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Assessing the efficacy of melatonin to curtail benzodiazepine/Z drug abuse

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ABSTRACT

The abuse of benzodiazepine (BZP) and Z drugs has become, due to the tolerance and dependence they produce, a serious public health problem. Thirty years ago, we demonstrated in experimental animals the interaction of melatonin with central BZD receptors, and in 1997 we published the first series of elderly patients who reduced BZP consumption after melatonin treatment. Almost every single neuron in the hypothalamic suprachiasmatic nuclei (SCN), the central pacemaker of the circadian system, contains γ-aminobutyric acid (GABA) and many results in animals point out to a melatonin interaction with GABA-containing neurons. In addition, central-type BZD antagonism, that obliterates $GABA_A$ receptor function, blunted most behavioral effects of melatonin including sleep. Melatonin is involved in the regulation of human sleep. This is supported by the temporal relationship between the rise of plasma melatonin levels and sleep propensity as well as by the sleep-promoting effects of exogenously administered melatonin. Both meta-analyses and consensus agreements give support to the therapeutic use of melatonin in sleep disorders. This action is attributed to MT_1 and MT_2 melatoninergic receptors localized in the SCN, as well as in other brain areas. This review discusses available data on 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, it is usually remarkably well tolerated and, in some studies, it has been administered to patients at very large doses and for long periods of time, without any potentiality of abuse. Further studies on this application of melatonin are warranted.

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1. Introduction

Insomnia is a very common disorder. It comprises unsatisfactory sleep, in terms of sleep onset, maintenance of sleep or early waking. Insomnia impacts heavily on the subjective well-being, skills and daily performance of patients and is amenable of diagnosis mainly through clinical observations and less through objective measurements [1].

Insomnia occurs despite having adequate opportunity for sleep and it is associated with clinically significant distress or impairments of daytime functioning including fatigue, decreased energy, mood disturbances or reduced cognitive functions (e.g., attention, concentration, memory).

Anxiety about sleep, repetition of precipitating stress, inadequate sleep hygiene and intrinsic vulnerability of neural mechanisms regulating sleep are factors involved in the persistence of insomnia [2]. The diagnosis of insomnia is made when sleep difficulties are present 3 nights or more per week and last for more than 3 months.

Insomnia is commonly associated with medical and psychiatric disorders, but the difficulties in elucidating cause-effect relationships, as well as the bidirectional relationship between insomnia and these disorders, has led current nosology systems (e.g., the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5) [3] to adopt the term "insomnia disorder" and simply use the comorbid disorder as a descriptor when appropriate. DSM-5 avoids the term "primary insomnia" to prevent the primary/secondary designation when the disorder co-occurs with other conditions. DSM-5 pays more attention to co-existing medical conditions to better emphasize when an individual has a sleep disorder warranting independent clinical attention, thus recognizing that co-existing medical conditions, mental disorders and sleep disorders are interactive and bidirectional [4].

The general detrimental effect of insomnia on health has long been established empirically. 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 [5], as well as of neurodegenerative disorders [6]. In cancer sleep disorders are very common [7] but they generally remained underdiagnosed and poorly treated [8].

Epidemiological studies have identified an association between insomnia, especially with reduced or fragmented sleep, and increased rate of accidents [9] and falls in the elderly [10]. Insomnia is associated with significant direct and indirect costs. The gross economic burden of this disorder has been estimated to be up to $107.5 billion per year in the USA [11].

While insomnia symptoms like disturbed sleep and particularly sleep fragmentation, increase with age, the prevalence of insomnia disorder itself is lower among older adults, probably due to the elderly less often reporting daytime impairment or distress associated with their disturbed sleep. Epidemiological results indicate that 12–20% of individuals over 65 years of age suffer insomnia and up to 40% are not satisfied with their sleep or report troubles in initiating or maintaining sleep [12–14]. Thus an increased use of hypnotics is seen in the elderly, i.e., 30–40% of older people use sedative hypnotic benzodiazepine (BZD) and related Z drugs for improving their sleep [15]. However, side effects of hypnotics in old people are common due to both a greater sensitivity of the aging nervous system as well as to decreased levels of serum albumin, the main protein that binds the drug in circulation. As a consequence the hypnotic drugs behave differently and in a less predictable way among elder people as compared with their younger counterparts [16,17].

Many aged patients are treated for longer periods or with higher doses of hypnotic drugs BZD/Z drugs than the 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 [18]. 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 [19].

Several studies have shown the importance of melatonin both for the initiation and for the maintenance of sleep [20–22]. In human beings the onset of melatonin secretion coincides with the timing of increase in nocturnal sleep propensity [23]. Since melatonin and BZD share some neurochemical mechanisms in brain, i.e., interaction with γ-aminobutyric acid (GABA) [24] and similar behavioral properties, e.g., a similar day-dependent anxiolytic activity [25], melatonin therapy has been postulated as a possible tool to decrease the dose of BZD needed in patients.

This review 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 August 5, 2015.

2. 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 [26]. BZD exerts broad inhibitory effects on brain functions including sleep promotion, anxiolysis, anticonvulsant effects, cognitive and motor impairment and reinforcing effects [27]. BZD exert their actions through activation of BZ_1 and BZ_2 receptor subtypes of the α_1-subunit of the $GABA_A$ receptor complex, the activation of BZ_1 accounting for their specific hypno-sedative, anxiolytic and anticonvulsant activities [28].

Meta-analyses like that of Ref. [29] support the efficacy of BZD in treating insomnia. In addition significant adverse effects like cognitive and psychomotor impairment, next-day hangover, rebound insomnia, anterograde amnesia and dependence have been documented turning controversial the use of BZD for treatment of insomnia in the elderly.

"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 [26,27]. Zolpidem, zopiclone and zaleplon all having high affinity and selectivity for the α_1-subunit of the $GABA_A$ receptor complex are included in this group [30]. Generally Z drug hypnotics, although effective in reducing sleep latency, are only moderately effective in increasing sleep efficiency [31]. For example, zolpidem improves sleep maintenance after administration, but its effect disappears later in the night [1,32]. In addition, zolpi-

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dem may induce adverse effects like headache, nausea and daytime drowsiness. Zaleplon is effective to decrease sleep latency [33] and together with zopiclone and its active stereoisomer eszopiclone have been shown effective and safe in patients with primary insomnia [30,34]. It must be noted that the use of all these agents are problematic in individuals prone to drug abuse.

The most commonly prescribed medications for sleep are BZD and Z-drug and a number of studies have indicated that 50–80% of nursing home residents have at least one prescription for psychotropic medication. For many of these substances (e.g., zolpidem, zopiclone, zaleplon, temazepam, triazolam) the recommended dosage for elder patients is about half that recommended for the young. The vast majority of studies advise to avoid long-acting BZD and to use hypnotics for as brief a period as possible in elder patients, in most cases not exceeding 2–3 weeks of treatment [27]. The clearest strategy is to taper the medication; abrupt cessation can only be justified if a very serious adverse effect supervenes during treatment. No clear evidence suggests the optimum rate of tapering, and schedules vary from 4 weeks to several months [27]. However, most patients continued to use BZD or drugs for long times due to their dependence potential.

Can we define the characteristics of the ideal hypnotic? It clearly should not only decrease sleep latency but 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. Melatonin fulfills many of these requirements as recognized in several consensus statements [1,35–37]. Meta-analysis publications also support such a conclusion [38,39] although not unanimously [40].

3. Basic physiology of melatonin

The metabolic machinery to synthesize melatonin occurs in a wide variety of tissues: however, circulating melatonin derives almost entirely from the pineal gland [41]. Melatonin synthesis in the pineal is regulated by the master clock located in the hypothalamic suprachiasmatic nucleus (SCN). Once synthesized in the pineal gland melatonin diffuses readily into the bloodstream, where it is bound to albumin [42]. Melatonin rapidly disappears from the blood with a biexponential half-life, with a first distribution half-life of 2 min and a second of about 20 min [43].

The liver clears 92–97% of circulating melatonin in a single pass [44]. The hepatic metabolism of melatonin comprises the hydroxylation in the C6-position by cytochrome P_{450} monooxygenases (isoenzymes CYP1A1, CYP1A2, and to a lesser extent CYP1B1) and a sulfate conjugation to be excreted as 6-sulphatoxymelatonin [43]. CYP1A2 and to a greater extent CYP2C19 also demethylate melatonin to its precursor *N*-acetylserotonin [45]. Specific melatonin deacetylases or less specific aryl acylamidases are also detectable in brain [41].

Approximately one third of the total metabolism of melatonin in the brain is attributed to oxidative pyrrole-ring cleavage to N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), which is then deformylated, either by arylamine formamidase or hemoperoxidases to N^1-acetyl-5-methoxykynuramine (AMK). Other oxidative catabolites like 2-hydroxymelatonin and cyclic 3-hydroxymelatonin are also formed [41]. AFMK and AMK form metabolites by interactions with reactive oxygen and nitrogen species thus behaving as antioxidants [46]. By this mechanism melatonin and its endogenous metabolites provide safeguarding of mitochondrial electron flux.

High affinity binding sites for melatonin were initially identified in our laboratory in bovine brain membranes by using ^{3}H-melatonin [47,48]. These initial observations were confirmed by later studies using 2-I^{125}-iodomelatonin as a radioligand [49]. 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 [50]. There are at least two G_i-protein-coupled membrane melatonin receptors in humans. The MT_2 receptor [51] is 60% identical in amino acid sequence to the MT_1 receptor. Additionally, a third receptor (GPR50) shares 45% of the amino acid sequence with MT_1 and MT_2 but does not bind melatonin [52].

MT_1 and MT_2 receptors have been localized in the SCN, the choroid plexus, cerebellar and prefrontal cortex, hippocampus, nucleus accumbens, basal ganglia, substantia nigra, ventral tegmental area, and retinal horizontal, amacrine and ganglion cells (summarized in ref. [53]). The MT_1 receptor is highly expressed in the human SCN [54] and mainly in SCN vasopressinergic neurons [55]. MT_2 seems not to be present in the human SCN [54]. This receptor subtype is expressed in the SCN of numerous mammals and, where present, is particularly important for circadian phase shifting [56,57]. Since circadian clock reset does occur in humans after administering melatonin [58,59] these changes must be ascribed to MT_1 signaling.

Through MT_1 receptors located in the SCN melatonin can promote sleep initiation via the hypothalamic sleep switch. This switch is thought to alternately activate either wake-related neuronal downstream pathways or to promote the sleep-related ones in a typical on-off response [60]. The sleep promoting part of the hypothalamic sleep switch includes a subset of sleep-active ventrolateral preoptic area (VLPO) neurons, a tightly clustered group of neurons that appears to promote slow wave sleep by suppression of the histaminergic arousal system, located in the tuberomammillary nucleus of the posterior hypothalamus. Furthermore, a subgroup of VLPO neurons promote rapid eye movement (REM) sleep through their inhibitory projection to monoaminergic dorsal raphe (serotonergic) and locus coeruleus (noradrenergic) nuclei in the brainstem [61]. The inhibitory projections from the VLPO to the histaminergic, serotonergic and noradrenergic components of the arousal system, use GABA and galanin neurotransmitters which are present in nearly 80% of VLPO neurons. Since melatonin, as below discussed, promotes GABAergic activity, it is possible that the methoxyindole activates VLPO neurons with the consequent suppression of arousal systems and sleep induction.

However, the sleep switch does not seem to represent the exclusive route of melatonin soporific action. The thalamus in particular contributes to melatonin effects by promoting spindle formation, a characteristic feature of the transition from sleep stage N2 to deeper sleep stages [62]. Moreover, the thalamus and other brain areas also feedback to the SCN.

4. Melatonin and brain gabaergic mechanisms

GABA-containing neurons are mostly interneurons in the majority of central neuronal circuits including the SCN [63]. 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 [64]. Because of this key distribution, it was thus logical to postulate GABA as the principal neurotransmitter of the circadian timing system [63].

A number of adaptive functions are made possible by the activity of inhibitory GABAergic neurons. It has been proposed that inhibition enables the CNS to produce variability in behavior and to adjust the extent and rate in which adaptative options take place [65].

GABA inhibits neuronal firing by increasing Cl^- conductance via activation of $GABA_A$ receptors. This receptor-channel complex is

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allosterically modulated by drugs like BZD or barbiturates whereas blockade of $GABA_A$ receptors by bicuculline generates epileptic activity. Another receptor ($GABA_C$ receptor) is associated, as the $GABA_A$ receptor, to a chloride channel through binding sites which are insensitive to bicuculline antagonism. A third type of receptors ($GABA_B$ receptors) coupled to K^+ channels also mediate neuronal inhibition by GABA.

Studies at the molecular level indicate that the $GABA_A$ receptor consists of at least 15 homologous subunits combined in various ways into pentamers. Although the stoichiometry and positional arrangements of the subunits remain unknown, the most abundant combination is $\alpha\beta\gamma$ with $\alpha1\beta2\gamma2$ predominating [66]. $GABA_C$ receptors comprise a similar pentameric structure as $GABA_A$ receptor sites, while $GABA_B$ receptors are of a metabotropic type, being a member of the G protein-coupled receptor family.

The depressive influence on CNS excitability exerted by the pineal is known since long [67]. In view that melatonin treatment prevented pinealectomy (Px)-induced seizures in gerbils [68] and kindled convulsions in rats [69] such inhibitory activity was attributed to melatonin. Melatonin potentiates the anticonvulsant action of phenobarbital and carbamazepine against electroshock-induced seizures in mice [70,71] and when given alone to adult rats, hamsters, guinea pigs, cats and baboons it has a demonstrable anticonvulsant action (for Ref. see [71]). Such anticonvulsant action of melatonin could be attributed to both MT_1 and MT_2 receptors [25,72–76] and similar anti-seizure effects were observed with the MT_1/MT_2 agonist ramelteon [77]. These antiexcitatory actions are also related to the anxiolytic, antihyperalgesic and antinociceptive effects of melatonergic agents [78–83].

The observation that brain GABA concentration increased after Px and that this increase was counteracted by melatonin was the first indication of a possible link between the pineal and brain GABAergic neurons [84]. Exogenously administered melatonin augmented pyridoxal phosphokinase activity in rat brain [84]. Results in rats, many of them obtained in our laboratory, indicate that central synapses employing GABA as an inhibitory transmitter are a target for pineal melatonin activity. These observations include: (i) the disruption by Px of circadian rhythmicity of brain GABA and BZD binding [85,86]; (ii) the reversal of Px-induced modifications of BZD and GABA binding by melatonin injection [87]; (iii) the increase in brain BZD and GABA binding by the long-term melatonin treatment [85,86,88]; (iv) the increase in brain GABA turnover rate after melatonin injection [89]; (v) the melatonin-induced, time-dependent increase in glutamic acid decarboxylase activity and Cl^- ion conductance in the medial basal hypothalamus-preoptic area, with maximal activity in the evening [90].

At a pharmacological concentration melatonin acts on $GABA_A$ 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 [91]. Indeed, melatonin competes for diazepam binding sites in rat, human and bovine brain membranes with micromolar affinity [92], suggesting a direct interaction within the BZ binding pocket, which is located at the α/γ subunit interface of the $GABA_A$ receptor complex.

In vivo, electrophysiological studies indicate that nanomolar concentrations of melatonin potentiate GABAergic inhibition of neuronal activity in the mammalian cortex [93]. In vitro, electrophysiological studies have shown that the MT_1 receptor is coupled to stimulation of GABAergic activity in hypothalamic slices, whereas the MT_2 receptor mediates an opposite effect in hippocampal slices [94]. The primary effect of melatonin in the rat SCN was to inhibit of neuronal activity [95], which is consistent with the relatively high expression of the MT_1 receptor subtype. $GABA_A$ receptor currents are also modulated by melatonin in neurons of carp retina [96] and chick spinal cord [97]. In cultured rat hippocampal neurons melatonin was able to enhance GABA-induced current and GABAergic miniature inhibitory postsynaptic currents through an effect inhibited by the BZD receptor antagonist flumazenil [98].

Although the above discussed results strongly endorse the view that GABA neurons are a target for melatonin action in brain, a second requirement must be fulfilled, namely that the functional obliteration of the neurotransmitter system should significantly modify the melatonin effect. The intraventricular injection of 6- hydroxydopamine and 5,7-dihydroxytryptamine, which deplete catecholamines and indoleamines, failed to alter melatonin entrainment of circadian rhythmicity in rodents indicating that monoamine brain pathways were not important for melatonin effect [99].

Several studies in our laboratory were addressed to examine whether the functional obliteration of the GABAergic system could significantly modify melatoninís behavioral effects. 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 their pro-convulsive activity. 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 flumazenil, 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 [79]. In subsequent studies, we analyzed the inhibitory effects of flumazenil on melatonin-induced depression of locomotor behavior and seizures induced by 3-mercaptopropionic acid [73,100]. The administration of flumazenil, 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 [78]. 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 flumazenil.

Other studies in the literature also supported the link of melatonin and GABA-mediated mechanisms in brain [101,102]. For example, BZD/$GABA_A$ antagonists block the sleep-inducing effect of pharmacological doses of melatonin in rats [103]. The ability of pharmacological concentrations of melatonin or BZD to inhibit the cAMP pathway via G protein-coupled BZ receptors [104] suggests yet another mechanism for modulation of GABAergic activity by melatonin.

Collectively, the above discussed results underline the importance of GABAergic mechanisms in sleep modulation by melatonin. The possibility that the sedative effects of pharmacological doses of melatonin also involve its allosteric interaction with BZD-$GABA_A$ receptors seemed warranted.

5. Melatonin and BZD use in insomnia disorder patients

The sleep-promoting activity of melatonin in humans has been known for years [105–107]. A number of studies pointed to a beneficial effect of melatonin in a wide variety of sleep disorders [20–22]. A recent meta-analysis involving 19 controlled studies and 1683 subjects has shown that melatonin was effective in reducing sleep latency and increasing total sleep time and sleep efficiency [39]. Prior data however, were controversial, supporting [38] or not [40] such a conclusion.

In several consensus statements [1,35–37] melatonin was recognized as fulfilling the properties of a useful sleep-promoting

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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 years [1]. Similar conclusions were put forth by Canadian and European pediatrics consensuses [1,35–37]. Brain imaging studies in wake subjects have revealed that melatonin modulates brain activity pattern to one resembling that of actual sleep [108].

Table 1 summarizes published data on melatonin/BZD interactions in clinical studies. Two types of reports have been published. On one hand, the efficacy of melatonin to curtail BZD use was assessed. On the other, melatonin was compared to BZD/Z drugs in their effects on sleep.

Our research group published in 1997 the first series of elderly patients who reduced BZP consumption after melatonin treatment. 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 50–75% and 4 (31%) discontinued it [109]. Of the 7 depressed and 7 demented patients who were receiving BZD, 2 (29%) in each group reduced BZD use by up to 50%. A case report supported 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 [110].

Two years later, 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 was published [111]. Fourteen out of 18 subjects who had received controlled-release melatonin, but only 4 out of 16 in the placebo group, discontinued BZD therapy [111]. Another 6-month-long, open label study from our research group 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 [112].

In another 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 [117].

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 [115]. 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 very low doses. To assess the efficacy of melatonin to reduce the use of BZD at these very low amounts we 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 [113]. In two steps BZD was tapered off and stopped after 4 weeks. Several subjective sleep parameters were assessed and found not to be different for both groups. The fact 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 [113].

Mild cognitive impairment (MCI) is an etiologically heterogeneous syndrome defined by cognitive impairment in advance of dementia. Two retrospective analyses of 60 [116] and 96 MCI outpatients [120], receiving or not daily 3–24 mg of a fast-release melatonin preparation p.o. at bedtime for 9–24 or 15–60 months

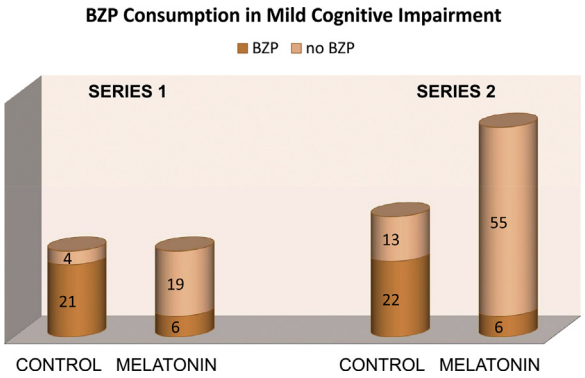

Fig. 1. Two retrospective analyses of 60 [116] and 96 MCI outpatients [120], receiving or not daily 3–24 mg of a fast-release melatonin preparation p.o. at bedtime for 9–24 or 15–60 months are shown. In both studies there was a significant improvement of cognitive and emotional performance and daily sleep/wake cycles.

were published by our research group (Fig. 1). 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.

Both in vitro and in vivo, melatonin prevented the neurodegeneration seen in experimental models of Alzheimer's disease (AD) and in a limited number of clinical trials melatonin was found to have a therapeutic value as a neuroprotective drug in treating AD and MCI patients (see for Ref. [127]). For these effects to occur, doses of melatonin about one order of magnitude higher than those required to affect sleep and circadian rhythmicity are needed.

In 2007 the approval by the European Medicines Agency (EMEA) of a sustained release form of 2 mg of melatonin (Circadin^{R}, Neurim, Tel-Aviv) for the treatment of insomnia in elderly people was an extraordinary event in melatoninís history. Melatonin has thus acquired a status that allows its incorporation into the vademecum of several European countries. The fact that melatonin shows no evidence of dependency, withdrawal, rebound insomnia or negative influence on alertness during the day was emphasized by EMEA.

A retrospective analysis of a German prescription database identified 512 patients who had initiated treatment with Circadin^{R} over a 10-month period [122]. From 112 patients in this group who had previously used BZD, 31% discontinued treatment with BZD 3-months after beginning controlled release melatonin treatment [122].

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 [19]. In this pharmacoepidemiological 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 [123].

A recent study examined the efficacy of controlled release melatonin to facilitate withdrawal of long-term BZP usage in patients with schizophrenia or bipolar disorder [126]. Patients were continuously guided to gradually reduce their usual BZP dosage. The

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Table 1
Clinical studies on the efficacy of melatonin to curtail BZD/Z drug use.

Subjects	Design	Studyís dura-tion	Treatment	Measured	Results	Ref.
41 patients (28 women, mean age 74 ± 12 years) 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 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%	[109]
A 43 year old woman who had suffered from insomnia for the past 11 years	Case report	1 year	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 BZD 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	[110]
34 primary insomnia outpatients aged 40–90 years who took BZD and had low urinary 6-sulphatoxy melatonin levels	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 BZD dosage 50% during week 2, 75% during weeks 3 and 4, and to discontinue BZD during weeks 5 and 6. Then melatonin was administered (single blind) for 6 weeks and attempts to discontinue BZD therapy were resumed. Follow-up reassessment was performed 6 months later	Sleep diary and recording of BZD use	14 of 18 subjects who had received melatonin, but only 4 of 16 in the placebo group, discontinued BZD therapy. Sleep-quality scores were higher in the melatonin group. Six additional subjects in the placebo group discontinued BZD after 6 months of treatment. At the follow-up 19 out of 24 patients who discontinued BZD kept good sleep quality	[111]
41 insomniac patients (28 females), mean age 60 ± 9.5 years. Twenty of 22 patients were on BZD treatment	Open-label study	6 months	3 mg melatonin p.o./daily at bed time	Sleep diary and recording of BZD use. Serum concentrations of prolactin, TSH, FSH, and estradiol and urinary 6-sulphatoxymelatonin excretion were measured by RIA	In 13 of 20 patients taking BZD together with melatonin, BZD use could be stopped, and in another 4 patients, BZD 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	[112]
45 patients (36 females, 70.5 ± 13.1 years old) regularly taking anxiolytic BZD 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, BZD dose was reduced by half and on day 28, it was halted	Sleep diary and recording of BZD use. Urinary 6-sulphatoxymelatonin measurement	No significant modifications of sleep or wakefulness were detected after BZD 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	[113]

Table 1 (*Continued*)

Subjects	Design	Studyís dura-tion	Treatment	Measured	Results	Ref.
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 h and at two hourly intervals between 13:00 and 17:00 h	A significant drug × 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	[114]
Of 503 long-term users of BZD asked to participate in a dis-continuation program, 38 patients (22 females) agreed to participate	Placebo controlled trial	1 year	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 BZD medication. The urine of all participants was tested for the presence of BZD	After one year 40% had stopped their BZD 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 BZD use, or awareness of problematic use	[115]
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 BZD treatment vs. 6 out 25 patients in the melatonin group	[116]
80 patients enrolled at a community methadone maintenance clinic recruited to a BZD withdrawal program	Double-blind cross-over control study to evaluate the effectiveness of melatonin in attenuating sleep difficulties during BZD withdrawal	13 weeks	Melatonin (5 mg/day, p.o.) or placebo: 6 weeks one arm, 1 week washout, 6 weeks other arm	Urine BZD; 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 BZD discontinuation rate. Sleep quality in patients who continued abusing BZD improved more in the 'melatonin first' group than in the 'placebo first' group, with no differences in sleep quality improvement in patients who stopped BZD. The data indicated that most improvement in sleep quality was attributed to BZD discontinuation. Although melatonin did not enhance BZD discontinuation, it improved sleep quality, especially in patients who did not stop BZD	[117]
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	[118]
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	[119]

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Subjects	Design	Studyís dura-tion	Treatment	Measured	Results	Ref.
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 BZD treatment vs. 22 out of 35 MCI patients not receiving melatonin	[120]
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, 5-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	[121]
112 insomniac outpatients classified according to their use of hypnotic BZD or BZD-like drugs	Retrospective study from a longitudinal database	Varied intervals	Melatonin (2 mg controlled release) p.o.	Discontinuation rate of BZD	31% of patients discontinued BZD after melatonin initiation. The discontinuation rate was higher in patients receiving two or three melatonin prescriptions	[122]
Pharmaco-epidemiologic analysis and evaluation of the impact of anti-BZD/Z-drugs campaigns in face of the availability of alternative pharmacotherapy (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 BZD/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	[19]
597 insomniac outpatients classified according to their use of hypnotic BZD or BZD-like drugs (mean age 62.7 years, 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 BZD 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	[123]
Randomly assigned 80 adult patients (ASA 1&2, American Society of Anesthesiologists 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 5 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 was comparable between combination drug and alprazolam alone. Addition of melatonin to alprazolam had superior anxiolysis compared with either drugs alone or placebo	[124]
86 patients with schizophrenia 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 vs. 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	[125]
15 healthy men and women aged 55–64 years	Double-blind, placebo-controlled, four-way cross-over trial	4 weeks	Controlled-release melatonin (2 mg p.o.), temazepam (20 mg p.o.), zolpidem (10 mg p.o.)	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 melatonin. Melatonin only reduced SWA during the first third of the night compared with placebo	[126]

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authors concluded that prolonged-release melatonin did not facilitate BZP withdrawal in patients with schizophrenia or bipolar disorder. Thus the underlying medical condition may affect substantially the results obtained.

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

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 after 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 neurobehavioral tasks than temazepam, indicating that melatonin is preferable to BZD in the management of circadian and sleep disorders [114].

Two studies have been performed 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 [118]. 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 [118].

In another study, effects of controlled-release melatonin and zolpidem on postural stability were assessed in healthy older adults [119]. 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 [119].

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, whereas temazepam and zolpidem significantly reduced it as compared with placebo. Melatonin only reduced slow wave activity 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 [126].

A study of 38 patients with Parkinson's disease without dementia with complaints on sleep disorders showed that 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 efficacy of melatonin in the treatment of sleep disorders in Parkinson's disease [121].

In a double blind placebo controlled study to assess whether the addition of melatonin to alprazolam had superior premedication effects compared to either drug alone, addition of drugs elicited superior anxiolysis compared with either drug alone or placebo when given 90 min before a standard anesthetic procedure [124]. Adding melatonin neither worsened the sedation score nor the amnesic effect of alprazolam alone [124].

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 50–100 min after administration). Melatonin was equally as effective as standard treatment with midazolam in reducing preoperative anxiety in adults [128].

Summarizing, the observations shown in Table 1 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 remarkably well tolerated, even at very large doses. Doses of 80 mg melatonin hourly for 4 h were given to healthy men with no undesirable effects other than drowsiness [129]. In healthy women receiving 300 mg melatonin/day for 4 months there were no side effects [130]. 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]. 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 [133]. 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 [134].

6. Conclusions

Translational medicine is a discipline in biomedical research and public health that aims to improve the health of individuals and the community by facilitating the "translation" of basic knowledge in biomedical sciences in diagnostic tools and treatment of diseases. On the one hand it implies direct knowledge of the basic sciences in producing new therapies and diagnostic procedures that direct treatment of human diseases. On the other hand, it seeks to ensure that new treatments and scientific knowledge reach patients and populations for whom they are designed, and are implemented properly. We hereby summarize the experience of our research group as a developer of a basic concept (melatonin—BZP interaction) in animals and as an initiator of the clinical application of melatonin to reduce BZP doses in insomniac patients. This exemplifies the concept of translational medicine performed in Argentina and with the support of CONICET, the University of Buenos Aires and the National Agency for Scientific and Technological Promotion.

The use of BZD/Z drugs as anxiolytics and hypnotics continues to arouse controversy. Their adverse effects have been 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 BZP/Z drugs do not apply to melatonin [1]. Melatonin exerts its promoting effect on sleep by amplifying day/night differences in alertness

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and sleep quality while displaying a modest sleep inducing effect as compared to that seen with BZD/Z drugs. Many times this outcome does not fit the preconception the consumer has for a sleeping pill as a strong sleep inducer [135]. It is thus necessary to change this view because of the lack of negative effects (addiction, dependence, etc.) that melatonin and its analogs have in contrast to the undesired complications of BZD/Z drug use.

The approval by the EMEA of melatonin as a prescription drug in 2007 has allowed getting pharmacoepidemiological information on this subject. Several studies have verified that more than 50% of insomniac patients treated with BZP stop its use upon melatonin treatment. Melatonin may thus become the therapy of choice to reduce dependence on BZP/Z drugs in the treatment of insomnia in older adults. Further studies on this application of melatonin are warranted.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phrs.2015.08.016.

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