and the
9 perinatal environment may offer a window into explaining heterogeneity in developmental
10 outcomes (Boyce & Ellis, 2005; Moffitt et al., 2005). Allelic variations influence susceptibility
11 to environmental context (i.e. Gene Environment (G x E) interactions) (Belsky & Pluess, 2009;
12 Caspi & Moffitt, 2006; Moffitt et al., 2005) and allelic variations in SLC6A4 (serotonin
13 transporter gene) in particular have been widely studied as a key moderator of early life
14 environmental influences. Caspi et al. (2003) reported that childhood maltreatment predicts adult
15 depression among individuals with at least one copy of the short allele. Building on this seminal
16 paper, the short allele has been widely studied as a crucial moderator of mental illness risk in
17 adulthood (Karg et al., 2011; Kendler, 2005; Kendler et al., 2005; Lesch, 2011; Schinka et al.,
18 2004). However, not all outcomes associated with having the short allele are negative (Risch et
19 al., 2009) and not all studies have replicated these relationships (Willis-Owen et al., 2005),
20 raising questions about the role of other factors that may underlie G x E interactions (Duncan,
21 2013), such as maternal mood disturbances and/ or perinatal SSRI exposure.

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

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

10 Beyond genetic factors, everyday context also matters. For example, a recent study
11 examined associations between day-to-day home environment and child self-regulation skills in
12 6 year olds (Dhaliwal et al., 2017; Dhaliwal et al., in press). Interestingly, children of mothers
13 with higher prenatal depressive symptoms (regardless of SSRI treatment) were less susceptible to
14 the everyday chaos at home (e.g., household noise, disorganization, etc). In contrast, children of
15 mothers with lower levels of prenatal mood symptoms were much more susceptible to the
16 household environment and in this setting this effect was moderated by prenatal exposure to
17 SSRIs. This suggests that prenatal SSRI exposure with lower depressive symptoms serves as a
18 risk factor for greater sensitivity to house chaotic environment, while prenatal maternal mood
19 regardless to SSRI exposure may “buffer” the child’s outcomes from the current house
20 environment. Taken together, both variation in genetics and environment (maternal depressive
21 symptoms and/ or SSRI exposure) can influence children’s outcomes and this needs to be the
22 focus of future research in order to determine risk and reliance.

23 **6. Limitations and Strengths**

1 Our aim was to provide a review of human and animal literature that reports effects of
2 perinatal SSRIs on anxiety and depression in offspring. In doing so we chose the most significant
3 measures of anxiety and depression in animal models and summarized these in Tables 2 and 3.
4 Other reviews on this topic have used only one behavioral test per study (e.g., Ramsteijn et al.,
5 2020 only use data from the first time a behavioral test was administered, unless there was a
6 learning component, to provide a “snap shot” of each study) or the overall results of a study
7 (Grieb & Ragan, 2019); whereas, we chose to treat each assessment within a study as a separate
8 task as it occurred at a different developmental time point. For example, Bairy et al., (2007)
9 measured anxiety during pre-weaning (P18) using one task and the juvenile stage (P30) using
10 two tasks. Thus, we counted all three tasks as only counting the first assessment point would
11 underestimate our knowledge of anxiety behaviors in rodents throughout their lifespan. We also
12 chose to focus on summarizing the research results and we chose not to weigh results according
13 to sample size as this was beyond the scope of the review; however, future researchers should
14 consider this option.

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

21 **7. Future Directions and Conclusion**

22 Our review of rodent studies suggests that results from perinatal exposure to both SSRIs
23 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.

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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 ≠ internalizing (emotional symptoms, peer problems) D-No AD ↑ 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 ↑ Depression, ≠ 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 ↑ 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 ↑ 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 ↑ 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 ≠ affective problems MDS ↑ affective problems	Controlled for prenatal and postpartum depressive symptoms
Oberlander et	33	SSRI	Prenatal	Prosp	3	CBCL	SSRI ↑ 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, ≠ = 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 ≠ 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 ≠ Anxiety (EPM, OFT) FLX ↑ Depression (FST: increased immobility; F only) FLX ≠ Depression (FST: M only)	Lisboa et al., 2007
P35	G0-P21	FLX 5mg/kg	OA	F/M	Wistar	-	FLX ↑ Anxiety (NSF: increased latency to feed) FLX ≠ 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 ↑ ↑ Anxiety (OFT: less time in open arms- Sprague-Dawley only, EPM: less time in open arms-both strains) FLX ↑ 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 ↓ ↓ Anxiety (OFT: more time in center, EPM: more time in open arms) ESC ≠ Depression (FST)	Altieri et al., 2015
P54	P7-21	ZIM 25mg/kg	IP	M	Wistar	-	ZIM ↑ Depression (FST: increased immobility)	Hilakivi et al., 1988b
P55	P1-21	FLX 10mg/kg	SC	M	Wistar	-	FLX ↓ 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 ↑ Anxiety (OFT: reduced central crossings, less time in center)	Bairy et al., 2007
P56	P0- 4	FLX 20mg/kg	SC	F/M	Wistar	-	FLX ↑ ≠ Anxiety (OFT: less time in center; EPM: ≠) FLX ↑ Depression (FST: increased immobility)	Ko et al., 2014
P56	G12-P12	FLX 25mg/kg	DW	M	C57BL/6	Prenatal stress	FLX ↓ ≠ Anxiety (EPM: more time in open arms; OFT: ≠) *FLX protected against effects of prenatal stress	Kiryanova et al., 2016
P56, P140	P7-18	ZIM 25mg/kg	IP	M	Wistar, Long-Evans	-	ZIM ↑ ↑ Depression (FST: increased immobility at both time points)	Hilakivi et al., 1987a
P60	P8-21	FLX 10mg/kg	IP	M	Sprague-Dawley	-	FLX ↑ Anxiety (OFT: less time in center)	Mnie-Filali et al., 2011
P60	G6-P20	CIT 10mg/kg	SC	F/M	Sprague-Dawley	-	CIT ↑ ↑ (F only) ≠ Anxiety (MB: increased marbles buried; OFT: less time in center (F only); EPM ≠) CIT ↑ Depression (FST: increased mobility)	Sprowles et al., 2016
P60	G6-P20	CIT 5mg/kg, FLX 5mg/kg,	SC	F/M	Sprague-Dawley	-	CIT ↑ ≠ ≠ Anxiety (MB: increased marbles buried; EZM: ≠; OFT: ≠) CIT ≠ Depression (FST) FLX ↑ ≠ ≠ Anxiety (MB: increased marbles buried; EZM: ≠; OFT: ≠)	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 ↑ ≠ Anxiety (NSF: increased latency to feed, EPM: ≠) FLUV ≠ ≠ Anxiety (NSF, EPM)	Noorlander et al., 2008
P90	P4-21	FLX 10mg/kg FLU 10mg/kg	IP	M	C57BL/6	-	FLX ≠ Anxiety (PFT) FLU ≠ Anxiety (PFT)	Zheng et al. 2011
P90	P8-21	CIT 5, 10, 20mg/kg	SC	M	Long	-	CIT ≠ Anxiety (EPM)	Harris et al., 2012
P90-100	P2-21	FLX 10mg/kg	OA	M	Sprague-Dawley	-	FLX ↑ ↑ Anxiety (EPM: less time in open arms, OFT: less time in center) FLX ↑ Depression (FST: increased immobility)	Sarkar et al., 2014
P90+	P2-11	FLX 10mg/kg	IP	F/M	129S6SvEv Tac	-	FLX ↑ ↑ Anxiety (OFT: less time in center, NSF: increased latency to feed) FLX ↑ Depression (FST: increased immobility)	Rebello et al., 2014
P90+	P2-21,	FLX 10mg/kg, CLOL 20mg/kg	IP	F/M	129S6/SvEv	-	FLX ↑ ↑ Anxiety (OFT: less time in center, NSF: increased latency to feed- only for P2-21 group) CLOL ↑ ↑ 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 ≠ ≠ 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 ≠ ≠ ≠ 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 ↑ Anxiety (NSF: increased latency to feed)	Smit-Rigter et al., 2012
P110+	P4-21	FLX 10mg/kg	IP	M	C57BL/6J	-	FLX ↑ ↑ Anxiety (OFT: less time in center, LD: less time in dark) FLX ↓ Depression (FST: decreased immobility)	Karpova et al., 2009
P119-P126	P8-21	LU 2.5, 5,10, 15 mg/kg	IP	M	Wistar	-	LU ≠ Anxiety (OFT) LU ↑ Depression (FST: increased immobility)	Hansen et al., 1997
P140	G0-P14	SER 5mg/kg	IP	F/M	C57BL/6	-	SER ≠ Anxiety (EPM)	Meyer et al., 2018
P140	P1-21	FLX 5mg/kg	SC	M	Sprague-Dawley	Prenatal stress	FLX ↑ ≠ Anxiety (OFT: less time in center, EZM: ≠) FLX ≠ 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 ≠ ≠ Anxiety (EZM, OFT) FLX ↑ 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**, ≠ = 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

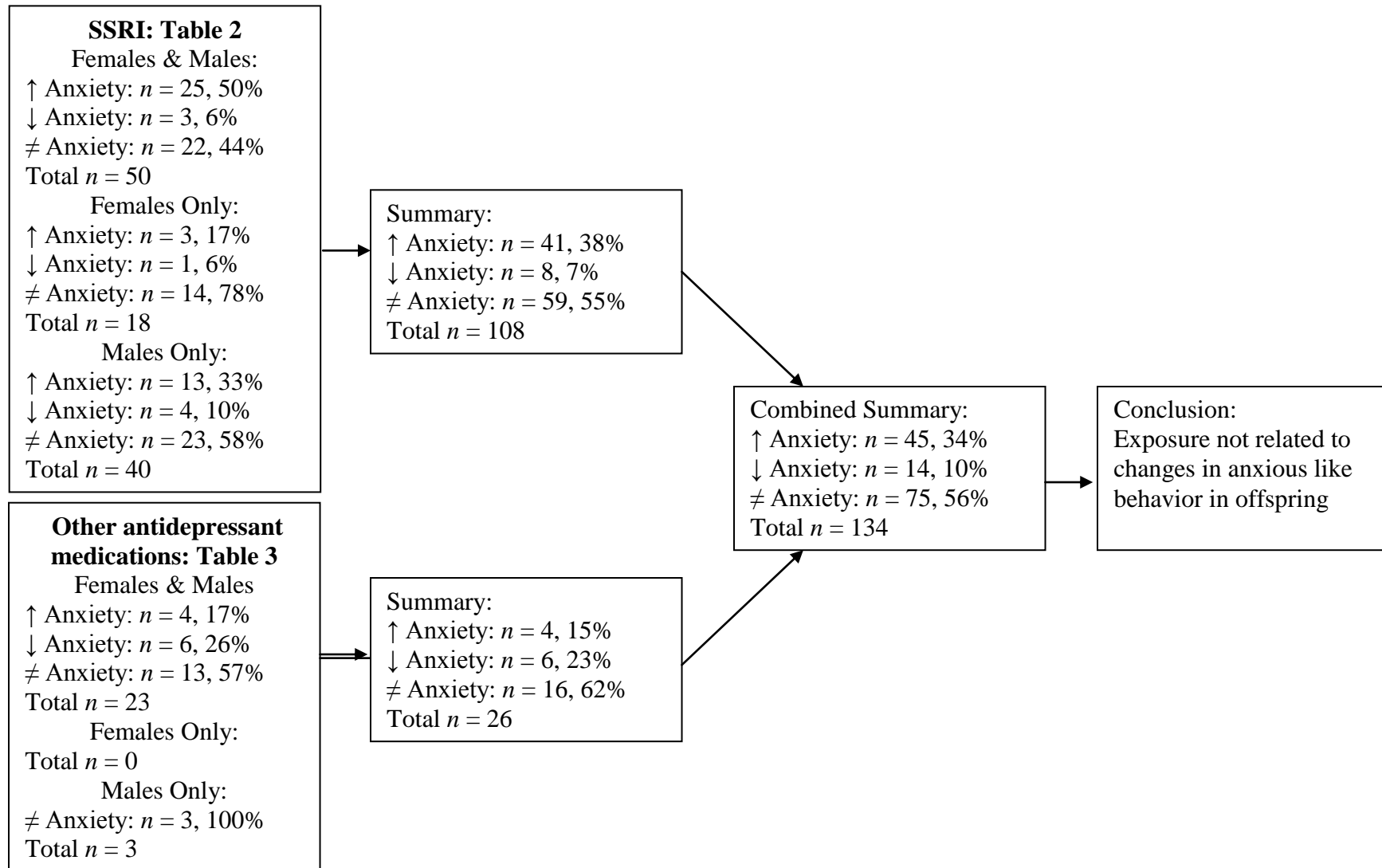
Summary of rodent research investigating other antidepressant medications to treat perinatal depression or anxiety and offspring anxiety and depressive behavior

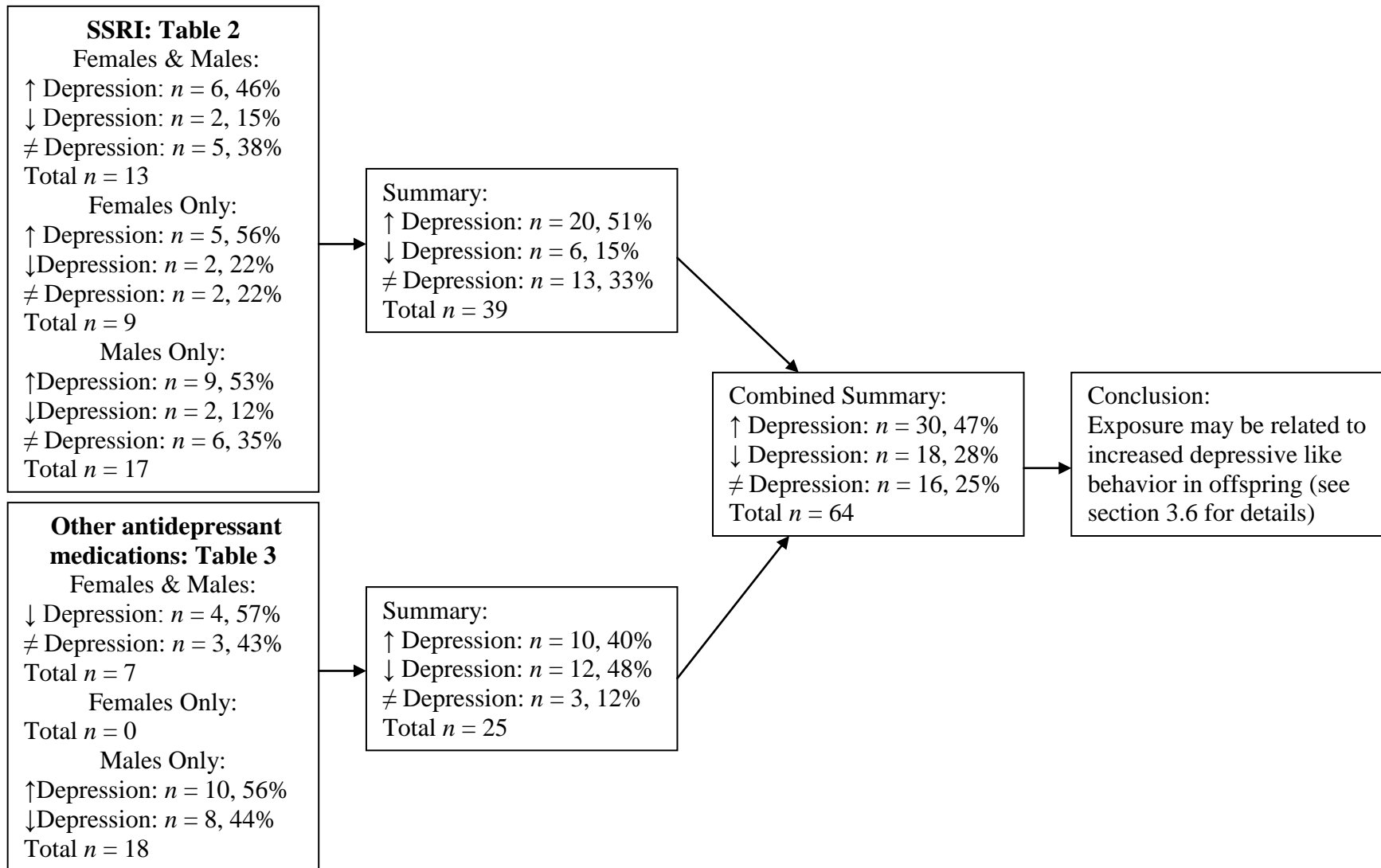
Test Dates	Time	Drug dose/day	Method admin	Sex	Strain	Maternal Stress	Results	Reference
							Juvenile Testing (P21-50)	
~P21+	P8-21	CLO 40mg/kg	IP	M	Wistar	Prenatal Stress	CLO ↑ Depression (FST: increased immobility)	Yang et al., 2008
P25	G9-21	BUS 3.5mg/kg or FLX 10mg/kg & BUS 3.5mg/kg	PI	M	Wistar	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 ≠ ≠ ≠ Anxiety (EPM, OFT, NSF) CLO ↑ ↑ ≠ Anxiety (EPM: less time in open arms, OFT: less time in center area, NSF: ≠)	Ansorge et al., 2008
P90	P8-21	CLO 15mg/kg	SC	M	Wistar	-	CLO ↑ ↑ 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 ↓ ↓ 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 ↑ ↑ 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 ↑ Depression (FST: increased immobility)	Vázquez-Palacios et al., 2005
P168	P8-21	CLO 15mg/kg	SC,	M	Wistar	-	CLO ↑ Depression (FST: increased immobility)	Velazquez-Moctezuma et al., 1992

Note. Arrows indicate significant differences (increases/ decreases) between medication exposed and controls on one task, ≠ = 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.

