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THERAPIES

HEADING: Clinical pharmacology

General practitioners' compliance with benzodiazepine discontinuation guidelines in patients treated with long-term lorazepam: a case-vignette cross-sectional survey

GPs compliance with BZD deprescribing guidelines

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Summary

Aim.- To study determinants associated with GPs' compliance with benzodiazepine discontinuation guidelines through a case-vignette of a patient with multimorbidity treated with long-term lorazepam for insomnia. *Methods.*- This cross-sectional survey was performed in a sample of French GPs. The questionnaire included items on their characteristics and questions related to the management of a case-vignette with long-term lorazepam use who was consulting for a prescription renewal. GPs who proposed a dedicated consultation to discuss discontinuation or progressive discontinuation were considered as "following guidelines", while they were considered as "out-of-guidelines" if they proposed immediate discontinuation or decided not to discontinue lorazepam. A backward selection process was used to select factors to be included in the final logistic regression model. The probabilities of out-of-guidelines practice and their 95% confidence interval (95% CI) were then plotted using a heatmap graph. *Results.*- Of 1,177 GPs, the majority (92.2%) were aware of the necessity to discontinue lorazepam and reported practice consistent with good practice guidelines. Women GPs aged under 50 years had the lowest estimated probability of out-of-guidelines practice. Conversely, men aged over 58 years with high consideration of patient preferences and low concern about the benefit-risk ratio of lorazepam had the highest probability of out-of-guidelines practice (27.3% [18.7%; 34.7%]). *Conclusion.*- GPs largely reported practice compliant with benzodiazepine discontinuation guidelines, although some GPs, mainly older men who overemphasise patient preferences, were more likely to adopt out-of-guidelines practice.

KEYWORDS

Surveys and questionnaires; General practitioners; Benzodiazepines; Practice guideline; Guideline adherence

Abbreviations

BRR: benefit-risk ratio

CATI: computer-assisted telephone interview

CI: confidence interval

GP: general practitioner

Min: minimum

Max: maximum

NICE: National Institute for Health and Care Excellence

PANEL3: 3rd observation panel on practices and conditions of general practice

Q1: 1st quartile

Q3: 3rd quartile

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

OR: odds ratio

Introduction

Good practice guidelines are intended to support and guide doctors in adopting the most appropriate therapeutic strategy, such as prescribing medicines with the most favourable benefit-risk ratio [1]. Their application can be challenging in some situations [2], such as in patients with multiple chronic diseases, who are exposed to poly medication and an increased risk of adverse events, drug-drug interactions, and medicine misuse [3,4].

Benzodiazepines are used to treat anxiety and severe sleep disorders and are among the most prescribed drug classes, although non-pharmacological alternatives exist [5–7]. Lorazepam is a benzodiazepine with anxiolytic, anti-anxiety, anticonvulsant, anti-emetic and sedative properties. When given orally, it is readily absorbed, with an absolute bioavailability of 90%. The peak of plasma concentration is reached in 2 hours, with a half-life of 14 hours [8]. These three elements explain its potential efficacy for insomnia, even if lorazepam is not formally approved for this indication. Given the lack of evidence of benzodiazepines long-term efficacy and because of the risks associated with their long-term use [9–13], regulatory rules and guidelines usually advise a treatment duration not exceeding 4-12 weeks [14–17]. Despite these recommendations, long-term benzodiazepines prescriptions concern 13.1% to 41.0% of users according to the definition retained (*e.g.* ≥ 4 weeks, ≥ 6 months) [18–21].

Thus, general practitioners (GPs) are likely to face situations in which benzodiazepines should be discontinued [22–24]. The French guidelines recommend a specific consultation focusing on methods of discontinuation, a progressive dose reduction, or a switch to diazepam [15]. The NICE guidelines are very similar and propose two approaches to discontinue benzodiazepines or Z-drugs: *i)* slow dose reduction, or *ii)* switching to an equivalent dose of diazepam, which is then tapered down [25].

Since most benzodiazepine prescriptions are given by GPs [26], it is also their responsibility to manage their discontinuation. They may face a dilemma in weighing up the advantages of the immediate and evident effects of benzodiazepines against the painful withdrawal syndrome that discontinuation or dose reduction may induce [27]. In these situations, the attitudes and practices of prescribers are crucial and may be influenced by their age, gender, perception of drug effectiveness, patients' expectations, and good practice guidelines [24,28]. GPs' practice in terms of drug discontinuation may also be influenced by patients' characteristics, such as their health condition and socioeconomic status.

The objective of the study was to study the determinants associated with GPs' compliance with benzodiazepine discontinuation guidelines through a case-vignette of a patient with multimorbidity and treated with long-term lorazepam for insomnia.

Methods

Data source and study population

This survey follows “Strengthening the Reporting of Observational Studies in Epidemiology” STROBE for cross-sectional studies guidelines [29] and was carried out as part of 3rd observation panel on practices and conditions of general practice (PANEL3), a nationally representative sample of 1,582 French GPs set up in 2014 to study GPs' perceptions, attitudes and practices. The sample was built using data from the French directory of health professionals by random draw using stratification by sex, age, workload, and GP density in the municipality of practice [30,31]. For the purpose of the present work, we used data from a questionnaire focusing on multimorbidity, administered in 2016. Thus, GPs who completed the first wave of surveys, still participating in 2016, were included in the present study [31,32].

Data collection

Professional interviewers collected data using a standardized questionnaire and a computer-assisted telephone interview (CATI) system. An online questionnaire was made available for GPs who were unable to participate in the telephone survey. GPs' sociodemographic characteristics were collected at the time of inclusion.

The questionnaire of this survey included general questions about GPs' practice, such as the proportion of their patients with multimorbidity. Their perceptions of current guidelines and trust in official sources of information on the benefits and risks of medicines were measured using 5-point Likert scales including “Do not know” answers.

To collect data related to GPs' perceptions and practices in a specific clinical context, a case-vignette was proposed. It corresponded to a woman with multiple chronic conditions

associated with polypharmacy and treated with lorazepam for 3 years for chronic insomnia, who consulted her GP for a prescription renewal. Eight versions of this case-vignette were available, in which age (54 or 82 years), socio-professional status (cleaner or manager) and stroke history (ischaemic stroke 2 years ago or no stroke) varied. These variations make it possible to study GPs conduct regarding different characteristics of the clinical case.

Before the survey start, a version of this vignette was randomly allocated to each GP in blocks of 8 in order to obtain a balanced number of GPs for each version. To do this, a random number was assigned to each GP in order to rank them in ascending order, the first version was assigned to the first 8 GPs, version two to the next eight GPs and so on. All GPs were all asked the same specific questions related to the management of this case, such as necessity for lorazepam discontinuation (required or not) and method of implementing it when the patient insisted for a prescription renewal. Moreover, a scale ranging from 0, not important, to 10, very important was used to evaluate GPs' perceptions of the importance of *i*) patient preferences, *ii*) lorazepam benefit-risk ratio, *iii*) patient's understanding of the risks of lorazepam, and *iv*) support from family and friends for making the decision to discontinue lorazepam (Appendix 1).

Main outcome

The main outcome was GPs' compliance with guidelines for managing a fictitious patient with long-term use of lorazepam for insomnia who insisted on a prescription renewal. Four answer modalities were proposed at the end of the case-vignette: *dedicated consultation to discuss discontinuation (1)*, *progressive discontinuation (2)*, *immediate discontinuation (3)*, or *decision not to discontinue (4)*. According to French guidelines [15], GPs' were grouped as follows: *i*) "following guidelines" (options 1 or 2) and *ii*) "out-of-guidelines" (options 3 or 4).

Statistical analysis

We described GPs characteristics and perceptions (*e.g.* perceptions of guidelines, trust in official sources) according to their compliance with guidelines using frequencies.

We categorized continuous variables, e.g. main criteria of importance for deciding to discontinue lorazepam, into quartiles (Min-Q1, Q1-Q3, Q3-Max).

To study the factors associated with out-of-guidelines practices, we first estimated odds ratios (ORs) and their 95% confidence intervals (95% CI) using univariate logistic regression models. We then included variables with p-values less than 0.25 in a multivariate regression model. Next, we performed a backward selection procedure and retained in the final model variables with p-values less than 0.10 or confounding variables. We used this final model to estimate probabilities of out-of-guidelines practice and calculated 95% CI using percentiles bootstrap method. To do so, we drew 1,000 random samples with replacement from the original sample and used the final model to re-estimate probabilities in each bootstrap sample. This iterative process produced 1,000 sets of probabilities according to GPs' characteristics and perceptions, and the 95% CI corresponding to the percentiles 2.5% and 97.5% of these values. We plotted the probabilities and their 95% CIs in a heatmap (*i.e.* graphic in which data values are depicted by colours) according to characteristics and perceptions of GPs.

We performed the analyses using weighted data to match our GP population with the nationwide one for stratification variables (age, gender, workload and density of GPs in the municipality of practice) at the time of the panel's constitution, in 2014. This data weighting minimises a potential selection bias related to non-participation [30,33].

We used R software (version 3.5.1, *R foundation for statistical computing, Vienna, Austria*) with *survey*, *tableone*, *ade4* and *FactoMineR* packages and SAS SURVEY procedures (SAS Enterprise Guide 6.1, *SAS Institute, North Carolina, USA*).

Results

Study population

Among the 1,582 GPs who agreed to join the panel in 2014 and completed the first wave of surveys, 1,266 (80.0%) were still participating in 2016, and 1,183 completed the multimorbidity questionnaire [30,31]. Six were excluded because of an unmeasured outcome so 1,177 were included (99.5%) in the study population (Fig. 1).

Participants were mainly men (69.2%), aged more than 58 years (37.0%), mainly worked in group practices (55.9%), with fixed national insurance consultation fee (91.3%), and did not practice alternative medicine such as homeopathy or acupuncture (89.7%). Most of them reported having $\leq 25\%$ or 25%-50% of their patients with multimorbidity (42.8% and 42.5%, respectively; Table 1).

Compliance with guidelines

Regarding the case-vignette, most GPs would have followed the guidelines (n = 1,085; 92.2%). Men (84.7% vs. 67.9%) and GPs aged over 58 years (55.4% vs. 35.4%) were more represented in the out-of-guidelines group. Moreover, GPs in the latter group worked in single practice more frequently (54.4% vs. 43.2%; Table 1).

Case-vignette characteristics were similar in the two groups of GPs (Table 2). Concerning GPs' perceptions, complexity of case-vignette, trust in official sources of information regarding benefit-risk ratio of drugs, and opinions regarding good practice guidelines were well balanced among the groups. Regarding criteria influencing GPs in their decision to discontinue lorazepam, GPs with out-of-guidelines practice less often valued patients' perception of the risks of lorazepam (low importance: 40.2% vs. 29.1%), and the support of family and friends (low importance: 43.5% vs. 31.9%) than the other GPs. GPs with out-of-guidelines practice more frequently considered their patients' preferences to be important (54.9% vs. 28.7%) and, among them (N = 50), almost all *decided not to discontinue lorazepam* (N = 43, 86.0%). They also considered the benefit-risk ratio of lorazepam to be important less frequently (19.8% vs. 26.8%) and, among them (N = 18), most proposed *immediate discontinuation* of lorazepam (N = 13, 72.2%; see Appendix 2 for related crude ORs).

Factors associated with compliance with good practice guidelines

Out-of-guidelines practice was independently associated with older age of GPs, high consideration of patient preferences and low consideration of the benefit-risk ratio of

lorazepam (Table 3). We found the highest estimated probability of out-of-guidelines practice in men aged over 58 years, who considered patient preferences as very important and had a low consideration of the benefit-risk ratio of lorazepam (27.3% [18.7%; 34.7%]). Conversely, we found the lowest probability of out-of-guidelines practice in women aged under 50 years, who considered patient preferences and the benefit-risk ratio as moderately important criteria regarding the decision to discontinue (0.6% [0.2%; 1.1%]; Fig. 2).

Discussion

Principal findings

The most important finding of our study is that most GPs managed the case-vignette in line with benzodiazepine discontinuation guidelines. Women GPs aged under 50 years reporting a counterbalanced consideration of both patient preferences and benefit-risk ratio of long-term lorazepam were more likely to comply with good practice guidelines. Conversely, men GPs aged over 58 years with high consideration of patient preferences and less concern about the benefit-risk ratio of lorazepam were more likely to adopt out-of-guidelines practice.

Benzodiazepines are among the medicines most frequently associated with inappropriate use, and for which discontinuation after one to three months of use is required [27]. Although scheduled discontinuation before treatment initiation is strongly recommended [15], we did not find any evidence in the literature about the actual implementation of this recommendation.

The high proportion of GPs reporting practice in line with the current good practice guidelines for the management of the case-vignette is highly encouraging. The small proportion of GPs who reported out-of-guidelines practice in the present sample had particular demographic characteristics such as age and gender, which is consistent with previous findings on the determinants of prescribing habits [34,35]. In our study, GPs aged over 58 years seemed more likely to be uncompliant with guidelines. This may be related to their longer experience, since they may have managed patients with multimorbidity more often, and hence rely on their field experience. In addition, they may not be familiar with recent guidelines or not entirely aware of their relevance, or they may question their

applicability [36]. Conversely, young GPs are less experienced and may tend to try to apply the guidelines even in complex patients [28].

In a study on the perspectives of deprescribing in primary care, Anderson *et al.* reported that the experience of GPs might contribute to their degree of self-confidence and to how they view drugs-related risks. They suggested that negative experiences on deprescribing might result in therapeutic inertia, while positive or neutral experiences might open their minds about deprescribing [37].

Our survey confirmed that women GPs have a pronounced tendency to follow guidelines on lorazepam discontinuation. This result is in line with previous reports, as women GPs have been found to spend more time with each patient, have better communication skills, and are more likely to follow evidence-based guidelines than men [38–40]. Moreover, the feminisation of the medical profession may also play a role in the evolution of practices between younger and older generations of GPs, as women are nowadays more represented in the younger age groups [41].

While the appropriate and rational use of medicines is a subject of growing interest in the medical community, more effort is needed to make it an integral part of medical studies [42,43]. Specific teaching, mainly focused on how to prescribe appropriate medicines [44], exists while the whole deprescribing process, which has been described as an integral part of the rational prescribing process [22], probably needs further efforts to be effectively adopted by the medical community.

Most of the GPs with out-of-guidelines practice devoted too much consideration to patient preferences and decided not to discontinue lorazepam. This may be due to the complexity of dealing with patients who are reluctant to stop a drug whose perceived effect is self-evident. Importantly, the deprescribing process should be patient-centred, although prescribers should give reasonable consideration to patient preferences [45]. This is particularly true for the use of benzodiazepines in insomnia, its severity being a risk factor for problematic use [46], although a French study suggested that the frequent or quasi-continuous use of benzodiazepines or z-drugs is not associated with dose escalation [47].

Even if GPs know that discontinuation is necessary, they may not know how to do it effectively, nor be able to convince patients to adhere to it. Indeed, as pointed out by Gentile *et al.* patient reluctance can feel like blackmail, as patient can threat to consult another practitioner [48]. Some facilitators have already been published [22,45,49,50]. For example, Scott *et al.* proposed algorithms for the decision to discontinue or renew medicines which are

useful for the management of polypharmacy [22]. They described a 5-step deprescribing protocol: (i) check the list of medicines taken by the patient, (ii) assess the overall risk of drug-induced harm, (iii) identify medicines that can be discontinued (*e.g.*, no valid indication, risks outweighing benefits), (iv) prioritize the medicines to be discontinued, and (v) implement and monitor the discontinuation [22]. McGrath *et al.* showed how to implement this deprescribing algorithm by using a detailed polymedicated clinical case-vignette [51]. Nevertheless, there is no consensus about the best interventions to adopt for the effective and durable discontinuation of benzodiazepines [52,53].

Out-of-guidelines GPs who showed high consideration for the benefit/risk ratio of long-term benzodiazepines most frequently proposed immediate discontinuation of lorazepam. GPs probably consider the risks related to long-term lorazepam use, such as falls [11,12] or dementia [9,10], more important than its potential withdrawal effects. This could be highly counterproductive, as rebound insomnia or anxiety are often interpreted as a sign of the effectiveness of benzodiazepines, leading to prescription renewal and creating a vicious circle [27,43].

Strengths and weaknesses

The main strength of this survey study is that the study population is large and representative of French GPs. Case-vignettes were used to collect GPs' perceptions and practices, thus giving an idea of their practices regardless of the constraints of consultations. The case-vignette included eight versions depending on the age of the case, socio-professional status, and stroke history, which also allowed to consider patients' characteristics.

The study also has some weaknesses. First, like all studies with declarative data, it was subject to a social desirability bias (*i.e.*, when participants answer questions in a way that will be considered favourable). In addition, despite the use of weights to obtain a representative sample of French GPs, participating GPs may be more invested in improving care than non-participants and therefore more likely to comply with guidelines. This may have overestimated the proportion of GPs following the guidelines in our study. Nevertheless, at the time of inclusion GPs were not informed of the different survey topics, and the two modalities (*i.e.*, out-of-guidelines, following guidelines) were not directly collected in the survey but were built *a posteriori*. Thus, the impact of these biases on the present study

should be minor. Second, even if case-vignettes are comparable to real situations, their use cannot guarantee that GPs' responses reflect their actual practice, even though they have been shown to be accurate to assess professional practice [35]. Finally, only some information on GPs' patient list characteristics was available (*e.g.* reported proportion of multimorbid patients), although this may influence their prescribing habits. For example, GPs with a high proportion of multimorbid patients should be more experienced because of a learning effect.

Implications for clinicians and policymakers

This study emphasises that some GPs may be more prone to out-of-guidelines practice in patients with long-term lorazepam for insomnia. The findings could allow policymakers to implement targeted measures taking into account barriers to deprescribing, such as uncertainty about the effects of discontinuation, limited GPs' time, or patient expectations.

This study also indicates that GPs who considered the benefit-risk ratio as an important criterion for their practice had a greater probability of discontinuing lorazepam immediately. Although GPs may be aware of the iatrogenic effects of some drugs, it is important to draw attention to the effects of withdrawal. Even if GPs are familiar with discontinuation guidelines and know that discontinuation is necessary, they may have difficulty in implementing it or in convincing patients to adhere to it. It is therefore crucial to highlight the importance of the appropriate prescribing of benzodiazepines and to schedule its discontinuation before the first benzodiazepine prescription. Initial training and further medical education about the right ways to discontinue benzodiazepines are thus crucial in this perspective.

Patients' beliefs and perceptions, such as fear of a relapse, and poor health literacy could be barriers toward discontinuation [54,55]. There is thus a need to inform patients about the risks associated with the long-term use of some drugs and the importance of discontinuing them under medical supervision.

Conclusion

This study shows that GPs are aware of the risks associated with the long-term use of lorazepam and suggests that they largely follow the current lorazepam discontinuation guidelines. However, some GPs, primarily older men who pay excessive attention to patient preferences, are more likely to adopt out-of-guidelines practice. Prevention targeted measures on GPs and patients about benzodiazepines discontinuation should thus be implemented.

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Contributors

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AS analysed and interpreted the data, and drafted the article. HC and PV designed and conceptualized the survey, developed the questionnaire, coordinated and supervised the data collection. HC, MT, AP and PV interpreted the data, revised the first draft of the manuscript, and investigated the accuracy of the results. FS interpreted the data, drafted the article, and investigated the integrity and accuracy of all aspects of the work. FS is the guarantor of the study. All authors revised the article critically for important intellectual content and gave final approval of the version to be published.

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Prior presentation

NA

Ethical approval

The *Commission nationale de l'information statistique* (National Authority for Statistical Information) approved the study. Approval ref: Paris, 3 June 2013, no. 82/H030.

Disclosure of interest

All authors declare no competing interests.

References

- [1] Institute of Medicine. Clinical practice guidelines: directions for a new program. Lohr KN, Field MJ, editors. Washington, D.C.: National Academies Press; 1990. 168 p. ISBN: 0-309-56001-2.
- [2] Luijckx H, Lucassen P, Van Weel C, Loeffen M, Lagro-Janssen A, Schermer T. How GPs value guidelines applied to patients with multimorbidity: A qualitative study. *BMJ Open* 2015;5:e007905.
- [3] World Health Organization (WHO). Multimorbidity: technical series on safer primary care. Geneva; 2016. <https://apps.who.int/iris/bitstream/handle/10665/252275/9789241511650-eng.pdf?sequence=1>. [Accessed 10 September 2021 (28 pp.)].
- [4] Aronson JK. In defence of polypharmacy. *Br J Clin Pharmacol* 2004;57:119–20.
- [5] Guina J, Merrill B. Benzodiazepines I: Upping the care on downers: the evidence of risks, benefits and alternatives. *J Clin Med* 2018;7:17.
- [6] Driot D, Ouhayoun S, Perinelli F, Grézy-Chabardès C, Birebent J, Bismuth M, et al. Non-drug and drug alternatives to benzodiazepines for insomnia in primary care: Study among GPs and pharmacies in a Southwest region of France. *Therapies* 2019;74:537–46.
- [7] Légereau L, Bonnard M, Tétart J, Barbaroux A. Training in medical hypnosis and prolonged use of benzodiazepines: The French national health insurance data. *Therapies* 2020 Nov 19:S0040-5957(20)30197-9. doi: 10.1016/j.therap.2020.11.004.
- [8] Ghiasi N, Bhansali RK, Marwaha R. Lorazepam. In: *xPharm: The Comprehensive Pharmacology Reference*. StatPearls Publishing; 2021. p. 1–5. ISBN 978-0-08-055232-3
- [9] Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, et al. Benzodiazepine use and risk of Alzheimer’s disease: case-control study. *BMJ* 2014;349:g5205.
- [10] Billioti de Gage S, Bégau B, Bazin F, et al. Benzodiazepine use and risk of dementia: prospective population based study. *BMJ*. 2012;345.
- [11] Pariente A, Dartigues JF, Benichou J, Letenneur L, Moore N, Fourrier-Réglat A. Benzodiazepines and injurious falls in community dwelling elders. *Drugs Aging* 2008;25:61–70.
- [12] Pierfitte C, Macouillard G, Thicoïpe M, Chaslerie A, Pehourcq F, Aïssou M, et al.

Benzodiazepines and hip fractures in elderly people: Case-control study. *Br Med J* 2001;322:704–8.

[13] Lapeyre-Mestre M. Benzodiazepines, cognitive decline and dementia: A review of causality criteria from published observational studies. *Therapies* 2019;74:407–19.

[14] NICE. BNF - Hypnotics and anxiolytics, treatment summary. 2020. <https://bnf.nice.org.uk/treatment-summary/hypnotics-and-anxiolytics.html> [Accessed 10 September 2021].

[15] Haute autorité de santé (HAS). Arrêt des benzodiazépines et médicaments apparentés : démarche du médecin traitant en ambulatoire. 2015. https://www.has-sante.fr/portail/upload/docs/application/pdf/2015-06/fiche_memo_arret_benzodiazepines_pour_mel_2015_06_16.pdf. [Accessed 10 September 2021 (5 pp.)].

[16] Legifrance. Arrêté du 7 octobre 1991 fixant la liste des substances de la liste I des substances vénéneuses à propriétés hypnotiques et/ou anxiolytiques dont la durée de prescription est réduite. 1991. <https://www.legifrance.gouv.fr/loda/id/LEGITEXT000020690355>. [Accessed 10 September 2021]

[17] Base de données publique des médicaments. Lorazépam Mylan 1 mg, comprimé pelliculé sécable. Résumé des caractéristiques du produit. 2021. <https://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=62505828&typedoc=R> [Accessed 10 September 2021]

[18] Panes A, Pariente A, Bénard-Larivière A, Lassalle R, Dureau-Pournin C, Lorrain S, et al. Use of benzodiazepines and z-drugs not compliant with guidelines and associated factors: a population-based study. *Eur Arch Psychiatry Clin Neurosci* 2020;270:3–10.

[19] Kurko T, Saastamoinen LK, Tuulio-Henriksson A, Taiminen T, Tiihonen J, Airaksinen M, et al. Trends in the long-term use of benzodiazepine anxiolytics and hypnotics: A national register study for 2006 to 2014. *Pharmacoepidemiol Drug Saf* 2018;27:674–82.

[20] Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry* 2015;72:136–42.

[21] Cunningham CM, Hanley GE, Morgan S. Patterns in the use of benzodiazepines in British Columbia: Examining the impact of increasing research and guideline cautions against long-term use. *Health Policy* 2010;97:122–9.

- [22] Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, et al. Reducing inappropriate polypharmacy: The process of deprescribing. *JAMA Intern Med* 2015;175:827–34.
- [23] Pollmann AS, Murphy AL, Bergman JC, Gardner DM, Gardner DM. Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: A scoping review. *BMC Pharmacol Toxicol* 2015;16:19.
- [24] Turner JP, Richard C, Lussier MT, Lavoie ME, Farrell B, Roberge D, et al. Deprescribing conversations: a closer look at prescriber-patient communication. *Ther Adv Drug Saf* 2018;9:687–98.
- [25] NICE. Benzodiazepine and z-drug withdrawal. 2020. <https://cks.nice.org.uk/topics/benzodiazepine-z-drug-withdrawal/>. [Accessed 10 September 2021].
- [26] ANSM. État des lieux de la consommation des benzodiazépines en France. 2017. http://www.pharmacovigilance-limoges.fr/sites/default/files/files/Documentation/ANSM_Rapport_Benzo_2017.pdf. [Accessed 10 September 2021 (60 pp.)].
- [27] Ng BJ, Le Couteur DG, Hilmer SN. Deprescribing benzodiazepines in older patients: impact of interventions targeting physicians, pharmacists, and patients. *Drugs Aging* 2018;35:493–521.
- [28] Wallis KA, Andrews A, Henderson M. Swimming against the tide: primary care physicians' views on deprescribing in everyday practice. *Ann Fam Med* 2017;15:341–6.
- [29] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573–7.
- [30] Le Maréchal M, Collange F, Fressard L, Peretti-Watel P, Sebbah R, Mikol F, et al. Design of a national and regional survey among French general practitioners and method of the first wave of survey dedicated to vaccination. *Med Mal Infect* 2015;45:403–10.
- [31] Carrier H, Zaytseva A, Bocquier A, Villani P, Verdoux H, Fortin M, et al. GPs' management of polypharmacy and therapeutic dilemma in patients with multimorbidity: A cross-sectional survey of GPS in France. *Br J Gen Pract* 2019;69:E270–8.
- [32] Carrier H, Zaytseva A, Bocquier A, Verger P, Barlet M, Chaput H, et al. Polymédication et pathologies chroniques multiples : opinions et pratiques des médecins

généralistes. DREES, études et résultats. 2017. <https://drees.solidarites-sante.gouv.fr/publications/etudes-et-resultats/polymedication-et-pathologies-chroniques-multiplies-opinions-et>. [Accessed 10 September 2021].

[33] Brion P, Caron N, Pietri-Bessy P. Redresser la non-réponse totale dans les enquêtes auprès des entreprises : les pièges à éviter. Illustration avec l'enquête innovation. Insee - Actes des journées méthodologie statistiques. 2005. http://www.jms-insee.fr/2005/S07_4_ACTE_BRION-CARON-PIETRI-BESSY_JMS2005.pdf. [Accessed 10 September 2021 (9 pp.)].

[34] Pichetti S, Sermet C, Godman B, Campbell SM, Gustafsson LL. Multilevel analysis of the influence of patients' and general practitioners' characteristics on patented versus multiple-sourced statin prescribing in France. *Appl Health Econ Health Policy* 2013;11:205–18.

[35] Saillour-Glénisson F, Kret M, Domecq S, Sibé M, Daucourt V, Migeot V, et al. Organizational and managerial factors associated with clinical practice guideline adherence: A simulation-based study in 36 French hospital wards. *Int J Qual Heal Care* 2017;29:579–86.

[36] Clerc I, Ventelou B, Guerville MA, Paraponaris A, Verger P. General practitioners and clinical practice guidelines: A reexamination. *Med Care Res Rev* 2011;68:504–18.

[37] Anderson K, Foster M, Freeman C, Luetsch K, Scott I. Negotiating “Unmeasurable Harm and Benefit”: Perspectives of General Practitioners and Consultant Pharmacists on Deprescribing in the Primary Care Setting. *Qual Health Res* 2017;27:1936–47.

[38] Phillips SP, Austin EB. The feminization of medicine and population health. *JAMA* 2009;301:863–4.

[39] Dahrouge S, Seale E, Hogg W, Russell G, Younger J, Muggah E, et al. A comprehensive assessment of family physician gender and quality of care. *Med Care* 2016;54:277–86.

[40] Roter DL, Hall JA. Physician gender and patient-centered communication: a critical review of empirical research. *Annu Rev Public Health* 2004;25:497–519.

[41] OECD. Ressources en santé : médecins par âge et sexe. 2019. <https://www.oecd-ilibrary.org/fr>. [Accessed 10 September 2021].

[42] Bégaud B, Costagliola D. Rapport sur la surveillance et la promotion du bon usage du médicament en France. 2013. https://solidarites-sante.gouv.fr/IMG/pdf/Rapport_Begaud_Costagliola.pdf. [Accessed 10 September 2021 (57 pp.)].

- [43] Montastruc JL, Montastruc F. Prescribe, but also know how to “deprescribe.” Vol. 22, *Prescrire Int* 2013;22:192.
- [44] Holloway KA. Combating inappropriate use of medicines. *Expert Rev Clin Pharmacol* 2011;4:335–48.
- [45] Holmes HM, Todd A. The role of patient preferences in deprescribing. *Clin Geriatr Med* 2017;33:165–75.
- [46] Manthey L, Lohbeck M, Giltay EJ, van Veena T, Zitman FG, Penninx BWJH. Correlates of benzodiazepine dependence in the Netherlands Study of depression and anxiety. *Addiction* 2012;107:2173–82.
- [47] Verger P, Cortaredona S, Jacqmin-Gadda H, Tournier M, Verdoux H. Eight-year follow-up of hypnotic delivery by adults aged 50 and older from an insurance database. *Sleep* 2017;40:1–11.
- [48] Gentile G, Lapeyre-Mestre M, Micallef J. Combatting the misuse of benzodiazepines and related Z drugs in French general practice: A clinical review. *BJGP Open* 2020;4:bjgpopen20X101014. doi: 10.3399/bjgpopen20X101014..
- [49] Scott IA, Gray LC, Martin JH, Pillans PI, Mitchell CA. Deciding when to stop: Towards evidence-based deprescribing of drugs in older populations. *Evid Based Med* 2013;18:121–4.
- [50] Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Review of deprescribing processes and development of an evidence-based, patient-centred deprescribing process. *Br J Clin Pharmacol* 2014;78:738–47.
- [51] McGrath K, Hajjar ER, Kumar C, Hwang C, Salzman B. Deprescribing: A simple method for reducing polypharmacy. *J Fam Pract* 2017;66:436–45.
- [52] Baandrup L, Ebdrup BH, Rasmussen JO, Lindschou J, Gluud C, Glenthøj BY. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. *Cochrane Database Syst Rev* 2018;3:CD011481.
- [53] Reeve E, Ong M, Wu A, Jansen J, Petrovic M, Gnjjidic D. A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people. *Eur J Clin Pharmacol* 2017;73:927–35.
- [54] Clyne B, Cooper JA, Boland F, Hughes CM, Fahey T, Smith SM. Beliefs about prescribed medication among older patients with polypharmacy: A mixed methods study in primary care. *Br J Gen Pract* 2017;67:e507–18.
- [55] Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and

enablers of deprescribing: A systematic review. *Drugs Aging* 2013;30:793–807.

Table 1. GPs' Characteristics (weighted data)

	N	Total	Practice	
			Out-of-guidelines, N = 92 (%)	Following guidelines, N = 1,085 (%)
<u>Characteristics</u>				
<u>Stratification variables</u>				
Gender	1,177			
Men		814 (69.2)	78 (84.7)	736 (67.9)
Age at inclusion in years (tertiles)	1,177			
<50		359 (30.5)	9 (9.8)	350 (32.3)
50-58		383 (32.5)	32 (34.8)	351 (32.3)
>58		435 (37.0)	51 (55.4)	384 (35.4)
Density of GPs in municipality of practice*	1,177			
<-19,3% of national average		296 (25.1)	29 (31.5)	267 (24.6)
From -19,3% to +17,7% of national average		587 (49.9)	44 (47.8)	543 (50.0)
>+17,7% of national average		294 (25.0)	19 (20.7)	275 (25.4)
Workload (number of consultations in 2012)*	1,177			
<3067		292 (24.8)	22 (23.9)	270 (25.0)
3067 - 6028		589 (50.0)	45 (48.9)	544 (50.0)
>6028		296 (25.2)	25 (27.2)	271 (25.0)
<u>Other characteristics</u>				
Types of practice	1,171			
Group practice†		655 (55.9)	41 (45.6)	614 (56.8)
Remuneration system	1,156			
Fixed national insurance fee		1,056 (91.3)	82 (91.1)	974 (91.4)
Additional fee		100 (8.7)	8 (8.9)	92 (8.6)
Non-exclusive practice of alternative medicine	1,171			
Yes		121 (10.3)	4 (4.4)	117 (10.8)
Reported proportion of patients with multimorbidity	1,160			
<25%		497 (42.8)	36 (40.0)	461 (43.1)
25% - 50%		493 (42.5)	42 (46.7)	451 (42.1)
>50%		170 (14.7)	12 (13.3)	158 (14.8)

*(Min-Q1 / Q1-Q3 / Q3-Max), † including multi-professional nursing home approved by regional health agencies

GP: general practitioner

Table 2. Perceptions and attitudes of GPs (weighted data)

	N	Practice	
		Out-of-guidelines, N = 92 (%)	Following guidelines, N = 1,085 (%)
<u>Characteristics of case-vignette</u>			
Age in years	1,177		
54		40 (43.5)	530 (48.8)
82		52 (56.5)	555 (51.2)
Socio-professional status	1,177		
Cleaner		42 (45.7)	561 (51.7)
Manager		50 (54.3)	524 (48.3)
Stroke history*	1,177		
Yes		48 (52.2)	527 (48.6)
No		44 (47.8)	558 (51.4)
<u>GPs' perceptions</u>			
Complexity of clinical case*	1,174		
Low (<5)		25 (27.2)	237 (21.9)
Moderate (5-7)		53 (57.6)	672 (62.1)
High (>7)		14 (15.2)	173 (16.0)
Trust in official sources for BRR assessment (tertiles)	1,130		
Low (<6)		35 (38.4)	336 (32.3)
Moderate (= 6)		40 (44.0)	498 (48.0)
High (>6)		16 (17.6)	205 (19.7)
Perception of guidelines	1,056		
Low overall perception (<i>not helpful and difficult to apply</i>)		21 (26.2)	217 (22.2)
Moderate overall perception (<i>helpful but difficult to apply</i>)		38 (47.6)	526 (53.9)
High overall perception (<i>helpful and applicable</i>)		21 (26.2)	233 (23.9)
<u>Criteria of importance for deciding to discontinue lorazepam</u>			
Importance of patients' perception of lorazepam risks*	1,172		
Low (≤ 6)		37 (40.2)	314 (29.1)
Moderate (6-9)		36 (39.1)	442 (40.9)
High (≥ 9)		19 (20.7)	284 (30.0)
Importance of support from family and friends*	1,169		
Low (≤ 2)		40 (43.5)	344 (31.9)
Moderate (2-6)		32 (34.8)	397 (36.9)
High (≥ 6)		20 (21.7)	336 (31.2)
Importance of patient preferences*	1,172		
Low (≤ 2)		19 (20.9)	284 (26.3)
Moderate (2-6)		22 (24.2)	487 (45.0)
High (≥ 6)		50 (54.9) [†]	310 (28.7)
Importance of benefit-risk ratio (BRR)*	1,171		
Low (≤ 7)		53 (58.2)	361 (33.4)
Moderate (7-10)		20 (22.0)	430 (39.8)
High (≥ 10)		18 (19.8) [‡]	289 (26.8)

* (Min-Q1 / Q1-Q3 / Q3-Max), † refrained from discontinuation (n=43, 86.0%); ‡ immediate discontinuation (N = 13, 72.2%).

BRR: benefit-risk ratio; GP: general practitioner

Table 3. Factors associated with GPs' practice in event of patient reluctance (weighted data, multivariate regression)

	Practice	
	Out-of-guidelines (N = 1,168) OR ^A (IC95%)	P-value
<i>GPs' characteristics</i>		
Gender		0.056
Men (ref. Women)	1.9 (1.0-3.6)	
Age at inclusion in years		0.002
50-58 (ref. <50)	3.0 (1.5-6.2)	
> 58 (ref. <50)	3.8 (1.8-8.1)	
<i>Criteria of importance for deciding to discontinue lorazepam</i>		
Importance of patient preferences		0.001
Low (ref. Moderate)	1.6 (0.8-3.4)	
High (ref. Moderate)	3.3 (1.8-6.1)	
Importance of benefit-risk ratio		0.007
Low (ref. Moderate)	2.8 (1.5-5.4)	
High (ref. Moderate)	1.7 (0.8-3.7)	

GP: general practitioner; OR^A: adjusted odds ratio

Legends for Figures

Figure 1 Flowchart of GP selection

Figure 2 Probabilities of out-of-guidelines practice according to GPs' characteristics and perceptions (weighted data, multivariate regression)

*Importance of benefit-risk ratio

APPENDICES

Appendix 1. Questionnaire (extract)

Appendix 2. Table S1. Factors associated with GPs' practice in event of patient reluctance
(weighted data, univariate regression)

Appendix 1. Questionnaire (extract)

NB: Only the parts of the questionnaire used to carry out this work are presented here. Characteristics of GPs were collected during the inclusion wave of the panel.

1. General questions: Part 1

Q1-1. What is the overall proportion of multimorbid patients in your practice?

₁ <25% ₂ 25-50% ₃ >50% ₄ Do not know ₅ NA

5. General questions: Part 3

Good practice guidelines exist for the management of various chronic diseases. Do you agree with the following proposals for the application of these guidelines in patients with multimorbidity? (*Random order*)

1 Strongly disagree, 2 Disagree, 3 Agree, 4 Strongly agree, 5 Do not know

	1	2	3	4	5	NA
Q5-4. The recommendations of different guidelines may contradict each other						
Q5-5. The application of recommendations of different guidelines can lead to drug-drug interactions						
Q5-6. The recommendations of guidelines are difficult to apply in multimorbid patients						
Q5-7. The recommendations of guidelines provide concrete help						

6. Case-vignette

Clinical case: A patient consults for a prescription renewal. Her hypertension is treated with ramipril and her hypothyroidism with levothyroxine. She is also treated with lorazepam for three years for frequent insomnia and paracetamol + tramadol and amitriptyline for pain related to a lumbosciatica. Apart from pain, the clinical examination is normal. (*Randomized cases*)

Case 1: 54 years old, cleaner.

Case 5: 54 years old, cleaner. Ischemic stroke 2 years ago treated by aspirin and rosuvastatin.

Case 2: 82 years old, retired cleaner.

Case 6: 82 years old, retired cleaner. Ischemic stroke 2 years ago treated by aspirin and rosuvastatin.

Case 3: 54 years old, manager.

Case 7: 54 years old, manager. Ischemic stroke 2 years ago treated by aspirin and rosuvastatin.

Case 4: 82 years old, retired manager.

Case 8: 82 years old, retired manager. Ischemic stroke 2 years ago treated by aspirin and rosuvastatin.

Q6-3. Do you think some of this patient's medicines should be discontinued?

₁ Yes ₂ No ₃ Don't know ₄ NA

If YES, which one(s)? (*Random order*)

	Yes	No	Do not know	NA
Q6-3-3. Lorazepam				

Q6-11. In case of prescription renewal, you explain to the patient that because of the risks of lorazepam, it would be better to discontinue but she says she absolutely needs it to sleep. What do you do? (*Note: Only one answer possible*)

- ₁ You propose a dedicated consultation to discuss the discontinuation
- ₂ You propose to start a very progressive discontinuation
- ₃ You propose an immediate discontinuation
- ₄ You decide not to discontinue
- ₅ Do not know
- ₆ NA

On a scale of 0 (Not important) to 10 (Very important), how important do you consider the following elements in making this decision? (Random order)

- Q6-12. Patient preferences /_/_/1 ₂ Do not know ₃ NA
- Q6-13. Benefit-risk ratio /_/_/1 ₂ Do not know ₃ NA
- Q6-14. Patient's understanding of the risks of lorazepam /_/_/1 ₂ Do not know ₃ NA
- Q6-15. Support from family and friends /_/_/1 ₂ Do not know ₃ NA

7. General questions: Part 7

Do you trust the following sources to give you reliable information about the benefits and risks of medicines? (*Random order*)

1 Highly untrustworthy, 2 Untrustworthy, 3 Trustworthy, 4 Highly trustworthy, 5 Do not know

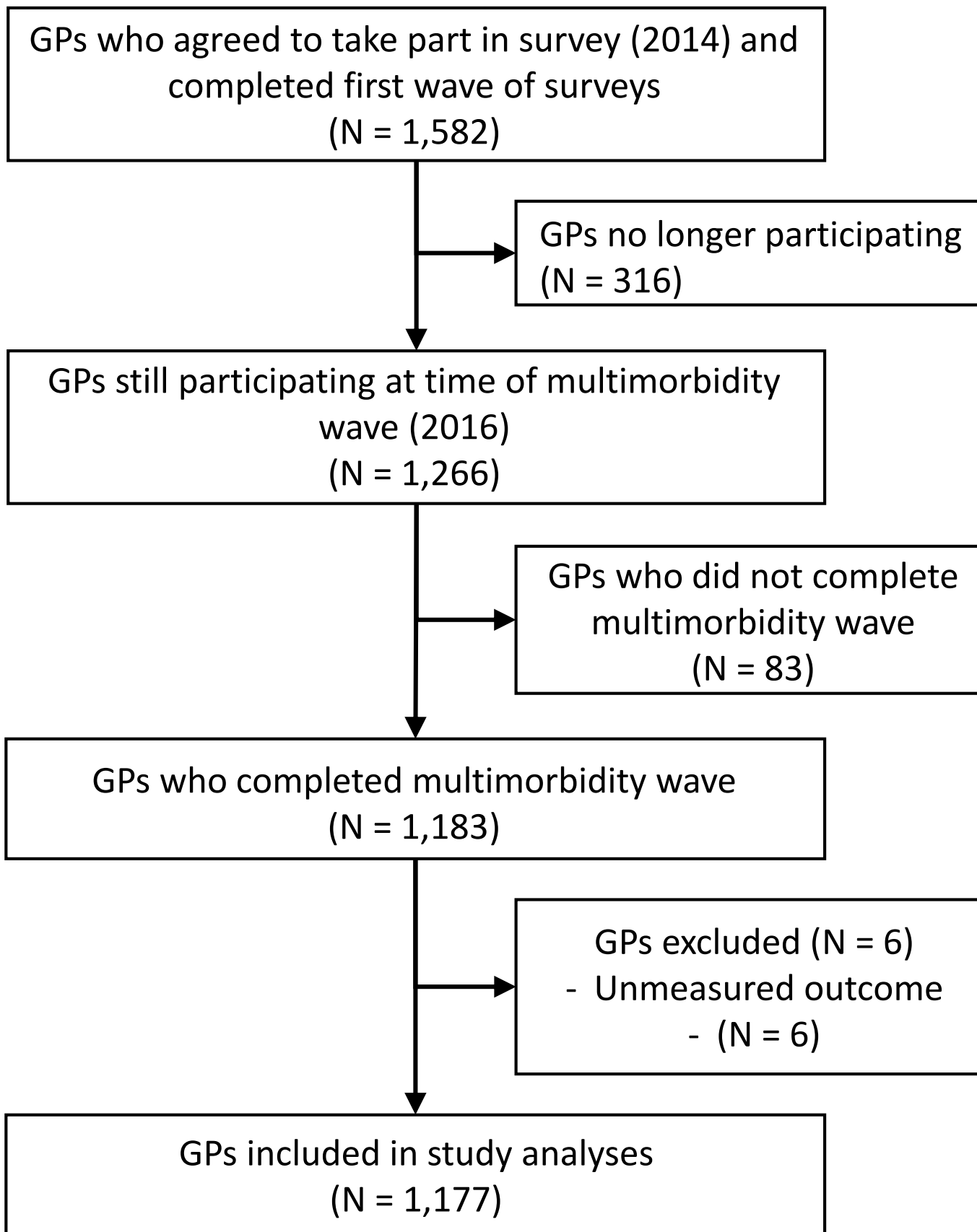
	1	2	3	4	5	NA
Q7-10. The French Ministry of Health						
Q7-11. The French Drug Safety Agency						

Appendix 2. Table S1. Factors associated with GPs' practice in event of patient reluctance (weighted data, univariate regression)

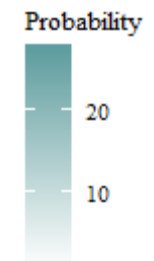
	Practice	
	Out-of guidelines OR (IC95%)	P-value
<u>Characteristics</u>		
<u>Stratification variables</u>		
Gender (N = 1,177)		0.002
Men (ref. Women)	2.6 (1.4-4.8)	
Age at inclusion in years (N = 1,177)		0.001
50-58 (ref. <50)	3.3 (1.7-6.7)	
> 58 (ref. <50)	4.9 (2.4-9.8)	
Density of GPs in municipality of practice (N = 1,177)		0.370
-19,3% to +17,7% of national average (ref. <-19,3%)	0.7 (0.4-1.3)	
> +17,7% of national average (ref. < -19,3%)	0.6 (0.3-1.3)	
Workload / number of consultations (N = 1,177)		0.911
3067 - 6028 (ref. <3067)	1.0 (0.5-2.0)	
> 6028 (ref. <3067)	1.1 (0.6-2.3)	
<u>Other characteristics</u>		
Types of practice (N = 1,171)		0.061
Individual practice (ref. Group practice)	1.6 (1.0-2.6)	
Remuneration system (N = 1,157)		0.845
Additional fee (ref. Fixed national insurance fee)	1.1 (0.4-2.7)	
Non-exclusive practice of alternative medicine (N = 1,171)		0.194
Yes (ref. No)	0.5 (0.2-1.5)	
Reported proportion of patients with multimorbidity (N = 1,160)		0.744
25% - 50% (ref. <25%)	1.2 (0.7-2.1)	
>50% (ref. <25%)	1.0 (0.5-2.1)	
<u>GPs' perceptions</u>		
Complexity of clinical case (N = 1,175)		0.548
5-7 (ref. <5)	0.7 (0.4-1.3)	
> 7 (ref. < 5)	0.7 (0.3-1.6)	
Trust in official sources for BRR assessment (n = 1,130)		0.570
Moderate – score = 6 (ref. Low – score <6)	0.8 (0.5-1.3)	
High – score >6 (ref. Low – score <6)	0.7 (0.4-1.5)	
Perception of guidelines (N = 1,056)		0.630
Moderate overall perception (ref. Low overall perception)	0.7 (0.4-1.4)	
High overall perception (ref. Low overall perception)	0.9 (0.4-1.9)	
<u>Criteria of importance for deciding to discontinue lorazepam</u>		
Importance of patient preferences (N = 1,172)		0.001
Low (ref. Moderate)	1.5 (0.7-3.1)	
High (ref. Moderate)	3.5 (1.9-6.3)	
Importance of BRR (N = 1,171)		0.001
Low (ref. Moderate)	3.2 (1.7-6.0)	
High (ref. Moderate)	1.4 (0.7-2.9)	
Importance of patients' perception of lorazepam risks (N = 1,172)		0.101
Low (ref. Moderate)	1.4 (0.8-2.5)	
High (ref. Moderate)	0.7 (0.4-1.4)	
Importance of support from family and friends (N = 1,169)		0.131
Low (ref. Moderate)	1.4 (0.8-2.5)	
High (ref. Moderate)	0.8 (0.4-1.5)	
<u>Characteristics of case-vignette</u>		
Age in years (N = 1,177)		0.401
82 (ref. 54)	1.2 (0.8-2.0)	
Socio-professional status (N = 1,177)		0.312
Cleaner (ref. Manager)	0.8 (0.5-1.3)	
Stroke history (N = 1,177)*		0.573
Yes (ref. No)	1.2 (0.7-1.9)	

BRR: benefit-risk ratio. ¥ Including multi-professional nursing home approved by regional health agencies.

* Ischemic stroke 2 years ago, for which she takes aspirin and rosuvastatin.



		<i>Criteria of importance for deciding to discontinue lorazepam</i>								
		Importance of patient preferences								
Sex	Age (years)	Low			Moderate			High		
		BRR* High	BRR* Moderate	BRR* Low	BRR* High	BRR* Moderate	BRR* Low	BRR* High	BRR* Moderate	BRR* Low
Women	<50	1.5 (0.6-2.7)	0.9 (0.3-1.7)	2.5 (0.9-4.6)	0.9 (0.4-1.8)	0.6 (0.2-1.1)	1.5 (0.7-2.8)	3 (1.3-5.5)	1.8 (0.7-3.2)	4.9 (2.2-8.4)
	50 – 58	4.4 (1.9-7.7)	2.6 (1.1-5)	7 (3.1-12.6)	2.8 (1.3-4.7)	1.7 (0.7-3)	4.5 (2.2-7.6)	8.6 (4.3-13.7)	5.3 (2.6-8.4)	13.4 (7.4-20.9)
	>58	5.5 (2.3-9.6)	3.3 (1.3-6.4)	8.8 (3.8-15)	3.5 (1.5-6.4)	2.1 (0.9-4)	5.7 (2.6-10)	10.8 (5-17.6)	6.7 (3.1-11.1)	16.6 (8.6-25.2)
Men	<50	2.8 (1.2-5)	1.7 (0.7-3.1)	4.5 (2.1-7.9)	1.8 (0.7-3.2)	1.1 (0.4-2)	2.9 (1.4-4.8)	5.6 (2.6-9.6)	3.4 (1.5-5.7)	8.9 (4.7-13.6)
	50 – 58	7.9 (4-12.6)	4.8 (2.3-7.7)	12.4 (6.7-18.4)	5.1 (2.6-8.3)	3.1 (1.5-5.2)	8.2 (5.1-11.8)	15.1 (8.7-22.1)	9.5 (5.5-13.8)	22.6 (15.4-30.2)
	>58	10 (5.2-15.3)	6.1 (2.9-10.2)	15.4 (8.8-22.6)	6.5 (3.2-10.8)	3.9 (1.7-6.6)	10.2 (6.2-15)	18.6 (10.8-27.4)	11.9 (6.6-17.6)	27.3 (18.7-34.7)



*Importance of benefit-risk ratio