REVIEW ARTICLE

Past and present in drug treatment of sleep disorders

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Abstract

Sleep disorders are frequent and disturbing, mostly chronic conditions. Despite the fact practice of sleep medicine is a young field. Sleep disorders were reduced to insomnia and even insomnia was not well studied until 1960ies. This article maps amazing development of sleep disorders treatment from the beginning till current date. The text covers both scientific and clinical perspectives on most frequent sleep related disorders including insomnias, hypersomnias, parasomnias, sleep related movement and breathing disorders, restless legs syndrome and circadian rhythm sleep disorders.

INTRODUCTION

Substantial growth in sleep disorders ethio-pathophysiology research started with discovery of benzodiazepines combined with positive economic and social situation in many countries. Benzodiazepines as the first efficient and relatively safe therapy of insomnia (and some other sleep disorders) gave the first impulse for clinical research and clinical practice of this interdisciplinary medical field. Some countries even constituted sleep medicine as independent specialty. Both United States and European sleep centers developed the sleep medicine concept. Rise in number of specialists and new sleep centers together with general awareness of sleep disorders followed. This positively influenced clinical pharmacologic research in common as well as rare sleep diseases. The most important milestones in pharmacotherapy of sleep disorders so far occurred before the end of 20th century.

2014 is the year of publication of the third edition of International Classification of Sleep Disorders. This new classification preserves six main groups of sleep disorders from the second edition published 9 years before: 1. insomnia, 2. sleep related breathing disorders, 3. central disorders of hypersomnolence, 4. circadian rhythm sleep-wake disorders, 5. parasomnias, and 6. sleep related movement disorders (American Academy of Sleep Medicine 2014). This grouping is made according to principal symptoms. This chapter respects the same grouping (except for circadian rhythm sleep-wake disorders).

Treatment of sleep diseases includes regime change, sleep hygiene, psychotherapy, pharmaco-

therapy and in case of sleep related breathing disorders positive pressure and non-invasive ventilation. This article is devoted to pharmacotherapy; other therapeutic approaches are therefore not mentioned in details, despite their importance.

Sleep disorders in childhood have no special categorization. Though frequent, their prevalence is not similar to those in adulthood. No high level studies concerning treatment of child sleep disorders exist and sleep disorders guidelines are not focused on patients of young age.

INSOMNIA

Insomnia is one of the most common sleep-wake disorders. Almost one third of the Western countries population reports some symptoms of insomnia during any given year (Ellis *et al.* 2012). Women report insomnia twice as often as men and women also more often report problems initiating sleep (Jaussent *et al.* 2011). The essential feature of insomnia disorder is dissatisfaction with sleep quantity or quality with complaints of difficulty initiating or maintaining sleep. Sleep complaints are accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning (DSM-5 2013). Different manifestations of insomnia can occur at different times of the sleep period. Sleep-onset insomnia involves difficulty initiating sleep at bedtime. Sleep maintenance insomnia involves frequent or prolonged awakenings throughout the night or early-morning awakening with an inability to return to sleep. Difficulty maintaining sleep is the most common single symptom of insomnia, followed by difficulty falling asleep, while a combination of these symptoms is the most common presentation overall (DSM-5 2013). Insomnia is uniquely associated with significant decrements in perceived physical and mental health (Roth *et al.* 2011). Additionally, older adults with insomnia may be at risk of cognitive decline (Pace-Schott & Spencer 2011).

Historical agents

The first synthetically produced sedative-hypnotic drug was chloral hydrate. Chloral hydrate was first synthesized in 1832, but it was not introduced into medicine until 1869, when its effectiveness in inducing sleep was first published (Liebreich 1869). Very soon, chloral hydrate substituted morphine and alkaloids, because of its easy synthesis and administration (Shorter 2005). Nevertheless, most widely used sedatives in the second half of the 19th century were the bromide salts introduced in 1857. Between the 1920s and the mid-1950s, practically the only drugs used as sedatives and hypnotics were barbiturates, synthesized in 1863. The first of the barbiturates to come onto the market was diethylbarbituric acid, also known as barbital (marketed as Veronal; Bayer company, patented in 1903) (López-Muñoz *et al.* 2005). During the next 40 years, more than 2500 different barbiturate preparations followed, including:

- phenobarbital (Luminal; Bayer company, patented in 1911)
- pentobarbital sodium (Nembutal; Bayer company, patented in 1916)
- amobarbital sodium (Sodium Amytal; Lilly, patented in 1924)
- butabarbital sodium (Butisol Sodium; Lilly, patented in 1932)
- secobarbital sodium (Seconal Sodium; Lilly, patented in 1934)
- thiopental sodium (Pentothal Sodium; Abbott, patented in 1939)

The first drug from chemical class of benzodiazepines (BZDs) – chlordiazepoxide – was patented in 1959. The following drug which became by the late 1960s the most successful drug in pharmaceutical history was diazepam launched in 1963. The BZDs were a highly successful drug class because they acted effectively, while at the same time relatively safe, although they were later marked as addictive. They virtually drove barbiturates from the field as hypnotics and sedatives of choice. By the 1990s, there were more than a hundred different benzodiazepines, among other popular were the following:

- oxazepam (introduced in 1965)
- flurazepam (introduced in 1970)
- clonazepam (introduced in 1975)
- flunitrazepam (introduced in 1976)
- lorazepam (introduced in 1977)
- midazolam (introduced in 1979)
- temazepam (introduced in 1981)
- alprazolam (introduced in 1981)
- triazolam (introduced in 1982)
- quazepam (introduced in 1985)
- estazolam (introduced in 1991)
- cinolazepam (introduced in 1993)

Benzodiazepine receptor agonists

There are two types of the current FDA (Food and Drug Administration) or EMA (European Medicines Agency) approved benzodiazepine receptor agonists (BzRAs) for insomnia. The older group with a benzodiazepine chemical structure includes the hypnotics: flurazepam, temazepam, triazolam, quazepam, estazolam (all FDA-approved) (Erman 2005); and cinolazepam, midazolam (both EMA-approved). These agents show no strong selectivity for a particular receptor subtype. The newer group with a non-benzodiazepine chemical structure (Z-drugs) includes zopiclone (introduced in Europe in 1986, not FDA-approved), zolpidem (introduced in Europe in 1988, in the US in 1993), zaleplon (introduced in 1999), and the es-enantiomer of zopiclone, eszopiclone (introduced in the US in 2005, not

licensed in the EU). These agents differ by their elimination half-lives: zopiclone and eszopiclone are intermediate-acting; zolpidem is short-acting; and zaleplon is ultrashort-acting (with an elimination half-life of just 1 hour). All non-benzodiazepine BzRAs are appropriate to treat sleep-onset insomnia, but their effects vanishes during the night (Lader 2011). These agents do not alter slow-wave sleep or REM sleep and the rebound insomnia following cessation is not as pronounced as in benzodiazepines.

The BzRAs are positive allosteric modulators of gamma-aminobutyric acid (GABA) responses at the $GABA_A$ receptor protein complex. Non-benzodiazepine BzRAs possess similar pharmacological properties by binding to benzodiazepine binding site on the $GABA_A$ receptor protein complex, even though they are not benzodiazepines (Montagna & Chokroverty 2012).

Relative incidence of reported addictions is similar for zolpidem and zopiclone and remarkably lower than that of benzodiazepines used for the treatment of insomnia (Hajak *et al.* 2003). There is some risk of tolerance and addiction development, but the risk can be reduced by intermittent BzRA use (Montagna & Chokroverty 2012).

Melatonin receptor agonists

Two well-established physiological effects of melatonin, promotion of sleep and entrainment of circadian rhythms are both mediated by two specific receptor proteins in the brain. Unlike the GABA-agonist drugs, exogenous melatonin neither suppress rapid eye movement (REM) sleep nor, in general, affect the distribution of sleep stages (Zhdanova *et al.* 2001).

Randomized clinical trials have failed to show an effect of supplemental melatonin on sleep efficiency in primary insomnia. Melatonin was more effective in reducing sleep onset latency in patients with delayed sleep phase syndrome than in primary insomnia (Buscemi *et al.* 2004). Because melatonin has a short elimination half-life (range from 0.5 to 2 hrs), attention has been focused either on the design of slow-release melatonin preparation (approved by the EMA in 2007) or on the development of more potent melatonin analogs with prolonged effects. The high-affinity melatonin MT1/MT2 receptors agonist, ramelteon (approved by the FDA in 2005), was effective in increasing total sleep time and sleep efficiency, as well as in reducing sleep latency, in insomnia patients (Pandi-Perumal *et al.* 2009).

The melatonergic antidepressant agomelatine, potent MT1/MT2 agonist and relatively weak serotonin $5\text{-}HT_{2C}$ receptor antagonist, was found effective in the treatment of depression-associated insomnia [see (Brzezinski 2014) for the review]. Other melatonergic compounds are currently developed.

Tasimelteon (approved by FDA in November 2013, intended to be launched in the second quarter of 2014) was granted orphan drug designation by the US FDA and the EMA for the treatment of blind individuals with non-24-hour sleep-wake disorder. Compared with melatonin, tasimelteon has slightly lower affinity for the melatonin MT1 receptor and a moderately higher affinity for the MT2 receptor (Dhillon & Clarke 2014).

Sedating antidepressants and atypical antipsychotics

The use of antidepressants to treat insomnia is widespread, but can be considered to be 'off-label' as none is licensed for insomnia; there are limited published data on the appropriate use of such agents in insomnia. Nonetheless, use of antidepressants and, increasingly, antipsychotics, is commonplace in insomnia therapy. Typically, doses used to treat insomnia are below the antidepressant dose. On the other hand, the safety profile of sedating antidepressants is not impressive compared to the BzRAs; however, most safety data is for antidepressant doses, not hypnotic ones.

Sedating tricyclic and tetracyclic antidepressants, which include amitriptyline, doxepin, nortryptiline, trimipramine, mianserin and others, act by inhibiting the uptake of norepinephrine and serotonin, and by blocking histamine and acetylcholine. They can increase total sleep time (TST) and N2 sleep stage, but suppress REM sleep. The tricyclics are known to impair cognition and psychomotor performance in antidepressant doses especially in the elderly (Kamel & Gammack 2006). Other first-generation antidepressants, the monoamine oxidase inhibitors, inhibit enzymes involved in metabolism of norepinephrine, serotonin, and dopamine either irreversibly or reversibly depending on the agent. These are not considered sedating but can disturb nighttime sleep with shorter TST and REM suppression, thereby worsening daytime symptoms (Sullivan 2010). Low-dose doxepin was FDA-approved (in 2010) for insomnia characterized by frequent or early-morning awakenings and an inability to return to sleep (Markov & Doghramji 2010).

Several serotonin-modulating antidepressants, such as trazodone and nefazodone, are used for insomnia, especially depression-associated insomnia (Mendelson 2005). Trazodone, a sedating antidepressant with inhibition of serotonin, alpha-1, increases TST. It may be associated with daytime hypersomnolence, cardiac arrhythmias, orthostatic hypotension, and, notably, priapism, which may limit its use. Although this agent may have use in those with comorbid depression, data in nondepressed patients with insomnia are limited and side effects including weight gain, dizziness, and psychomotor impairment have led to relatively high rates of discontinuance (Everitt *et al.* 2013). Nefazodone is similar to trazodone in its serotonin receptor blockade, but is less active at alpha-1 receptors and has no activity at histamine receptors. Drowsiness is a dose-dependent side effect (Robinson *et al.* 1996).

Mirtazapine, a selective alpha-2, serotonin, and histamine receptor blocker (Nutt 1997), is another antide-

pressant associated with daytime sedation and increase in TST. Weight gain and restless legs syndrome may be a deal breaking side effect in some patients.

Sedating newer antipsychotics have also been increasingly used in the treatment of insomnia, especially comorbid insomnia, but have not been studied extensively for this purpose. Quetiapine, a dopamine, serotonin, and norepinephrine antagonist, and olanzapine, a cholinergic, histaminergic, and dopaminergic antagonist, have been used for the purpose of sleep promotion (Sullivan 2010). Robust studies evaluating the safety and efficacy of sedating newer antipsychotics for the treatment of insomnia are lacking.

First-generation histamine antagonists

There are little published data on the efficacy of first-generation histamine antagonists (with activity at H1 receptors) in insomnia, and adverse effects may be considerably high in some populations. Promethazine, diphenyhydramine and other H1 antagonists are usual sleep-promoting agents in over-the-counter distribution in the United States. These substances cross the blood-brain barrier and act in central nervous system histamine receptors. The somnolence caused by these agents interferes with natural circadian sleep-wake cycle (Yanai *et al.* 2012). H1 antagonists has been shown to extend sleep duration (Roth 2005). These agents, however, are associated with rapid tolerance to hypnotic effect; residual daytime sedation associated with long half-life; and anticholinergic side effects. They should be used with great caution in the elderly and in those with narrow-angle glaucoma (Sullivan 2010).

Psychological and behavioral therapies for insomnia

Most sleep-promoting agents are not FDA and/or EMA approved for the treatment of insomnia. For off-label use agents, scarce data exist about efficacy for improvement of sleep, and little or no data exist on long-term improvement of daytime functions or medical outcomes for any prescription drugs.

Psychological and behavioral therapies for persistent insomnia include sleep restriction, stimulus control therapy, relaxation training, cognitive therapy, and a combination of those methods, referred to as cognitive behavior therapy (CBT). Evidence from controlled clinical trials indicates that the majority of patients (70% to 80%) with persistent insomnia respond to treatment, and approximately half of them achieve clinical remission (Morin 2011).

SLEEP RELATED BREATHING DISORDERS

Sleep related breathing disorders include obstructive sleep apnea disorders, central sleep apnea syndromes, sleep related hypoventilation disorders and sleep related hypoxemia disorder.

From the pharmacotherapy point of view, one has to consider negative pharmacologic influence on sleep breathing first. There is a clinical experience that benzodiazepines may aggravate sleep apnea due to the decreased arousal response to hypoxia and hypercapnia. Exogenous testosterone worsens sleep related breathing disorders in hypogonadal men predominantly through non-anatomic effect (Liu *et al.* 2003).

Many drugs were studied in attempt to increase respiratory drive, but no drug has sufficiently evident, robust and safe effect to be recommended for clinical practice. Medroxyprogesterone and progesterone both have mild effect especially in obesity hypoventilation syndrome confirmed by small-scale clinical studies. Protriptyline, a tricyclic antidepressant, may modestly decrease the number of apneas and hypopneas in patients with obstructive sleep apnea (Brownell *et al.* 1982). Though the drug may increase genioglossus tone, predominant mechanism of action is likely its suppression of REM sleep. Although this drug may be a reasonable alternative option in patients with mild, predominantly REM associated obstructive sleep apnea; the drug is often poorly tolerated.

A residual sleepiness may persist in sufficiently treated patients. Modafinil was successfully tested in this indication (Kingshott *et al.* 2001; Pack *et al.* 2001; Black & Hirshkowitz 2005) but one must know that modafinil does not treat the primary disease and that the improvement of residual sleepiness may diminish compliance to the positive airway pressure therapy (Kingshott *et al.* 2001).

All together, there are no milestones in pharmacological treatment of sleep related breathing disorders despite the fact that this group of diseases is the most frequently investigated and treated in specialized sleep disorder centers. The greatest therapeutic achievement in this group of diseases was the introduction of continuous positive airway pressure in 1981 (Sullivan *et al.* 1981).

CENTRAL DISORDERS OF HYPERSOMNOLENCE

Central disorders of hypersomnolence include a group of disorders in which the primary complaint is excessive daytime sleepiness (EDS) not caused by disturbed nocturnal sleep or misaligned circadian rhythms (American Academy of Sleep Medicine 2014). This chapter deals with narcolepsy type 1 (narcolepsy with cataplexy) and type 2 (narcolepsy without cataplexy) and idiopathic hypersomnia. EDS is defined as the reduced ability to stay awake and alert during normal daytime hours, resulting in lapses of sleepiness or sleep. EDS seriously decreases quality of life for affected patients (Ozaki *et al.* 2012).

Narcolepsy is a disabling lifelong sleep disorder characterized by excessive daytime sleepiness and abnormal rapid-eye movement (REM) sleep manifestations, including cataplexy, sleep paralysis, hypnagogic hallucinations and sleep onset REM periods. **Nar-**

colepsy type 1 has a prevalence of 0.02–0.067%. The loss of hypothalamic hypocretin-producing neurons at the diseases onset is the main ethiopathogenic factor of narcolepsy type 1. This disease is associated with a Human Leukocyte Antigen (HLA) and T-cell receptor (TCR) polymorphisms, suggesting that an autoimmune process targets a single peptide unique to hypocretin cells via specific HLA-peptide-TCR interactions. Recent data have shown a robust seasonality of the disease and associations with streptococcus pyogenes, influenza A H1N1 infection and H1N1 vaccination in children, pointing towards processes such as molecular mimicry or bystander activation as crucial for disease development (Kornum *et al.* 2011). Etiopathogenesis of **narcolepsy type 2** is not clear.

EDS is the most inconveniencing symptom in both forms of narcolepsy with mean sleep latency <8 min at Multiple Sleep Latency Test (MSLT). The second MSLT diagnostic criterion is the presence of two or more sleep-onset REM periods (SOREMPs) (American Academy of Sleep Medicine 2014). Night sleep is disturbed by periodic limb movements in sleep (PLMS) and REM sleep behavior disorder (RBD). Narcolepsy type 1 has low or undetectable level of hypocretin in cerebrospinal fluid (Mignot *et al.* 2002). Cerebrospinal fluid hypocretin in narcolepsy type 2 is at normal levels. HLA subtype DQB1*06:02 is positive in 95% of narcolepsy type 1, but only in 40% of narcolepsy type 2. Because this allele is also positive in 18–35% of general population this parameter has only supportive value for the differential diagnosis (Mignot *et al.* 1997). Narcolepsy type 1 is associated with higher body mass index (Sonka *et al.* 2010).

Because of a large number of findings suggesting that narcolepsy has an autoimmune basis, the intravenous immunoglobulins were administered in some cases and case series of narcolepsy type 1. The first application was performed by Lecendreux et al in Paris. The experiment was considered successful (Lecendreux *et al.* 2003) and inspired specialist to use high dosage of intravenous immunoglobulins within first weeks after narcolepsy type 1 symptoms onset. Results are somehow promising (Dauvilliers *et al.* 2009) but inconsistent and a controlled study is needed. No other etiologic treatment of narcolepsy exists.

Symptomatic treatment focuses on two main areas – the treatment of sleepiness and cataplexy and other symptoms of dissociated REM sleep.

Treatment of sleepiness

A short nap prevents unwanted sleep in narcolepsy, thus scheduled short naps are advised as nonpharmacologic EDS treatment where optimal nap time schedule and duration is individual.

Caffeine is a xanthine derivative and non-specific antagonist of adenosine receptors. Caffeine's stimulatory effect is rather mild and has been recommended to manage sleepiness for many centuries as mentioned by Willis in 17th century (Willis 1672).

Ephedrine was the first drug to be used effectively in the treatment of narcolepsy. It was introduced independently by the Czech psychiatrist Janota (Janota 1930) and by American neurologists Doyle and Daniels (Doyle & Daniels 1931). The effect on sleepiness was mild and ephedrine had side effects such as palpitation, tachycardia, headache and elevated blood pressure. Due to its frequent abuse, ephedrine was withdrawn from markets by the end of 20thcentury.

Amphetamine was introduced into the treatment of narcolepsy in 1935 (Prinzmetal & Bloomberg 1935). Amphetamine increases catecholamine (dopamine and norepinephrine) release and inhibits reuptake. Both the L- and D-isomers have been used for the treatment of narcolepsy, either in isolation or as a racemic mixture. The D-isomer is a slightly more potent stimulant (Parkes & Fenton 1973). Amphetamines are of the most effective drugs treating sleepiness but they have side effects such as anorexia, palpitations, tachycardia, irritability and psychosis. The addiction potential is high and this is why amphetamines are no longer available in many countries. Amphetamine derivative compounds – metamphetamine and methylphenidate are still used for treatment in narcolepsy. Pemoline, another amphetamine derivative was less potent, well tolerated but it is no longer available in developed countries because of its liver toxicity. Metamphetamine is the most efficacious and most potent amphetamine derivative (available in some countries only).

Methylphenidate is a piperazine derivative of amphetamine with acceptable safety profile and relatively short duration of action (approximately 3–4 hours). Methylphenidate was introduced for the treatment of narcolepsy in 1959 (Yoss & Daly 1959) and since then widely used and recommended by valuable guidelines.

Years of clinical practice as well as two level-2 studies and one level-3 study (all of short duration) justifies the use of amphetamine, methamphetamine, dextroamphetamine and especially methylphenidate (Littner *et al.* 2001; Billiard *et al.* 2006; Wise *et al.* 2007). Despite the lack of information on addiction development in patients with narcolepsy, this risk should be taken into account. Tolerance toward amphetamine and its derivatives is likely to develop in one third of the cases.

Phenmetrazin and dexphenmetrazine were mentioned for the first time in 1960 (Bochnik & Spiegelberg 1960) and were widely used especially in central Europe until 1990ies. Their efficacy was comparable to the efficacy of amphetamines (Roth & Broughton 1980). Phenmetrazin vanished from markets because of side effects and the risk of abuse.

Mazindol is an imidazolidine derivative with similar pharmacological effects as amphetamines. The first report on the use in narcolepsy came in 1979 (Parkes & Schachter 1979). It is a weak dopamine releasing agent

that also blocks dopamine and norepinephrine reuptake. There were five reports on the use of mazindol in treating EDS in narcoleptic patients. Mazindol is an anorexisant and its adverse effects include dry mouth, nervousness, constipation, and less frequently nauseas, vomiting, headache, dizziness, tachycardia and excessive sweating. Rare cases of pulmonary hypertension and valvular abnormalities have been reported. For this reason mazindol has been withdrawn from the market in many countries.

Selegiline is a potent irreversible monoamino oxidase B selective inhibitor, which is metabolized into various compounds, including amphetamine and metamphetamine. There are two controlled studies (Hublin *et al.* 1994; Mayer *et al.* 1995) documenting the effect of selegiline on EDS and cataplexy. Dietary restrictions, incompatibility with triptans and serotonin-specific reuptake inhibitors and tricyclic antidepressants limit its routine use.

Modafinil is the most common drug recommended and used in sleepiness therapy (Billiard *et al.* 2006; Morgenthaler *et al.* 2007). Modafinil is an original French compound. It was available for a individual care in France since 1984 and approved there in 1992 (in other countries nearly 10 years later). The first report dates back to 1988 (Bastuji & Jouvet 1988), the first double-blind study was published in 1994 (Billiard *et al.* 1994) and later it has been studied in double-blind, placebo-controlled fashion on a large number of narcoleptic patients. Exact working mechanism remains unclear; it is supposed that it acts by blocking norepinephrine and dopamine re-uptake transporters. Modafinil is safe and well tolerated; it's most frequent undesirable effects – headache, nausea, loss of appetite and nervousness – are infrequent. In terms of tolerance and addiction risk, long-term experience of its administration to narcoleptics is encouraging. However, there is also clinical experience that shows need for dosage increase after a long-term use in some patients. In European Union the use of modafinil has been recently restricted only to narcoleptic adults because of reports of serious skin and allergic reactions. The age limitation has been criticized by expert group based on their own experience (Lecendreux *et al.* 2012). Armodafinil (Lankford 2008) is recently developed R-enantiomer of modafinil with prolonged action and similar efficacy and safety profile.

Sodium oxybate (gamma hydroxybutyrate) is a potent and well tested drug treating EDS in narcolepsy. It must be pointed out that its anti-EDS effect is not immediate and it appears within 4–6 weeks.

Pitolisant is an inverse agonist of H3 receptor and its efficacy and safety in narcolepsy have been recently documented in a large European multicentre double-blind, randomised, parallel-group controlled trial (Dauvilliers *et al.* 2013). Pitolisant is a promising drug but currently not mentioned by guidelines and still waiting for approval by health care regulation authorities.

Treatment of cataplexy and other symptoms of dissociated REM sleep

The milestone in cataplexy treatment was the use of antidepressants. Japanese narcolepsy specialists were the first who reported the effect of antidepressants – namely tricyclic antidepressant imipramine (Akimoto *et al.* 1960). Another tricyclic antidepressant clomipramine (still recommended by valid guidelines and frequently used) was firstly mentioned by Montpellier´s group (Passouant *et al.* 1973). New antidepressant generations – selective serotonin reuptake inhibitors (fluoxetine, es/citalopram, fluvoxamine) and selective serotonin and norepinephrine reuptake inhibitors (venlafaxine and atomoxetine), were used as they become available. Antidepressants are still the most common cataplexy treatment drugs but the evidence of efficacy is not based on controlled studies. Long clinical experience and quite old reports is the only available source (Billiard *et al.* 2006; Morgenthaler *et al.* 2007). Side effect profile of these drugs is well known from psychiatry.

Sodium oxybate, sodium salt of gamma-hydroxybutyrate was approved for the treatment of narcolepsy with cataplexy after the year 2000, but first clinical reports on gamma-hydroxybutyrate in narcolepsy were published much before. The first report was made by Broughton and Mamelak, they administered gamma-hydroxybutyrate to their patients in an attempt to improve their nocturnal sleep and experienced (unintentional) improvement of EDS (Broughton & Mamelak 1979). Next trials showed efficacy of this drug in all narcolepsy type 1 symptoms (Scrima *et al.* 1989; Lammers *et al.* 1993). Some ten years later a new pharmacologic preparation of gamma-hydroxybutyrate named sodium oxybate was successfully tested in multiple highest level controlled studies. The advantage of sodium oxybate is the improvement all fundamental symptoms of narcolepsy type 1 – EDS, cataplexy, hypnagogic hallucinations, sleep paralysis and disturbed nocturnal sleep (Boscolo-Berto *et al.* 2011). Serious pharmacological interactions of sodium oxybate are unknown, but alcohol and other centrally acting inhibitors are strictly forbidden. Sodium oxybate is not recommended in sleep apnea. Sodium oxybate is known for its central inhibitory effect and for its abuse potential and addiction risk.

Idiopathic hypersomnia is characterized by EDS, no cataplexies and less than two SOREMPs in MSLT. Stimulants are used with success despite the lack of highest level studies, in particular: methylphenidate and modafinil in a dosage similar to that in narcolepsy (Ali *et al.* 2009; Lavault *et al.* 2011). These drugs are also mentioned in respective guidelines (Morgenthaler *et al.* 2007).

CIRCADIAN RHYTHM SLEEP DISORDERS

The only notable drug used to treat this group of disorders is melatonin. For more detailed description see the insomnia section of this review.

PARASOMNIAS

Parasomnias are undesirable physical events or experiences that occur while falling asleep, within sleep or during arousals from sleep. There are three main groups of parasomnias: NREM-related disorders (confusional arousals, sleep walking, sleep terrors and sleep related eating disorder), REM-related parasomnias (REM sleep behavior disorder – RBD, recurrent isolated sleep paralysis and nightmare disorder) and finally the group of other parasomnias (American Academy of Sleep Medicine 2014). This review is focused on two first groups only; pharmacologic intervention for the third group of disorders is not available at the moment.

NREM parasomnias are also called disorders of arousal (from NREM sleep). They are frequent in childhood and naturally cease by reaching adolescence. Same individual may experience more than one type of arousal parasomnias. The underlying pathophysiology is basically state dissociation. The brain is partially awake and partially in NREM sleep. The brain is awake enough to perform very complex, and often protracted motor functions and vocalizations, but asleep enough to be unable to maintain conscious awareness, thinking, perception and behavior at normal level. Given the usual benign character of these disorders and their common favorable course, special treatment is not necessary in most patients. Regime change with avoidance of provoking factors, sleep hygiene, psychotherapeutic intervention, hypnotic and relaxation techniques are usually recommended. Tricyclic antidepressants and benzodiazepines may be effective but should be administered if the activity is dangerous for the individual or extremely disruptive to family members. Paroxetine and trazodone have been reported effective in isolated cases (Mahowald & Cramer Bornemann 2005). The effect of above mentioned drugs must be evaluated and if there is no improvement the therapy must be changed.

RBD is a new disease described in 1986 by Schenck et al as a disturbance of REM sleep muscle atonia, leading to the enactment of dream content. This condition leads to sleep disruption, injuries of the patient and/or his bed partner and frequently to unpleasant dreams (Schenck *et al.* 1986). RBD can occur as independent disease (idiopathic RBD) or as comorbid parasomnia in Parkinson´s disease, dementia with Lewy bodies, multiple system atrophy (all these diseases are caused by pathological storage of alfasynuclein in neurons and glial cells). There is a growing body of evidence that patients suffering from idiopathic RBD are at high risk of the development of neurodegenerative disease with parkinsonism and dementia, approximately 25–40% in 5 years and 40–65% in 10 years (Postuma *et al.* 2013).

There are five interesting pharmacologic aspects of RBD.

1. Monoamine oxidase inhibitors, tricyclic antidepressants, serotonergic synaptic reuptake inhibitors, and noradrenergic antagonists can induce or aggravate RBD symptoms (Gagnon *et al.* 2006).
2. Antidepressants (except bupropion) trigger symptoms of RBD in up to 6% of users. It is of great interest to understand whether antidepressant associated RBD is an independent pharmacologic syndrome or a sign of possible prodromal neurodegeneration. According to the prospective cohort study in 100 patients with RBD (27%of patients were using antidepressants, the rest was not medicated). Parkinsonism and dementia rates were highest in non-medicated group, antidepressant medicated patient parkinsonism and dementia rates were significantly lower but still higher than in members of the control group (Postuma *et al.* 2013).
3. A drug widely used in RBD symptoms treatment – clonazepam was first mentioned in the original description of RBD (Schenck *et al.* 1986). The treatment of RBD by clonazepam is supported by a large clinical experience.
4. Melatonin in RBD was tested for the first time by Kunz and Bes (Kunz & Bes 1999) and later by others. The effect of melatonin (3 mg in the evening) was confirmed by randomized, double blind, placebo-controlled cross-over study (Kunz & Mahlberg 2010) and it is of special interest that this study showed that melatonin-related improvement of RBD symptoms persisted 5 weeks after the end of the treatment period.
5. The fact that subjects suffering from RBD are at high risk to develop a neurodegenerative disease opens the door for testing agents suggested to have a neuroprotective or disease-modifying potential (Schenck *et al.* 2013). This neuroprotection represents a great challenge of contemporary clinical neuropharmacology research and the drugs targeting melatonin receptors will perhaps play a role in this field.

SLEEP RELATED MOVEMENT DISORDERS

Sleep related movement disorders are characterized by simple, usually stereotyped movements that disturb sleep or its onset (American Academy of Sleep Medicine 2014). The group of sleep related movement disorders includes namely restless legs syndrome/Willis-Ekbom disease RLS/WED, periodic limb movement disorder, sleep related leg cramps, sleep related bruxism and sleep related rhythmic movement disorder. RLS/WED is classified in this group mainly because of its close association with periodic limb movements in sleep (PLMS). There is robust knowledge of treatment strategy for RLS/WED and PLMS, other conditions are far less clear from this point of view.

RLS/WED

The National Institute of Health (NIH) consensus panel defined RLS/WED as (i) an urge to move the limbs with or without sensations, (ii) worsening at rest,

(iii) improving with activity, and (iv) worsening in the evening or night. Supportive clinical features for RLS are a positive family history for RLS/WED, an initial response to dopaminergic therapy and the presence of PLMS (Allen *et al.* 2003).

PLMS are highly regular, jerky, stereotyped, unilateral or bilateral movements, usually extensions of the big toe, often accompanied by flexions of the hip, knees and ankles. PLMS are detected within night polysomnography and the patient is usually unaware of PLMS.

The prevalence of RLS/WED is according to multiple studies in Europe and North America between 5 and 10% and the symptoms occur at least twice a week and cause at least moderate distress in 1.5% to 2.7% of the population. Women are affected more frequently than men; the prevalence is higher in older people. Approximately a half of patients have familial history of RLS. Genome-wide association studies identified six genetic variants including MEIS1 and BTBD9 with potential relationships to iron. Brain iron level is low in RLS and neuropathological studies have shown significant decreases in dopamine D2 receptors in the putamen that correlated with RLS/WED severity, and increased tyrosine hydroxylase in the *substantia nigra*. An overly activated dopaminergic system was reported in both animal and cell models of iron insufficiency thus suggesting that in at least a subgroup of RLS patients altered iron metabolism plays a role in the disorder (Dauvilliers & Winkelmann 2013). Clinically RLS/WED is considered as idiopathic or secondary (associated to iron deficiency, end stage of renal insufficiency, pregnancy and multiple sclerosis). New data show the higher prevalence of hypertension, cardiovascular disease, and cerebrovascular disease in RLS (Ferini-Strambi *et al.* 2013). RLS has bidirectional ethiological relationship with depression (Szentkiralyi *et al.* 2013). There is a clear indication to treat the patient suffering from RLS/WED to achieve better quality of life and to reduce the risk of cardiovascular diseases and/or depression due to untreated RLS/WED.

The management of RLS/WED should start with behavioral recommendation (sleep hygiene, regular physical activity and avoiding caffeine). Most antidepressant agents (namely selective serotonine reuptake inhibitors and mirtazapine) may be associated with initiation or worsening of RLS/WED. However, if antidepressants are deemed necessary, the symptoms can usually be treated in the same way as idiopathic RLS/WED. Alternatively, use of bupropion can be considered because this antidepressant with dopamine agonist properties does not seem to induce or worsen RLS/WED (Bayard *et al.* 2011). RLS may also be provoked by neuroleptic agents, dopamine-blocking antiemetics (such as metoclopramide). The second step is the determination of iron levels. If the plasmatic level of iron is low or the serum ferritin concentration is lower than 45 μg/L the replacement of iron is recommended (Silber *et al.* 2013).

Documented pharmacological treatment of RLS/WED may go back over three centuries to Willis' successful treatment of a severely affected patient with opiates (Willis 1672; Willis 1683). The modern era of pharmacotherapy of RLS/WED and PLMS began with reports that benzodiazepines could alleviate RLS/WED and PLMS (Matthews 1979; Boghen 1980; Oshtory & Vijayan 1980). In 1980ies, three other major classes of medications, the dopaminergic agents (Akpinar 1982; Montplaisir *et al.* 1986; von Scheele 1986; Akpinar 1987; Sandyk *et al.* 1987), opioids (Hening *et al.* 1986) and the anticonvulsants (Lundvall *et al.* 1983; Telstad *et al.* 1984) were reported to be effective in these conditions.

Benzodiazepines took place in RLS/WED treatment in 20th century. One of the most recommended used to be clonazepam (Montagna *et al.* 1984). Clonazepam based studies in PLMS ended up with contradictory results (Ohanna *et al.* 1985; Mitler *et al.* 1986) and clonazepam is not anymore recommended in modern guidelines for these conditions.

The first dopaminergic compound used in RLS/WED treatment was levodopa/benserazide (Akpinar 1982). Akpinar was the first to perform a double-blind placebo controlled, crossover trial of 200 mg administration of levodopa at night (Akpinar 1987). He experienced a significant reduction of awakenings and an improvement of subjective sleep parameters. Marked reduction of PLMS as well as an improvement of subjective symptoms was reported by Montplaisir's group in the first polysomnographic double blind controlled study in RLS/WED (Brodeur *et al.* 1988). Since then several short-term and long-term studies including placebo controlled studies showed efficacy of levodopa administered together with a dopa-decarboxylase inhibitor, either benserazide or carbidopa in idiopathic RLS/WED and RLS/WED associated with uremia. These studies successfully tested immediate and slow release levodopa and results are summarized in reviews and guidelines (Hening *et al.* 1999; Hening *et al.* 2004; Vignatelli *et al.* 2006).

Hereafter levodopa was combined with entacapone and this therapy decreased PLMs in a dose-related manner in RLS/WED patients and this effect was more pronounced than the effect of placebo or slow release levodopa alone (Polo *et al.* 2007).

Levodopa has several side effects typical for dopaminergic drugs. One particularly troubling adverse effect with levodopa (and with other dopaminergic agents in lower intensity) is augmentation. Described for the first time by Allen and Earley (Allen & Earley 1996), augmentation consists of worsening of the sensory and motor symptoms of RLS, which tend to appear earlier and earlier in time and also tend to spread, involving previously unaffected regions of the body. This is different from the rebound of symptoms into the day that sometimes occurs when levodopa is administered in the evening or night. Augmentation may set in after a few weeks or months of drug use, and may be progressive.

Immediate attention is required and a reduction of the dosage or discontinuation of the medication is needed. Augmentation was found in 17% to 60% of patients treated with levodopa, more frequent in those with higher dosage. Levodopa is still indicated in patients using the treatment in "as needed" mode (Silber *et al.* 2013).

The dopaminergic agents mentioned in this paper are ergot and non-ergot derivatives. Ergot derivatives are the following: alfa-dihydroergocryptine, bromocriptine, cabergoline, lisuride, pergolide and terguride with predominantly D2 receptor agonist properties and partial or complete D1 agonist properties (except cabergoline). Non-ergot dopamine agonists promipexole, ropinirole, rotigotine, piribedil and talipexone have agonistic affinity for D2 and D3 receptor (rotigotine also for D1).

Pergolide was considered to be very promising drug, its effect was proved by four studies of Level 1 evidence. Series of serious complications of pergolide use which are typical of ergot medications – the development of pleuropulmonary fibrosis or cardiac valvulopathy caused that pergolide is no longer recommended (Aurora *et al.* 2012). Other ergot derivatives had different level of evidence of the effect and safety in RLS/WED and PLMS and were less used in daily practice: alfa-dihydroergocryptine (Tergau *et al.* 2001), bromocriptine (Walters *et al.* 1988), cabergoline (Trenkwalder *et al.* 2007), transdermal lisuride (Benes 2006), terguride (Sonka *et al.* 2003). Cabergoline is the only ergot derivative which can be used in the treatment of RLS/WED nowadays, but only if other treatment fails and close supervision is required (Aurora *et al.* 2012).

The efficacy of ropinirole in RLS/WED was first reported in a small open label study in 1999 (Ondo 1999). Five randomized controlled trials have been published and all confirmed high efficacy and low incidence of augmentation. Ropinirole is recommended because its efficacy and tolerability, side effects are self limited with the cessation of ropinirole therapy (Aurora *et al.* 2012; Garcia-Borreguero *et al.* 2012; Garcia-Borreguero *et al.* 2013; Silber *et al.* 2013).

The first publication mentioning the effect of pramipexole in RLS/WED was published in 1998 (Lin *et al.* 1998) and the next year Montplaisir's group published results of the first placebo controlled randomized study with pramipexole (Montplaisir *et al.* 1999). The efficacy and safety profile of pramipexole is favourable and these are the reasons pramipexole is recommended by present guidelines (Aurora *et al.* 2012; Garcia-Borreguero *et al.* 2012; Garcia-Borreguero *et al.* 2013; Silber *et al.* 2013).

Rotigotine as the treatment of RLS/WED was first described in 2004 (Stiasny-Kolster *et al.* 2004). Since then the evidence of its efficacy grow up and rotigotine is the only drug with short-term and also long-term randomized controlled Level 1 studies and even one open-label, 5-year, long-term study. Rotigotine is a safe and efficient drug. The drug administered in form of a patch is in some subjects less tolerated, the others consider it as an advantage. The profile of side effects is similar to other non-ergot dopaminergic drugs (Garcia-Borreguero *et al.* 2012; Garcia-Borreguero *et al.* 2013).

Despite the fact that opioids were the first described effective drug group, experimental evidence about their effect in RLS/WED is rather small. This situation is perhaps caused by low commercial interest (old drugs are no more protected by patents), to the known and sometime overestimated risk of side effects and also problems rising from formal difficulties of handling opioids in some countries. Opioids side effects include respiratory depression, especially in pre-existing respiratory compromise and addiction but from the RLS/WED point of view their general advantage is a low risk of augmentation.

Reports of successful tests with opioids in RLS/WED concern oxycodone (Walters *et al.* 1993), methadone (Ondo 2005) and tramadol (Lauerma & Markkula 1999). Methadone displayed in contrast to dopaminergic agents no augmentation within long-term follow-up (Silver *et al.* 2011). A successful randomized controlled trial with open-label extension with fixed-dose combination of prolonged release oxycodone-naloxone in patients with RLS/WED where previous treatment failed has been published recently (Trenkwalder *et al.* 2013). Combination of oxycodone with naloxone lowers some undesirable effects of oxycodone.

The group of α2δ ligands used in RLS/WED is now represented by following drugs. Gabapentin was mentioned for the first time in the RLS/WED contextin 1997 (Adler 1997). It is frequently used but results from randomized placebo controlled Level 1 studies are lacking maybe because RLS/WED usage of gabapentin started many years after its primary launch in other indications. Gabapentin enacarbil – a prodrug of gabapentin was reported in RLS/WED for the first time in 2009 (Kushida *et al.* 2009)and nowadays its evidence of efficiency precedes gabapentin (Aurora *et al.* 2012). Both are well tolerated. Pregabaline in RLS/WED was mentioned for the first time in 2007 in subjects suffering from RLS/WED and comorbid neuropathic pain (Sommer *et al.* 2007). Later studies showed pregabalin as sufficiently efficient drug in patients without comorbid diseases (Allen *et al.* 2010; Garcia-Borreguero *et al.* 2010). Pregabalin has a good safety profile and has low augmentation rate (Allen *et al.* 2014).

RLS/WED is quite common chronic illness, modern treatment procedures documentation is therefore widely available and number of resources grows. The most important pharmacotherapeutic intervention is the first use of levodopa in RLS/WED performed by Turkish military physician Akpinar (Akpinar 1982) that started experiments with medication primarily developed to treat Parkinson's disease.

CONCLUSION

Despite the fact that the last decade did not lead to any groundbreaking pharmacotherapeutic discovery in sleep medicine, new molecular biology based methods look more than promising and may soon help to create entirely new therapeutic strategies.

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