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ADDICTOVIGILANCE

Inputs of pharmacoepidemiology in addictovigilance: How do they fit together?

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Summary The French Addictovigilance Network has been using data from the French Health insurance since the late 1990s to assess prescription drug abuse. In this narrative review, we illustrate the inputs of pharmacoepidemiology in addictovigilance based on the experience of the French Addictovigilance Network. The review focuses on pharmacoepidemiology using the French National Health Data System. We propose three examples: the MEGADOSE study, which aimed to conduct the first nation-wide, systematic, repeated assessment of doctor shopping;

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the DANTE study, which aimed to assess trends in analgesic use, focusing on the prevalence of use and the demographic profiles of analgesic users by age and sex; and the ZORRO study, which aimed to assess the impact of secure prescription forms on the use of zolpidem and other sedatives. These examples show how pharmacoepidemiology fits in the multifaceted monitoring conducted by the French Addictovigilance Network and complements the other data sources of this framework. This approach improves signal detection, confirmation, and quantification. It also makes it possible to overcome the limitations of each data source taken individually.

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Abbreviations

SNDS French National Health Data System

Introduction

Monitoring of prescription drug abuse addresses an issue that is often hidden. A single data source is therefore rarely enough to assess such a complex phenomenon. The current best practice is to use multiple detection systems to assess prescription drug abuse by various populations in a timely, sensitive, and specific manner [1]. Using various tools to mine epidemiological data, assess the pharmacological properties of the drugs, and assess the social contexts where the drugs are used enables to detect emerging trends earlier and intervene more quickly to protect the public from associated risks [2]. Pharmacoepidemiology can fit in this framework, by enabling to quantify prescription drug abuse in the general population.

Moreover, drug risk assessment is intrinsically linked to the population's exposure to these drugs. The pathway to prescription drug abuse often begins with initial therapeutic use, followed by misuse for therapeutic purposes, and eventually leads to a loss of control by the patient. This progression has been well established through addictovigilance monitoring of opioid analgesics (e.g., tramadol, oxycodone, and transmucosal fentanyl) and, more recently, pregabalin [3–5]. Pharmacoepidemiology also enables to assess the dynamics of drug exposure at a detailed level (e.g., including formulations, doses, frequency of dispensing, prescribing physicians, and dispensing pharmacies).

As a result, the French Addictovigilance Network has been using data from the French Health insurance since the late 1990s to assess prescription drug abuse [6,7], in addition to spontaneous reporting and other specific programs (e.g. OSIAP [8], OPPIDUM [9], DRAMES/DTA [10], and ASOS [11]), soumission chimique [12]. In this narrative review, we illustrate the inputs of pharmacoepidemiology in addictovigilance based on the experience of the French Addictovigilance Network. The review focuses on pharmacoepidemiology using the French National Health Data System (SNDS).

How did it start?

Development of pharmacoepidemiological studies has significantly advanced with the increased accessibility of claims databases. Initially designed to monitor Health Insurance expenditures for administrative and political purposes, these databases were quickly identified as a premier data source for pharmacoepidemiology. In France, the health insurance system provides mandatory, universal coverage to the population, irrespective of socio-economic status, including low-income and the unemployed people. Different Health Insurance schemes cover various population (e.g., employees, farmers, or students). The resulting databases are centralized and can now be linked to hospital data and cause of death records within the SNDS [13]. This forms one of the largest medico-administrative databases in the world, covering nearly the entire French population (i.e., about 68 million people in 2024).

Thanks to regional collaborations with the French Health Insurance at the end of the 1990s, the French Addictovigilance Network conducted the first population-based studies to assess patterns of psychoactive drug use and characterize patient profiles. These studies aimed to, e.g.: describe prescriptions of methadone maintenance treatment in Southeast France in 1999 [14]; characterize patient profiles on buprenorphine maintenance treatment in Southeast France in 1999 [15]; and assess patterns of buprenorphine use in ambulatory care and retention rate in new users during a 24-week follow-up in Southwest France in 2000 [16].

Since then, extensive research has been conducted using data from the French Health Insurance to develop specific methods to assess prescription drug abuse from the SNDS [6,7]. A recent systematic review that described the use of the SNDS for research in the field of mental health found that pharmacoepidemiology accounted for about 80 % of the articles, of which about 1/3 concerned addictovigilance [17].

Examples of the inputs of pharmacoepidemiology in addictovigilance in the past decade in France

Systematic assessment of doctor shopping

Drug-abusing patients may develop drug-seeking behaviors to satisfy their needs. Among these behaviors, doctor shop-

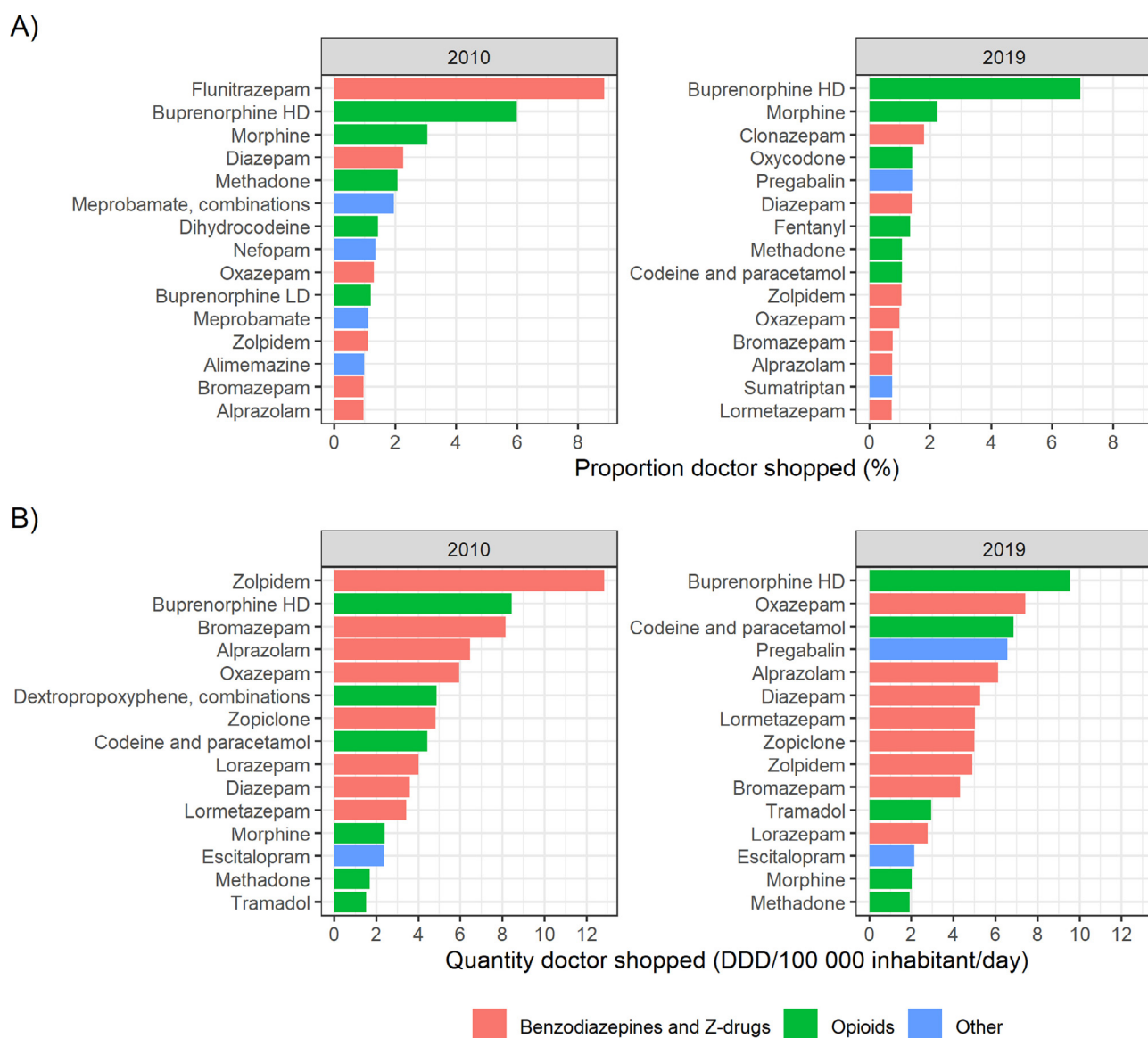


Figure 1. Ranking of psychoactive prescription drugs according to the proportion doctor shopped (A) and the quantity doctor shopped (B) in France in 2010 and 2019 according to the MEGADOSE study [23].

ping has long been described. Nevertheless, most studies focused upon a single drug or a single pharmacological class, mainly opioids in the USA [18,19]. Doctor shopping involves obtaining overlapping prescriptions from multiple prescribers for the same drug, leading to higher doses than those prescribed by each prescriber individually. Consequently, a single prescriber is unaware that other prescribers are also prescribing the same drug. The lack of medical management in addition to high doses increase the risks for adverse outcomes, such as high-risk use, overdose, and death [20–22].

In this context, the MEGADOSE study aimed to conduct the first nation-wide, systematic, repeated assessment of doctor shopping [23]. In this repeated cross-sectional study, dispensings of more than 200 psychoactive prescription drugs were extracted from the SNDS in 2010, 2015 and 2019. Detection and quantification of doctor shopping were based on an algorithm designed to identify overlapping prescrip-

tions resulting from repeated visits to different physicians [24].

Analyses included about 200 million dispensings to about 30 million patients each year. The median age was about 60 years and women accounted for about 57 % of patients. Opioids and benzodiazepines and Z-drugs had the highest proportions doctor shopped. Flunitrazepam had the highest proportion doctor shopped in 2010 (8.85 %), while buprenorphine had the highest in 2019 (6.92 %) (Fig. 1A). Several drugs from other pharmacological classes also exhibited high proportions doctor shopped, in particular pregabalin (1.40 % in 2019). The proportion doctor shopped increased for opioids during the study period, in particular for oxycodone (from 0.71 to 1.41 %), fentanyl (from 0.83 to 1.34 %), and tramadol (from 0.37 to 0.59 %). The proportions doctor shopped accounted for heterogeneous quantities doctor shopped due to marked differences in use levels across drugs (Fig. 1B). In most cases, the quantity doctor shop-

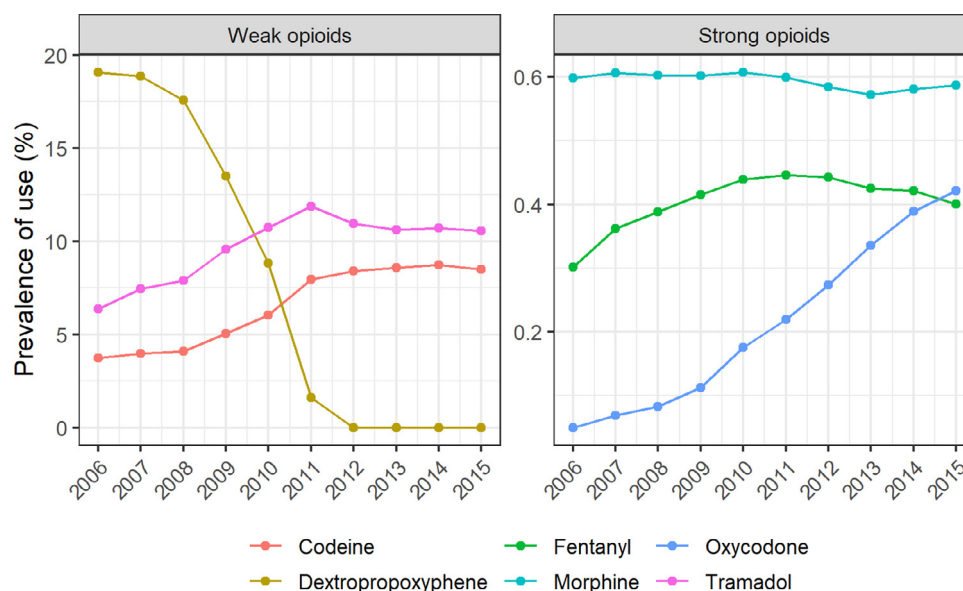


Figure 2. Prevalence of use of opioid analgesics in France from 2006 to 2015 according to the DANTE study [29].

ped was higher for benzodiazepines and Z-drugs than for opioids. When considering both indicators, pregabalin had the sharpest increase in the proportion doctor shopped (from 0.28 to 1.40 %), in parallel with a sharp increase in quantity (from 0.7 to 6.6 DDD/100,000 inhabitants/day). Oxycodone had the sharpest increase in the quantity doctor shopped (from 0.1 to 1.1 DDD/100,000 inhabitants/day), in parallel with a sharp increase in the proportion doctor shopped (from 0.71 to 1.41 %). Similar trends, though to a lesser extent, were observed for fentanyl and tramadol. Detailed results for all drugs can be explored interactively at <https://soeiro.gitlab.io/megadose/>.

Overall, these results constitute a national overview of the dynamics of prescription drug abuse in the general population. Implementing systematic, regular monitoring of doctor shopping would offer crucial information for more effectively targeting regulatory interventions and assessing their impact. Finally, this drug-centered approach (i.e., aggregating patient-level behaviors into drug-level indicators) aligns with the signal detection efforts of the French Addictovigilance Network, in collaboration with the French Medicine Agency. The ongoing MONITO study pursue this monitoring with more recent data and to refine the results (e.g., by stratifying by formulations, doses, or geographical areas). In addition, the METEOR study, also ongoing, aims to further characterize health trajectories (i.e., incidence of drug abuse and impact on hospitalizations and deaths) of new users of gabapentinoids (i.e., pregabalin and gabapentin), opioid analgesics (i.e., morphine, oxycodone, fentanyl, and tramadol), and opioid agonist treatments (i.e., buprenorphine and methadone).

Trends of opioid and non-opioid analgesic use

Analgesics are among the most widely used drugs worldwide. Their use has been increasing steadily in France over the past 15 years [25–27]. Several pain management plans have been implemented since 1998 to address the under-

treatment of pain, particularly cancer pain. These plans have raised awareness of the importance of treating pain and have transformed pain management practices. In addition, significant changes in the availability of analgesics on the French market have occurred in recent years, in particular:

- new pharmaceutical forms, strengths, and generics has been marketed, leading to a high number of available products (e.g., more than hundred tramadol containing products);
- indication of oxycodone and fentanyl have been extended to non-cancer pain;
- dextropropoxyphene, i.e., the most widely used opioid analgesic in the 2000s, was withdrawn in France in 2011 [28].

In this context, the DANTE study aimed to assess trends in analgesic use, focusing on the prevalence of use and the demographic profiles of analgesic users by age and sex [29]. In this repeated cross-sectional study using a 1/97 sample of the SNDS, all prevalent user of analgesics (i.e., peripheral analgesics, weak opioid analgesics and nefopam, and strong opioid analgesics) aged 18 and older were included from 2006 to 2015.

The annual prevalence of analgesic use increased from 55.6 % in 2006 ($n=218,579$) to 59.8 % in 2016 ($n=253,976$). It was higher in women (66.3 % in women vs. 52.6 % in men in 2015) and it increased with age except in patients aged 85 years and older. Overall, paracetamol was the most used (52.6 % in 2015). Among opioid analgesics, dextropropoxyphene was the most used bar far in 2006, but its use steadily decreased until its withdrawal in 2011 (Fig. 2). Concurrently, the prevalence of codeine and tramadol use sharply increased, making them the most used opioid analgesics in 2015. Overall, the decline in weak opioid analgesic use, driven by the dextropropoxyphene withdrawal, was not fully compensated by the increase in other drugs. Among strong opioid analgesics, morphine was the most used since 2006 (0.6 %), with a stable prevalence of use over the decade. The

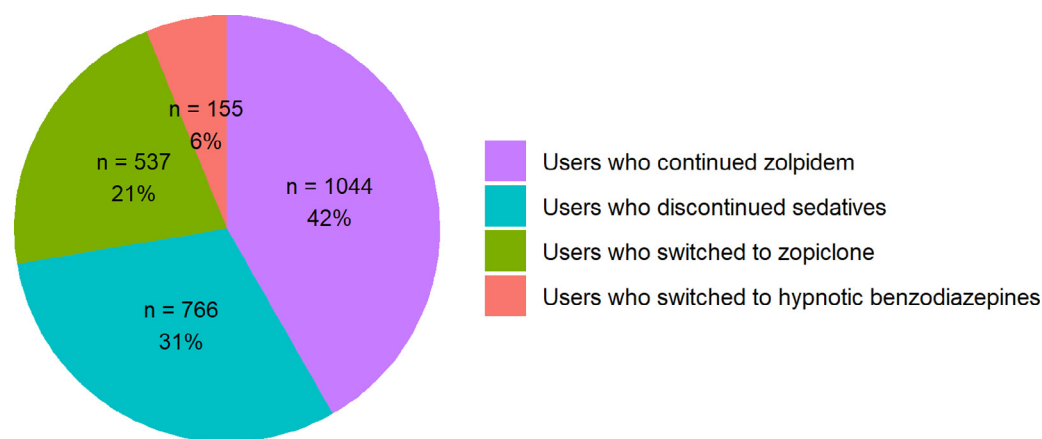


Figure 3. Distribution of the four clusters of zolpidem users in France from October 2016 to December 2018 according to the ZORRO study [39]. The French Medicine Agency announced on 2017/01/11 that zolpidem will have to be prescribed on secure prescription forms as of 2017/04/10.

prevalence of fentanyl use was low. The prevalence of oxycodone use constantly increased, matching that of fentanyl in 2015. Although this prevalence remained low, there were still ten times more patients who were dispensed oxycodone in 2015 compared to 2006. The increase in oxycodone use was primarily driven by an increase in women and in patients aged 65 years and older, particularly those aged 85 years and older.

Further analysis focused on analgesic switching in chronic users of dextropropoxyphene [30]. Overall, 63,671 patients had a dispensing of dextropropoxyphene/paracetamol reimbursement in the year prior to its withdrawal, including 7.1% who were identified as chronic users. Among the patients who were taking dextropropoxyphene/paracetamol alone at the time of its withdrawal: 1/4 switched to a peripheral analgesic; 1/4 switched to a combination of peripheral analgesic and opioid; 1/4 switched to another opioid; and 1/4 discontinued their treatment (14.1%) or died (7.9%).

Overall, prevalence of analgesic use was high in France over the study period, mainly for peripheral analgesics, while opioid analgesics were used much less frequently. These studies also showed that regulatory interventions can significantly impact pattern of drug use and require vigilance. While there are emerging signals of opioid abuse in France, the country still appears to be far from an opioid crisis. However, given these signals and the international context, there is a need to implement preventive and harm-reduction measures in France. This includes training health professionals in pain management and identifying substance use disorders.

Impact of regulatory intervention on zolpidem

Zolpidem was initially marketed as an “alternative” to benzodiazepines, with early clinical trials showing no evidence of abuse and dependence [31]. It subsequently became one of the most prescribed hypnotics in France. However, cases abuse and dependence of zolpidem have since been identified [32–34], in particular:

- users who abuse high doses seeking paradoxical effects (e.g., euphoria, exaltation and hyperactivity);

- chronic users for therapeutic purpose who increase doses due to tolerance. In response, the French Medicine Agency announced on 2017/01/11 that zolpidem will have to be prescribed on secure prescription forms as of 2017/04/10. This intervention resulted in a significant decrease in the prevalence of zolpidem use [35,36].

One year after the enforcement, the prevalence of zopiclone prescriptions had sharply increased [37]. This prompted the need to further assess the impact of the regulatory intervention.

In this context, the ZORRO study aimed to assess the impact of secure prescription forms on the use of zolpidem and other sedatives (zopiclone, benzodiazepines, and antihistamines) [38,39]. In this cohort study on a 1/97th permanent representative sample of the SNDS, all patients aged 18 years and older and long-term users of zolpidem before the intervention (i.e., patients who were dispensed zolpidem at least once in October, November, and December 2016) were included.

Overall, 2502 patients were included. The mean age was 66 years and most patients were women (66.8%). Using state sequence analysis, a four-cluster typology was found (Fig. 3): users who continued zolpidem ($n=1044$, 42%); users who discontinued sedatives ($n=766$, 31%); users who switched to zopiclone ($n=537$, 21%); and users who switched to hypnotic benzodiazepines ($n=155$, 6%). Switch to zopiclone and hypnotic benzodiazepines were mainly long term. In multivariate analysis, women were more likely to belong to continue zolpidem (1.44 [1.20 to 1.72]). Patients with treatment for addictive or psychiatric disorders were more likely to switch to zopiclone (1.23 [1.01 to 1.50]) or hypnotic benzodiazepines (1.33 [0.95 to 1.87]). Extensive use of zolpidem before the intervention was associated with continued use of zolpidem (4.13 [3.12 to 5.52] for ≥ 180 DDD).

Further analysis focused on the impact of the intervention on patterns of zolpidem use [40]. Respectively 15,550 and 8301 zolpidem users were identified before and after the intervention. Using latent class analysis, similar profiles of zolpidem users were identified before and after the intervention: non-problematic users, who were the most

prevalent; users whose drug use suggest psychiatric disorder; and potential problematic users, who accounted for a lower absolute number of patients after the intervention.

The intervention appeared to have long-term effectiveness in decreasing zolpidem use and also had a broad impact on prescriptions of other sedatives. It suggests that physicians perceived the intervention as a warning about the risks of zolpidem, which led to a decrease in the number of zolpidem prescriptions, as previously seen for flunitrazepam in 2001 [41]. In addition, the intervention also appeared to have a positive impact on the patterns of zolpidem use.

Where are we now?

After two decades of utilization, the value of these databases for assessing the abuse of psychoactive drugs is now widely acknowledged [6,7]. These studies are crucial because they enable to assess prescription drug abuse at a national level, in the general population, and for all psychoactive drugs. Given the proliferation of data sources and the increasing volume of available information, the primary challenge lies in extracting relevant information from a medical and a public health standpoint. Therefore, from the initial hypotheses to the interpretation of results, these studies are conducted in light of all available pharmacological knowledge.

In France, the added value of the pharmacoepidemiological surveillance of prescription drug abuse is its integration within the complementary data sources of the French Addictovigilance Network. To fully understand its contribution, it is needed to highlight the complementarity of these results with the routine systems of the French Addictovigilance Network.

As a public health vigilance system, the primary objective of addictovigilance is the detection of previously unknown safety signals [42,43]. This objective drives the implementation of the French Addictovigilance Network programs, which are designed to be both sensitive and responsive. This approach is further strengthened by the close collaboration between the French Addictovigilance Network and various field actors (e.g., addictologists, algologists, toxicologists, in addition to physicians and pharmacists). The detection of tropicamide abuse (i.e., intravenous use of high doses seeking for its central anticholinergic effects) is an illustrative example among many others of the capacity to detect signals early, even those of low magnitude [44]. The signal was identified following the report of falsified prescriptions in Southwest France.

In addition to these reactive methods, pharmacoepidemiological approaches can provide comprehensive results in the general population. These characteristics make pharmacoepidemiology particularly well suited for quantifying risks, and thus for confirming, comparing, and prioritizing signals. It can thus also facilitate more effective targeting and prioritization of regulatory interventions. Furthermore, pharmacoepidemiology is also capable of signal detection, as demonstrated with oxycodone. In fact, the first signal of oxycodone abuse in France was identified in 2008 through interregional comparisons of doctor shopping for opioid analgesics [45].

Conclusion

Pharmacoepidemiology fits in the multifaceted monitoring conducted by the French Addictovigilance Network and complements the other data sources of this framework. This approach improves signal detection, confirmation, and quantification. It also makes it possible to overcome the limitations of each data source taken individually.

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Disclosure of interest

The authors declare that they have no competing interest.

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