

REVIEW

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# Alertness in patients with treatment-resistant depression: interface between sleep medicine and psychiatry—review article

Dusan Kolar<sup>1\*</sup>  and Michael V. Kolar<sup>2</sup>

## Abstract

**Background:** Treatment-resistant depression (TRD) is a significant problem in clinical practice and reason for the lack of functional recovery among depressed patients. Sleep disturbances and poor alertness are common residual symptoms.

**Main body of the abstract:** Many patients with refractory depression experience residual symptoms, such as insomnia, daytime sleepiness, and poor alertness. This is a literature review and we searched the electronic databases, including PubMed, the Cochrane database, Ovid MEDLINE, PsycINFO, and Google Scholar of all studies published between 2000 and 2020.

The literature on the relationship between sleep quality and alertness in a patient with depression is very sparse. One possible reason could be the difficulty in defining alertness as a mental function. Alertness itself has been described as a state of responsiveness to both interoceptive and external stimuli. Subjective and objective measures of alertness, daytime somnolence, and quality of sleep are presented. Adjunctive treatment with stimulant medications (methylphenidate, amphetamine, modafinil) to the standard antidepressant medications might be warranted in patients in patients with daytime sleepiness, decreased alertness, fatigue, and poor work performance.

**Short conclusion:** Patients with treatment-resistant depression usually suffer from poor quality of sleep and decreased alertness. Stimulant medications may help with alertness, daily functioning, and work performance.

**Keywords:** Alertness, Insomnia, Sleep quality, Depression, Treatment-resistant depression

## Background

Treatment-resistant depression (TRD) typically refers to inadequate response to at least two antidepressant trials of adequate doses and duration [1]. A correct determination of what constitutes TRD requires consensus on criteria of treatment response, including adequate dose, duration of treatment, and patient compliance on the number of adequate trials required before a patient is determined to be nonresponsive [2].

TRD is a common condition with up to 50 to 60% of MDD patients not achieving adequate response following antidepressant treatment [1].

A strong relationship between inflammation and depression has been observed. In patients with depression, markers of inflammation have been shown to be higher than in non-depressed individuals [3]. Sleep loss may cause the elevation of cellular inflammation and elevated levels of CRP (C-reactive protein) and IL-6 (interleukin 6) were associated with sleep impairment. Although the strong relationship between sleep disturbance, inflammation, and depression is obvious, the precise interaction between them remains unclear [4].

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Disordered sleep has been shown to disturb many aspects of emotional life including emotion regulation capacity. On the other hand, there is evidence that maladaptive emotion regulation is associated with depression and depressed individuals demonstrate increased use of maladaptive emotion regulation strategies [5]. Therefore, sleep disturbance in this way may worsen symptoms of depression and may contribute to the treatment resistance of depression.

Insomnia and sleep have a bidirectional relationship with depression and anxiety. Depression and anxiety affect sleep quality and the severity of insomnia [6]. Depressed patients with sleep disturbance are likely to present more severe symptoms and difficulties in treatment [4].

This paper presents a literature review of all available studies on alertness in patients with treatment-resistant depression published in the last 20 years.

## Methods

This was a literature review of the electronic database in PubMed, the Cochrane database, Ovid MEDLINE, PsycINFO, and Google Scholar of all studies using the following keywords: “depression and alertness”; “treatment-resistant depression and alertness”; “treatment-resistant depression, quality of sleep, alertness”; and “stimulant medications, antidepressants, and alertness” in the period from 2000 and 2020. We searched for randomized controlled trials, non-randomized controlled prospective studies, meta-analyses, systematic literature reviews, and case studies.

## Results

The literature on alertness in patients with treatment-resistant depression is very sparse, particularly in terms of the lack of randomized controlled trials.

We found only 3 studies specifically investigating alertness in patients with depression and a number of other relevant studies on sleep disturbances and quality of sleep affecting alertness in patients with treatment-resistant depression as it will be presented in the following sections.

### Sleep disturbance, quality of sleep, alertness, and treatment-resistant depression

Insomnia, the subsequent daytime sleepiness and decreased alertness are common residual symptoms of depression. Fatigue, excessive daytime sleepiness, and poor alertness as a result of sleep deprivation and poor sleep quality are likely the most common symptoms of depressive disorder [7]. These symptoms negatively influence patients' quality of life, their work performance, and ability to return to work, and as a result, many of them are on long-term disability. Remission of depression cannot

be fully achieved until insomnia and daytime sleepiness are resolved [8].

There are a number of sleep abnormalities among patients with major depressive disorder (MDD), including increased sleep-onset latency, frequent awakenings, decreased sleep efficiency, early morning awakenings, and decreased total sleep time. Disturbances in sleep architecture such as decreased REM latency and increased REM density, decreased slow-wave sleep, and increased intra-sleep awakenings are common in untreated patients with depressed moods [9].

Research studies suggest that poor non-depressed sleepers reported more daytime difficulties than good sleepers [10]. Poor sleep quality negatively influences attention and executive functions [11].

Sleep quality and daytime sleepiness correlate with fatigue severity measured with the Fatigue Severity Scale [12]. Sleepiness is defined as a tendency to fall asleep, drowsiness, and decreased alertness, whereas fatigue is usually operationalized as lack of energy, weakness, and feeling of exhaustion associated with impaired physical and/or cognitive functioning [13, 14]. Fatigue and symptoms of depression have a strong and significant impact on levels of alertness [15].

Diminished alertness, poor attention, and lack of concentration associated with excessive daytime sleepiness may cause substantial morbidity and mortality related to occupational injury and motor vehicle accidents [16].

Considering these relationships, sleep difficulties and alertness are important features of treatment-resistant depression, yet research in this area is only emerging.

Daytime sleepiness is not the same as poor alertness. Excessive sleepiness is a pathologically increased tendency to fall asleep, uncontrollable sleep, and increased need to take naps [15], and this condition is more present in obstructive sleep apnea (OSA).

Numerous studies report an association between depression and sleep apnea. Obstructive sleep apnea (OSA) is a common breathing-related sleep disorder, but it is often unrecognized and thereby underdiagnosed [17].

It is important to emphasize the difference between insomnia as a symptom of depression and sleep fragmentation often associated with insomnia due to breathing-related sleep abnormalities in patients with OSA. Polysomnography (PSG) findings in patients with major depression demonstrate an increase in sleep latency, decrease in slow-wave sleep, and a shortened REM latency, whereas the sleep of patients with OSA is fragmented and contains a lot of transitional sleep stages (stage 1) at the expense of REM sleep and slow-wave sleep [18]. However, these disorders are often comorbid, which further complicates the assessment and impact on daytime alertness of patients who suffer from both conditions.

The literature on the relationship between sleep quality and alertness in depression is very sparse. One possible reason may be the difficulty in defining alertness as a mental function. Sustained attention or vigilance is a cognitive construct that refers to the ability to maintain alertness over a period of time [19]. Alertness itself has been described as a state of responsiveness to both interoceptive and external stimuli. An alert individual is aware of the environment, capable of focusing on a task, neither sleepy nor fatigued, and able to concentrate and be motivated [20]. Alertness includes facets of attention, vigilance, and cognitive performance [15].

Based on the model of a combined network of alertness and visuospatial attention, Schock and colleagues demonstrated that decreased alertness in depression promotes visuospatial deficit in the left hemifield reflected as a rightward bias of spatial attention [21].

An important challenge in investigating alertness is the lack of established indicators of daytime alertness level. Matousek and colleagues demonstrated in their study that there was no correlation between scores of subjective symptoms in the daytime (lack of feeling refreshed in the morning, low working capacity, sleepiness, low mood, anxiety symptoms) and presumptive EEG alertness indicators [22].

A study on cognitive deficits in patients with primary insomnia revealed the following impairments in cognitive performances: mild to moderate impairments on specific cognitive functions, including working memory (retention and manipulation), episodic memory, problem-solving, reaction time, information processing, and selective attention. There were no differences in alertness, divided attention, sustained attention, vigilance, and general cognitive functioning as compared to healthy adults [23].

On the contrary, as compared with patients with primary insomnia, patients with major depressive disorder demonstrate common cognitive impairments in alertness, information processing speed, sustained and divided attention, spontaneous flexibility, verbal learning, and declarative memory. Memory deficits and other neurocognitive impairments are similar in unipolar depression and bipolar disorder [24, 25].

The results of Kayumov and colleagues' study showed that there is a significant difference between alertness in depressed patients and patients with sleep apnea. They proposed that alertness can be subcategorized into two types: maladaptive alertness usually seen in patients with depression and anxiety and associated with poor performance, and adaptive alertness without impaired daytime functioning. Depressed patients with disturbed sleep show greater daytime alertness, but it is maladaptive and associated with poor performance, while patients with sleep apnea and disturbed sleep do have more difficulties in maintaining daytime alertness [26].

### **How to measure alertness, daytime sleepiness, and sleep quality in patients with treatment-resistant depression?**

There are different instruments to assess the subjective and objective quality of sleep, daytime sleepiness, and alertness. The instruments for the quality of sleep, fatigue, and excessive sleepiness are well described and validated in sleep medicine, and measures of alertness are not sufficiently developed.

Objective sleep quality is usually determined by overnight polysomnography (PSG) and there is plenty of studies in this field. Subjective sleep quality is usually assessed using the Pittsburgh Sleep Quality Index (PSQI). This is a 19-items questionnaire with seven subcategories: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction [27].

*Subjective methods* of assessment of sleepiness, alertness, and fatigue include the Epworth Sleepiness Scale [28], Fatigue Severity Scale [29], Toronto Hospital Alertness Test (THAT), and ZOGIM Alertness Scale (ZOGIM-A).

Alertness could be assessed using the Toronto Hospital Alertness Test [20] and ZOGIM Alertness Scale [20].

Toronto Hospital Alertness Test (THAT) is a 10-item self-report measure which requires approximately 5 min for completion. It is designed to measure perceived alertness during the past week. Subjects rate all items on a 6-point scale ranging from 0 (not at all) to 5 (all the time).

Toronto Hospital Alertness Test (THAT) has been valid and has high re-test reliability in the determination of trait alertness level [20, 15]. In a study conducted by Shahid and colleagues, alertness measured using the THAT scale was significantly correlated with depressive symptoms, fatigue levels, and anxiety. As there is a significant correlation between alertness measured by THAT and depression, it is hypothesized that symptoms of depression are predictive of levels of alertness [15].

ZOGIM Alertness Scale (ZOGIM-A) is a 10-item self-report scale designed to measure the impact of various influences on subjective alertness (e.g., sleep loss, caffeine), anticipated benefits of increased alertness, and the proportion of daytime experience during which subject functions with a high level of alertness. The scale evaluates a respondent's experiences with alertness over the course of the day. The ZOGIM-A was created as an efficient and inexpensive alternative to laboratory measures such as the Maintenance of Wakefulness Test [27].

*Objective methods* of assessment of daytime sleepiness and alertness include Multiple Sleep Latency Test (MSLT) and Maintenance Wakefulness test (MWT). MSLT is a validated objective measure of the ability or tendency to fall asleep while the MWT measures the ability to stay awake for a defined time [30].

Maintenance of Wakefulness Test measures patient's ability to stay awake in a quiet, dark, and non-

stimulating room while sitting in a comfortable chair. The test consists of four 40-min trials at 2 h intervals. The MWT 40-min protocol may be used to assess an individual's ability to remain awake when his or her inability to remain awake constitutes a public or personal safety issue [30].

As alertness included aspects of attention, vigilance, and cognitive performance [15], a *brief cognitive assessment* should be an integral part of the comprehensive assessment of alertness in the context of sleep disturbances. Brief cognitive assessment should assess at least critical domains of attention and processing speed.

The Visual Cancellation Test measures visual attention, visual neglect, and organizational process. Participants look at an array of 100 symbols and cross out specific targets.

The Digit Span Test in the Wechsler batteries is used to measure working memory, immediate verbal recall, and auditory attention; participants listen to and then repeat a series of digits in order forward for the first part of the task and then backward order for the second part [31].

The Continuous Performance Test (Conners) is a task-oriented computerized assessment of attention-related problems. This test is a good measure of sustained attention or vigilance and requires the participant to press a button following repetitions of identical stimuli (i.e., two four-digit numbers) and resist responding to distractors [31].

### Treatment recommendations

An appropriate and comprehensive assessment of the patient including clinical assessment, sleep study, MSLT, or MWT is required for all patients with depression and accompanied sleep disturbances, poor quality of sleep, daytime sleepiness, decreased alertness, and impaired daily functioning. This assessment will provide an outline of possible treatment options.

A few different classes of medications could be helpful in improving alertness in patients with treatment-resistant depression. Suggested treatment options will be discussed based on the available evidence.

First of all, if a comorbid obstructive sleep apnea is diagnosed, treatment will include the continuous positive airway pressure (CPAP). Even patients with undiagnosed sleep apnea may benefit from sleep study and starting treatment with the continuous positive airway pressure, in addition to their treatment for depression.

Bupropion as a dual norepinephrine and dopamine reuptake inhibitor significantly improves cognitive function, global function, and measures of work productivity in patients with major depressive disorder. It is less likely how escitalopram exerts all these effects on cognition [32]. Some other antidepressants such as mirtazapine may also improve daytime alertness and driving safety

despite its sedating effects [33]. Vortioxetine, 5-HT<sub>3</sub>/5-HT<sub>7</sub> receptor antagonist may also improve cognitive performance in patients with MDD [34].

Adjunctive treatment with stimulant medications (methylphenidate, amphetamines) to the standard antidepressant medications might be warranted in carefully selected patients with treatment-resistant depression. By increasing dopamine levels in the brain, stimulant medications improve alertness and concentration [35]. Lisdexamfetamine significantly improves residual symptoms of depression including inattention, executive dysfunction, and daily functioning in patients with the major depressive disorder [36]

Modafinil, similar to methylphenidate and amphetamines, with its dopaminergic and noradrenergic effects, increases alertness, improves fatigue, mood, and overall cognitive functioning [37]. Modafinil may alleviate the effects of sleep deprivation when sustained alertness and sustained performance are needed [35]. This medication has no addictive properties like amphetamines.

We should be careful with overusing stimulant medications as just cognitive enhancers because of its addictive potential and lack of sustained benefits [38] and limit the usage of this class of medication only for patients with residual symptoms of depression, such as decreased alertness, poor concentration, and resulting in poor work performance.

Melatonin is a pineal gland hormone which influences the maintenance of circadian rhythms. The mechanisms through which melatonin can exert neuroprotective and cognitive-enhancing effects include anti-inflammatory and antioxidant properties, but it also may enhance neuroplasticity [39].

Similar to melatonin, agomelatine, another melatonergic analog drug acting as an MT<sub>1</sub> and MT<sub>2</sub> agonist and 5-HT<sub>2C</sub> antagonist, stabilizes abnormal circadian rhythmicity, prevents sleep disruption, and has precognitive effects through increasing neuroplasticity [40].

### Discussion

Treatment-resistant depression (TRD) is a common condition and up to 50 to 60% of MDD will not reach remission with adequate antidepressant treatment [1]. Insomnia and the subsequent decreased alertness, daytime sleepiness, and fatigue are common residual symptoms of depression [7]. It is obvious that the quality of sleep is also impacted and poor sleep quality, in turn, negatively influences attention and executive functions [11]. Poor alertness, inattention, and decreased concentration may cause substantial morbidity and mortality related to occupational injury and motor vehicle accidents [16]. Sustained attention is a cognitive construct that refers to the ability to maintain alertness over a period of time [19]. Alertness itself has been described as a state of responsiveness to both interoceptive and

external stimuli [20]. Alertness includes aspects of attention, vigilance, and cognitive performance [15]. Kayumov and colleagues [26] very appropriately categorized alertness into maladaptive alertness which is usually present in patients with depression and associated with poor performance and adaptive alertness. Besides this group of authors and Shapiro's teams, there are no other published papers on the alertness in specifically patients with refractory depression. Toronto Hospital Test (THAT and ZOGIM are the only instruments that measure alertness directly. All other described instruments present indirect measures for alertness. Therefore, further validation of the THAT and ZOGIM would be very important. A brief cognitive assessment should be an integral part of the comprehensive assessment of alertness in patients with sleep disturbances. With regard to treatment options for patients with poor alertness in the context of treatment-resistant depression, it is quite expected that stimulant medications, bupropion, and modafinil with its dopaminergic and noradrenergic effects could improve alertness. The role of melatonin and agomelatine should be further elucidated.

## Conclusion

Literature on alertness in patients with treatment-resistant depression is very sparse, particularly in terms of randomized controlled trials. Treatment-resistant depression is a significant problem in clinical practice and the reason for the lack of functional recovery among depressed patients. Many patients experience residual symptoms of depression, such as insomnia, poor alertness, daytime sleepiness, and lack of energy. These symptoms negatively influence patients' quality of life, their occupational functioning, and ability to return to work, and as a result, many patients are on long-term disability. Therefore, a thorough assessment and an appropriate treatment are needed. Besides CPAP for patients with comorbid OSA and antidepressants, stimulant medications (MPH, amphetamines) and modafinil are possible treatment options for this population of patients.

## Abbreviations

TRD: Treatment-resistant depression; MWT: Maintenance of Wakefulness Test; MSLT: Multiple Sleep Latency Test; THAT: Toronto Hospital Alertness Test; OSA: Obstructive sleep apnea

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## Authors' contributions

MK performed the literature review for the paper and did some editing of the finalized manuscript. DK wrote this paper. Both authors read and approved the final manuscript.

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## Declarations

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No human subjects were included.

### Consent for publication

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### Competing interests

The authors declare that they have no competing interests.

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