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CLINICAL REVIEW

Medication induced sleepwalking: A systematic review

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SUMMARY

Medications that trigger sleepwalking may inadvertently put the patient at risk of injury to themselves and/or others, and contribute to poor treatment adherence. The aim of this study was to systematically review the literature to identify drugs that may increase the risk of sleepwalking. A search of CINAHL, EMBASE, PsycINFO, PubMed, and ScienceDirect was conducted with the keywords 'sleepwalking' OR 'somnambulism'. Of the original 83 sourced papers, 62 met the inclusion criteria and were subsequently included for review. Twenty-nine drugs, primarily in four classes—benzodiazepine receptor agonists and other gamma aminobutyric acid (GABA) modulators, antidepressants and other serotonergic agents, antipsychotics, and β-blockers—were identified as possible triggers for sleepwalking. The strongest evidence for medication-induced sleepwalking was for zolpidem and sodium oxybate. All other associations were based on case reports. This research highlights the importance of considering sleepwalking in risk profiles in clinical trials, particularly for drugs that enhance GABA activity at the $GABA_A$ receptor, enhance serotonergic activity, or block the activity of noradrenaline at β receptors. The results also have implications for prescribers to consider sleepwalking as a potential adverse effect and ensure that: 1) the patient is educated about a safe sleep environment; 2) they are encouraged to report the onset or exacerbation of sleepwalking, and 3) alternative treatments are considered if sleepwalking occurs.

Medication induced sleepwalking: A review of the evidence

Sleepwalking, or somnambulism, occurs in non-rapid eye movement (NREM) sleep, predominantly during slow wave sleep (SWS) [1] and appears as a disorder of arousal regulation [see [2] for a review]. While frequently innocuous, it can result in injury to the sleepwalker, to others, and sometimes even death [e.g., [3–5]]. The estimated prevalence of sleepwalking is 5.0% (95% CI 3.8–6.5) in children and 1.5% (95% CI 1.0–2.3) in adults [6]. There is no difference in lifetime prevalence rates of sleepwalking between adults and children [6], suggesting that first time sleepwalking is relatively uncommon in adulthood. Adult-onset sleepwalking may therefore signify environmental or neurological disease triggers, (for example Parkinson's disease [7]).

Although there are no evidence-based treatments for sleepwalking, a range of pharmacological interventions are used to treat the condition, including anticholinergics, antiepileptics, antipsychotics, benzodiazepines, melatonin, selective serotonin reuptake inhibitors, and barbiturates [8]. However, as will be evident from the present review, a number of these medications may actually trigger sleepwalking. A better understanding of the association between medication use and sleepwalking is likely to aid treatment planning, as well as shed light on the underlying mechanisms involved in causing sleepwalking events.

Neurobiology of sleepwalking

Increased interruption of the typical progression of sleep neurophysiology during SWS, and reduced slow wave intensity during early sleep cycles, are commonly observed in sleepwalkers [9–12]. At the level of specific arousal events within SWS, sleepwalkers show greater frequency of arousal to auditory stimulation, despite preserved arousal thresholds [13]. Furthermore, increased slow and high frequency brain activity and higher density of slow waves immediately preceding a sleepwalking event [14–16], as well as a high proportion of delta activity post-arousal have been observed [2,17]. Together, these results suggest abnormal arousal and arousal response predominantly in SWS as the core neurophysiological features of sleepwalking.

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Curiously, sleepwalkers do not show the typical SWS rebound following periods of sleep deprivation [18]. Rather, long periods of sleep deprivation, greater than 24 h, appear to trigger sleepwalking behavior, with sleepwalking events also containing more overt and complex behavior following sleep deprivation [18,19]. This suggests that the processes impacted by sleep deprivation may act in a feed-forward manner to further promote sleepwalking in predisposed individuals. Sleep deprivation is known to result in autonomic hyperactivation to stimulation [20–23] as well as reduced inhibitory control mechanisms [24–27]. Recently, reduced blood flow in the inferior temporal gyrus, an area of the brain implicated in response inhibition [28], was shown in sleepwalkers following sleep deprivation when compared to healthy controls [29]. Indeed, sleepwalkers show impaired wake inhibitory control behavior when compared to non-sleepwalkers following sleep deprivation [30]. Using transcranial magnetic stimulation to examine the excitability of the motor cortex during wakefulness in sleepwalkers and controls, Oliviero et al. found reduced inhibition consistent with impaired GABAergic neuronal inhibition and reduced cholinergic activation [31]. Specifically, this pattern of activity could explain disinhibited motor activity coincident with difficulty arousing from sleep in sleepwalkers.

Medications can affect the neurobiology that precipitates sleepwalking

Such neurobiological mechanisms are important to understand in the context of pharmacological treatment for sleepwalking [8], but also for understanding medication-induced sleepwalking occurrences. There are a number of purported mechanisms whereby prescribed medications may trigger sleepwalking in vulnerable individuals. Sedative pharmacological interventions, for example, are hypothesized to reduce the duration of SWS, when sleepwalking typically occurs, thereby limiting opportunities for sleepwalking. Benzodiazepines, potentiate the effects of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) throughout the central nervous system (CNS), resulting in anxiolytic, sedative, hypnotic, muscle relaxant and antiepileptic effects [32] and reduced slow wave sleep duration [33]. Antidepressants are also thought to reduce sleepwalking either through their anxiolytic properties [34] or by reducing the partial arousal that is characteristic of sleepwalking [35]. Anticholinergic medication is used to address a proposed cholinergic mechanism in sleepwalking [e.g., [36]]. Antipsychotics are thought to decrease slow wave sleep, and therefore also limit sleepwalking occurrences [37].

Reports of medication-induced sleepwalking have appeared across the last four decades, however, to date, such reports have not been systematically reviewed. Systematically summarizing the reported effects is likely to provide important information for improving the estimation of adverse drug reactions, identifying classes of drugs that may trigger sleepwalking, and may also improve our understanding of underlying mechanism of the condition. Toward this end, the aim of this study is to systematically review the evidence for medications causing sleepwalking.

Method

This systematic review examined studies that reported prescribed medication linked to sleepwalking behavior. The following databases were included in the identification of relevant studies: CINAHL, EMBASE, PsycINFO, PubMed, and ScienceDirect. Initial search terms were ‘sleepwalking’ or ‘somnambulism’. Studies were included if they reported clinical trials, cases studies or case reports involving prescribed drug-induced sleepwalking in any field. Studies were excluded if: 1) they included forensic samples—to avoid cases confounded by possible secondary gains; or 2) if they only reported sleep eating or sleep driving—to avoid confounding possible behaviors that occurred with subsequent amnesia caused by drugs, without sleepwalking. The combined lists were screened for relevant titles and abstracts and all potentially relevant titles were examined. We identified other pertinent studies through citation tracking, review of reference lists of retrieved articles and our knowledge of the literature. The search dates were from the database start date through to 1 May 2016.

The initial literature search was conducted by the first author. The third author reviewed all studies independently. There was 100% agreement between authors on included and excluded studies. The data extracted comprised study characteristics (authors, publication year, and population), study design, participant characteristics (sex and age) and sleepwalking history of participants. Our findings were synthesized and described narratively.

Results

Fig. 1 displays the flow of information through the different phases of the systematic review. A total of 62 studies describing medication-induced sleepwalking were identified. All but four studies were case reports. One case study of paroxetine-induced sleepwalking was published in two different journals [38,39]—only one is discussed [39] in this review.

Table 1 provides a summary of the class of drug, drug name, number of studies for each drug type, year published, study design, number of sleepwalkers, participant sex, and age for each study that found medication-related sleepwalking. Twenty-nine drugs were reported to be associated with sleepwalking. These were primarily from the following drug classes: benzodiazepine receptor agonists, atypical antipsychotics, antidepressants and other serotonergic agents and β-blockers. The majority of studies reported on adults with no prior history of sleepwalking. A qualitative synthesis of the evidence for the association between each class of drug and the individual drugs and sleepwalking is considered below.

Benzodiazepine receptor agonists and other GABA modulators

The review of zolpidem-related sleepwalking identified cross-sectional surveys [40,41], marketing or open trials [42–44], and case reports—16 with adults [45–58] and two with adolescents [59,60]. The two post-marketing reviews of adult patients found the incidence of zolpidem-induced sleepwalking rates were 0.5% [42] and 1.1% [43]—in children the rate was 2.2% [44]. In a psychiatric sample, it was 5.1% [41].

Case reports included patients with complex medical histories or who were concurrently taking other medications [41,45,47,49–51,60–63] and patients who were otherwise healthy aside from their presenting problem [48,53,55,56]. There was one report of zolpidem interacting with an anticonvulsant medication prior to sleepwalking [50]. Only one case study reported alcohol being combined with zolpidem to precipitate sleepwalking [56]. Individual case reports showed that while there are cases of sleepwalking as a consequence of higher than recommended doses of zolpidem [48,51,63], more commonly zolpidem precipitated sleepwalking at the recommended dose [45,46,49,52,53,55,61,62]. Only one case study reported a previous history of sleepwalking during childhood [53]; all others reported participants experiencing sleepwalking for the first time subsequent to taking zolpidem [48–50,52,55,60–62]. There were no case reports that included a history of sleepwalking during adulthood.

In contrast to the substantial literature on zolpidem, the systematic review identified only two case reports that described sleepwalking associated with zaleplon [64,65] and one for

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