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Melatonin and Benzodiazepine/ Z Drug Abuse

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Abstract

A temporal relationship between the nocturnal rise in melatonin secretion and the increase in sleep propensity at the beginning of the night, coupled with the sleep-promoting effects of exogenous melatonin, supports the view that melatonin is involved in the regulation of sleep. Both meta-analyses and consensus agreements give credibility to the therapeutic use of melatonin in sleep disorders. Administration of melatonin will cue the circadian phase of sleep/wake cycles in a variety of disorders including jet lag problems, shift work maladaptation, advanced and delayed sleep phase disorders, major affective disorder, seasonal affective disorder and disrupted rhythms in attention deficit hyperactivity disorder, autism, and schizophrenia. This action is attributed to MT_1 and MT_2 melatonin receptors present in the hypothalamic suprachiasmatic nucleus (SCN) and in other brain areas. Almost every single neuron in the SCN contains GABA and many results in animals point out to a melatonin interaction with GABA-containing neurons. In addition, central-type benzodiazepine (BZD) antagonism, that obliterates $GABA_A$ receptor function, blunted melatonin behavioral effects including sleep. The sleep promoting activity of melatonin is relevant because the BZD and type Z drugs usually prescribed as sleep promoters have many adverse effects, such as next-day hangover, dependence and impairment of memory. This Chapter discusses available data on the efficacy of melatonin to curtail chronic BZD/ Z drug use in insomnia patients.

Key words: insomnia, melatonin, benzodiazepines, Z drugs, drug abuse.

Key points:

The efficacy of BZD/ Z drugs in treating insomnia is hampered by adverse effects including dependence and BZD / Z drug abuse has become a public health problem

A limited number of studies support the efficacy of melatonin to curtail chronic BZD/ Z drug use in insomnia patients

A major advantage is that melatonin has a very safe profile and is usually remarkably well tolerated

Further studies on this application of melatonin are warranted.

INTRODUCTION

Insomnia is a common disorder that includes unsatisfactory sleep, either in terms of sleep onset, sleep maintenance or early waking. It is also a disorder that affects the day and subjective well-being, skills and performance. Like pain, insomnia is a subjective disorder amenable of diagnosis through clinical observations rather than through objective measurements [1;2]. Insomnia occurs despite having adequate opportunity for sleep and it is associated with clinically significant distress or impairments of daytime functioning involving fatigue, decreased energy, mood disturbances and reduced cognitive functions (e.g., attention, concentration, memory).

Factors influencing the persistence of insomnia include iteration of precipitating stress, anxiety about sleep, maladaptive sleep habits or an intrinsic vulnerability of the neural mechanism for regulating sleep [3]. The diagnosis of insomnia is made when sleep difficulties are present 3 nights or more per week and last for more than 3 months. The diagnostic procedure for insomnia, and its co-morbidities, should include a clinical interview consisting of a sleep history (sleep habits, sleep environment, work schedules, circadian factors), the use of sleep questionnaires and sleep diaries, questions about somatic and mental health, a physical examination and additional measures if indicated (i.e. blood tests, electrocardiogram, electroencephalogram). Polysomnography can be only used to evaluate other sleep disorders if suspected (i.e. periodic limb movement disorder, sleep-related breathing disorders), in treatment-resistant insomnia, for professional at-risk populations and when substantial sleep state misperception is suspected. Cognitive behavioral therapy for insomnia is recommended as the first-line treatment for chronic insomnia in adults of any age [2].

The general detrimental effect of insomnia on health has long been established. Epidemiological studies have shown that disturbed sleep - comprising short, low-quality, and mistimed sleep - increases the risk of metabolic diseases, especially obesity and type 2 diabetes mellitus [4] as well as neurodegenerative disorders [5]. Epidemiological studies have also identified an association between insomnia, especially with reduced or fragmented sleep, and increased rates of accidents [6] and falls in the elderly [7].

Epidemiological surveys indicate that up to 40% of individuals over 65 years of age are not satisfied with their sleep or report problems initiating and maintaining sleep, and that 12-20% complain of persistent insomnia [8-10]. This leads to increased use of hypnotics for the elderly, which is a cause for concern [11]. Up to 30 to 40% of older people use sedative hypnotic benzodiazepine (BZD) and related Z drugs and often show side effects of hypnotics due to both a greater sensitivity of the nervous system and decreased serum albumin, that binds the drug. Thus, the older population responds to hypnotic drugs differently and less predictable than their younger counterparts [12;13].

Many aged patients are treated for longer periods or with higher doses of hypnotic BZD / Z drugs than are generally recommended. The failure to adjust the individual dose to the pharmacokinetic and pharmacodynamic changes cause by the progressive aging and comorbid medical problems can make treatment more difficult and potentially risky [14]. Thus, the chronic and widespread use of BZD /

Z drugs has become a public health problem which has led to campaigns to reduce their prescription, especially in Europe [15].

Several studies have shown the importance of melatonin both for the initiation and for maintenance of sleep [16-18]. In human beings the onset of melatonin secretion coincides with the timing of increase in nocturnal sleep propensity [19]. Since melatonin and BZD shared some neurochemical, i.e. interaction with γ-aminobutyric acid (GABA)-mediated mechanisms in brain [20] and behavioral properties, e.g., a similar day-dependent anxiolytic activity [21], melatonin therapy has been postulated as a possible tool to decrease the dose of BZD needed in patients [22].

This Chapter discusses available data on the efficacy of melatonin to curtail chronic BZD use in insomnia patients. Medical literature was identified by searching databases including (MEDLINE, EMBASE), bibliographies from published literature and clinical trial registries/databases. Searches were last updated January 6, 2018.

BZD AND RELATED DRUGS IN INSOMNIA

BZD are a group of compounds that exert their therapeutic effect on sleep through allosteric modulation of the $GABA_A$ receptor complex [23]. BZD exert broad inhibitory effects on brain function including sleep promotion, anxiolysis, anticonvulsant effects, cognitive and motor impairment and reinforcing effects [24]. BZD exert their actions through activation of BZ_1 and BZ_2 receptor subtypes of the $GABA_A$ complex, the activation of BZ_1 accounting for their specific hypno-sedative, anxiolytic and anticonvulsant activities [25]. The α_1-subunit of the $GABA_A$ receptor mediates the sedative and anxiolytic effects of BZD [24] (Figure 1).

The efficacy of BZD in treating insomnia is supported by several meta-analyses, e.g. [26], but significant adverse effects like cognitive and psychomotor impairment, anterograde amnesia, next-day hangover, rebound insomnia and dependence have also been documented. Because of their adverse effects the use of BZD for treatment of insomnia in the elderly has become controversial [27;28].

Z drugs are a group of agents that are not part of the BZD chemical class but act via the same mechanism – they enhance GABA-mediated inhibition through allosteric modulation of the GABA-A receptor [23;24]. This group includes drugs like zolpidem, zaleplon and zopiclone all having high affinity and selectivity for the α_1-subunit of the $GABA_A$ receptor complex. Zolpidem improves sleep maintenance shortly after administration, but the effect disappears at later in the night [1]. It may cause adverse effects like daytime drowsiness, dizziness, headache and nausea. The pyrazolopyramidine derivative zaleplon is effective to decrease sleep latency and to improve sleep quality. Zopiclone and its active stereoisomer eszopiclone have both been shown effective and safe in patients with primary insomnia. In general Z drug sedative hypnotics, although effective in reducing sleep latency, are only moderately effective in increasing sleep efficiency and total sleep time [29]. These agents are problematic in those prone to abuse potential [27;28].

International studies indicate that 50-80% of nursing home residents have at least one prescription for psychotropic medication. The most commonly prescribed medications for sleep are BZD and Z-drugs. Utilization rates vary dramatically from country to country and from institution to institution. In general,

recommendations for the pharmacotherapy of insomnia in elderly patients include using a reduced dosage. For some substances (e.g. zolpidem, zopiclone, zaleplon, temazepam and triazolam) the recommended dosage is half that recommended for younger patients. The vast majority of studies of these medications are short-term, i.e. < or =2 weeks. Clinicians are advised to avoid long-acting BZD and to use hypnotics for as brief a period as possible, in most cases not exceeding 2-3 weeks of treatment [24;27;28].

Can we define the characteristics of the ideal hypnotic? It clearly should not only decrease sleep latency but should also increase total sleep time and sleep efficiency [1]. In addition, the ideal hypnotic drug should not produce undesired side effects such as impairment of memory, cognition, next psychomotor retardation and day hangover effects or potentiality of abuse (Figure 2).

Melatonin fulfills many of these requirements as recognized in several consensus statements [1;30-33]. Meta-analysis publications also support such a conclusion [34;35] although not unanimously [36].

Controlled-release melatonin is recommended as a first-line agent in older insomniacs [1]; the Z drugs (zolpidem, eszopiclone, and zaleplon) should be reserved for use if the first-line agents are ineffective. BZD are not recommended because of their high abuse potential and the availability of better alternatives. Although the orexin receptor antagonist suvorexant appears to be relatively effective, it is no more effective than the Z drugs and much more expensive [37]. However, further studies on melatonin and its analogs are needed as indicated in the recent guidelines for the treatment of insomnia developed by the European Sleep Research Society [2] and by the American Academy of Sleep Medicine [27].

BASIC STUDIES ON MELATONIN RELEVANT TO SLEEP REGULATION

The discoverer of melatonin, Aaron Lerner, initially reported soporific effects of melatonin, noting that drowsiness and sleep enhancement followed administration of doses of 200 mg and 1 g of melatonin [38]. Since then numerous studies have demonstrated melatonin's value as a hypnotic agent. In low doses (such as 0.5 to 3 mg) administered melatonin can function as a cue for the sleep-wake cycle acting in the opposite manner to light so that when given prior to sleep onset it advances the timing of sleep onset, but when given after waking it can lead to a delay in sleep timing. Phase response curves for both melatonin and light have been obtained [39].

Melatonin regulates circadian rhythms in both brain and periphery. Administration of melatonin will cue the circadian phase in a variety of disorders including jet lag problems, shift work maladaptation, advanced and delayed sleep phase disorders, major affective disorder, seasonal affective disorder and disrupted rhythms in attention deficit hyperactivity disorder, autism, and schizophrenia. Preclinical studies have established that melatonin has significant neuroprotective effects and clinical trials have been proposed for preventive treatment of neurodegenerative diseases [39].

Melatonin blood levels normally increase during darkness rising to a peak around 2 to 3 AM and then decreasing with virtually no melatonin detectable during light. Although produced in many tissues of the body, serum melatonin originates almost exclusively from the pineal gland where production is driven by neural inputs from

the suprachiasmatic nucleus (SCN) functioning as the master body clock [40]. The inherent rhythm of the SCN is synchronized both by the light/dark cycle via neural inputs from the retina and by melatonin acting via two protein linked melatonin receptors MT_1 and MT_2. In many laboratory animals melatonin's phase shifting (chronobiotic) effects, are mainly produced by MT_2 receptors. However, MT_2 receptors are poorly expressed in the human SCN, so that phase shifting may be ascribed to MT_1 receptors.

Binding sites for melatonin were initially identified in a wide variety of central and peripheral tissues using ^{3}H-melatonin [41-43] and later 2-I^{125}-iodomelatonin [44]. Molecular cloning of the first high affinity membrane melatonin receptor (MT_1) was accomplished using a cDNA library from a dermal cell line of amphibian melanophores [45]. This initial finding led to the discovery that that there are at least two G_i-protein coupled membrane melatonin receptors in humans. The second receptor (MT_2) [46] is 60% identical in amino acid sequence to the MT_1 receptor. Additionally, a third receptor, now called GPR50, shares 45% of the amino acid sequence with MT_1 and MT_2 but does not bind melatonin [47]

In the mammalian brain, MT_1 and MT_2 receptors have been reported in the SCN, prefrontal cortex, cerebellar cortex, hippocampus, basal ganglia, substantia nigra, ventral tegmental area, nucleus accumbens and in retinal horizontal, amacrine and ganglion cells and choroid plexus (summarized by [48]). The MT_1 receptor is highly expressed in the human SCN [49] and mainly in vasopressinergic neurons. MT_2 was not detected in an earlier investigation of the human SCN [49]. This receptor subtype is expressed in the SCN of numerous mammals and, where present, is particularly important for circadian phase shifting [50;51]. Since circadian clock reset does occur in humans after administering melatonin [52;53] these changes must be ascribed to MT_1 signaling.

Since melatonin is a lipophilic substance, once it is synthesized in the pineal gland it diffuses readily into the bloodstream, where it is bound to albumin [54]. Melatonin rapidly disappears from the blood with a half-life that is biexponential, with a first distribution half-life of 2 min and a second of 20 min [55]. Circulating melatonin is metabolized mainly in the liver which clears 92-97% of circulating melatonin in a single pass [56]. Melatonin is first hydroxylated in the C6-position by cytochrome P_{450} monooxygenases (isoenzymes CYP1A1, CYP1A2, and to a lesser extent CYP1B1) and thereafter conjugated with sulfate to be excreted as 6-sulphatoxymelatonin, glucuronide conjugation being extremely limited [55]. CYP1A2 and to a greater extent CYP2C19 also demethylate melatonin to its precursor *N*-acetylserotonin [57]. Specific melatonin deacetylases or less specific aryl acylamidases [40] are also present in brain.

Because melatonin has a relatively short half-life (30-45 min) prolonged release melatonin and several synthetic melatonin analogs which are agonists of MT_1/MT_2 receptors and have a longer half-life have been developed. Circadin, a prolonged-release form of melatonin (2 mg), has been approved by the European Medicines Agency (EMA) as monotherapy for insomnia in 55 years old patients and over. It is formulated to provide peak levels 3 h after dosing, plateauing at 3.5 h and then gradually falling [58]. Blood levels thus approximate physiologic nocturnal patterns of melatonin.

Available evidence tends to indicate that melatonin has a more potent sleep-inducing action at a higher dose than the low doses typically used as a chronobiotic to trigger sleep onset. Sleep latency is significantly shortened, and sleep quality and morning alertness are improved following treatment of affected patients in that age group. In contrast, effects on sleep maintenance and duration do not show significant changes [59].

In several consensus statements [1;30-32] melatonin was recognized as fulfilling the properties of a useful sleep -promoting agent. For example, the consensus of the British Association for Psychopharmacology on evidence-based treatment of insomnia, parasomnia and circadian rhythm sleep disorders concluded that melatonin is the first-choice treatment when a hypnotic is indicated in patients over 55 yr. [1]. Similar conclusions were put forth by Canadian and European pediatrics consensuses [1;30-32]. Brain imaging studies in wake subjects have revealed that melatonin modulates brain activity pattern to one resembling that of actual sleep [60].

The melatonergic agonist ramelteon is effective in helping initiate and thus improving sleep in insomniacs with minimal side effects. Several reports indicate that ramelteon can both prevent and treat delirium [61]. The melatonin agonist, tasimelteon, has been approved to treat non-24 hour sleep-wake disorders, often caused by blindness [62]. For major affective disorder the melatonergic agonist agomelatine which also has 5-HT_{2C} antagonistic properties, not only ameliorates the symptoms of depression but also the quality and efficiency of sleep [63]. In common with other naphthalenic drugs, there is a risk of severe hepatotoxicity and is contradicted in those with liver disease. Another melatonin agonist, TIK-301, is under development; TIK-301 also has 5-HT_{2C} and 5-HT_{2B} receptor antagonism and potentially has antidepressant properties.

MELATONIN AND BRAIN GABAERGIC MECHANISMS

GABA-containing neurons are mostly interneurons in the majority of central neuronal circuits including the SCN [64]. GABAergic neurons are also important in other components of the circadian timing system, e.g., GABA co-exists with neuropeptide Y in the intergeniculate leaflet of the thalamic lateral geniculate complex as well as in certain horizontal cell interneurons and ganglion cells of the retina [65]. Because of this key distribution, it was thus logical to postulate GABA as the principal neurotransmitter of the circadian timing system [64].

Through activation of $GABA_A$ receptors, GABA inhibits neuronal firing by increasing Cl^- conductance (Figure 1). Blockade of $GABA_A$ receptors by bicuculline generates neuronal epileptic activity. The receptor-channel complex, which has been sequenced, is allosterically modulated by drugs like BZD or barbiturates. In addition to its effect on Cl^- channels, GABA also inhibits neuronal activity by activating $GABA_B$ receptors coupled to K^+ channels. A third type of receptor ($GABA_C$ receptor) is associated, as the $GABA_A$ receptor, to a chloride ionophore through binding sites which are insensitive to bicuculline antagonism.

The pineal gland exerts a depressive influence on CNS excitability [66]. This activity is attributed to melatonin, since pharmacological doses of the hormone prevent pinealectomy (Px)-induced seizures in gerbils [67] as well as kindled convulsions in rats [68]. In murine seizure models, melatonin has been documented to potentiate the anticonvulsant action of phenobarbital and

carbamazepine against electroshock seizures in adult animals [69;70]. Melatonin has also been reported to exert an anticonvulsant action when given alone to adult rats, mice, hamsters, guinea pigs cats and baboons (for ref. see [70]).

Both MT_1 and MT_2 receptors appear to be involved in sedating and antiexcitatory effects of melatonin. This has been mainly studied in relation to anticonvulsant actions [21;71-75]. The anticonvulsant activity of melatoninergic agents seems to be mediated by MT_1 and/or MT_2 membrane receptors since similar effects were observed with the MT_1 / MT_2 agonist ramelteon [76]. These antiexcitatory actions may be also related to additional anxiolytic, antihyperalgesic and antinociceptive effects of melatonergic agents [77-83].

The first indication of a possible link between the pineal and brain GABAergic neurons was provided by Anton Tay et al. [84] who reported increased GABA levels in rat brain following Px, and depressed levels after melatonin injection. Exogenously administered melatonin increases pyridoxal phosphokinase activity in rat brain [84]. Results in rats indicate that central synapses employing GABA as an inhibitory transmitter are a target for pineal melatonin activity because: (a) Px disrupts circadian rhythmicity of brain GABA and BZD binding [85;86]; (b) low doses of melatonin counteract Px-induced modifications of BZD and GABA binding [87]; (c) chronic melatonin treatment increases brain BZD and GABA binding [85;86;88]; (d) melatonin administration accelerates brain GABA turnover rate [89]; (e) melatonin increases glutamic acid decarboxylase activity and Cl^- ion conductance in the medial basal hypothalamus-preoptic area, with maximal activity in the evening [90].

Melatonin competes for diazepam binding sites in rat, human and bovine brain membranes with micromolar affinity [91]. Similarly, pharmacological doses of melatonin act on BZD-$GABA_A$ receptors to enhance both in vitro and in vivo binding of GABA, and to inhibit allosterically the binding of the caged convulsant t-butyl bicyclophosphorothionate on GABA-gated chloride channels in rat brain [92]. The binding site for melatonin on the BZD-$GABA_A$ receptor complex is not known, but its ability to competitively inhibit diazepam binding suggests a direct interaction within the BZ binding pocket, which is located at the α/γ subunit interface of the BZD-$GABA_A$ receptor complex.

There is in vivo electrophysiological evidence that nanomolar concentrations of melatonin can potentiate GABAergic inhibition of neuronal activity in the mammalian cortex [93]. In vitro electrophysiological studies have indicated that the MT_1 receptor is coupled to stimulation of GABAergic activity in the hypothalamus, whereas the MT_2 receptor mediates an opposite effect in the hippocampus [94]. The primary effect of melatonin in the rat SCN appears to be inhibition of neuronal activity [95], which is consistent with the relatively high expression of the MT_1 subtype in the circadian clock and the fact that this receptor is linked to enhancement of GABAergic activity [94]. $GABA_A$ receptor currents are also modulated by melatonin in neurons of chick spinal cord [96] and carp retina [97]. In a study aiming at assessing the effect of melatonin on the GABA-induced current and GABAergic miniature inhibitory postsynaptic currents in cultured rat hippocampal neurons, melatonin was effective only when GABA and melatonin were applied together [98]. This enhancement was mediated via high-affinity BZD sites as BZD receptor antagonist flumazenil inhibited it.

In principle, to demonstrate that a neurotransmitter system is involved in the mediation of a given melatonin effect, two requirements should be fulfilled: (a) the neurotransmitter system should show dynamic changes because of melatonin injection; (b) functional obliteration of the neurotransmitter system should significantly modify the melatonin effect. It should be stressed that monoamine pathways within the brain seem not to be important for melatonin entrainment of circadian rhythmicity in rodents, since the intraventricular injection of 6-hydroxydopamine and 5,7-dihydroxytryptamine, which deplete catecholamines and indoleamines, failed to alter entrainment [99].

To achieve an effective inhibition of $GABA_A$-mediated mechanisms a rather indirect procedure had to be employed, because the use of $GABA_A$ antagonists, like bicuculline or picrotoxin, was precluded due to the convulsive state produced in the animals. The central type BZD antagonist flumazenil was thus employed. In a study aiming to determine whether melatonin-induced analgesia in rats could be inhibited by flumazenil, melatonin exhibited maximal analgesic effects at late evening and the administration of fIumazenil, although unable by itself to modify pain threshold, blunted the analgesic response. This indicated that the time-dependent melatonin analgesia was sensitive to impairment of $GABA_A$-mediated mechanisms [78]. In subsequent studies, the inhibitory effects of flumazenil on melatonin-induced depression of locomotor behavior and 3-mercaptopropionic acid seizures were analyzed [72;100]. The administration of fIumazenil, although unable by itself to modify locomotor activity or seizures, significantly attenuated the inhibitory effects of melatonin. A similar result was observed when the anxiolytic and pro-exploratory melatonin properties were assessed in rats using a plus-maze procedure [77]. Melatonin displayed maximal effects at night, with absence of effects at noon and a weak activity at the beginning of the light phase, an effect also blunted by administration of fIumazenil. Other studies also supported the link of melatonin and GABA-mediated mechanisms in brain [101;102].

In view of the importance of GABAergic mechanisms in sleep modulation, it is likely that the sedative effects of pharmacological doses of melatonin involve its allosteric interaction with BZD-$GABA_A$ receptors (Figure 1). This view is supported by evidence that BZD/$GABA_A$ antagonists block the sleep inducing effect of pharmacological doses of melatonin in experimental animals [103]. The ability of pharmacological concentrations of melatonin or BZDs to inhibit the cAMP pathway via putative G protein-coupled BZ receptors [104] suggests yet another neuropharmacological mechanism for modulation of GABAergic activity. In a recent study the relationship of nocturnal concentrations of melatonin and GABA with insomnia after stroke were examined in insomniac and non insomniac patients recruited during rehabilitation phase. Nocturnal concentrations of melatonin and GABA were lower, and the severity of stroke was higher, in the insomnia group. Correlation analysis demonstrated that the nocturnal concentrations of melatonin and GABA were associated with insomnia after stroke [105].

MELATONIN AND BZD USE IN INSOMNIA DISORDER PATIENTS

Tables 1 and 2 summarize published data on melatonin/BZD interactions in clinical studies. Table 1 report data on the comparison of melatonin with BZD/Z drugs in their effects on sleep. Table 2 summarizes the efficacy of melatonin to

curtail BZD.

INSERT TABLE 1 HERE

Several studies compared melatonin and BZD/Z drug efficacy (Table 1). In a study aimed to assess subjective sleepiness and cognitive performance after administering 5 mg melatonin, 10 mg temazepam or placebo, greater changes in performance were evident following temazepam administration than melatonin administration, relative to placebo. Administration of melatonin or temazepam significantly elevated subjective sleepiness levels. The authors concluded that melatonin administration induced a smaller deficit in performance on a range of neurobehavioural tasks than temazepam, indicating that melatonin is preferable to BZD in the management of circadian and sleep disorders [106].

Two studies have undertaken in healthy volunteers to compare the effect of controlled-release melatonin with that of zolpidem. In one of those studies, 16 healthy volunteers were randomized for a double-blind, placebo controlled, single-dose, 4-way crossover study of controlled release melatonin and zolpidem (10 mg) or their combination [107]. Subjects were tested 1 h, 4 h and next morning after dosing. Psychomotor functions, memory recall, and driving skills were assessed. No impairment of performance after melatonin was detected whereas zolpidem impaired psychomotor and driving performance 1 h and 4 h post-dosing as well as early memory recall. Melatonin co-administration exacerbated the zolpidem effect [107]

In another study, effects of controlled-release melatonin and zolpidem on postural stability were assessed in healthy older adults [108]. Twenty-four volunteers, aged 55-64 years, were randomized for a double-blind, placebo controlled, single-dose, three-way crossover study. Body sway was tested by the area of the 95% confidence ellipse enclosing the center of pressure (A95) and its path length. No effect of melatonin on A95 was detected. In contrast, zolpidem significantly increased the A95 and path length pointing out to the feasible disturbance of postural stability caused by the drug [108].

To establish whether the effects of controlled-release melatonin (2 mg) on the nocturnal sleep EEG were different to those of temazepam (20 mg) and zolpidem (10 mg), 16 healthy men and women aged 55-64 years participated in a double-blind, placebo-controlled, four-way cross-over trial. Nocturnal sleep was assessed with polysomnography and spectral analysis of the EEG. In an entire night analysis controlled-release melatonin did not affect slow wave activity (SWA), whereas temazepam and zolpidem significantly reduced SWA compared with placebo. Melatonin only reduced SWA during the first third of the night compared with placebo. The authors concluded that the effects of melatonin on the nocturnal sleep EEG are minor and are different from those of temazepam and zolpidem [111].

A study of 38 patients with Parkinson's disease without dementia with complaints on sleep disorders, both melatonin (3 mg) and clonazepam (2 mg) reduced sleep disorders. However, the daytime sleepiness was significantly increased in the clonazepam group and not affected by melatonin. The authors underlined the treatment efficacy of melatonin in the treatment of sleep disorders in Parkinson's disease [109].

To evaluate whether the addition of melatonin to alprazolam had superior

premedication effects compared to either drug alone, a prospective, double blind placebo controlled trial randomly assigned 80 adult patients (ASA 1&2, American Society of Anesthesiologists physical status classification) with a Visual Analogue Score for anxiety ≥ 3 to receive a tablet containing a combination of alprazolam 0.5 mg and melatonin 3 mg, alprazolam 0.5 mg, melatonin 3 mg, or placebo orally 90 min before a standard anesthetic [110]. Primary end points were change in anxiety and sedation score at 15, 30, and 60 min after premedication, and number of patients with loss of memory for the five pictures shown at various time points when assessed after 24 h. Addition of melatonin to alprazolam had superior anxiolysis compared with either drug alone or placebo. Adding melatonin neither worsened sedation score nor the amnesic effect of alprazolam alone [110].

INSERT TABLE 2 HERE

As early as in 1997 two observations pointed to the possible beneficial effect of melatonin to decrease the dose of BZD used by patients (Table 2). Fainstein et al. [114] reported in a short term (3 weeks) open label treatment with fast release melatonin (3 mg) that included 22 insomniacs, 9 depressed and 10 demented patients, 4 (31%) of the 13 insomniac patients who were receiving BZD reduced BZD use by 50 to 75% and 4 (31%) discontinued it. Of the 7 depressed and 7 demented patients who were receiving BZD, 2 (29%) in each group reduced BZD use by up to 50% [114].

Dagan et al. published a case report on the efficacy of 1 mg of controlled release melatonin to completely cease any BZD use in a 43 year old woman who had suffered from insomnia for the past 11 years [115]. All previous attempts to stop BZD treatment in this patient had resulted in withdrawal symptoms and a renewal of the insomnia. Treatment with melatonin enabled the patient to completely cease any BZD use within two days, with an improvement in sleep quality and no side effects.

In a double-blind, placebo controlled, study followed by a single blind period of 34 primary insomnia outpatients aged 40-90 years who took BZD and had low urinary 6-sulphatoxy melatonin levels, 14 out of 18 subjects who had received controlled-release melatonin, but only 4 out of 16 in the placebo group, discontinued BZD therapy [116]. An open label study further supported the efficacy of fast release melatonin in decreasing BZD use, i.e. 13 out of 20 insomnia patients taking BZD together with melatonin (3 mg) could stop BZD use while another four patients decreased BZD dose to 25–66% of initial doses [117].

In a study evaluating the effectiveness of melatonin in attenuating sleep difficulties during BZD withdrawal most improvement in sleep quality was attributed to drug discontinuation. Although melatonin did not enhance BZD discontinuation it improved sleep quality, especially in patients who did not stop BZD [121].

The above reported observations were not supported by the results of a placebo controlled trial of 38 long-term users of BZD. After 1 year 40% had stopped their BZD use, both in the intervention group on melatonin and in the placebo control group [119]. It must be noted that many times, old patients with minor sleep disturbance received, on a long-term basis, anxiolytic BZD or sedative-hypnotic BZD in low doses.

To assess the efficacy of melatonin to reduce the use of BZD in low doses one of us

carried out a double blind placebo controlled study on 45 patients randomized to receive either fast release melatonin (3 mg) or placebo for six weeks [118]. In two steps BZD was tapered off and stopped after four weeks. Several subjective sleep parameters were assessed and found not to be different for both groups. That the patients included in this study were taking BZD on reasons other than an established sleep disturbance was indicated by the lack of subjective changes in sleep quality after reduction or suppression of BZD dose. Melatonin, however, was not devoid of activity: it advanced sleep onset and decreased significantly variability of sleep onset time as compared to placebo [118].

Mild cognitive impairment (MCI) is an etiologically heterogeneous syndrome defined by cognitive impairment in advance of dementia. Two retrospective analyses of 60 [120] and 96 MCI outpatients [123], receiving or not daily 3-24 mg of a fast-release melatonin preparation p. o. at bedtime for 9-24 or 15-60 months were published. In both studies there was a significant improvement of cognitive and emotional performance and daily sleep/wake cycles. The comparison of the medication profile in both groups of MCI patients indicated that about 10% in the melatonin group received BZD vs. 63% in the non-melatonin group, thus supporting administration of fast release melatonin to decrease BZD use.

A retrospective analysis of a German prescription database identified 512 patients who had initiated treatment with controlled release melatonin (2 mg) over a 10-month period. From 112 patients in this group who had previously used BZD, 31% discontinued treatment with BZD 3-months after beginning controlled release melatonin treatment [124].

In a study aimed to analyze and evaluate the impact of anti-BZD/Z-drugs campaigns and the availability of alternative pharmacotherapy (melatonin) on the consumption of BZD and Z-drugs in several European countries it was reported that campaigns failed when they were not associated with the availability of melatonin in the market [15]. In this pharmacoepidemiologic study the reimbursement of melatonin supports better penetration rates and a higher reduction in sales for BZD/Z-drugs.

A post marketing surveillance study of controlled release melatonin (2 mg) was recently performed in Germany. It examined the effect of 3 weeks of treatment on sleep in 597 patients. Most of the patients (77%) who used traditional hypnotics before melatonin treatment had stopped using them and only 6% of naïve patients started such drugs after melatonin discontinuation [125].

Therefore, most data favor the potential utility of melatonin to reduce BZD/Z-drug consumption in insomniac patients. The number of studies is however limited and further data on this application of melatonin are warranted.

A recent meta-analysis was performed to assess whether melatonin offers an atoxic alternative to BZD in ameliorating anxiety in the pre- and postoperative period. Randomized, placebo-controlled or standard treatment-controlled, or both, studies that evaluated the effect of preoperatively administered melatonin on preoperative or postoperative anxiety were compared. This systematic review identified 12 randomized controlled trials including 774 patients that assessed melatonin for treating preoperative anxiety, postoperative anxiety or both. The authors concluded that when compared to placebo, melatonin given as premedication (tablets or sublingually) can reduce preoperative anxiety in adults

(measured 50 to 100 minutes after administration). Melatonin was equally as effective as standard treatment with midazolam in reducing preoperative anxiety in adults [130].

Summarizing, the observations shown in Tables 1 and 2 support the use of melatonin as a valid alternative for BZD abuse. A major advantage for melatonin use is that it has an excellent safety and tolerability record, showing no difference from placebo. Emergent adverse events including gastrointestinal, cardiovascular, and body weight effects were absent.

Melatonin is usually remarkably well tolerated and, in some studies, it has been administered to patients at very large doses. Melatonin (300 mg/day for up to 3 years) decreased oxidative stress in patients with amyotrophic lateral sclerosis [131]. In children with muscular dystrophy, 70 mg/day of melatonin reduced cytokines and lipid peroxidation [132]. Doses of 80 mg melatonin hourly for 4 h were given to healthy men with no undesirable effects other than drowsiness [133]. In healthy women given 300 mg melatonin/day for 4 months there were no side effects [134]. A randomized controlled double-blind clinical trial on 50 patients referred for liver surgery indicated that a single preoperative enteral dose of 50 mg/kg melatonin was safe and well tolerated [135]. In a recent case report on a patient with primary progressive multiple sclerosis followed for 4 years with the only administration of 50 to 300 mg of melatonin per day a partial recovery of the disease was documented [136].

CONCLUSIONS

The ultimate goal of antiinsomnia therapy is symptomatic and functional recovery that helps a return to everyday life. However, a large proportion of patients under BZD treatment fail to achieve a complete and sustained recovery and are left with residual symptoms that make relapse or recurrence more likely. Most treatment guidelines recognize a symptom-free state as the best definition of insomnia remission, despite functional recovery often lagging behind symptomatic improvement. Given the importance of all three dimensions of functioning (emotional, cognitive and social) in everyday activities such as work, and the impact that impaired daily functioning by insomnia may have on a patient's life, it is clear that more attention should be paid to functioning when assessing treatment´s response.

The use of BZD anxiolytics and hypnotics continues to excite controversy. Views differ from expert to expert and from country to country as to the extent of the problem, or even whether long-term BZD use actually constitutes a problem. The adverse effects of these drugs have been extensively documented and their effectiveness is being increasingly questioned. Discontinuation is usually beneficial as it is followed by improved psychomotor and cognitive functioning, particularly in the elderly. The potential for dependence and addiction have also become more apparent.

In this respect most safety concerns with use of hypnotics do not apply to melatonin [1]. Melatonin agonists also show promise in some forms of insomnia. Accordingly, it is now even more imperative that long-term BZD users be reviewed with respect to possible discontinuation. Strategies for discontinuation start with primary-care practitioners, who are still the main prescribers.

An important point when dealing with the effects of melatonin on sleep is to understand that they are different from BZD/Z drugs in that they exert a promoting effect on sleep by amplifying day/night differences in alertness and sleep quality and displaying a modest sleep inducing effect, quite mild as compared to that seen with the BZD. Certainly because of the long time in the market and on the lack of new alternatives for treatment of insomnia the preconception that the consumer has for a sleeping pill is that of a strong sleep inducer, something that the melatonin family of compounds will hardly accomplish [137]. Therefore, a very important educational goal would be to change this view because of the lack of negative effects (addiction, dependence, etc.) the melatonin analogs have in contrast to the well-known complications of BZD.

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Table 1. Clinical studies comparing melatonin vs. BZP / Z drugs.

Subjects	Design	Study´s duration	Treatment	Measured	Results	Reference(s)
16 healthy, young subjects (10 females; mean age: 21.4 ± 6 years)	Randomized, double-blind crossover study	3 days	Subjective sleepiness was measured at hourly intervals using a visual analogue scale. At 12:00 h subjects were administered a capsule containing 5 mg melatonin, 10 mg temazepam or placebo.	After sleeping overnight in the laboratory, subjects completed a battery of tests at hourly intervals between 08:00 and 11:00 hours and at two hourly intervals between 13:00 and 17:00 hours.	A significant drug x time interaction was evident on the unpredictable tracking, spatial memory and vigilance tasks. Greater changes in performance were evident following temazepam administration than melatonin administration, relative to placebo. Administration of melatonin or temazepam significantly elevated subjective sleepiness levels, relative to placebo. The findings demonstrated that melatonin administration induces a smaller deficit in performance on a range of neurobehavioural tasks than temazepam.	[106]
16 healthy volunteers aged ≥55 years	Randomized, double-blind, placebo controlled, single-dose, 4-way crossover study	1 day	Melatonin controlled release (2 mg p.o.), zolpidem (10 mg p.o.) or their combination	Psychomotor functions, memory recall, and driving skills. Subjects were tested 1 h, 4 h and next morning after dosing.	No impairment of performance after melatonin. Zolpidem impaired psychomotor and driving performance 1 h and 4 h post-dosing, and early memory recall. Melatonin co-administration exacerbated zolpidem effect.	[107]
24 healthy volunteers, aged 55-64 years)	Randomized, double-blind, placebo controlled, single-dose, three-way crossover study	1 day	Melatonin controlled release (2 mg p.o.), zolpidem (10 mg p.o.) or their combination	Body sway tested by the area of the 95% confidence ellipse enclosing the center of pressure (A95) and its path length. Subjects were tested 30 min before, 1.5 and 4 h after dosing.	No effect of melatonin on A95. It increased path length at 4 h post-dose in open but not closed eyes condition. Zolpidem significantly increased the A95 and path length.	[108] }

Subjects	Design	Study´s duration	Treatment	Measured	Results	Reference(s)
38 patients with Parkinson's disease with complaints on sleep disorders (mean age, 67.3±4.8 years; 15 males)	Open-label study	6 weeks	Melatonin (3 mg p.o.) vs. clonazepam (2 mg p.o.)	Quality of sleep was assessed with the Parkinson's disease sleep scale (PDSS) and the Epworth Sleepiness Scale as well as with overnight polysomnographic study at baseline and at the end of the trial. All patients underwent neuropsychological testing using MMSE, five-word test, digit span and the Hamilton scale	Compared to baseline, melatonin and clonazepam reduced sleep disorders in patients. However, the daytime sleepiness (was increased in the clonazepam group. Patients treated with melatonin had better scores on the MMSE, five-word test, Hamilton scale at the end of the study period as compared with the clonazepam group. The number of REM sleep epochs remained lower in patients treated with clonazepam	[109]
Randomly assigned 80 adult patients (ASA 1&2, American Society of Anaesthes-iologists physical status classification) with a Visual Analogue Score (VAS) for anxiety > 3	Prospective, double blind placebo controlled trial	24 h	A tablet containing a combination of alprazolam 0.5 mg and melatonin 3 mg, alprazolam 0.5 mg, melatonin 3 mg, or placebo orally 90 min before a standard anesthetic.	Primary end points were change in anxiety and sedation score at 15, 30, and 60 min after premedication, and number of patients with loss of memory for the five pictures shown at various time points when assessed after 24 h.	Combination drug produced the maximum reduction in anxiety VAS from baseline at 60 min. Sedation scores at various time points and number of patients not recognizing the picture shown at 60 min after premedication were comparable between combination drug and alprazolam alone. Addition of melatonin to alprazolam had superior anxiolysis compared with either drugs alone or placebo.	[110]
15 healthy men and	Double-blind, placebo-	4 weeks	controlled-release melatonin (2 mg p.o.), temazepam (20 mg	Polysomnography and spectral analysis of the EEG	Temazepam and zolpidem significantly reduced slow wave activity (SWA) as compared to placebo. Temazepam significantly reduced SWA compared with	[111]

Subjects	Design	Study´s duration	Treatment	Measured	Results	Reference(s)
women aged 55-64 years	controlled, four-way cross-over trial.		p.o.), zolpidem (10 mg p.o.)		melatonin. Melatonin only reduced SWA during the first third of the night compared with placebo.	
82 critically-ill with mechanical ventilation >48 hours and Simplifed Acute Physiology Score II>32 points were examined	Double-blind randomized placebo-controlled trial		Patients were randomized 1:1 to receive, at 8 p.m. and midnight, melatonin (3+3mg) or placebo p.o., from the third ICU day until ICU discharge.	Primary outcome was total amount of enteral hydroxyzine administered	Melatonin treated patients received lower amount of enteral hydroxyzine. Other neurological indicators (amount of some neuroactive drugs, pain, agitation, anxiety, sleep observed by nurses, need for restraints, need for extra sedation, nurse evaluation of sedation adequacy) improved, with reduced cost for neuroactive drugs.	[112]
92 children aged 5-14 years, scheduled for elective surgery, were randomly assigned to two pre-medication groups	Prospective, randomized, double-blind study		oral melatonin (0.5 mg/kg) or oral midazolam (0.5 mg/kg) premedication before induction of anesthesia with propofol	The effect of premedication on the required infusion of propofol was assessed. As a secondary outcome, the effect of premedication on the preoperative sedation level and on the post anaesthesia recovery score was evaluated.	Oral administration of melatonin significantly reduced doses of propofol required for induction of anaesthesia, more than midazolam ($P < 0.001$). No statistically significant differences were found in the pre- and post-anesthesia sedation score ($P = 0.387$ and $P = 0.525$, respectively) between the two groups.	[113]

Table 2. Clinical studies on the efficacy of melatonin to curtail BZP / Z drug use.

Subjects	Design	Study´s duration	Treatment	Measured	Results	Reference(s)
41 patients (28 women, mean age 74 ± 12 yr.) with sleep disturbance including 22 insomniacs, 9 depressed and 10 demented patients.	Open-label study	3 weeks	3 mg melatonin p.o./daily at bed time	Daily logs of sleep and wake quality completed by the patients or their caretakers	Four (31%) of the 13 insomniac patients who were receiving BZP reduced BZP use by 50 to 75% and 4 (31%) discontinued it. Of the 7 depressed and 7 demented patients who were receiving BZP, 2 (29%) in each group reduced BZP use by up to 50%.	[114]
A 43-year-old woman who had suffered from insomnia for the past 11 years	Case report	1 yr.	1 mg of controlled release melatonin p.o./daily at bed time	Subjective evaluation of sleep quality. Urinary 6-sulphatoxymelatonin measurement.	Treatment with melatonin enabled the patient to completely cease any BZP use within two days, with an improvement in sleep quality and no side effects. Examination of urinary 6-sulphatoxymelatonin levels before the melatonin treatment indicated that the levels were very low and lacked the typical circadian rhythm of excretion. Reexamination of 6-sulphatoxymelatonin levels during melatonin treatment revealed the existence of a normal circadian rhythm of excretion.	[115]
34 primary insomnia outpatients aged 40-90 years who took BZP and had low urinary 6-	Randomized, double-blind, placebo controlled study followed by a single blind period.	18 months	Patients received melatonin (2 mg controlled release p.o.) or placebo for 6 weeks. They were encouraged to reduce BZP dosage 50% during week 2,	Sleep diary and recording of BZP use	14 of 18 subjects who had received melatonin, but only 4 of 16 in the placebo group, discontinued BZP therapy. Sleep-quality scores were higher in the melatonin group. Six additional subjects in the placebo group discontinued BZP after 6 months of treatment. At the follow-up 19 out of 24 patients who discontinued BZP kept good sleep quality.	[116]

Subjects	Design	Study´s duration	Treatment	Measured	Results	Reference(s)
sulphatoxy melatonin levels			75% during weeks 3 and 4, and to discontinue BZP during weeks 5 and 6. Then melatonin was administered (single blind) for 6 weeks and attempts to discontinue BZP therapy were resumed. Follow-up reassessment was performed 6 months later			
41 insomniac patients (28 females), mean age 60 ± 9.5 yr. Twenty of 22 patients were on BZP treatment.	Open-label study	6 months	3 mg melatonin p.o./daily at bed time	Sleep diary and recording of BZP use. Serum concentrations of prolactin, TSH, FSH, and estradiol and urinary 6-sulphatoxymelatonin excretion were measured by RIA	In 13 of 20 patients taking BZP together with melatonin, BZP use could be stopped, and in another 4 patients, BZP dose could be decreased to 25–66% of the initial dose. Serum hormone concentration did not change, nor were any indications of hematologic or blood biochemistry alteration found. Urinary 6-sulphatoxymelatonin correlated negatively with age, but not with the intensity of sleep the disorder or the outcome of treatment.	[117]
45 patients (36 females, 70.5 ± 13.1 years old) regularly taking anxiolytic BZP in low doses were studied.	Randomized, double-blind, placebo controlled study	6 weeks	3 mg melatonin p.o./daily at bed time. On day 14 of treatment, BZP dose was reduced by half and on day 28, it was halted.	Sleep diary and recording of BZP use. Urinary 6-sulphatoxymelatonin measurement.	No significant modifications of sleep or wakefulness were detected after BZP withdrawal. As compared to basal, there was a general lack of changes in quality of wakefulness or sleep in patients taking melatonin or placebo. Melatonin advanced sleep onset by 27.9 ± 11.9 min and decreased significantly the variability of sleep onset time. The urinary concentration of 6-sulphatoxymelatonin prior to the study did not correlate with any parameter examined.	[118]

Subjects	Design	Study´s duration	Treatment	Measured	Results	Reference(s)
Of 503 long-term users of BZP asked to participate in a dis-continuation program, 38 patients (22 females) agreed to participate.	Placebo controlled trial	1 yr.	5 mg melatonin or placebo which had to be taken p.o. 4 h before patients went to bed.	During this period participants received 4 questionnaires about their use of BZP medication. The urine of all participants was tested for the presence of BZP.	After one year 40% had stopped their BZP use, both in the intervention group on melatonin and in the placebo control group. Comparing stoppers and non-stoppers did not reveal significant differences in BZP use, or awareness of problematic use.	[119]
60 mild cognitive impairment (MCI) out patients	Open-label, retrospective study	9-24 months	35 patients received daily 3-9 mg of a fast-release melatonin preparation p.o. at bedtime. Melatonin was given in addition to the standard medication	Daily logs of sleep and wake quality. Initial and final neuropsychological assessment.	Beck Depression Inventory score improved in melatonin-treated patients, concomitantly with an improvement in wakefulness, sleep quality and neuropsychological assessment. Twenty-one out of 25 MCI patients not treated with melatonin received BZP treatment vs. 6 out 25 patients in the melatonin group.	[120]
80 patients enrolled at a community methadone maintenance clinic recruited to a BDZ withdrawal program	Double-blind cross-over control study to evaluate the effectiveness of melatonin in attenuating sleep difficulties during BZP withdrawal	13 weeks	Melatonin (5 mg/day, p.o.) or placebo: 6 weeks one arm, 1-week washout, 6 weeks another arm.	Urine BZP; self-reported Pittsburgh Sleep Quality Index and the Center for Epidemiologic Studies Depression questionnaires administered at baseline, and at 6, 7 and 13 weeks.	Sixty-one patients (77.5% in the 'melatonin first' condition and 75% in the 'placebo first' condition) completed 6 weeks of treatment, showing a similar BZP discontinuation rate. Sleep quality in patients who continued abusing BZP improved more in the 'melatonin first' group than in the 'placebo first' group, with no differences in sleep quality improvement in patients who stopped BZP. The data indicated that most improvement in sleep quality was attributed to BZP discontinuation. Although melatonin did not enhance BDZ discontinuation, it improved sleep quality, especially in patients who did not stop BDZ.	[121]

Subjects	Design	Study´s duration	Treatment	Measured	Results	Reference(s)
22 older adults (7 men, 15 women over 65) with a history of sleep disorder complaints Fourteen of these subjects were receiving hypnotic drug therapy	Prospective, randomized, double-blind, placebo-controlled, crossover trial	4 months	Participants received 2 months of melatonin (5 mg/day p.o.) and 2 months of placebo.	Sleep disorders were evaluated with the Northside Hospital Sleep Medicine Institute (NHSMI) test, discarding secondary insomnia and evaluating sleep quality. Behavioral disorders were evaluated with the Yesavage Geriatric Depression Scale (GDS) and Goldberg Anxiety Scale (GAS). Patients discontinuing hypnotic drugs were also recorded.	Melatonin treatment improved sleep quality scores. Depression and anxiety also improved significantly after melatonin administration. Nine out of 14 subjects receiving hypnotic drugs were able to discontinue this treatment during melatonin but not placebo administration; one discontinued hypnotic drugs during both melatonin and placebo administration, and four were unable to discontinue hypnotic therapy.	[122]
96 MCI outpatients	Open-label, retrospective study	15-60 months	61 patients received daily 3-24 mg of a fast-release melatonin preparation p.o. at bedtime. Melatonin was given in addition to the standard medication	Daily logs of sleep and wake quality. Initial and final neuropsychological assessment.	Beck Depression Inventory score improved in melatonin-treated patients, concomitantly with an improvement in wakefulness, sleep quality and neuropsychological assessment. Only 6 out of 61 patients treated with melatonin needed concomitant BZP treatment vs. 22 out of 35 MCI patients not receiving melatonin.	[123]
112 insomniac outpatients classified according to their use of hypnotic BZP or BZP-like drugs	Retrospective study from a longitudinal database	Varied intervals	melatonin (2 mg controlled release) p.o.	Discontinuation rate of BZP	31% of patients discontinued BZP after melatonin initiation. The discontinuation rate was higher in patients receiving two or three melatonin prescriptions	[124]

Subjects	Design	Study´s duration	Treatment	Measured	Results	Reference(s)
Pharma-coepidemiol-ogic analysis and evaluation of the impact of anti-BZD/Z-drugs campaigns in face of the availability of alternative pharma-cotherapy (melatonin)		Varied intervals	Annual sales data from 9 European countries were extracted from the IMS sales database	To determine whether trends in use of treatment options were attributed to campaigns and/or availability and affordability of safer alternatives on the market.	Campaigns aiming to reduce the use of BZP/Z-drugs failed when they were not associated with the availability and market uptake of melatonin. The reimbursement of melatonin supports better penetration rates and a higher reduction in sales for BZD/Z-drugs.	[15]
597 insomniac outpatients classified according to their use of hypnotic BZP or BZP-like drugs (mean age 62.7 yr., 68% previously treated with hypnotics, 65% women).	Post-marketing surveillance study in Germany	3 weeks	melatonin (2 mg controlled release) p.o.	Sleep diary and recording of BZP use.	Most of the patients (77%) who used traditional hypnotics before melatonin treatment had stopped using them and only 5.6% of naive patients started such drugs after melatonin discontinuation.	[125]

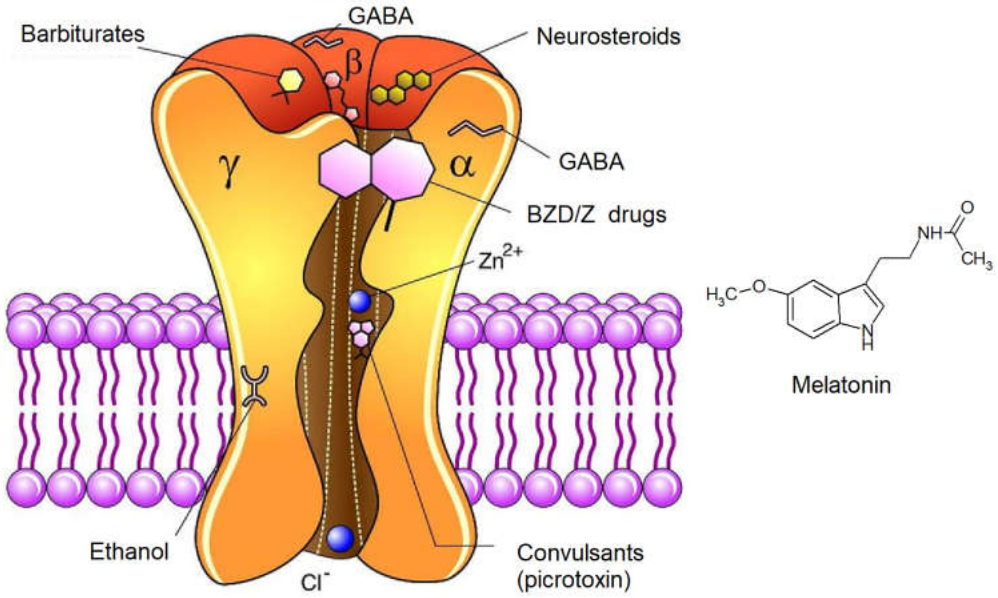
Subjects	Design	Study´s duration	Treatment	Measured	Results	Reference(s)
86 patients with schizo-phrenia or bipolar disorder (21-74 years)	Randomized, placebo-controlled, blinded, trial	24 weeks	controlled-release melatonin (2 mg p.o.).	The primary outcome was mean benzodiazepine daily dosage at 24 weeks. Secondary outcomes included pattern of benzodiazepine dosage over time, benzodiazepine cessation proportion, and benzodiazepine withdrawal symptoms.	BZP cessation proportion was 38.1% (16/42) in the melatonin group versus 47.7% (21/44) in the placebo group (OR 0.64; 95% CI 0.26 to 1.56; P = 0.32). Prolonged-release melatonin had no effect on BZP withdrawal symptoms.	[126]
48 patients with schizo-phrenia or bipolar disorder were studied	Randomized, double-blind study	24 weeks	Prolonged-release melatonin (2 mg) or placebo p.o. once daily. All participants gradually tapered usual benzodiazepine dosage	72 h of actigraphic assessment of activity-rest cycles performed pre and post tapering	Melatonin significantly increased the interdaily stability and at a trend level decreased the intradaily variability compared with placebo.	[127]
78 patients with schizo-phrenia or bipolar disorder were studied	Randomized, double-blind study	24 weeks	Prolonged-release melatonin (2 mg) or placebo p.o. once daily. All participants gradually tapered usual benzodiazepine dosage	23 patients underwent sleep recordings (one-night polysomnography) while 55 patients were assessed by subjective sleep quality ratings	Melatonin had no effect on objective sleep efficiency, but significantly improved self-reported sleep quality. Reduced benzodiazepine dosage at the 24-week follow-up was associated with a significantly decreased proportion of stage 2 sleep.	[128]
80 patients with schizo-phrenia or bipolar disorder were studied	Randomized, double-blind study	24 weeks	Prolonged-release melatonin (2 mg) or placebo p. o. once daily. All participants gradually tapered usual benzodiazepine dosage	Brief Assessment of Cognition in Schizophrenia (BACS) was used to assess neurocognitive performance with additional assessments of subjective well-being and psychosocial functioning	BACS composite and subscale scores (except motor speed) significantly improved in parallel with benzodiazepine dose reduction, but there was no additional effect of melatonin. Cognitive performance was still markedly impaired post-tapering compared with normative data. Neither benzodiazepine withdrawal nor treatment group affected subjective well-being or psychosocial functioning	[129]

FIGURE LEGENDS

Figure 1. Schematic representation of the GABA type A receptor.

Figure 2. Theoretical properties of the ideal hypnotic drug,

Figure 1. Schematic representation of the GABA type A receptor.



Melatonin

Figure 2. Theoretical properties of the ideal hypnotic drug.