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EXPLORATORY ASSESSMENT OF BEHAVIORAL ALTERATIONS IN YOUNG RATS AFTER INTRAUTERINE BENZYDAMINE EXPOSURE

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Abstract: Substance use is a major global public health issue with important medical, social, and economic consequences. Drug use during pregnancy is particularly concerning, as this period involves increased biological vulnerability for both mother and fetus. Intrauterine exposure to psychoactive substances may lead to severe and sometimes irreversible effects. Benzydamine misuse for recreational purposes, often referred to as "benzydamine trips," has been documented globally, particularly among adolescents. It was hypothesized that intrauterine benzydamine exposure would lead to sex-specific deficits in cognitive and exploratory behavior in adolescence. In this study, 40 female Wistar rats were mated (2:1 ratio) and randomly assigned to two groups: one received recreationally relevant doses of benzydamine during pregnancy. Offspring behavior was assessed using the Novel Object Recognition (NOR) test for memory and the Elevated Plus Maze (EPM) for exploratory and anxiety-related behavior. Biochemical analyses were performed at the end of the experiment. The EPM showed no significant group differences in time spent in open or closed arms. Females displayed slightly higher locomotor activity, and treated females spent more time in open arms compared to males and untreated females. This is the first study evaluating offspring exposed prenatally to recreational doses of benzydamine. The findings suggest that benzydamine may impair memory and alter behavior, with more evident effects in females.

Keywords: benzydamine, novel object recognition, discrimination index, elevated plus maze, behavior

1. Introduction

Substance use is a major public health problem worldwide, with significant medical, social and economic implications. This category includes both classic illicit substances, such as opioids, cannabis, cocaine or amphetamines, and certain over-the-counter (OTC) medications, which, although perceived as safe, can have psychoactive effects and can be addictive when used inappropriately (Chiappini et al. 2021, Ősz et al. 2023, La Nou et al. 2024). The increased accessibility of these substances, associated with insufficient information for the population, contributes to the trivialization of consumption and the underestimation of short- and long-term risks. In parallel, many OTC drugs, such as those containing codeine, pseudoephedrine or sedative antihistamines, are frequently used outside therapeutic indications, in high doses or for prolonged periods, precisely because of their euphoric or sedative effects (Ősz et al. 2023). This practice is often found among teenagers and young adults but is not exclusive to these categories.

A particularly worrying aspect is the use of narcotics and potentially abusive drugs during pregnancy. Pregnancy is a period of increased biological vulnerability, for both mother and fetus, and intrauterine exposure to psychoactive substances can have severe and sometimes irreversible consequences (Franks et al. 2020). Narcotic substances easily cross the placental barrier, affecting fetal development, especially during critical stages of organogenesis and maturation of the central nervous system.

A relevant example of an often overlooked OTC drug with narcotic potential is benzydamine, a topical nonsteroidal anti-inflammatory drug commonly used as a solution, spray, or vaginal suppository. Although indicated for its analgesic and antiseptic properties, benzydamine can produce psychoactive effects when administered orally in high doses, including visual and auditory hallucinations, confusion, psychomotor agitation, and delusional behavior (Ősz et al. 2023). These effects are explained by the substance's interaction with serotonergic and dopaminergic receptors.

Benzydamine abuse has been reported particularly among adolescents and young adults, favored by its high accessibility, low cost, and lack of strict release control, compared to other psychoactive substances (Ősz et al. 2023). Epidemiological studies from Central and Eastern Europe and Latin America indicate an increase in the recreational use of benzydamine, which is sometimes perceived as a "legal" alternative to classic illicit drugs (Opaleye et al 2009, Zaprutko et al. 2016).

From an epidemiological perspective, the use of OTC drugs with narcotic potential represents a significant component of substance abuse, especially among young people. Data from the World Health Organization and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) suggest that between 3% and 6% of adolescents have experienced at least once the misuse of an OTC drug with psychoactive effects [8]. In women of reproductive age, the exact prevalence is likely underestimated, due to underreporting and low perception of risk.

In the context of pregnancy, epidemiological data on the use of benzydamine is limited, but the existence of maternal neuropsychiatric effects raises questions about fetal safety, especially in the case of uncontrolled systemic administration. Given the lack of robust clinical studies on prenatal exposure, the precautionary principle requires avoiding the use of benzydamine orally or in inappropriate doses during pregnancy (Ősz et al. 2023).

The inclusion of benzydamine in the discussion of "atypical" drugs highlights the need to broaden the classical definition of substances of abuse and strengthen prevention strategies to include not only illicit drugs but also OTC medications. From a public health perspective, recognition and monitoring of this phenomenon are essential to reduce the associated risks, especially in vulnerable populations.

To our knowledge, this is the first study that aims to verify the effects of benzydamine on the central nervous system in the offspring of female rats treated during pregnancy with benzydamine at doses used for recreational purposes.

2. Materials and Methods

Animals and treatment

Benzydamine (Tantum Rosa, powder for solution for vaginal irrigation, Angelini Pharma, Italy) was purchased from the Romanian pharmaceutical market. Forty female Wistar rats (mean body weight: 253 ± 23 g), 6-month-old were obtained from the Animal Facility of George Emil Palade University of

Medicine, Pharmacy, Science and Technology of Târgu Mureș.

Female Wistar rats were housed with males at a ratio of 2:1, and pregnancy was confirmed by the presence of sperm in vaginal smears (gestation day 1 – GD1). The sample size (n=40 females) was chosen based on previous exploratory behavioral studies to ensure adequate power for detecting sex-specific differences in offspring. Pregnant female rats were randomly allocated to two experimental groups: one received benzydamine at a dose representative of recreational human exposure (BZY, 261 mg/kg), while the control (CTRL) group received vehicle only. Medication was included in the food and administered daily, between 8:00 AM and 10:00 AM. This dose represents a recreationally relevant human exposure.

Body weight was recorded once a week for dose adjustment. Offsprings from the two maternal treatment groups were housed in pairs according to their mothers' treatment and gender. Offspring were handled daily from postnatal day 7 onward to minimize stress and reduce the risk of maternal rejection. Animals were maintained under standard environmental conditions (12 h light/dark cycle, ambient temperature 20 ± 2 °C, relative humidity 60% ± 10%), with unrestricted access to standard laboratory rodent pellets and water throughout the study. At the end of the experiment, all animals were decapitated under anesthesia with isoflurane (3%) in order to collect samples of blood for further investigations.

All experimental procedures were conducted in accordance with the European Directive 2010/63/EU on the protection of animals used for scientific purposes. The study protocol was reviewed and approved by the Ethics Committee for Scientific Research of the George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mureș (approval no. 2073/15.02.2023).

Behavioral assessment

Behavioral assessments on offsprings were done in different days when their age corresponded to the adolescence period in humans (4 weeks). Behavioral testing and video analysis were performed by researchers unblinded to the treatment groups.

Novel Object Recognition

Novel object recognition test (NOR) was used to evaluate memory. The objects used were about the same height. They were placed at an equal distance of 30 cm from the corners, diametrically opposite and after each analysis were wiped with 70% alcohol to limit the appearance of any olfactory bias.

Initially, two identical objects were placed for each rat for a period of 7 minutes. At the end of this period, they were returned to the personal cage, at which point the box and objects were cleaned. Subsequently, after 4 hours, the procedure was repeated, but one of the familiar objects was replaced with a new one for evaluating the retention process. This test lasted for 5 minutes. Exploratory activity was considered valid when rodents sniff objects or touch them with their front paws but without leaning on or sitting on them. For behavioral evaluation EthoVision XT, Noldus IT, Wageningen, The Netherlands, version 11.5 was used. Discrimination index (DI) represents the difference of exploration time of the new object (EB) compared to the familiar object (EA) compared to the total time spent exploring the two objects in the retention process, DI = (EB - EA) / (EA + EB) (Rajagopal et al. 2014, Antunes and Biala 2012).

Elevated Plus Maze

The assessment of the exploratory behavior was performed with the aid of the Elevated Plus Maze test (EPM). This device comprises a plus-shaped maze, with two opposite open arms (50 × 10 cm) and two closed arms (50 × 10 × 40 cm). The distance from the floor was set at 60 cm height. The rats were placed at the crossroad, facing the open arm. After each rat, the maze was cleaned with 70% alcohol, and the activity was recorded for 5 min. The time spent in open and/or closed arms and in the center zone, rearing, and head dipping were recorded (Kraeuter et al. 2019, Knight et al. 2021).

Biochemical analysis

Biochemical analyses were performed using an Element RC Clinical Chemistry Analyzer (Scil), using the General Health Rotor for albumin (ALB), total protein (TP), globulins (GLOB), total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine (CREA), Blood Urea Nitrogen (BUN), glucose (GLU), total cholesterol (TC), calcium (Ca^{2+}), phosphate (PHOS), potassium (K^+), and sodium (Na^+), measurements.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software (San Diego, California USA, ver. 9). The Shapiro-Wilk test was performed to test the normality of the data and values were expressed as mean ± SEM or median [min – max] where appropriate. For the statistical analysis a t test or Mann-Whitney test were performed. The significance level was set at *p* value less than 0.05.

3. Results and discussions

To our knowledge, this is the first study to verify the effects of intrauterine exposure to recreational doses of benzydamine on the central nervous system of rat offspring. Our findings suggest that prenatal exposure leads to distinct behavioral alterations in adolescence, characterized by memory deficits and a reduction in anxiety-like inhibitory avoidance, particularly in females.

In the NOR test, differences in discrimination indices were observed, though the statistical significance was not definitive across all groups. To evaluate the motor activity in the retention trial, the t test revealed no significant differences between groups. For better representation we compared control group and experimental groups separately (CTRL F (858.7 ± 42.04 cm) vs EXP F (878.3 ± 77.73 cm), CTRL M (637.4 ± 169.1 cm) vs EXP M (752.9 ± 48.82 cm) as shown in **Figure 1A** and **1B**. Following the determination of DI (**Fig. 1C** and **1D**), no significant differences were found between the groups included in the study. However a better result was observed for the male groups, which may be influenced by the distance traveled (CTRL F (-0.333 ± 0.108) vs EXP F (-0.278 ± 0.0855), CTRL M (0.331 ± 0.41) vs EXP M (0.055 ± 0.118)). The overall trend suggests that benzydamine may alter memory retention processes. This cognitive impairment can be interpreted through benzydamine's ability to stabilize neuronal membranes and inhibit basal excitability. Such alterations in neuronal signaling during critical periods of hippocampal development may disrupt the synaptic plasticity required for long-term object recognition.

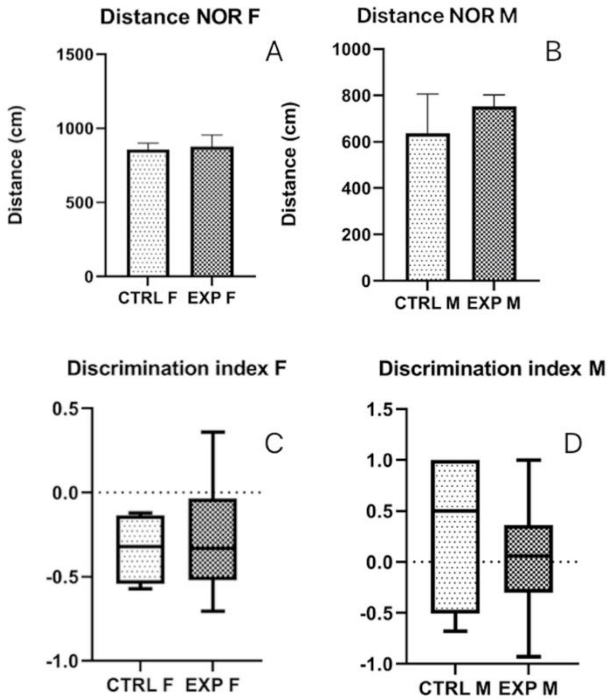

Fig. 1. Distance and discrimination index between the offsprings resulted from treated and not treated mothers. CTRL F – female control, EXP F – experimental female, CTRL M – male control, EXP M – experimental male, NOR – novel object recognition.

No experimental studies were found in the literature evaluating the effect of benzydamine in the context of NOR test, but review studies suggest a negative effect on memory (Ősz et al. 2023), and further studies should evaluate whether this is due to memory impairment or impairment of interest in exploration. Regarding motor activity, due to the toxicological profile, moderate doses of benzydamine favor psychomotor agitation, and high doses can lead to an inhibition of motor activity, by inducing a state of confusion and disorientation. The results of the present study do not show significant differences between groups, but it is observed that in both the treated and control groups, the motor activity of females is slightly increased.

The EPM did not reveal any statistically significant difference between the groups for the time spent in open arms, **Figure 2A-D**. However, in both sexes, the time spent in the open arms was lower in the control groups than in the experimental groups, consistent with the distance traveled. The head dipping frequency differed between the CTRL F (4.5 ± 1.258 s) and EXP F (10.83 ± 1.424 s) as can be seen in Figure 2K. It is worth mentioning that rearing time was longer for EXP M than for the CTRL M, Fig. 2N.

Locomotor activity in the EPM is similar to that in the NOR test, with females traveling slightly longer distances. Regarding the time spent in the open arms of the maze, it is greater for treated females, both compared to males and to untreated females. One study from the literature demonstrated that females had a less anxious behavior (Knight et al. 2021). These data should be viewed in correspondence with the activity in the closed arms, where times are similar for all groups, which suggests that these data are not due to hyperactivity, but to exploratory behavior. While this initially appears as an anxiolytic effect, it likely represents behavioral disinhibition. The rearing behavior supports a shift in how these animals process novel environments and risk.

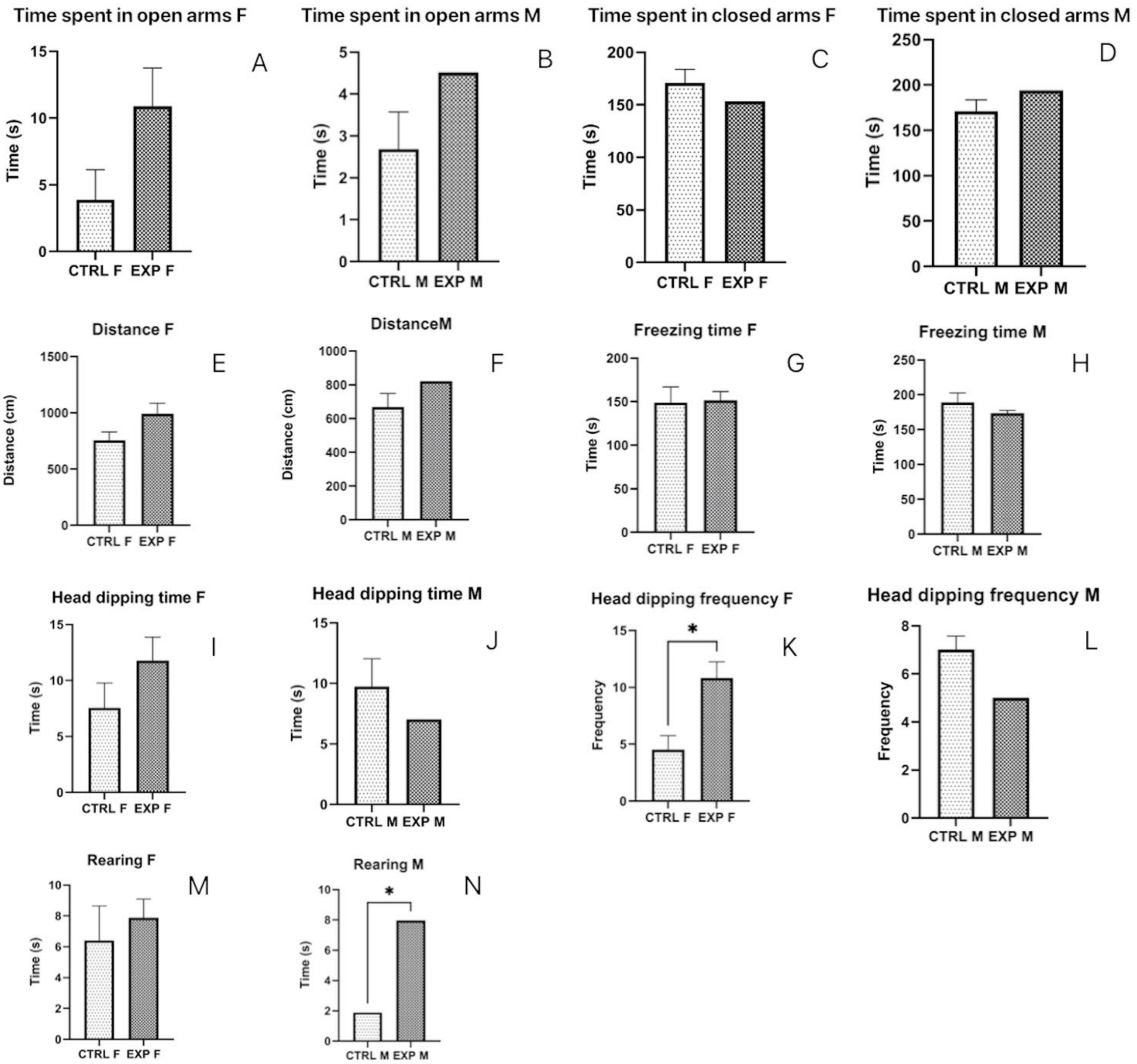

Fig. 2. Parameters comparison between between the offsprings resulted from treated and not treated mothers. CTRL F – female control, EXP F – experimental female, CTRL M – male control, EXP M – experimental male. $^{*}p < 0.05$.

The increased exploratory activity and head dipping suggest an interference with the limbic-striatal reward pathways, potentially mediated by benzydamine's structural similarity to indoleamines like serotonin and its reinforcing properties.

Recent studies indicate that benzydamine also acts via a central cannabinoidergic mechanism, specifically interacting with CB1 receptors to modulate glutamatergic transmission in the prefrontal cortex. In rat brain slices, benzydamine-induced longterm depression-like responses in the prelimbic cortex-to-nucleus accumbens circuitry were significantly reduced by the CB1 receptor antagonist AM251 (Avvisati et al. 2018).

A study demonstrated that methadone administration produced effects in offspring of both sexes, whereas buprenorphine administration influenced behavior only in females, as observed in the EPM test (Chen et al. 2015). It has also been reported that exposure to methadone may impair long-term spatial memory in offspring (Kongstorp et al.

2020). Furthermore, prenatal exposure to methadone or buprenorphine has been associated with an increased risk of anxiety-like behaviors in offspring (Nyberg et al. 2024). Similarly, exposure to amphetamine was linked to reduced performance in the Morris Water Maze test, although this effect was observed only in females (Šlamberová et al. 2014).

Biochemical analyses indicated some systemic alterations, most notably the increase in alkaline phosphatase (ALP) in both males and females exposed to benzydamine and a decrease in blood urea nitrogen (BUN) in males. The other parameters were not statistically different (**Table 1**). The lower BUN levels (p = 0.022) in treated males might indicate shifts in protein metabolism or renal filtration efficiency following prenatal drug stress.

Higher ALP levels in young rats often reflect altered bone metabolism or hepatic stress during rapid growth phases. Numerous scientific studies highlight the fact that the use of narcotics can have significant toxic effects on the liver. Following hepatic biotransformation processes, many narcotics are transformed into reactive metabolites that may have an increased cytotoxic potential, with changes in biochemical parameters. One mechanism by which these changes in liver function occur is represented by oxidative stress, and long-term exposure can cause alterations in liver function (Atici et al. 2005, Valente et al. 2012). An increasing trend in AST levels was also observed in females exposed to benzydamine, but the ALT levels were not altered.

Consequently, the perception of benzydamine as a "safe" over-the-counter medication contributes to its misuse. However, our results underscore the potential for irreversible behavioral alterations in offspring following recreational use during pregnancy.

This study has several limitations that should be considered when interpreting the findings. First, the work was explicitly designed as an exploratory assessment and as acknowledged in the manuscript, it represents the first attempt to examine behavioral outcomes in offspring after prenatal exposure to recreational doses of benzydamine, which limits direct comparison with previous experimental literature and makes the current results necessarily preliminary. Second, the behavioral assessment was also limited in scope. The study relied on only two tests, NOR for memory-related performance and EPM for exploratory or anxiety-like behavior, both performed during a single developmental window corresponding to adolescence at approximately 4 weeks of age. While these paradigms are established and useful, they capture only a narrow portion of neurobehavioral function and do not allow firm conclusions regarding broader domains such as social behavior, impulsivity, reward sensitivity, attention, sensorimotor gating, spatial learning, or long-term executive function. Third, as was explicitly stated above, behavioral testing and video analysis were performed by researchers unblinded to treatment groups, which can introduce bias. In addition, the use of a single benzydamine dose, the absence of pharmacokinetic confirmation of fetal exposure, the lack of mechanistic brain analyses, and the limited characterization of maternal factors constrains causal interpretation and translational generalization.

Table 1. Biochemical parameters

Parameter	Gender	Control	Experimental	*p* Value [c]
ALB	F	3.900 ± 0.0817	3.940 ± 0.0476	0.668
	M	3.700 [3.600 – 3.700]	3.700 [2.900 – 4.000]	
TP	F	5.500 ± 0.1225	5.630 ± 0.07753	0.264
	M	5.450 ± 0.0289	5.283 ± 0.0908	0.407
GLOB	F	1.800 [1.800 – 2.000]	1.600 [1.500 – 2.200]	0.15
	M	1.850 [1.800 – 1.900]	1.600 [1.200 – 2.000]	0.062
AST	F	82 [69 – 87]	88.50 [81 – 141]	0.056
	M	96.25 ± 11.64	82.54 ± 6.97	0.38
ALT	F	52 [47 – 59]	52 [47 – 71]	0.768
	M	54.5 [47 – 61]	50.50 [38 – 62]	0.468
ALP	F	223.5 [201 – 256]	303.50 [283 – 425]	0.002*
	M	358 ± 7.842	435.60 ± 18.21	0.064
Crea	F	0.2 [0.1 – 0.2]	0.250 [0.1 – 0.4]	0.166
	M	0.250 [0.2 – 0.3]	0.2 [0.1 – 0.4]	0.384
BUN	F	18.51 [16.20 – 20.69]	17.48 [14.85 – 19.94]	0.454
	M	17.07 ± 0.3572	15.06 ± 0.3682	0.022*
GLU	F	162.9 ± 1.896	167.8 ± 4.947	0.651
	M	162 ± 4.602	158 ± 3.764	0.564
TC	F	73.76 ± 3.425	82.23 ± 3.091	0.143
	M	47.07 ± 3.723	56.81 ± 2.225	0.069
Ca^{2+}	F	10.22 ± 0.228	10.32 ± 0.1165	0.674
	M	10.18 [10.18 – 10.31]	10.21 [7.520 – 11.04]	0.865
PHOS	F	8.470 ± 0.3659	8.058 ± 0.2456	0.381
	M	10.23 [9.530 – 10.55]	9.80 [5.980 – 10.79]	0.187
K^+	F	5.498 ± 0.3371	5.175 ± 0.0938	0.222
	M	5.215 [4.850 – 5.600]	5.660 [3.690 – 6.810]	0.173
Na^+	F	148.9 ± 0.3582	148.6 ± 0.0734	0.175
	M	149.1 [148.3 – 149.3]	148.9 [144.3 – 151.2]	0.797

F – females, M – males, ALB – albumin, TP – total proteins, GLOB – globulin, AST – aspartate aminotransferase, ALT – alanin aminotransferase, ALP – alkaline phosphatase, Crea – creatinine, BUN – blood urea nitrogen, GLU – glucose, TC – total cholesterol, PHOS – phosphate.

Conclusions

To our knowledge this is the first study in the literature which assessed the behavior of the offsprings resulted from mother which were on treatment with recreational doses of benzydamine during the pregnancy. In conclusion, benzydamine should be considered a substance which is able to alter memory but also the behavior, effects more evident in females. Time spent in open arms in EPM, head dipping frequency and rearing behavior suggest a reduction in anxiety. The exploratory and innovatory character of the present study limits the possibility of direct comparison to data from the literature, highlighting the necessity of future studies.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Conceptualization, GJ and B-EO; Data curation, GJ and ZG; Formal analysis, C-EV and B-EO; Funding acquisition, B-EO; Investigation, GJ and ZG; Methodology, GJ and ZG; Project administration, C-EV and B-

EO; Resources, B-EO; Software, GJ and ZG; Supervision, C-EV and B-EO; Validation, C-EV and B-EO; Visualization, GJ; Writing – original draft, GJ; Writing – review & editing, ZG, C-EV and B-EO.

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Generative AI Statement:

During the preparation of this work the author(s) used ChatGPT in order to *improve language, grammar*. After using ChatGPT, the author(s) reviewed and edited the content as needed and are fully responsible for the originality and integrity of the content of the manuscript.

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