Benzodiazepine discontinuation with prolonged-release melatonin: hints from a German longitudinal prescription database

Dieter Kunz, Sébastien Bineau†, Khaled Maman, Dominique Milea & Mondher Toumi
†International Epidemiology Department, Global Outcomes Research Division, Lundbeck SAS, Paris, France

Objective: Prolonged-release (PR) melatonin is approved in Europe for the treatment of insomnia in patients aged 55 years and above. The objective of the study was to describe its prescription patterns and its impact on hypnotics use in routine clinical practice.

Research design and methods: This is a retrospective study analyzing PR melatonin prescription data from a German longitudinal database (IMS® Disease Analyzer). All patients initiating PR melatonin over the 10 months after approval (April 2008 – February 2009) were included. Patients were classified according to their use of hypnotic benzodiazepines or benzodiazepine-like drugs (BZD/Z) in the 3-month period before and after PR melatonin initiation.

Results: Of the 512 eligible patients, 380 (74%) were aged ≥ 55 years, 344 (67%) women and 112 (22%) previous BZD/Z users. Most of the latter (79/99, 79.8%) had used BZD/Z for at least 180 days. Approximately one-third (35/112, 31%) discontinued BZD/Z after PR melatonin initiation, and the BZD/Z discontinuation rate was higher in patients receiving two or three PR melatonin prescriptions than in patients receiving only one prescription (10/24 = 42% vs 25/88 = 28%, p = 0.21). Of the 400 patients without prior BZD/Z use, 39 (10%) received BZD/Z during the follow-up.

Conclusions: Based on the observed 31% discontinuation rate, PR melatonin may help to facilitate BZD/Z discontinuation in older insomniacs.

Keywords: benzodiazepines, drug discontinuation, insomnia, patient profile, prolonged-release melatonin

1. Introduction

Insomnia is defined as disturbed sleep comprising difficulties in initiating and maintaining sleep and waking up too early, as well as non-restorative or poor-quality sleep [1]. Its diagnosis is further subdivided into primary insomnia (in the absence of comorbid conditions) and secondary insomnia if an association with other diseases can be determined. These are often not only neurological or psychiatric problems, but also some cardiovascular, pulmonary and gastrointestinal disorders [1]. Sleep disturbances lead to an increased risk of physical and mental health problems, and cognitive abilities are reduced, including attention and memory [2].

More than one-third of the population aged 65 years and older complains of insomnia symptoms in Germany, Italy and UK [3]. For severe insomnia requiring treatment, a prevalence of 6 - 22% was reported in different European countries (Germany, Belgium, Great Britain, Ireland and Sweden) [4]. Non-restorative sleep has been reported to occur in about 10% of the general population in a large
European epidemiological cross-sectional study (> 25,000 participants) [5]. The high prevalence of insomnia is associated with a substantial economic burden on society. According to recently published study, total annual costs were estimated to be $6.6 billion in Quebec [6].

Sedative or hypnotic drugs such as benzodiazepines and benzodiazepine receptor agonists, so-called Z-drugs (zolpidem, zaleplon, zopiclone, eszopiclone), which bind to gamma-aminobutyric acid-A (GABA-A) receptors, are most commonly prescribed for the treatment of insomnia [5,7,8]. A meta-analysis of the risks and benefits of these therapeutic options in older people found not only statistically significant improvements in sleep, but also a statistically significant greater risk of adverse events [7]. In people of more than 60 years, chronic sedative use carries the risk of exacerbation of preexisting psychomotor or cognitive impairment, which may result in increased risks of falls, motor vehicle collisions, household accidents or confusion and memory problems [7]. These safety concerns about the treatment of insomnia with hypnotic drugs as well as the possibility of dependence are also a significant public health issue [9]. Prolonged use of benzodiazepines and benzodiazepine receptor agonists is not recommended, but discontinuation of their use is often difficult, especially for long-term users because of, for example, their addiction potential and rebound insomnia [10].

Prolonged-release melatonin (PR melatonin) is a new non-sedative hypnotic with a mode of action different from other hypnotics. It has demonstrated clinical efficacy on sleep and morning alertness, with a good safety profile [11,12]. No evidence of dependence, withdrawal effects, rebound insomnia or negative influence on daytime alertness was observed with its use [11,13,14]. As it is a formula-

ded to be available for each included patient.

2.4 Base-case analysis
Patients were classified according to their use of benzodiazepine hypnotics (BZD; ATC code N05CD) or benzodiazepine-like drugs (referred to as ‘Z’ drugs, ATC code N05CF) at baseline and/or during the follow-up period [18]. Each category was defined by documentation of at least one prescription filled during the baseline/follow-up period. The definitions used for the hypnotic BZD/Z status of the patients are listed in Table 1. Patients were grouped according to their use of hypnotic BZD/Z drugs (previous, no previous, continuous, discontinuous, new or never) (Figure 1) during the baseline and/or the follow-up period. In addition, the data analysis considered the patient history of the prescription of psychotropic drugs comprising anxiolytics, antidepressants, neuroleptics, antiepileptics and anti-dementia drugs. ATC codes N05B, N06A, N05A, N03 and N06D, respectively [18].

2.5 Sensitivity analysis
Several univariate sensitivity analyses were performed on the compilation of BZD/Z drugs (both anxiolytic and/or hypnotic BZD/Z drugs with ATC codes N05BA, N03AE, N05CD or N05CF vs only hypnotic BZD/Z drugs alone with ATC codes N05CD or N05CF) [18], on higher number of previous BZD/Z prescriptions (at least two vs one) and over a longer follow-up period (6 vs 3 months after the index date) in order to test the robustness of findings.

2.6 Statistics
Descriptive analyses presented absolute and relative frequency for categorical variables and mean ± standard deviation (SD) for continuous variables. t-Tests and chi-square tests were applied to test for statistical significance. Two-sided p-values of less than 0.05 were considered to be significant. Data were analyzed with SAS software version 9.1 (SAS Institute Inc., Cary, NC, USA).
Between April 2008 and February 2009, 1382 patients were initiated on PR melatonin. Of these, 512 patients met inclusion criteria with a minimum 3-month history and a minimum 3-month follow-up and comprised our study sample. Thereof 200 patients received their prescription from 46 neurologists and 312 patients from 158 GPs or internists. As depicted in Figure 1, 400 patients (78%) did not receive prescriptions for any hypnotic BZD/Z drugs during the baseline period (group with no previous BZD/Z use), and 361 of those patients (90%) remained without hypnotic BZD/Z prescription during the follow-up period (subgroup who never used BZD/Z). Among the 112 patients (21.9%) who had received a hypnotic BZD/Z prescription during the baseline period (group with previous BZD/Z use), 35 patients (31.3%) did not receive any hypnotic BZD/Z drugs during the PR melatonin follow-up period; that is, these patients discontinued BZD/Z use (discontinuation subgroup).

Demographics and baseline characteristics are summarized in Table 2. The mean age was 63 ± 14 years and 380 patients (74.2%) were 55 years or older. Patients in the group with previous BZD/Z use were older than patients in the group without previous BZD/Z use (66 vs 62 years; p = 0.01). The majority of patients were women (n = 344/512, 67.2%). Slightly more patients in the previous BZD/Z group were women compared with the group without previous BZD/Z use (n = 80/112, 71.4% vs n = 264/400, 66.0%), but this difference was not statistically significant (p = 0.28).

A diagnosis was documented at the index date (first PR melatonin prescription) for 296 patients (57.8%). Sleep disorder was diagnosed for 231 patients at the issue date of the PR melatonin prescription (78.0%), increasing to 325 patients when including patients with diagnoses made 12 months before the index date. No statistically significant baseline differences were observed between any of the subgroups (Table 2).

The most prevalent diagnoses other than insomnia in the total cohort within a 1-month period around the index date were hypertension (n = 160/512, 31.3%), back pain (n = 136/512, 26.6%), disorders of lipoprotein metabolism (n = 109/512, 21.3%) and ischemic heart disease (n = 58/512, 11.3%) (Table 2). Depression was more common among the group of previous BZD/Z users (n = 54/112, 48.2%) than in the group without previous BZD/Z use (n = 132/400, 33.0%; p = 0.003). The subgroup of patients who continued BZD/Z use (n = 39/77, 50.6%) had a higher incidence of depression than the subgroup of patients who discontinued BZD/Z use (n = 15/35, 42.9%; p = 0.44). The highest prevalence of hypertension was in the subgroup with new use of BZD/Z drugs (n = 17/39, 43.6%), who also had the highest prevalence of lipoprotein metabolism disorders (n = 12/39, 30.8%).

In the group with previous BZD/Z drug use and with an observation period of at least 1-year prior to index date available, the majority of patients were long-term users (n = 79/99, 79.8%); that is, they had used BZD/Z drugs for at least 180 days before their first PR melatonin prescription: 87.3% (n = 62/71) in the continuation subgroup and 60.7% (n = 17/28) in the BZD/Z discontinuation subgroup, p = 0.003 (Table 2).

Analysis of the history of psychotropic drug use revealed that 56.6% of patients had used antidepressants (n = 290/512), 47.7% had taken anxiolytics (n = 244/512), 19.9% neuroleptics (n = 102/512), 10.4% antiepileptics (n = 53/512) and 2.3% anti-dementia drugs (n = 12/512) (Figure 2). The percentage of patients taking antidepressants, anxiolytics or neuroleptics was significantly higher (p < 0.0001) in the group with previous BZD/Z use (n = 83/112, 74.1%, n = 112/112, 100%, and n = 37/112, 33.0%, respectively) than in the group without previous BZD/Z prescriptions (n = 267/400, 51.8%, n = 132/400, 33.0%, and n = 65/400, 16.3%, respectively). The history of psychotropic drug use was quite similar between the subgroups with continued and discontinued BZD/Z use. A statistically significant difference was observed within the group without previous BZD/Z use, with more anxiolytic use in the subgroup with new BZD/Z prescriptions (n = 26/39, 66.7%) compared with the subgroup without new BZD/Z prescriptions (n = 106/361, 29.4%; p < 0.0001).

One PR melatonin package contains 20 tablets and lasts for 20 days. Most patients (n = 422/512, 82.4%) received only one prescription of PR melatonin within the 3-month follow-up period, while 10.7% (n = 55/512) obtained two prescriptions and 6.8% (n = 35/512) three prescriptions within the 3-month follow-up period (Table 3). The highest proportion of patients with three prescriptions was found in the BZD/Z discontinuation subgroup with 17.1% (n = 6/35) and the lowest in the subgroup of new BZD/Z drug users with 2.6% (n = 1/39). The rate of BZD/Z discontinuation was higher in patients receiving two or three PR melatonin prescriptions (n = 10/24, 41.7%) than in patients receiving only one prescription (n = 25/88, 28.4%) but the difference was not statistically significant (p = 0.21). Stratification of PR melatonin prescriptions by type showed that 59.4% (n = 303/501) of patients received prescriptions

| Table 1. Definition of hypnotic BZD/Z status used for classification of patients. |
|---|---|
| | At least one hypnotic BZD/Z prescription |
| | Baseline period | Follow-up period |
| Previous | Yes | n/a |
| No previous | No | n/a |
| Continuation | Yes | Yes |
| Discontinuation | Yes | No |
| New | No | Yes |
| Never | No | No |

BZD/Z: Benzodiazepines or benzodiazepine-like drugs; n/a: Not applicable.
Patients with prescription of prolonged-release melatonin

n = 512

Previous BZD/Z
n = 112

Continuation
n = 77

Discontinuation
n = 35

No previous BZD/Z
n = 400

Never
n = 361

New
n = 39

Figure 1. Prolonged-release (PR) melatonin patients: flow chart according to their BZD/Z use 3 months before (baseline) and 3 months after (follow-up) PR melatonin initiation.

BZD/Z: Benzodiazepines or benzodiazepine-like drugs.

Table 2. Demographics and baseline characteristics of patients with PR melatonin prescriptions.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Previous BZD/Z</th>
<th>No previous BZD/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 512</td>
<td>n = 112</td>
<td>n = 400</td>
</tr>
<tr>
<td></td>
<td>All Cont.</td>
<td>Discont.</td>
<td>All New Never</td>
</tr>
<tr>
<td>Age (years; mean ± SD)</td>
<td>63 ± 14</td>
<td>66 ± 13</td>
<td>62 ± 14 65 ± 14 62 ± 14</td>
</tr>
<tr>
<td>Patients ≥ 55 years</td>
<td>380 (74.2)</td>
<td>89 (79.5)</td>
<td>291 (72.8) 29 (74.4) 262 (72.6)</td>
</tr>
<tr>
<td>Female patients</td>
<td>344 (67.2)</td>
<td>80 (71.4)</td>
<td>264 (66.0) 25 (64.1) 239 (66.2)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>186 (36.3)</td>
<td>54 (48.2) 39 (50.6) 15 (42.9)</td>
<td>132 (33.0) 13 (33.3) 119 (33.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>160 (31.3)</td>
<td>35 (31.3) 25 (32.5) 10 (28.6)</td>
<td>125 (31.3) 17 (43.6) 108 (29.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>136 (26.6)</td>
<td>28 (25.0) 25 (32.5) 3 (8.6)</td>
<td>108 (27.0) 11 (28.2) 97 (26.9)</td>
</tr>
<tr>
<td>Disorders of lipoprotein metabolism</td>
<td>109 (21.3)</td>
<td>24 (21.4) 17 (22.1) 7 (20.0)</td>
<td>85 (21.3) 12 (30.8) 73 (20.2)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>58 (11.3)</td>
<td>15 (13.4) 8 (10.4) 7 (20.0)</td>
<td>143 (0.8) 7 (17.9) 36 (10.0)</td>
</tr>
<tr>
<td>Diagnosis associated with the PR melatonin prescription at the index date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients (n)</td>
<td>296 62 47 15</td>
<td>234 24 210</td>
<td>184 (78.6) 20 (83.3) 164 (78.1)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>231 (78.0)</td>
<td>47 (75.8) 36 (76.6) 11 (73.3)</td>
<td>12 (5.1) 1 (4.2) 11 (5.2)</td>
</tr>
<tr>
<td>Depression</td>
<td>17 (5.7)</td>
<td>5 (8.1) 2 (4.3) 3 (20.0)</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>Unknown cause morbidity</td>
<td>9 (3.0)</td>
<td>3 (4.8) 3 (6.4) -</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>Others</td>
<td>39 (13.2)</td>
<td>7 (11.3) 6 (12.8) 1 (6.7)</td>
<td>32 (13.7) 3 (12.5) 29 (13.8)</td>
</tr>
</tbody>
</table>

History of BZD/Z drug use (observation ≥ 365 days prior to ID)

| Number of patients (n) | 99 71 28 | n/a n/a n/a |
| Short-term user         | 13 (13.1)| 5 (7.0) 8 (28.6) | - - - |
| Intermediate user       | 7 (7.1)  | 4 (5.6) 3 (10.7) | - - - |
| Long-term user          | 79 (79.8)| 62 (87.3) 17 (60.7) | - - - |

Data are expressed as number (n) or as n (%), if not otherwise indicated. ID means index date. Comorbidities were defined as diagnosis other than insomnia within a 1-month window around the index date. ICD-10 codes are as follows: sleep disorder G47, F51; depression F32, F33; unknown/unspecific cause morbidity R69, hypertension I10; back pain M54; disorder of lipoprotein metabolism E78; ischemic heart disease I24, I25 [17]. Short-term BZD/Z users had prescription of BZD/Z drugs ≤ 90 days, intermediate users > 90 days and < 180 days, and long-term users ≥ 180 days before their first PR melatonin prescription.

BZD/Z: Benzodiazepines or benzodiazepine-like drugs; PR: Prolonged release.
reimbursed by statutory health insurance (SHI), and 37.4% (n = 191/510) of patients paid the PR melatonin prescription by themselves.

Several sensitivity analyses were performed to check the robustness of results (Table 4). When the definition of BZD/Z drug use was broadened from purely hypnotic to anxiolytic and/or hypnotic BZD/Z drugs (ATC codes N05BA, N03AE, N05CD or N05CF), there was a slightly higher BZD/Z discontinuation rate, but the overall values were similar compared with the baseline analysis (n = 51/149, 34.2% vs n = 35/112, 31.3%; p = 0.61). If the analysis was restricted to patients who had received at least two prescriptions of anxiolytic and/or hypnotic BZD/Z drugs, the BZD/Z discontinuation rate was slightly lower (n = 20/79, 25.3% vs n = 35/112, 31.3%; p = 0.37). The evaluation of a 6-month follow-up was not meaningful because there were too few patients in single subgroups (n = 7).

4. Discussion

It is estimated that more than 1.1 – 1.2 million (out of approximately 80 million) people in Germany are taking benzodiazepine derivatives for months and years despite regulatory limitations on use for more than 14 – 30 days, presumably because they become dependent on them [19]. Besides representing one of the most disabling psychiatric disorder with substantial side effects (e.g., hip fracture by

Figure 2. Percentage of patients with a history of psychotropic drug use: ATC codes of psychotropic drugs are antidepressants N06A; anxiolytics N05B; neuroleptics N05A; antiepileptics N03; anti-dementia: N06D [18].

BZD/Z: Benzodiazepines or benzodiazepine-like drugs.

Table 3. Frequency of PR melatonin prescriptions within 3-month follow-up and reimbursement information.

<table>
<thead>
<tr>
<th></th>
<th>Total Previous BZD/Z</th>
<th></th>
<th>No previous BZD/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 512</td>
<td>n = 112</td>
<td>n = 77</td>
</tr>
<tr>
<td><strong>Number of prescriptions during follow-up period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One prescription</td>
<td>422 (82.4)</td>
<td>88 (78.6)</td>
<td>63 (81.8)</td>
</tr>
<tr>
<td>Two prescriptions</td>
<td>55 (10.7)</td>
<td>11 (9.8)</td>
<td>7 (9.1)</td>
</tr>
<tr>
<td>Three prescriptions or more</td>
<td>35 (6.8)</td>
<td>13 (11.6)</td>
<td>7 (9.1)</td>
</tr>
<tr>
<td><strong>Reimbursement information for PR melatonin prescriptions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reimbursed by SHI</td>
<td>303 (59.4)</td>
<td>67 (59.8)</td>
<td>49 (63.6)</td>
</tr>
<tr>
<td>Not reimbursed by SHI</td>
<td>191 (37.5)</td>
<td>42 (37.5)</td>
<td>25 (32.5)</td>
</tr>
<tr>
<td>Giveaway sample</td>
<td>16 (3.1)</td>
<td>2 (2.7)</td>
<td>3 (3.9)</td>
</tr>
</tbody>
</table>

Data are expressed as number n (%). Total number n refers to the PR melatonin prescriptions with an associated diagnosis at the issue date.

*Missing data regarding the type of prescription n = 2 for 'Never' group of patients.

SHI: Statutory health insurance; BZD/Z: Benzodiazepines or benzodiazepine-like drugs; PR: Prolonged release.
Benzodiazepine discontinuation with prolonged-release melatonin

Table 4. Sensitivity analyses.

<table>
<thead>
<tr>
<th>Total</th>
<th>Previous BZD/Z</th>
<th>No previous BZD/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 512</td>
<td>n = 112</td>
<td>n = 77</td>
</tr>
<tr>
<td>Base-case analysis: 3-month follow-up and at least one previous hypnotic BZD/Z prescription</td>
<td>512 (100)</td>
<td>112 (21.9)</td>
</tr>
<tr>
<td>3-month follow-up and at least one previous anxiolytic and/or hypnotic BZD/Z prescription</td>
<td>512 (100)</td>
<td>149 (29.1)</td>
</tr>
<tr>
<td>3-month follow-up and at least two previous anxiolytic and/or hypnotic BZD/Z prescription</td>
<td>512 (100)</td>
<td>79 (15.4)</td>
</tr>
</tbody>
</table>

Data are expressed as number n (%). ATC codes are for hypnotic BZD/Z drugs N05CD and N05CF and for anxiolytic BZD/Z drugs N05BA and N03AE [18].

 nightly falls), benzodiazepine dependency causes a substantial socioeconomic burden, and the direct cost of BZD/Z drugs prescribed as a result of dependency amounted to an estimated €25 million in 2009 from the perspective of SHIs [20,21].

Among the 22% previous BZD/Z users in our study, approximately one-third (31%) did not receive any prescriptions of BZD/Z drugs in the 3-month period following PR melatonin initiation; that is, they are presumed to have discontinued BZD/Z drug use. This result is consistent with previous clinical findings suggesting that PR melatonin can potentiate the effects of GABA-A receptor modulators (e.g., benzodiazepine and benzodiazepine-like hypnotics), and coadministration of melatonin during the withdrawal period might be thus useful to facilitate discontinuation of hypnotic drugs [3,22,23]. Interestingly, the efficacy of fast-release melatonin to help the discontinuation of the use of benzodiazepines in patients with insomnia was not demonstrated [24]. Moreover, due to the short half-life of fast-release melatonin, maintaining effective bodily concentrations of melatonin throughout the night requires either high doses or repeated administration of low doses of the hormone. PR melatonin may be more effective because it mimics physiological patterns of melatonin secretion, thereby providing sufficient melatonin levels throughout the night [25].

Moreover, in our study, about 90% of the patients with no previous BZD/Z use remained without BZD/Z use also in the 3-month period following PR melatonin initiation suggesting that PR melatonin treatment may be useful in preventing BZD/Z use in insomniacs and sufficient to resolve insomnia symptoms in a substantial group of patients.

About 61% of patients in the discontinuation subgroup were long-term BZD/Z users. This percentage is significantly lower than that in the continuation subgroup (87%), but indicates that long-term BZD/Z users also discontinued BZD/Z intake. Overall, the difficulty to quit BZD/Z drug use after a long time period is known [26]. It has to be taken into account that BZD/Z discontinuation is a challenging process for both patients and their physicians and requires additional support to facilitate withdrawal, such as patient education, supervised medication tapering or psychological training, for example, cognitive behavioral therapy [10,24,26]. Results from a long-term outcome study on the discontinuation of BZD/Z for insomnia showed a relapse rate of 43% during the 2-year follow-up period, despite additional patient support. The number of relapses increased during the 3- and 9-month observation periods [10]. Future research is needed to examine the impact of PR melatonin on BZD/Z discontinuation for more than 3 months after initiation.

In our study, a higher BZD/Z discontinuation rate of 42% (n = 10/24) was observed among patients taking two or more prescriptions of PR melatonin compared with 28% discontinuation in patients taking only one prescription of PR melatonin (n = 25/88). This suggests a positive effect of longer use of PR melatonin on discontinuation of BZD/Z drug use. This group had the highest percentage of patients (48%) paying for PR melatonin by themselves. The reason might be that until recently PR melatonin was licensed only as short-term (3 weeks) treatment for primary insomnia in patients aged 55 years and older. This indication has been extended by the European Commission to 13 weeks [27]. This extension of duration of prescription might contribute in insomniac patient to improve current performance of PR melatonin in addressing BZD/Z discontinuation.

Some limitations to our study have to be considered. The database extraction includes prescription data of GPs, office-based internists and neurologists but not psychiatrists. However, it is known that about 80% of antidepressants are prescribed by the GP [28]. The study was retrospective in design and comprised patients from the early launch phase of PR melatonin, resulting in patient subgroups with small numbers. The study related to prescription data over a time period of only 3 months,
which might be too short to judge discontinuation rates of BZD/Z drug use without taking later relapses into account [26]. In addition, it cannot be ruled out that some patients may have changed their GP in order to obtain the BZD/Z drugs they are used to.

5. Conclusions

This is the first analysis of real-life data to provide a profile of patients receiving PR melatonin in clinical practice in Germany. The results suggest a positive temporal relationship between prescription of PR melatonin and discontinuation of BZD/Z drugs. Based on the 31% discontinuation rate observed in this analysis, PR melatonin may have the potential to facilitate the discontinuation of BZD/Z use or to prevent BZD/Z use in patients with insomnia. Further studies are required on the short- and long-term use of PR melatonin in defined patient populations to confirm these findings.

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Declaration of interest

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Bibliography


17. ICD-10 codes German Modification 2007, 2007


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Affiliation
Dieter Kunz1 MD PhD,
Sébastien Bineau†2 MD MSc,
Khaled Maman3 MSc,
Dominique Milea2 PharmD PhD,
Mondher Toumi4 MD PhD
1Author for correspondence
2Department of Sleep Medicine, St. Hedwig-Krankenhaus, Berlin, Germany
3International Epidemiology Department, Global Outcomes Research Division, Lundbeck SAS, 43-45, Quai du Président Roosevelt, 92445 Issy-Les-Moulineaux, France
Tel: +33 1 79 41 29 27; +33 6 66 67 80 56; E-mail: sebi@lundbeck.com
3Creativ Research, Paris, France
4University Claude Bernard Lyon I, Lyon, France