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AN OBSERVATIONAL CROSS-SECTIONAL STUDY TO ESTIMATE USE OF MODAFINIL /ARMODAFINIL IN PATIENTS ATTENDING PSYCHIATRY OPD OF TERTIARY CARE HOSPITAL IN CENTRAL INDIA

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ABSTRACT **Background:-** Psychiatric patients frequently complains of daytime drowsiness, weakness, lethargy, fatigue due to various psychotropic medications or due to underlying psychopathology. This not only severely impair productivity and performance, but may also have detrimental effects on social functioning and overall quality of life. Modafinil/armodafinil is an effective medication that can be used to overcome these complains.

Material and Method:- An observational cross-sectional study was done at a tertiary care hospital by randomly selecting 111 patients following up in psychiatry opd who were on modafinil/armodafinil for various indications. Specially prepared proforma to collect information including socio-demographic aspects, clinical profile were obtained. Patients were evaluated by using clinical global impression scale,data was pooled, tabulated and statistical analysis was done in terms of frequency and percentage.

Result :- Study showed majority of participants were young, in age group of 21-35 yrs n= 45(40.54). with an average of 40.97 years having average 9.91 years of schooling and average per capita income of 2647.30 rupees. The clinical profile of participants showed majority involvement of patients with schizophrenia n=62 (55.86%) mainly receiving modafinil n=86 (77.48%) at a maximum dosage of 100mg, n= 71 (63.97) used for excessive daytime sedation n= 79 (71.17%). Mean % of improvement of 76 was found and 93.7% participants did not show any side effect to use of modafinil/armodafinil.

Conslusion :- Modafinil/armodafinil is a safe and effective alternative to improve quality of life of patients attending psychiatric OPD with various diagnostic indications Modafinil used in dose of 100 mg for atleast 3months showed more than 70% improvement in drowsiness, fatigue, lethargy like symptoms. Around 97% respondent reported no side effects and minor side effects were successfully treated symptomatically.

KEYWORDS : Modafinil, Armodafinil, Schizophrenia, Daytime sleepiness.

INTRODUCTION:-

Modafinil is a non amphetamine type central nervous stimulant drug[1]. Central nervous system stimulants are the drugs whose primary action is to stimulate the CNS globally or to improve specific brain functions. Modafinil is a psychostimulant that is used for promoting wakefulness in narcolepsy, obstructive sleep apnoea, various psychiatry illnesses, night-shift (call centre) workers and other professionals who want to improve alertness and keep awake[2,3]. It is claimed to increase attention span and improve accuracy compromised by fatigue and sleepiness. Armodafinil is the R enantiomer of modafinil. having longer half life and used for similar indications[4].

Modafinil is the active metabolite of adrafinil and is in use since 2003 as waking drug having a half life of 12 to15 hours. Modfinil is thought to exhibit wake-promoting properties by stimulating release of serotonin, dopamine, and norepinephrine in the cortex [5] . It induces quite waking without rebound sleepiness. It has weak addiction potential and tolerance. Additionally, the lack of euphoria among patients receiving modafinil makes it an attractive option for use in clinical practice [6,7,1] . This makes it unique medicine to normalise excess daytime sleepiness associated with various psychiatric and non-psychiatry conditions and to improve vigilance and cognitive outputs.

Patients attending psychiatry opd frequently complains of daytime drowsiness, weakness, lethargy, fatigue due to various psychotropic medications or due to underlying psychopathology[8]. Fatigue and excess daytime sedation due to any reason not only severely impair productivity and performance, but may also have detrimental effects on social functioning and overall quality of life. Modafinil/armodafinil is an effective medication that can be used to overcome these adverse effect and enhance overall functioning and quality of life of patients with psychiatric condition[9,10]. Only a few Indian studies were found related to modafinil/armodafinil and none studying the effectiveness and its user profile, hence the study was undertaken to estimate the use of modafinil /armodafinil in patients attending psychiatry opd of tertiary care hospital of central India.

MATERIAL & METHODS :-

Study design: This observational cross-sectional study was done at a government run tertiary care hospital and teaching institute amongst patient attending psychiatry opd. Prior institutional ethics committee approval was obtained.

Study Population and sample characteristics:- The sample consist of randomly selected 111 patients following up in psychiatry opd who were on modafinil/armodafinil for various indications, fulfilling the inclusion criteria and who gave consent for participating in the study were assessed.

Inclusion & Exclusion criteria- Patients attending psychiatry opd with any psychiatry illness who were on modafinil/ armodafinil at least for period of 3 months and gave consent for participation in the study. Patient not willing to give consent and patient not having objective data were excluded from the study.

Procedure of study : Specially prepared proforma to collect information including sociodemographic aspects, clinical profile ,diagnosis, indication to start modafinil/armodafinil, duration of treatment ,maximum dosage , improvement, side effect after starting modafinil , if stopped- reason to stoppage of modafinil/armodafinil were obtained by a qualified psychiatrist by personal interview and documentation review. Patients were evaluated by using clinical global impression scale [11] data was pooled, tabulated and subjected to statistical analysis. Statistical analysis was done in terms of frequency and percentage

RESULT :-

In our study sociodemographic profile (Table -1) showed majority of participants were young in age group of 21-35 yrs n= 45(40.54). with an average of 40.97 years having average 9.91 years of schooling and average per capita income of 2647.30 rupees.

Table 1. Sociodemographic Profile

Sr.No		Frequency(n)	Percentage (%)	Mean
1	**Age in years**			
	21-35	45	40.54	40.97±13.69
	36-50	37	33.33	

	51-65	27	24.33	
	66-80	2	1.8	
2	**Years of schooling**			
	< 7	25	22.52	9.91±3.37
	8- 10	44	39.64	
	11-12	20	18.02	
	>12	22	19.82	
3.	**Employment**			
	Unemployed	34	30.63	
	Self employed	27	24.32	
	Service	19	17.12	
	Housewife	31	27.93	
4.	**Per Capita Income (Rupees)**			
	<2000	61	54.95	**Mean**
	2000-4000	38	34.25	2647.30±1694.23
	4000-6000	5	4.5	
	6000-8000	5	4.5	
	8000-10000	2	1.8	

The clinical profile (Table-2) of participants showed majority involvement of patients with schizophrenia n=62 (55.86%) receiving mainly receiving modafinil n=86 (77.48%) at a maximum dosage of 100mg n= 71 (63.97) used for excessive daytime sedation n= 79 (71.17%). Mean % of improvement of 76 was found and 93.7% participants did not show any side effect to use of modafinil/ armodafinil.

Table 2 :- Clinical Profile of Patients receiving Modafinil /Armodafinil

1.	**Diagnosis**	**Frequency (n)**	**Percentage (%)**
	Schizophrenia	62	55.86
	Major Depression	31	27.93
	Bipolar Mood Disorder	7	6.31
	Anxiety Disorder	3	2.7
	Obsessive Compulsive Disorder (OCD)	2	1.8
	Panic Disorder	3	2.7
	Somatic Symptom Disorder	2	1.8
	Behavioural and psychological symptoms of Dementia (BPSD)	1	0.9
2.	**Drug Used**		
	Modafinil	86	77.48
	Armodafinil	25	22.52
3.	**Maximum Dose of Modafinil**	**Frequency**	**Percentage**
	100mg	71	63.97
	200mg	15	13.51
	Maximum Dose of Armodafinil	Frequency	Percentage
	50mg	7	6.3
	150mg	18	16.22
4.	**Indication**		
	Excess Daytime Sleepiness	79	71.17
	Lethargy	15	13.51
	Fatigue	5	4.5
	Augmentation to Antidepressant	9	8.12
	Lack of Attention	3	2.7
5.	**Duration of Treatment**	3	2.7
	3-6 Months	58	52.25
	6-9 Months	10	9.01
	9-12 Months	29	26.13
	>12 Months	14	12.61
	Mean	9.15±6.87	
6.	**% Improvement reported**		
	75-100	65	58.56
	50-75	38	34.23
	25-50	8	7.21
	<25	0	0
	Mean 76%±18%		
7.	**Side Effect**		
	Nil	108	97.3
	Headache	1	0.9
	Mental Weariness	1	0.9
	Slurring of Speech	1	0.9

DISCUSSION :-

In our study majority of respondents 45 (40.54%) were in the age group 21-35 years, Only 2 (1.8%) were in the age group of 66-80 years. The mean age of study population was 40.97±13.69 years. In a study conducted by Kaplan S et al [12] on study of modafinil and risk of cardiovascular effects, majority of population was in younger age group with mean age of study population was 39±14.2 years with very less population beyond 60 years and less than 18 years. This signifies the prescribing pattern of modafinil/ armodafinil in younger working population and avoidance in extremes of age group probably due to risky cardiovascular side effect.

Education of respondents was noted in the form of years of schooling. Mean years of schooling of the study population were 9.91±3.37. Majority of respondent in study i.e. 44(39.64%) were educated for 8 to 10 years ,25(22.52%) respondents were educated for 7 years or less and very less number were educated for 12 or more years. In a government hospital in India, the health services are mostly availed by patients from poor socioeconomic background with low educational qualification and very small number of patients come from upper socioeconomic background.

Majority of respondent who participated in study 34(30.63%) were unemployed, 31(27.93%) were housewives, 27(24.32%) were self-employed, followed by 19(17.12%) who were in service. This may be because of various factors. Participants in the study were having sever mental illness like schizophrenia, major depression, bipolar disorder, ocd. The disease may be affecting the capacity of that individual to work. Some were not working owing to excess daytime sedation. This explains majority of participants in the study being unemployed or involved in less cognitively challenging work.

Mean per capita income of study population was 2647.30±1694.23 rupees. Of all th participants 61(54.95%) respondent were having per capita income below rupees 2000, and only 2(1.8%) having per capita income rupees 8000-10000. This again indicates that in a government hospital in India, the health services are mostly availed by patients from poor socioeconomic background with low educational qualification and a smaller number of patients come from upper socioeconomic background.

As seen in Table 2 ,amongst the study participants 62(55.86%) respondent were diagnosed as schizophrenia, 31(27.93%) as major depression, 7 (6.31) as bipolar mood disorder, 3(2.7%) as anxiety disorder, 3(2.7%) as panic disorder, 2(1.8%) as OCD, 2(1.8%) as somatic symptom disorder and 1(0.9%) as BPSD. Use of modafinil in psychiatric patients has been studied by Spence, S. A.et al (2011)[13]. who had studied use of modafinil in chronic schizophrenia patients showing modafinil modulating anterior cingulate gyrus in these patients. In other study by Calabrese, J. R. et al (2010) [14] modafinil was used as an adjuvant in bipolar depression to demonstrated significantly greater improvement in depressive symptoms. There were no Indian studies showing use of modafinil/armodafrinil in various psychiatric conditions. Our study outlines use of modafinil/ armodafinil in other common mental illness like anxiety, ocd, panic and somatoform disorder and BPSD.

Various researchers have studied use of modafinil in non psycgiatric disorders like Shangyan H., Kuiqing L (2017) [15] studied effect of modafinil on fatigue in multiple sclerosis. Lillicrap, T. P .et al (2018)[16] studied use of modafinil to improve quality of life in stroke survivors. Another study done by Roth T. et al (2006) [17] on use of armodafinil in obstructive sleep apnoea syndrome, Battleday R.M. et al (2015)[18] , Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects and found very encouraging results.

Table 3. Frequency distribution of respondent according diagnosis and indication for modafinil/armodafinil

Indication	**Excess Daytime Sleepiness n (%)**	**Lethargy**	**Fatigue**	**Augmentation to Antidepressant**	**Lack of Attention**	**Total**
Diagnosis						
Schizophrenia	59(95.16)	3 (4.84)	0	0	0	62
Major Depression	9 (29.03)	8(25.81)	4(12.90)	9 (29.03)	1 (3.23)	31
Bipolar Mood Disorder	7(100.00)	0	0	0	0	7

Anxiety Disorder	1 (33.33)	2(66.67)	0	0	0	3
Obsessive Compulsive Disorder	1 (50)	0	0	0	1(50)	2
Panic Disorder	1 (33.33)	1 (33.33)	1(50)	0	1 (33.33)	3
Somatic Symptom Disorder	1(50)	0	0	0	0	2
Behavioural and psychological symptoms of dementia (BPSD)	1(100.00)	0	0	0	0	1
Total	79(71.17)	15(13.51)	5(4.50)	9 (8.11)	3 (2.71)	111

In our study out of 111 respondents studied ,79(71.17%) respondent received modafinil/ armodafinil for excess daytime sleepiness, 15(13.51%) respondent received for lethargy, 9(8.12%) received for augmentation to antidepressants, 5(4.5%) received for fatigue, followed by 3(2.7%) for lack of attention. Of those 79(71.17%) respondent received modafinil/armodafinil for excess daytime sleepiness majority were patient of Sever mental illness namely 59(95.16%) schizophrenia, 9 (29.03%) patients of major depression,and . 7(100%) patients of bipolar disorder patients . Whereas patients with Common Mental Illness rarely received modafinil/ armodafinil for excess daytime sedation. This might be due to use of high dosage and sedating medication and need for rapid control of aggressive symptoms.

Even after extensive search we were unable get studies done in India and abroad for comparison which studied use of modafinil in for various indications like excess daytime sleepiness, fatigue, lethargy, augmentation to antidepressants etc.

Mean duration of treatment of study population was 9.15±6.87 months. Maximum duration was 48 months and minimum were 3 months.In a study done by Roth T. et al (2006) [17] on use of armodafinil in obstructive sleep apnoea syndrome, respondent were assessed for 12 week

Table 4 :- Frequency distribution of respondent according to CGI scale assessment

Efficiency by CGI Scale	Description	Frequency	Percentage
1	Very Much Improved	65	58.56
2	Much Improved	38	34.23
3	Minimally Improved	8	7.21
4	No Change	0	0
5	Minimally Worse	0	0
6	Much Worse	0	0
7	Very Much Worse	0	0

As per table 4 CGI- impression scale was used for assessing improvement. 65(58.56%) respondent reported "very much improvement (score 1)", 38(34.23%) respondent reported "much improvement (score 2)", 8(7.21%) reported "minimal improvement (score3)". No patient reported worsening of symptoms.

In a study conducted by Spence, S. A. et al (2005) [13] where modafinil was studied in patient of chronic schizophrenia for improving cognitive functions (working task memory). Patient reported significant improvement in working memory on modafinil. In another study done by Roth T. et al (2006) [17] on use of armodafinil in obstructive sleep apnoea syndrome,showed significant improvement in sleepiness, fatigue and cognitive activities and no worsening of symptoms. In study by Calabrese, J. R. et al (2010) [14] on use of modafinil as an adjuvant in bipolar depression, showed improvement in depression and did not show any worsening or development of any other symptom.

Mean percentage improvement of study population was 76%±18%. Of all 65(58.56%) respondent reported 75-100% improvement, 38(34.23%) respondent reported 50-75% improvement, 8(7.21%) respondent reported 25-50% improvement and no patient reported worsening of symptoms.

As per table 2, majority respondent i.e. 108(97.3%) respondent reported no side effects,and only 1(0.9%) respondent reported headache,mental weariness and slurring of speech on high dosage i.e.200mg of modafinil. Which responded well to reduction of dosage. Thus Modafinil was found to be effective and showed minimal side effect.

Only single case of acute Psychosis was reported in study conducted by Spence, S. A.et al (2005) [13] where modafinil was studied in patient of chronic schizophrenia for improving cognitive functions. Similarly study by Billiard M. and Broughtonb R.(2018) [19], stated that modafinil has never been shown to develop tolerance and side effects are very few, generally due to prolong use or abuse. A study done by Alacam H. et al (2016) [20] on modafinil dependence it was stated that modafinil use in ADHD patients may lead to dependence and abuse. No respondent stopped taking modafinil/armodafinil during or before assessment as per a study on overexposure of modafinil by Kristin A. et al[21] in 2014, no death was reported due to overexposure of modafinil.

Those who have received modafinil/armodafinil for 3 months or more were studied for improvement. Majority respondent reported significant improvement ranging from 70% - 100%.And 16 respondent out 111 reported 100% improvement.

CONCLUSION

In current study, we found that modafinil/armodafinil was used in almost all major psychiatric disorders for various indications. Most common indication of use was for excess daytime sedation due to use of psychotropic medications. Many were patients of depression who were started on modafinil/armodafinil as augmenting agent, for chronic fatigue and lethargy. Our study showed that modafinil used in dose of 100 mg for atleast 3months showed more than 70% improvement in drowsiness, fatigue, lethargy like symptoms. Around 97% respondent reported no side effects and minor side effects were successfully treated symptomatically.

Excess daytime sedation in patients on psychotropic medications is a common side effect. Many patients become noncompliant to treatment because of excess sedation. It also interferes in their socio-occupational performance. Psychotropic medicine though helps the patient to come out of illness, excess sedation decreases quality of life. Some patients who are on antidepressants doesn't show improvement even after full trial of antidepressants. In such cases, modafinil/ armodafinil is safe and effective way to deal with these problems. It not only improves wakefulness but also improves cognitive performance and helps to increase compliance to psychotropic medications. Thus modafinil/armodafinil is a safe and effective alternative to improve quality of life of patients attending psychiatric OPD with various diagnostic indications.

Limitations

Study was conducted in one government hospital with as small sample size hence study cannot be generalized. Childhood population was not studied in the current study. So whether to use modafinil/armodafinil in adolosent psychiatric patients is not clear. Likelihood of abuse potential in patient with psychiatric disorder was not assessed in current study.

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