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SHORT REPORT

Preliminary evidence that vortioxetine may improve sleep quality in depressed patients with insomnia: a retrospective questionnaire analysis

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Insomnia is a frequent symptom in depressed patients. It can present with difficulty in initiating and/or maintaining sleep. We retrospectively evaluated a group of 15 patients affected by major depressive disorder and complaining of insomnia, who started vortioxetine (VOR) treatment for their depressive symptoms. The following questionnaires were captured at baseline and follow-up: Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale and Beck Depression Inventory. Pittsburgh Sleep Quality Index total score significantly decreased between follow-up and baseline ($P < 0.01$), and in several subitems related to sleep quality and continuity. Moreover, Epworth Sleepiness Scale decreased between follow-up and baseline ($P < 0.01$). Finally, Beck Depression Inventory reduction was also evident between follow-up and baseline ($P < 0.01$). This retrospective analysis showing the significant effect of VOR on both depressive symptoms and insomnia in patients showing comorbid major depressive disorder and insomnia invites further research in order to confirm this preliminary evidence. We hypothesize that the VOR mechanism of action may explain the improvement of subjective sleep, other than depressive symptoms.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Vortioxetine is a novel atypical antidepressant recently approved for the treatment of major depressive disorder. It presents a different mechanism of action since it regulates several 5-hydroxytryptamine receptors. Insomnia is frequently observed in patients affected by major depressive disorder, but no studies investigated the effect of vortioxetine on sleep.

WHAT THIS STUDY ADDS

- This preliminary study documented the beneficial effect of vortioxetine on subjective sleep and daytime sleepiness in patients affected by major depressive disorder, although it needs to be further confirmed. Moreover, we did not document sleep disorders related to vortioxetine treatment, as restless legs syndrome and rapid eye movement sleep behavior disorder. Further polysomnographic studies are invited to test the positive effect of vortioxetine on sleep in patients with major depressive disorder.

Introduction

Sleep complaints are frequent in patients affected by major depressive disorder (MDD). Accordingly, they affect an estimated 70–90% of patients with depression [1]. Moreover, sleep impairment may worse depressive symptoms and impair quality of life of depressed patients [2]. Polysomnographic studies have identified the dysregulation of rapid eye movement (REM) sleep in patients affected by MDD, as the reduction of REM latency coupled with the increment of REM sleep [3]. Sleep fragmentation and reduced slow wave sleep (SWS) may further impair sleep architecture in MDD patients [4].

Treating insomnia comorbid with depression may be challenging considering that many antidepressant medications can adversely affect sleep quality and continuity [5, 6]. In particular, widely used antidepressants, such as selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI), have been associated with sleep dysregulation [6]. In agreement with this observation, patients affected by MDD and treated by SSRI or SNRI show the increase of nocturnal wakefulness, the presence of sleep fragmentation, and the suppression of REM sleep [6].

Vortioxetine (VOR) is a recently approved drug for treating MDD [7–10]. It is a novel atypical antidepressant since it is both a serotonin modulator and stimulator [11]. Although the mechanism of action is not understood as stated by the Food and Drug Administration, it has supposed a multimodal mechanism of action, since this drug may modulate several serotonergic (5-hydroxytryptamine: 5-HT) targets [8–10]. Briefly, VOR is an antagonist of 5-HT_3, 5-HT_7 and 5-HT_{1D} receptors, a partial agonist of 5-HT_{1B} receptors, and an agonist of 5-HT_{1A} receptors [7]. Although the efficacy and safety of VOR treatment have been already demonstrated on depressive symptoms in trials comparing this drug *vs*. placebo [7], no studies investigated the effect of VOR on sleep in depressed patients.

Therefore, the aim of the present retrospective single centre analysis was to evaluate the effectiveness of VOR treatment on sleep quality, daytime sleepiness and depressive symptoms evaluated by means of subjective validated questionnaires in depressed patients with insomnia.

Methods

The present report is a retrospective observational single-centre data collection based on individual charts review of drug-naïve patients affected by comorbid MDD, diagnosed according to DSM 5–2013, and insomnia, diagnosed according to ICSD3–2014 criteria, who were admitted at our Sleep Medicine Centre from February 2016 to August 2017 [12, 13]. Diagnoses were achieved by anamnesis and clinical interview, also based on the questionnaires routinely performed at our centre. All patients included in this observational retrospective study were treated for MDD by 10 mg of VOR, as common clinical practice and indication. The research followed the tenets of the Declaration of Helsinki, and the Independent Ethical Committee of the University Hospital of Rome Tor Vergata approved the study protocol (experimental registry 115/17). We included in this retrospective observational analysis patients aged ≥18 years who visited our Sleep Medicine Centre and were affected by MDD, who were not already taking neurological or psychiatric medications before the first visit, and who started VOR at the baseline visit. We excluded from this analysis patients with previous history of primary sleep disorders diagnosed by polysomnography, such as obstructive sleep apnoea syndrome, and patients with diagnosis of neurological or psychiatric conditions other than MDD and insomnia.

Since it is common clinical practice at our Sleep Medicine Centre to fix visits before starting a new therapy and after 6 months of treatment, for this retrospective study we collected and analysed data considering those time points. VOR titration was performed according to clinical practice, starting with 5 mg day^{-1} and increasing to 10 mg day^{-1} after 1 week. Therefore, the following data were analysed: age, sex, time since MDD onset, subjective questionnaires. In particular, we reviewed: (i) the Pittsburgh Sleep Quality Index (PSQI), which is a well-recognized and approved instrument able to measure quality of sleep and the effect of sleep medications [14, 15]; (ii) the Epworth Sleepiness Scale (ESS), which is a simple tool to evaluate diurnal sleepiness [16–18]; (iii) the Beck Depression Inventory (BDI), which is a questionnaire measuring depressive symptoms [19]. PSQI is a self-rated questionnaire assessing sleep quality and disturbances over a 1-month period. It is a 24-item scale that measures sleep disturbances according to seven items: subjective sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbances (C5), use of sleep medication (C6) and daytime dysfunction (C7). The scores from these seven items are added together, creating a global score. A total score of >5 is considered as an indicator of relevant sleep disturbances [14, 15]. ESS is an eight-item self-reported questionnaire measuring daytime sleepiness, with a possible score ranging from 0 to 24 [16–18]. BDI is a subjective

questionnaire measuring the symptoms of depression [19]. We considered two BDI scores, one including all the subitems and the second one named BDI#16, obtained excluding from the total score the subitem 16, which investigates sleep during depressive symptoms.

The statistical analysis was performed using commercial software Statistica 10.0 program, Statsoft Inc, Tulsa, OK, USA. PSQI, ESS and BDI scores obtained at baseline and follow-up were considered for the statistical analysis. Descriptive data was expressed as mean and standard deviation for quantitative analyses. The effectiveness of VOR treatment on subjective sleep questionnaires was evaluated by using the paired Wilcoxon test. *P* value set at <0.05 was considered as significant.

We also correlated delta scores (mean change between follow-up and baseline) of BDI#16 and PSQI total score by using the Spearman's rank correlation test.

Results

Forty-nine patients complaining about depression and insomnia were evaluated at our Centre between February 2016 and March 2017. Among them, 34 patients were already under antidepressant medications and thus were excluded from this retrospective analysis; the remaining 15 patients showed the inclusion criteria and thus were included in the analysis for this retrospective observation, since they were drug-naïve and started VOR at the baseline visit. All the patients performed PSQI, ESS, and BDI before starting VOR treatment and after 6 months of therapy. Demographic and clinical data of patients represented in Table 1.

Comparing data obtained at baseline and follow-up also controlling for age and time from symptoms onset, we documented the significant reduction of PSQI total score between baseline and follow up (13.8 ± 1.9 *vs*. 4.73 ± 2.05, $P < 0.01$, Table 1), and in the subitems 1 ($P < 0.01$, Table), 2 ($P < 0.01$, Table 1), 3 ($P < 0.01$, Table 1), 4 ($P < 0.01$, Table 1), 6 ($P < 0.05$, Table 1) and 7 ($P < 0.01$, Table). Considering the PSQI total score, we documented a pathological cut-off in all 15 patients at baseline, which reduced to normality in nine patients at follow-up. Moreover, ESS decreased between follow-up and baseline ($P < 0.01$, Table 1). Finally, BDI reduction was also evident between follow-up and baseline ($P < 0.01$, Table 1). We also tested the change of BDI#16, which is the BDI total score less than subitem 16 owing to sleep impairment related to depressive symptoms, and documented the significant reduction of this score between baseline and follow-up ($P < 0.01$, Table 1). The correlation analysis between delta scores of BDI#16 and PSQI total score did not document significant relationships (R = 0.1, $P = 0.71$).

Notably, no patient treated by VOR reported at follow-up sleep disorders, such as REM sleep behaviour disorder (RBD) or restless legs syndrome (RLS).

Discussion

The present retrospective single-centre study investigated the effectiveness of VOR treatment on depressive and insomnia symptoms in patients affected by comorbid MDD and insomnia. Notably, we documented the beneficial effect of VOR treatment on subjective sleep quality and daytime somnolence in our patients' group. Accordingly, VOR improved subjective sleep efficiency and continuity without affecting daytime functioning and diurnal alertness. Consistently, daytime sleepiness improved during VOR treatment.

The treatment of MDD may be challenging in patients complaining both depression and insomnia, since antidepressants may have detrimental effects on sleep architecture [6, 20, 21]. Several studies investigated sleep in patients affected by MDD documenting that sleep disruption is frequently reported [3]. PSG studies confirmed the negative impact of several antidepressants, such as SSRI and SNRI, on sleep architecture [6, 20, 21]. In the past years, trazodone has shown good efficacy in treating sleep disorders accompanied by a depressive state [22]. It has been hypothesized that the agonism on the 5-HT_{1A} receptors may positively modulate sleep, in particular when it is coupled with the antagonisms on the other 5-HT receptors [22]. VOR has been proved as a possible alternative antidepressant treatment due to its superiority on depressive symptoms compared to placebo. In keeping with its mechanism of action, VOR may enhance cholinergic, dopaminergic, and noradrenergic neurotransmission in both frontal cortex and ventral hippocampus [23]. In particular, VOR differently acts on the 5-HT

Table 1

Clinical, demographic and questionnaire data of patients

Patients (*n* = 15) Mean ± SD				
Age (years)		43.6 ± 11.5		
Sex		9 F, 6 M		
Time from symptom onset (months)		9.5 ± 3.4		
		Baseline	**Follow-up**	***P***
PSQI	1	2.53 ± 0.52	0.53 ± 0.64	0.007
	2	2.33 ± 0.49	0.67 ± 0.62	0.0004
	3	2.4 ± 0.74	0.93 ± 0.6	0.0004
	4	1.53 ± 0.74	0.73 ± 0.6	0.003
	5	1.33 ± 0.49	1.13 ± 0.35	NS
	6	0.93 ± 1.03	0.27 ± 0.46	0.007
	7	2.73 ± 0.46	0.47 ± 0.52	0.0004
PSQI	Tot.	13.8 ± 1.97	4.73 ± 2.12	0.0004
BDI	Tot.	18.8 ± 1.9	9.2 ± 3.03	0.0004
	BDI#16	16.47 ± 1.88	8.93 ± 2.84	0.0006
	#Item 16	2.33 ± 0.49	0.27 ± 0.45	0.0006
ESS	Tot.	9.33 ± 3.24	3 ± 1.77	0.001

BDI, Beck Depression Inventory; BDI#16, the BDI total score less than subitem 16; ESS, Epworth Sleepiness Scale; F, female; M, male; NS, not significant; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation

receptors, by promoting the neurotransmission mediated by 5-HT_{1A} and 5-HT_{1B} receptors; moreover, it inhibits the activity of 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors. Consistently, not only the agonism to the 5-HT_{1A} and 5-HT_{1B} receptors, but also the antagonisms on 5-HT_3 receptors may promote sleep. In particular, the suppression of serotonergic activity by blocking 5-HT_3 receptors may improve non-REM sleep and increase SWS [24]. By contrast, the antagonism on 5-HT_7 and 5-HT_{1D} receptors suppresses REM sleep [24].

It has been documented that antidepressant medications, such as SSRIs, improve subjective sleep and daytime sleepiness [25]. Nevertheless, no study has yet investigated the effect of VOR on sleep in patients affected by MDD. A single study, using paroxetine (SSRI) as a comparator, evaluated the effect of VOR *vs*. paroxetine on sleep in healthy subjects [26]. The reduction of REM sleep was documented either in subjects treated by VOR or in subjects treated by paroxetine, but this REM sleep suppression was less evident in volunteers treated by 20 mg of VOR [26]. Considering that VOR is approved and used in common clinical practice at the dose of 10 mg and that VOR treatment induces a REM sleep suppression which seems to be dose-dependent, we may suppose that the 10 mg of VOR used in our patients' group may partially save sleep architecture. These data have been confirmed by studies performed in animal models showing that VOR may preserve sleep architecture more than SSRI; in particular, VOR has fewer effects than the other antidepressants on both REM sleep and non-REM to wake transitions, which are considered two measures of sleep fragmentation [24].

It is widely known that patients affected by MDD show REM sleep dysregulation, featured by the increase of REM sleep time and the reduction of REM latency [3]. However, this total REM sleep time increase results inefficient and does not improve the subjective perception of sleep quality [3]. Conversely, Non-REM sleep alteration is featured by the increase of superficial and not restorative sleep, associated with the reduction of deep sleep, in particular SWS [27]. In keeping with these observations, patients affected by MDD frequently show difficulty in initiating sleep, sleep fragmentation, early awakening in the morning and nonrestorative sleep. Other signs of sleep deterioration in depressed patients are the reduction of total sleep time, the presence of nightmares, and daytime sleepiness [26–28]. Several biological mechanisms have been recognized at the basis of sleep alteration in depressed patients [3]. Neuroendocrinal factors, circadian genes deregulation, and cholinergic, serotonergic and noradrenergic neurotransmission impairment have been documented [27]. Therefore, the modulation of serotonergic receptors may positively change sleep in depressed patients. Accordingly, not only the effects of VOR on different serotonergic receptors, but also on the cholinergic and noradrenergic neurotransmitting systems, may explain its positive effect on sleep quality and continuity in patients showing comorbid depression and insomnia.

It is conceivable that the improvement of the depressive state may be responsible for nocturnal sleep stabilization. Accordingly, insomnia comorbid with depression is frequently treated by antidepressants, which are targeted at restoring the depressive state. Consistently, the subjective measurement of sleep may be inappropriate in evaluating the sleep architecture and polysomnography remains the best instrument able to identify sleep macrostructure changes. In keeping with this evidence, polysomnographic studies are invited in evaluating the effects of antidepressants on sleep, since antidepressants may cause RLS, periodic limb movements and RBD, which may additionally alter sleep quality [6, 20]. Notably, in this study, no patient treated by VOR complained of sleep disorders at follow-up; in particular, no clinical suspicion of RBD or RLS was evident.

We are aware that this analysis has several limitations: (i) the effect of VOR on sleep was not prospectively assessed but retrospectively analysed based on subjective sleep questionnaires; (ii) subjective sleep and diurnal sleepiness were evaluated without PSG confirmation; (iii) the diagnosis of depression and insomnia was achieved in a Sleep Medicine Centre, where the subjective questionnaires were limited and the clinical interview focused primarily on sleep complaints; (iv) data were not systematically captured but documented in routine clinical records; (v) the sample of patients included is small and achieved in a single outpatient Sleep Medicine Centre; (vi) the design of this observation does not permit a population of patients treated by placebo or active comparator (antidepressants) and therefore a causal inference cannot be established.

Despite the limitations of our study, this first clinical retrospective investigation evaluating the effectiveness of VOR treatment on depressive and insomnia symptoms invites future prospective studies aimed at evaluating the impact of VOR on sleep architecture, also by using polysomnography.

Considering that insomnia is the most common subjective complaint in depressed patients [29, 30] and that depression has been shown to alter sleep structure [21], the main implication of this study is the efficacy of VOR treatment on depressive and insomnia symptoms in patients affected by comorbid MDD and insomnia. Notably, VOR improves subjective sleep quality and continuity in depressed patients. Hence, considering that sleep impairment is a frequent comorbid symptom in patients affected by MDD, we suggest the possible use of VOR for treating depressive symptoms and improving sleep quality in patients showing comorbid depression and insomnia. However, future studies investigating sleep by using polysomnography, the gold standard tool able to study sleep architecture, are invited in order to confirm this preliminary observation.

Competing Interests

There are no competing interests to declare.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

N.B.M. is the principal investigator of this manuscript; C.L. and F.P. were the two subinvestigators of this manuscript.

Contributors

L.M., A.D., and N.M. analyzed the data. C.L. and F.P. prepared the manuscript. L.F.-S. and F.I. critically revised the manuscript. N.B.M supervised the study.

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