

A Placebo Controlled Trial on Add-on Modafinil on the Anti-psychotic Treatment Emergent Hyperglycemia and Hyperlipidemia

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ABSTRACT

Modafinil is non stimulant drug which is marketed for mainly Narcolepsy and daytime drowsiness. The clinical experience and Summary of Product Characteristics (SPC) of the drug also mentions Anorexia as one of the side effects. Anorexia can have a direct impact on the carbohydrate and fat intake, which may, in turn, regulate antipsychotic induced dyslipidemia and Hyperglycaemia. **Aim:** To compare the effects of Modafinil- ADDON with Placebo add on with olanzapine, Clozapine and Risperidone in drug naive subjects and people who were started on the drugs within 15days of assessment. **Materials and Methods:** Randomized, Double blind, Placebo controlled study, which was conducted at two centres, one at department of Psychiatry, S.V Medical College, Tirupati and the other at Asha hospitals, Hyderabad. Seventy two patient were randomised, sixty three patients have completed the total study period of three months. The dose of Modafinil was 200 mgs constantly as Flexible doses of Olanzapine, Clozapine and Risperidone as per clinical need was given. A baseline, three week and twelve week assessments of Fasting blood Glucose and fasting Serum cholesterol were made and the groups were compared on these parameters. **Results:** From baseline to week 3 there was a significant raise in Fasting serum cholesterol followed by a fall from week 3 to week 12 in the Modafinil addon group, though it could not be considered a drug for hypercholesteremia like Statins in controlling hyperlipidaemia. The implications of these findings were discussed.

Key words: Atypical anti-psychotic, clozapine, dyslipidemia, glycemic dysregulation, metabolic syndrome, modafinil

INTRODUCTION AND REVIEW OF THE EXISTING LITERATURE

Since, the introduction of conventional antipsychotics in the treatment of various psychotic disorders in late 1950's quest for better molecules continued. The

reasons for the betterment resulted in the introduction of second generation antipsychotics (SGA's), which are supposed to be more patient friendly with lesser extra pyramidal symptoms lesser chances of inducing tardive dyskinesia and better impact on affective, cognitive and negative symptoms of schizophrenia. The initial enthusiasm about SGA's within 5 years had settled down toward skeptical optimism to control the unwanted and potentially endangering metabolic side-effects.^[1-7]

Among the newer drugs except for aripiprazole and to some extent ziprasidone all other drugs produce significant weight gain and predispose the individual for hyperglycemia and hyperlipidemia. The land mark

Access this article online	
Website: www.ijpm.info	Quick Response Code 
DOI: 10.4103/0253-7176.130982	

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study on antipsychotic efficacy, safety and tolerability namely CATIE study had clearly shown that 74% of patients discontinued the treatment before 18 months of trial.^[6] Intolerability was one of the major reason for the discontinuation, weight gain and metabolic effects with olanzapine was established in phase II, part of the study. However, the trend for metabolic syndrome is also noticed with clozapine, risperidone and olanzapine and to some extent with quetiapine, ziprasidone.^[4]

Modafinil is a novel, non-amphetamine psychostimulant though it is not a typical sympathomimetic amine and has only weak affinity for dopamine uptake carrier site. It also acts on anterior hypothalamic nucleus and adjacent area. It is currently being promoted for excessive daytime sleepiness that occurs in narcolepsy and also sleep apnea. In 5% of cases it is known to produce anorexia and increase the alertness.

As this drug also has got anorexia and weight loss as adverse events, it would be worthwhile to see, whether add-on therapy of modafinil with atypical, especially olanzapine, risperidone, clozapine (widely prescribed atypical in India) would in any way influence the metabolic side-effects such as hyperglycemia and hyperlipidemia (Summary of Product Characteristics of modafinil).^[8]

MATERIALS AND METHODS

Objectives

Primary objective

1. To evaluate the effect of add on modafinil therapy on fasting blood glucose (FBG) and serum cholesterol levels in patients receiving olanzapine, risperidone or clozapine as compared with placebo add-on.

Secondary objectives

1. To evaluate the tolerability of modafinil.
2. To study whether modafinil affects the efficacy of atypical antipsychotics.

Study sample

At baseline there were 72 patients, out of that only 63 completed the total study period. All patients after fulfilling the inclusion and exclusion criteria were taken into the study. Written Informed consent was obtained after explaining the study procedure in detail. They were given the choice to voluntarily withdraw from the study without ascribing any reason. The institutional ethics committee had accorded approval for the study.

Inclusion criteria

1. Any sex, aged above 18 years.

2. Patients who were on atypical antipsychotics namely risperidone or olanzapine or clozapine for less than 2 weeks, irrespective of diagnosis.
3. Those patients who could read and understand the informed consent form (ICF).

Exclusion criteria

1. History of consuming any anti-obesity drugs or following weight reduction regimens.
2. History of having taken atypical antipsychotics for more than 3 months in the last past 5 years.
3. History of any co-existing metabolic illness including all endocrinal disorders.
4. History of patients consuming corticosteroids, anabolic steroids and oral contraceptive pills.
5. History of dual diagnosis on axis I on Diagnostic and statistical manual (DSM)-IV
6. Prolonged history of concomitant use of sedatives or tranquilizers.
7. When patient was kept on a mood stabilizer or an antidepressant.
8. Patients who were highly uncooperative, destructive or suicidal.
9. Patients who were stuporosed or required electroconvulsive therapy.

Scales used in the study

Efficacy assessment scales

mainly carried out to find out whether modafinil interfered with the therapeutic effect of atypical antipsychotic on psychoses.

1. Brief psychiatric rating scale (BPRS).
2. Clinical global impression (CGI).

Biochemical assessments

FBG assessment was carried out at the local laboratory by using a fasting glucose estimation kit, which uses a technique called glucose oxidase-peroxidase enzyme method. In which enzyme peroxides is used to estimate the glucose level.

For fasting cholesterol estimation also readymade kit called CHOD-PAP kit for the estimation of total cholesterol and PRE-CHOD-PAP kit for high density lipoprotein-cholesterol estimation were used. Same kits were used throughout the study period.

Methodology

After selection of the subjects, who fulfilled the exclusion and inclusion criteria were explained the nature of the possibility of participation in the study highlighting their contribution to explore adverse events of some of the drugs prescribed for their ailments. Once they had understood and accepted the implications of the study in detail, a written informed consent was obtained. After

signing the ICF, the patient was randomized either to modafinil or placebo, which was performed by the third party, which manufactured and supplied the placebo.

The assessments were carried out again at week 3 and week 12. The doses of olanzapine, risperidone and clozapine were kept flexible according to patient clinical condition. The dose of modafinil was kept fixed at 200 mg.

Tolerability of modafinil

All the adverse events those occurred during the study period were promptly noted and required action was taken. Deviation from the treatment protocol was noted. Whenever, there was a risk to patient the doses were altered. Patient safety was kept in mind throughout the period of the study. Only those cases that have completed the 12 weeks study were taken up for statistical assessment. The reasons for the deviations and dropouts were evaluated separately.

Statistical methods

After unblinding the data was coded. Analysis of data was performed by using the Statistical Package for Social Sciences 10.0 version. The placebo group and the modafinil group characteristics were made out by using the descriptive statistics such as frequencies, means and standard deviations. Non-parametric statistics like paired *t* test was used, for within the group comparisons at baseline, at the end of the study and between the groups comparison.

OBSERVATIONS

The total number of patients, who had signed the written ICF during the recruitment period and accepted to participate in the study from two centers in Tirupati and Hyderabad, amounted to 72. They were randomly assigned to either modafinil or placebo as add-on for a period of 12 weeks. At the end of the study, it was found that only 63 completed the study protocol and considered for the analysis. They were analyzed on socio-demographical, disease related, physical and sleep parameters for the period of the study.

- Patients completed the total study period — 63.
- Patients who did not completed the study — 9.

Out of nine patients who did not complete the protocol the reasons for non-completion were ascertained as far as possible.

Common causes for the non-completion

Reason	Placebo	Modafinil
Exacerbation of psychosis — one	0	1
Patients lost to follow-up — two	1	1
Headache — four (mild in severity)	1	3
Trouble falling asleep — two	0	2

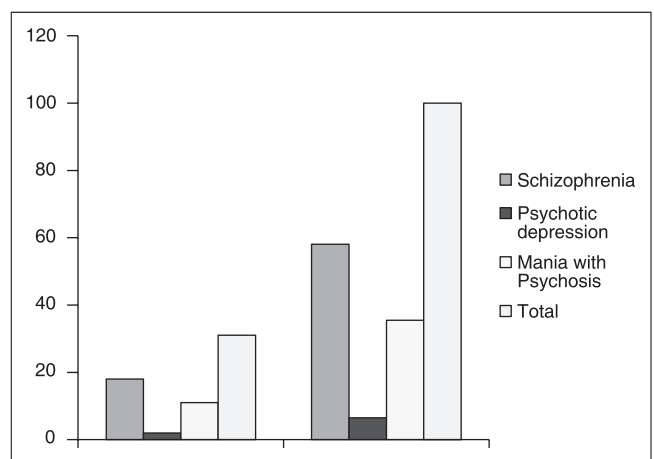
Among the completed patients, the analysis was carried out on these two groups of placebo and modafinil to test the hypothesis [Tables 1-9].

The population of placebo group and modafinil group did not differ in any statistically significant manner on the following socio-demographic parameters namely, age, sex, socioeconomic status, marital status and education.

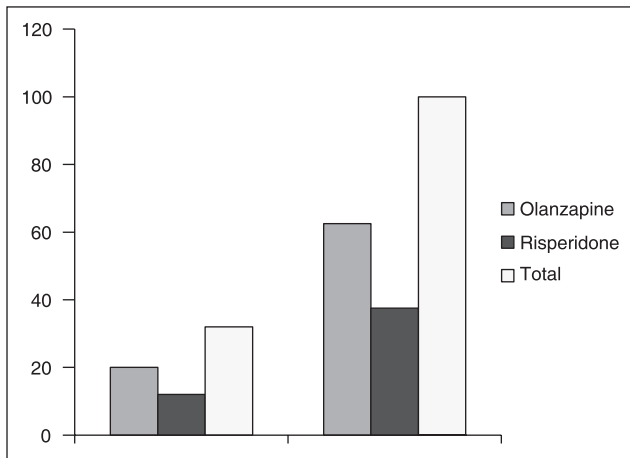
Both the groups did not vary significantly on clinical diagnosis or doses of atypicals as per the tables given below:

Diagnosis (modafinil group)	Frequency	Percent
Schizophrenia	18	56.3
Psychotic depression	5	15.6
Delusional disorder	2	6.3
Acute psychosis	3	9.4
Mania with psychosis	4	12.5
Total	32	100.0

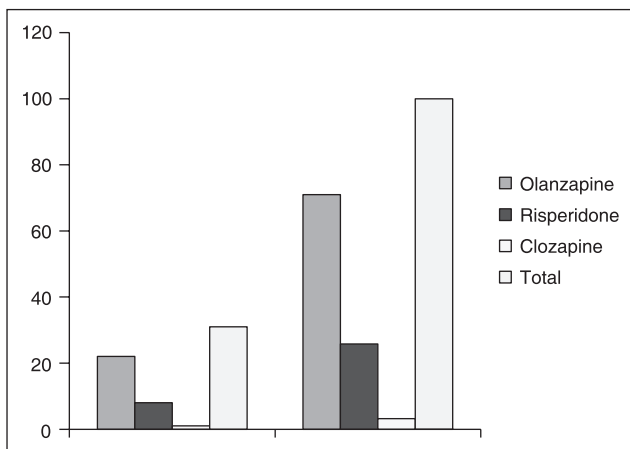
Diagnosis (placebo group)	Frequency	Percent
Schizophrenia	18	58.1
Psychotic depression	2	6.5
Mania with psychosis	11	35.5
Total	31	100.0



Antipsychotic used (modafinil group)	Frequency	Percent
Olanzapine	20	62.5
Risperidone	12	37.5
Total	32	100.0



Antipsychotic used (placebo group)	Frequency	Percent
Olanzapine	22	71.0
Risperidone	8	25.8
Clozapine	1	3.2
Total	31	100.0



Base line parameters of modafinil and placebo groups

From Tables 10 and 11, it was obvious that there was no difference between groups on baseline efficacy group parameters.

Comparison of efficacy parameters between modafinil group and placebo group at the end of week 12 compared to baseline on BPRS and CGI values

Description	Paired differences mean	SD	Significance
BPRS in modafinil group at baseline versus week 12	-82	9-33	-721 not significant
CGI at baseline versus week 12	-3529	8618	-111 not significant

BPRS–Brief psychiatric rating scale; CGI–Clinical global impression; SD–Standard deviation

This showed that modafinil did not interfere with the anti-psychotic efficacy throughout the period of study.

Table 1: Fasting blood sugar: Baseline

Groups	Value	Standard deviation	Significance
Placebo group (n=31)	88.5	14.729	0.114
Modafinil group (n=31)	78	31.777	Not significant

Fasting blood sugar levels at the entry into the study did not differ significantly between the groups

Table 2: Fasting blood sugar: Differences between baseline and week 3 between the groups

Baseline to week 3	Paired differences		Significance
	Mean	SD	
Placebo	-0.7000	17.3785	0.859
Modafinil			Not significant

SD – Standard deviation

Table 3: Between the baseline to week 12 fasting blood sugar

Baseline to 12 week comparison	Paired differences		Two tailed significance
	Mean	SD	
Placebo	0.82	9.33	0.721
Modafinil			Not significant

There were no significant differences when blood glucose levels were compared between the placebo and modafinil groups at both at week 3 and week 12; SD – Standard deviation

Table 4: Fasting blood sugar comparison within the group throughout the study: In the placebo group

Description	Mean	SD	Significance
Between baseline to week 3	-0.6000	18.3576	0.872*
Baseline to week 12	4.4091	19.4316	0.299*

*It showed that in the placebo group throughout the study there were no changes noticeable in the group from baseline to week 12; SD – Standard deviation

Table 5: Fasting blood sugar comparison within the group throughout the study: In the modafinil group

Description	Mean	SD	Significance
Between baseline to week 3	-2.2000	15.3487	0.480*
Baseline to week 12	-8.1600	36.8835	0.480*

*It again showed even in modafinil group throughout the study there were no noticeable changes from baseline to week 12; SD – Standard deviation

Table 6: Fasting serum cholesterol: Baseline

Groups	Value	Standard deviation	Significance
Placebo group	154.78	18.94	0.661
Modafinil group	152.25	22.51	Not significant

Fasting serum cholesterol levels at the entry into the study did not differ significantly between the groups.

Table 7: Serum cholesterol: Comparison between the groups from baseline to week 3 and week 12 paired differences using paired t-test

Description	Comparison	Mean	SD	Significance
Baseline to week 3	Placebo	6.800	41.3274	0.471*
	Modafinil			
Baseline to week 12	Placebo	-2.1111	38.3925	0.818*
	Modafinil			

*There were no significant changes in the serum cholesterol when measured at week 3 and week 12 in comparison with baseline values, between the placebo and modafinil groups; SD – Standard deviation

Table 8: Serum cholesterol comparison from baseline to week 3 and week 12 within the placebo group as opposed to modafinil group

Placebo group	Mean	SD	Significance
Baseline to week 3	-4.8750	30.4493	0.441*
Baseline to week 12	-8.5500	34.5002	0.282*

*In the placebo group there were no differences as compared with baseline with either week 3 or week 12; SD – Standard deviation

Table 9: Serum cholesterol comparison from baseline to week 3 and week 12 within the placebo group as opposed to modafinil group

Modafinil group	Mean	SD	Significance level
Baseline to week 3	-13.3600	20.3713	0.003**
Baseline to week 12	-8.1200	22.6593	0.086**

**In the modafinil group, there were statistically significant differences between baseline to week 3 when serum cholesterol levels raised and by week 12 the levels fell down in a significant manner

Table 10: Mean and SD of modafinil group efficacy rating scales (base line)

Efficacy rating scales	N	Mean	SD
BPRS	32	38.47	8.84
CGI	32	3.38	0.75

BPRS – Brief psychiatric rating scale; CGI – Clinical global impression; SD – Standard deviation

Table 11: Mean and SD of placebo group efficacy rating scales (base line)

Efficacy rating scales	N	Mean	SD
BPRS	31	38.00	12.04
CGI	31	3.35	0.98

BPRS – Brief psychiatric rating scale; CGI – Clinical global impression; SD – Standard deviation

DISCUSSION

Impact of modafinil on resolution of psychotic features

From the results, it was obvious that modafinil no way interfered with antipsychotic action of the drug. It was proved by the significant improvement of BPRS and CGI-S scores when compared from baseline to week 3

and also at end of the study that was at week 12. There was no significant difference between placebo and modafinil in improving the psychotic features. It clearly proves that modafinil did not have any potential to exacerbate the psychosis. Hence in conclusion, modafinil could be safely administered with atypical antipsychotics.

Common adverse events noted in the study period

During the total 12 weeks of study period only few adverse effects were noted, which were only mild in intensity and resolved on their own over a period of time. Following were the adverse events noted:

Headache, disturbed sleep, mild gastro intestinal difficulties, agitation and decreased appetite.

None of these adverse events required any active intervention. There was only one case of re-emergence of Mania in the study. The blind was broken and when patient was found to be on modafinil, he/she was taken away from the study. Later it was found out that it could have been due to poor compliance and after admission and reinstatement of the anti-psychotic regimen the illness remitted successfully. This finding is unlike what was observed with anti-obesity drugs.^[8,9]

Impact of modafinil on fasting blood sugar and fasting serum cholesterol

In this study, an attempt was also made to correlate; weight loss achieved with modafinil could be translated into biochemical terms. In fact that FBG does not showed any significant change in both groups. However, FSC showed significant changes in patients with modafinil group. From baseline to week 3, there was a significant raise in FSC and from week 3 to week 12 again there was a fall in FSC. Similar biochemical changes that could be possible due to the direct effect of the modafinil are not available. Hence, modafinil could not be considered a drug for hypercholesterolemia like statins in controlling hyperlipidemia.

Though topiramate was tried a some of the drugs to control antipsychotic induced obesity, no studies were available, which studied agents controlling hyperglycemia and hyperlipidemia associated with antipsychotic usage.^[8]

Though fenfluramine, amantadine and roboxetene a Nor Epinephrine (NE) specific reuptake inhibitor could be potential candidates there role would be limited as they could either worsen psychotic features and may produce a manic shift in bipolar disorders.^[9]

In this study, no attempt was made to measure any cognitive changes with modafinil in comparison to placebo as the population constituted the multiple

diagnoses and more than one antipsychotic; already some studies are in progress which is looking at modafinil as a cognitive enhancer in schizophrenia.

In conclusion, the results of this study suggest that modafinil even at a dosage of 200 mg is efficacious adjuvant treatment in controlling atypical antipsychotic induced weight gain and some of the metabolic parameters. It was found to be well-tolerated without major side-effects. Further clinical research is necessary to prove the fact that modafinil is an effective add on therapy. A higher dose of modafinil should also be explored in those who could tolerate it.

CONCLUSIONS

Present study was a randomized, placebo controlled trail, using a double-blind technique. Findings point out the modafinil could be a potential candidate in selected group of patients to decrease some of the unwanted adverse events such as weight gain, daytime drowsiness and metabolic syndrome produced by atypicals. However, as the sample size was small and many atypicals were included and the population studied was not homogeneous for the duration of drug therapy and as the study duration was 12 weeks, this study finding definitely requires future replication.

In the light of present findings a multi-center randomized study using a good comparator like topiramate, which had proven efficacy in decreasing weight have to be under taken, using a bigger sample.

Limitations of the study

This was a convenient sample.

Consented people, at least few of them were more motivated and modafinil might have motivated them to change their food habits and life-style.

A large sample than this concentrating on one atypical drug would have decisively answered the hypothesis.

Crossover at the end of 12 weeks from placebo to modafinil and vice versa for the next 12 weeks would have strongly established the role of modafinil as a useful adds on.

No active comparator was used as a third arm to make sure that changes with modafinil were not apparent.

The dosage of modafinil was fixed in the study. A flexible dosage ranges higher than 200 mg might have further influenced the outcome of the study.

The improvement in psychosis, might have contributed as body image changes were not studied between the groups.

Drug attitude inventory could not be applied – hence acceptability of modafinil as an add-on could not be studied.

ACKNOWLEDGMENT

The author acknowledged all the help rendered by M/S Sun Pharmaceuticals for their interest and co-operation.

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How to cite this article: Prasuna PL, Vijay Sagar KJ, Sudhakar TP, Rao GP. A placebo controlled trial on add-on modafinil on the anti-psychotic treatment emergent hyperglycemia and hyperlipidemia. *Indian J Psychol Med* 2014;36:158-63.

Source of Support: Nil, **Conflict of Interest:** This study was funded partially for provision of placebo and look alike modafinil tablets by M/S Sun Pharmaceuticals, Mumbai and expenditure incurred toward biochemical centers for all the subjects had been reimbursed by the same company.