

## Comparative Effect of Aripiprazole Versus Risperidone on Sperm Motility and Morphology in Rats

Mohammed Saarti, Mohammed D Mahmood\*, Loay A. Alchalaby

College of Pharmacy, University of Mosul, Mosul, Iraq

\*mohameddaowd@uomosul.edu.iq

### Abstract

**Background:** Atypical antipsychotics are preferred over typical antipsychotics in the treatment and management of schizophrenia due to their reduced adverse effects like the extrapyramidal symptoms and akathisia. On the critical analysis of multiple available authentic pieces of evidence, it has been highlighted that the prolonged use of risperidone and aripiprazole has induced reproductive toxicity and sperm deformity. **Objectives:** Through this study, we aim to establish the comparison between the effect of aripiprazole versus risperidone on sperm motility and morphology in rats by a randomized control trial. **Methods:** Male rats were used for the experiment which was divided into two equal groups; group one was the aripiprazole group and the second group was of risperidone. The sample was collected by the right epididymis of rats immediately after exciting the rats. **Results:** The detailed analysis on the properties of sperm including sperm vitality, linear and curve velocity and the path of velocity was done by using sperm quality analyzers. On results, it was found that aripiprazole induced better sperm velocity compared to risperidone and had a reduced deformity rate which has proven to be safer and less toxic compared to risperidone. However, sexual dysfunction should be evaluated particularly evaluated. **Conclusion:** Prescribing antipsychotics require careful selection based on individualization of patients and adverse effects of each antipsychotics.

**Keywords:** Aripiprazole, Risperidone, Sperm, SQA vision, Sperm motility.

### Introduction

Schizophrenia is a commonly known psychiatric issue with a severe mental disability which is associated with symptoms like hallucination, troubled thinking, and delusion categorized as positive symptoms and negative symptoms like volition (lack of motivation), failure to express and sense pleasure (anhedonia), and social reluctance (Delcourte *et al.*, 2018). Atypical antipsychotics are preferred over typical antipsychotics in the treatment and management of schizophrenia due to their reduced adverse effects like the extrapyramidal symptoms and akathisia (Arango *et al.*, 2020). However, the adverse effects of atypical antipsychotics on multiple functions including the reproductive system, metabolism, serum lipid, etc. are under examination.

Aripiprazole belongs to the atypical antipsychotic class of drugs which has a unique chemical composition that makes it more tolerable and efficient compared to other typical antipsychotics like haloperidol (Preda and Shapiro, 2020). The mechanism of action of Aripiprazole enables it to have both a partial agonist as well as an antagonist impact on dopaminergic receptors, it has an antagonist effect on the postsynaptic D2 receptors and an agonist impact of presynaptic D2 receptors, precisely (Han, Huang and Deng, 2009). It has also been proved to be a partial antagonist to 5-HT<sub>2A</sub> and a partial agonist of 5-HT<sub>1A</sub> receptors. The following properties entitle it as a 5-HT and a dopamine stabilizer. Usage of Aripiprazole against schizophrenia and psychosis has resulted in reduced extrapyramidal symptoms in patients such as dyskinesia, Parkinsonism, dystonic reactions, etc. resulting from

blockage of D2 receptors (Kikuchi *et al.*, 2021). Studies mention that aripiprazole fine-tunes dopaminergic transmission by influencing the hyper and hypoactivation of dopaminergic receptors (Stahl, 2008).

Risperidone, a derivative of benzisoxazole is a complex antipsychotic compound that too belongs to atypical, second generation antipsychotic and is a drug of choice for the management of schizophrenia and bipolar disorder (Ardıç *et al.*, 2021). Reportedly this drug efficiently deals with schizophrenia with no known extrapyramidal symptoms. Risperidone has an affinity for both the serotonin 5-HT<sub>2A</sub> receptors and dopamine D2 receptors which enables it to reduce the symptoms of Parkinsonism (Drobnis and Nangia, 2017). Other than the reduced extrapyramidal symptoms it also stands out for its faster onset of action against psychosis and greater efficiency to decrease the negative symptoms of schizophrenia (Hassanane *et al.*, 2012).

On the critical analysis of multiple available authentic pieces of evidence, it has been highlighted that the prolonged use of risperidone and aripiprazole (E.Z. and A.K., 2017) has induced reproductive toxicity. Such a study shows that antipsychotic antidepressants and anticonvulsants compromise the quality of semen and as well as sexual function through various ways like increasing the level of prolactin in men, decreasing testosterone, and even sexual dysfunction (Solomon *et al.*, 2019). Adverse effects on the reproductive system due to risperidone also include the changes in the histology of testicular tissues, decrease in sperm morphology, and histopathological degeneration in testis by altering the hormonal level and inducing oxidative stress (Nørr *et al.*, 2016).

The commercially available antipsychotics and antidepressants that are commonly prescribed were the targets of our study (Faisal *et al.*, 2019, Abdulqader *et al.*, 2022, Faisal *et al.*, 2022). Through this study, we aim to establish the comparison between the effect of aripiprazole versus risperidone on sperm motility and morphology in rats by a randomized control trial.

## Methodology

**Animal:** Male rats were used for the experiment. Each rat was around 10 to 12 weeks old. The average weight of rats was approximately 200g to 300g, they were kept under a controlled environment with 12 hours light cycle followed by 12 hours dark cycle. The temperature was kept at  $23 \pm 1$  °C and humidity level approximately  $50 \pm 5\%$ . Food and water were supplied to the rats as per need and all the protocols of the animal's ethical committee were strictly followed.

**Drugs:** Risperidone C<sub>23</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>2</sub> belongs to the second-generation antipsychotic drug which is used to treat multiple diseases including Schizophrenia. It has a molar mass of 410.485 g/mol and a half-life of 20 hours when consumed orally and 3–6 days in the IM route. Aripiprazole C<sub>23</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> is an atypical antipsychotic which is primarily used to treat schizophrenia and bipolar disorder. The molar mass of aripiprazole is 448.385 g/mol and the half-life is of 72 hours.

All the rats were divided into two equal groups; group one was the aripiprazole group and the second group was of risperidone. The sample was collected by the right epididymis of rats immediately after exciting the rats. Blood and fats were cleaned by epididymis at 37°C. 0.5 cm of the cauda epididymis was isolated and sperms were allowed to swim for an estimated

one minute. 5  $\mu$ l sperms were placed on a slide which was further dried and stained with spermblue for further analysis. The detailed analysis on the properties of sperm including sperm vitality, linear and curve velocity and the path of velocity was done by using sperm quality analyzers (SQA).

**Histopathological analysis:** The Histopathological analysis of the testis was done by slicing the testis into sections and taken further by fixation procedure using 4% paraformaldehyde. The specimens of the tissue were hydrated in alcohol and embedded for one hour in LR white and ethanol. Later they were studied under a microscope.

**Sperm comet assay:** The damage to the DNA and evaluation of the deformity of sperms was done by the Sperm comet assay method. Microscopic slides were suspended in 1% agarose in 75  $\mu$ l of 1% (w v-1) low melting agarose. Before the slide was transferred to lysis solution, 85  $\mu$ l of it was applied on the surface of the slide, the slides were kept under room temperature. After the completion of the lysis procedure, the slides were washed thrice and electrophoresis was performed for the next thirty minutes.

**Statistical analysis:** All the data is statically significant with the mean  $\pm$  standard deviation (SD)  $p \leq 0.05$ . Statistical analysis was performed using two-way ANOVA followed by Student's t-test and using Friedman test on IBM SPSS version 22.

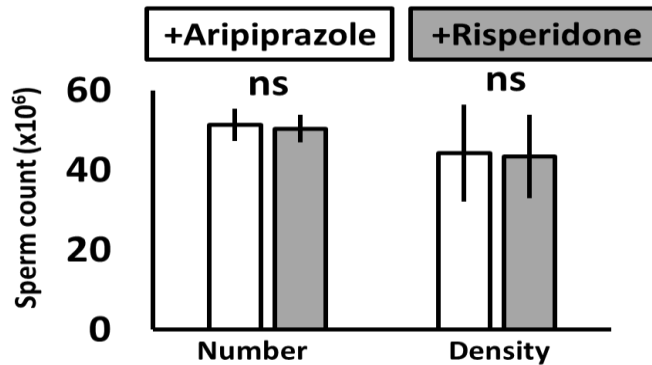
## Results

Analysis of the physical appearance of the semen samples revealed no differences between the physical parameters of the tested group (Table 1)

**Table 1:** Physical examination of semen in studied groups.

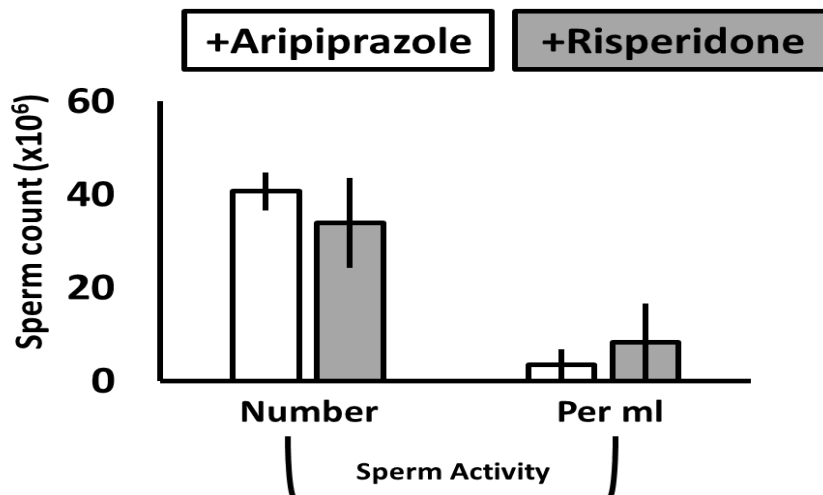
Physical parameter	+Aripiprazole	+Risperidone
<b>Appearance</b>	Milk White	Milk White
<b>Viscosity</b>	Normal	Normal
<b>Liquefaction Status</b>	Completely	Completely
<b>pH</b>	7.4	7.4
<b>Volume (ml)</b>	2	2
<b>Liquefaction Time (minute)</b>	30	30

Analysis of sperm count revealed that the number of sperm in the total sample and density is similar between aripiprazole and risperidone group with non-significant difference existing between them ( $p < 0.05$ ) (figure 2).



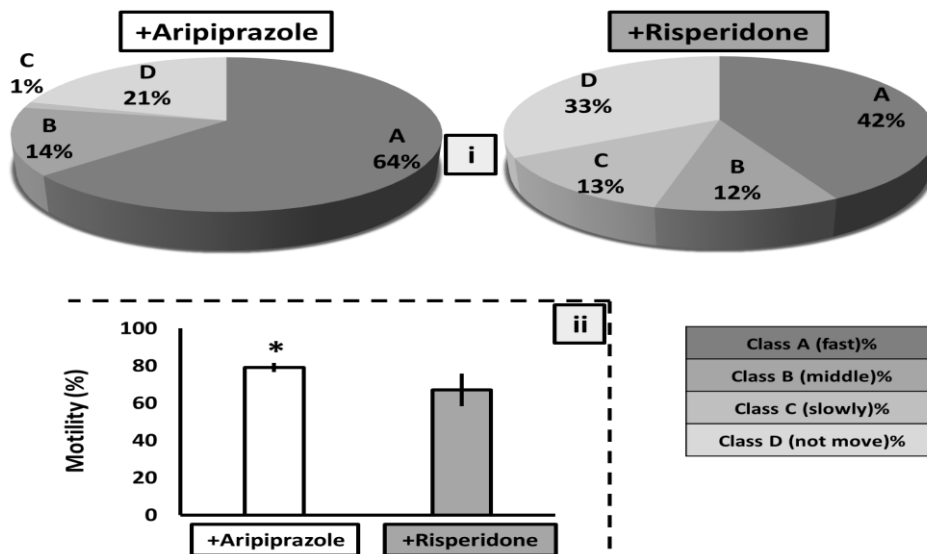
**Figure 2:** Effects of aripiprazole versus risperidone on sperm count and density. Data expressed as mean±SD, ns=non-significant.

The sperm activity has been tested in the aripiprazole and risperidone groups. Non-significant ( $p>0.05$ ) differences exist between both groups in terms of the total number of sperm or per ml (figure 3).



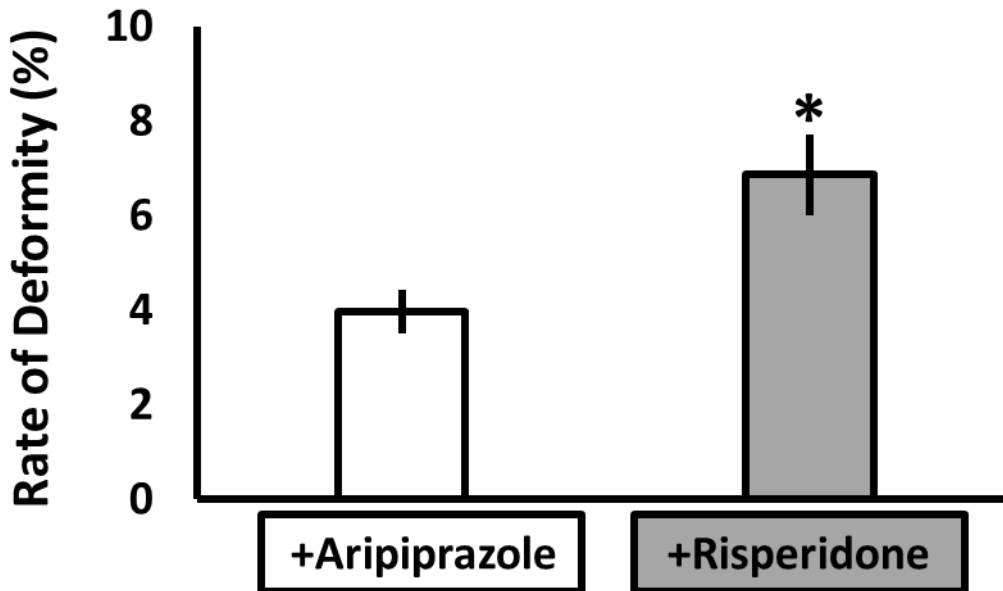
**Figure 3:** Effects of aripiprazole and risperidone on sperm count. Data expressed as mean±SD, \* $p<0.05$ .

Motility has significantly ( $p<0.05$ ) reduced in risperidone compared to the aripiprazole group. Stratification of the results has shown that the percentage of the fast motility was higher in aripiprazole than risperidone with higher non-moves perms in the risperidone group compared to aripiprazole (figure 4).



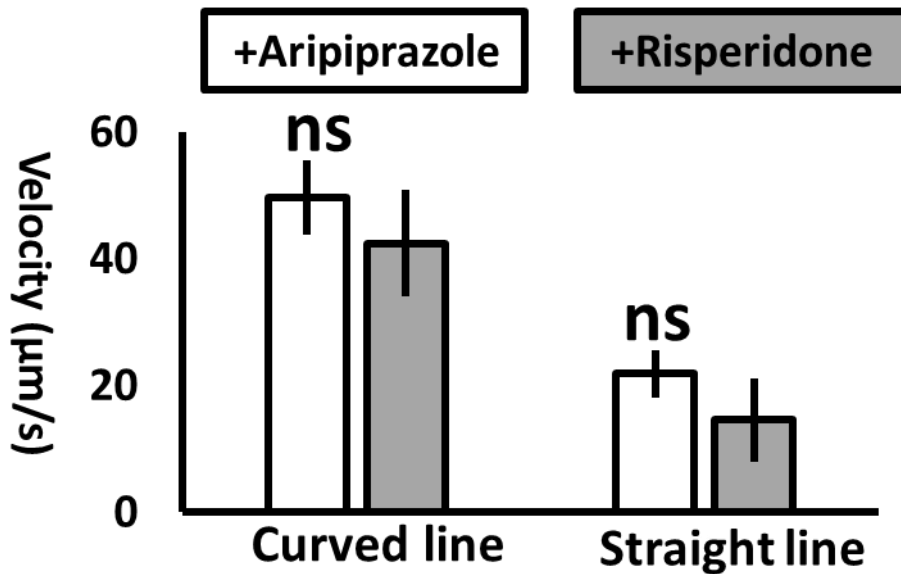
**Figure 4:** Risperidone reduced sperm motility in rats compared to aripiprazole. Risperidone decreased different motility behaviors of sperm (fast, middle, slowly) compared to aripiprazole. The no-movement sperm represent the highest levels of the overall percentage in the risperidone group. [i] percentage of fast, middle, slow, and non-moved sperm in the tested sample. [ii] Percentage of motility in aripiprazole versus risperidone group, data expressed as mean±SD, \*p<0.05.

The rate of the deformity was significantly higher in the risperidone compared to the aripiprazole group (Figure 5)



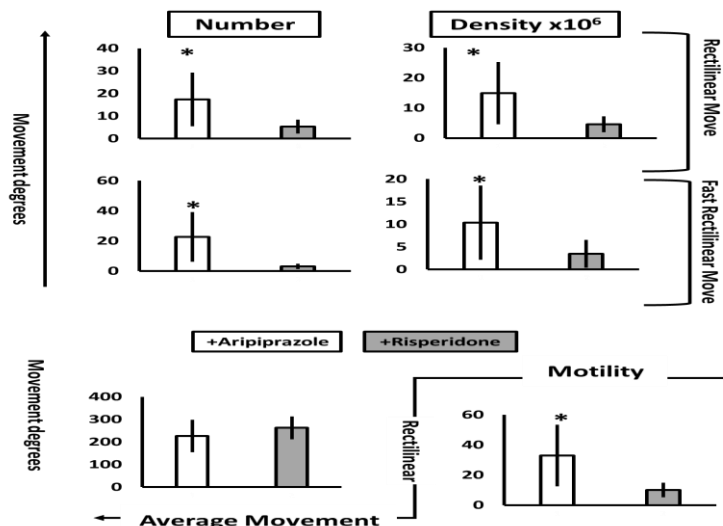
**Figure 5:** Risperidone increased sperm deformity compared to aripiprazole. Data expressed as mean ± SD, \*p<0.05.

Measurement of velocity of sperm movements in aripiprazole group versus risperidone has shown slightly non-significant (p<0.05) higher speed of movement in per the second measurement in both curved or straight path of movement (Figure 6).



**Figure 6:** Aripiprazole induced better sperm velocity compared to risperidone. Data expressed as mean±SD, ns=non-significant.

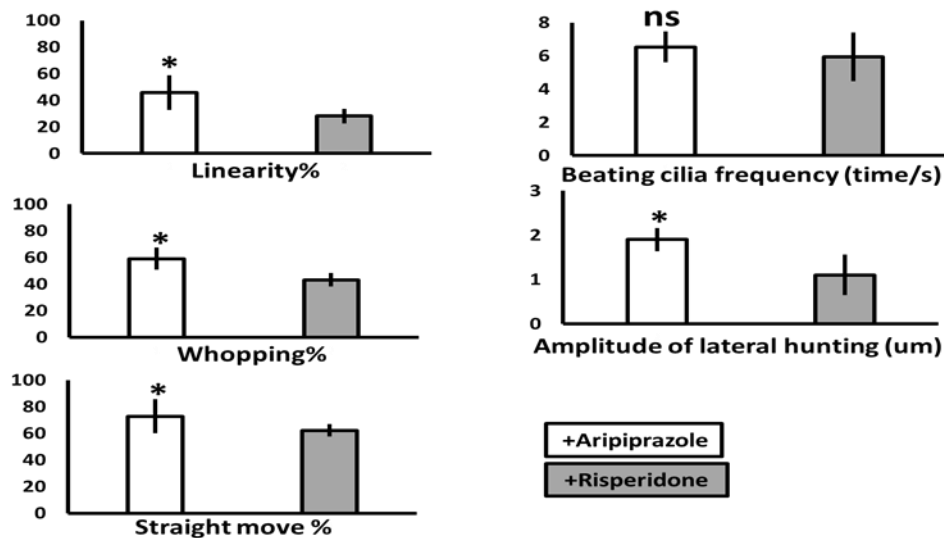
Measurement of rectilinear movement of sperm revealed that the general rectilinear movement and the fast rectilinear movement is significantly better in aripiprazole versus risperidone group both at density level or in the general whole sample, similarly motility is significantly higher in aripiprazole group compared to risperidone, whereas the general movement showed non-significant differences (Figure 7)



**Figure 7:** Risperidone decreased the rectilinear movement parameters compared to aripiprazole. Data expressed as mean±SD, \*p<0.05.

The behaviors of sperm movement in aripiprazole versus risperidone revealed that aripiprazole has shown significantly higher synchronized movement in aripiprazole compared to the risperidone group in terms of linearity, whopping, or straight movement. The amplitude of lateral hunting is significantly higher in the aripiprazole compared to the risperidone group,

nevertheless, the cilia beating frequency showed non-significant differences between aripiprazole and risperidone (figure 8).



**Figure 8:** Movement synchronization behaviors of sperm in aripiprazole versus risperidone group. Data expressed as mean±SD, \*p<0.05.

## Discussions

The results from our study stated that there was no major difference in the count of sperms and the density of sperms in the groups of rats which received either aripiprazole or risperidone. A similar study with respect to risperidone which was conducted to evaluate the influence of risperidone on the reproductive system of rats stated as follows; after the ascending pattern of risperidone dose form 1.25, 2.5, and 3 mg/kg administered in rats through oral route for twenty-eight days represented that the level of follicle-stimulating hormone in blood and testosterone was reduced in the group of high dose. The level of Glutathione (GSH) was also reduced and Malondialdehyde (MDA) was markedly increased, the following changes highlighting the increased oxidative stress and concluding to the fact that risperidone causes reproductive toxicity in male rats (Gormus *et al.*, 2021).

Likewise, on a comparative study of risperidone with other antipsychotic known as olanzapine in male schizophrenic patients, it was found that risperidone caused more elevation of PRL causing Hyperprolactinemia compared to olanzapine, this is a potential factor in alteration of reproductive hormones like testosterone and gonadotropins, this study also indicates that the use of risperidone is more likely to cause sexual dysfunction (Konarzewska *et al.*, 2009). The marked difference in the deformity of sperms with less in aripiprazole and more in risperidone is also supported by the other evidences like that of a detailed analysis which stated that risperidone has the potential to encourage infertility and impotence (Oriakpono and Anuforo, 2020, Shanmugasundaram *et al.*, 2019). The following results and discussion highlight the requirement of keen observation and evaluation of sexual dysfunction in patients under the treatment course of the following drug as the adverse effects are highly reported.

The general perspective of our study towards the drug aripiprazole has been quite favorable. On the examination of the velocity of sperms, we found that Aripiprazole induced better



sperm velocity compared to risperidone as well as the deformity rat has found to be relatively very low. Although there is enough evidence that indicates the adverse effects of aripiprazole in males which includes the escalation in prolactin (PRL) level resulting in reproductive toxicity (Sogawa *et al.*, 2016).

A comparison between aripiprazole and risperidone and their influence on testosterone levels said that hyperprolactinemia was evidently seen in the aripiprazole group with a 75% margin on contrary to it, hyperprolactinemia was absent in the group which received risperidone. Around 65% of the patients who received risperidone had serum prolactin concentrations above 20 ng/ml whereas it was not seen at all in the aripiprazole group. The following results further stated that the Prolactin concentrations are highly associated with the quantity of dopamine antagonist and opposite relation has been seen in the case of dopamine partial agonist (Tasaki *et al.*, 2021).

### Conclusion

From the following study it has been concluded that irrespective of the benefits of atypical antipsychotics on diseases like Schizophrenia and bipolar disorder, they are associated with reproductive toxicity, decreased sperm quality, and potentially increasing sperm deformity. In a comparison of aripiprazole and risperidone, aripiprazole has proven to be safer and less toxic compared to risperidone.

### References

- [1] Abdulqader SW, Faisal IM, Saeed MG, Merkhan MM. Fluvoxamine Provide a Gastro-Protection Against Vitiated Insult. *Indian Journal of Forensic Medicine & Toxicology*. 2022 Jan;16(1):1047.
- [2] Arango C, Ng-Mak D, Finn E, Byrne A, Loebel A. Lurasidone compared to other atypical antipsychotic monotherapies for adolescent schizophrenia: a systematic literature review and network meta-analysis. *European child & adolescent psychiatry*. 2020 Sep;29(9):1195-205. <https://doi.org/10.1007/s00787-019-01425-2>
- [3] Pawan Kumar Tiwari, P. S. . (2022). Numerical Simulation of Optimized Placement of Distributed Generators in Standard Radial Distribution System Using Improved Computations. *International Journal on Recent Technologies in Mechanical and Electrical Engineering*, 9(5), 10–17. <https://doi.org/10.17762/ijrme.v9i5.369>
- [4] Ardic CM, Ilgin S, Baysal M, Karaduman AB, Kılıc V, Aydoğan-Kılıç G, Uçarcan Ş, Atlı-Eklioglu O. Olanzapine induced reproductive toxicity in male rats. *Scientific Reports*. 2021 Feb 26;11(1):1-1. <https://doi.org/10.1038/s41598-021-84235-4>
- [5] Delcourte S, Ashby Jr CR, Rovera R, Kiss B, Adham N, Farkas B, Haddjeri N. The novel atypical antipsychotic cariprazine demonstrates dopamine D2 receptor-dependent partial agonist actions on rat mesencephalic dopamine neuronal activity. *CNS Neuroscience & Therapeutics*. 2018 Dec;24(12):1129-39. <https://doi.org/10.1111/cns.12867>
- [6] Drobnis EZ, Nangia AK. Male reproductive functions disrupted by pharmacological agents. *Impacts of Medications on Male Fertility*. 2017:13-24. [https://doi.org/10.1007/978-3-319-69535-8\\_3](https://doi.org/10.1007/978-3-319-69535-8_3)



- [7] Drobnis EZ, Nangia AK. Psychotropics and male reproduction. Impacts of Medications on Male Fertility. 2017:63-101. [https://doi.org/10.1007/978-3-319-69535-8\\_8](https://doi.org/10.1007/978-3-319-69535-8_8)
- [8] Chaudhary, D. S. . (2022). Analysis of Concept of Big Data Process, Strategies, Adoption and Implementation. International Journal on Future Revolution in Computer Science & Communication Engineering, 8(1), 05–08. <https://doi.org/10.17762/ijfrcsce.v8i1.2065>
- [9] Faisal IM, Almukhtar HM, Merkhan MM, Alobaidi RW. Comparative anti-inflammatory effect of risperidone versus olanzapine in schizophrenic patients. Indian J. Publ. Health Res. Develop.. 2019 Aug 1;10(8):964-9.
- [10] Gormus G, Ilgin S, Baysal M, Karaduman AB, Kılıc V, Aydogan-Kılıç G, Karagoz O, Atlı-Eklioglu O. Risperidone induced reproductive toxicity in male rats targeting leydig cells and hypothalamic–pituitary–gonadal axis by inducing oxidative stress. Andrologia. 2021 Feb;53(1):e13813. <https://doi.org/10.1111/and.13813>
- [11] Han M, Huang XF, Deng C. Aripiprazole differentially affects mesolimbic and nigrostriatal dopaminergic transmission: implications for long-term drug efficacy and low extrapyramidal side-effects. International Journal of Neuropsychopharmacology. 2009 Aug 1;12(7):941-52. <https://doi.org/10.1017/S1461145709009948>
- [12] Hassanane MS, Hafiz N, Radwan W, El-Ghor AA. Genotoxic evaluation for the tricyclic antidepressant drug, amitriptyline. Drug and chemical toxicology. 2012 Oct 1;35(4):450-5. <https://doi.org/10.3109/01480545.2011.642382>
- [13] Kikuchi T, Maeda K, Suzuki M, Hirose T, Futamura T, McQuade RD. Discovery research and development history of the dopamine D2 receptor partial agonists, aripiprazole, and brexpiprazole. Neuropsychopharmacology Reports. 2021 Jun;41(2):134-43. <https://doi.org/10.1002/npr2.12180>
- [14] Konarzewska B, Wołczynski S, Szulc A, Galinska B, Popławska R, Waszkiewicz N. Effect of risperidone and olanzapine on reproductive hormones, psychopathology and sexual functioning in male patients with schizophrenia. Psychoneuroendocrinology. 2009 Jan 1;34(1):129-39. <https://doi.org/10.1016/j.psyneuen.2008.08.015>
- [15] Norr L, Bennedsen B, Fedder J, Larsen ER. Use of selective serotonin reuptake inhibitors reduces fertility in men. Andrology. 2016 May;4(3):389-94. <https://doi.org/10.1111/andr.12184>
- [16] Agarwal, A. . (2022). Symmetric, e-Projective Topoi of Non-Solvable, Trivially Fourier Random Variables and Selberg’s Conjecture. International Journal on Recent Trends in Life Science and Mathematics, 9(1), 01–10. <https://doi.org/10.17762/ijlsm.v9i1.136>
- [17] Oriakpono OE, Anuforo C, Belita O. Response of selected reproductive parameters and prolactin levels of male Albino Wistar rats exposed to antipsychotic drugs. World J of Pharm and Pharm Sci 2020; 9(10): 353-363. DOI: 10.20959/wjpps202010-17445
- [18] Preda A, Shapiro BB. A safety evaluation of aripiprazole in the treatment of schizophrenia. Expert opinion on drug safety. 2020 Dec 1;19(12):1529-38. <https://doi.org/10.1080/14740338.2020.1832990>

- [19] Sada W. Abdulqader, Ibrahim M. Faisal, M. G. Saeed, Marwan M. Merkhan. Fluvoxamine Suppressed Oxidative Stress associated with Tissue Erosion. *Research Journal of Pharmacy and Technology*. 2022; 15(2):819-4. 10.5958/0974-360X
- [20] Shanmugasundaram N, Nivedhya J, Karthik MS, Ramanathan S. Risperidone-induced retrograde ejaculation and lurasidone may be the alternative. *Industrial Psychiatry Journal*. 2019 Jan;28(1):152. doi: 10.4103/ipj.ipj\_8\_19
- [21] Sogawa R, Shimomura Y, Minami C, Maruo J, Kunitake Y, Mizoguchi Y, Kawashima T, Monji A, Hara H. Aripiprazole-associated hypoprolactinemia in the clinical setting. *Journal of Clinical Psychopharmacology*. 2016 Aug 1;36(4):385-7. doi: 10.1097/JCP.0000000000000527.
- [22] Palagan Senopati Sewoyo, I Made Kardena. (2022). Canine Transmissible Venereal Tumor: Treatment Review and Updates. *Revista Electronica De Veterinaria*, 01 - 07. Retrieved from <https://www.veterinaria.org/index.php/REDVET/article/view/133>
- [23] Solomon R, Shvartsur R, Azab AN. The association between psychotropic drug use and fertility problems among male subjects. *Journal of Psychiatric Practice®*. 2019 Jan 1;25(1):22-33. <https://doi.org/10.1097/PRA.0000000000000353>
- [24] Stahl SM. Do dopamine partial agonists have partial efficacy as antipsychotics?. *CNS spectrums*. 2008 Apr;13(4):279-82. <https://doi.org/10.1017/S1092852900016382>
- [25] Tasaki M, Yasui-Furukori N, Yokoyama S, Shinozaki M, Sugawara N, Shimoda K. Hypoprolactinemia and hyperprolactinemia in male schizophrenia patients treated with aripiprazole and risperidone and their relationships with testosterone levels. *Neuropsychopharmacology Reports*. 2021 Sep;41(3):379-84.