Impact of Modafinil Add-on with Atypical Anti-psychotics on Excessive Daytime Drowsiness

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ABSTRACT

Background: Atypical antipsychotic drugs are known to cause many side effects which include daytime drowsiness. So many add on drugs are tried to reduce the same. Materials and Methods: 72 patients who were on atypical antipsychotic drugs were randomly assigned to either Modafinil or placebo and were followed for a period of 12 weeks. Daytime drowsiness, was taken at baseline, week 3, and at week 12 by using VAS, EDD scales. Results: The results were analyzed and showed that the Modafinil add on therapy significantly reduced the daytime Drowsiness. Conclusions: Modafinil could be a potential candidate in selected group of patients to decrease some of the unwanted adverse events like daytime drowsiness produced by atypical antipsychotics.

Key Words: Atypical antipsychotic drugs, Daytime drowsiness, Modafinil, Visual Analogue Scale, Adverse events

INTRODUCTION

Since the introduction of conventional anti-psychotics in the treatment of various psychotic disorders in late 1950’s, the quest for better molecules continued. The reasons for the betterment resulted in the introduction of second generation anti-psychotics (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 the schizophrenia. The initial enthusiasm about SGA’s within 5 yrs had settled down towards skeptical optimism to control the unwanted and potentially endangering metabolic side-effects.

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. They also produce significant daytime drowsiness, which interferes with patients’ daily occupational activities.

The landmark study on anti-psychotic efficacy, safety, and tolerability namely CATIE study had clearly shown that 74% of the patients discontinued the treatment before 18 months of trial. Intolerability was one of the major reasons for the discontinuation; weight gain and metabolic effects with Olanzapine were 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.

The other major side-effect that discourages the patient to continue the treatment is the daytime drowsiness. Though with dose titration, this side-effect can be minimized, most of the patients do not continue the treatment because it interferes with their daytime work performance. To improve the compliance with atypical anti-psychotics and to give the patients a better
quality of life, it becomes imperative that we should find various strategies including pharmacotherapy and diet control.

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 in sleep apnea. In 5% of cases, it is known to produce anorexia and increase the alertness.

In this study, an attempt is made to explore whether a non-amphetamine drug like modafinil would help in reducing daytime drowsiness.

**Review of literature**

**Atypical anti-psychotics versus conventional anti-psychotics**

Conventional antipsychotic agents which have been the mainstay of treatment in schizophrenia and other psychotic disorders for over 40 years have a number of limitations. This had prompted a search for new agents with greater efficacy and fewer side-effects. So, the serotonin dopamine antagonists (SDA) (Janssen et al., 1988) came into the practice, which is at present the mainstay of treatment in patients with schizophrenia and other psychoses.

But, atypical anti-psychotics are also not without side-effects. Atypicality mainly refers to infrequent occurrence of extrapyramidal syndromes in clinical setting. During recent years, it was found that akathisia is still common and tardive dyskinesia is also not uncommon with atypical drugs as earlier thought. Hence, second generation anti-psychotics would be a better name that was suggested for this group of drugs.

Atypicals are not without other unwanted side-effects. Most of the patients commonly gain weight to abnormal and unwanted proportions (Allison et al.). They also experience excessive daytime drowsiness. The estimated prevalence of obesity in this population is three-fold to that of the general population (Coodin S, 2001). An unhealthy diet and lifestyle, environmental factors, negative syndrome, and direct effects of anti-psychotic medication may predispose schizophrenics to weight gain.

Most of the patients on atypical anti-psychotic like olanzapine, risperidone, clozapine etc., commonly experience excessive daytime sleepiness as a common adverse effect, which interferes with their daytime work performance and affect their quality of life. This along with abnormal weight gain may be one of the factors responsible for non-compliance.

**Evidence**

This review of literature assesses the various body weight gain liabilities associated with atypical anti-psychotics, as well as the effects of body weight gain on quality of life. Most study reviews indicate that clozapine and olanzapine were associated with more body weight gain than the other atypicals.

**Modafinil**

In this study, it was hypothesized that modafinil, a centrally acting alpha 1 adrenergic drug, which was approved by US Food and Drug Administration as a treatment for narcolepsy, other conditions associated with sleep apnea syndromes and sleep shift conditions shall help in minimizing the unwanted drowsiness. As the clinical experience and SPC of the drug also mentions anorexia as one of the side-effects, it was further hypothesized that it shall also control the weight gain associated with the atypical anti-psychotic therapy. This loss of weight that may take place is considered as a direct result of lesser carbohydrate and fat intake by the subject.

Modafinil is a memory-improving and mood-brightening novel psycho-stimulant. It enhances wakefulness and vigilance, but its pharmacological profile is notably different from the amphetamines. Modafinil is less likely to cause jitteriness, anxiety, excess loco motor activity or lead to rebound hypersomnolence than the traditional stimulants. Subjective experience of most of the patients had been that it felt smoother and cleaner. The half-life of modafinil is between 12-15 hrs. It is a safe, effective, and well-tolerated agent.

Modafinil induces wakefulness in part by its action in the anterior hypothalamus. Its dopamine-releasing action in the nucleus accumbens is weak and dose-dependent. Modafinil has central alpha 1 adrenergic agonist effects and inhibits the reuptake of noradrenaline by the noradrenergic terminals on sleep-promoting neurons of ventrolateral preoptic nucleus (VLPO); more significant ability is to increase excitatory glutamatergic transmission. This reduces local GABAergic transmission.

Modafinil is clinically proved drug for treatment of narcolepsy, a neurological disorder marked by uncontrollable attacks of daytime sleepiness.

In Jan 2004, modafinil is approved by USFDA for the treatment of excessive sleepiness associated with obstructive sleep apnea, and shiftwork sleep disorder, apart from its original application for narcolepsy.
most common adverse events reported in clinical studies were headache, most were transient and mild to moderate intensity.

Anectodal evidences about modafinil’s usefulness
In the only study, that was reported, by Makela (2003)[1], in 3 cases that the use of modafinil was successful in treating sedation induced by anti-psychotic medication. In this proposed study, based on this available information on modafinil, an attempt was made to study the utility of add-on of modafinil to patients with treatment-emergent unwanted adverse events with olanzapine, risperidone, and clozapine. These drugs were chosen, because they are the commonly prescribed atypical drugs for their cost-effectiveness in India.

MATERIALS AND METHODS

Type and design of the study
Present study is a randomized, double-blind, placebo-controlled study,

This was conducted at 2 centers; one at the department of Psychiatry, S. V. Medical College, Tirupati and another at Asha Hospitals, Hyderabad.

All patients who fulfilled the inclusion and exclusion criteria were explained about the study in detail, and a written informed consent was obtained. The patients were assigned blindly to one of the treatment arms placebo or modafinil, by sponsor.

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

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

The results were analyzed statistically and discussed. Limitations and strengths of study were also mentioned.

Study sample
At baseline, there were 72 patients, out of that, only 63 completed the total study period. All the 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 anti-psychotics for less than 2 weeks, irrespective of diagnosis.
3. Those patients who could read and understand the ICF.

Exclusion criteria
1. History of consuming any anti-obesity drugs or regimens.
2. History of having taken atypical anti-psychotics 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 steroid, and oral contraceptive pills.
5. History of dual diagnosis on axis 1 on DSM IV
6. Prolonged history of concomitant use of sedatives or tranquilizers.
7. When the patient was kept on a mood stablizer or an anti-depressant.
8. Patients who were highly uncooperative, destructive, or suicidal.
9. Patients who were stuporosed or required ECT.

Sleep disorders rating scales
1. Visual Analog Scale (VAS)-Subjective scale.
2. Excessive Daytime drowsiness scale (EDD) — Objective scale

Statistical methods
After unblinding, the data was coded. Analysis of data was done by using SPSS 10.0 version. The placebo group and the modafinil group characteristics were made out by using the descriptive statistics like 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 informed consent form during the recruitment period and accepted to participate in the study from 2 centers in Tirupati and Hyderabad, amounted to 72. They were randomly assigned to either modafinil or placebo as an 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 were considered for the analysis. They were analyzed on socio-demographical, disease-related sleep parameters of the study.

Patients completed the total study period — 63
Patients who did not complete the study — 9
Out of 9 patients who did not complete the protocol the reasons for non-completion were ascertained as far as possible.

Headache and trouble falling asleep appeared to be 2 main reasons for these patients to withdraw early from the study in modafinil group. Except for these 2 reasons, there was not much difference between placebo and modafinil group.

The unblinding was done by the sponsor who had provided modafinil, the investigational product, and a similar-looking placebo capsules. This was done after the last subject completed the study protocol after a written request from the investigating sites.

After unblinding, it was found that among the 63 subjects who completed the protocol, 31 were allocated to placebo and 32 to modafinil.

All the analysis was carried out on these 2 groups to test the hypothesis.

Comparisons were made between modafinil and placebo groups at baseline and also within the groups over 12-week period. The following conclusions were obtained:

**In placebo group**
1. Sleep parameters like VAS1 [quality of sleep] showed significant improvement from baseline to week 3 and to week 12.
2. VAS2 [daytime drowsiness] was increased over a period of time, that is from baseline to week 3 and also at week 12.

**In modafinil group**
Whereas in modafinil group,
1. Sleep parameters VAS 1 [quality of sleep] was improved significantly.
2. VAS2 [daytime drowsiness] decreased significantly over a period of time.

Efficacy parameters like BPRS, CGI-S improved significantly in both the groups. It clearly shows that modafinil did not exacerbate or worsen the existing psychotic features.

**DISCUSSION**

**Impact of modafinil on resolution of psychotic features**
From the results, it was obvious that modafinil no way interfered with anti-psychotic action of the drug in majority of the subjects. Only one case of exacerbation of psychosis was noted in the study; patient was on modafinil; patient was taken out of the study because of psychosis and was treated promptly. Modafinil could be safely administered with atypical anti-psychotics.

**Other common adverse events noted during 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 disturbances
- Agitation
- Decreased appetite
- Exacerbation of psychosis

**Impact of modafinil on daytime sedation**
In this study, 2 scales to measure the drowsiness were used. A subjective scale having 2 components, one is to assess the sleep quality and other is to assess the daytime drowsiness. Another was objective scale where examiner asks few structured questions to decide about the duration of the drowsiness and also intensity of the excessive daytime drowsiness.

In the study, only on subjective scale, there was improvement in the quality of sleep and also improvement in the daytime drowsiness in modafinil group. But, same findings were not found with the objective scale.

The improvement of quality of sleep could have been due to the fact that patients improved in their psychotic features. But, in the modafinil group, there was a significant decrease in the daytime drowsiness. The same was not reflected when this finding was looked in objective manner using EDD scale (the objective scale). This particular finding requires further exploration, as the patient suffering from psychosis, when they responded to a structured questionnaire, might not have answered adequately. However, in future studies, the correlation between subjective and objective scales must be studied and the reasons ascertained.

**CONCLUSION**

Present study was a randomized, placebo-controlled trial, using a double-blind technique. Findings point out that modafinil could be a potential candidate in selected group of patients to decrease some of the unwanted adverse events like daytime drowsiness produced by atypical anti-psychotics. 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.
REFERENCE

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