Received: 24 January 2023 | Revised: 27 April 2023 | Accepted: 6 May 2023

DOI: 10.1111/acps.13582

Acta Psychiatrica Scandinavica WILEY

ORIGINAL ARTICLE

Risk of suicide attempt and suicide associated with benzodiazepine: A nationwide case crossover study

Marie Tournier[1,2] | **Anne Bénard-Laribière**[1] | **Fabrice Jollant**[3,4] | **Emilie Hucteau**[1] | **Papa-Yatma Diop**[1] | **Ana Jarne-Munoz**[1] | **Antoine Pariente**[1,5] | **Emmanuel Oger**[6] | **Julien Bezin**[1,5]

[1]University of Bordeaux, INSERM, BPH, Team AHeaD, U1219, Bordeaux, France

[2]Hospital Charles Perrens, Bordeaux, France

[3]Moods Research Team, INSERM UMR-1178, CESP, Le Kremlin-Bicêtre, France

[4]Department of Psychiatry, School of Medicine, University Paris-Saclay & Academic Hospital (CHU) Bicêtre, APHP, Le Kremlin-Bicêtre, France

[5]CHU de Bordeaux, Clinical Pharmacology Unit, INSERM, U1219, Bordeaux, France

[6]EA 7449 REPERES (Pharmacoepidemiology and Health Services Research), Rennes 1 University, Rennes, France

Correspondence
Marie Tournier, University of Bordeaux, Bordeaux Population Health Research Centre, INSERM U1219, Case 121, PHARMACIE 4, 3ème étage, 146 rue Léo Saignat, 33076 Bordeaux cedex, France.
Email: mtournier@ch-perrens.fr

Funding information
French Medicines Agency (ANSM), Grant/Award Number: 2019S015

Abstract

Background: Previous studies that found an association between benzodiazepines and suicidal behaviours were confounded by indication bias.

Aims: To limit this bias, a case crossover study (CCO) was conducted to estimate the risk of suicide attempt and suicide associated with benzodiazepines.

Method: Patients ≥16 years, with hospitalised suicide attempt or suicide between 2013 and 2016, and at least one benzodiazepine dispensing within the 120 days before their act were selected in the nationwide French reimbursement healthcare system databases (SNDS). For each patient, frequency of benzodiazepine dispensing was compared between a risk period (days −30 to −1 before the event) and two matched reference periods (days −120 to −91, and −90 to −61).

Results: A total of 111,550 individuals who attempted suicide and 12,312 suicide victims were included, of who, respectively, 77,474 and 7958 had recent psychiatric history. Benzodiazepine dispensing appeared higher in the 30-day risk period than in reference ones. The comparison yielded adjusted odds ratios of 1.74 for hospitalised suicide attempt (95% confidence interval 1.69–1.78) and 1.45 for suicide (1.34–1.57) in individuals with recent psychiatric history, and of 2.77 (2.69–2.86) and 1.80 (1.65–1.97) for individuals without.

Conclusion: This nationwide study supports an association between recent benzodiazepine use and both suicide attempt and suicide. These results strengthen the need for screening for suicidal risk carefully before initiation and during treatment when prescribing benzodiazepines. Registration No. EUPAS48070 (http://www.ENCEPP.eu).

KEYWORDS

benzodiazepines, reimbursement healthcare databases, self-controlled study, suicide and suicide attempt

1 | INTRODUCTION

Psychiatric disorders and symptoms are among the main risk factors for suicidal behaviours.[1] Even though some pharmacological and psychological treatments showed preventive effectiveness, most drugs used to treat them did not show a clear effectiveness in preventing suicidal behaviours and some of them might increase suicide risk.[2–7] The impact of benzodiazepines on the risk of suicidal behaviours is unknown.[8] Previous studies found a positive and significant association between benzodiazepine exposure and both suicide death and suicide attempts, in the general population or in patients with psychiatric disorders as well.[9–13] They were however affected by potential indication bias where the causal association links the outcome to the condition being treated but not to exposure to treatment. Authors adopted various designs to minimise this bias, such as cohorts[14–16] or matched case–control studies[13,17] with statistical adjustments for sleep disturbances, mood disorders, history of suicidal behaviours, other psychotropic drugs and other risk factors for suicide. Some showed a dose-effect relationship, both short- (1 week) and long-term (up to 1 year).[13,15,18,19] However, residual confounding by indication could not be ruled out. Mechanisms that might be involved in this association remain unclear and are subject to various assumptions. They might be causal, direct (disinhibition, cognitive impairment, dissociative behaviour, parasomnia) or indirect (depression, rebound insomnia or anxiety).[8,12] Moreover, as the relationship was shown cumulative in some studies, the role of repeated withdrawal or of long-term lowering of the brain activation level that might limit the ability to compensate some pre-existing cognitive disturbances might be suggested.[20] In this context of uncertainty, this study aimed at estimating the risk of suicide attempt and suicide death associated with recent exposure to benzodiazepines in patients with or without recent psychiatric history using methods minimising confounding factors.

Significant outcomes

- The association between benzodiazepines and suicidal behaviours has to be clarified to inform evidence-based practice guidelines for suicidal risk management.
- The occurrences of suicide attempt or suicide were associated with recent exposure to benzodiazepine (i.e., in the previous 30 days) compared with former exposure.
- Benzodiazepine prescription should be avoided in patients presenting with suicidal ideation without careful clinical assessment and monitoring.

Limitations

- The present study did not allow assessing a potential dose-effect relationship between benzodiazepine and suicidal behaviours and was only designed to investigate a short-term association.
- The study did not allow distinguishing between the various hypotheses of mechanisms underlying such an association: suicidal ideation triggering, facilitating effect on the transition from ideation to act, cognitive impairment, dissociative behaviour, parasomnia, or psychiatric symptoms worsening.

2 | MATERIALS AND METHODS

2.1 | Study design

A nationwide study was conducted using data from the French reimbursement healthcare system (SNDS) from 1 January 2013 through 31 December 2016. A case crossover (CCO) study compared the presence of benzodiazepine exposure immediately before the suicidal outcome (risk period) with exposure within reference periods earlier in time for each individual with suicidal outcome. This within-person comparison design allows self-adjusting over a short period for individual factors not typically recorded in medicoadministrative healthcare databases and not likely to change over such a short period of time, such as psychiatric symptoms or disorders (insomnia, depression, anxiety), substance or alcohol use, social isolation, financial difficulties, or family history of suicide. This design is especially adapted to study acute events and intermittent exposures.[21] An important assumption of the CCO design is that intermittent exposures have stable prevalence over time; potential exposure-trend bias was thus examined in a sensitivity analysis.

The CCO analyses were performed in patients with an identified suicide attempt or suicide and with at least one dispensing of benzodiazepine in the preceding 120 days. Since benzodiazepine treatment is issued for a maximum of 30 days in France, we considered periods of 30 days for exposure assessment. The odds of benzodiazepine use were compared between the risk period (days −30 to −1 before the suicidal act) and two matched reference periods (days −120 to −91, and −90 to −61 before the suicidal

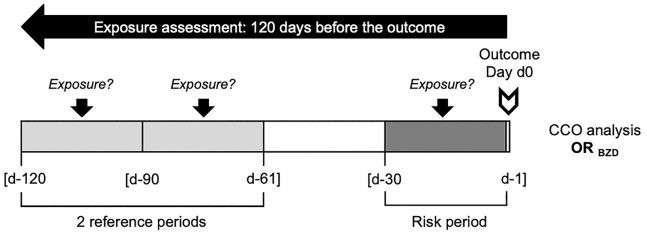

FIGURE 1 Diagram of the case-crossover design for studying the association between benzodiazepine dispensing and the occurrence of suicide attempt or suicide.

act). Benzodiazepines dispensed on the day of the act were not considered. A washout gap of 30 days between risk and reference periods prevented any residual effect of an exposure in reference periods on the act (Figure 1).

2.2 | Data source

French Health Insurance SNDS database consists of three nationwide databases: the national health insurance database (DCIR), the national hospital discharge database (PMSI), and the national causes-of-death registry (BCMD).[22,23]

The DCIR database comprises the anonymous and exhaustive recording of all reimbursements of outpatient-dispensed healthcare expenditure, including drugs, physician visits, lab tests or imaging investigations. Indications for prescribing are not available in the database. The database includes medical diagnoses related to long term chronic diseases and disabilities eligible for full reimbursement of health care. The PMSI database provides some medical information (including diagnoses) on all admissions to private and public settings in France; this database is linked with data from DCIR by the personal identification number, a unique identifier assigned to all French residents. Drugs administered during hospital stays are not available in the database. Causes of death are linked to DCIR and PMSI databases only after a delay of 4 years due to long manual data quality validation procedures of manuscript death certificates. The study focused on the beneficiaries of the general health insurance scheme for employees and retirees (77% of the French population), as exhaustive information on the date of death, necessary for linkage to causes-of-death data, is only available for this scheme.

2.3 | Suicide attempt and suicide death

The suicidal outcomes were hospitalised suicide attempts and suicide deaths. In the SNDS database, only acts leading to a hospitalisation can be studied. Hospitalised suicide attempts were identified through the hospital discharge codes from the international classification of diseases, 10th revision (ICD-10; X60-X84 for intentional self-harm). The date of hospital admission was used as the date of outcome (index date). Suicides were identified through the causes-of-death registry as those with an ICD-10 codes X60-X84 as well. The date of death was the index date. While intentional self-harm does not equal to suicide attempt or suicide, the fact that only hospitalised acts or death are measured here suggest that most of them were considered severe and probably suicidal. For individuals who died in hospital with a diagnostic code of suicide attempt, the outcome was considered as a suicide and the date of hospital admission as the index date. This method has been performed in previous studies.[24,25]

2.4 | Exposure to benzodiazepines

All benzodiazepines indicated for anxiety and for insomnia, as well as the related drugs zolpidem and zopiclone, were considered (Table S1). Injectable forms were not considered in the present study, as well as benzodiazepines exclusively used as an anticonvulsant or anaesthetic (clonazepam, midazolam). As benzodiazepines cannot be obtained over-the-counter and that their dispensing always leads to reimbursement in France, their use was identified from reimbursements information. Therefore, patients were considered exposed within one of the studied periods of interest if they have been reimbursed for at least one dispensing of a benzodiazepine during this period. The day of benzodiazepine dispensing was used as a proxy for drug initiation.

2.5 | Study populations

Eligible participants were all patients who carried out a suicide attempt or suicide (outcome) between 1 January 2013 and 31 December 2016 (index date); were aged 16 and over at that date; and had at least one benzodiazepine dispensing in the 120 days preceding the index date. Exclusion criteria were a history of hospitalisation with an intentional self-harm code in the 6 months preceding the observation period (patients with a recent self-harm behaviour might be more likely to both receive a benzodiazepine treatment and repeat such a behaviour); and at least one dispensing for midazolam or clonazepam in the observation period or in the year before.

In these, the risk of suicide attempt and suicide was assessed within two populations: patients who were not treated for a psychiatric disease over the year preceding the period of exposure assessment (i.e., the observation period, Figure 1), and patients who were treated for a psychiatric disease over this period. The latter were

defined as patients fulfilling at least one of the following criteria in the year preceding the observation period: hospitalisation in a psychiatry department; long-term disease or disability status for one or more psychiatric disorders; at least one dispensing of psychotropic drugs (antidepressants, or antipsychotics, or lithium, or anticonvulsants used as mood stabilisers, i.e., carbamazepine, valproate, valpromide, and lamotrigine).

By agreement of the French Data Protection Supervisory Authority (CNIL), neither ethics committee approval nor informed consent were required for this observational study based on anonymized French medicoadministrative databases.

2.6 | Statistical analysis

Conditional logistic regression models were used to estimate the crude and adjusted odds ratios of suicidal behaviours associated with benzodiazepine over the risk period compared with the reference periods. Given the short observation period (120 days), age and comorbidities were considered fixed over all periods (risk and reference). Models were adjusted for time-varying confounders, that is, drugs likely to impact the risk of suicidal acts (antidepressants, antipsychotics, mood stabilisers, non-benzodiazepine anxiolytics and hypnotics) (Table S2); exposure to these drugs was defined as dispensing within risk or reference periods. Moreover, they were considered as proxy for acute psychiatric episodes and statistical adjustment allowed minimising confounding by indication. Subgroup analyses were conducted according to sex, age (<25 years, 25–65 years, and >65 years), and benzodiazepine elimination half-life (<20 h and ≥20 h). To assess the impact of benzodiazepine exposure independently of other psychotropic drugs, analyses were also performed in patients with and without other psychotropic drugs within the observation period.

Sensitivity analyses concerned: varying lengths of risk and reference periods (15 and 45 days); performing another CCO analysis using cyamemazine (a phenothiazine neuroleptic widely used as an anxiolytic and hypnotic in France) as a negative control with similar risk of indication bias. Cyamemazine is the most prescribed antipsychotic drug in France, for its sedative and anxiolytic component.[26] For this purpose, the main CCO analysis among benzodiazepine users was restricted to those who did not have cyamemazine dispensing during the observation period; similarly, a second CCO was conducted among cyamemazine users who did not have benzodiazepine dispensing within the observation period. The associations between cyamemazine and suicidal behaviours reflected confounding by indication bias and was used to amend the associations between benzodiazepines and suicidal behaviours. Finally, the ratio of adjusted odds ratios (adjusted odds ratio for CCO in benzodiazepine users, divided by adjusted odds ratio for CCO in cyamemazine users) yielded an estimate for the association of benzodiazepine use and the risk of suicidal outcomes controlled for the risk of indication bias (Appendix S1 and Figure S1). In addition, a case–case-time-control model was performed to examine whether the main CCO analysis was confounded by a time trend in benzodiazepine use (Appendix S2 and Figure S2).

Data were analysed using SAS Enterprise Guide® statistical software (SAS Institute, version 9.4, NC, United States).

3 | RESULTS

The selection of patients with suicide attempt or suicide eligible is detailed in Figure 2. Their main characteristics are described in Table 1.

3.1 | Population without a recent psychiatric history

The CCO analysis included 34,076 patients hospitalised for suicide attempt and 4354 suicide victims with at least one benzodiazepine dispensing in the previous 120 days. Within the risk period (days −30 to −1 before suicidal outcome), general practitioners prescribed the majority of benzodiazepines (77% (30,722/39,877 benzodiazepine dispensings) among patients who attempted suicide, and 75.2% (3859/5133 dispensings) among suicide victims). Benzodiazepine dispensing was more frequent within the 30 days before suicide attempt (adjusted odds ratio 2.77; 95% confidence interval 2.69–2.86) and suicide death (1.80; 1.65–1.97) than in the reference periods.

The association between suicide attempt or suicide and recent benzodiazepine dispensing varied across subgroup analyses (Figure 3). The strongest association was found in men hospitalised for suicide attempt (3.08; 2.93–3.23). Age-stratified estimates suggested a greater association between benzodiazepines and suicide (2.13; 1.89–2.40) in patients aged 25–65 years. A similar association with benzodiazepines was observed in those aged under 25 years with respect to suicide attempt (3.92; 3.62–4.25). Owing to the low number of cases regarding suicide under 25 years ($n = 66$), the association could not be computed. The association of suicide with recent exposure to short half-life benzodiazepines was higher than that with recent exposure to longer half-life benzodiazepines (1.85; 1.68–2.04 vs. 1.29; 1.12–1.48, respectively).

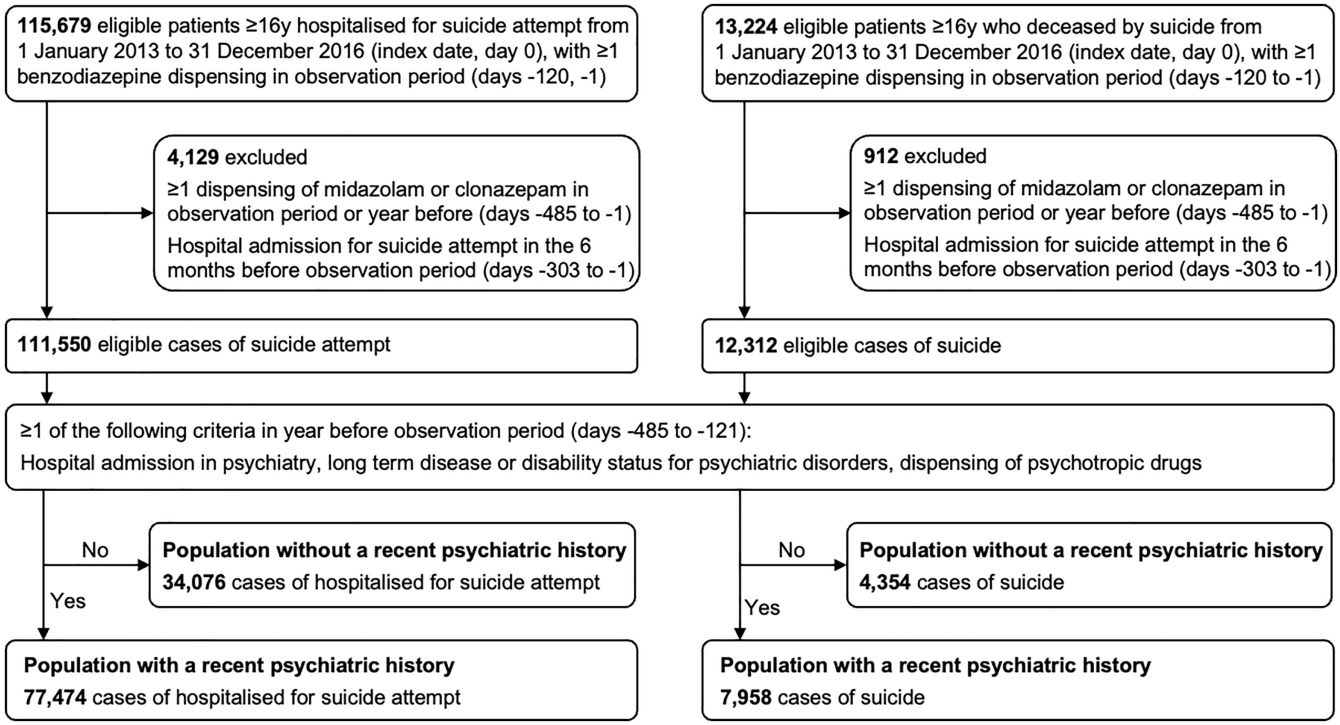

FIGURE 2 Flow-chart of cases with suicide attempt or suicide, and according to recent psychiatric history.

In patients with no other psychotropic drug use, an increased odds ratio was found for suicide attempt (3.17; 3.06–3.29) and for suicide (1.88; 1.70–2.09) in presence of recent benzodiazepine exposure compared with former exposure. In patients taking other psychotropic drugs in addition to benzodiazepines, an increased odds ratio was also found for suicide attempt (1.90; 1.79–2.02) and for suicide (1.60; 1.35–1.90), adjusting for the use of antidepressants, antipsychotics, mood stabilisers, and non-benzodiazepine anxiolytics and hypnotics.

3.2 | Population with a recent psychiatric history

A total of 77,474 cases of suicide attempt hospitalisation and 7958 cases of suicide death with at least one benzodiazepine dispensing in the previous 120 days were included in the analyses. Within the risk period, roughly 60% of benzodiazepines were prescribed by a general practitioner (57.9% (78,612/135,670 benzodiazepine dispensings) among patients who attempted suicide, and 56% (7250/12,952 dispensings) among suicide victims). Benzodiazepine dispensing was more frequent within the 30 days before suicide attempt (1.74; 1.69–1.78) and suicide (1.45; 1.34–1.57) than in the reference periods.

Men had a stronger association between benzodiazepines and suicide attempt than women (1.95; 1.86–2.03 vs. 1.64; 1.59–1.69) (Figure 3). Also, patients aged under 25 years and aged 25–65 years had higher odds ratios of suicide attempt in the presence of recent benzodiazepine use than those aged 65 years and more (1.88; 1.70–2.07 and 1.78; 1.73–1.83 vs. 1.45; 1.35–1.56). The odds ratio of suicide in the presence of recent exposure to short half-life benzodiazepines was higher than that in the presence of recent exposure to long half-life benzodiazepine for suicide (1.48; 1.36–1.60 vs. 1.18; 1.08–1.29).

In patients with no other psychotropic drugs, an increased odds ratio was found for suicide attempt (2.31; 2.17–2.46) and for suicide (1.45; 1.20–1.75) when benzodiazepine was dispensed in the 30 days preceding suicidal outcome. In patients taking other psychotropic drugs in addition to benzodiazepines, an increased odds ratio was also found for suicide attempt (1.64; 1.59–1.68) and for suicide (1.45; 1.33–1.58), adjusting for the use of these other drugs.

3.3 | Sensitivity analyses

Sensitivity analyses confirmed the robustness of our main findings (Figure 3; detailed results provided in Tables S3 and S4). Sensitivity analyses varying the length of the periods (15 and 45 days) produced similar results. Sensitivity analysis exploring the possibility of residual confounding bias by indication, using cyamemazine as a

TABLE 1 Baseline characteristics of the populations with and without a recent psychiatric history.

	Population without a recent psychiatric history		Population with a recent psychiatric history	
	Suicide attempt $N = 34{,}076$ *n* (%)	Suicide $N = 4354$ *n* (%)	Suicide attempt $N = 77{,}474$ *n* (%)	Suicide $N = 7958$ *n* (%)
Age (m, SD)	44.8 (18.0)	61.2 (18.4)	48.8 (15.0)	56.7 (16.0)
Male sex	14,240 (41.8)	3382 (77.7)	25,651 (33.1)	4649 (58.4)
Social deprivation index[a]				
Quintile 1 (the least deprivation)	3939 (12.7)	504 (12.1)	9921 (13.7)	1021 (13.6)
Quintile 2	5172 (16.6)	673 (16.2)	11,969 (16.5)	1226 (16.3)
Quintile 3	6170 (19.8)	831 (20.0)	15,511 (21.4)	1605 (21.4)
Quintile 4	7280 (23.4)	995 (23.9)	17,055 (23.5)	1845 (24.6)
Quintile 5 (the most deprivation)	8530 (27.4)	1153 (27.7)	18,021 (24.9)	1817 (24.2)
Number of different non-psychotropic drugs used in the 6 months before the observation period (median, IQR)	6 (2–10)	7 (3–12)	7 (4–12)	7 (3–12)
Characteristics in the 12 months before the observation period				
Stay in non-psychiatric department	10,230 (30.0)	1448 (33.2)	34,507 (44.5)	3545 (44.5)
Stay in psychiatric department			23,371 (30.2)	2380 (29.9)
Public psychiatric consultation			27,666 (35.7)	2319 (29.1)
Private psychiatric consultation			2094 (2.7)	264 (3.3)
Other psychotropic dispensing				
Antidepressant			67,960 (87.7)	6992 (87.9)
Antipsychotic			33,439 (43.2)	3609 (45.4)
Mood stabiliser[b]			13,263 (17.1)	1181 (14.8)
Non-BZD anxiolytic and hypnotic			22,331 (28.8)	1930 (24.3)
Drug for alcohol or substance use disorders			10,841 (14.0)	860 (10.8)

Abbreviations: BZD, benzodiazepines; IQR, inter quartile range.
[a]Unknown for French overseas territories.
[b]Lithium, valproate, valpromide, carbamazepine, and lamotrigine.

negative control, confirmed the association found in the main analysis. For suicide attempt, the analysis yielded a ratio of adjusted odds ratio (adjusted odds ratio for CCO in benzodiazepine users, divided by adjusted odds ratio for CCO in cyamemazine users) of 1.80 (1.53–2.12) among the population with a recent psychiatric history, and of 2.15 (1.76–2.64) in the other population. For suicide, ratio of adjusted odds ratio was 1.66 (1.03–2.70) in the population with a recent psychiatric history but could not be computed in the population without a recent psychiatric history owing to the low number of suicides among individuals exposed to cyamemazine in this population (Figure 3).

Finally, the main results were replicated in the case–case-time-control analysis, in both the population without a recent psychiatric history (ratio of adjusted odds ratio of 2.56 (2.44–2.69) for suicide attempt, and of 1.35 (1.13–1.62) for suicide), and the population with a recent psychiatric history (ratio of adjusted odds ratio of 1.77 (1.70–1.85) for suicide attempt, and of 1.36 (1.18–1.57) for suicide; Figure 3).

4 | DISCUSSION

4.1 | Main results

Recent exposure to benzodiazepine (i.e., in the previous 30 days) was significantly associated with the occurrence of suicide or suicide attempt requiring a hospitalisation compared with former exposure. This association was found in patients with and without a recent psychiatric history, but was stronger in people without. Sensitivity analyses led to similar findings, including the use of a negative control (cyamemazine) to minimise bias of confounding by

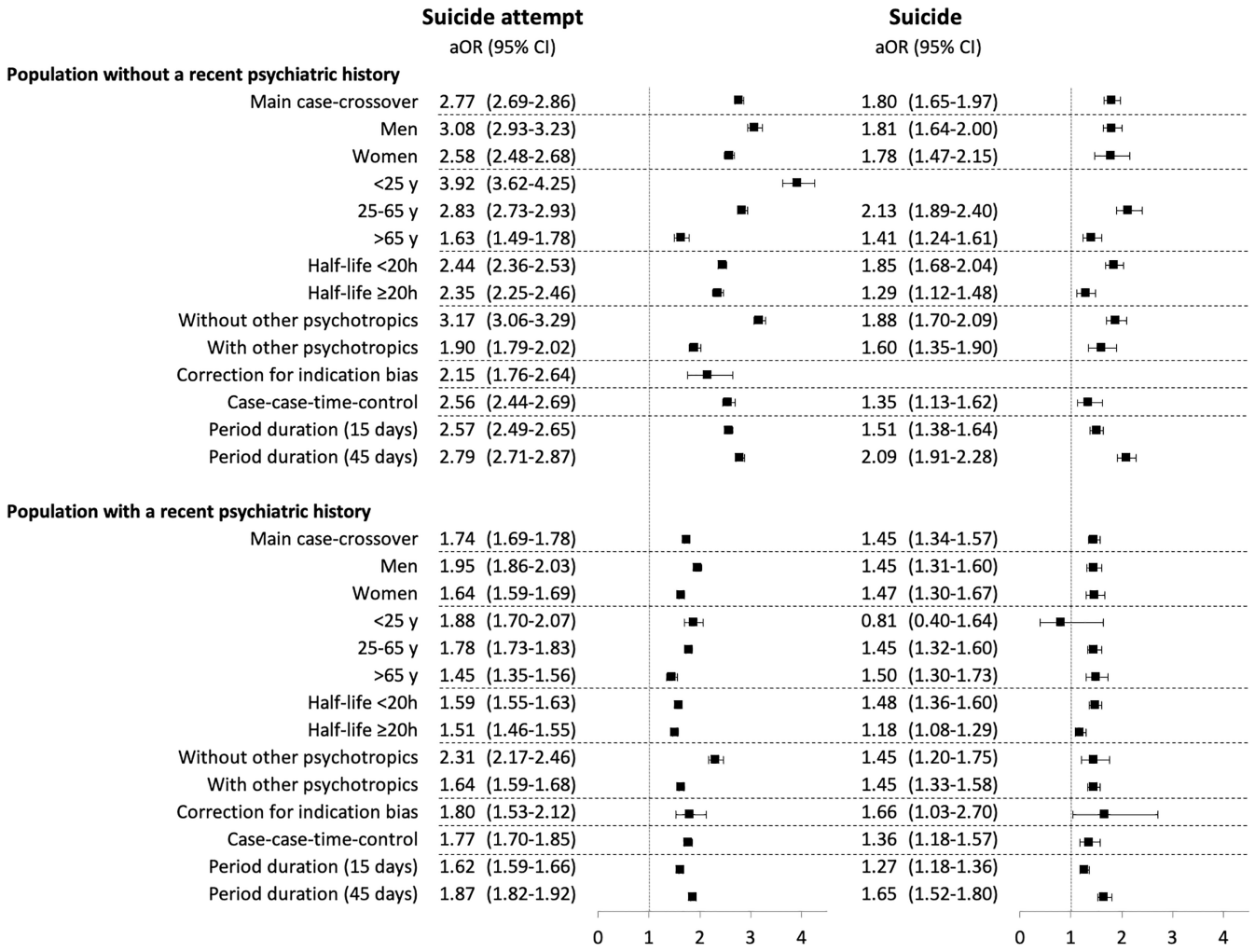

FIGURE 3 Association between both suicide attempt and suicide and benzodiazepine. Estimates presented are adjusted odds ratio (OR) with their 95% confidence interval, and ratio of OR for sensitivity analyses.

indication. The association between suicidal outcomes and recent exposure to benzodiazepine was higher in men than in women, when short half-life drugs were used, and in patients receiving no other psychotropic drugs. The odds ratio of suicide attempt when exposed to benzodiazepine was higher in people aged under 65 years, and the odds ratio of suicide as well but only when they had no recent psychiatric history.

4.2 | Strengths and limitations

This study is based on large nationwide database. Design and numerous sensitivity analyses minimised biases and particularly confounding by indication. However, some limitations should be mentioned. Benzodiazepines overdose is a frequent method of suicidal behaviour in France, particularly of suicide attempt, and their dispensing might make the method available instead of triggering suicidal act. To avoid this bias, benzodiazepine dispensings that occurred on the day of suicidal acts were not considered. Moreover, in suicide cases, overdoses were rare in these samples; violent methods accounted for 92.2% of cases in patients without a recent psychiatric history and 89.2% of cases in patients with a recent psychiatric history. The database did not allow including suicide attempts that did not require hospitalisation.[27] However, the most severe and life-threatening acts are hospitalised and therefore included in analyses. Moreover, the ICD-10 coding system does not allow distinguishing between non-suicidal and suicidal intentional self-harming acts. However, deliberate self-harms leading to hospitalisation or death are very likely to correspond to suicidal behaviours. Similarly, some suicides might be missing as some deaths might be misclassified as accidental or of unknown cause. As in any observational study, dispensing does not mean drug ingestion. Some patients might be dispensed benzodiazepine without any intake

and, conversely, some patients might use some pills that were dispensed a long time ago. All these information biases should impact the associations found only if they are differential and, in this case, associations would be underestimated. Finally, some time-dependent risk factors for suicidal behaviours were not available in the database and residual confounding cannot be ruled out.

4.3 | Interpretation of results

The study found an association between recent dispensing of benzodiazepines and both suicide attempts and death, providing further support for a potential contribution of benzodiazepines to suicidal risk. Design, statistical adjustments and sensitivity analyses allowed considering time-invariant characteristics, such as personal and family psychiatric history, and individual factors unlikely to change over a short period of time, such as psychiatric symptoms or disorders; therefore, minimising confounding by indication that was the main limitation of previous studies.[8] Despite similar indications, the association found remained after adjustment for non-benzodiazepine anxiolytics or hypnotics and was significantly stronger than the association between cyamemazine and suicide attempt or suicide. The present study did not allow assessing a potential dose-effect relationship and was only designed to investigate a short-term association, future research should focus on a cumulative risk over time with benzodiazepine exposure. Similarly, the study did not allow distinguishing between the various hypotheses of mechanisms: suicidal ideation triggering, facilitating effect on the transition from ideation to act, cognitive impairment, dissociative behaviour, parasomnia, or psychiatric symptoms worsening.

In the present study, the association between both suicide attempt and suicide death and recent dispensing of benzodiazepines or of other psychotropic drugs was stronger in people without any recent psychiatric history. Patients with a recent psychiatric history might benefit from other types of care and support such as psychotherapy and from previously acquired self-help skills with a good preventive effectiveness such as safety planning.[28] Others particular associations found are more difficult to explain based on the present study. The particular effect found with short half-life drugs might relate to repeated withdrawals or with more varying level of exposure and stronger associations found in men and non-elderly might be linked to a proneness to impulsive behaviours. This has to be further investigated. To conclude, even though potential mechanisms of the association between benzodiazepines and suicidal acts are not elucidated, mounting arguments should make the prescribers aware and cautious especially as treatment exposure complied the short duration recommended by practice guidelines. Additional safety precautions might be relevant in men, with short half-life drugs and when the benzodiazepine is prescribed as monotherapy. All prescribers of benzodiazepines should be regularly trained to the assessment of suicidal risk, particularly general practitioners as they initiated most benzodiazepine treatments in the population we studied. In the week before suicide death, a third of victims contacted health services, most often their general practitioners for mental health purpose.[29]

ACKNOWLEDGEMENTS

We thank Moussa Laanani (French National Health Insurance, Paris, France) for his valuable comments on the method used for the identification of suicidal acts in the SNDS database.

FUNDING INFORMATION

Supported by the French Medicines Agency (ANSM) (grant number 2019S015), in the context of a partnership with the Health Product Epidemiology Scientific Interest Group (EPI-PHARE). The ANSM played no role in the study design, conduct, and results interpretation or discussion. This publication represents the views of the authors and does not necessarily represent the opinion of the ANSM.

CONFLICT OF INTEREST STATEMENT

Co-authors declare no conflict of interest.

ORCID

Marie Tournier https://orcid.org/0000-0002-5054-5805
Anne Bénard-Laribière https://orcid.org/0000-0002-9071-6314
Fabrice Jollant https://orcid.org/0000-0001-5809-4503

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13582.

DATA AVAILABILITY STATEMENT

Data are made available by the national healthcare insurance system for academic purpose. No additional data available by author (French law to access SNDS https://www.snds.gouv.fr).

REFERENCES

1. Macalli M, Navarro M, Orri M, et al. A machine learning approach for predicting suicidal thoughts and behaviours among college students. *Sci Rep*. 2021;11(1):11363.

2. Tournier M. A need for personalised suicidology: pharmacoepidemiology. In: Courtet P, ed. *Understanding suicide*. Springer International Publishing; 2016:403-413.
3. Wilkinson ST, Trujillo Diaz D, Rupp ZW, et al. Pharmacological and somatic treatment effects on suicide in adults: a systematic review and meta-analysis. *Depress Anxiety*. 2022;39(2):100-112.
4. Zalsman G, Hawton K, Wasserman D, et al. Suicide prevention strategies revisited: 10-year systematic review. *Lancet Psychiatry*. 2016;3(7):646-659.
5. Jiang T, Rosellini AJ, Horvath-Puho E, et al. Using machine learning to predict suicide in the 30 days after discharge from psychiatric hospital in Denmark. *Br J Psychiatry*. 2021;219(2):440-447.
6. Chen PH, Tsai SY, Chen PY, et al. Mood stabilizers and risk of all-cause, natural, and suicide mortality in bipolar disorder: a nationwide cohort study. *Acta Psychiatr Scand*. 2022;147:234-247.
7. Sorensen JO, Rasmussen A, Roesbjerg T, Verhulst FC, Pagsberg AK. Suicidality and self-injury with selective serotonin reuptake inhibitors in youth: occurrence, predictors and timing. *Acta Psychiatr Scand*. 2022;145(2):209-222.
8. McCall WV, Benca RM, Rosenquist PB, et al. Hypnotic medications and suicide: risk, mechanisms, mitigation, and the FDA. *Am J Psychiatry*. 2017;174(1):18-25.
9. Ahlm K, Saveman BI, Bjornstig U. Drowning deaths in Sweden with emphasis on the presence of alcohol and drugs – a retrospective study, 1992-2009. *BMC Public Health*. 2013;13:216.
10. Brower KJ, McCammon RJ, Wojnar M, Ilgen MA, Wojnar J, Valenstein M. Prescription sleeping pills, insomnia, and suicidality in the National Comorbidity Survey Replication. *J Clin Psychiatry*. 2011;72(4):515-521.
11. Darke S, Deady M, Duflou J. Toxicology and characteristics of deaths involving zolpidem in New South Wales, Australia 2001-2010. *J Forensic Sci*. 2012;57(5):1259-1262.
12. Dodds TJ. Prescribed benzodiazepines and suicide risk: a review of the literature. *Prim Care Companion CNS Disord*. 2017;19(2):16r02037.
13. Shih HI, Lin MC, Lin CC, et al. Benzodiazepine therapy in psychiatric outpatients is associated with deliberate self-poisoning events at emergency departments-a population-based nested case-control study. *Psychopharmacology (Berl)*. 2013;229(4):665-671.
14. Lecat N, Fourrier-Reglat A, Montagni I, et al. Association between anxiolytic/hypnotic drugs and suicidal thoughts or behaviors in a population-based cohort of students. *Psychiatry Res*. 2020;291:113276.
15. Tiihonen J, Mittendorfer-Rutz E, Torniainen M, Alexanderson K, Tanskanen A. Mortality and cumulative exposure to antipsychotics, antidepressants, and benzodiazepines in patients with schizophrenia: an observational follow-up study. *Am J Psychiatry*. 2016;173(6):600-606.
16. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. *Arch Gen Psychiatry*. 2012;69(5):476-483.
17. Cato V, Hollandare F, Nordenskjold A, Sellin T. Association between benzodiazepines and suicide risk: a matched case-control study. *BMC Psychiatry*. 2019;19(1):317.
18. Cho CH, Jee HJ, Nam YJ, An H, Kim L, Lee HJ. Temporal association between zolpidem medication and the risk of suicide: a 12-year population-based, retrospective cohort study. *Sci Rep*. 2020;10(1):4875.
19. Sun Y, Lin CC, Lu CJ, Hsu CY, Kao CH. Association between zolpidem and suicide: a nationwide population-based case-control study. *Mayo Clin Proc*. 2016;91(3):308-315.
20. Pariente A, de Gage SB, Moore N, Begaud B. The benzodiazepine-dementia disorders link: current state of knowledge. *CNS Drugs*. 2016;30(1):1-7.
21. Maclure M, Fireman B, Nelson JC, et al. When should case-only designs be used for safety monitoring of medical products? *Pharmacoepidemiol Drug Saf*. 2012;21(Suppl 1):50-61.
22. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: from the systeme national d'information interregimes de l'Assurance Maladie (SNIIRAM) to the systeme national des donnees de sante (SNDS) in France. *Rev d'epidemiol Sante Publique*. 2017;65-(Suppl 4):S149-S167.
23. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 2017;26(8):954-962.
24. Droitcourt C, Nowak E, Rault C, et al. Risk of suicide attempt associated with isotretinoin: a nationwide cohort and nested case-time-control study. *Int J Epidemiol*. 2019;48(5):1623-1635.
25. Laanani M, Imbaud C, Tuppin P, et al. Contacts with health services during the year prior to suicide death and prevalent conditions a nationwide study. *J Affect Disord*. 2020;274:174-182.
26. Kovess-Masfety V, Balusson F, Leray E, Husky M, Scailteux LM. Prescription patterns of first- and second-generation antipsychotic drugs in the French population. *Fundam Clin Pharmacol*. 2020;34(5):603-611.
27. Jollant F, Hawton K, Vaiva G, Chan-Chee C, du Roscoat E, Leon C. Non-presentation at hospital following a suicide attempt: a national survey. *Psychol Med*. 2020;52(4):1-8.
28. Stanley B, Brown GK, Brenner LA, et al. Comparison of the safety planning intervention with follow-up vs usual care of suicidal patients treated in the emergency department. *JAMA Psychiat*. 2018;75(9):894-900.
29. John A, DelPozo-Banos M, Gunnell D, et al. Contacts with primary and secondary healthcare prior to suicide: case-control whole-population-based study using person-level linked routine data in Wales, UK, 2000-2017. *Br J Psychiatry*. 2020;217(6):717-724.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tournier M, Bénard-Laribière A, Jollant F, et al. Risk of suicide attempt and suicide associated with benzodiazepine: A nationwide case crossover study. *Acta Psychiatr Scand*. 2023;1-9. doi:10.1111/acps.13582