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## THERAPIES

### HEADING: THERAPEUTICS

#### **Non-drug and drug alternatives to benzodiazepines for insomnia in primary care: study among GPs and pharmacies in a Southwest region of France.**

Alternatives to benzodiazepines for insomnia

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## Summary

*Objectives.-* Benzodiazepines and related drugs are the most commonly prescribed drugs in the treatment of insomnia, and referral to psychotherapy is rare when recommended as first line treatment for chronic insomnia. The frequency of referral to psychologists, of use of alternative drugs to benzodiazepines, either prescribed by general practitioners (GPs) or dispensed by community pharmacies, is unknown in France. We aimed to describe the non-pharmacological approaches recommended, such as cognitive behavioral therapies (CBT), and the drugs, including alternatives drugs to benzodiazepines, used by GPs and community pharmacies for patients complaining of insomnia.

*Methods.-* A cross-sectional study was conducted during 3 months in 2015 on the management of individual GPs' patients and pharmacies' customers consecutively consulting for insomnia in the Midi-Pyrénées region of southwest France. Participating GPs and pharmacists completed a form, for each patient, on their management (drugs, sleeping advices, referral to psychotherapy).

*Results.-* Fifty-five GPs included 263 patients and 43 community pharmacies included 354 customers in the study. Among patients, 193 (73,4%) had already used benzodiazepine. Thirty-eight patients (14.4%) and 2 customers (0.5%) were recommended non-drug therapies (mostly CBT). Benzodiazepines were prescribed 188 times (69.1% of the prescriptions) by GPs. Alternative drugs prescribed were mostly antihistamines (n = 26; 9.6%) and antidepressants (n=17; 6.3%). Antihistamines were the most commonly dispensed drugs by pharmacists (n=149; 39.4%).

*Conclusions.-* While non-pharmacological treatments, such as CBT, are safe and widely recommended, benzodiazepines and antihistamines remain widely used despite the lack of long term benefit and the risk of adverse drug reactions.

## KEYWORDS

Community pharmacy services; General Practitioners; Hypnotics and sedatives; Patient care management; Psychotherapy; Sleep initiation and maintenance disorders

## **Abbreviations**

CBT: cognitive behavioral therapies

GRADE: Grading of Recommendations Assessment, Development and Evaluation system

GPs: general practitioners

OTC: over-the- counter

SD: standard deviation

SIIRAM: French health insurance database (*système national d'information inter-régimes de l'Assurance maladie*)

URML: Regional Union of Liberal Physicians

Z-drugs: non benzodiazepine drugs

## Introduction

Hypnotics drugs exposure and sleep disorders are highly prevalent in Europe and North America [1–3]. Benzodiazepines and related drugs (Z-drugs), are effective in the management of acute insomnia but they expose patients to many adverse drug reactions [4–7].

There is a tendency among general practitioners (GPs) to limit the prescription of benzodiazepines [3], but campaigns aiming to reduce the use of benzodiazepines and related drugs failed in many European countries, especially because of the difficulties in accessing alternative treatments [8]. Nonetheless, a trend towards decreasing benzodiazepines use has been observed in France since 2012, but remains high (13% of the population was exposed at least once in 2015) [3].

Many alternative drugs for insomnia have been discussed and are widely used [9], such as antihistamines, herbal medicine [10], homeopathy, antidepressants [11] and melatonin [12]. In France, as in many other European countries, most of these drugs can be obtained by prescription or directly in community pharmacies without prescription (“over-the-counter” [OTC]). Benzodiazepines and related drugs, antidepressants, and antipsychotics can only be obtained by physician’s prescription. Very little data exist on the efficacy and safety of alternative drugs to benzodiazepines such as antihistamines [13–15]. The same is true for other treatments such as aromatherapy [16], herbal medicines [10], homeopathy [17]. Melatonin’s efficacy is modest [18]. Despite the lack of strong evidence for the effectiveness of antidepressants in insomnia [11], they are widely prescribed in Great Britain [19]. This is despite the fact that safe and effective non-pharmacological treatments exist for the management of insomnia, such as cognitive behavioral therapies (CBT) [20], which are widely promoted in international guidelines [21] and are the only long term effective treatment while benzodiazepines and any other drug have only proved their effectiveness in acute insomnia [22]. The latest European guideline for the diagnosis and treatment of insomnia was developed by a task force of the European Sleep Research Society in 2016 [21]. They conducted an umbrella review of meta-analyses on PubMed and The Cochrane Library, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the evidence and to guide recommendations. The table 1 contains an extract of the summary of these guideline recommendations on the treatments of insomnia and their evidence. Off-label use of drugs for insomnia is frequent among GPs, probably due to the lack of safe and effective pharmacological alternatives to benzodiazepines, and the difficulty for GPs to refer patients for psychotherapy [19]. Yet, the off-label use of drugs is associated with an increased risk of adverse

drug reactions [22]. Patients are also at risk from self-medication, increasing the risk of adverse drug reactions [23] and drugs interactions, since physicians often ignore patients' self-medication practices.

To our knowledge, no study has ever described the alternative management to benzodiazepines and related drugs for insomnia, in parallel between GPs and community pharmacies, using actual prescription and dispensing data, in France.

We aimed to describe drugs used, including alternatives to benzodiazepines and related drugs, non-pharmacological treatments and no treatment for insomnia in primary care. We studied in parallel GPs' prescriptions, and drugs and advice dispensed by community pharmacies, for patients or customers complaining of insomnia, in a southwest region in France.

## Method

We conducted a descriptive cross-sectional study in a southwest region of France among GPs and community pharmacies, to assess their management of patients or customers complaining of insomnia during the study period. This study received ethical approval from the ethical committee of the academic department of family medicine of Toulouse III University, France, on April 12, 2015.

### Study among GPs

The study among GPs was conducted between May and June 2015, in the southwest region of Midi-Pyrénées in France, where 3 million inhabitants live. A sample of volunteer GPs (2230 GPs in the Midi-Pyrénées region in 2015) was selected, not randomly, among the exhaustive records of the Regional Union of Liberal Physicians (*Union régionale des médecins libéraux* [URML]) computerized database of all GPs. GPs were then contacted by e-mail to present the study and ask for their consent. GPs with a non-exclusively ambulatory family practice were excluded. An online consent form to participate to the study and a questionnaire to described GPs' professional and demographic characteristics was sent out to all the selected GPs in May 2015.

Consenting GPs received by e-mail a link to a patient inclusion form in order to collect clinical and prescribing data for each patient included. In addition, GPs had to send their anonymized prescriptions for insomnia. One to 10 of their patients aged over 18, and consulting repeatedly for an insomnia complaint, or for an insomnia prescription renewal, were included during one month. Patient data collected from the first consultation for insomnia was kept if the patient consulted several times.

Patients and GPs data were anonymously collected. Patients' non-opposition to this anonymous data collection was asked during the consultation. The data collection form was tested by a panel of five GPs. Forms could be returned in paper or in electronic format. The deadline for returning the questionnaires was June 30, 2015.

In order to ensure the representativeness of the included patient, we decided to include at least 200 patients. We could estimate that a minimum of 43 GPs had to be recruited to include at least 200 patients. To estimate the number of GPs to include, no previous study on drugs dispensing/prescriptions patterns was available : there is only data on what GPs' conclude at the end of their consultation (1.47% of the French GPs' consultation conclude that their patient had a sleep disorder [24]). On the basis of the worse hypothesis, we assumed that a GP sees at least 80 patients per week. It represents 1,17 consultations concluding to a sleep disorder in a week (4.7 patients in one month). We decided to recruit at least 60 GPs to ensure the inclusion of these patients, considering that not all GPs would necessarily include as many patients as requested, or would drop out. To assess the representativeness of the recruited GPs, age and gender were compared with those of Midi-Pyrénées region GPs in 2015. Access to the French health insurance database (*système national d'information inter-régimes de l'Assurance maladie* [SNIIRAM]) was provided by the URML in order to perform this comparison. When a data request is done on this database, practice location of GPs cannot be obtained if age is also requested. We chose to keep age and gender to perform our comparison.

### **Study among community pharmacies**

The study was conducted the same year, between February and April 2015, among a sample of community pharmacies' customers in the department of the Haute-Garonne in the Midi-Pyrénées region. The Haute-Garonne is the most populous area in the region, with 1.3 million inhabitants. This department includes the capital city of the region, Toulouse, with 441,000 inhabitants. All the 409 community pharmacies of the department, identified in the national book phone, were

contacted by phone to present the study and collect their consent. In Toulouse, all community pharmacies that agreed to participate were included. In the other smaller town of the department, more rural, only the first two community pharmacies of one city that agreed to participate were included to ensure representativeness of urban and rural areas.

The pharmacists or their assistant were asked to recruit one to 20 customers over 18 requesting a treatment for insomnia without medical prescription, or complaining of insomnia. Customers with a prescription were excluded. After a study presentation by phone or during a meeting, an explanation on forms for the community pharmacy's staff, including consent forms for customers, and drug/advice dispensed forms, were given. The community pharmacy's staff filled the part of the form including name of the dispensed drug, if applicable, sleeping advice and non-drug recommendations. The customer filled in sociodemographic data, clinical data, and other drug or non-pharmacological treatments previously used for insomnia. These questionnaires were anonymous and customers' consent was asked before filling the forms. Before the study, the customer's form was tested by a panel of 5 people in the general population. No data were available to calculate the minimum number of community pharmacists to be recruited to include a minimum number of 200 customers. We decided to include at least 40 community pharmacists.

## **Analysis**

Web forms were created using LimeSurvey<sup>®</sup> software (1.90+ Build 9406 version, Hambourg, Germany). Age was described with mean and standard deviation (SD). To compare the characteristics of the sample of GPs to the whole region GPs' characteristics, , Chi2, or exact Fisher tests were performed when relevant. For comparison of continuous variables, Student's T test, or Wilcoxon's test was used when relevant. P-value <0.05 was considered as statistically significant. Data analysis was performed with EPIDATA Entry<sup>®</sup> (version 3.1, Epidata software association, Odense, Denmark) and Analysis<sup>®</sup> (V2.2.2 183).

## **Results**



During the study period, on the 2230 GPs contacted with the list of the URML, 71 GPs gave their consent to participate to the study. Among them, 55 included 263 patients and 43 community pharmacies included 354 customers with complete patients' forms. On the 354 customers included, 65 (18.3%) were in the capital city of the region (Toulouse). Flowcharts in Fig. 1 and Fig. 2 illustrate the inclusion process of patients and customers.

Customers and patients' characteristics are reported in Table 2. Female was the most represented gender among patients, 193 (73,4%) had already been prescribed a benzodiazepine, 125 (47,5%) an alternative drug to benzodiazepines. Most patients (215; 81.7%) had already taken a sleeping drug for insomnia. Sleep advice had already been given to 135 patients (51,3%) and 100 (19,8%) had already benefited from non-drug therapies. Pharmacies' customers were mostly females (70.1%) and a majority (272; 76,8%) reported chronic insomnia. Most of them had already consult their GPs for sleep disorders (n = 198; 55.9%) and 191 (53.9%) had already taken a medicine. GPs' characteristics are reported in Table 3. Those who had included at least one patient (n=55; 77.5%) were not significantly representative on age and gender of the Midi-Pyrénées region (more proportion of females, younger). There was no significant difference between GPs who had included patients and those who had not.

Non-drug treatments used or advice provided are reported in Table 4. Thirty-four patients (12.9%) and 9 customers (2.5%) didn't receive any drug therapy. Thirty-eight patients (14.4%) were prescribed non-drug therapies, mostly CBT and relaxation/meditation, and two customers (0.5%) were recommended non-drug therapies. Sleep hygiene advice was given to 97 patients (36.9%), and 206 customers (58.2%). Thirty-five patients (13.3%) were prescribed two drugs for sleeping or more on the same prescription. Fifty-six customers (15.8%) were advised to visit a physician for their insomnia.

Drugs prescribed by GPs or dispensed in community pharmacies are reported in Table 3. A total of 272 drugs prescriptions were given, and 378 were dispensed in pharmacies. Among the patients, 229 (87.1%) received one drug or more for insomnia. Benzodiazepines or related drugs were prescribed to 173 patients (65.8%), corresponding to 188 prescriptions (69.1%). The most commonly prescribed alternative drugs by GPs were antihistamines for 26 patients (9.6%), mostly hydroxyzine (n = 16; 5.9%), antidepressants for 17 patients (6.3%), homeopathy for 11 patients (4.0%), herbal medicine for 10 patients (3.8%). Antipsychotic drugs, melatonin, and paracetamol were the least prescribed. Oligotherapy and aromatherapy was never prescribed.

Several drugs dispensed in pharmacies contained multiple pharmaceutical substances. The most commonly dispensed drugs were antihistamines (n=149; 39.4%), mostly doxylamine, followed by herbal medicine (n = 127; 32.2%), and melatonin (n = 83; 21.0%). Homeopathy, oligotherapy, and

aromatherapy were the least dispensed. The drug provided had already been dispensed previously for 136 customers (37,2%). More than a half of the customers had already warned their GPs of their insomnia (n = 198; 55,9%).

## Discussion

### Main findings

In this study, very few patients or community pharmacies' customers received a non-pharmacological treatment. Proportionally more patients didn't receive any medical prescription (around 12%) than customers who didn't buy any drug therapy (less than 3%), even though pharmacists provided more sleep advice than GPs.

Among those being prescribed a treatment, an alternative drug to benzodiazepines or related was prescribed for almost 29% of the patients, whereas almost 70% of the patients were prescribed a benzodiazepine or a Z-drug. Antihistamines were the most prescribed alternative drug (almost 10% of all the prescriptions). They were also the most dispensed drugs in the community pharmacies and represented more than 40% of the drugs dispensed, which is consistent with GPs prescriptions habits. Benzodiazepines, antidepressants and neuroleptics must be prescribed by a physician to be dispensed by pharmacists in France, which explains why none of these drugs were dispensed by pharmacies without a prescription.

### Strengths and limitations

To the best of our knowledge, no study has ever described alternatives managements to benzodiazepines among GPs and pharmacists in France, using prescription and dispensing data in a French region. Rather than asking GPs about their prescriptions habits, we performed a practical study collecting anonymously prescription data for each consulting patient or customer. For the community pharmacies study, pharmacies' staff were asked to fill names of drugs on the forms to achieve reliability and validity of the data on drugs dispensed.

Our study is limited by selection bias: our sample was not drawn randomly but was based on the voluntariness of the GPs contacted by the URML regional list. Thus, the most involved GPs must have been selected. This was illustrated by the non-representativeness of the GPs: our sample was younger and included more females. We may have selected the most involved GPs in research who are on average 10 years younger, similar to the age bias in our sample [25]. The younger age in this sample can explain the more important number of women, since the average age of female GPs is lower in this region (47 vs. 56 years). Health professionals included in this study may also have modified their prescriptions' habits to comply more with recommendations during the course of the study. Nonetheless GPs/pharmacists or patients' data were anonymously collected which may have limited any bias of desirability. Moreover, GPs included an average of 4.8 patients when they had to include up to ten patients. Nonetheless, this average number of patient was consistent with our most pessimistic hypothesis [24], and we have been able to assess GPs' actual practices among a sample of 263 patients. Also, GPs may not have included all consecutive patients and select them. We can hypothesize that patients consulting for several health problems, including sleep disorders, making consultations time-consuming, may have been excluded or forgotten. The sixteen GPs who did not include a patient probably illustrate this. Thus, these confounding factors and selection or measurement bias do not allow a relevant statistical comparison between pharmacies and GPs' management habits. Our results are consistent with other data on prescription and drug dispensing habits of GPs [1,19,26,27] but also of pharmacists [28]. Our cross-sectional approach prevented any long term follow-up to determine drug prescription duration. In France, benzodiazepines cannot be prescribed for more than 28 days to prevent misuse. Thus, asking the prescription's duration may not have been relevant: in France, even if a physician prescribes more than 28 days, the pharmacist cannot legally reuse the prescription for another 28 days of benzodiazepines' treatment. We could not analyze the number, characteristics, and reasons for customers declining to participate in the study. This prevented us from calculating the refusal rate and controlling the potential selection bias in the community pharmacies study.

## **Comparison with existing literature**

In France, no study comparing drugs prescribed by GPs or dispensed OTC by pharmacists on prescriptions or dispensing data was found. One study in Germany compared GPs and pharmacists' perceptions on benefits and harms of benzodiazepines and Z-drugs, but did not investigate real practices [29], the same in Australia with a qualitative study among GPs and pharmacists [30].

Pharmacists had a more critical view on these drugs' harmfulness than GPs [29]. In Italy, a study with a design similar to ours showed a limited use of non-drug therapies, with frequent use of non-benzodiazepines drugs. A survey among all GPs in Norway also showed similar problems with limited use of non-pharmacological treatment [27]. In United-Kingdom, a questionnaire survey investigated GPs' management of insomnia in 2005 [31] and more recently in 2014 [19]. These studies did not deal with community pharmacies dispensed drugs. One major difference with France is the large use of amitriptyline: 31% of the GPs declared prescribing them commonly, whereas this drug represented 2.6% of our sample prescriptions [19]. Antidepressants are not licensed for insomnia, due to the lack of evidence of their effectiveness [32]. British GPs provided much more sleep hygiene advice, yet psychotherapies provision remain limited [19]. One study in Australia described community pharmacies' drug dispensing for insomnia [28]. Their results were consistent with ours: antihistamines were the most dispensed drugs, followed by herbal medicines [28]. However, non-drug techniques were recommended slightly more frequently [28]. These results on antihistamines are also consistent with the British GPs practices [19]. Antihistamines have a moderate efficacy on mild insomnia [14]. They cause residual daytime sedation and dizziness, due to their long half-life and their anti-cholinergic effects [33]. Misuse was also reported among patients with chronic consumption, especially with doxylamine [13]. The off-label use of drugs is also problematic, with its increased risk of adverse drug reactions [22]. Self-medication also increases the risk of adverse drug reactions due to their inappropriate use [23].

These inappropriate prescriptions practices seem risky, since effective and safe non-pharmacological treatment, such as CBT, can be proposed for insomnia [20]. Non-pharmacological treatment is now commonly recommended as first-line treatment for chronic insomnia in France [34], and many other European countries, with a good benefit-risk ratio [21].

### **Implication for research and practice**

Our results demonstrate the difficulties for GPs to comply with recommendations. Improvement of clinical outcomes were shown when the guidelines were taken into account by physicians [35], particularly in mental health care [36]. One of the main problems remain the limited use of non-pharmacological management of insomnia, such as psychotherapy [19], despite the evidence of its effectiveness [20], and patients' preference for them [37]. Nonetheless, there are many limiting factors to their provision in practice, such as the cost, the time spent by patients, the short supply of

trained professionals [38], and also a lack of knowledge and awareness of these therapies by physicians [19]. Striving to solve these problems, at the national authorities' level, by improving reimbursement for instance, but also at the GP's level, by improving information on these therapies and their ability to implement them for instance, would be beneficial for patients.

## **Conclusion**

This is a first study that aimed to describe the unknown use of alternative drugs to benzodiazepines and non-drug therapies in the management of insomnia among French GPs and pharmacists in a Southwest region of France. CBT and sleep hygiene advice, are seldom recommended while benzodiazepines and antihistamines remain widely dispensed despite the lack of long term benefit and their risk of serious adverse drug reactions.

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## **Disclosure of interests**

The authors declare no conflict of interests.

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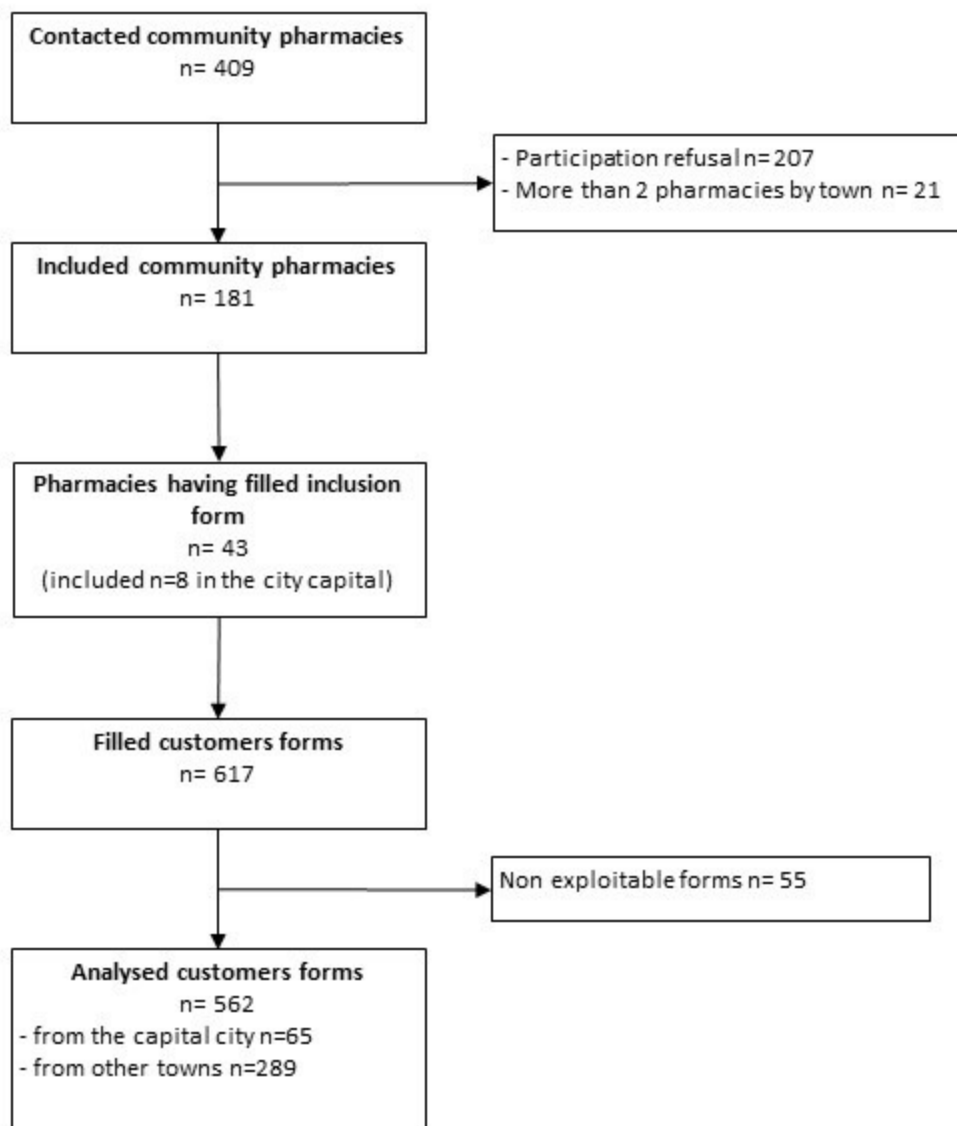
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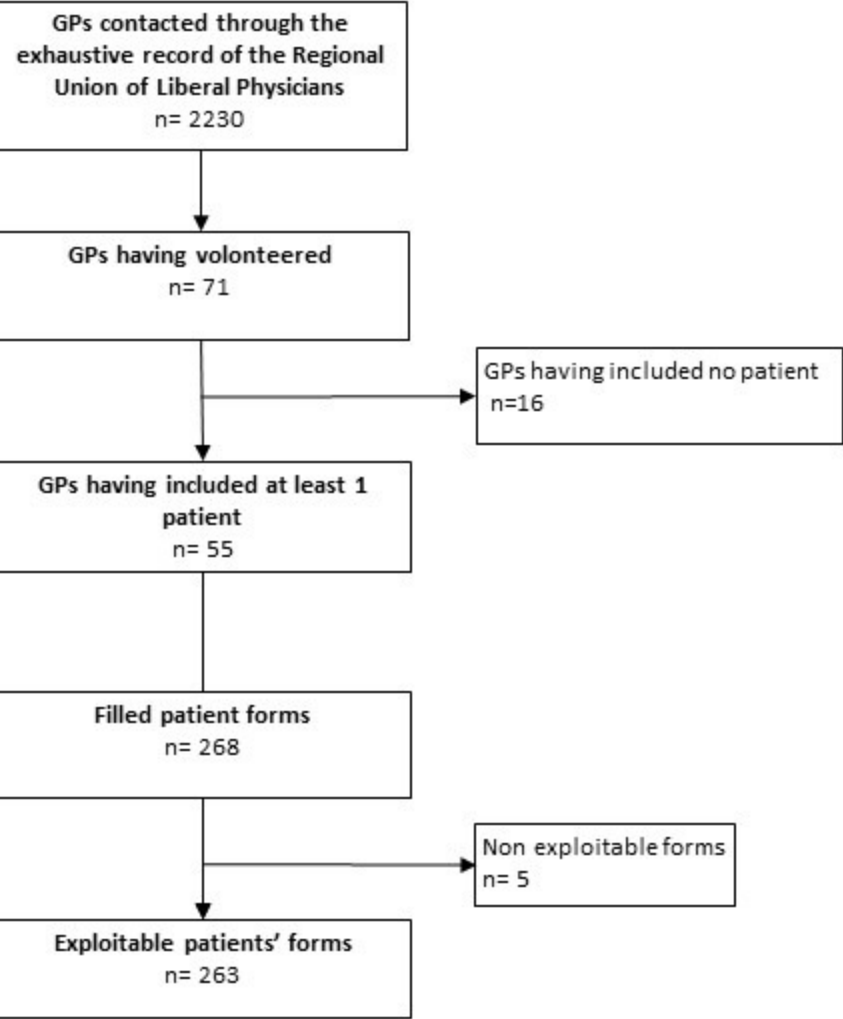
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**Figure 1** Flow-chart of pharmacies inclusion and customer's forms collected



**Figure 2** Flow-chart of GP's inclusion and patients' forms collected



**GPs** : General practitioners

**Table 1** Assessment of different treatments in insomnia : extract of a summary of the 2017 European guideline for the diagnosis and treatment of insomnia [21]

- **Cognitive behavioural therapy** for insomnia is recommended as the first-line treatment for chronic insomnia in adults of any age (*strong recommendation, high-quality evidence*).

A pharmacological intervention can be offered if cognitive behavioural therapy for insomnia is not sufficiently effective or not available.

- **Benzodiazepines, benzodiazepine receptor agonists and some antidepressants** are effective in the shortterm treatment of insomnia ( $\leq 4$  weeks; *weak recommendation, moderate-quality evidence*).
- **Antihistamines, antipsychotics, melatonin and phytotherapeutics** are not recommended for insomnia treatment (*strong to weak recommendations, low- to very-low-quality evidence*).
- **Light therapy and exercise** need to be further evaluated to judge their usefulness in the treatment of insomnia (*weak recommendation, lowquality evidence*).
- **Complementary and alternative treatments** (e.g. homeopathy, acupuncture) are not recommended for insomnia treatment (*weak recommendation, very-low-quality evidence*).

**Table 2** Characteristics of included patients and customers

|                                      | GP's patients | Pharmacie's customers |
|--------------------------------------|---------------|-----------------------|
|                                      | (n = 263)     | (n = 354)             |
|                                      | <i>n (%)</i>  | <i>n (%)</i>          |
| <b>Sex</b>                           |               |                       |
| female                               | 174 (66,2)    | 248 (70,1)            |
| male                                 | 34 (33,8)     | 106 (29,9)            |
| <b>Previous sleeping drug intake</b> | 215 (81,7)    | 191 (53,9)            |
| <b>Medical history</b>               |               |                       |
| No history                           | 80 (30,4)     | -                     |
| chronic sleep disorder               | 86 (32,7)     | 272 (76,8)            |
| depression                           | 113 (43,0)    | -                     |
| substance use disorder               | 29 (11,0)     | -                     |
| <i>benzodiazepines</i>               | 9 (3,4)       | -                     |
| <i>alcohol</i>                       | 15 (5,7)      | -                     |
| <i>tobacco</i>                       | 8 (3,0)       | -                     |
| <i>drogues illicites</i>             | 6 (2,3)       | -                     |
| <i>autres</i>                        | 4 (1,5)       | -                     |
|                                      | <i>m ±SD</i>  | <i>m±SD</i>           |
| <b>Age</b>                           |               |                       |
| (years)                              | 58,6 ±18,6    | 51,0±17,1             |

GP: general practitioner; M: mean; n: number; SD: standard-deviation

**Table 3** Characteristics of included GP's

|                      | All GPs      | GPs having<br>included at least 1<br>patient | GPs having<br>included no<br>patient |            | All GPs in the<br>Midi-Pyrénées<br>region |            |
|----------------------|--------------|--|--------------------------------------|------------|---|------------|
|                      | N = 71       | N = 55                                       | N = 16                               |            | N = 3193                                  |            |
|                      | <i>n (%)</i> | <i>n (%)</i>                                 | <i>n (%)</i>                         | <i>p</i> * | <i>n (%)</i>                              | <i>p</i> * |
| <b>Sex</b>           |              |  |                                      |            |   |            |
| female               | 37 (52.1)    | 30 (54.5)                                    | 6 (37.5)                             | 0.36       | 1194 (37.4)                               | <0.0001    |
| male                 | 34 (47.9)    | 25 (45.5)                                    | 10 (62.5)                            |            | 1999 (62.6)                               |            |
| <b>Practice area</b> |              |  |                                      |            |   |            |
| urban                | 20 (27.8)    | 14 (25.5)                                    | 5 (31.3)                             | 0.28       | NA  | -          |
| semi-urban           | 37 (51.4)    | 32 (58.2)                                    | 6 (37.5)                             |            | NA  |            |
| rural                | 14 (19.4)    | 9 (16.4)                                     | 5 (31.3)                             |            | NA  |            |
|                      | <i>m ±SD</i> | <i>m ±SD</i>                                 | <i>m ±SD</i>                         |            | <i>m±SD</i>                               |            |
| <b>Age (years)</b>   | 45.3±10.8    | 43.6±10.4                                    | 49.9±11.0                            | 0.054      | 53.3±10.9                                 | <0.0001    |

GP: general practitioner; m: mean; n: number; NA: data not available; SD: standard-deviation

\* comparison with the group of GPs having included at least 1 patient

**Table 4** Drugs or Non-drugs treatments prescribed by GPs or dispensed OTC in community pharmacies

|  | By GP's  | By Pharmacists                              |
|--|--|---|
|  | number of drugs prescribed :<br><b>n = 272</b> | number of drugs dispensed<br><b>n = 378</b> |
|  | <i>n (%)</i>                                   | <i>n (%)</i>                                |
| <b>Non-drugs therapies</b>               | 38 (14,4)                                      | 2 (0,5)                                     |
| <i>Cognitive behavioral therapy</i>      | 14 (5,3)                                       | 0   |
| <i>Other psychotherapy</i>               | 6 (2,3)  | 0   |
| <i>Sophrology</i>                        | 9 (3,4)  | 0   |
| <i>Meditation, relaxation</i>            | 11 (4,2)                                       | 2 (0,5)                                     |
| <b>Sleep hygiene advice</b>              | 97 (36,9)                                      | 206 (58,2)                                  |
| <b>Referral to a physician</b>           | -  | 56 (15,8)                                   |
| <b>Sleep schedule</b>                    | 10 (3,8)                                       | -   |
| <b>Number of treatments <sup>†</sup></b> |  |   |
| 0  | 34 (12,9)                                      | 9 (2,5)                                     |
| ≥1                                       | 229 (87,1)                                     | 345 (97,5)                                  |
| ≥2                                       | 35 (13,3)                                      | -   |
| <b>Antihistamines</b>                    | 26 (9,6)                                       | 149 (39,4)*                                 |
| <i>Hydroxyzine</i>                       | 16 (5,9)                                       | -   |
| <i>Doxylamine</i>                        | 7 (2,6)  | 133 (35,2)                                  |
| <i>Alimemazine</i>                       | 3 (1,1)  | 1 (0,3)                                     |
| <b>Herbal medicine</b>                   | 10 (3,7)                                       | 127 (33,6)*                                 |
| <b>Melatonin</b>                         | 5 (1,8)  | 83 (22,0)*                                  |
| <b>Oligotherapy</b>                      | 0  | 41 (10,8)*                                  |
| <b>Homeopathy</b>                        | 11 (4,0)                                       | 46 (12,2)*                                  |
| <b>Aromatherapy</b>                      | 0  | 5 (1,3)*                                    |
| <b>Antidepressants</b>                   | 17 (6,3)                                       | -   |
| <i>MAOI (amitriptyline, dosulepine)</i>  | 7 (2,6)  | -   |
| <i>Mianserine</i>                        | 5 (1,8)  | -   |
| <i>SSRI (fluvoxamine, escitalopram)</i>  | 2 (0,7)  | -   |
| <i>SNRI (venlafaxine)</i>                | 1 (0,4)  | -   |
| <i>Other</i>                             | 2 (0,7)  | -   |
| <b>Antipsychotics</b>                    | 6 (2,2)  | -   |
| <i>Cyamemazine</i>                       | 4 (1,5)  | -   |
| <i>Loxapine</i>                          | 1 (0,4)  | -   |
| <i>Risperidone</i>                       | 1 (0,4)  | -   |
| <b>Other drugs</b>                       | 3 (1,1)  | -   |
| <i>Etifoxine</i>                         | 1 (0,4)  | -   |
| <i>Codeine</i>                           | 1 (0,4)  | -   |
| <i>Paracetamol</i>                       | 1 (0,4)  | -   |
|  |  | -   |
| <b>Benzodiazepines or related</b>        | 188 (69,1)                                     | -   |
| <i>Benzodiazepines</i>                   | 86 (31,6)                                      | -   |
| <i>Z-drugs</i>                           | 102 (37,5)                                     | -   |

\* Some drugs contain several pharmaceutical substances. Each substance was counted separately

‡ percentage is reported on the number of patients

GP: general practitioner; MAOI: monoamine oxidase inhibitor; OTC: over-the-counter; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor