Prescription of approved hypnotics for insomnia decreased by more than 50%, whereas of antidepressive agents outstripped that of hypnotics. However, there is little data on their efficacy to treat insomnia, and many of these medications may be associated with known side effects. Antidepressants are associated with various effects on sleep patterns, depending on the intrinsic pharmacological properties of the active agent, such as degree of inhibition of serotonin or noradrenaline reuptake, effects on 5-HT1A and 5-HT2 receptors, action(s) at alpha-adrenoceptors, and/or histamine H1 sites. Mirtazapine is a noradrenergic and specific serotonergic antidepressive agent that acts by antagonizing alpha-2 adrenergic receptors and blocking 5-HT2 and 5-HT3 receptors. It has high affinity for histamine H1 receptors, low affinity for dopaminergic receptors, and lacks anticholinergic activity. In spite of these potential beneficial effects of mirtazapine on sleep, no placebo-controlled randomized clinical trials of mirtazapine in primary insomniacs have been conducted. Mirtazapine was associated with improvements in sleep on normal sleepers and depressed patients. The most common side effects of mirtazapine, i.e. dry mouth, drowsiness, increased appetite and increased body weight, were mostly mild and transient. Considering its use in elderly people, this paper provides a revision about studies regarding mirtazapine for sleep disorders.

KEYWORDS: sleep; antidepressive agents; sleep disorders; treatment.

A prescrição de hipnóticos aprovados para insônia diminuiu em mais de 50%, enquanto de antidepressivos ultrapassou a dos primeiros. Entretanto, existem poucos dados sobre a sua eficácia no tratamento da insônia, e muitas dessas medicações podem estar associadas com efeitos adversos desconhecidos. Antidepressivos estão associados com vários efeitos nos padrões do sono, o que depende basicamente das propriedades farmacológicas dos agentes ativos, tais como o grau de inibição dos receptores de serotonina ou noradrenalina, os efeitos nos receptores 5-HT1A e 5-HT2, a(s) ação(ões) no receptor alfa-adrenérgico e/ou sítios histaminérgicos. A mirtazapina é um antidepressivo específico, noradrenérgico e serotonérgico que atua antagonizando os receptores alfa-2 adrenérgicos e bloqueando os receptores 5-HT2 e 5-HT3. Tem uma afinidade elevada para os receptores histaminérgicos H1, baixa afinidade para os receptores dopaminérgicos e carece de atividade anticolinérgica. Apesar destes efeitos benéficos potenciais da mirtazapina no sono, não há ensaios clínicos randomizados controlados com placebo sobre a mirtazapina em insônia primária até o momento. A mirtazapina foi associada com melhorias no sono em indivíduos insones e em pacientes com depressão. Os efeitos colaterais mais comuns da mirtazapina, como boca seca, sonolência, aumento de apetite e aumento de peso corporal, foram, sobretudo, rápidos e transitórios. Considerando seu uso frequente na população geriátrica, este manuscrito traz uma revisão acerca do uso da mirtazapina em transtornos do sono.

PALAVRAS-CHAVE: sono; antidepressivos; transtornos do sono; tratamento.
Mirtazapine as a hypnotic

INTRODUCTION

Analyses of clinical practices conducted in the past decades have shown that the prescription of approved hypnotics decreased by more than 50%, whereas antidepressants outstripped that of hypnotics. Three of the four most commonly used medications for insomnia are antidepressive agents, including trazodone, amitriptyline, and mirtazapine. Prescribers believe that antidepressive agents are more effective, safer, and cause less dependence or fewer side effects when compared with hypnotic medications. However, there is little data on their efficacy to treat insomnia, and many of these medications may be associated with known side effects.

ANTIDEPRESSIVE AGENTS AND SLEEP

Antidepressive agents are associated with various effects on sleep patterns in users of this medication class. This wide range of responses depends on the intrinsic pharmacological properties of the active agent, such as inhibition degree of serotonin or noradrenaline reuptake, effects on 5-HT1A and 5-HT2 receptors, and action(s) at alpha-adrenoceptors and/or histamine H1 sites. Although some of them can cause insomnia, many antidepressive agents have sedating properties, thus they become an option for the treatment of insomnia and other sleep disorders. Antidepressants that increase serotonin function decrease the amount of REM sleep predominantly in the beginning of the treatment. Thus, serotonin 5-HT2-receptor antagonists reduce sleep fragmentation and promote slow-wave sleep. Inhibition of alpha 2-adrenoceptors increases noradrenaline availability, and therefore may be associated with sleep fragmentation. Blockade of the receptor sites of alpha 1-adrenoceptors and histamine H1 may facilitate sleep promotion.

MIRTAZAPINE EFFECTS ON SLEEP

Mirtazapine is a tetracyclic piperazino-azepine, which has a different structure from any other currently available antidepressive agents. It has a dual mode of action. It is a noradrenergic and specific serotoninergic antidepressant, which acts by antagonizing alpha-2 adrenergic receptors and by blocking 5-HT2 and 5-HT3 receptors. Mirtazapine has high affinity for histamine H1 receptors, low affinity for dopaminergic receptors, and lacks anticholinergic activity.

With regard to its impact on sleep patterns, mirtazapine seems to produce effects on the electroencephalogram that are significantly different from those of other antidepressive agents. The prominent anti-histaminergic properties of this medication may result in a sedative effect, which also seems to be mediated by 5-HT2 receptor blockade. Sedation is more pronounced at 15 mg-day doses than at doses ≥ 30 mg per day, probably due to exacerbation of noradrenergic neurotransmission at increased doses. Another factor that may also contribute to the sleep-improving mirtazapine property is the increased synthesis of melatonin because of noradrenergic action.

In spite of these potential beneficial effects of mirtazapine on sleep, no placebo-controlled randomized clinical trials about mirtazapine in primary insomniacs have been conducted yet. In normal sleepers, it has been shown to decrease sleep latency, increase total sleep time and the amount of deep sleep compared with placebo. Aslan et al. demonstrated that mirtazapine was associated with improvements in sleep efficiency and reduced wake time after the onset of sleep (WASO) compared with placebo, in healthy subjects.

Insomnia traits in the context of depression also generally reduce the use of mirtazapine. In placebo-controlled studies, mirtazapine has been reported to improve subjective complaints of sleep disturbance in depressed patients. In this scenario, two open-label studies using sleep polysonmographic records showed decrease in sleep latency (p = 0.009), increase in total sleep time (1 hour), and increase in sleep efficiency (9%) from baseline levels (p = 0.004 and p = 0.003, respectively).

Mirtazapine was likewise shown to result in more rapid and favorable relief of insomnia symptoms versus venlafaxine and fluoxetine, in a study that included polysomnographic monitoring. A follow-up investigation about sleep changes and endocrine traits during treatment of depressed patients with mirtazapine found decreased secretion of cortisol and increased secretion of melatonin throughout the night among antidepressant users. This biochemical milieu is compatible with the clinical findings characterized by sleep parameters with increased total sleep time, improved sleep efficiency, and reduced time spent awake.

SIDE EFFECTS AND TOXICITY

The incidence of the most common mirtazapine side effects was reviewed in a meta-analysis conducted by Fawcett and Barkin. Dry mouth (25%), drowsiness (23%), increased appetite (11%), and increased body weight (10%) were more frequent in the intervention group compared with placebo. However, they were mostly mild and transient. In comparison with other classes of antidepressive agents in terms of individual adverse events, a meta-analysis evidenced that mirtazapine was significantly more likely to cause weight gain, increased appetite (RR = 3.68) or somnolence (RR = 1.62) compared with selective serotonin uptake inhibitors. Nevertheless, patients may develop tolerance to the sedating effects of mirtazapine.
There are some reports of restless leg syndrome (RLS) as a mirtazapine side effect in depressed patients, which is more frequent than the use of other antidepressive agents. The pathophysiology of mirtazapine-associated RLS is unclear but may be associated with dopaminergic hypofunction. Considering that RLS may lead to sleep disturbances, this side effect could interfere with the treatment of depression and sleep disorders.

No clinically significant alterations in heart rate or blood pressure were reported in clinical trials with mirtazapine, even in geriatric patients. Unlike selective serotonin reuptake inhibitors, mirtazapine is associated with a very low incidence of sexual dysfunction. The antidepressant effects of mirtazapine were studied in geriatric patients, and the medication was well tolerated. Depressed elderly patients on mirtazapine treatment were less likely to take sedative or hypnotic drugs. Excessive sedation seems to be the main effect of a mirtazapine overdose.

CONCLUSIONS

Potential improvements in sleep patterns caused by antidepressant medications, such as mirtazapine, make these drugs possible alternatives to treat insomnia. Compared with trazodone, the most frequently used antidepressive agent for insomnia, mirtazapine has the advantage of fewer cardiovascular adverse effects and anticholinergic activity.

Lack of placebo-controlled, double-blind trials on the effects of antidepressive agent as a hypnotic drug on patients with insomnia is probably a result of the absence of interest from the pharmaceutical industries in assessing the effectiveness and safety of drugs no longer under patent reserves. Even more worrisome is the fact that health authorities seem to neglect the actual health practices and the evidence that the literature has produced so far.

Because of data shortage that still hampers evidence-based recommendations, further long-term comparative studies are needed to define the role of mirtazapine versus placebo (or other agents) in the management of primary insomnia, possibly focused on those population groups that are particularly vulnerable to sleep disorders, such as elderly individuals and demented patients.

CONFLICT OF INTERESTS

The authors have no financial conflicts of interest to declare apart from Einstein F. Camargos, Ph.D., who is currently receiving personal payment from Novartis Pharma as speaker.

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