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Sleep Pattern and Sleep Quality Observed With Tab. Diazepam and Tab. Alprazolam in Patients Treated For Insomnia

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Abstract:

Background: *The duration and pattern of sleep varies considerably among individuals. Insomnia is characterised by acute or chronic inability to initiate or maintain sleep adequately at night (1). Benzodiazepine-receptor agonists are the most effective and well-tolerated class of medications for insomnia. While there are significant differences among different BZDs, in general, they hasten onset of sleep, reduce intermittent awakening and increase total sleep time. The likely hood of rebound insomnia and tolerance can be minimized by short durations of treatment, intermittent use, or gradual tapering of the dose.*

Aim/ Objective: *To observe the effects of Tab. Diazepam and Tab. Alprazolam on Sleep pattern and sleep quality in patients with insomnia*

Materials and Methods: *Patients who are on T. Diazepam(5-10mg) or T. Alprazolam (0.5-2mg) were assessed for sleep pattern at baseline, at 15 days and at the end of one month. Quality of sleep was evaluated using pittsburgh sleep quality index scale which includes subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction.*

Results and Conclusion: *The results of our study reveal that there was a significant difference in sleep pattern and quality of sleep at first follow-up and was consistent till the last follow-up (at the end of one month). It was observed that there was improvement in the primary disease. So, the final score of the sleep pattern parameters is because of the resultant activity of direct drug action and improvement in the underlying disease.*

Keywords: *Insomnia, Diazepam, Alprazolam, pittsburgh sleep quality index scale (PSQI)*

I. Introduction

Insomnia is the most common complaint causing distress, frequently because of a fear or a feeling of not being able to fall asleep at bedtime and can impair work-related productivity because of daytime fatigue or drowsiness(3). Common causes of insomnia include concomitant psychiatric disorders, significant psychosocial stressors, excessive alcohol use, caffeine intake, and nicotine use. Management of all patients with insomnia should include identifying the cause of the insomnia, patient education on sleep hygiene, and stress management. Any unnecessary pharmacotherapy should be eliminated (4). Non pharmacologic interventions for insomnia frequently consist of short-term behavioural therapies, stimulus control therapy, sleep restriction, relaxation therapy, cognitive therapy, paradoxical intention, and education on good sleep hygiene(5) .

Pharmacologic therapy for mild insomnia includes Antihistamines (Diphenhydramine), sedating Antidepressants(amitriptyline, doxepin, nortriptyline and Trazodone),Melatonin receptor agonists (Ramelteon).Anti histamines are less effective and have anticholinergic side effects(6),antidepressants may cause daytime sedation and weight gain. Ramelteon most commonly resulted in head ache,dizziness and somnolence(7). Benzodiazepines are the anxiolytics of choice in the acute management of generalized anxiety and insomnia. Commonly used Benzodiazepines for sleep disturbances are Alprazolam, Diazepam,Lorazepam and Midazolam.Alprazolam and Lorazepam has intermediate physical half-life.Diazepam has long physical half-life(8). Midazolam has short physical half-life hence mostly used Intravenously . The intermediate acting drugs are useful as sedatives for insomnia.This study was therefore carried out to evaluate the effects of long-term (one month) administration of a commonly prescribed BZDs Diazepam(5-10mg), Alprazolam(0.5-2mg) on sleep pattern and on sleep quality for sleep disorders using a battery of simple tests that can be conveniently applied to the Indian population.

II.AIM

To study the effects of Tab. Diazepam (5-10mg), Tab. Alprazolam (0.5-2mg) on sleep pattern and sleep quality .

III. Materials & Methods

Study design– Prospective observational study
Study period - April 2016- Aug 2016
Study duration - One month/ patient
Place of study - Dept. of Psychiatry, Stanley medical college
Study population – 30 patients in each group

IV. Selection criteria

4.1 Inclusion criteria:

- Both sexes
- Age group between 15 and 60 yrs
- Only patients with whom rapport can be established
- Patients with anxiety disorders, mild depression, obsessive compulsive disorder, phobia and psychosomatic disorders who were prescribed BZDs are included
- Patients who give informed consent to participate in this study.

4.2 Exclusion criteria:

- Patients below 18 yrs and above 60 yrs
- Patients with major psychiatric illness
- Patients on other centrally acting drugs which may impair sleep and memory like antipsychotics
- Patients with serious systemic disorders like HIV, TB
- Patients who were on any other BZDs at the time of enrollment to the study.
- Pregnant and lactating women

V. Methodology

Those patients who were willing to participate in the study were divided into two groups according to their medication.

Group A	Tab .Diazepam (5-10mg) at bed time
Group B	Tab. Alprazolam (0.5–2 mg) at bed time

The aim and procedure of the study were explained to the patients. Written informed consent was obtained in the local vernacular language from the patients. Patients were asked questions related to the study, translated in their own language. Patient's personal data like name, age, hospital number, educational status, occupation, mother tongue were noted at the first visit. Also the symptoms, duration of illness, past drug history and family history were also noted. Vital data and details of systemic examination were recorded. A note of the diagnosis and treatment prescribed was recorded in the proforma at each visit. Adverse drug reaction and clinical progress observed by investigator or reported by the patient was also recorded in the proforma. Pittsburgh sleep quality scale was employed to assess the sleep pattern and sleep quality of the patients. Baseline sleep evaluation is done on 0 day on starting therapy, at the end of 15days and at the end of 1month of drug therapy. Diagnosis of case and dosage given are recorded.

Tests

The Pittsburgh sleep quality scale (9) was employed to assess the sleep quality of patients. The questions relate to their usual sleep habits during the specified period (0day, 15days, 30days). It consists of seven subsets. Each has a maximum score of 3(worse) and the minimum score of 0 (better). The subsets are as follows:

1. **Subjective Sleep Quality:** This consists of one question with Minimum score=0(better);Maximum score =3(worse)
2. **Sleep Latency**: This consists of two subsets and the each score is added together and scores given. Minimum score=0(better);Maximum score =3(worse)
3. **Sleep Duration**: It consists of one simple question with hours (>7 hours) =Minimum score=0(better); (<5 hours = Maximum score =3(worse)
4. **Sleep Efficiency**: It consists of information on going to bed, time taken to fall asleep, getting up time in the morning, hours of actual sleep at night. It is calculated as (Number of hours slept/ Number of hours spent in bed) x100=sleep efficiency (%). >85%=Minimum score=0(better); < 65 %=Maximum score =3(worse).
5. **Sleep Disturbances**: It consists of one question with ten subsets. Minimum score=0(better);Maximum score =3(worse)

6. **Use Of Sleeping Medication**: This consists of one question with Minimum score=0(better);Maximum score =3(worse)
7. **Day Time Dysfunction**: This consists of two questions and the individual scores should be added and further scored. Minimum score=0(better);Maximum score =3(worse)
   Psqi Total=sleep quality + latency + duration + sleep efficiency + disturbance + need medicines to sleep+ daytime dysfunction
   Minimum Score = 0 (better); Maximum Score =7*3= 21(worse)

Interpretation:
Total < 5 associated with better sleep quality
Total > 5and <10associated with good sleep quality
Total > 11 associated with poor sleep quality

VI. Results

Data was statistically analyzed and compiled. Patients were divided into two groups based on their medication.

- Age and Sex distribution does not show any difference between the groups.
- All subsets of sleep pattern and sleep quality tests significantly improved at the first and second follow up in both the study groups and the p' value is highly significant. (<0.001)
- The improvement in sleep pattern and sleep quality were to the same level in both the groups at the end of 15 days and at the end of 1 month. In other words, no significant difference was noted in subsets between the two groups and the p' value is not significant. (>0.05)
- No patient in either group complained of serious adverse effects.

The mean quality sleep score of each subset in both the groups was tabulated as shown below.

Table 1: Mean quality sleep score obtained with Diazepam (group A) at baseline; at 15 days & at the end of 1 month

subset	PSQI	0days	15 days	30 days
1	Subjective sleep quality	1.333	0.533	0.533
2	Sleep latency	2.166	1.866	2.133
3	Sleep duration	0.733	0.966	0.733
4	Sleep efficiency	1.466	0.633	0.633
5	Sleep disturbances	1.666	0.866	0.866
6	Use of sleeping medication	2.666	2.733	2.666
7	Daytime dysfunction	1.866	1.066	1.066
	Total	11.90	8.666***	8.633***

p value<0.05 * p value < 0.01 ** p value < 0.001***

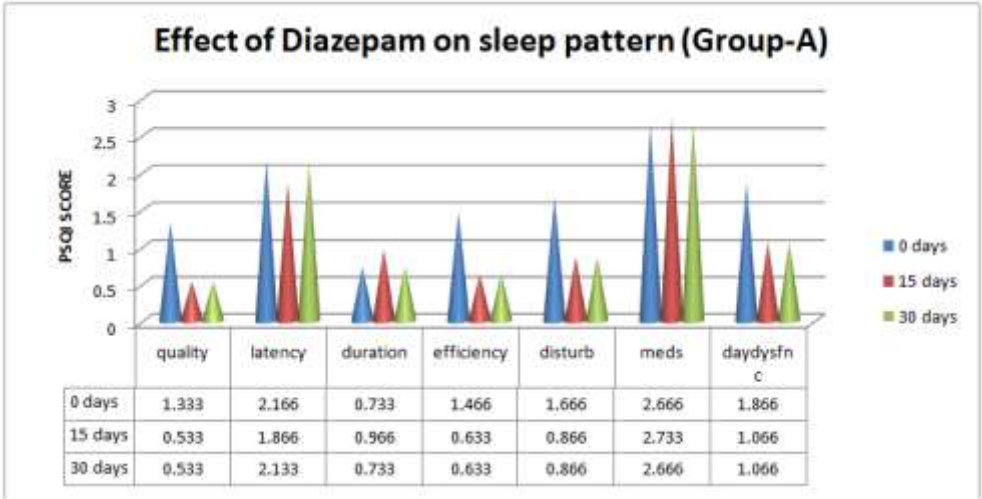

Fig 1 : Effect of Diazepam on sleep quality subtests in (Group A) at baseline; at 15 days & at the end of 1 month

Table 2: Mean quality sleep score obtained with Alprazolam(group B) at baseline, at 15 days & at the end of 1 month

Subset	PSQI	0 days	15days	30 days
1	Subjective sleep quality	1.966	1.333	1.333
2	Sleep latency	1.466	0.666	0.566
3	Sleep duration	2.333	1.866	1.933
4	Sleep efficiency	2.366	1.933	1.966
5	Sleep disturbances	2.133	1.333	1.266
6	Use of sleeping medication	2.066	1.533	1.633
7	Daytime dysfunction	2.533	1.066	1.066
	Total	14.86	10.70^{***}	10.76^{***}
p value <0.05 * p value < 0.01 ** p value < 0.001***				

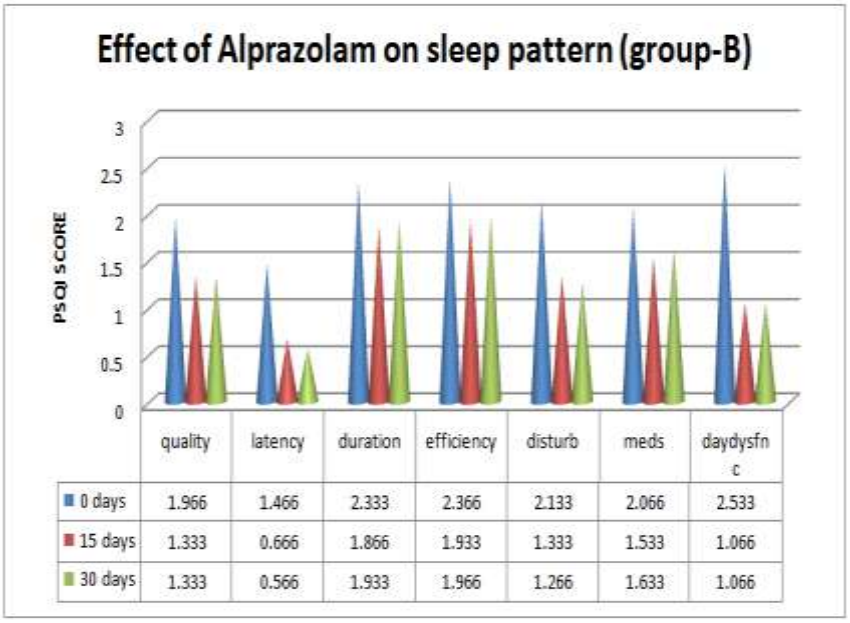

Fig: 2 Effect of Alprazolam on sleep quality subtests (Group B) at baseline, at 15 days & at the end of 1 month.

Table no: 3 Significant quality sleep score compared with Diazepam (groupA) and Alprazolam(group B) at the end of 1 month

Subset	PSQI	**Diazepam**	**Alprazolam**
1	Subjective sleep quality	0.533***	1.333***
2	Sleep latency	2.133**	0.566***
3	Sleep duration	0.733***	1.933**
4	Sleep efficiency	0.633**	1.966**
5	Sleep disturbances	0.866***	1.266**
6	Use of sleeping medication	2.666**	1.633**
7	Daytime dysfunction	1.066***	1.066**
p value < 0.001***(highly significant), p value < 0.01**(significant),			

VII. Discussion

Insomnia is subjectively characterized as a complaint of difficulty falling asleep, difficulty maintaining sleep, or experiencing non restorative sleep. Insomnia lasting two or three nights is considered to be transient insomnia, whereas short-term insomnia usually resolves in less than 3 weeks. Insomnia is considered to be chronic when it lasts longer than 1 month (10). Most commonly used effective sedative-hypnotics, for insomnia are Benzodiazepine receptor agonists. All benzodiazepine receptor agonists bind to GABA-A receptors in the brain resulting in stimulatory effects on GABAergic transmission and hyper polarization of neuronal membranes. Traditional benzodiazepines have sedative, anxiolytic, muscle relaxant, and anticonvulsant properties; newer non benzodiazepine GABA agonists possess only sedative properties. Benzodiazepines relieve insomnia by reducing sleep latency and increasing total sleep time. Benzodiazepines increase stage 2 sleep while decreasing REM, stage 3, and stage 4 sleep.

Benzodiazepines are very safe, and fatal overdoses are rare unless they are taken in combination with central nervous system (CNS) depressants or alcohol.Onset of action is depends on rate of absorption and it varies with various BZDs. Diazepam is rapidly absorbed orally. This characteristic, along with high lipid solubility, may explain the popularity of diazepam.

Duration of action of the benzodiazepines varies as a function of the active metabolites they produce. Lorazepam do not produce active metabolites and have intermediate half lives of 10–20 hours. Flurazepam and Diazepam produce active metabolites, have half-lives of 20–120 hours. Shorter-acting compounds, such as alprazolam and oxazepam, can produce daytime anxiety, early morning insomnia, and, with discontinuation, rebound anxiety and insomnia(11).In our study, Diazepam and Alprazolam had produced significant improvement of subset scores of pittsburgh sleep quality index scale. Sleep pattern and sleep quality improved in both Diazepam and Alpazolam groups. This improvement is statistically significant when compared to the baseline scores of the same group. These findings are significant and are of clinical importance.Group A showed significant improvement in Sleep duration, Sleep disturbances at night, Day time dysfunction due to sleepiness and overall subjective sleep quality compared with baseline (0 Days) and with Group B. There is no significant difference between 15 days and 30 days interval.The above effects may be because of its longer half life causing effective sleep duration and reduced disturbance during sleep .It is also due to its active metabolites it produce causing nil interdose rebound anxiety so improving the day time dysfunction due to sleepiness , so improving overall subjective sleep quality .(Table 1,3).Group B showed significant reduction in sleep latency and improvement in overall subjective sleep quality compared with base line(0 days) and with Group A. There is no significant difference between 15 days and 30 days interval.

This explains the Fast and short acting nature of Alprazolam causing rapid sleep onset improving sleep latency and overall subjective sleep quality. It does not produce much improvement in sleep disturbance at night and in day time sleepiness may be because it do not produce any active metabolites in turn causing inter dose rebound anxiety at night so affecting day time performance . (Table 2,3).No patients reported any major adverse effects and all were adhered to the treatment .Both the groups were similar in adherence using medication for sleep .This may be due to the patients awareness towards treatment, better health education status and also the smooth sleep pattern produced by the BZDs. A further study is essential to assess the effect of Diazepam, Alprazolam and other BZDs on sleep Quality in longer term basis and effects when combined with other medications.

VIII. Conclusion

It is concluded that Diazepam and Alprazolam causes significant improvement in sleep pattern and in sleep quality which was assessed by PSQI during the one month study period and the final score of the parameters are because of the resultant activity of direct drug action and improvement in the underlying disease.

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X. Annexure

PSQI scale used in this study.

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

   USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

   USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

   HOURS OF SLEEP PER NIGHT _____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...cannot get to sleep within 30 minutes	☐	☐	☐	☐
(b) ...wake up in the middle of the night or early morning	☐	☐	☐	☐
(c) ...have to get up to use the bathroom	☐	☐	☐	☐
(d ...cannot breathe comfortably	☐	☐	☐	☐
(e) ...cough or snore loudly	☐	☐	☐	☐
(f) ...feel too cold	☐	☐	☐	☐
(g) ...feel too hot	☐	☐	☐	☐
(h) ...had bad dreams	☐	☐	☐	☐
(i) ...have pain	☐	☐	☐	☐
(j) Other reason(s), please describe				
How often during the past month have you had trouble sleeping because of this?	☐	☐	☐	☐

PSQI Page 1

	Very good	Fairly good	Fairly bad	very bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room, but not same bed	Partner in same bed
10. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...loud snoring	☐	☐	☐	☐
(b) ...long pauses between breaths while asleep	☐	☐	☐	☐
(c) ...legs twitching or jerking while you sleep	☐	☐	☐	☐
(d) ...episodes of disorientation or confusion during sleep	☐	☐	☐	☐
(e) Other restlessness while you sleep; please describe	☐	☐	☐	☐

_____

_____

PSQI Page 2