

# Neurodevelopmental and neurobehavioral sequelae associated with in utero exposure to second-generation antidepressants: A systematic review

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## ABSTRACT

Most of the clinical and non-clinical literature revealed an association between maternal use of classical/first-generation antidepressants such as tri/tetra-cyclic antidepressants (TCAs) and monoamine oxidase inhibitors and impaired neurodevelopment in children along with adverse pregnancy outcomes. Although several second-generation antidepressant drugs (ADs) of various classes have been introduced recently, their potential to affect neurodevelopment and neurobehavioral development in newborns has not been investigated. This systematic review intends to provide an overview of the findings of neurodevelopmental and neurobehavioral effects following prenatal exposure to second-generation antidepressants, taking into account pharmaceutical company-conducted clinical trials, case reports, non-clinical studies, and academic publications that have been published to date. With the accompanying keywords of pregnancy, neurodevelopment, neurobehavior, and ADs, a systematic evaluation of published research on neurodevelopmental/neurobehavioral outcomes including cognition, speech, emotion, and motor coordination in early life was undertaken between January 1980 and April 2022. We searched Pub Med, Clinicaltrials.gov, Cochrane Library and Web of Science for potentially relevant articles published in English and included 32 articles in this review. On analyzing 32 articles pertaining to selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRIs) and atypical ADs use during pregnancy, its clinical and non-clinical implications showed no difference in neurodevelopmental outcomes between those exposed and controls, despite some reports of abnormalities in motor, cognitive, speech, emotion, and social behavior, as well as neurodevelopmental and neurobehavioral outcomes. However, scholarly articles on neurodevelopmental/neurobehavioral studies are still limited to drawing an appropriate conclusion. Therefore, there is an urgent need to study the long-term impact of SSRIs, SNRIs, and atypical ADs use in pregnancy on the betterment of both mother and fetus, respectively.

## 1. INTRODUCTION

Depression, a common mental disorder, has affected a large population of the world [1]. Previous studies reveal that approximately 70% of women are more likely to suffer from depression than men during their childbearing age, from adolescence to pre- and post-menopausal age [2]. Approximately 10% of expectant mothers and 13% of young mothers have had a mental condition, and in developing nations, these percentages are much higher, at about 15.6% during pregnancy and 19.8% after giving birth [3].

There are considerable risks involved if depression is not treated during pregnancy. The untreated pregnant population poses an increased risk of maternal and neonatal adverse outcomes such as fetal

distress, preterm birth, low birth weight, and birth defects [4]. Another aspect of untreated depression in pregnancy is the possible effect of maternal depression on the pregnancy and fetus, associated with adverse neurodevelopmental outcomes such as motor, speech, and neurobehavioral impairments, including cognitive, social engagement, immature regulatory behaviors, and negative emotionality [5]. The growing body of clinical literature indicates that untreated cases of maternal depression may lead to suicidal attempts as a significant cause of maternal mortality [6]. Therefore, medication for maternal depression should be of great concern during the pre- and perinatal period. Children of mothers diagnosed with a mood or anxiety disorder that used selective serotonin reuptake inhibitors (SSRIs) and/or selective norepinephrine reuptake inhibitors (SNRIs) during pregnancy were at risk for developmental vulnerability and language and cognitive difficulties [7].

For therapeutic management of depression, antidepressant drugs (ADs), namely, classical/first-generation and second-generation, are available in the world market [Table 1]. Globally, the numbers of clinical depressive cases are escalating rapidly in the general population,

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**Table 1:** List of antidepressants available and their development in the time scale.

First generation (classical) antidepressants		Second generation antidepressants		
Monoamine oxidase inhibitors (MAOIs)	Tricyclic antidepressants (TCAs)	Selective serotonin reuptake inhibitors (SSRIs)	Serotonin norepinephrine reuptake inhibitors (SNRIs)	Atypical antidepressants
Phenelzine (1961)	Melitracen (1950s)	Fluoxetine (1987)	Venlafaxine (1997)	Trazodone (1981)
Tranylcypromine (1962)	Amitriptyline (1961)	Sertraline (1991)	Duloxetine (2004)	Bupropion (1985)
Isocarboxazid (1998)	Amitriptylinoxide (1961)	Paroxetine (1992)	Desvenlafaxine (2008)	Amoxapine (1992)
Selegiline (2006)	Desipramine (1964)	Fluvoxamine (1994)	Milnacipran (2009)	Mirtazapine (1997)
	Lofepramine (1977)	Citalopram (1998)	Levomilnacipran (2009)	Atomoxetine (2002)
	Nortriptyline (1977)	Escitalopram (2002)	Viloxazine (2021)	Nefazodone (2003)
	Trimipramine (1979)			Vilazodone (2011)
	Imipramine (1982)			Vortioxetine (2013)
	Clomipramine (1989)			Esketamine (2020)

MAOIs: Monoamine oxidase inhibitors, TCAs: Tricyclic antidepressants, SSRIs: Selective serotonin reuptake inhibitors, SNRIs: Serotonin norepinephrine reuptake inhibitors.

including pregnant women, despite the availability of various typical and atypical ADs, thus causing a treatment gap for effective control of the depressed population [8]. At present, SSRIs and SNRIs are a safer and influential class of drugs as compared to tri or tetra-cyclic antidepressants (TCAs), or monoamine oxidase inhibitors (MAOIs) for the treatment of depression in pregnant women. SSRIs or SNRIs during pregnancy have shown a four-fold increase between 1996 and 2005, with approximately 2–8% of pregnant women receiving this treatment [9,10]. Hence, clinicians or health care providers are highly concerned about pharmaco-therapeutic management of pre- and perinatal depression, considering the safety profile of developing fetus and pregnancy outcomes.

Most clinical studies revealed that infants prenatally exposed to SSRIs are at high risk for developing psychopathology, involving abnormal social behavior and adolescent depression [11-13], but no association with attention-deficit/hyperactivity disorder [14,15]. Therefore, *in utero* exposure to ADs must be a severe consideration for pregnant women taking ADs prescriptions. Furthermore, it is expected that clinicians must be aware of the recent studies on the potential risk of *in utero* exposure to second-generation ADs during the fetus's brain development and its long-term neurobehavioral outcomes. However, patients with major depression have inadequate responses or intolerant side effects to first-line treatment with SSRIs and SNRIs frequently prescribed with atypical ADs [16]. Several narrative reviews [17-22] have described a substantial increase in clinical and non-clinical studies examining various neurobiological outcomes of *in utero* SSRI exposure. However, a thorough literature survey indicates a paucity of review articles on the impact of exposure to second-generation ADs during pregnancy and its impact on long-term neurodevelopment outcomes in children. Therefore, the present review aims to scrutinize the available literature on the neurodevelopmental and neurobehavioral potential of commonly prescribed second-generation ADs in clinical and experimental models as translational research.

## 2. CHARACTERISTICS OF SECOND-GENERATION ANTIDEPRESSANTS

Various parameters such as drug structure, molecular weight, pharmacokinetics, pharmacodynamics, and mechanism of action are used to classify ADs. First-generation ADs include TCAs and MAOIs, and MAOIs were the first to be introduced clinically as ADs. The

MAOIs work by binding covalently to monoamine oxidase enzyme resulting in non-competitive and irreversible inhibition. Despite the fact that most TCAs lack selectivity, they work by reducing the uptake of monoamines by nerve terminals, competing with carrier protein for its binding site, and, to a lesser extent, inhibiting the absorption of noradrenaline and serotonin (5-HT), with a much less pronounced effect on dopamine uptake [23,24].

Among second-generation ADs, SSRIs were the first introduced medication for clinical use. They have better durability, efficacy, and safety than first-generation ADs (TCAs or MAOIs) and are safer at high doses exposure. To prevent serotonin from being reabsorbed into the presynaptic terminal, SSRIs block the presynaptic plasma membrane serotonin transporter (SERT). Therefore, due to a rise in synaptic dopamine content, it initially prevents reuptake and extended serotonergic neurotransmission. Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram are some of the common SSRIs. All SSRIs involving those with an additional effect on norepinephrine reuptake (SNRIs) have a similar mechanism of action despite being different in molecular structures, including duloxetine, desvenlafaxine, venlafaxine, and milnacipran [25,26]. Atypical antidepressants (including trazodone, bupropion, mirtazapine, vilazodone, and vortioxetine) are a group of relatively new and unique antidepressants that works with a different mode of action which is poorly understood and vary from drug to drug. It works by affecting the balance of various neurotransmitters such as dopamine, serotonin, and norepinephrine in the brain, so they don't fall into the typical categories of antidepressants which includes MAOIs, TCAs, SSRIs, and SNRIs [27]. Among all available ADs, SSRIs and SNRIs are most commonly used for treating depression [28].

## 3. METHODS

### 3.1. Search and Inclusion Criteria

This study is designed to review all possible and potential literature available on *in utero* exposure to second-generation ADs and neurodevelopment outcomes in infants during initial years and neurobehavioral changes in young offspring. A thorough computerized search of the literature was performed on controlled clinical trials conducted by the pharmaceutical companies (product monograph of the drugs), case-control reports, cohort studies, prospective or retrospective studies in clinical and non-clinical (animal) domains, and review articles published in reputed journals in English; experimental trials published

in various journals related to psychopathology, neurodevelopment, neuroscience, medicine, neurology, cognition, etc. including recent World Health Organization data fact sheets published up to April 30, 2022. We searched Pub Med, Clinicaltrials.gov, Cochrane Library, and Web of Science for potentially relevant articles published in English. The following keywords and/or their combinations were used for search purposes: Pregnancy, gestation, *in utero*, maternal, antidepressant, SSRIs, SNRIs, atypical ADs, brain or neurodevelopment, developmental neurotoxicity, drug safety, placental passage, pregnancy outcomes, neurobehavioral outcomes, motor development, cognition, learning, memory, intelligent quotient (IQ), anxiety, depression, major depressive disorder (MDD), social interaction, and individual name of the second-generation ADs as mentioned in Table 1. Ethical committee approval is not required for this review paper as it is solely based on the literature search from various sources.

### 3.2. Exclusion Criteria

In this article, we have excluded the studies for the following reasons: (1) If they were abstract, (2) if they reported a citation that lacked full text or was not available in English, (3) if the published study has no comparison groups or lacked the outcomes of interest, (4) if there is no SSRIs, SNRIs or atypical ADs treatment, and (5) if they reported inadequate assessments of neurodevelopmental/neurobehavioral outcomes between groups (e.g., outcomes assessments timings and units of measurements were not specified).

## 4. RESULTS

Database searches retrieved 1535 citations. Removal of duplicates followed by review of titles abstracts and full texts yielded 32 relevant studies reporting neurodevelopment and neurobehavioral outcomes following exposure to second-generation antidepressant compared to control/untreated group. The number of titles, abstracts, and full papers excluded is shown in the PRISMA flow chart [Figure 1]. Table 2 contains comprehensive information on the research, including study size, exposure, exposure period, doses range, and results for neurodevelopmental and neurobehavioral outcomes.

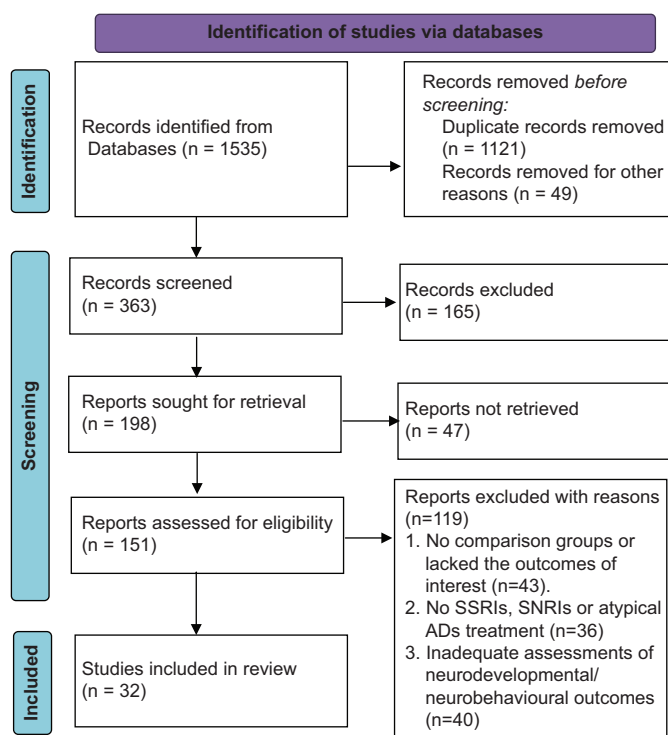
### 4.1. SSRIs

#### 4.1.1. Fluoxetine

This drug got approval in 1987 by the US food and drug administration (FDA) to treat MDD. The safety of using fluoxetine during pregnancy is unclear, and it comes under the pregnancy category C (human studies are lacking, and animal studies are either positive for fetal risk or lacking as well). The mechanism of action of fluoxetine is not known precisely but is believed to act by inhibiting the reuptake of serotonin, therefore increasing its concentration in the brain [29].

##### 4.1.1.1. Clinical studies

The data available on neurodevelopmental outcomes following the use of fluoxetine in pregnant women are limited. Nulman *et al.*, 1997, 2002, and 2012 reported that *in utero* exposure to fluoxetine does not affect preschool children's cognitive ability, language development, and behavior [30-32]. In contrast, a study by Casper *et al.*, 2003, reported impaired psychomotor development in children prenatally exposed to fluoxetine, paroxetine, and other SSRIs compared to non-exposed children [33]. There were statistically significant variations in the scores on the Bayley Scales of Infant Development (BSID-III) subscales evaluating gross motor, social-emotional, and adaptive behavior in exposed infants [34,35].



**Figure 1:** PRISMA flow diagram for systematic review of antidepressants treatment.

##### 4.1.1.2. Animal studies

Available studies exploring the neurodevelopmental outcomes following the gestational exposure of this drug in rats suggest a delay in motor development [36] and induce anxiety-like and depressive-like behavioral alterations in offspring [37,38], but no other developmental problems were recorded. Some studies reported reduced social behavior and increased anxiety in adulthood in the exposed group compared to the non-exposed group [39-41]. Some other studies on rodents also revealed that maternal exposure to fluoxetine caused a significant increase in aggression, increase in motor activity, a reduction in sexual behavior, and emotional problems [39,42,43]. These changes appear to be influenced by fluoxetine exposure during pregnancy after proliferating neurons in the hippocampus are damaged, resulting in morphological abnormalities in the cerebral cortex [39]. In contrast, other studies showed no significant effects on locomotor activity, spontaneous alternation, passive avoidance, or water maze performance [44,45].

#### 4.1.2. Sertraline

Sertraline was licensed in 1991 by US FDA for the treatment of MDD. The safety of this drug use during pregnancy is unclear [46], and it belongs to the pregnancy category C. Sertraline is the most commonly prescribed SSRI in pregnant women [47].

##### 4.1.2.1. Clinical studies

There are relatively few investigations on the effects of sertraline exposure during pregnancy on neurodevelopment. Following prenatal exposure to sertraline and other SSRIs in comparison to non-exposed individuals, Austin *et al.* and Suri *et al.* found no statistically significant changes in infant neurodevelopmental outcomes, either cognitive or motor [48,49]. Another study by Oberlander *et al.*, 2007, shows no

**Table 2:** Summary of neurobehavioral and neurodevelopmental effects induced by second generation antidepressant drugs.

Author and year	ADs and sample size	Exposure period	Doses per day/dose range	Species	Outcomes
Clinical studies					
Nulman <i>et al.</i> , 1997 [30]	FLU (n=55)	First trimester/ throughout pregnancy	NS	Human	No developmental problems
Heikkinen <i>et al.</i> , 2002 [60]	CIT (n=11)	During pregnancy and lactation	20–40 mg	Human	Normal development at 1 year
Nulman <i>et al.</i> , 2002 [31]	FLU (n=40)	Throughout pregnancy	20–80 mg	Human	No change in global IQ, language, behavior in comparison to control
Casper <i>et al.</i> , 2003 [33]	SER (48%); FLU (23%); PAR (26%); FLV (3.2%)	Throughout pregnancy (45%); first trimester (21%) and third trimester (74%)	SER (113.2 mg); FLU (20 mg); PAR (17.2 mg); FLV (50 mg)	Human	Lower motor scores in exposed group as compared to nonexposed group
Misri <i>et al.</i> , 2006 [55]	PAR (n=14); FLU (n=5); SER (n=3)	During pregnancy and lactation	PAR (23–28 mg); FLU (18–22 mg); SER (91 mg)	Human	Levels of internalizing behaviors did not differ significantly between exposed and unexposed children
Oberlander <i>et al.</i> , 2007 [50]	PAR (n=13); FLU (n=6); SER (n=3)	During pregnancy	PAR (20 mg); FLU (20 mg); SER (75 mg)	Human	No significant difference in externalizing behavior
Oberlander <i>et al.</i> , 2010 [54]	PAR (n=15); FLU (n=4); SER (n=5); CIT (n=6); VEN (n=3)	Third trimester	PAR (2–45 mg); FLU (10–40 mg); SER (25–175 mg); CIT (20–40 mg); VEN (38–150 mg)	Human	Increased internalizing behavior and anxiety/depressed symptoms in children at 3 years of age
Pedersen <i>et al.</i> , 2010 [65]	FLU (n=88); CIT (n=86); PAR (n=76); SER (n=86); TCAs (n=28); Other ADs, including VEN (n=29); More than one SSRIs (n=12)	At any point of pregnancy	NS	Human	Small developmental delay in gross motor function milestones in exposed groups
Galbally <i>et al.</i> , 2011 [51]	SER (n=8); FLU (n=1); FLV (n=1); CIT (n=3); ESC (n=1); PAR (n=1); VEN (n=4) and MIR (n=1)	First trimester	SER (50–200 mg); FLU (20 mg); FLV (100 mg); CIT (20 mg); ESC (10 mg); PAR (10 mg); VEN (75–150 mg); MIR (60 mg)	Human	Lower motor score in exposed group
Suri <i>et al.</i> , 2011 [49]	FLU (38%), SER (36%) and other ADs (26%)	During pregnancy	FLU (22.5 mg); SER (90.5 mg); Other ADs (NS)	Human	No significant differences were observed in early infant neurobehavioral development
Nulman <i>et al.</i> , 2012 [32]	SER (n=11); PAR (n=20); CIT (n=15); FLU (n=15); FLV (n=1); VEN (n=62)	Throughout pregnancy (n=81); Mothers exposed in 1 <sup>st</sup> , 2 <sup>nd</sup> , and/ or 3 <sup>rd</sup> trimesters (n=43)	SSRIs (0.40–4.00 mg) And VEN (0.25–3.75 mg)	Human	Children of control function better but no difference between treated and untreated group of depressed mothers
Austin <i>et al.</i> , 2013 [48]	SER (n=11); FLU (n=6); CIT (n=5); ESC (n=2); PAR (n=1); FLV (n=1) VEN (n=4)	During pregnancy (at least for 1 month)	SER (25–150 mg); FLU (20–40 mg); CIT (10–20 mg); ESC (5 mg); PAR (20 mg); FLV (100 mg); VEN (150–300 mg)	Human	No difference between exposed and unexposed infants in any of the neurodevelopment outcomes
Bellantuono <i>et al.</i> , 2013 [72]	DUL (n=1)	Throughout pregnancy	60 mg	Human	Normal infant development
Hanley <i>et al.</i> , 2013 [35]	SSRIs (n=31)	Throughout pregnancy	NS	Human	Significantly lower scores of exposed infants on gross motor, social emotional and adaptive behavior
Hanley <i>et al.</i> , 2015 [12]	FLU (n=5); PAR (n=16); SER (n=7); CIT (n=6); VEN (n=10)	During pregnancy	NS	Human	Higher internalizing behavior and anxious/depressed symptoms; No significant difference in externalizing scores
Preclinical or animal studies					
Vorhees <i>et al.</i> , 1994 [45]	FLU	GD 7–20	1; 5; 12 mg/kg (oral: Gavage)	Sprague Dawley rat	No significant effects on locomotor activity, passive avoidance, or water maze performance

(Contd...)

**Table 2:** (Continued).

Author and year	ADs and sample size	Exposure period	Doses per day/dose range	Species	Outcomes
Singh <i>et al.</i> , 1998 [43]	FLU	GD 13–21	10 mg/kg (IP)	Charles Foster rat	Significantly increased in aggression
Stewart <i>et al.</i> , 1998 [44]	FLU	GD 8–20	12.5 mg/kg (oral)	Sprague Dawley rat	No significant alteration in behaviour
Coleman <i>et al.</i> , 1999 [56]	PAR	GD 0–16.5	30 mg/kg (oral: Food bar)	CD-1 mouse	Increase in male aggression but no significant differences in early development task (or in locomotor) and exploratory activities throughout development
Chritensen <i>et al.</i> , 2000 [57]	PAR	GD 0–P 1	30 mg/kg (oral: Food bar)	CD-1 mouse	No impact on cognition
Bairy <i>et al.</i> , 2007 [36]	FLU	GD 6–20	8; 12 mg/kg (oral)	Wistar rat	Transient delay in motor development and favorable effect on learning and memory
Cagiano <i>et al.</i> , 2008 [39]	FLU	GD 13–20	5; 10 mg/kg (SC)	Wistar rat	Alteration of short-term retention memory, increased anxiety level and altered emotionality found in exposed group
Noorlander <i>et al.</i> , 2008 [40]	FLU; FLV	GD 8–18	FLU (0.3; 0.6; 0.8 mg/kg; IP); FLV (4.2 mg/kg; IP)	C57BL/6 mouse	FLU exposure resulted increase in depressive and anxiety related behavior, but FLV exposure didn't showed any alteration
Sahoo <i>et al.</i> , 2010 [74]	MIR	GD 6–20	3.6; 7.2 mg/kg (oral: Distilled water)	Wistar rat	No significant difference in cognition level but subtle changes in motor development and anxiety level
Olivier <i>et al.</i> , 2011 [41]	FLU	GD 11–P1	12 mg/kg (oral: Gavage)	Wistar rat	Induced significant increase in anxiety during adulthood and decrease in social play behavior at 4 weeks of age
Smit-Rigter <i>et al.</i> , 2012 [37]	FLU	GD 8–18	0.6 mg/kg (IP)	C57BL/6 mouse	Induced anxiety-like behavior in wild type offspring
Bourke <i>et al.</i> , 2013 [63]	ESC	GD 0–P 1	12.2–17.3 mg/kg (SC: osmotic minipump)	Sprague Dawley rat	No change in anxiety level between group in adulthood
Ehrlich <i>et al.</i> , 2015 [62]	ESC	GD 0–P 1	12.2–17.3 mg/kg (SC: Osmotic minipump)	Sprague Dawley rat	Reduced social interaction in adolescents but not in adulthood
Singh <i>et al.</i> , 2015 [68]	VEN	GD 5–19	25; 40; 50 mg/kg (oral gavage: distilled water)	Charles-Foster rats	Increased anxiety-like behavior in offspring
Singh <i>et al.</i> , 2016 [38]	FLU	GD 13–20	5 and 10 mg/kg/day (IP)	Charles Foster rat	Dose dependent significant increase in immobility time in FST and reported depressive-like behavior in rat offspring
Svirsky <i>et al.</i> , 2016 [42]	FLU	GD 1–P1	10 mg/kg (SC)	CD-1 mouse	Increased aggression in adult males but no effect on social exploration and recognition memory
Lozano <i>et al.</i> , 2021 [52]	SER	GD 13–20	20 mg/kg (oral gavage)	Wistar rat	Reduced exploratory behavior (anxious profile) and delayed negative geotaxis responses in male offspring

NS: Not specified, SC: Subcutaneous, IP: Intraperitoneal, SSRIs: Selective serotonin reuptake inhibitors, FLU: Fluoxetine, SER: Sertraline, PAR: Paroxetine, FLV: Fluvoxamine, CIT: Citalopram, ESC: Escitalopram, VEN: Venlafaxine, MIR: Mirtazapine, DUL: Duloxetine, GD: Gestation day, P: Postnatal day, FST: Forced swimming test, IQ: Intelligent quotient, TCAs: Tri/tetra-cyclic antidepressants, ADs: Antidepressant drugs.



significant difference in externalizing behavior (subscale that examines the degree of aggression, attention, and hyperactivity) between the treated and untreated groups [50]. These findings lack association with the previous studies suggesting impaired psychomotor development in the exposed group compared to the non-exposed group [33,51].

#### 4.1.2.2. Animal studies

Animal studies regarding neurodevelopmental outcomes following prenatal exposure to sertraline are limited. A study by Lozano *et al.*, 2021, reported that perinatal sertraline exposure delayed somatic and reflex development in rats and reduced exploratory behavior (anxious profile) in male offspring [52].

#### 4.1.3. Paroxetine

US FDA approved this drug in 1992 to treat MDD. This drug is not recommended during pregnancy, and it comes under the pregnancy category D (investigational or post marketing data show risk to the fetus). It also works by blocking serotonin reuptake, thereby increasing its activity in the brain [53].

##### 4.1.3.1. Clinical studies

Neurodevelopmental outcomes data following administration of this drug during pregnancy are confined. A study carried out on children with prenatal exposure reported higher levels of internalizing behavior (subscale that examines emotional responses, including assessment of anxiety and depressed behaviors) but no significant differences in the externalizing or attention scores [12,54]. However, some studies that evaluated children who were prenatally exposed to paroxetine indicated no significant difference in internalizing and externalizing behavior between groups [50,55].

##### 4.1.3.2. Animal studies

Developmental effects of embryonic exposure to paroxetine on postnatal development were first studied by Coleman *et al.*, 1999, in mice [56]. They found no differences in locomotor activities but reported increased anxiety levels, particularly in adult males. Christensen *et al.*, 2000, gave paroxetine to mice through food during pregnancy, observed the offspring up to adulthood, and found no difference in neurobehavioral and cognitive tests except for some delayed learning in adolescence compared to the non-exposed group [57].

#### 4.1.4. Fluvoxamine

Initially, fluvoxamine was approved by US FDA in 1994 specifically for treating obsessive-compulsive disorder, and it is also used for treating depression and anxiety disorders. This drug is categorized in pregnancy category C [58].

##### 4.1.4.1. Clinical studies

Studies regarding prenatal exposure to fluvoxamine and its effect on long-term neurodevelopmental outcomes in the offspring are limited.

##### 4.1.4.2. Animal studies

Pre-clinical studies investigating prenatal exposure to SSRIs regarding different neurodevelopment outcomes are scanty. Noorlander *et al.*, 2008, reported fluvoxamine has relatively low placental transfer compared to fluoxetine. They further examined fluvoxamine-exposed offspring and found no alteration in behavior and SERT levels. In contrast, fluoxetine-exposed offspring showed long-term alteration in SERT levels and displayed depressive and anxiety-related behavior in adulthood [40].

#### 4.1.5. Citalopram

US FDA licensed citalopram (Celexa) in 1998 to treat MDD [59]. This drug is categorized in pregnancy category C.

##### 4.1.5.1. Clinical studies

At present, there are no adequate and well-informed studies on the long-term consequences of early-life exposure to citalopram on neurodevelopment in humans. Considerable research of Heikkinen *et al.*, 2002, indicated normal development in a small group of children exposed to citalopram during pregnancy and followed up for 1 year [60].

##### 4.1.5.2. Animal studies

Animal studies in this regard are not available.

#### 4.1.6. Escitalopram

US FDA licensed this drug in 2002 to treat MDD [61]. It is an (S)-stereoisomer of citalopram. The safety of this drug use during pregnancy is unclear, and this drug comes under pregnancy category C.

##### 4.1.6.1. Clinical studies

There are no adequate and well-controlled studies available for long-term neurodevelopmental outcomes following prenatal exposure to escitalopram.

##### 4.1.6.2. Animal studies

Neurodevelopmental studies of this drug in the exposed animal are limited. Ehrlich *et al.*, 2015, administered escitalopram to rats during pregnancy and observed its impact on the neurodevelopment of delivered pups in adolescence and adulthood [62]. This study reported reduced social interaction in adolescents but not in adulthood. Another study on rats found no change in anxiety levels between exposed and unexposed groups in adulthood [63].

## 4.2. SNRIs

#### 4.2.1. Venlafaxine

Venlafaxine (brand name Effexor) was approved in 1993 by the US FDA to treat MDD. It is kept in the SNRI class of ADs. The mechanism of action is not clearly understood but is believed to be related to the potentiation of neurotransmitter activity in the brain. This drug is categorized in pregnancy category C [64].

##### 4.2.1.1. Clinical studies

Limited studies are available regarding prenatal exposure to venlafaxine and its impact on long-term neurodevelopmental outcomes in the exposed offspring. Some studies suggested no difference in IQ, motor development, and behavior of venlafaxine-exposed children compared with children of non-depressed mothers [32,48]. Other studies also showed no differences in externalizing behavior between exposed and non-exposed groups, but higher internalizing and anxious behaviors were reported in SRI exposed children at both 3 and 6 y of age [12,50]. Pedersen *et al.*, 2010, assessed children's developmental milestones using a questionnaire at 6 and 19 months of age and reported a slight delay in gross motor developmental milestones, but it will overcome with increasing age [65]. Some studies, however, have linked behavioral problems in children to untreated maternal depression [66,67].

##### 4.2.1.2. Animal studies

In this aspect, there is few research available. In open field exploratory behavior (OFT), Singh *et al.* found higher anxiety-like and stereotypical

behaviors, indicating altered neurobehavioral patterns in early rat pups [68]. Alterations in developing serotonergic and noradrenergic neurotransmitter systems caused by *in utero* venlafaxine exposure could be a source of behavioral disturbances [69,70].

#### 4.2.2. Duloxetine

Duloxetine (brand name Cymbalta) was approved in 2004 by the US FDA to treat MDD. It is kept in the SNRI class of ADs, and its mechanism of action is not clearly defined. This drug is categorized in pregnancy category C [71].

##### 4.2.2.1. Clinical studies

Studies regarding neurodevelopmental outcomes following the administration of this drug during pregnancy are confined. A research that accesses *in utero* duloxetine exposure following an infant until nine months after the treatment reported normal infant development on all domains of cognition, language, motor, and psychomotor scales [72].

##### 4.2.2.2. Animal studies

There are no published data regarding duloxetine prenatal exposure in animals and its long-term effects on the offspring developing brain.

### 4.3. Atypical Antidepressants

#### 4.3.1. Mirtazapine

Mirtazapine was initially approved for the treatment of MDD in the Netherlands in 1994 and received FDA approval in 1997. This drug is categorized in pregnancy category C. The mechanism of action is not fully understood but may affect central adrenergic and serotonergic activity [73].

##### 4.3.1.1. Clinical studies

There are no adequate data available for the use of this drug in pregnancy.

##### 4.3.1.2. Animal studies

Limited animal studies are conducted in this regard. Sahoo *et al.*, 2010 reported no significant difference in cognition level between control and exposed groups, whereas subtle changes were observed in motor development and anxiety level of prenatally exposed pups [74].

#### 4.3.2. Vilazodone

Vilazodone was approved for medical use by the US FDA in 2011 to treat MDD. This drug is categorized in pregnancy category C, and the safety profile of this drug use during pregnancy is not yet clear. It is kept in the serotonin modulator and stimulator (SMS) class of ADs and is believed to work both as SSRIs and an agonist of the 5-HT<sub>1A</sub> receptor [75].

##### 4.3.2.1. Clinical studies

There are no sufficient and reputable research on this medication usage during pregnancy.

##### 4.3.2.2. Animal studies

Animal studies regarding the prenatal exposure of vilazodone and its long-term effects on the developing brain of neonates are not available. However, the product monograph of the drug indicates the excretion of vilazodone in the milk of lactating rats [75].

#### 4.3.3. Vortioxetine

Vortioxetine is sold under the brand name brintellix, which got approval for medical use in 2013 by the US FDA and European Medicines

Agency to treat MDD. This drug is categorized in pregnancy category C. The mechanism of action is not precise for this drug and works by enhancing serotonergic activity in the Central nervous system by inhibiting serotonin's reuptake. It is a multimodal agent classified as a SMS, including 5-HT<sub>3</sub> receptor antagonism and 5-HT<sub>1A</sub> receptor agonism. Use of this drug during pregnancy and lactation is generally not recommended [76,77].

##### 4.3.3.1. Clinical studies

There are no sufficient and well-controlled studies on pregnant women available.

##### 4.3.3.2. Animal studies

There are no published data regarding vortioxetine prenatal exposure in animals and its long-term consequences on the offspring's developing brain and behavior.

## 5. DISCUSSION

A thorough clinical/pre-clinical literature survey on prenatal exposure to second-generation ADs (SSRIs, SNRIs, and atypical ADs) and their effects on neurodevelopment and neurobehavioral impairments in adolescent/young offspring is inconsistent in drawing a definite conclusion. Many clinical studies demonstrated non-substantial changes in the brain development and associated neurodevelopmental disorders followed by functional disturbances in children after *in utero* exposure to second-generation ADs [48,49]. In contrast, a large amount of non-clinical studies carried out in various animal models mimicking clinical characteristics revealed substantive changes in neurodevelopmental and neurobehavioral/functional sequelae in young offspring [52,68]. Therefore, extrapolation of animal data to humans is an intricate procedure, and difficult to draw an overt affirmation for determining the drug doses due to various confounding factors such as the mechanism of action of ADs, the metabolic rate of animals, gender variability, and strain susceptibility. Second-generation ADs target binding of serotonin specific receptors (5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub>, 5-HT<sub>1A</sub>, etc.) in the case of SSRIs, norepinephrine receptors (2 adrenergic receptors) along with serotonergic receptors in SNRIs, and other receptors (dopamine D<sub>2</sub> receptor, melatonin receptors, N-methyl-D-aspartate receptor, etc.) for atypical ADs [78].

It is presumed that therapeutic doses of an antidepressant may be useful for a deceased mother, but it could be harmful to the developing brain, which may lead to neurodevelopmental disturbances and psychopathological changes in the children and young offspring as a long-lasting impact of the drug if administered during pregnancy (1<sup>st</sup>, 2<sup>nd</sup>, and/or 3<sup>rd</sup> trimester). These drugs may cross the placental and blood-brain barrier swiftly at significant concentrations [4,60], which may disrupt the neurotransmitter levels during fetal brain development.

Neurotransmitters (serotonin, dopamine, and norepinephrine) have a phylogenetically ancient role in neural transmission [79]. Specifically, serotonin (5-HT) has a diverse role in brain development [80] and is crucial in cognitive processes such as memory and learning [81]. Thereby, even a minor alteration in the 5-HT level during critical developmental periods significantly impact brain development, behavior, long-lasting emotional health [82] and promote aggressive and/or anxiety-related behaviors [83,84]. Preclinical studies also showed that early-life modification of serotonin levels induces behavioral changes [85]. The activation or inhibition of certain 5-HT receptors can affect hippocampal adult neurogenesis [86]. 5-HT<sub>1A</sub> receptors can be up or down-regulated in the fetal brain; therefore, they

are likely to be functioning before birth [87] and a disruption in early development can affect brain structure which repairs much later in life.

With the widespread use of SSRI antidepressant medications among women of childbearing age, pregnant, or nursing, there is a need to understand the long-term effects of SSRI exposure on their children, as SSRI exposure is one of the most important environmental factors regulating 5-HT levels in the developing brain [88]. The therapeutic benefits of ADs are thought to cause long-lasting changes in cellular physiology by changing 5-HT signaling and influencing neurogenesis. While these SSRI-induced adaptations are required to manage maternal depression efficiently, SSRI exposure in pregnancy may have long-term harmful effects on the offspring. Therefore, there should be more clinical and pre-clinical studies to measure its risk to the long-term neurobehavioral development of offspring.

## 6. CONCLUSIONS AND FUTURE DIRECTIONS

There has been limited study on the effects of prenatal AD exposure on adolescent neurobehavioral development, and the evidence that is available is inadequate to draw any conclusive results. However, it would be suspected that exposure to second-generation ADs during pregnancy would interfere with brain development and related functional disturbances in the young offspring as these drugs can cross placental and blood-brain barriers swiftly. The use of SSRIs, SNRIs, and atypical ADs during pregnancy is not entirely risk-free, and it's evident that poor maternal mental health has an adverse effect on child development. However, it is difficult to measure the exact impact of maternal mental illness on a child's developing brain. Hence, accurate and well-controlled studies should be designed to profoundly evaluate this issue and ensure future benefits for pregnant women as maternal health and fetal well-being concomitantly.

## 5. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

## 9. DATA AVAILABILITY

The references were used to gather all the information in the manuscript.

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