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Research Article

A prospective study on sleep disorders related to antidepressant drugs use in a tertiary care teaching hospital

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ABSTRACT

Background: Prescription of antidepressants has been increased from the last decade and responsible for producing sleep disorders as adverse drug reactions (ADRs). Sleep disorders can be divided into 3 large groups: (1) insomnia, (2) primary complaint of daytime sleepiness, and (3) Association of disruptive behaviours during sleep, the disorders of arousal. So active surveillance is needed to access these ADRs.
Aims and Objective: To analyze the sleep disturbances as ADRs of various antidepressants prescribed to the patients attending psychiatry outpatient department (OPD).
Methods: This prospective study was conducted on patients aged ≤74 years attending Department of Psychiatry OPD and were prescribed Antidepressants for the duration of 8 months (December, 2013-July, 2014). The ADRs reported were confirmed by WHO UMC Causality Assessment Scale.
Results: Total number of patients enrolled on the basis of inclusion and exclusion criteria (n=50). Total number of ADRs related to drugs prescribed were found to be n=69. Total number of patients with sleep disturbances as ADRs were found to be n=28.
Conclusion: The drug, most frequently implicated to cause sleep disturbances, was mirtazapine. Increased sleep was the most common ADR, found to occur. Unusual ADRs such as sleep talking was also seen.

Keywords: Sleep disturbances, Antidepressants, Mirtazapine

INTRODUCTION

Nowadays, major depressive disorder is reported to be the most common ailment among all psychiatric disorders.[1] The overall prevalence of depression in India is 15.1% and is found to be higher in females.[2] Drugs used for the treatment of depression have been increased from the last decade and report also says that in the past 20 years the rate of taking antidepressants will be increased to 04 times,[3] due to the huge increase in the use of antidepressants, they are responsible for producing so many ADRs such as sleep disorders, dry mouth, blurred vision, weight gain, drowsiness, and sleep disorders. Among these, sleep disorders are one of the most common ADRs. Sleep disorders can generally be divided into 3 large groups: (1) insomnia, (2) those with a primary complaint of daytime sleepiness, and (3) those associated with disruptive behaviors during sleep, the disorders of arousal.[1,2] Thus, active surveillance is required to access these ADRs.

Equally we recognize that all the antidepressants cause some degree of perturbation in the normal sleep cycle, so they are surviving to affect sleep inevitably. Current evidence suggests that this result depends on the class of antidepressant used and their dosage. The extent of variation between the effects of antidepressants on sleep may be related to their mechanism of action. Various mechanisms are important in the effects of antidepressant treatment on sleep. Increments in the availability of serotonin and norepinephrine appear to be connected with the inhibition of REM sleep, but also with increases in sleep fragmentation.[4] The mechanisms thought to be responsible for sleep effects in tricyclic antidepressants (TCAs) vary with specific compounds. Most TCAs inhibit the reuptake of both serotonin and noradrenaline, but the relative extent that they do this varies and may explain some of the differences in sedation and REM sleep suppression. All TCAs except lofepramine block histamine H1 receptors, and all but desipramine block α1- adrenoceptors. The blockade of histamine H1 receptors may be linked to sleep promotion.[5]

EEG studies of sleep confirm that selective serotonin reuptake inhibitors of α1-adrenoceptors are more potential to explain the sedative properties of TCAs, as might the 5-HT2 blockade action, as seen with amitriptyline and trimipramine. SSRIs immediately suppress REM sleep, and go forward to do so throughout the treatment; REM parameters return to normal once the SSRI is discontinued.[6] The observed effects on sleep of SSRIs are believed to be referable to the effects of increased levels on 5-HT1A and 5-HT2 receptors. Activation of 5-HT1A receptors is likely responsible for REM suppression,[7] but is unlikely to mediate sleep fragmentation. Mirtazapine blocks α2-autorecptors, 5-HT2 receptors, and H1 receptors. α2-adrenoceptor inhibition increases noradrenaline, thus suppressing REM sleep and disrupting sleep continuity while the other actions tend to promote sleep. The improvements in sleep with mirtazapine are most likely to be the result of 5-HT2 receptor inhibition.[8]

Aims and objective

The objective of this study is to monitor and evaluate the ADRs specially related to sleep disturbances caused by antidepressants prescribed to patients attending the psychiatry outpatient department (OPD) of Teerthanker Mahaveer Medical College, Hospital and Research Center, Moradabad, U.P.

METHODS

This prospective study was conducted on patients aged ≤74 years attending Department of Psychiatry OPD at Teerthanker Mahaveer Medical College, Hospital and Research Center, Moradabad. Only those patients who were prescribed Antidepressant drugs for the duration of 8 months (December, 2013-July, 2014) and fulfilled the inclusion and exclusion criteria, were included in the study. The patients on concomitant drugs were excluded from the study. The patients were assessed for any type of ADR reported by the health professionals. The ADRs reported were confirmed by WHO UMC Causality Assessment Scale. Written informed consent was taken from each participant just prior to study. The study was commenced only after approval from the Institutional Ethical Committee.

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RESULTS

Adverse drug reactions (ADRs) were confirmed in 50 patients after causality assessment. Of 50 patients, 22 were male, and 28 were female (Table 1).

The above information clearly indicates that depression was found to be more common in females (56%) as compared to males (44%). Among the age groups 15-29, 61.53% females were suffering from depression as compared to 38.46% males of the same age group. Similarly, in the age group 30-44, 66.66% females compared with antidepressants to only 33.33% males. In the age group 45-59, this trend slightly falls to females affected 57.14% as compared to 42.85% of males (Table 1).

Total 69 antidepressants were prescribed to 50 patients enrolled in our study, SSRIs was most commonly prescribed (37 out of 69) among patients with depression, which cumulatively make 53% of total prescribed agents followed by mirtazapine prescribed in 25 (36.26%), followed by TCAs 04 (5.8%), followed by serotonin-norepinephrine reuptake inhibitor 03 (4.34%) (Table 2 and Figure 1).

Table 1: Demographic detail of study population.

Age group (years)	Male (%)	Female (%)	Number of patients (%)
0-14	02 (66.66)	01 (33.33)	03 (06)
15-29	05 (38.46)	08 (61.53)	13 (26)
30-44	04 (33.33)	08 (66.66)	12 (24)
45-59	06 (42.85)	08 (57.14)	14 (28)
60-74	05 (62.50)	03 (37.50)	08 (16)
Total	22 (44)	28 (56)	50 (100)

Table 2: Antidepressants prescribed in n=50 patients.

Class	Antidepressant agent	No. of agents prescribed	% of total prescriptions
SSRIs	Mirtazapine	25	36.26
	Sertraline	20	28.98
	Escitalopram	08	11.59
	Fluoxetine	04	5.79
	Paroxetine	02	2.89
	Citalopram	03	4.34
SNRIs	Venlafaxine	03	4.34
TCAs	Desipramine	03	4.34
	Amitriptyline	01	1.44
Grand total		69	100

SNRIs: Serotonin-norepinephrine reuptake inhibitor, SSRIs: Selective serotonin reuptake inhibitors, SRM: Serotonin receptor modulators

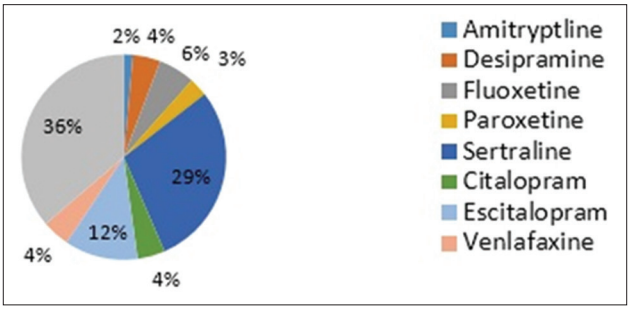

Figure 1: No. of agents prescribed.

As far as individual drugs are concerned, mirtazapine was prescribed to 25 patients (36.26%), followed by sertraline 20 (28.98%), followed by escitalopram 08 (11.59%), followed by fluoxetine 04 (5.79%), followed by desipramine, citalopram, and venlafaxine prescribed to 03 patients each (4.34% each), followed by paroxetine 02 (2.89%) and amitriptyline 01 (1.44%) (Table 2 and Figure 1).

On observation of sleep disturbances, we found that the patient prescribed with amitriptyline, i.e., 01 (100%) shows sleep disorders. Desipramine was prescribed to n=3 patients, and no ADRs were reported. SSRIs especially fluoxetine were prescribed to patients (n=4) with no report of any ADRs. Paroxetine prescribed to n=2 patients and in both the cases (100%), ADRs of sleeping disorder were noted. Sertraline was prescribed to n=20 patients, of which, n=7 patients showed (35%) ADRs related to sleep disorders. Citalopram was given to n=3 patients and all of them (100%) showed ADRs related to sleep disorder whereas, escitalopram prescribed to n=8 patients and only 2 patients were (25%) found to have sleeping disorders as ADRs. Venlafaxine was given to n=3 patients, and only n=1 patient (33.3%) has ADR related to sleep. Mirtazapine was mostly prescribed in n=25 patients, and nearly half of it, i.e. n=12 (48%) patients have sleep ADRs (Table 3 and Figure 2).

On the categorization of ADRs of sleep disorders into 3 major groups, i.e., (1) insomnia, (2) those with a primary complaint of daytime sleepiness, and (3) those associated with disruptive behaviors during sleep the disorders of arousal, we observe the results which are summarized in Table 4.

Table 3: Agent wise % of sleeping ADR.

Class	Antidepressant agents	No. of agents prescribed	No. of patients having sleep disturbance (n=28) (%)
TCAs	Amitriptyline	1	01 (100)
	Desipramine	3	0
	Total	4	
SSRIs	Fluoxetine	4	0
	Paroxetine	2	02 (100)
	Sertraline	20	07 (35)
	Citalopram	3	03 (100)
	Escitalopram	8	02 (25)
	Total	37	
SNRIs	Venlafaxine	3	01 (33.3)
SRMs	Mirtazapine	25	12 (48)
	Total	69	28 (40.5)

SNRI: serotonin-norepinephrine reuptake inhibitor, SSRIs: Selective serotonin reuptake inhibitors, DTS: Daytime sleepiness, ADRs: Adverse drug reaction, TCAs: Tricyclic antidepressants

Only n=1 ADR was noted with Amitriptyline, and that was of daytime sleepiness. Desipramine and fluoxetine showed no ADRs related to sleep disorder. Paroxetine showed that sleep disorder n=2 times and in both cases insomnia with disruptive behavior were noted. Sertraline resulted in the total n=7 ADRs of sleep disorders, all n=7 showed insomnia as ADR, but n=2 of them also showed daytime sleepiness as ADR. Citalopram resulted in total n=3 ADRs related to sleep disorders, and all were linked to daytime drowsiness. Escitalopram showed that n=2 ADRs of sleep disorder and both were of insomnia. Only ADR related to sleep disorder due to Venlafaxine was of insomnia and disruptive behavior. Mirtazapine showed most number of ADRs related to sleep disorder and all were of daytime sleepiness. Graphical representation of these results is shown in Figure 3.

DISCUSSION

This prospective study revealed that a patient prescribed with amitriptyline showed daytime sleepiness as an ADR (Table 3). A previous study showed that patients presented better improvement in early morning awakenings, and nocturnal awaking with amitriptyline (100-150 mg) than imipramine (100-150 mg).[9] Likewise, another study observed that amitriptyline (75 mg) was linked with significantly shorter sleep latency, but more drowsiness than fluoxetine (20 mg).[10] In another study conducted

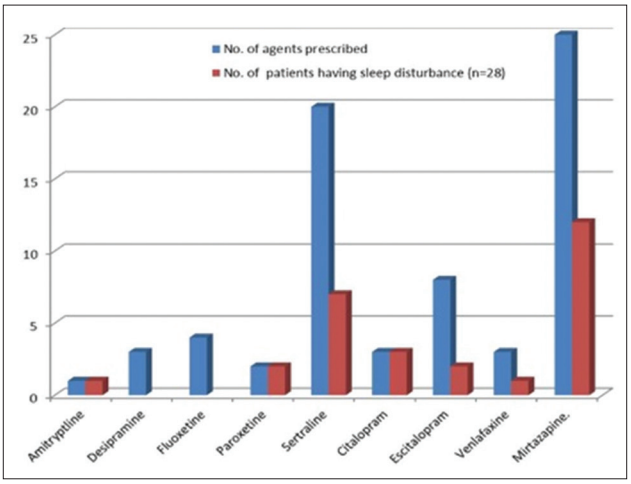

Figure 2: Adverse drug reaction noted with each agent.

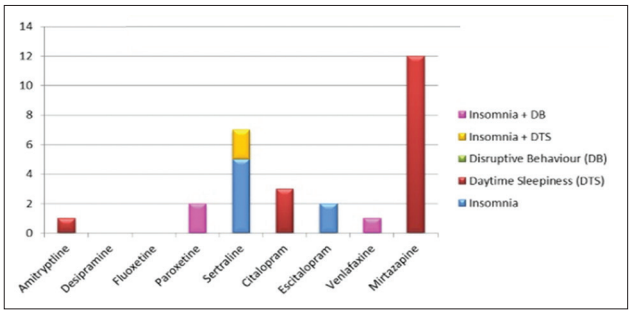

Figure 3: Group wise distribution of sleeping adverse drug reaction, to respective agents.

Table 4: Categorization of ADRs according to sleep disorder groups.

Class	Agent	Total ADRs	DTS	Insomnia	Insomnia+DB	Insomnia+DTS	Disruptive behavior DB
TCAs	Amitriptyline	01	01	-	-	-	-
	Desipramine	00	-	-	-	-	-
SSRIs	Fluoxetine	00	-	-	-	-	-
	Paroxetine	02	-	-	02	-	-
	Sertraline	07	-	05	-	02	-
	Citalopram	03	03	-	-	-	-
	Escitalopram	02	-	02	-	-	-
SNRIs	Venlafaxine	01	-	-	01	-	-
SRMs	Mirtazapine	12	12	-	-	-	-
	Total (%)	28 (100)	16 (57.2)	07 (25)	03 (10.7)	02 (7.1)	-

SNRI: serotonin-norepinephrine reuptake inhibitor, SSRIs: Selective serotonin reuptake inhibitors, DTS: Daytime sleepiness, ADRs: Adverse drug reaction, TCAs: Tricyclic antidepressants

by Kupfer et al., 1991 demonstrated that desipramine (100-200 mg) significantly reduces sleep latency after just one day of treatment but significantly increase again as treatment proceeds. The same study says that desipramine was associated with shorter sleep latency than fluvoxamine (200 mg).[11] In another study, desipramine (50-250 mg) was associated with more nocturnal waking, shorter sleep, and less efficient sleep than amitriptyline (50-150 mg).[12] In our study, no such effects on sleep were noted by use of Desipramine. Wolf et al., 2001 demonstrated that fluoxetine (20 mg) was associated with less efficient, shorter and more disrupted sleep than trimipramine (150 mg).[13] Our study showed no sleep disorders with the use of fluoxetine. Another study found that sleep time was less, and disruption greater, for paroxetine (20-40 mg) when compared to nefazodone (400-600 mg).[14] In our study, Paroxetine makes about 2.89% of total prescriptions, but all of them complained of insomnia and disruptive sleep. Jindal et al., 2003 found that sertraline (mean 142 mg) suppressed REM sleep and increased sleep latency (although not significantly), compared to placebo.[15] Other study demonstrated that sertraline (50-100 mg) was associated with fewer reports of trouble in sleep initiation than fluoxetine (20-40 mg), but with poorer perceptions on waking.[16] Similarly, sertraline in our study comprises 28.98% of all prescribed drugs, 35% of these shows ADRs related to sleep disturbances among these 35% all complaints of insomnia while about 1/4th of them also complaints of daytime sleeping with insomnia. A previous study found that citalopram (20-80 mg) was associated with significant improvements in HAMD sleep scores, relative to placebo although daytime sleepiness was a significantly greater problem for those taking citalopram than for placebo.[17] In our study, patients who received citalopram have daytime sleepiness as ADR. Another study showed that HAMD sleep scores were also significantly poorer for venlafaxine (75-375 mg) than mirtazapine (15-60 mg).[18] Similarly our study revealed that venlafaxine causes insomnia with disruptive behavior as ARD related to sleep disturbances in 1/3rd of patients. In our study, mirtazapine was most commonly prescribed agent individually 36.26% of total agents, and nearly half of them, i.e., 48% show daytime sleepiness as ADR related to sleep disturbance. Earlier analyses comparing mirtazapine to other antidepressants indicated less nocturnal disturbance and better sleep efficiency than with fluoxetine[6] or paroxetine,[19] and better HAMD sleep scores than with paroxetine[20] or venlafaxine.[18]

CONCLUSION

The drug most frequently implicated to cause sleep disturbances (in 48% of patients) as increased sleep was mirtazapine, followed by sertraline (37%) as insomnia and daytime sleep and escitalopram (25%) as insomnia alone. Increased sleep or daytime sleep was the most common ADR found to occur which alone comprised 57.2% of all sleep-related ADRs, followed by insomnia alone (25%) and insomnia with disruptive behavior combined (10.7%). Disruptive behavior alone is not noted in any case. Desipramine and fluoxetine showed no ADR related to sleep disturbance in our study. Nevertheless, we acquire that more robust reporting with larger study size is needed as this shall enable us to detect the category of sleep disturbance, based on polysomnography.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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