Risk of first ischaemic stroke and use of antidopaminergic antiemetics: nationwide case-time-control study

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ABSTRACT

OBJECTIVE

To estimate the risk of ischaemic stroke associated with antidopaminergic antiemetic (ADA) use.

DESIGN

Case-time-control study.

SETTING

Data from the nationwide French reimbursement healthcare system database Système National des Données de Santé (SNDS).

PARTICIPANTS

Eligible participants were ≥18 years with a first ischaemic stroke between 2012 and 2016 and at least one reimbursement for any ADA in the 70 days before stroke. Frequencies of ADA reimbursements were compared for a risk period (days -14 to -1 before stroke) and three matched reference periods (days -70 to -57, -56 to -43, and -42 to -29) for each patient. Time trend of ADA use was controlled by using a control group of 21 859 randomly selected people free of the event who were individually matched to patients with stroke according to age, sex, and risk factors of ischaemic stroke.

MAIN OUTCOME MEASURES

Association between ADA use and risk of ischaemic stroke was assessed by estimating the ratio of the odds ratios of exposure evaluated in patients with stroke and in controls. Analyses were adjusted for time varying confounders (anticoagulants, antiplatelets, and prothrombotic or vasoconstrictive drugs).

RESULTS

Among the 2612 patients identified with incident stroke, 1250 received an ADA in the risk period and 1060 in the reference periods. The comparison with the 5128 and 13 165 controls who received an ADA in the same periods yielded a ratio of adjusted odds ratios of 3.12 (95% confidence interval 2.85 to 3.42). Analyses stratified by age, sex, and history of dementia showed similar results. Ratio of adjusted odds ratios for analyses stratified by ADA was 2.51 (2.18 to 2.88) for domperidone, 3.62 (3.11 to 4.23) for metopimazine, and 3.53 (2.62 to 4.76) for metoclopramide. Sensitivity analyses suggested the risk would be higher in the first days of use.

CONCLUSIONS

Using French nationwide exhaustive reimbursement data, this self-controlled study reported an increased risk of ischaemic stroke with recent ADA use. The highest increase was found for metopimazine and metoclopramide.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antipsychotics are central antidopaminergic drugs; typical and atypical antipsychotics have been associated with an increased risk of ischaemic stroke

Domperidone, metopimazine and metoclopramide are peripherally acting antidopaminergics used as antiemetics; metopimazine and metoclopramide are also low potency central antidopaminergics

Whether the risk of stroke highlighted for antipsychotics could extend to other antidopaminergics including antiemetics is not known

WHAT THIS STUDY ADDS

Use of antidopaminergic antiemetics is associated with an increased risk of ischaemic stroke

The highest risk was observed for metopimazine and metoclopramide

The central effect of metopimazine and metoclopramide and their potential action on cerebral blood flow could explain this higher risk

Introduction

The risk of ischaemic stroke with centrally acting antidopaminergic antipsychotics has been highlighted in large observational studies, especially in older patients and among people with dementia.[1-3] The risk is considerable at the start of treatment, 12 times higher in the first month of use, and progressively declines over time and falls to baseline after three months of treatment.[4-6] Dopamine receptor antagonism is the main determinant of antipsychotic action. Although antipsychotics also block a variety of other receptors (muscarinic, histaminergic, serotoninergic, adrenergic), possible mechanisms by which these drugs might cause stroke could relate to this dopamine antagonism.[6] Research is lacking on the risk of stroke for non-antipsychotic dopamine receptor antagonists, such as antidopaminergic antiemetics (ADAs). ADAs are peripheral D2 receptor antagonists with a direct effect on the chemoreceptor trigger zone, which lies outside the blood-brain barrier. However, some ADAs, such as metoclopramide, cross the blood-brain barrier and are also low potency central antidopaminergics. Moreover, stroke occurrence can be triggered by mechanisms that do not require any crossing of the blood-brain barrier because blood vessels are located outside the blood-brain barrier. ADAs are widely used in general practice for the treatment of nausea and vomiting of different causes (migraine, chemotherapy or radiotherapy, postoperative). Given the well known risk of ischaemic stroke associated with antidopaminergic antipsychotics and the widespread use of ADAs, we assessed the association between ischaemic stroke and ADAs in a real world setting.

Methods

We conducted a nationwide study from 1 January 2012 to 31 December 2016 using data from the French

reimbursement healthcare system (Système National des Données de Santé (SNDS), formerly SNIIRAM). We used a case-time-control design, which implies the conduct of two self-adjusted analyses, a case crossover analysis, and a time trend control crossover analysis. The case crossover design derives from the case-control approach; it can be considered for the study of short transient exposures and acute effects when 'the best control for each case is the case itself with, as reference, exposure data from another point in time'.[7] In this case only analysis, cases are used as their own control, which allows self-adjusting over a short period for individual time invariant characteristics that are not recorded in medico-administrative healthcare databases, such as average physical activity, diet, habitual health behaviours, or body mass index. A caveat to this case crossover approach is that the estimated odds ratios for associations, obtained solely from the exposure of cases at different points in time, could represent the increase in drug use associated with the event occurrence and the natural increase in drug use over time. The case-time-control design was developed to allow this potential bias to be eliminated.

In this design, the first case crossover analysis performed in cases is completed by a second and similar analysis performed in controls free of the disease and selected at a time corresponding to that of inclusion of the cases considered for the initial case crossover analysis. This second crossover analysis performed in time trend controls and its results are used to remove from the odds ratios obtained in the case crossover the part of the associations that could relate to a natural increase in drug use. In the context of this study, such a bias relating to a time trend in exposure could have occurred, especially because of a general decreasing trend in ADA use over the study period,[8] but also because of a seasonal trend related to acute gastroenteritis epidemics.[9] This approach justified the performance of a case-time-control analysis, including a case crossover analysis and a time trend control crossover analysis (fig 1).

The case crossover analysis was performed in patients who presented with an ischaemic stroke and received an ADA at one moment in time. Because marketing approval for ADAs is only for short term use, we considered periods of 14 days for exposure assessment. To estimate the association within each period, the probability of ADA use was compared between a risk period (days -14 to -1 before stroke) and three matched reference periods (days -70 to -57, -56 to -43, and -42 to -29 before stroke). A 14 day washout gap between risk and reference periods prevented any residual effect of an exposure in reference periods on the event.

The time trend control crossover analysis was performed in a time trend control group composed of randomly selected people individually matched up to 10 patients according to sex, age at patient's index date, and risk factors of stroke in the two years preceding the index date (hypertension, dyslipidaemia, diabetes, chronic kidney disease, atrial fibrillation, ischaemic heart disease, depression, and smoking). Controls were recruited at the same time as the patients with stroke to take into account the time trend of ADA use, and were assigned the corresponding patient's index date.

Data source

The French health insurance SNDS database, linked with the national hospital discharge database (PMSI), contains information on at least 99% of the French population. The database consists of the anonymous and exhaustive recording of all reimbursements to outpatients for dispensed healthcare, including drugs, physician visits, laboratory tests, or imaging investigations. For each reimbursed drug, data collected in the database include date of dispensing, active ingredients, route of administration, pill dosage, number of pills per packaging, but not the prescribed daily dosage. The date of dispensing corresponds to the day on which treatment is delivered. Indications for prescribing and the results of medical procedures or laboratory tests are not available on the database. However, SNDS includes medical diagnosis information relating to costly and severe long term diseases eligible for full reimbursement of healthcare and discharge diagnosis from hospital. Details on the French medico-administrative databases have been described in greater detail elsewhere.[10]

This study focused on the beneficiaries of the major health insurance scheme for employees (salaried workers and their relatives, retired salaried workers and their relatives); that is, 77% of the French population for whom the SNDS database has comprehensively recorded data since 2006.

Ischaemic stroke

The outcome of interest was an incident hospital admission for ischaemic stroke identified through hospital discharge codes as the primary discharge diagnosis from the international classification of diseases, 10th revision (ICD-10; I63.0-I63.5, I63.8, I63.9). Because the identification of transient ischaemic attacks in medico-administrative databases is less reliable, we decided not to consider them for this analysis and to focus only on ischaemic stroke.[11] The onset of stroke (index date) was defined as the date of the first hospital admission for stroke.

Exposure

The studied ADAs were domperidone, metopimazine, and metoclopramide. All of these drugs act as D2 antagonists at the chemoreceptor trigger zone and at the gastric level. Metopimazine and metoclopramide also penetrate the blood-brain barrier, in contrast to domperidone, which is consequently less prone to producing central adverse effects. Injectable forms were not considered because their use is almost exclusively in hospital settings. Patients were considered to have received one of these drugs during a period of interest if they had been reimbursed for at least one dispensing during this period. All prescribed ADA dispensings lead to reimbursement in France. The day of ADA dispensing was used as a proxy for start of treatment.

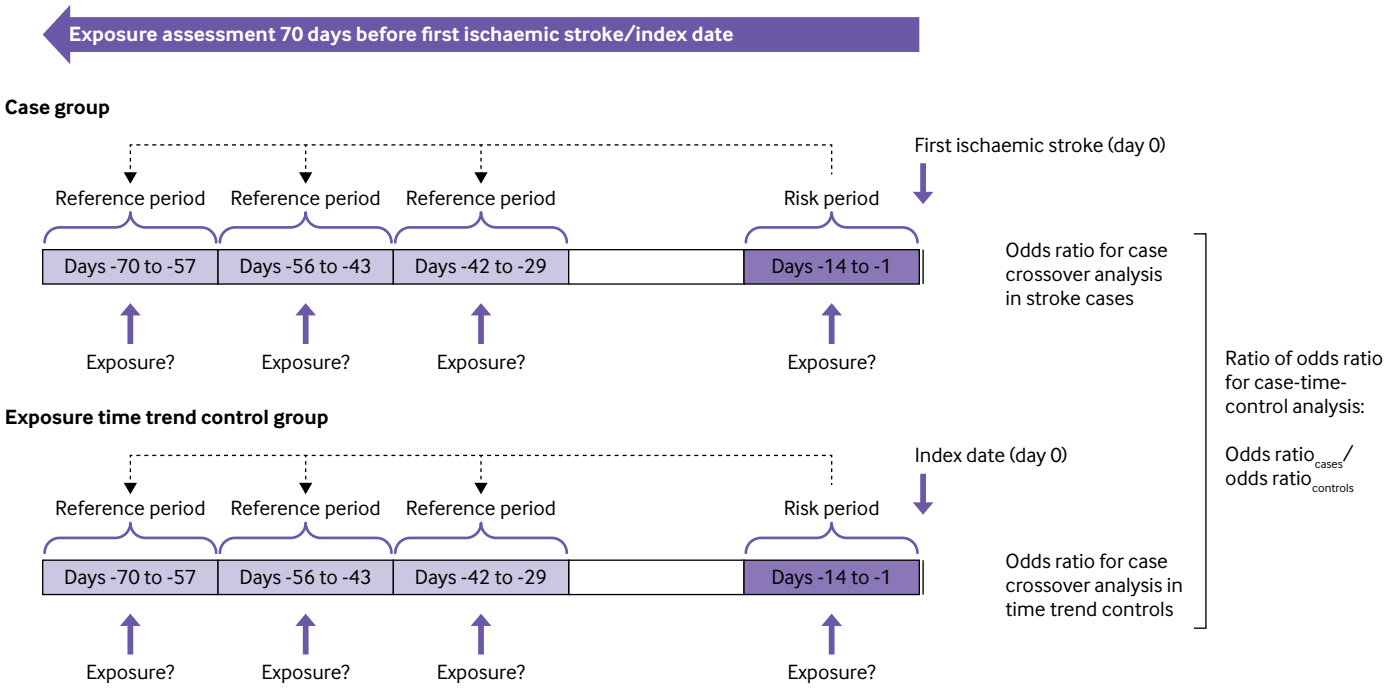

Fig 1 | Diagram of the case-time-control design for studying the effect of antidopaminergic antiemetic use on risk of first ischaemic stroke

Study population

Eligible participants were all patients registered on the database who had a diagnosis of first ischaemic stroke between 1 January 2012 and 31 December 2016 (index date); were aged ≥18 at that date; had no history of cerebrovascular disease before the index date (identified through long term diseases and hospital discharge codes from ICD-10 (I60-I64, I69, G45); were affiliated with the major health insurance scheme at least during the year of outcome occurrence; had at least one reimbursement for any ADA (domperidone, metoclopramide, metopimazine) in the 70 days before ischaemic stroke occurrence (the observation period); and no reimbursement for these drugs in the year before the observation period. Exclusion criteria were a history of cancer; at least one reimbursement for the fixed association metoclopramide aspirin in the observation period or in the year before because the potential impact of metoclopramide might be inaccurately assessed in this setting; hospital admission in the observation period because data on ADA use in hospital were not available from the database. The same eligibility criteria were applied when identifying the time trend control group (with the exception of the event of interest).

Statistical analysis

We used a conditional logistic model to estimate matched odds ratios and 95% confidence intervals among patients with stroke and controls.[7] Given the short observation period (70 days), age and comorbidities were considered fixed during all periods (risk and reference). Our model was adjusted for time varying confounders, which were drugs that enhance the risk of stroke (including drugs with prothrombotic effects, non-steroidal anti-inflammatory drugs, and vasoconstrictive drugs such as triptans and ergot derivatives indicated for migraine attack), or protect against it (anticoagulants and antiplatelet drugs); table S1 provides a full list of covariates. A patient was considered to have received one of the ADAs when a reimbursement for the drug occurred during risk or reference periods. The case crossover analyses compared exposure frequencies from the risk period and the three reference periods for each patient with stroke, and each time trend control. The case-time-control ratio of adjusted odds ratios (adjusted odds ratio for case crossover in stroke cases divided by adjusted odds ratio for case crossover in time trend controls) yielded an estimate for the association of ADA use and the risk of ischaemic stroke which was not biased by the time trends in ADA use.

We also conducted subgroup analyses according to sex, age (<70 years and ≥70 years), history of dementia, and the type of ADA used (domperidone, metopimazine, metoclopramide) among patients who used only one type of ADA during the observation period. Because gastroenteritis could be treated by ADA and might lead to important dehydration, which conveys a subsequent risk of ischaemic stroke, we also performed subgroup analysis according to periods of gastroenteritis epidemics.[12]

We performed several sensitivity analyses: using risk periods of seven days (days -7 to -1) and 21 days (days -21 to -1; reference periods adapted accordingly); and extending the population to patients with a history of

hospital admission during the 70 days before the index date.

We specifically explored the potential for protopathic bias related to the prescription of ADAs for stroke prodromes and therefore associated with the subsequent diagnosis of stroke by performing sensitivity analyses that censored for exposure assessment during the last days before the date of the event. We censored the day of stroke plus the two preceding days (risk period: days -14 to -3), and the day of stroke plus the six preceding days (risk period: days -14 to -7; reference periods adapted accordingly). Data were analysed using SAS Enterprise Guide statistical software (SAS Institute, version 9.4, North Carolina, United States).

Patient and public involvement

There was no specific patient or public involvement activity planned for this study. This did not result from lack of funding or specific difficulty; the study indeed did not encounter difficulty in access to data. Simply, the study was part of the 2021 research programme of the DRUGS-SAFER Center. The Center is funded by the French Drug Agency ANSM and its research programme is defined yearly based on the propositions made by the Center's researchers and on the needs identified by the GIS EPI-PHARE, a structure founded jointly by the ANSM and the French Health Insurance. No patient or public involvement is planned a priori for the studies conducted by the Center using the nationwide data from the French Health Insurance system (SNDS).

Results

In total, 2824 patients with first ischaemic stroke who received ADA during the observation period (70 days before stroke) fulfilled eligibility criteria. Of these, 2612 were matched to at least one control and included in the analyses (fig 2).

Table 1 describes the main characteristics of the matched patients with stroke, time trend controls, and non-matched patients with stroke. The mean (standard deviation) age of matched patients was 71.9 years (16.2), and 33.9% (885/2612) were men. Figure 3 shows dates when ADA treatment was started over the observation period; a peak of treatment initiation was observed in the few days before stroke (fig S1 provides distribution of ADA initiation among controls).

Among patients with stroke, 1250 received ADA in the risk period (days -14 to -1 before stroke), and 1060 in at least one reference period (days -70 to -57, -56 to -43, and -42 to -29 before stroke). The population of time trend controls comprised 21 859 people. Among them, 5128 and 13 165 received ADA at least once in the risk and reference periods, respectively. This yielded a case-time-control ratio of adjusted odds ratios of 3.12 (95% confidence interval 2.85 to 3.42; table 2). Analyses stratified by age (<70 years and ≥70 years), sex, history of dementia, and gastroenteritis epidemic periods showed similar results. The highest case-time-control ratio of adjusted odds ratios was observed in men: 3.59 (3.06 to 4.20; table S2).

During the observation period, 97.3% (2542/2612) of patients with stroke received a single type of ADA. Of these, and after a new matching process including the type of ADA, the case-time-control ratio of adjusted odds ratios was 2.51 (2.18 to 2.88) for domperidone, 3.62 (3.11 to 4.23) for metopimazine, and 3.53 (2.62 to 4.76) for metoclopramide (table 2).

A sensitivity analysis that used risk and reference periods of seven days showed a higher risk of 4.66 (4.14 to 5.25); a period of 21 days showed a lower risk (2.59, 2.37 to 2.82). The results of a sensitivity analysis that included patients with a history of hospital admission in the 70 days before stroke did not differ from the main analysis (table S3). For the sensitivity analyses that explored the possibility of protopathic bias, the ratio of adjusted odds ratios was 2.32 (2.09 to 2.57) when censoring the date of stroke plus the two preceding days for exposure assessment; when we censored the day of stroke plus the six preceding days, the ratio of adjusted odds ratios was 1.75 (1.53 to 2.00; table S4).

Discussion

Principal findings

We investigated the relation between the use of ADAs and the risk of ischaemic stroke by performing a nationwide case-time-control study. We found evidence that new users of ADA presented with an increased risk of stroke shortly after treatment started. The risk appeared to increase for all ADAs, the highest increase being found for metopimazine and metoclopramide. The results were similar in subgroup analyses stratified by age, sex, history of dementia, and gastroenteritis epidemic periods.

Strengths and weaknesses of the study

The major strength of this study is the use of a self-controlled design that eliminates between-person confounding for time invariant factors. This design has great value when unmeasured confounding is a major concern, especially when using medico-administrative databases for which environmental factors are not usually collected. This approach allowed us to self-adjust for time fixed risk factors over the short observation period that are not captured in the database, such as physical activity, diet, habitual health behaviours, and body mass index. Moreover we used the case-time-control design, which was conceived to remove bias due to exposure time trends from the case crossover estimate.[7] Even if confounding by indication cannot be completely ruled out using case only designs, the additional analyses performed that considered periods of gastroenteritis epidemics did not support a confounding relating to the gastroenteritis indication. Furthermore, we adjusted for exposure to drugs indicated for the treatment of migraine attacks (non-steroidal anti-inflammatory drugs, triptans, and ergot derivatives) as time dependent covariates, which could reduce the impact of such bias, if any. Moreover, to assess the robustness of the main analysis and circumvent a potential protopathic bias, we performed sensitivity analyses in which we censored for exposure

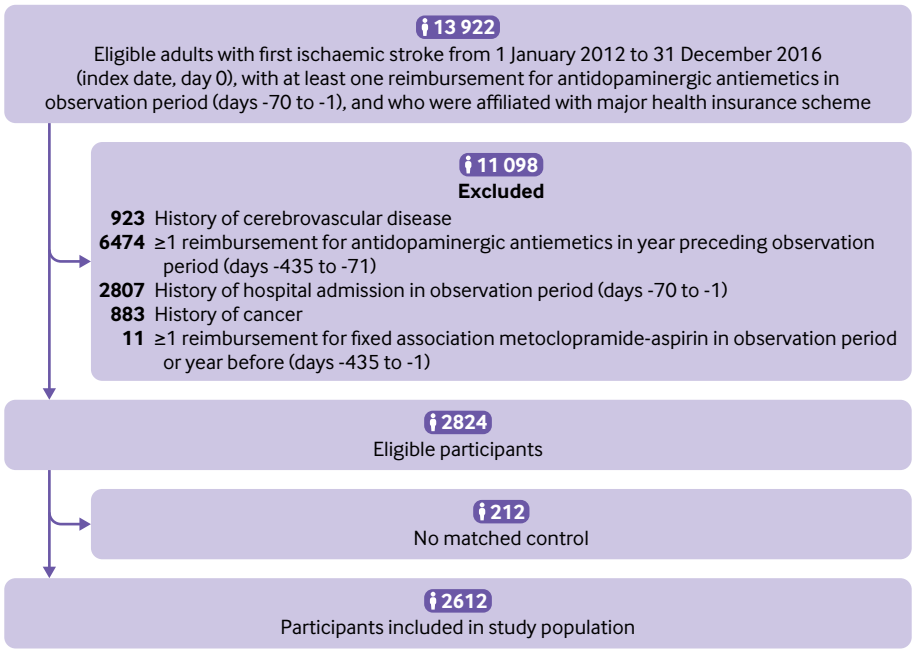

Fig 2 | Flow chart of eligible participants included in study population

assessment in the days preceding the date of hospital admission for stroke. The association between ADA use and the risk of ischaemic stroke was also observed in these sensitivity analyses, which does not support the hypothesis of a protopathic bias.

Another strength of this study is that we used the SNDS, which is a comprehensive database for all out-of-hospital healthcare expenditures, covering more than 99% of the French population (almost 66 million people); it also includes comprehensive information on hospital stays. Although the SNDS is not primarily intended for research, ICD-10 codes for ischaemic stroke showed a high diagnostic accuracy.[13 14] Therefore, misclassifications relating to coding errors should be minimal. However, as case identification was only possible from hospital admission diagnoses, our analysis could not take into account patients who died before hospital admission.

Table 1 | Characteristics of patients with stroke and matched time trend controls, and non-matched patients. Data are numbers (percentages) unless stated otherwise

Characteristics	Non-matched patients (n=212)	Matched patients (n=2612)	Time trend controls (n=21 859)
Age (years), mean (SD)	81.8 (13.7)	71.9 (16.2)	70.2 (16.3)
Men	95 (44.8)	885 (33.9)	7063 (32.3)
Hypertension*	178 (84.0)	1808 (69.2)	14 382 (65.8)
Dyslipidaemia*	110 (51.9)	967 (37.0)	7503 (34.3)
Chronic kidney disease*	181 (85.4)	629 (24.1)	4546 (20.8)
Smoking*	90 (42.5)	577 (22.1)	3967 (18.6)
Diabetes*	101 (47.6)	558 (21.4)	3867 (17.7)
Depression*	87 (41.0)	532 (20.4)	3784 (17.3)
Atrial fibrillation*	150 (70.8)	220 (8.4)	895 (4.1)
Ischaemic heart disease*	107 (50.5)	219 (8.4)	1038 (4.8)
Heart failure	42 (19.8)	153 (5.9)	590 (2.7)
Obesity	22 (10.4)	94 (3.6)	552 (2.5)
Alcohol addiction	2 (0.9)	46 (1.8)	225 (1.0)

*Matching variables.

This study also has some limitations that are inherent when performing observational studies using medico-administrative databases. Firstly, ADA use was assessed using reimbursement data, from which the actual ADA use can only be assumed; the day of ADA dispensing has been used as a proxy for start of drug treatment as usually done in observational studies based on health insurance data. ADAs are used to treat symptoms of nausea and vomiting of variable origin. With the exception of preventive treatment for chemotherapy or radiotherapy induced nausea and vomiting, ADAs are prescribed for the immediate relief of symptoms, and start of treatment is expected to be close to the date of drug dispensing. Because the situation differs for preventive treatment in patients receiving chemotherapy or radiotherapy when it is more difficult to assume the date of treatment initiation from the date of dispensing, patients with a history of cancer were not included in the study population. We also assumed that the potential misclassification of the exposure, relating to actual drug use or treatment start, should be non-differential between risk and reference periods, and so would not affect the association estimates.

Secondly, the database provides exhaustive recording of prescribed and reimbursed drugs. If all ADAs can be prescribed, and domperidone and metoclopramide can only be obtained by medical prescribing, metopimazine is also available over the counter. Therefore, all exposures to this ADA have not been captured. However, here again, there is no reason to believe that this misclassification would differ between risk and reference periods. Thirdly, the database does not include information on prescribed daily dose or on prescription duration. In this context,

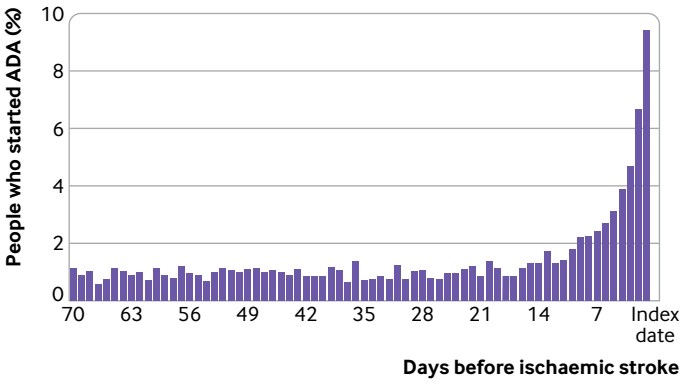

Fig 3 | Proportion of people who started antidopaminergic antiemetic (ADA) treatment during the 70 days before ischaemic stroke (n=2612). Total of histogram bars equals 100%

owing to the large range of possible daily dosages (from 10 to 30 mg/day for domperidone or metoclopramide, and from 7.5 to 30 mg/day for metopimazine), we considered it would not be appropriate to presume daily dosages from dispensed drug quantities and therefore irrelevant to perform dose-response analysis from the database.

Finally, the database does not contain information on ischaemic stroke subtypes. This lack of information precluded further investigation of possible mechanisms by which ADAs might cause stroke; it also prevented us from further exploring a potential protopathic bias. This bias is a concern because it could be hypothesised that stroke potential prodromic symptoms of nausea could have led to ADA use. However, such prodromes are mostly encountered in posterior fossa ischaemic strokes and having information on stroke subtypes would therefore have been of great value to explore such bias.[15] Because we did not have this information, we had to perform sensitivity analyses in which we censored for exposure assessment in the days preceding the date of hospital admission for stroke to avoid this potential bias. The results are important for our conclusions. The association found in the main analysis was consistently found in these sensitivity analyses; however, substantial variations were observed in the association estimate, with a decrease in the estimate progressing with the intensity of exposure assessment censoring. Two competing hypotheses could explain this phenomenon. The first would relate it to a protopathic bias by which the closest exposures would be consecutive to early symptoms of the disease. Under this hypothesis, the increase in the risk of stroke potentially attributable to ADA use would still remain important but might correspond to only a 1.5-fold increase. The second hypothesis would relate this decrease to the exact hypothesis initially proposed for this risk increase owing to the findings for conventional or atypical antipsychotics; that is, an increase that would especially concern the first days of use. The decrease would therefore be assumed to strengthen the results of the main analysis and the estimate of a 3.5-fold increase. To distinguish between these hypotheses we require information on the nature of the ischaemic stroke, data that are lacking from the database. Therefore, because the association was consistently found in all analyses, a clear indication exists that the risk of ischaemic stroke is associated with the use of ADAs. However, we found substantial variations in the association estimates, and so additional studies are needed. To complete the evidence provided, these studies should consider the types of ischaemic stroke and use other designs that could also provide information on outcome incidences.

Table 2 | Results of the main analysis. Crude and adjusted ratio of odds ratios for overall ADA use, and stratified by type of ADA. Data are numbers unless stated otherwise

		ADA use		Odds ratio (95% CI)	
ADA use	No of people	Risk period	Reference period*	Crude	Adjusted
Overall ADA use					
CCO cases	2612	1250	1060	3.59 (3.31 to 3.91)	3.55 (3.26 to 3.87)
CCO controls	21 859	5128	13 165	1.14 (1.10 to 1.18)	1.14 (1.10 to 1.18)
CTC ratio	—	—	—	3.16 (2.89 to 3.46)	3.12 (2.85 to 3.42)
Domperidone					
CCO cases	1150	502	511	3.02 (2.66 to 3.42)	3.00 (2.63 to 3.40)
CCO controls	8888	2158	5308	1.19 (1.13 to 1.25)	1.19 (1.13 to 1.26)
CTC ratio	—	—	—	2.54 (2.22 to 2.91)	2.51 (2.18 to 2.88)
Metopimazine					
CCO cases	939	476	348	4.10 (3.56 to 4.71)	4.08 (3.54 to 4.70)
CCO controls	6824	1524	4026	1.12 (1.06 to 1.19)	1.13 (1.06 to 1.20)
CTC ratio	—	—	—	3.65 (3.14 to 4.24)	3.62 (3.11 to 4.23)
Metoclopramide					
CCO cases	267	134	92	4.33 (3.32 to 5.65)	4.22 (3.22 to 5.54)
CCO controls	1558	368	914	1.20 (1.06 to 1.35)	1.20 (1.06 to 1.35)
CTC ratio	—	—	—	3.63 (2.71 to 4.86)	3.53 (2.62 to 4.76)

Odds ratios were adjusted for prothrombotic or vasoconstrictive drugs, anticoagulants and antiplatelet drugs.
*Patients who received ADA treatment in at least one reference period.
ADA=antidopaminergic antiemetic; CCO=case crossover; CTC=case-time-control.

Strengths and weaknesses in relation to other studies, discussing important differences in results

Our results are consistent with those highlighted for centrally acting antidopaminergics (that is, antipsychotics). The consistency relates to the association of an increased risk of ischaemic stroke and the short term onset of this increase after start of treatment. The literature especially highlights the risk of antipsychotics in older people and in those with dementia. In our study, we did not find evidence of a higher risk in these populations; the increased risk was found to be similar across age groups and irrespective of any history of dementia. Finally, publications that have specifically investigated the association between ADA use and the risk of ischaemic stroke seem to be lacking.

Meaning of the study: possible explanations and implications for clinicians and policymakers

As highlighted in the studies exploring the risk of stroke in people receiving antipsychotics, the short term onset after start of treatment does not advocate for mechanisms mediated by metabolic effects. A risk mediated by the arrhythmogenic effects of antidopaminergic drugs, whether centrally acting or not, can be hypothesised. However, the higher

risk found for drugs crossing the blood-brain barrier suggests a potential central effect, possibly through an action on cerebral blood flow.[16] Our results show that the risk of ischaemic stroke appears to be associated with ADA use. However, further causal inference research is needed to confirm this association in other settings, and to integrate ischaemic stroke subtype information in the analyses to help determine the extent of the risk increase that can be attributed to ADAs.

Conclusion

Using French nationwide exhaustive reimbursement data, this self-controlled study reported an increased risk of ischaemic stroke with recent ADA use. This risk appeared to be higher in the first days of ADA use. All ADAs were associated with an increased risk, the highest increase being found for metopimazine and metoclopramide.

Contributors: All authors conceived and designed the study. EH performed data management and statistical analyses. ABL, JB, and AP ensured project and study management. ABL drafted the manuscript. All authors contributed to interpretation of the data and revised the manuscript. All authors approved the final manuscript. AP and JB are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: all authors had financial support from the French Medicines Agency ANSM for the submitted work; JK has been paid for lectures for Pfizer company, JK did consultancy for Roche and Pfizer companies; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: By agreement of the French Data Protection Supervisory Authority (Commission Nationale de l'Informatique et des Libertés), neither ethics committee approval nor informed consent was required for this observational study based on anonymised French medico-administrative databases.

Data sharing: No additional data available by author (French law to access SNDS https://www.snds.gouv.fr).

Dissemination to participants and related patient and public communities: As the study we performed used data from an anonymised electronic health database, direct communication of the results towards patients whose data were used for the analyses cannot be performed. The study results have been transmitted to the French Medicine Agency (ANSM) which funds the DRUGS-SAFER programme. In addition to the manuscript herein published, the ANSM has been sent a final study report, a report which the DRUGS-SAFER Center is authorised to publish on its webpage (https://drugssafer.fr/). As the DRUGS-SAFER programme is coordinated by the Inserm research team AHeaD (Inserm Research Center Bordeaux Population Health, BPH), findings will also be communicated via press release by Inserm (https://presse.inserm.fr/) and on the BPH website (https://www.bordeaux-population-health.center/). Finally, study information will be shared with clinicians and patients through national and international conferences (in pharmacoepidemiology or cardiology) and the study publication will be communicated on social media (@DrugsSafe, @1APariente).

The lead author (AP) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Web appendix: Supplementary material