ORIGINAL ARTICLE

Maternal Exposure to Antidepressants Vilazodone and Vortioxetine: Effects on Neurodevelopment of Young Rat Offspring

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Abstract

Background: Vilazodone (VLZ) and Vortioxetine (VOX) are newer antidepressants often used for treating major depressive disorder, but potential therapeutic safety for brain development in pregnant women is almost negligible due to paucity of clinical and non-clinical data. **Objectives:** The current work was planned to investigate possible linkages between neurodevelopmental delay and prenatal exposure to equivalent therapeutic doses of VLZ and VOX. **Materials and Methods:** Pregnant Wistar rats were orally gavaged with VLZ and VOX (1 mg/kg, and 2 mg/kg body weight [BW]) from gestation day 6 to 21. The dams delivered naturally and reared their litters until postnatal day 21 during which neurodevelopment reflexes were recorded. **Results:** Prenatally VLZ-and VOX-exposed rats showed significant (1) reduction in BW, (2) delay in forelimb grasping, (3) delay in the day of apparition of cliff avoidance, (4) delay in response in negative geotaxis only in VOX group, (5) deficit in grip strength, and (6) delayed eye opening. **Conclusion:** Our findings suggest that early life exposure to VLZ and VOX might be involved in the retardation and maturation of some reflexes which imply an existing association between early life VLZ and VOX exposure with an increased risk of developmental vulnerability.

Key words: Antidepressant, depression, neurodevelopment, pregnancy, rat, vilazodone, vortioxetine

INTRODUCTION

About 0.28 billion people worldwide suffer from depression, which is a major cause of mental impairment and greatly increases the global burden of disease.[1] According to the majority of epidemiological research, women are more prone than males to have major depression.[2,3] Pregnancy is one of the most vulnerable times, including almost 20% of women experiencing depression in their life.[4] The prevalence rate for depression during pregnancy has been reported to range from 4% to 25% in various clinical studies.[5-8]

Pregnant women suffering from depression may require proper medication, as maternal depression is linked to a slew of negative health consequences for both mother and child.[9] In addition to increasing impulsivity, altering social interactions, and causing cognitive, behavioral, and emotional issues for the mother,[10,11] maternal depression untreated can adversely affect pregnancy outcomes such as prematurity, intrauterine growth restriction, and low birth weight.[12,13] Importantly, pregnant women who experience depression are more susceptible to postpartum depression and suicidality.[14,15] Therefore, antidepressant (ADs) medication is required to minimize or prevent adverse implications for the benefit of both pregnant mother and developing fetus.

For therapeutic management of depression, pharmacological agents of different classes are available in the world market to treat and effectively control the different forms of depressive symptoms. Among the various classes of ADs, tri-or tetra-cyclic ADs (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and atypical or "newer generation" ADs are accessible in the pharmaceutical market. In pregnancy, SSRIs tend to be regarded safer and more effective than MAOIs and TCAs.[16-18] The frequency of AD exposure within pregnant women spike from 0.2% in 1997 to 3.2% in 2009, with a prevalence of 2.7% during

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Received: 02-12-2022
Revised: 02-02-2023
Accepted: 16-02-2023

the first trimester and 2.6% after. As much as 88.7% of pregnancy-related exposures were attributed to SSRIs, which accounted for the 16-fold increase.[19,20]

Furthermore, the literature indicates that ADs exposure during early life can interfere and/or interact with developmental processes of the brain as it may cross the blood-brain barrier and placenta at considerable amounts.[21,22] According to studies, women who took SSRIs during pregnancy had a 20% heightened incidence of preterm delivery and low birth weight than women who never took ADs.[23-25] Prenatal and early postnatal exposure to ADs were discovered to be linked to neurodevelopmental disorders.[26,27]

In the recent past, some new drugs belong to SSRIs, SNRIs, and/or atypical class such as vilazodone (VLZ) (2011) and vortioxetine (VOX) (2013) have been made available in the world market as an alternate source of existing ADs considering their improved efficacy and safety concerns.[28,29] The majority of SSRIs and SNRIs work primarily through the monoamine neurotransmitters serotonin, norepinephrine, and dopamine (DA), resulting in a unimodal or dual mode of action (monoamine transporter inhibition).[30] The atypical ADs and VOX, on the other hand, have a multimodal mode of action that combines regulation of 5-HT receptor activation with inhibition of the serotonin transporter (SERT), whereas VLZ is classed as a serotonin partial agonist reuptake inhibitor.[31] Although mechanism of action of these new drugs is similar to SSRIs or SNRIs, but their receptor binding pattern has been improved over to those ADs which were causing adverse effects on various aspects of pregnancy outcomes and developmental defects in offspring at childhood and adolescent stage.[32,33]

Several studies demonstrated that prenatal exposure to SSRIs or SNRIs may cause subtle delays in neurodevelopment in offspring,[34-36] but it is astonishing that no study of this sort has been yet conducted to evaluate the impact of prenatal exposure to atypical ADs, such as VLZ and VOX, on the various aspects of offspring brain development. Therefore, the safety of VLZ and VOX exposure during pregnancy, particularly with relation to child neurodevelopment, has not yet established.

Therefore, based on the necessity to establish a link between prenatal exposure to VLZ and VOX with fetal brain development, with therapeutically appropriate dosages in a prenatal rat model, this study seeks to examine the developmental neurotoxic potential of VLZ and VOX.

MATERIALS AND METHODS

Animals

Wistar female laboratory inbred nulliparous rats weighed 180 ± 10 g were used in this study. In a typical laboratory setting (24 ± 2°C, 12/12 h light/dark cycle, and 60% relative humidity), transparent polypropylene cages (39 × 24 × 15 cm) with rice bran as bedding were used to house the animals. There was *ad libitum* access to food and water for the rats. University of Allahabad's Institutional Animal Ethics Committee, located in Prayagraj, India, authorized the procedure for experimental use of rats, which were maintained and utilized as per guidelines of Animal Welfare Act.

Pregnancy determination

Male and female rats were let to mate overnight (ratio 2♀:1♂), and the following morning (at 08.00 h), vaginal swabs were checked for sperm to determine whether gestation commenced gestation day (GD-0). The females who tested positive for sperm were subsequently utilized in the tests and kept separately in cages of the same size.

Drug dosages

The drugs VLZ (brand name Vilodon, Msn Laboratories Pvt Ltd., India) and VOX (brand name Brintellix, H. Lundbeck A/S, Denmark) were purchased from the local pharmaceutical market. The therapeutic dosage range for VLZ in humans is 10–40 mg/day (0.167–0.66 mg/kg body weight [BW]/day), while, for VOX, it is 5–20 mg/day (0.083–0.33 mg/kg BW/day).[28,29] VLZ and VOX have maximum recommended human doses of 0.66 mg/kg BW and 0.33 mg/kg BW, respectively. The experimental doses of both drugs were calculated on the basis of body surface area per day (mg/m^2), and for inter conversion of unit (mg/m^2 to mg/kg), conversion factor was applied.[37] The dosages of VLZ and VOX were, thus, calculated to be 1 mg/kg/day and 2 mg/kg/day. The selected doses of VLZ and VOX were within the range of human therapeutic doses. Further, daily doses of VLZ and VOX were calculated as per escalation of BW of the pregnant dams accordingly, till GD-21.

Experimental design

All sperm-positive female dams (n = 36) were divided into Group-I (VLZ 1 mg/kg) and Group-II (VLZ 2 mg/kg, n = 6/per group), Group-III (VOX 1 mg/kg), and Group-IV (VOX 2 mg/kg, n = 6/per group). The corresponding controls (n = 6/group) of VLZ and VOX groups were also maintained concomitantly.

Both drugs were dissolved in distilled water and administered through gavage from GD-6 to GD-21 to pregnant dams once day (at 09.00 h) using a cannula. The same route and time were used to provide an identical amount of vehicle to control pregnant dams. All the dams were permitted to deliver normally and culled (n = 8 pups per litter), according to the experimental protocol.

Up to postnatal day (PND) 21, pups were raised with their respective mothers, during which neurodevelopment reflexes were recorded. The offspring (n = 1 male pup/dam) of each group were weighed at birth and then once a week until they reached the age of PND 21.

Neurodevelopment/reflex development tests

The tracking of developmental milestones was begun after observation of maternal behavior at PND-6 to prevent disrupting the nest and altering mother behavior. On the male pups, all developmental evaluations and neonatal behaviors were carried out during the light period (09.00–16.00). Between 9:00 and 11:00 h for 12 successive days (PND 6–18), a daily assessment of pup's reflex and other developmental landmarks were conducted until the selected pups in the litter had attained the developmental milestones. The following reflex tests were carried out chronologically: Limb grasping, surface righting reflex, cliff avoidance response, negative geotaxis, and grip strength response. The pups' developmental milestones, such as auditory startle and eye opening, were assessed until they completed the task. To reduce stress, pups were separated from their mothers for no more than 5 min throughout the neurological reflex development study. The time took by the pup to complete the reflex was used to evaluate the development reflexes.[38,39]

A standard battery of tests adapted from Fox (1965) and Tanaka *et al*. (2012) were used to examine neonatal reflexes. From PND-6 onward, 3–4 pups from each litter were assessed daily. The following aspects were daily examined in the same pup until PND-18:

Forelimb grasp reflex (PND 6–10)

The reflex was deemed fully completed when the pups were able to grip the body of a 16-gauge needle when it was brushed against the base of their forepaw.

Righting reflex (PND 6–10)

On a leveled surface, the pups were laid on its back. The time it takes for a pup to return back to its four limbs is known as the righting reflex. The time limit was set at 10 s.

Cliff avoidance (PND 6–10)

Pups were placed over a 30-cm precipice with their nose and forepaws placed over it. They were measured for how much time it took them to pull back from the edge.

Negative geotactic response (PND 6–12)

On an inclined surface covered with wire mesh, the pups were laid head down (45°). For 60 s, each pup was observed turning and moving toward the higher end of the surface.

Grip strength response (PND 6–12)

Grip demands tremendous strength, mostly in the fingers and paws, to maintain their BW on a metal rod. The pups were, therefore, encouraged to dangle by their forepaws from a horizontal bar that was 30 cm over a thick bed of cotton (for minimum time of 15 s).

Auditory startle (PND11–14)

The pup's capacity to display a full-body startle response was assessed when a loud finger snap occurred at around 10 cm.

Eye openings (PND14–18)

The day both eyes were visible was recorded.

Statistical analysis

For the righting reflex, cliff avoidance, and grip strength responses, the assessment of the time taken by each pup to complete the task was performed. Results for the subsequent tests are shown as a percentage of pups that successfully completed the task. Standard errors and means (mean ± Standard error mean) were used to depict all data. A two-way analysis of variance (ANOVA) was used to analyze the variables (treatment condition and time), with time serving as the repeated measures. All statistical values were subjected to a significance level of $p < 0.05$. Microsoft Excel and the GraphPad Prism8 software (California Corporation) were used for all calculations.

RESULTS

Effect of prenatal VLZ and VOX exposure on the postnatal growth and development of offspring

In VLZ group, two-way ANOVA indicated significant impact on treatment ($F [2, 60] = 30$, $P < 0.001$) and PNDs ($F [3, 60] = 286$, $P < 0.001$), as well as a significant interaction between treatment and PNDs ($F [6, 60] = 5.3$, $P < 0.001$). In the same manner, two-way ANOVA showed significant impact on treatment ($F [2, 60] = 94$, $P < 0.001$) and PNDs ($F [3, 60] = 513$, $P < 0.001$), as well as a significant interaction between treatment and PNDs ($F [6, 60] = 11$, $P < 0.001$) in VOX group. *Post hoc* Tukey's test detects significant difference between VLZ treated (2 mg/kg) and control pups at PND 14 and 21, while at PND 7, 14, and 21 in VOX-treated (2 mg/kg) pups. VOX-and VLZ-exposed pups appear to have substantial weight loss in drug-exposed groups as compared to corresponding control groups [Figure 1].

Neurodevelopmental reflex testing

Forelimb grasp reflex

In VLZ-exposed group, two-way ANOVA indicated significant impact of the early treatment ($F [2, 75] = 7.7$,

$P < 0.001$) and PNDs (F [4, 75] = 17, $P < 0.001$), whereas, in VOX-exposed group, two-way ANOVA showed significant impact of the early treatment (F [2, 75] = 9.98, $P < 0.001$) and PNDs (F [4, 75] = 17.5, $P < 0.001$), as well as significant interaction between early treatment and PNDs (F [8, 75] = 3.61, $P \leq 0.001$). Forelimb grasp reflex is slightly delayed in exposed groups in comparison to control [Figure 2].

Righting

Prenatal VLZ and VOX treatment did not significantly affect righting reflex of offspring (data not shown).

Cliff avoidance

In VLZ groups, two-way ANOVA revealed significant effects of treatment (F [2, 345] = 39, $P < 0.001$) and PNDs (F [4, 345] = 64,

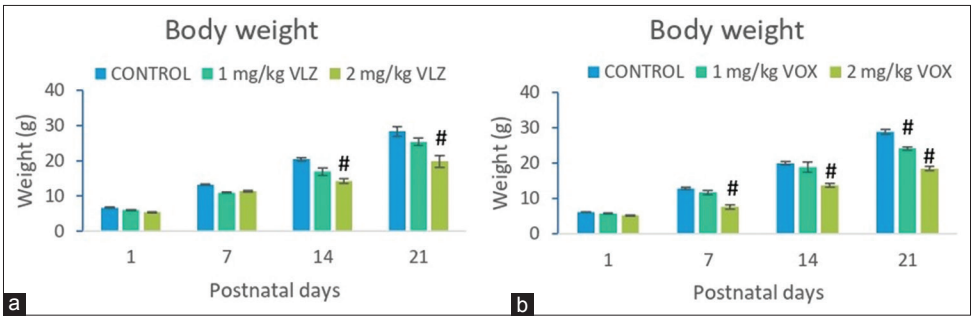

Figure 1: Effect of (a) VLZ and (b) VOX on neonatal growth from PND 1-21. All data represent Mean ± SE. value (n = 6 per group). Symbol # indicates level of significance at $P < 0.001$ between control and exposed groups for two-way ANOVA followed by Tukey's multiple comparison test

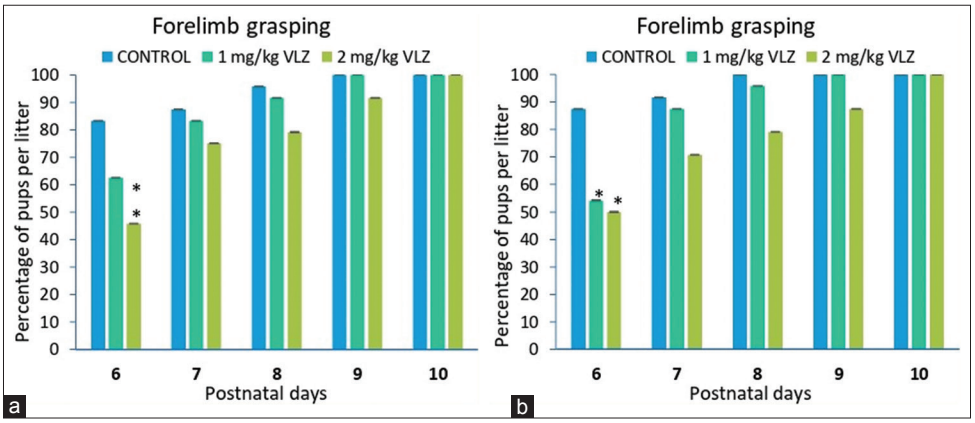

Figure 2: Effect of (a) VLZ and (b) VOX on forelimb grasping from PND 6-10 (Mean of 6 Litters per Treatment). All data represent Mean ± SE. value. Symbols * and ** indicate level of significance at $p < 0.05$, and $p < 0.01$, respectively, between control and exposed groups for two-way ANOVA followed by Tukey's multiple comparison test

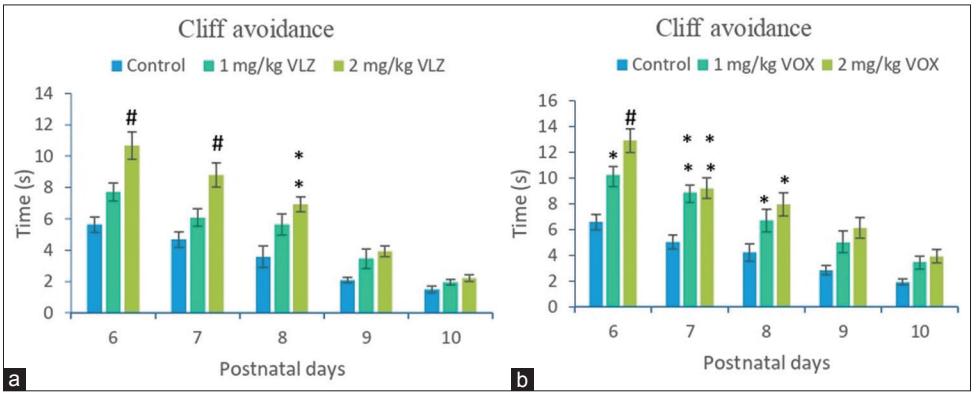

Figure 3: Effect of (a) VLZ and (b) VOX on cliff avoidance response from PND 6–10 (Mean of 6 litters per treatment). All data represent Mean ± SE. value. Symbols*, ** and # indicate level of significance at $P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively, between control and exposed groups for two-way ANOVA followed by Tukey's multiple comparison test

$P < 0.001$), as well as significant interaction between treatment and PNDs (F [8, 345] = 2.9, $P < 0.01$). In VOX-treated group, two-way ANOVA showed significant effects of treatment (F [2, 345] = 44, $P < 0.001$) and PNDs (F [4, 345] = 45, $P < 0.001$), but no significant interaction between treatment and PNDs (F [8, 345] = 1.6, $P > 0.05$) was observed. These results indicate delay in the day of apparition of this neurological reflex in VOX-and VLZ-exposed animals [Figure 3].

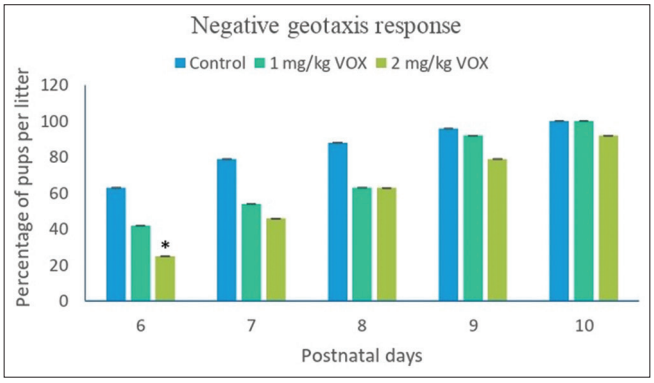

Figure 4: Effect of VOX on negative geotaxis response from PND 6–10 (Mean of 6 litters per Treatment). All data represent Mean ± SE. value. Symbol * indicate level of significance at $P < 0.05$ between control and exposed groups for two-way ANOVA followed by Tukey's multiple comparison test

Negative geotaxis response

In VLZ group, there is no significant effect was observed (data not shown). While, in VOX group, two-way ANOVA indicated significant effects of early treatment (F [2, 75] = 15, $P < 0.001$) and PNDs (F [4, 75] = 29, $P < 0.001$). At PND 6, VOX-treated and control rats showed a substantial difference, indicating a delay in response [Figure 4].

Grip strength response

In VLZ group, two-way ANOVA indicated significant impact of treatment (F [2, 483] = 56, $P < 0.001$) and PNDs (F [6, 483] = 56, $P < 0.001$). Similarly, two-way ANOVA showed significant effects of treatment (F [2, 483] = 14, $P < 0.001$) and PNDs (F [6, 483] = 34, $P < 0.001$), in VOX group. The data obtained show that there is a significant deficit in grip strength in VLZ groups and Tukey's *post hoc* showed substantial difference at PND 12 ($P < 0.05$) in VOX groups [Figure 5].

Auditory startle

Neither group showed significant differences (data not shown).

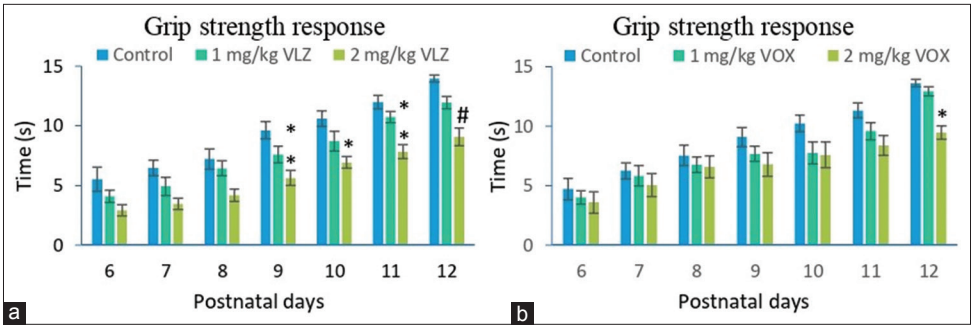

Figure 5: Effect of (a) VLZ and (b) VOX on grip strength response from PND 6–10 (Mean of 6 litters per treatment). All data represent Mean ± SE. value. Symbol*, ** and # indicate level of significance at $P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively, between control and exposed groups for two-way ANOVA followed by Tukey's multiple comparison test

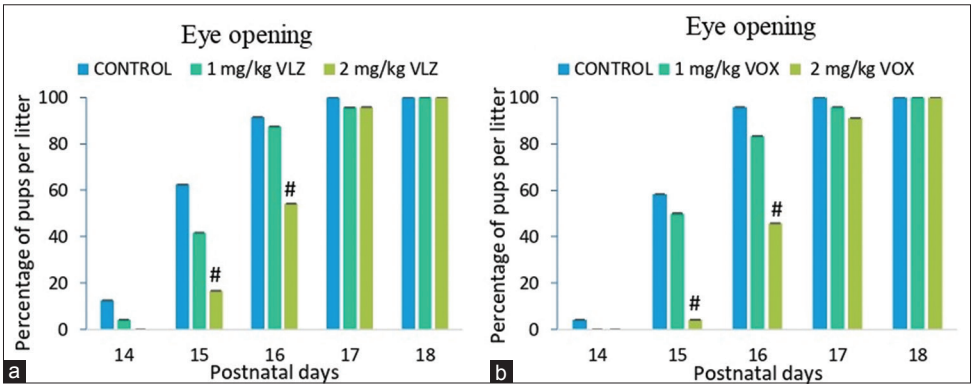

Figure 6: Effect of (a) VLZ and, (b) VOX on eye opening from PND 14–18 (Mean of 6 litters per treatment). All data represent Mean ± SE. value. Symbol # indicates level of significance at $P < 0.001$, between control and exposed groups for two-way ANOVA followed by Tukey's multiple comparison test

Eye opening

No control or exposed rats had opened their eyes before PNDs 9–13 (data not shown). Figure 6 displays the overall percentage of rats who were able to open their eyes between PNDs 14 and 18. It is evident that control rats opened their eyes a little earlier than rats exposed to VLZ and VOX. Two-way ANOVA revealed significant interaction between early treatment and PNDs in both VLZ group ($F [12, 105] = 3.6$, $P < 0.001$) and VOX group ($F [12, 105] = 3.65$, $P < 0.001$).

DISCUSSION

The findings of this study showed that prenatal exposure to equivalent therapeutic doses of two atypical ADs, VLZ, and VOX during sensitive phase of brain development induced substantial changes in postnatal BW gain in pups until 3 weeks of age, and expressed mild delayed response in selected neurodevelopmental characteristics of reflexes (limb grasping, surface righting reflex, cliff avoidance response, negative geotaxis, and grip strength response) and pups' developmental milestones (auditory startle and eye opening). These changes were found in a dose-dependent manner. Our results indicate that lower dose (1 mg/kg BW) of VLZ and VOX could not induce significant effects on developing pups, whereas higher therapeutic dose (2 mg/kg BW) of these agents induced substantial impact on postnatal development and growth pattern of pups in comparison with control pups.

It is well established that 5-HT and DA have a role in controlling food intake.[40] In anorexic animals, the hypothalamic ventromedial nucleus exhibits elevated 5-HT levels and reduced DA levels, along with increased levels of the dopaminergic receptors D1 and D2.[41] Therefore, the decreased weight of pups observed at PND 7, 14, and 21 may be due to changes in serotonergic and/or dopaminergic neurotransmission by VLZ and VOX exposure during prenatal brain development. Similar finding of significant weight loss in citalopram exposed pups was also reported.[42]

In addition, a modest delay in reflex development was observed in VLZ-and VOX-exposed rats compared to rats exposed to vehicles, as evidenced by lengthened withdrawal latency in the cliff avoidance test and delayed gripping. It is in accordance with the findings of Deiró *et al*., who found that rats treated to sertraline and citalopram postnatally experienced a delay in reflex development.[43,44] It was also reported that rats exposed to fluoxetine prenatally had longer turning latencies in negative geotaxis[45] which is similar to our results in VOX group. In addition, compared to rats exposed to vehicles, the VLZ-and VOX-exposed rats performed less well in the grip strength test, indicating poor muscularity.

AD exposure during pregnancy may interfere with and/or disrupt brain development due to the fact that it passes the placental barrier and blood-brain barrier at substantial concentrations[21,22] and during the critical stages of brain development, disruption of normal neurotransmitter signaling can cause enduring changes in the proliferation, differentiation, and growth of their target cells, potentially providing the underlying mechanism for neurodevelopmental abnormalities.[46] Importantly, variations in serotonin (5-HT) levels during development can have lasting effects on neurodevelopment.[47]

Neurotrophins have also been found to affect brain development among many other potential processes. Neurotrophins are crucial in the regulation of neuropeptides, such as melatonin, urocortin, oxytocin, and serotonin, which are small proteins molecule that play a key role in processes such as placental development, appetite regulation, and hormone regulation.[48,49] Therefore, any changes in these neurotrophins' concentrations may increase the likelihood of developing neurodevelopmental abnormalities later in life as well as a variety of pregnancy-related issues. During pregnancy, maternal exposure can alter the production and expression of neuropeptides that regulate fetal brain growth and development.[50]

A clear understanding of the mechanisms responsible for the postnatal BW deficit and delayed reflex development of ADs exposed rats is still unclear. Thus, it is likely that multiple factors may be involved in these pathways, which requires further investigation.

CONCLUSION

The *in utero* exposure to VLZ and VOX results in delayed postnatal BW gain and reflex development in rat offspring. In particular, we have seen a substantial delay in forelimb grasping, cliff avoidance, grip strength, and eye opening in VLZ-exposed groups. The identical results were seen in the VOX-exposed group, except for a noticeable delay in the negative geotaxis response at PND 6. It confirmed our hypothesis that there is an association between prenatal exposure to VLZ and VOX and fetal brain development. From a neurodevelopmental point of view, it may thus be concluded that both medications have mild effects on pups' neurodevelopment when used therapeutically during pregnancy. Further, both clinical and non-clinical investigations are required to ascertain the long-term neurotoxic potential of newly introduced atypical ADs, that is, VLZ and VOX which will be helpful to pregnant population.

ACKNOWLEDGMENT

Authors are thankful to the University Grant Commission-Council of Scientific and Industrial Research (UGC-CSIR) for providing financial assistance as a Junior Research

Fellowship to Priyanka Agrawal [Grant No. 964/(CSIR-UGC NET DEC 2017)] and UGC-CRET fellowship, University of Allahabad to Pallavi Singh [Grant No. 498/RES/19/246].

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Source of Support: Nil. **Conflicts of Interest:** None declared.