Nature and Science

Websites:
http://www.sciencepub.net/nature
http://www.sciencepub.net

Emails:
naturesciencej@gmail.com
editor@sciencepub.net

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Study about the possible toxic Effects resulting from the combined administration of both Aripiprazole and Fluvoxamine on the liver of both male and female albino rats

Mohamed Ibrahem Ahmed[1], Fouad Helmy El-Dabah[1], Ahmed Fathy Abd El-Aziz[1] and Said Abd El-Raheem Said[2]

[1]Departments of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[2]ClinicalPpathology and Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
E-Mail: drmohamedibrahem201@gmail.com

Abstract: Background: Aripiprazole is an atypical antipsychotic that is being used to treat psychosis for a long time in combination with other medications that may activate or suppress the hepatic enzyme CYP3A4 and cause hepatotoxicity or activity loss. **Objective:** Recognizing the effect of aripiprazole and fluvoxamine on liver functions in albino rats of both sexes and elucidating the effect of combined administration of aripiprazole and fluvoxamine on liver functions in albino rats of both sexes. **Materials and Methods:** One hundred fifty (150) adult healthy male and female albino rats were used, weighing 150-200g and obtained from the Faculty of Medicine's animal house at Assiut University in the Arab Republic of Egypt. They were housed in clean capacious macro-lane cages in standard lab conditions, which included a well-aerated environment with appropriate temp and relative humidity, excellent lighting with alternating 12-hour light/dark cycles, and standard water and food. **Results:** The combination of aripiprazole with fluvoxamine at 1/20 from oral rats Lethal dose 50(LD50) of both drugs in both male and female albino rats showed significant the hepatic damage and significant elevation in liver function compared with aripiprazole and fluvoxamine alone treated groups which is supported by histopathological reports**. Conclusion:** there were significant hepatotoxic effects when aripiprazole was given in combination with fluvoxamine.

[Mohamed Ibrahem Ahmed, Fouad Helmy El-Dabah, Ahmed Fathy Abd El-Aziz and Said Abd El-Raheem Said **Study about the possible toxic Effects resulting from the combined administration of both Aripiprazole and Fluvoxamine on the liver of both male and female albino rats.** *Nat Sci* 2021;19(9):1-11]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature 1. doi:10.7537/marsnsj190921.01.

Keywords: Aripiprazole, Fluvoxamine, Albino Rats.

1. Introduction

Psychosis is a psychological disease which affects social functioning, perception, and thinking. The sickness can be fatal in the worst-case condition (**Al Diwani et al; 2017).** Psychotic manifestations , such as hallucinations and delusions, have been observed in a variety of neurodegenerative illnesses, which include Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies (DLB), and frontotemporal dementia **(Fischer et al; 2018).**The psychotic symptoms prevalence indicates a potential public health concern. A psychotic disorder is predicted to affect one out of every 150 persons at some point in their lives **(Moreno-Kustner; 2018).**

Antipsychotic drugs is a highly efficient therapy for reducing psychotic symptoms and preventing relapses in those who are suffering from psychosis **(Leucht et al; 2017) and (Huhn et al; 2019).** After antipsychotic treatment, a considerable percentage of sufferers with first-episode psychosis (FEP) obtain complete symptom remission **(Zhu et al; 2017).** Because of their superior safety and effectiveness, second-generation antipsychotics have a benefit over first-generation antipsychotics. For certain refractory patients and those with Treatment-Resistant Depression, combining and augmenting antipsychotic drugs could be a choice (**Melnik et al., 2010) and (Strawbridge et al., 2019).**

Combining these antipsychotic medications with antidepressants that either suppress or activate CYP enzymes can lead in either a greater plasma level with negative impacts (mostly liver damage) or a reduced plasma level with a decreased therapeutic benefit **(Abilify; 2019)**. Therefore, when combining antipsychotic medications with other medications that are metabolized via such liver enzymes, caution should be exercised.

In the therapy of psychosis accompanying bipolar emotional disorders, generalized tonic clonic seizures, obsessive compulsive disorders, as well as

depression, antidepressant medicines (tricyclic agents or selective serotonin reuptake inhibitors) and mood-stabilizing agents were widely used alongside antipsychotic treatments. Clinical hepatotoxicity has been linked to such combinations **(Shastry et al; 2013)**.

Aripiprazole is a structurally and pharmacologically unique second-generation antipsychotic (SGA) from prior SGAs **(Briles et al; 2012)**. Aripiprazole is predominantly eliminated through the liver, where it undergoes dehydrogenation, N dealkylation, and hydroxylation, primarily via the CYP3A4 and CYP2D6 enzyme systems. As a result, when aripiprazole is taken with CYP3A4 and CYP2D6 inhibitor or stimulators of CYP3A4, dose adjustment is advised **(Abilify; 2019)**. When aripiprazole is combined with CYP3A4 inducers like carbamazepine, for example, the dosage ought to be doubled**.** If aripiprazole is co-given with CYP3A4 inhibitors (like ketoconazole) or CYP 2D6 inhibitors (like fluoxetine or paroxetine), the dosage ought to be lowered to half of the usual dosage, or to a quarter if it is given with the both CYP3A4 inhibitors and CYP 2D6 inhibitors, or when a poor metabolizer receives any of such two **(Casey and Canal; 2017) and (Abilify; 2019)**.

Fluvoxamine is a powerful selective serotonin reuptake inhibitor which acts by boosting serotonin levels in the brain **(Slaton et al; 2015)**. Fluvoxamine, known as inhibitor of CYP3A4 that strongly metabolized in the liver. It's used to treat depression and anxiety disorders such OCD, panic disorders, social phobia, and PTSD **(Lin et al; 2017).**

Aripiprazole has been used in the long-term psychosis therapy with other medicines that may activate or inhibit the hepatic enzyme CYP3A4, that might result in hepatotoxicity or activity loss **(Abilify; 2019)**. Therefore the present study aimed at elucidating the possible toxic effects which may arise from the combined administration of both drugs together on the liver functions.

2. Materials and Methods

Chemicals:

Aripiprazole and fluvoxamine maleate gift sample from elit pharmaceuticals. Aripiprazole in addition to fluvoxamine have been freshly made in distilled water by suspending them with 0.6% Carboxymethylcellulose prior to being administered orally daily by Gavage to animals for three months.

Animals:

One hundred fifty (150) adult healthy male and female albino rats weighing 150 200g were used, and they were acquired from the animal house at Assiut University's Faculty of Medicine in Egypt. They were kept in clean, capacious macro-lane cages (5 per cage, 60x40x25 cm) in standard lab conditions, which included a well-aerated environment with appropriate temp and relative humidity, as well as good lighting with regular light/dark cycles. All rats were given normal rat diet during the experimental period with free access to water.

The animals were classified into five groups, each group divided into males and females:

1) Control group **(control –ve group I**): Each animal were given water and food freely given for 3 consecutive months.

2) Control group **(control +ve group II**): Each animal were given 0.5ml of distilled water orally by gavage for 3 consecutive months.

3) Treated group **(Aripiprazole-treated group III):** Each animal were given 41.25 mg/kg/day of Aripiprazole dissolved in distilled water (which represents 1/20 of LD50) orally by gavage for 3 consecutive months.

4) Treated group **(Fluvoxamine-treated group IV):** Each animal were given 55 mg/kg/day of Fluvoxamine dissolved in distilled water (which represents 1/20 of LD50) orally by gavage for 3 consecutive months.

5) Treated group (**Combined-treated group V):** Each animal were given 41.25 mg/kg/day of Aripiprazole and 55mg/kg/day of Fluvoxamine dissolved in distilled water (which represent 1/20 of LD50) orally by gavage for 3 consecutive months.

The rats were weighted at the beginning of the study and then after 3monthes at the last treatment, to calculate the suitable and accurate dose of the drug, according to the weight and to determine the effect of each group on the weight of the rats. At the end of this period and under ether anesthesia all animals were sacrificed after 24 hours of the last dose. The removal of the gallbladder and ligaments then the liver was extracted from the abdominal cavity. The liver were weighed and then placed in a container of water to determine the liver volume by measuring the volume of displaced fluid. The blood was undergone centrifugation; and serum for separation, and subjected to analysis of the following parameters:

(I) Physical parameters:

Parameters including body weight loss and liver weight gain were used to assess liver damage. The experimental animals' body weights were measured pre and post chronic therapy, and the percentage shift in body weight has been used to assess liver damage. Animals were slaughtered after the final dose, and the liver weight and volume were assessed.

(II) Biochemical analysis:

Two ml of blood samples were collected from the retro-bulbar plexuses of veins of inner canthus of eyes of each rat of control and treated rat groups by using fine capillary tubes in a glass vial (Vacationer tubes) without adding anticoagulant (5ml capacity). Blood samples were held on ice and serum was obtained by centrifugation of blood samples at 3000rpm for 5 minutes. Serum samples were stored at -20^{O}C until the time of biochemical analysis. Serum aspartate aminotransferase, serum glutamic-pyruvic transaminase, alkaline phosphatase, serum albumin and total bilirubin were determined in the serum of both male and female rats of all groups using commercially available diagnostic kits according to manufactures instructions (Life Span Biosciences, USA) using automated biochemical analyzer.

(III) Histopathological examination:

The male and female rats in all groups were sacrificed by decapitation using light ether anesthesia. Tissue samples from the liver have been preserved in 10% formalin, embedded in paraffin, and sectioned with a slidge microtome to produce 4 µm thick paraffin sections. Tissue sections have been collected on glass slides, deparaffinized in xylene, hydrated in a descending sequence of ethyl alcohol, stained with hematoxylin and eosin stains (H & E), dehydrated in an ascending sequence of ethyl alcohol, cleared in two changes of xylene, mounted with DPX, and investigated under a light microscope.

Statistical Analysis:

The mean ± standard error of the mean were used to represent all of the data (S.E.M.). Graph pad prism 5.0 was used for statistical analysis, with one-way analysis of variance (ANOVA) followed by Turkey's posttest. The minimal level of significance has been determined to be P< 0.05.

3. Results

(A) Physical parameters:

Hepatotoxicity is assessed using a chronic therapy model. To determine the extent of liver damage, the liver volume, liver weight, and bodyweight were all measured. The liver weight and volume rate in the aripiprazole with fluvoxamine group increased significant (P< 0.01) when compared to aripiprazole and fluvoxamine alone treated groups, at 1/20 from oral rate lethal dose 50(LD_{50}) of both medications indicated liver damage (Table 1 and 2). A significant decrease in body weight in aripiprazole with fluvoxamine group at 1/20 from oral rates Lethal dose 50(LD_{50}) of both drugs was observed when compared to aripiprazole and fluvoxamine alone treated groups (P <0.001) (Table 3).

Table 1: significant Liver weight (g) changes after chronic treatment in different groups in both male and female albino rats.

Groups	liver weight after chronic treatment							ANOVA	
	Range			Mean	±	SD	% of change	f	P-value
Control -ve	3.129	-	3.295	3.21	±	0.03		734.173	<0.001*
Control +ve	3.128	-	3.296	3.21	±	0.03			
Fluvoxamine	3.19	-	3.321	3.26	±	0.05	1.5		
Aripiprazole	3.179	-	3.469	3.37	±	0.10	4.7		
Combined aripiprazole and fluvoxamine	3.97	-	4.541	4.27	±	0.17	24.8		
Tukey's test									
	control -ve			control +ve				Fluvoxamine	Aripiprazole
control +ve	1.000								
Fluvoxamine	0.248			0.244					
Aripiprazole	<0.001*			<0.001*				<0.001*	
combined Aripiprazole and fluvoxamine	<0.001*			<0.001*				<0.001*	<0.001*

Table 2: Difference in Liver volume (ml) after chronic treatment in different groups in both male and female albino rats.

Groups	liver volume after chronic treatment							ANOVA	
	Range			Mean	±	SD	% of change	f	P-value
Control –ve	5.162	-	5.321	5.21	±	0.03		203.985	<0.001*
Control +ve	5.161	-	5.32	5.22	±	0.03			
Fluvoxamine	5.176	-	5.398	5.28	±	0.05	1.14%		
Aripiprazole	5.201	-	5.498	5.37	±	0.07	2.79%		
Combined aripiprazole and fluvoxamine	5.57	-	6.987	6.51	±	0.47	19.82%		
Tukey's test									
	control -ve			control +ve				Fluvoxamine	Aripiprazole
control +ve	1.000								
Fluvoxamine	0.797			0.813					
Aripiprazole	0.032*			0.035*				0.395	
combined Aripiprazole and fluvoxamine	<0.001*			<0.001*				<0.001*	<0.001*

Table3: significant body weight changes after chronic treatment in different groups in both male and female albino rat (P <0.001).

Groups	Body weight after chronic treatment							ANOVA	
	Range			Mean	±	SD	% of change	f	P-value
Control –ve	190	-	223	205.70	±	8.36		107.506	<0.001*
Control +ve	191	-	221	205.60	±	8.29			
Fluvoxamine	162	-	192	180.13	±	10.46	12.4		
Aripiprazole	160	-	193	177.00	±	11.58	13.9		
Combined aripiprazole and fluvoxamine	158	-	183	167.03	±	7.12	18.8		
Tukey's test									
	control -ve			control +ve				Fluvoxamine	Aripiprazole
control +ve	1.000								
Fluvoxamine	<0.001*			<0.001*					
Aripiprazole	<0.001*			<0.001*				0.689	
Combined aripiprazole and fluvoxamine	<0.001*			<0.001*				<0.001*	<0.001*

(B) Biochemical parameters:

AST, ALT and ALK PH were significantly higher when aripiprazole was administrated with fluvoxamine and in aripiprazole and fluvoxamine treated groups at 1/20 from oral rats Lethal dose 50(LD50) of both drugs in both male and female albino rats versus control groups (P = 0.011 and P <0.001). However AST, ALT and ALK PH were significantly higher (P <0.001) when aripiprazole was administrated in combination with fluvoxamine than aripiprazole and fluvoxamine groups in both male and female albino rats. There were insignificant differences in AST, ALT and ALK PH between control +ve and control –ve groups (Table 4-6). Total bilirubin was significantly higher in aripiprazole and combined (aripiprazole and fluvoxamine) than control -ve. (P=0.032 and <0.001 respectively) and then control +ve. (P=0.039and <0.001 respectively). Total bilirubin was significantly higher in combined (aripiprazole and fluvoxamine) than fluvoxamine. (P=0.002) (Table 7).

Table 4: The effect of combining of (aripiprazole with fluvoxamine), aripiprazole and fluvoxamine on biochemical parameters (AST).

Groups	SGOT(AST)							ANOVA	
	Range			Mean	±	SD	% of change	f	P-value
Control -ve	14	-	43	27.07	±	7.71		51.963	<0.001*
Control +ve	18	-	46	32.00	±	7.80			
Fluvoxamine	30	-	211	70.70	±	40.81	54.7		
Aripiprazole	34	-	324	130.73	±	84.53	75.5		
Combined aripiprazole and fluvoxamine	76	-	283	187.00	±	66.52	82.9		
Tukey's test									
	control -ve			control +ve			Fluvoxamine		Aripiprazole
control +ve	0.996								
Fluvoxamine	0.011*			0.032*					
Aripiprazole	<0.001*			<0.001*			<0.001*		
combined Aripiprazole and fluvoxamine	<0.001*			<0.001*			<0.001*		<0.001*

Table 5: The effect of combining of (aripiprazole with fluvoxamine), aripiprazole and fluvoxamine on biochemical parameters (ALT).

Groups	SGPT(ALT)							ANOVA	
	Range			Mean	±	SD	% of change	f	P-value
Control -ve	10	-	33	23.13	±	6.15		58.741	<0.001*
Control +ve	13	-	35	25.50	±	5.72			
Fluvoxamine	28	-	87	44.93	±	17.45	43.2		
Aripiprazole	26	-	145	65.73	±	31.22	61.2		
Combined aripiprazole &fluvoxamine	54	-	136	86.37	±	22.60	70.5		
Tukey's test									
	control -ve			control +ve			Fluvoxamine		Aripiprazole
control +ve	0.990								
Fluvoxamine	<0.001*			<0.001*					
Aripiprazole	<0.001*			<0.001*			<0.001*		
combined Aripiprazole and fluvoxamine	<0.001*			<0.001*			<0.001*		<0.001*

Table 6: The effect of combining of (aripiprazole with fluvoxamine), aripiprazole and fluvoxamine on biochemical parameters (ALK PH).

Groups	ALK PH							ANOVA	
	Range			Mean	±	SD	% of change	f	P-value
Control -ve	20	-	135	90.13	±	40.30		34.502	<0.001*
Control +ve	22	-	140	96.20	±	42.91			
Fluvoxamine	47	-	218	153.90	±	45.83	37.49		
Aripiprazole	64	-	216	167.03	±	48.04	42.41		
Combined aripiprazole and fluvoxamine	61	-	278	208.63	±	54.62	53.89		
Tukey's test									
	control -ve			control +ve				Fluvoxamine	Aripiprazole
control +ve	0.987								
Fluvoxamine	<0.001*			<0.001*					
Aripiprazole	<0.001*			<0.001*				0.811	
combined Aripiprazole and fluvoxamine	<0.001*			<0.001*				<0.001*	0.005*

Table 7: The effect of combining of (aripiprazole with fluvoxamine), aripiprazole and fluvoxamine on Serum Total bilirubin.

Groups	Total bilirubin							ANOVA	
	Range			Mean	±	SD	% of change	f	P-value
control -ve	0.19	-	1.53	0.83	±	0.36		10.052	<0.001*
control +ve	0.2	-	1.4	0.84	±	0.31			
Fluvoxamine	0.5	-	1.43	0.97	±	0.26	13.4		
Aripiprazole	0.4	-	1.5	1.06	±	0.37	20.8		
combined Aripiprazole and fluvoxamine	0.7	-	1.5	1.27	±	0.24	33.9		
Tukey's test									
	control -ve			control +ve				Fluvoxamine	Aripiprazole
control +ve	1.000								
Fluvoxamine	0.409			0.454					
Aripiprazole	0.032*			0.039*				0.781	
combined Aripiprazole and fluvoxamine	<0.001*			<0.001*				0.002*	0.089

(C) Histopathology Report:

Table (8): showed that total histopathology was significantly different among the five groups (P<0.001). Total histopathology was higher in fluvoxamine, aripiprazole and combined aripiprazole and fluvoxamine than control -ve and control +ve (P <0.001). In aripiprazole and combined aripiprazole and fluvoxamine than fluvoxamine (P <0.001) and in combined aripiprazole and fluvoxamine than aripiprazole. (P = 0.024).

In the control groups, histolopathogical investigation of the liver reveals normal lobular architecture and histology (Fig 1,2).

In Fluvoxamine treated group at 1/20 from oral rats Lethal dose 50(LD50), The Liver revealed mildly edematous portal tracts with mild portal inflammatory infiltration, average portal veins and average hepatocytes in peri-portal area, mildly dilated central veins with scattered apoptotic hepatocytes in peri-venular area (Fig 3,4).

In groups treated with aripiprazole alone at 1/20 from oral rats Lethal dose 50(LD50), The liver showed mildly edematous portal tracts with mild portal inflammatory infiltrate, markedly dilated portal veins, mildly dilated central veins, and scattered apoptosis with moderate vacuolar degeneration of hepatocytes in peri-portal and peri-venular areas (Fig 5,6).

In the group treated with aripiprazole with fluvoxamine at 1/20 from oral rats Lethal dose 50 (LD50) of both drugs, Histopathological examination of liver showed markedly expanded portal tracts with marked portal and peri-portal inflammatory infiltrate, marked apoptosis with moderate vacuolar degeneration of hepatocytes in peri-portal area which confirms the severe hepatic damage (Fig 7,8).

Table 8: statistical Histopathological significance in different groups.

Groups	**Total histopathology**							ANOVA	
	Range			**Mean**	**±**	**SD**	**% of change**	**f**	**P-value**
Control -ve	0	-	2	0.70	±	0.70		96.093	<0.001*
Control +ve	0	-	2	0.70	±	0.70			
Fluvoxamine	0	-	7	3.07	±	2.70	77.2%		
Aripiprazole	0	-	8	6.13	±	2.06	88.6%		
Combined aripiprazole and fluvoxamine	4	-	10	7.47	±	1.57	90.6%		
Tukey's test									
	control -ve			**control +ve**				**Fluvoxamine**	**Aripiprazole**
control +ve	1.000								
Fluvoxamine	<0.001*			<0.001*					
Aripiprazole	<0.001*			<0.001*				<0.001*	
combined Aripiprazole and fluvoxamine	<0.001*			<0.001*				<0.001*	0.024*

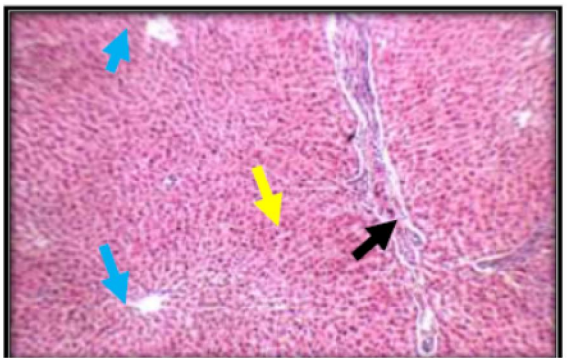

Figure 1: (Control +ve group): liver showing average portal tract (black arrow), average central vein (blue arrow) and average hepatocytes (yellow arrow) (H&E X 200)

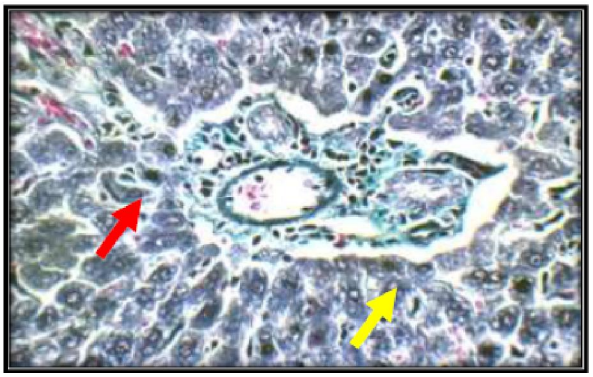

Figure 2: (Control – ve group): liver showing average collagen distribution in portal tract (red arrow) and in peri-portal area (yellow arrow) (Masson trichrome X 400)

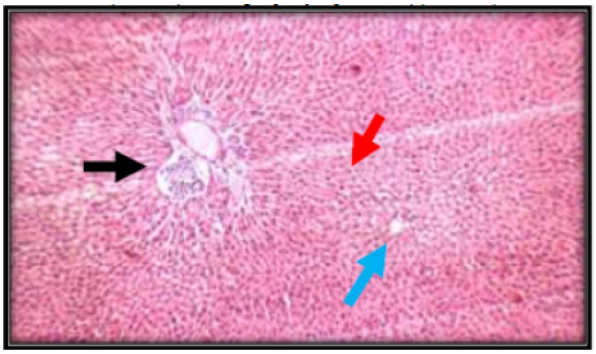

Figure 3: (Fluvoxamine group): liver showing mildly edematous portal tract with mild portal inflammatory infiltrate (black arrow), average central veins (blue arrow) and average hepatocytes (red arrow) (H&E X 200)

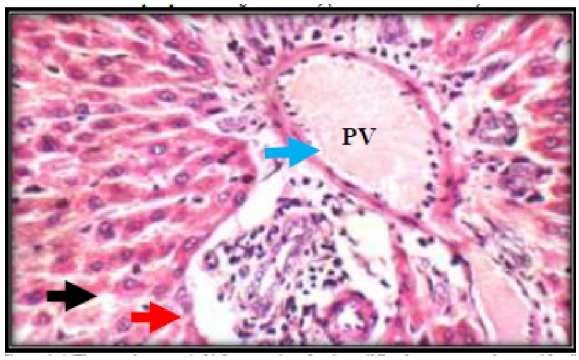

Figure 4: ((Fluvoxamine group): high power view showing mildly edematous portal tract with mild portal inflammatory infiltrate (black arrow), average portal vein (PV), average bile ducts (red arrow), and average hepatocytes in peri-portal area (blue arrow) (H&E X 400)

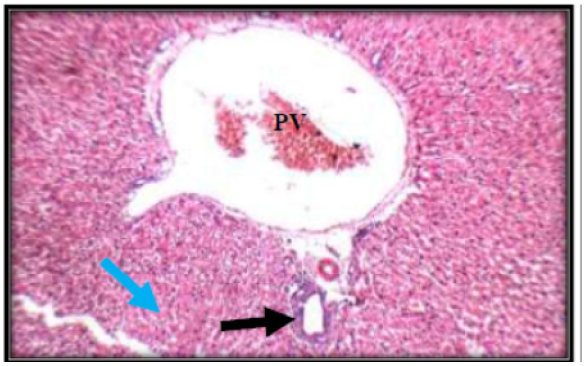

Figure 5: (Aripiprazole group): liver showing mildly edematous portal tract with mild portal inflammatory infiltrate (black arrow) and markedly dilated congested portal veins (PV), and moderate vacuolar degeneration of hepatocytes in peri-portal area (blue arrow) (H&E X 200)

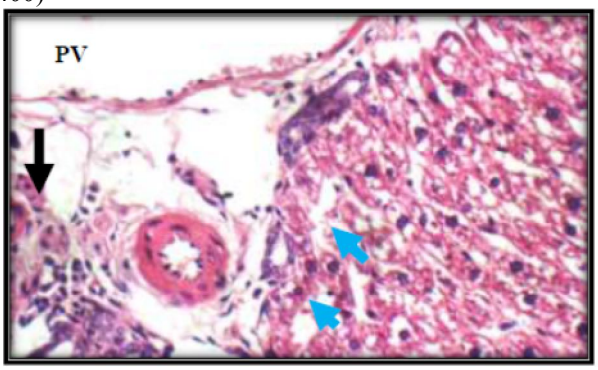

Figure 6: (Aripiprazole group): high power view showing mildly edematous portal tract with mild portal inflammatory infiltrate (black arrow) and markedly dilated portal veins (PV), and moderate vacuolar degeneration of hepatocytes in peri-portal area (blue arrow) (H&E X 400)

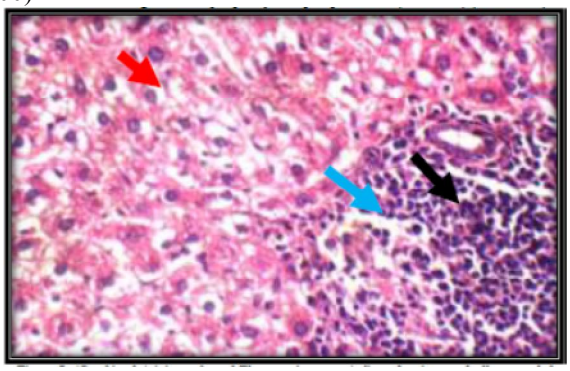

Figure 7: (Combined Aripiprazole and Fluvoxamine group): liver showing markedly expanded portal tract with marked portal and peri-portal inflammatory infiltrate (black arrow), and scattered apoptosis (blue arrow) with moderate vacuolar degeneration of hepatocytes in peri-portal area (red arrow) (H&E X 400)

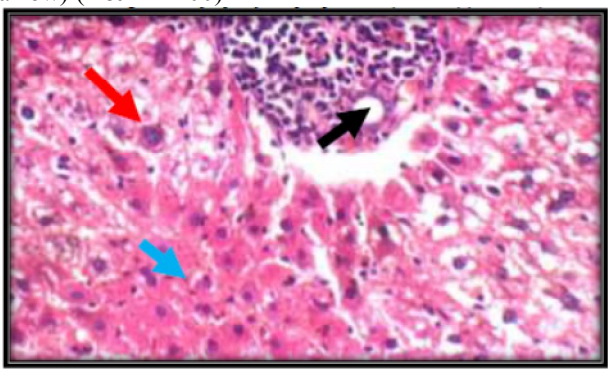

Figure 8: (Combined Aripiprazole and Fluvoxamine group) another view showing mildly expanded portal tract with marked portal and peri-portal inflammatory infiltrate (black arrow), and marked apoptosis (blue arrow) with moderate vacuolar degeneration of hepatocytes in peri-portal area (red arrow) (H&E X 400)

4. Discussion

Antipsychotic drugs are the foundation of psychosis therapy and must be initiated as soon as a precise diagnosis is made. Antipsychotic medicines were widely researched for the therapy of schizophrenia **(Huhn et al; 2019)** and seem to be useful for other kinds of psychosis as well. Antipsychotics have been shown in studies to be beneficial for bipolar mania with psychosis **(Yildiz et al; 2011)**, depression with psychotic features (combination therapy with antidepressants) **(Wijkstra et al; 2013)**, Parkinson disease psychosis, and psychosis related to dementia **(Lochheadet al; 2016).** Because of their superior safety and effectiveness, atypical antipsychotics possess an edge over typical antipsychotics. For certain refractory patients and those with Treatment-Resistant Depression, a combination of augmenting antipsychotics could be a choice **(Melnik et al., 2010) and (Strawbridge et al., 2019).**

Fluvoxamine is a very effective and selective serotonin reuptake inhibitor which works by boosting serotonin levels in the brain **(Slaton et al; 2015)**. Fluvoxamine, a well-known CYP3A4 inhibitor, is heavily metabolized in the liver. It's used to treat significant anxiety and depression disorders such OCD, panic disorders, social phobia, and PTSD **(Lin et al; 2017).** Atypical antipsychotics, such as aripiprazole, are utilized in the long-term therapy of psychosis in conjunction with other medicines that may activate or suppress the hepatic enzyme CYP3A4, which may result in hepatotoxicity or activity loss. **(Abilify, 2019)**.

The present study revealed increased level of biochemical parameters like serum aspartate aminotransferase (AST), serum glutamic-pyruvic transaminase (ALT), alkaline phosphatase (ALK PH), and indicating significant liver damage when fluvoxamine was administered at 1\20 of LD50 level. Our findings were validated by a study **(Galal et al., 2016)**, revealed that oral treatment of rats with fluvoxamine at both Low therapeutic dose (LTD) and high therapeutic dose (HTD) exhibited a considerable increase in ALTthat might be related to fluvoxamine's detrimental impact on the hepatocyte, which increased the permeability of its cell membrane, resulting in increased ALT release into circulation. Our findings were supported by (Ebuehi et al. 2013), who reported that four weeks of oral citalopram and fluoxetine treatment increased serum aspartate aminotransferase (AST) and serum glutamic-pyruvic transaminase (ALT) activity in rats.

The current research discovered an increase in the of biochemical parameters like serum aspartate aminotransferase (AST), serum glutamic-pyruvic transaminase (ALT), alkaline phosphatase (ALK PH) suggesting significant hepatic damage when aripiprazole has been provided in conjunction with fluvoxamine than aripiprazole and fluvoxamine groups at 1/20 of oral Lethal dose. Serum albumin was significantly higher in combined aripiprazole and fluvoxamine than other groups. Total bilirubin was significantly higher in combined aripiprazole and fluvoxamine than aripiprazole and fluvoxamine groups at 1/20 of oral Lethal dose (LD50). Our findings were validated by a study **(Shastry et al., 2013)** as they revealed that there was a highly significant elevation in serum aspartate aminotransferase (AST), serum glutamic-pyruvic transaminase (ALT), alkaline phosphatase (ALK PH) levels in the aripiprazole/fluvoxamine group at both therapeutic dose (TD) and maximum therapeutic dose (MTD) levels and there were no similar elevations detected in the aripiprazole with carbamazepine treated groups. At TD, total bilirubin levels increased significantly in the aripiprazole with carbamazepine groups. When compared to rats treated with aripiprazole alone, significant increases in MTD were found. Increased levels of biochemical liver enzyme indicators imply hepatic damage. **(Shastry et al., 2013).**

The combined aripiprazole and fluvoxamine group had higher liver weight, liver volume, and body weight loss than the aripiprazole and fluvoxamine groups, indicating that the combination of aripiprazole and fluvoxamine causes more drug-induced liver damage. Our findings were confirmed by those of (Shastry et al., 2013), who reported a significant increase in the liver weight and liver volume of animals in the aripiprazole with fluvoxamine group at both the TD and MTD levels, signifying liver damage, when compared to the aripiprazole-treated group.

In The present study the histopathological of the liver showed that portal vein, peri-portal area, central vein, peri-venular area and fibrosis were significantly higher in combined aripiprazole and fluvoxamine than fluvoxamine and aripiprazole treated grougs than control –ve and then control +ve .however it were marked higher significance in combined aripiprazole and fluvoxamine group than fluvoxamine and aripirazole treated groups. But there were insignificant differences between control -ve and control +ve. These histopathological investigations of the liver reveal chronic inflammatory cells as well as portal inflammation, indicating liver damage.

However, in the study of **(Shastry et al., 2013)**, histological investigation of the liver in the control group demonstrated the preservation of normal lobular architecture and histology. There was no significant portal inflammation or hepatocyte damage

in groups treated with aripiprazole alone at TD; however the portal tract demonstrated minor aggregation of chronic inflammatory cells at MTD. At TD, there was no significant portal inflammation or hepatocellular damages in the aripiprazole with carbamazepine group, however at MTD, there were small aggregation of chronic inflammatory cells as well as mild periportal inflammation. The portal tract revealed modest aggregates of chronic inflammatory cells and moderate portal inflammation in the group administered with aripiprazole with fluvoxamine at TD, whereas moderate to severe portal inflammation has been seen at MTD, confirming the significant liver damage in the aripiprazole with fluvoxamine group **(Shastry et al., 2013)**.

Fluvoxamine also inhibits CYP3A4 and CYP2D6. (Aripiprazole and fluvoxamine co-administration has been found to produce liver damage through CYP3A4 inhibition and aripiprazole buildup) **(Shastry et al. 2013).** Therefore, fluvoxamine and clozapine or aripiprazole ought to be avoided if feasible, or recommended with caution when co-administration is necessary.

Even at therapeutic dosages, ADs and APs, which are used to treat a variety of psychiatric diseases like depression, schizophrenia, and anxiety, can cause hepatotoxicity. Over 160 psychiatric medicines were linked to hepatic adverse impacts. In a recent investigation, psychiatric medicines were found to be responsible for 7.6% of DILI instances in a group of 185 patients (**Licata et al. 2017).**

Conclusion;

There was significant toxic effects resulting from the combined administration of both Aripiprazole and Fluvoxamine on the liver of both male and female albino rats, due to inhibition of aripiprazole-metabolizing enzyme CYP3A4. Therefore caution must be exercised when aripiprazole is combined with fluvoxamine for the therapy of psychosis. It is necessary to keep track of adverse effects such as hepatotoxicity and reduced efficacy. In such a case, dosage titration and correction might be required.

References

[1]. **Abilify.** US prescribing information. [cited 2019 May 5]. Available from: Aripiprazole summary of product characteristics and prescribing information (FDA).

[2]. **Al Diwani AA, Pollak TA, Irani SR, Lennox BR (2017) Psychosis:** an autoimmune **disease**? Immunology 152(3): 388-401.

[3]. **Briles JJ, Rosenberg DR, Brooks BA, et al.** Review of the safety of second-generation antipsychotics: are they really "atypically" safe for youth and adults? Prim Care Companion CNS Disord. 2012; 14(3): PCC.11r01298.

[4]. **Casey AB, Canal CE.** Classics in chemical neuroscience: aripiprazole. ACS Chem Neurosci. 2017;8(6):1135–1146.

[5]. **Ebuehi OA, Akinbode AA, Erinfolami AR, Badaru AA, Yusuf MA, Ojajuni MO (2013)** Citalopram and fluoxetine affects blood chemistry, haematology and brain serotonin in rats. Nig Q J Hosp Med 23: 94–98.

[6]. **Fischer CE, Ageuera-Ortiz L.** Psychosis and dementia: risk factor, prodrome, or cause? Int Psychogeriatr 2018; 30:209–219.

[7]. **Gala A. A. A. l, Alam R. T. M. & Abd El-Aziz R. M (2016)** Adverse effects of long-term administration of fluvoxamine on haematology, blood biochemistry and fertility in male albino rats. Life Sci J 10: 2924–2934.

[8]. **Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al.:** Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 2019; 394: 939–51.

[9]. **Licata A, Minissale MG, Calvaruso V, Craxì A (2017)** DILI and epidemiology. Eur Rev Med Pharmacol Sci 21:112–121.

[10]. **Lin WT, Liao YJ, Peng YC, et al.** Relationship between use of selective serotonin reuptake inhibitors and irritable bowel syndrome: A population-based cohort study. World J Gastroenterol. 2017 May 21; 23(19):3513-3521.

[11]. **Lochhead JD, Nelson MA, Maguire GA.** The treatment of behavioral disturbances and psychosis associated with dementia. Psychiatr Pol 2016; 50(2):311–322.

[12]. **Melnik T, Soares BG, Puga ME and Atallah AN. (2010):** "Efficacy and safety of atypical antipsychotic drugs (quetiapine, risperidone, aripiprazole and paliperidone) compared with placebo or typical antipsychotic drugs for treating refractory schizophrenia": Overview of systematic reviews. Sao Paulo Med J.p. 128:141–66.

[13]. **Moreno-Kustner, B., Martin, C., & Pastor, L. (2018).** Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. PLoS ONE, 13(4), e0195687.

[14]. **Shastry, C. S., Shafeeque, A. A., & Ashwathnarayana, B. J. (2013).** Effect of combination of aripiprazole with carbamazepine and fluvoxamine on liver functions in experimental animals. Indian journal of pharmacology, 45(2), 121.

[15]. **Slaton RM, Champion MN, Palmore KB.** A review of paroxetine for the treatment of vasomotor symptoms. J Pharm Pract. 2015 Jun; 28(3):266-74.

[16]. **Strawbridge, R., Carter, B., Marwood, L., Bandelow, B., Tsapekos, D., Nikolova, V.L., Taylor, R., Mantingh, T., De Angel, V., Patrick, F., Cleare, A.J., Young, A.H., 2019.** Augmentation therapies for treatmentresistant depression: Systematic review and meta-analysis. Br. J. Psychiatry 214, 42–51.

[17]. **Yildiz A, Vieta E, Leucht S, Baldessarini RJ.** Efficacy of antimanic treatments: meta-analysisof randomized, controlled trials. Neuropsychopharmacology 2011; 36(2):375–389.

[18]. **Zhu Y, Li C, Huhn M, et al.:** How well do patients with a first episode of schizophrenia respond to antipsychotics: a systematic review and meta-analysis. Eur Neuropsychopharmacol 2017; 27: 835–44.

9/3/2021