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EFFECT OF WITHANIA SOMNIFERA (ASHWAGANDHA) ON LIPID PROFILE PARAMETERS IN MDD (MAJOR DEPRESSIVE DISORDER) PATIENTS WHO ARE ON SERTRALINE.

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ABSTRACT

Aim and Objectives: Aim: To study the effect of administration of sertraline alone and sertraline with ashwagandha on Lipid Profile Parameters in patients with MDD (Major Depressive Disorder). **Objectives:**1. To estimate the effect of sertraline on Lipid Profile Parameters in patients with MDD. 2. To estimate the effect of co-administration of ashwagandha with sertraline on Lipid Profile Parameters. 3. To compare Lipid Profile 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 according to inclusion and exclusion criteria. After enrolling, participants were randomly allocated in either of the groups. One who are taking routine treatment with sertraline (Sertraline Group) and another who are given ashwagandha with their routine treatment with sertraline (Sertraline + Ashwagandha Group). All Lipid Profile 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 Total Cholesterol, Triglyceride, VLDL and LDL were significantly increased. Whereas there was no significant difference in value of HDL. In sertraline + ashwagandha group values of Total Cholesterol and LDL were significantly decreased. Whereas there was no significant difference in values of Triglyceride, VLDL and HDL levels before and after three months of treatment. **Conclusion:** we can conclude prolonged sertraline treatment can derange the lipid profile parameters (Total cholesterol, Triglyceride, VLDL and LDL) and concurrent administration of Ashwagandha can prevent this derangement of lipid profile parameters. However, Sertraline or sertraline + ashwagandha does not have any effect on HDL levels.

KEY WORDS: Antidepressants, Ashwagandha, Depression, Lipid profile, MDD, Sertraline.

INTRODUCTION

Major depression is characterized by symptoms like sad mood, loss of interest and pleasure, low energy, worthlessness, guilt, psychomotor retardation or agitation, change in appetite and/or sleep, melancholia, suicidal thoughts, etc.[1] In India, 197.3 million people suffered mental illnesses in 2017, of which 45.7 million had depression and 44.9 million had anxiety. In 2017, mental illnesses of various severity impacted one in seven Indians. The proportional contribution of mental disorders to

the total disease burden in India has almost doubled since 1990.[2] With a female to male ratio of roughly 5:2, the lifetime prevalence of depression in the general population worldwide is as high as 20%.[3]

Patients with major depressive disorder are commonly treated with antidepressant medications, though in specific circumstances they may also get psychotherapy or counselling. Selective serotonin reuptake inhibitors (SSRIs) are a class of medications used as first-line pharmacotherapy for depression and numerous other psychiatric disorders due to their safety, efficacy, and tolerability.[4] Sertraline is the most frequently prescribed antidepressant agent from SSRIs group to manage and treat social anxiety disorder, premenstrual dysphoric disorder, panic disorder, obsessive-compulsive disorder, and post-traumatic stress disorder.[5]

Dry mouth, insomnia, nausea, headache, diarrhoea / loose stools, agitation, fatigue, tremor are most common acute side effects with the use of sertraline.[6] Also some evidences which suggest that there are metabolic side effects with sertraline due to its prolonged use. Sertaline is an effective and frequently prescribed medication for treating serious depression, appears to have a negative impact on the lipid profile.[7] A clinical study found that sertraline raised levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C).[8]

Withania somnifera is also known as Ashwagandha, Winter cherry and Ginseng. It is an ayurvedic herb from Solanaceae family which utilized for ages in India as an adaptogenic herb to increase general health. In Sanskrit Ashwagandha means ‘the smell of a horse’. This plant's many parts are utilized in herbal medicine.[9] Ashwagandha has so many pharmacological effects on various human systems. It is effective in mental disorders, Parkinson's disease, epilepsy, insomnia, rheumatism, arthritis, erectile dysfunction, depressive disorders, diabetes etc. It has sedative, diuretic, and anti-inflammatory properties, and is wellknown for boosting stamina, endurance, and acting as an adaptogen with potent immunostimulatory and anti-stress effects.[10]

There are some studies available which suggests ashwagandha can reduce various lipids in hyperlipidemic patients and normalize the lipid profile. Withania Somnifera root powder, it can significantly decrease serum cholesterol, triglycerides, LDL (low density lipoproteins), and VLDL (very low-density lipoproteins) cholesterol, showing that the root of W. somnifera is a potential source of hypolipidemic agents.[11]

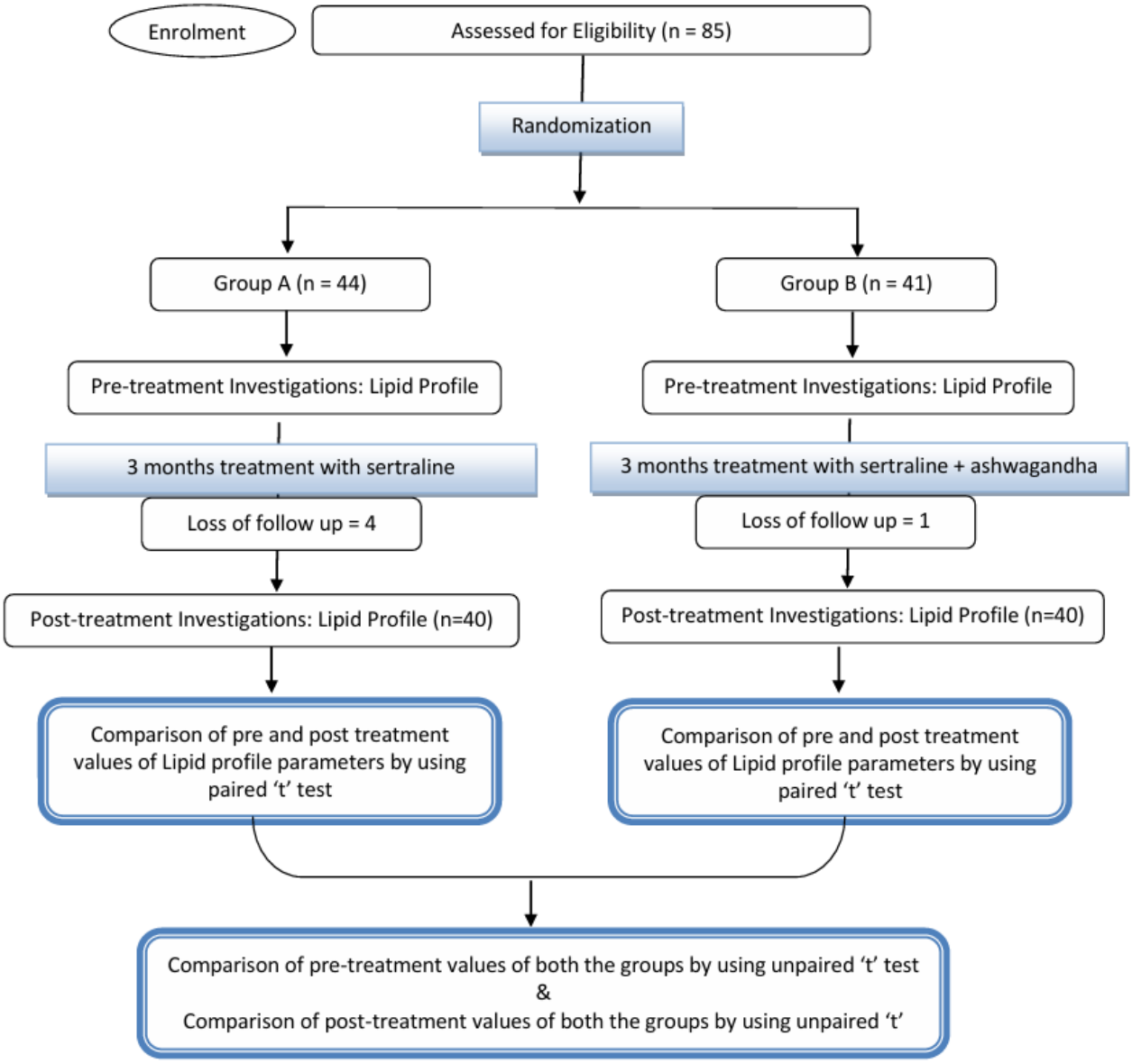
So, in this study we planned to evaluate the effect of sertraline on various parameters of Lipid profile like Total cholesterol, triglyceride, VLDL, LDL and HDL. And effect of combination of sertraline + ashwagandha on these parameters in patients suffering from Major Depressive Disorder (MDD) and compared both the group with each other. The purpose of combining ashwagandha with sertraline is it is having well proven antidepressant activity[12] which can give benefit to MDD patients. And second thing ashwagandha can play protective role to prevent the metabolic changes faced by some patients who are on prolonged treatment with sertraline.

MATERIALS AND METHODS

The present Study was conducted in Psychiatry Department in Krishna Hospital & Krishna Institute of Medical Sciences, Karad after taking the approval from Institutional Ethics committee (IEC). Study was conducted between Feb, 2021 to August 2022. This was an open labelled, randomized, comparative, prospective, interventional study involving 85 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 hyperlipidemia, 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 blood lipid parameters were excluded from this study.
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 total cholesterol – Enzymatic Method, Serum triglyceride – Enzymatic method, Serum HDL-C – Enzymatic method, Serum VLDL – Calculated, Serum LDL-C – 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.



RESULTS

All 80 patients completed a three months of antidepressant therapy. Out of the 80 patients, 43 were males and 37 were females. Comparison of two groups is as following:

In sertraline group, there was significant difference in values of Total Cholesterol, Triglyceride, VLDL and LDL levels before and after three months of treatment with Sertraline and they were significantly increased. Whereas there was no significant difference in values of HDL levels before and after three months of treatment with Sertraline. (Table 1)
In sertraline + ashwagandha group, there was significant difference in values of Total Cholesterol and LDL levels before and after three months of treatment with Sertraline + Ashwagandha and they were significantly decreased. Whereas there was no significant difference in values of Triglyceride, VLDL and HDL 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 lipid profile parameters in sertraline & sertraline + ashwagandha groups before initiation of respective treatment. However, there was significant difference in Total Cholesterol, Triglyceride, VLDL and LDL 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, 4, 5 and 6). Whereas there was no significant difference in values of HDL of two groups after drug treatment (Table 7).

DISCUSSION

Antidepressant drugs are frequently used to treat patients with major depressive disorder. Some of the drugs used to treat depression include SSRIs, SNRIs, MAOIs, tricyclic antidepressants (TCAs), norepinephrine and dopamine reuptake inhibitors.[13] SSRIs are most commonly prescribed first line medication in MDD patients. To treat depression sertraline is one of the most often recommended SSRIs (Selective Serotonin Reuptake Inhibitors) for the treatment of Major Depressive Disorders due to its safety and tolerability. Antidepressant medication therapy will always be ongoing for prolonged period. Despite being a highly safe treatment, it does have some side effects that can arise from its prolonged use. Therefore, it is important to understand Sertraline's long-term side effects.
Numerous studies have shown that sertraline can produce metabolic adverse effects after its long-term use. A clinical study found that sertraline raised levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C)[8] and use of sertraline, fluoxetine and fluvoxamine raised cholesterol levels.[14] In a different study, sertraline and paroxetine raised the levels of low-density lipoprotein cholesterol (LDL-C) in patients with depression.[15] Sertraline increased total cholesterol and LDL-C but had no effect on HDL-C while citalopram increased just HDL-C, and paroxetine increased total cholesterol, HDL-C, and LDL-C levels in patients with panic disorder.[16]
In our observation there was statistically significant difference in values of Total Cholesterol, Triglyceride, VLDL and LDL levels before and after three months of treatment with Sertraline and they were significantly increased whereas there was no significant difference in values of HDL levels before and after three months of treatment with Sertraline. (Table: 3 to 7) In one study by Beyazyüz M et al. have shown in their study that Total cholesterol was significantly increased after treatment with Sertraline for 16 weeks which is matching with our study.[17] In another study by Murat Kesim et al. have shown that Sertraline significantly increased Triglyceride levels after 12 weeks of treatment but Sertraline does not affect HDL-C levels which is known as cardioprotective cholesterol which is also similar findings to our study.[8] Wei F et al. have shown that long-term use of sertraline may have a measurable adverse impact on cardiovascular risk in adults as it was significantly increasing LDL-C levels which is risk factor for atherosclerotic diseases.[15]
In our study, we observed that there was significant difference in values of Total Cholesterol and LDL levels (Table: 3 & 6) before and after three months of treatment with Sertraline + Ashwagandha and they were significantly reduced whereas there was no significant difference in values of Triglyceride, VLDL and HDL levels (Table: 4, 5 & 7) before and after three months of treatment with Sertraline + Ashwagandha. In one study by Raut AA, Rege NN, et al. they have found, there was significant reduction in Total Cholesterol and LDL Cholesterol levels after

administration of Ashwagandha.[18] Our results support the results of above study. While There are no studies available which shows combine effect of Sertraline + Ashwagandha on Lipid Profile.
In a study by Raut AA, Rege NN, et al. showed that total cholesterol, Triglyceride and LDL cholesterol levels significantly decreased which has included healthy volunteers and ashwagandha is given for 30 days, which is exactly the same findings as our study.[18] Ashwagandha extract can considerably lower total cholesterol levels in wistar rats, according to an animal study by Visavadiya et al.[19] Which shows that ashwagandha has significant hypolipidemic activity in terms of Total cholesterol and LDL cholesterol. LDL Cholesterol is responsible for atherosclerotic changes.[20] Therefore, continuous sertraline therapy should be administered with caution to patients who are already at risk for cardiovascular disorders. It demonstrates that Ashwagandha does not lower triglyceride and VLDL levels; rather, it can only prevent triglyceride levels from rising as a result of prolonged Sertraline use.
When we compared HDL levels in Sertraline group and Sertraline + Ashwagandha group there was no significant difference in values of HDL before as well as after respective treatment. In one study Murat Kesim et al. they have found that Sertraline does not affect HDL-C levels which is known as cardioprotective cholesterol.[8] Which reveals that there was no effect of Sertraline as well as Sertraline + Ashwagandha on serum HDL levels. Through a variety of processes, including enhancing reverse cholesterol transport, anti-inflammatory, and anti-oxidant mechanisms, high density lipoprotein cholesterol (HDL-C) is known to protect against the future development of CVD.[21]
An additional risk factor that raises the mortality and morbidity rates in psychiatric patients is dyslipidemia. Some studies have found associations between depressive symptoms and low levels of high-density lipoprotein (HDL) values or high triglyceride levels. Significant correlations between the use of SSRIs and low HDL, elevated total cholesterol, elevated triglyceride levels, and elevated risk for diabetes have been reported.[22] In these conditions if prolonged sertraline treatment is given it can worsen the condition. Addition of ashwagandha in the treatment can play protective role in this condition and prevent this type of dyslipidemia. Another advantage of adding ashwagandha in treatment is Ashwagandha had significant antidepressant action[12] which can be beneficial for depressive patients.

CONCLUSION

From results of our study, we can conclude prolonged sertraline treatment can derange the lipid profile parameters (Total cholesterol, Triglyceride, VLDL and LDL) and concurrent administration of Ashwagandha can prevent this derangement of lipid profile parameters. However, Sertraline or sertraline + ashwagandha does not have any effect on HDL levels.

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

Table 1: Pre and Post treatment levels of Lipid Profile after Sertraline administration.

Sr. No.	Variable	Mean ± SD		t - value	p - value
		Before Treatment	After Treatment		
1.	Total Cholesterol (mg/dl)	162.03 ± 30.98	180.95 ± 28.11	2.694	0.0103*
2.	Triglyceride (mg/dl)	112.58 ± 57.26	182.70 ± 123.58	3.490	0.0012*

3.	VLDL (mg/dl)	24.90 ± 14.32	35.15 ± 25.81	2.218	0.0324*
4.	LDL (mg/dl)	83.12 ± 25.09	97.10 ± 27.72	2.121	0.0403*
5.	HDL (mg/dl)	50.67 ± 8.95	52.80 ± 10.46	0.950	0.3477

p<0.05 = *Significant difference

Table 2: Pre and Post treatment levels of Lipid Profile after Sertraline + Ashwagandha administration.

Sr. No.	Variable	Mean ± SD		t - value	p - value
		Before Treatment	After Treatment		
1.	Total Cholesterol (mg/dl)	161.18 ± 30.47	147.68 ± 23.96	2.593	0.013*
2.	Triglyceride (mg/dl)	108.48 ± 38.76	96.67 ± 30.42	1.708	0.095
3.	VLDL (mg/dl)	24.22 ± 10.26	21.60 ± 12.55	1.001	0.332
4.	LDL (mg/dl)	95.65 ± 31.45	82.40 ± 26.09	2.597	0.013*
5.	HDL (mg/dl)	53.05 ± 9.46	53.6 ± 9.24	0.297	0.767

p<0.05 = *Significant difference

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

Total Cholesterol (mg/dl)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	162.03 ± 30.98	161.18 ± 30.47	0.123	0.901
After	180.95 ± 28.11	147.68 ± 23.96	5.697	<0.001*
Paired t Test t value	2.694	2.593		
Paired t Test p value	0.0103*	0.013*		

p<0.05 = *Significant difference

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

Triglyceride (mg/dl)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	112.58 ± 57.26	108.48 ± 38.76	0.375	0.708
After	182.70 ± 123.58	96.67 ± 30.42	4.259	0.001*
Paired t Test t value	3.490	1.708		
Paired t Test p value	0.0012*	0.095		

p<0.05 = *Significant difference

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

VLDL (mg/dl)	Sertraline Group (n = 40)	Sertraline + Ashwagandha Group (n = 40)	Unpaired t Test	
			t - value	p - value
Before	24.90 ± 14.32	24.22 ± 10.26	0.224	0.807
After	35.15 ± 25.81	21.60 ± 12.55	2.986	0.003*
Paired t Test	2.218	1.001		

t value			
Paired t Test p value	0.032*	0.332	

p<0.05 = *Significant difference

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

LDL (mg/dl)	**Sertraline Group (n = 40)**	**Sertraline + Ashwagandha Group (n = 40)**	**Unpaired t Test**	
			t - value	p - value
Before	83.12 ± 25.09	95.65 ± 31.45	1.970	0.052
After	97.10 ± 27.72	82.40 ± 26.09	2.442	0.016*
Paired t Test t value	2.121	2.597		
Paired t Test p value	0.0403*	0.013*		

p<0.05 = *Significant difference

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

HDL (mg/dl)	**Sertraline Group (n = 40)**	**Sertraline + Ashwagandha Group (n = 40)**	**Unpaired t Test**	
			t - value	p - value
Before	50.67 ± 8.95	53.05 ± 9.46	1.156	0.251
After	52.80 ± 10.46	53.60 ± 9.24	0.362	0.717
Paired t Test t value	0.950	0.297		
Paired t Test p value	0.3477	0.767		

p<0.05 = *Significant difference

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