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EFFECT OF WITHANIA SOMNIFERA (ASHWAGANDHA) ON LIVER FUNCTION PARAMETERS IN MDD (MAJOR DEPRESSIVE DISORDER) PATIENTS TAKING SERTRALINE.

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ABSTRACT

Aim and Objectives: **Aim:** To study the effect of administration of sertraline alone and sertraline with ashwagandha on liver function parameters in patients with MDD (Major Depressive Disorder).. **Objectives:** 1. To estimate the effect of sertraline on Liver Function parameters in patients with MDD. 2. To estimate the effect of co-administration of ashwagandha with sertraline on liver function parameters. 3. To compare liver function parameters of both the groups before and after treatment. **Material and Methods:** This was an open labelled, randomized, comparative, prospective study involving 80 newly diagnosed patients with MDD (Major depressive Disorder) according to inclusion and exclusion criteria. After enrolling, patients were randomly allocated in either of the groups. One who are taking routine treatment with sertraline (Sertraline Group) and another who are given ashwagandha 250mg twice a day with their routine treatment with sertraline (Sertraline + Ashwagandha Group). All liver function parameters were investigated before starting the treatment and reinvestigated after a period of 3 months of drug treatment in both the groups. **Results:** In sertraline group, values of SGOT, SGPT, Total Protein and Globulin levels were significantly increased. Whereas there was no significant difference in values of other parameters. In sertraline + ashwagandha group, there was no significant difference in values of any liver function parameters before and after three months of treatment. **Conclusion:** We can conclude prolonged treatment with sertraline can increase few liver function parameters i.e., SGOT, SGPT, Total proteins and Globulin which can be prevented by using ashwagandha with the sertraline. However, sertraline + ashwagandha does not have any effect on any liver parameters.

KEY WORDS: Antidepressants, Ashwagandha, Liver function test, MDD (Major depressive Disorder), Sertraline.

INTRODUCTION

The symptoms of major depression include melancholia, suicidal thoughts, low energy, guilt, worthlessness, psychomotor retardation or agitation, low energy, sad mood, and lack of interest and pleasure.¹ According to estimates, depression affects 3.8% of the world's population, 5.0% of adults and 5.7% of people over the age of 60. There are almost 280 million people are suffering from depression globally.² Patients with major depressive disorder are commonly treated with antidepressant medications, though in specific circumstances they may also get psychotherapy or counselling. The main aim of treatment is remission.³ Some of the drugs used to treat depression include tricyclic antidepressants (TCAs), SNRIs, SSRIs, MAOIs, norepinephrine and dopamine reuptake inhibitors.⁴ The SSRIs, a class of medications that is most frequently used to treat depression. Due to their safety, effectiveness, and tolerability, they are frequently used as first-line pharmacotherapy for depression and many other mental illnesses.⁵

Due to better tolerability and safety of sertraline and other serotonin reuptake inhibitors they are superior to that of tricyclic antidepressants. Sertraline has a wide therapeutic index and limited anticholinergic activity because of which it is most frequently prescribed antidepressant agent from SSRIs group.⁶ Sertraline side effects most frequently include nausea, dry mouth, loose stools or diarrhoea, sleeplessness, dizziness, tremor, fatigue, agitation, and somnolence.⁷ In previous study Ebuehi OA et al. which was conducted on rabbit they have shown that levels of serum and liver SGOT, SGPT and alkaline phosphatase were increased after giving sertraline for 28 days.⁸ It may do metabolic changes in terms of altered liver profile. The rate of asymptomatic increase in blood transaminases (SGOT and SGPT) secondary to sertraline use, according to data from the premarketing review of sertraline, is 0.8%, with the majority of instances occurring within the first 9 weeks of drug beginning.⁹ Despite of this, liver function derangement due to sertraline is rare and effect of sertraline on liver function parameters is yet not clear which needs to be studied as it is very frequently used antidepressant agent.

Ayurvedic herb *Withania somnifera* (Solanaceae family) has been utilized for ages in India as an adaptogenic herb to increase general health. This plant's many parts are utilized in herbal medicine. Although the seeds, shoots, juice, and leaves have all been utilized traditionally, the root is used medicinally.¹⁰ There are so many pharmacological effects of ashwagandha which are documented. It has sedative, diuretic, and anti-inflammatory properties, and is well known for boosting stamina, endurance, and acting as an adaptogen with potent immunostimulatory and anti-stress effects.¹¹ Ashwagandha is used to treat conditions like the common cold and cough, ulcers, emaciation, diabetes, conjunctivitis, epilepsy, insomnia, Parkinson's disease, leprosy, mental disorders, rheumatism, arthritis, intestinal infections, bronchitis, and erectile dysfunction.¹² Effect of Ashwagandha on liver function parameters is not yet clear. But some studies have shown that ashwagandha can reduce serum SGOT and SGPT levels^{13, 14} and it can also decrease total protein, albumin, albumin: globulin (A : G) ratio after eight weeks treatment with Ashwagandha.¹⁵

So, this study was aimed to evaluate the effect of sertraline and effect of combination of sertraline + ashwagandha on Liver function parameters. The purpose of combining ashwagandha with sertraline is it is having well proven antidepressant activity which can give benefit to MDD (Major Depressive Disorder). It may play protective role to prevent if any liver parameter derangement.

MATERIALS AND METHODS

The present Study was conducted in Psychiatry Department in Krishna Hospital & Krishna Institute of Medical Sciences. Study was conducted between February, 2021 to August, 2022. This was an open labelled, randomized, comparative, prospective, interventional study involving 80 newly diagnosed patients with MDD (Major depressive Disorder) according to inclusion and exclusion criteria. Institutional ethics committee (IEC) approval was taken prior to the initiation of the study vide letter No. KIMSDU/IEC/01/2021 dt 17.02.2021. Written informed consent was taken before enrolling patient into study.

Patients of either gender diagnosed with major depressive disorder age between 18 to 60 years who were willing to give informed consent and received Sertraline for treatment were included for this study. Patients with other comorbid conditions like liver cirrhosis, hyperthyroidism, pregnant and lactating females and females on hormonal contraceptives, patients with alcohol dependence syndrome and chronic smoker and subjects who are on other chronic drug therapy which can alter liver function parameters were excluded from this study.

After enrolling, patients were divided into two groups. Those patients were allocated in either of the group randomly (40 patients in each group). Dose of ashwagandha was decided after consultation with ayurvedic consultant.

Sertraline Group – Patients who are taking routine treatment with sertraline (40 patients)

Sertraline + Ashwagandha Group – Patients who are taking Ashwagandha 250 mg twice a day with their routine treatment with sertraline (40 patients)

Baseline blood sample was collected before starting treatment for various liver function parameters. 4 ml venous blood was collected in plain vacutainer (red) from the subjects by veni puncture under all aseptic precautions. All the biochemical parameters were investigated in the Biochemistry laboratory (NABL accredited), Krishna Institute of Medical Sciences, Karad. All the biochemical parameters included in present study were estimated by the following methods: Serum SGOT – IFCC method, Serum SGPT – IFCC method, Serum alkaline phosphatase – p-NP-AMP method, Serum Total proteins – Biuret method, Serum Albumin – BCG method, Serum Globulin – Calculated, Serum Total Bilirubin – DIAZO method, Serum Direct Bilirubin – DIAZO method, Serum Indirect Bilirubin – Calculated

For follow up and refilling of prescription, patients visited the Psychiatry OPD of the hospital after every fifteen days. Telephonic follow up was taken at every fifteen days to check the adherence to the treatment as well as to ask about any adverse effect. All the parameters were rechecked for each patient after a period of 3 months of drug treatment. After collection of data, both the groups were

compared with each other by using unpaired ‘t’ test and before and after treatment data was compared by using paired ‘t’ test. $P < 0.05$ was considered as a significant value.

RESULTS

All 80 patients completed a three months of antidepressant therapy. Out of the 80 patients, 43 were males and 37 were females.

In sertraline group, there was significant difference in values of SGOT, SGPT, Total Protein and Globulin levels before and after three months of treatment with Sertraline and they were significantly increased. Whereas there was no significant difference in values of Alkaline Phosphatase, Albumin, Total Bilirubin, Direct Bilirubin and Indirect Bilirubin levels before and after three months of treatment with Sertraline. (Table 1)

In sertraline + ashwagandha group, there was no significant difference in values of SGOT, SGPT, Alkaline Phosphatase, Total Protein, Albumin, Globulin, Total Bilirubin, Direct Bilirubin and Indirect Bilirubin levels before and after three months of treatment with Sertraline + Ashwagandha. (Table 2)

When we compared both the group with each other there was no significant difference in values of all liver parameters who received sertraline & sertraline + ashwagandha before initiation of respective treatment. However, there was significant difference in SGPT ($t=2.075$, $p=0.041$) and total proteins ($t=2.438$, $p=0.017$) levels of two groups after drug treatment for a period of three months and their levels were significantly low in sertraline + ashwagandha group as compared to sertraline group (Table 4 and 6). Whereas there was no significant difference in values of other liver parameters i.e., SGOT, Alkaline Phosphatase, Proteins (globulin & albumin) and bilirubin (Direct, Indirect or Total) of two groups after drug treatment. (Table 3, 5, 7, 8, 9, 10 and 11)

DISCUSSION

Sertraline is the most frequently prescribed antidepressant agent from SSRIs group. It can ease symptoms of moderate to severe depression.

Sertraline rarely causes liver damage, and it seems to do so less frequently than with other selective serotonin reuptake inhibitors.¹⁶ Liver function usually returns to normal shortly after stopping sertraline in cases of sertraline-induced hepatic damage. However, it varies from person to person how long it takes for liver function to return to normal. It has been observed to take 6 months after stopping the medicine.¹⁷

In our observation the values of SGOT, SGPT, Total Proteins and Globulin levels were significantly increased whereas there was no significant difference in values of other liver parameters (Albumin, Alkaline Phosphatase and bilirubin) (Table 1). In study by Ebuehi OA et al. which was conducted on rabbit shown that levels of serum and liver SGOT, SGPT and alkaline phosphatase were increased after giving sertraline for 28 days. which is similar finding in our study also.⁸ But these increase in levels with sertraline in their study were less as compared to other antidepressant drugs like amitriptyline and imipramine but they were more than clozapine.

In our study, we observed that there was no significant difference in values of any liver function parameter (SGOT, SGPT, Alkaline Phosphatase, Total Protein, Albumin, Globulin, Total Bilirubin, Direct Bilirubin and Indirect Bilirubin) levels before and after three months of treatment with sertraline + ashwagandha (Table 2). So, use of ashwagandha with sertraline is not showing raise in SGOT, SGPT, Total proteins and Globulin which were raised with the use of sertraline alone. There are no studies available which shows combine effect of sertraline + ashwagandha on liver profile. But in an animal study *Withania somnifera* (ashwagandha) root extract improved serum AST and ALT levels to normal.¹³ Through its antioxidant activity, *Withania somnifera* demonstrates promising hepatoprotective properties and it restore the liver function parameters which can alter by other drugs.¹⁸ Extract of ashwagandha root has improved serum ALT, AST and protein levels as well as cholesterol significantly after treatment of 28 days. Which indicates that ashwagandha has significant hepatoprotective property.¹⁹

When we compared both the group with each other there was no significant difference in values of all liver parameters who received sertraline &

sertraline + ashwagandha before initiation of respective treatment. However, there was significant difference in SGPT ($t=2.075$, $p=0.041$) and total proteins ($t=2.438$, $p=0.017$) levels of two groups after drug treatment for a period of three months and their levels were significantly low in sertraline + ashwagandha group as compared to sertraline group (Table 3 and 4). Whereas there was no significant difference in values of other liver parameters i.e., SGOT, Alkaline Phosphatase, Proteins (globulin & albumin) and any type of bilirubin (Direct, Indirect or Total) of two groups after drug treatment. The levels of SGOT, SGPT, total proteins and globulin which were elevated in the Sertraline group, whereas they were not raised in Sertraline + Ashwagandha group after three months of treatment (Table 1 & 2). Ebuehi OA et al also reported the similar findings.⁸ Though derangement of liver function parameters is rare which can be prevented by adding ashwagandha if any. The purpose of combining ashwagandha with sertraline is it is having well proven antidepressant activity¹¹ which can give benefit to MDD (Major Depressive Disorder). And second thing ashwagandha can play protective role to prevent the metabolic changes faced by some patients who are on prolonged treatment with sertraline.

So, it reveals that Ashwagandha does not lower SGPT and Total Proteins levels; rather, it can only stop the rise in SGPT and total proteins levels which is due to prolonged sertraline use.

CONCLUSION

From results of our study, we can conclude that prolonged treatment with sertraline can increase few liver function parameters i.e., SGOT, SGPT, Total proteins and Globulin. This rise in parameters can be prevented by using ashwagandha with the sertraline. However, Sertraline or sertraline + ashwagandha does not have any effect on other liver parameters i.e., Alkaline Phosphatase, Proteins (globulin & albumin) and bilirubin (Direct, Indirect or Total).

LIMITATIONS OF STUDY

As we have studied metabolic changes, other related physical parameters (i.e., Weight, Waist circumference, BMI etc.) can be included. As it was a

OPD based study it was difficult to give specific diet recommendations to all patients and follow up was for short duration.

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Conflict of interest: None

TABLES

Table 1: Pre and post treatment levels of Liver Function Parameters after Sertraline administration.

Sr. No.	Variable	Mean \pm SD		t - value	p - value
		Before Treatment	After Treatment		
1.	SGOT (IU/L)	26.35 \pm 10.87	33.55 \pm 17.50	2.231	0.0315*
2.	SGPT (IU/L)	22.30 \pm 9.59	35.32 \pm 36.69	2.176	0.0357*
3.	Alkaline Phosphatase (U/L)	95.20 \pm 27.93	89.50 \pm 30.45	0.859	0.3956
4.	Total Protein (g/dl)	7.30 \pm 0.43	7.50 \pm 0.44	2.330	0.0251*
5.	Albumin (g/dl)	4.07 \pm 0.27	4.04 \pm 0.28	0.515	0.6096
6.	Globulin (g/dl)	3.19 \pm 0.50	3.47 \pm 0.44	2.712	0.0099*
7.	Total Bilirubin (mg/dl)	0.50 \pm 0.28	0.64 \pm 0.45	1.645	0.1080
8.	Direct Bilirubin (mg/dl)	0.19 \pm 0.10	0.24 \pm 0.15	1.471	0.1492
9.	Indirect Bilirubin (mg/dl)	0.30 \pm 0.18	0.40 \pm 0.31	1.707	0.0958

p<0.05 = *Significant difference

Table 2: Pre and Post treatment levels of Liver Function Parameters after Sertraline + Ashwagandha administration.

Sr. No.	Variable	Mean \pm SD		t - value	p - value
		Before Treatment	After Treatment		
1.	SGOT (IU/L)	28.32 \pm 9.32	28.12 \pm 9.53	0.090	0.928
2.	SGPT (IU/L)	26.65 \pm 12.13	22.72 \pm 11.33	1.449	0.155
3.	Alkaline Phosphatase (U/L)	91.07 \pm 20.44	84.50 \pm 18.36	1.792	0.080
4.	Total Protein (g/dl)	7.41 \pm 0.48	7.26 \pm 0.44	1.341	0.187
5.	Albumin (g/dl)	4.12 \pm 0.27	3.98 \pm 0.58	1.336	0.189

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6.	Globulin (g/dl)	3.28 ± 0.53	3.36 ± 0.44	0.685	0.497
7.	Total Bilirubin (mg/dl)	0.56 ± 0.34	0.68 ± 0.44	1.357	0.182
8.	Direct Bilirubin (mg/dl)	0.22 ± 0.13	0.25 ± 0.14	0.931	0.357
9.	Indirect Bilirubin (mg/dl)	0.34 ± 0.23	0.43 ± 0.32	1.400	0.169

p<0.05 = *Significant difference

Table 3: Comparison of SGOT levels in before and after administration of Sertraline and Sertraline + Ashwagandha

SGOT (IU/L)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	26.35 ± 10.87	28.32 ± 9.32	0.870	0.386
After	33.55 ± 17.50	28.12 ± 9.53	1.723	0.088
Paired t Test t value	2.231	0.090		
Paired t Test p value	0.0315*	0.928		

p<0.05 = *Significant difference

Table 4: Comparison of SGPT levels in before and after administration of Sertraline and Sertraline + Ashwagandha

SGPT (IU/L)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	22.30 ± 9.59	26.65 ± 12.13	1.779	0.079
After	35.32 ± 36.69	22.72 ± 11.33	2.075	0.041*
Paired t Test t value	2.176	1.449		
Paired t Test p value	0.0357*	0.155		

p<0.05 = *Significant difference

Table 5: Comparison of Alkaline Phosphatase levels in before and after administration of Sertraline and Sertraline + Ashwagandha

Alkaline Phosphatase (U/L)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	95.20 ± 27.93	91.07 ± 20.44	0.754	0.452
After	89.50 ± 30.45	84.50 ± 18.36	0.889	0.376
Paired t Test t value	0.859	1.792		
Paired t Test p value	0.3956	0.080		

p<0.05 = *Significant difference

Table 6: Comparison of Total Protein levels in before and after administration of Sertraline and Sertraline + Ashwagandha

Total Proteins (g/dl)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	7.30 ± 0.43	7.41 ± 0.48	1.080	0.283
After	7.50 ± 0.44	7.26 ± 0.44	2.438	0.017*
Paired t Test t value	2.330	1.341		
Paired t Test p value	0.0251*	0.187		

p<0.05 = *Significant difference

Table 7: Comparison of Albumin levels in before and after administration of Sertraline and Sertraline + Ashwagandha

Albumin (g/dl)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	4.07 ± 0.27	4.12 ± 0.27	0.828	0.410
After	4.04 ± 0.28	3.98 ± 0.58	0.589	0.557
Paired t Test t value	0.515	1.336		
Paired t Test p value	0.6096	0.189		

p<0.05 = *Significant difference

Table 8: Comparison of Globulin levels in before and after administration of Sertraline and Sertraline + Ashwagandha

Globulin (g/dl)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	3.19 ± 0.50	3.28 ± 0.53	0.781	0.437
After	3.47 ± 0.44	3.36 ± 0.44	1.118	0.267
Paired t Test t value	2.712	0.685		
Paired t Test p value	0.0099*	0.497		

p<0.05 = *Significant difference

Table 9: Comparison of Total Bilirubin levels in before and after administration of Sertraline and Sertraline + Ashwagandha

Total Bilirubin (mg/dl)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value

Before	0.50 ± 0.28	0.56 ± 0.34	0.861	0.391
After	0.64 ± 0.45	0.68 ± 0.44	0.402	0.688
Paired t Test t value	1.645	1.357		
Paired t Test p value	0.1080	0.182		

p<0.05 = *Significant difference

Table 10: Comparison of Direct Bilirubin levels in before and after administration of Sertraline and Sertraline + Ashwagandha

Direct Bilirubin (mg/dl)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	0.19 ± 0.10	0.22 ± 0.13	1.157	0.250
After	0.24 ± 0.15	0.25 ± 0.14	0.308	0.758
Paired t Test t value	1.471	0.931		
Paired t Test p value	0.149	0.357		

p<0.05 = *Significant difference

Table 11: Comparison of Indirect Bilirubin levels in before and after administration of Sertraline and Sertraline + Ashwagandha

Indirect Bilirubin (mg/dl)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	0.30 ± 0.18	0.34 ± 0.23	0.866	0.389
After	0.40 ± 0.31	0.43 ± 0.32	0.425	0.671
Paired t Test t value	1.707	1.400		
Paired t Test p value	0.095	0.169		

p<0.05 = *Significant difference

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