

# Antipsychotic drugs and risk of acute pancreatitis: A nationwide case–control study

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## Abstract

**Introduction:** Use of antipsychotic drugs, especially second-generation agents, has been suggested to cause acute pancreatitis in multiple case reports; however, such an association has not been corroborated by larger studies. This study examined the association of antipsychotic drugs with risk of acute pancreatitis.

**Methods:** Nationwide case–control study, based on data from several Swedish registers and including all 52,006 cases of acute pancreatitis diagnosed in Sweden between 2006 and 2019 (with up to 10 controls per case;  $n = 518,081$ ). Conditional logistic regression models were used to calculate odds ratios (ORs) in current and past users of first-generation and second-generation antipsychotic drugs (dispensed prescription <91 and ≥91 days of the index date, respectively) compared with never users of such drugs.

**Results:** In the crude model, first-generation and second-generation antipsychotic drugs were associated with increased risk of acute pancreatitis, with slightly higher ORs for past use (1.58 [95% confidence interval 1.48–1.69] and 1.39 [1.29–1.49], respectively) than for current use (1.34 [1.21–1.48] and 1.24 [1.15–1.34], respectively). The ORs were largely attenuated in the multivariable model—which included, among others, alcohol abuse and the Charlson comorbidity index—up to the point where only a statistically significant association remained for past use of first-generation agents (OR 1.18 [1.10–1.26]).

**Conclusion:** There was no clear association between use of antipsychotic drugs and risk of acute pancreatitis in this very large case–control study, indicating that previous case report data are most likely explained by confounding.

## KEYWORDS

antipsychotic agents, case–control studies, incidence, pancreatitis, population-based

## 1 | INTRODUCTION

The clinical spectrum of acute pancreatitis varies from a mild, self-limiting illness to a severe or fatal disease.<sup>1</sup> Besides well-established risk factors, most notably gallstone disease and alcohol abuse,<sup>1</sup> the use of several medical drugs has been suspected as a cause of acute pancreatitis.<sup>2–4</sup>

More than 40 case reports have been published on the association between antipsychotic drugs and risk of acute pancreatitis, with the bulk of them detailing the second-generation (atypical) agents Clozapine and Olanzapine.<sup>5–9</sup> However, data from well-controlled pharmacoepidemiological studies are sparse and somewhat inconsistent with case report data. While a multinational European case-control study (724 cases) observed an increased risk of acute pancreatitis with use of antipsychotic drugs (the included agents were, however, not specified),<sup>10</sup> a Swedish case-control study (462 cases) found no such association with use of first-generation (conventional) phenothiazines after adjustment for potential confounders.<sup>11</sup> In addition, in a Danish case-control study (3083 cases), only use of first-generation—but not second-generation—antipsychotic drugs was associated with an increased risk of acute pancreatitis.<sup>12</sup> Finally, in a Swedish case-control study that included 6161 cases and categorized the exposure according to main clinical usage (antiemetic/anxiolytics or other antipsychotics) as well as according to generation (first or second), there was no association between current use of antipsychotic drugs and risk of acute pancreatitis in multivariable-adjusted models.<sup>13</sup>

By conducting a nationwide case-control study, with more than nine times the number of cases than in any previous study, we sought to further examine the association of first-generation and second-generation antipsychotic drugs with risk of acute pancreatitis. In addition, we examined whether these associations differed by type of acute pancreatitis (i.e., gallstone-related and non-gallstone-related).

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

The Swedish Pancreatitis Cohort (SwePan), for which details have been published elsewhere,<sup>14</sup> is a nationwide cohort that was designed to study (i) the incidence and long-term complications of acute pancreatitis and (ii) different risk factors of acute pancreatitis. It includes 95,632 cases of acute pancreatitis diagnosed in Sweden between 1990 and 2019, together with 952,632 acute

### Significant outcomes

- Zero point eight and 1.6% of the acute pancreatitis cases were current users of first-generation and second-generation antipsychotic drugs, respectively; the corresponding estimates among control subjects were 0.6% and 1.2%.
- No association was observed between current or past use of second-generation agents and risk of acute pancreatitis after adjustment for potential confounders.
- A positive association was observed between past—but not current—use of first-generation agents and risk of acute pancreatitis after adjustment for potential confounders.

### Limitations

- Due to the register-based study design, a certain degree of exposure and outcome misclassification is expected.
- Residual confounding by alcohol consumption, cigarette smoking, and obesity is inevitable, as these variables were only accounted for via diagnosis codes.
- Some risk factors for acute pancreatitis, such as diet, were not accounted for.

pancreatitis-free individuals matched on age, sex, and municipality of residence. The SwePan contains data from the following Swedish registers: the National Patient Register,<sup>15</sup> the National Prescribed Drug Register,<sup>16</sup> the National Cancer Register,<sup>17</sup> the National Cause of Death Register,<sup>18</sup> the Register of the Total Population,<sup>19</sup> and the Register on Participation in Education.<sup>20</sup>

The current study was restricted to incident cases of acute pancreatitis diagnosed between 2006 and 2019 ( $n = 52,006$ ), since the National Prescribed Drug Register has only had complete national coverage since 1 July 2005. Ethical approval for the SwePan was granted by the Central Ethics Review Board in Stockholm, Sweden (2010/920–31/4; 2015/0090–32).

### 2.2 | Case and control identification

In the National Patient Register, which has had complete national coverage on all inpatient care since 1987, we identified all individuals who had been hospitalized for a first-time episode of acute pancreatitis during the study

period. None of the individuals had a history of pancreatitis (acute or chronic) or pancreatic cancer (data obtained from the National Cancer Register) prior to the start of the study period (see Online Resource 1 for details, including the Swedish clinical modification of the International Classification of Diseases and Related Health Problems [ICD-SE] codes). The code K85 in the 10th version of the ICD-SE represents acute pancreatitis, and it has been shown to have a good validity in the National Patient Register (positive predictive value ranging from 83% to 98%).<sup>21</sup> Gallstone-related acute pancreatitis was defined as episodes with gallstone-related disease (ICD-SE-10: K800-9, K851) or gallstone-related surgery (7th version of the Swedish Classification of Operations and Major Procedures: JKA20-21, JKB00-01, JKE00, JKE02, JKE12, JKE18, JKE25, UJK02, UJK05), either during the hospital admission for acute pancreatitis or within the first 3 months of hospital discharge. All other episodes were defined as non-gallstone-related acute pancreatitis. In an effort to minimize residual confounding by alcohol abuse on the exposure-outcome associations, we also identified a subgroup of patients with alcohol-related acute pancreatitis (used in sensitivity analyses only). This subgroup was defined by a diagnosis of alcohol-induced acute pancreatitis (ICD-SE-10: K852) or a diagnosis of acute pancreatitis in combination with a diagnosis related to alcohol abuse (at any time before the index date or during the index hospital stay; see Online Resource 1 for details and ICD-SE codes).

For each case subject, survivor sampling was used to randomly select up to 10 control subjects via the Register of the Total Population. The matching variables were age, sex, and municipality of residence. The control subjects were alive and residing in Sweden at the date of hospitalization for their index case. None of the control subjects had a history of pancreatitis (acute or chronic) or pancreatic cancer prior to the start of the study period.

To avoid misdiagnosis between acute pancreatitis and pancreatic cancer, the case and control subjects who were diagnosed with pancreatic cancer within 1 year of the index date were excluded.

### 2.3 | Exposure assessment

Data on dispensed prescriptions for antipsychotic drugs (Anatomical Therapeutically Chemical [ATC] code N05A) were obtained via the National Prescribed Drug Register. Only exposure prior to the index date was considered, which was set to the date of hospitalization for the case subjects and to the corresponding date for their matched control subjects. First-generation agents included Dixyrazine (N05AB01), Levomepromazine

(N05AA02), Melperone (N05AD03), Prochlorperazine (N05AB04), Fluphenazine (N05AB02), Perphenazine (N05AB03), Flupenthixole (N05AF01), Thioridazine (N05AC02), Chlorpromazine (N05AA01), Haloperidol (N05AD01), Pimozide (N05AG02), Zuclopenthixol (N05AF05), and Chlorprothixene (N05AF03). (Nota bene: No case or control subject had a prescription of Penfluridol [N05AG03].) The first-generation agents were further categorized as low-potency (Chlorpromazine, Chlorprothixene, Levomepromazine, Melperone, Thioridazine, Dixyrazine), intermediate-potency (Perphenazine, Prochlorperazine, Zuclopenthixol), and high-potency (Flupenthixole, Fluphenazine, Haloperidol, Pimozide) according to their potential to block dopamine receptors. Second-generation agents included Clozapine (N05AH02), Olanzapine (N05AH03), Quetiapine (N05AH04), Risperidone (N05AX08), Paliperidone (N05AX13), Ziprasidone (N05AE04), Arpiprazole (N05AX12), Sulpiride (N05AL01), and Amisulpride (N05AL01). (Nota bene: No case or control subject had a prescription of Levosulpiride [N05AL07].) Separate categorization of Clozapine and Olanzapine, that is the antipsychotic agents most commonly linked to acute pancreatitis in case report data,<sup>5-9</sup> was also performed.

Use of antipsychotic drugs was defined as “current” (a dispensed prescription within 90 days of the index date), “past” (a dispensed prescription earlier than 90 days of the index date), and “never” (no dispensed prescription between 1 July 2005 and the index date). The categories were exclusive and ordered hierarchically (current use above past use). The 90-day cut-off value was chosen because drugs for long-term use are normally dispensed for 3-month periods in Sweden.

### 2.4 | Covariate assessment

In addition to the matching variables (age, sex, and municipality of residence), information was collected on country of birth (Sweden, other), educational level (<10, 10–12, >12 years), the Charlson comorbidity index (0, 1, 2, ≥3; see Online Resource 2 for details), alcohol abuse (no, yes), use of antidepressants (ATC code N06A; never, past, current) and mood stabilizers (ATC code N03 [antiepileptic drugs] and N05AN [Lithium]; never, past, current), the total number of dispensed drugs (unique in seven positions of the ATC classification and prescribed within 6 months of the index date<sup>22</sup>), and psychiatric condition (none, psychosis, bipolar or unipolar depression). Presence of the listed diseases or conditions was determined by a recorded diagnosis in the National Patient Register at any time before the index date, except for cancer status, for which a recorded diagnosis in the

National Cancer Register within 5 years of the index date was used (see Online Resource 1 for details and ICD-SE codes).

## 2.5 | Statistical analysis

Conditional logistic regression was performed to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of acute pancreatitis by use of first-generation and second-generation antipsychotic drugs. All first-generation agents were further analyzed according to potency to block dopamine receptors (low, intermediate, high), while the second-generation agents Clozapine and Olanzapine were further analyzed as a separate exposure category.

Two statistical models were constructed: Model 1, which only included the matching variables (age, sex, and municipality of residence); and Model 2, which also included country of birth, educational level, the Charlson comorbidity index, alcohol abuse, and psychiatric condition. In addition, rather than adjusting for use of mood stabilizers and antidepressants, due to a high collinearity with use of antipsychotics, we restricted the analysis to case and control subjects without current use of mood stabilizers and antidepressants in a separate model. Similarly, in order to minimize polypharmacy bias, the analysis was restricted to case and control subjects with a prescription history (in the 6 months preceding the index date) of five or fewer unique drugs in another model. All regression models were mutually adjusted for first-generation and second-generation antipsychotic drugs.

To allow for a longer time-interval between the inception of the National Prescribed Drug Register and the start of the study, thereby minimizing the potential for exposure misclassification during the register's first year, we performed a sensitivity analysis restricted to 1 January 2007 and 31 December 2019. In another sensitivity analysis, the definition of current use of antipsychotic drugs was changed to a dispensed prescription within (i) 100 days, (ii) 90 days plus a margin of 14 days, and (iii) 100 days plus a margin of 14 days. Subgroup analyses were performed by the type of acute pancreatitis (gallstone-related or non-gallstone-related) and psychiatric condition (none or psychosis and/or bipolar or unipolar depression; with the purpose to examine confounding-by-indication<sup>23</sup>) as well as by age (<64 or ≥64 years) and sex.

## 3 | RESULTS

The analytical cohort included 52,006 cases of acute pancreatitis and 518,081 control subjects (Online

Resource 3), for whom demographic, comorbid, and pharmaceutical characteristics are shown in Table 1. Compared with control subjects, case subjects were slightly less well-educated and had a markedly higher burden of comorbid conditions, especially with respect to alcohol abuse (9.0% vs. 2.9%). As expected, given the observed differences in prevalence of psychiatric and other comorbid conditions, the overall use of different drugs, including that of antipsychotics, mood stabilizers, and antidepressants, was more common in case subjects than in control subjects.

The antipsychotic drugs prescribed and dispensed to the study population are tabulated in Table 2 (current use) and Online Resource 4 (ever use). Among current users of the case subjects, the most common first-generation agents were Levomepromazine, Haloperidol, and Flupenthixole and the most common second-generation agents were Risperidone, Quetiapine, and Olanzapine. The same distribution was seen in the control subjects, with the exception of Zuclopenthixol being more common than Flupenthixole among first-generation agents. Subjects with a diagnosis of psychosis and/or bipolar or unipolar depression, that is, the main patient groups for antipsychotic drug treatment, had an extensive comorbidity burden compared with subjects without such diagnoses (alcohol abuse, 15.8 vs. 2.8%; Charlson comorbidity index ≥3, 13.2 vs. 8.0%).

The ORs of acute pancreatitis by use of antipsychotic drugs are shown in Table 3. In the crude model, adjusted for the matching variables only, first-generation and second-generation agents were associated with increased risk of acute pancreatitis, with slightly higher ORs for past use than for current use. The ORs were largely attenuated in the multivariable model, to the point where only a statistically significant association remained for past use of first-generation agents (OR 1.18 [95% CI 1.10–1.26]). (Nota bene: Further categorization of past use according to time since the last dispensed prescription is shown in Online Resource 5). Accounting for confounding by (i) co-current use of mood stabilizers and antidepressants and (ii) polypharmacy had negligible influence on the results (Online Resource 6). The multivariable-adjusted ORs of acute pancreatitis were increased for first-generation agents with low potency to block dopamine receptors (OR for current and past use 1.21 [1.03–1.41] and 1.28 [1.18–1.40], respectively) but not for first-generation agents with intermediate or high potency to do so (Online Resource 7). In addition, when looking at Clozapine and Olanzapine as a separate exposure category, the risk of acute pancreatitis was increased for past use but not for current use (multivariable-adjusted OR 1.26 [1.14–1.39] and 0.93 [0.81–1.07], respectively).

The association between use of antipsychotic drugs and risk of acute pancreatitis did not change in the

**TABLE 1** Characteristics of the case patients with a first-time episode of acute pancreatitis and the matched control subjects in Sweden between 2006 and 2019.

Characteristics	Cases		Controls	
	(n = 52,006)		(n = 518,081)	
<b>Demographics</b>				
Male sex, n (%)	26,967	(51.8)	268,519	(51.8)
Age (years), median (interquartile range [IQR])	64	(48–76)	64	(48–76)
Education >12 years, n (%)	11,244	(21.6)	145,214	(28.0)
Born in Sweden, n (%)	42,709	(82.1)	437,940	(84.5)
<b>Comorbidities</b>				
Charlson comorbidity index $\geq 3$ , n (%) <sup>a</sup>	7362	(14.2)	39,661	(7.7)
Alcohol abuse, n (%) <sup>b</sup>	4706	(9.0)	15,103	(2.9)
Psychosis, n (%) <sup>c</sup>	840	(1.6)	6364	(1.2)
Bipolar or unipolar depression, n (%) <sup>c</sup>	3811	(7.3)	22,936	(4.4)
<b>Drug use<sup>d</sup></b>				
First-generation antipsychotics <sup>e</sup>				
Current use, n (%)	431	(0.8)	2962	(0.6)
Past use, n (%)	1236	(2.4)	7161	(1.4)
Second-generation antipsychotics <sup>f</sup>				
Current use, n (%)	841	(1.6)	5983	(1.2)
Past use, n (%)	946	(1.8)	6062	(1.2)
Mood stabilizers (current use), n (%)	2090	(4.0)	12,379	(2.4)
Antidepressants (current use), n (%)	6433	(12.4)	46,536	(9.0)
Number of total drugs, median (IQR) <sup>g</sup>	7	(3–10)	5	(2–8)

<sup>a</sup>Based on Swedish clinical modification of the International Classification of Diseases and Related Health Problems codes for a number of chronic diseases (see Online Resource 1 for details).

<sup>b</sup>Based on Swedish clinical modification of the International Classification of Diseases and Related Health Problems codes for a number of alcohol-related disorders (see Online Resource 1 for details).

<sup>c</sup>Based on Swedish clinical modification of the International Classification of Diseases and Related Health Problems codes for psychosis, bipolar depression, and unipolar depression (see Online Resource 1 for details).

<sup>d</sup>Current use: last prescription within 90 days of index date; Past use: last prescription more than 90 days of index date.

<sup>e</sup>Dixyrazine, Levomepromazine, Melperone, Prochlorperazine, Fluphenazine, Perphenazine, Flupenthixole, Thioridazine, Chlorpromazine, Haloperidol, Pimozide, Zuclophenthixol, or Chlorprothixene.

<sup>f</sup>Clozapine, Olanzapine, Quetiapine, Risperidone, Paliperidone, Ziprasidone, Arpiprazole, Sulpiride, or Amisulpride.

<sup>g</sup>Unique drugs prescribed during the last 6 months before the index date.

sensitivity analyses that applied a different follow-up period (2007 to 2019) and a different definition of current use (<101, <105, or <115 days of the index date) (Online Resource 8). The results interpretation was also similar in subgroup analyses by sex (Online Resource 8). However, the exposure-outcome association differed in subgroup analyses by age, with increased risk in younger subjects (for first-generation and second-generation agents) and decreased risk in older subjects (for second-generation agents), and by underlying psychiatric disease, with increased risk in subjects without psychosis and/or bipolar or unipolar depression (for first-generation agents, especially for past use thereof) (Online Resource 8).

Forty-nine and 51% of the acute pancreatitis cases were considered to be gallstone-related and non-gallstone-related, respectively, for which Table 4 presents the subtype-specific ORs by use of antipsychotic drugs. No exposure-outcome association was observed with respect to second-generation agents (irrespective of subtype of acute pancreatitis) or with respect to gallstone-related acute pancreatitis (irrespective of generation of agents), while there were increased risks for non-gallstone-related acute pancreatitis by current and past use of first-generation agents (OR 1.19 [1.03–1.37] and 1.25 [1.14–1.37], respectively). Exclusion of case subjects (and their corresponding control subjects) who were considered to have had an alcohol-related etiology ( $n = 3684$  and  $36,823$ , respectively) did not change the ORs for non-

**TABLE 2** Antipsychotic drugs currently used by the study population<sup>a</sup>.

Antipsychotic drugs	Cases		Controls	
	n	(%)	n	(%)
First-generation	431	(0.8)	2962	(0.6)
Dixyrazine (N05AB01)	14	(0.0)	64	(0.0)
Levomepromazine (N05AA02)	130	(0.2)	714	(0.1)
Melperone (N05AD03)	18	(0.0)	152	(0.0)
Prochlorperazine (N05AB04)	13	(0.0)	34	(0.0)
Fluphenazine (N05AB02)	1	(0.0)	14	(0.0)
Perphenazine (N05AB03)	28	(0.1)	240	(0.0)
Flupenthixole (N05AF01)	49	(0.3)	374	(0.1)
Thioridazine (N05AC02)	1	(0.0)	12	(0.0)
Chlorpromazine (N05AA01)	0	(0.0)	7	(0.0)
Haloperidol (N05AD01)	110	(0.2)	887	(0.2)
Pimozide (N05AG02)	0	(0.0)	4	(0.0)
Zuclopenthixol (N05AF05)	43	(0.1)	397	(0.1)
Chlorprothixene (N05AF03)	24	(0.0)	63	(0.0)
Second-generation	841	(1.6)	5983	(1.2)
Clozapine (N05AH02)	16	(0.0)	342	(0.1)
Olanzapine (N05AH03)	219	(0.4)	1458	(0.3)
Quetiapine (N05AH04)	230	(0.4)	1045	(0.2)
Risperidone (N05AX08)	295	(0.6)	2691	(0.5)
Paliperidone (N05AX13)	10	(0.0)	42	(0.0)
Ziprasidone (N05AE04)	8	(0.0)	62	(0.0)
Arpiprazole (N05AX12)	62	(0.1)	342	(0.1)
Sulpiride (N05AL01)	1	(0.0)	1	(0.0)

<sup>a</sup>Most recent prescription (<91 days) before index date.

gallstone-related acute pancreatitis in a meaningful way (data not shown).

## 4 | DISCUSSION

In this nationwide case-control study, we observed no overall association between second-generation antipsychotic drugs and risk of acute pancreatitis after adjustment for potential confounders. In contrast, first-generation antipsychotic drugs (especially agents with a low potency to block dopamine receptors) were associated with a slightly increased risk of acute pancreatitis in general and of non-gallstone-related acute pancreatitis in particular, even after adjustment for potential confounders.

The notion of second-generation antipsychotic drugs as causes of acute pancreatitis, originating from multiple case reports on the subject,<sup>5-9</sup> has received little support from well-controlled pharmacoepidemiological studies. Gasse

**TABLE 3** Odds ratios (ORs) and 95% confidence intervals (CIs) of acute pancreatitis by use of antipsychotic drugs before index date.

Antipsychotic drugs	Crude OR (95% CI) <sup>a</sup>	Adjusted OR (95% CI) <sup>b</sup>
First-generation		
No use	1 (reference)	1 (reference)
Current use (<91 days)	1.34 (1.21–1.48)	1.04 (0.93–1.16)
Past use (≥91 days)	1.58 (1.48–1.69)	1.18 (1.10–1.26)
Second-generation		
No use	1 (reference)	1 (reference)
Current use (<91 days)	1.24 (1.15–1.34)	0.99 (0.91–1.07)
Past use (≥91 days)	1.39 (1.29–1.49)	1.03 (0.96–1.11)

<sup>a</sup>Conditional logistic regression analysis including the matching variables only (age, sex, and municipality of residence). All estimates were mutually adjusted for the use of first- and second-generation antipsychotic drugs (no use, current use, past use).

<sup>b</sup>Conditional logistic regression analysis including the matching variables, education level (<10, 10–12, and >12 years), country of birth (Sweden, other), the Charlson comorbidity index (0, 1, 2, and ≥3 comorbidities), alcohol abuse (no, yes), and psychiatric disease (none, psychosis, and bipolar or unipolar depression). All estimates were mutually adjusted for the use of first- and second-generation antipsychotic drugs (no use, current use, past use).

et al., who analyzed data from 3083 Danish patients with acute pancreatitis (of whom 20 were exposed to second-generation agents), observed no association between second-generation agents and risk of acute pancreatitis.<sup>12</sup> A null association was also seen by Bodén et al, who used the same Swedish registers as in our study but restricted to the period between 2006 and 2008 (6161 cases [of whom 110 were exposed to second-generation agents]).<sup>13</sup> Despite this, acute pancreatitis is listed as an adverse reaction in the product information of several second-generation antipsychotic drugs (as reviewed by Sosnowski et al.<sup>4</sup>).

Consistent with the above-mentioned studies, we observed a positive association in crude models and a null association in multivariable models for second-generation antipsychotic drugs with respect to acute pancreatitis (52,006 cases [of whom 1787 were exposed to second-generation agents]). This finding was consistent across subtypes of acute pancreatitis (i.e., gallstone-related and non-gallstone-related), not to mention that current users of Clozapine and Olanzapine had no increased risk of acute pancreatitis (i.e., the second-generation agents most commonly detailed in case reports<sup>5-9</sup>). Taken together, and even though adverse reactions cannot be categorically ruled out, especially since disease recurrence has been reported after drug rechallenge,<sup>5,7</sup> the bulk of the case reports on second-generation agents are most likely explained by confounding by other factors, such as alcohol,<sup>1,24</sup> cigarettes,<sup>25</sup> and obesity.<sup>26</sup>

**TABLE 4** Odds ratios (ORs) and 95% confidence intervals (CIs) of subtypes of acute pancreatitis by use of antipsychotic drugs before index date.

Antipsychotic drugs	Subtype of acute pancreatitis			
	Gallstone-related <sup>a</sup>		Non-gallstone-related <sup>b</sup>	
	Crude OR (95% CI) <sup>c</sup>	Adjusted OR (95% CI) <sup>d</sup>	Crude OR (95% CI) <sup>c</sup>	Adjusted OR (95% CI) <sup>d</sup>
First generation				
No use	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Current use (<91 days)	1.15 (1.03–1.29)	0.86 (0.72–1.02)	1.69 (1.48–1.93)	1.19 (1.03–1.37)
Past use (≥91 days)	1.26 (1.13–1.41)	1.08 (0.98–1.20)	1.92 (1.77–2.09)	1.25 (1.14–1.37)
Second generation				
No use	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Current use (<91 days)	0.97 (0.82–1.15)	1.00 (0.88–1.13)	1.33 (1.20–1.47)	1.01 (0.91–1.13)
Past use (≥91 days)	1.24 (1.12–1.38)	1.05 (0.94–1.18)	1.52 (1.38–1.67)	1.03 (0.93–1.14)

<sup>a</sup>Restricted to 25,543 cases and 254,573 controls.

<sup>b</sup>Restricted to 26,463 cases and 263,508 controls.

<sup>c</sup>Conditional logistic regression analysis including the matching variables only (age, sex, and municipality of residence). All estimates were mutually adjusted for the use of first- and second-generation antipsychotic drugs (no use, current use, and past use).

<sup>d</sup>Conditional logistic regression analysis including the matching variables, education level (<10, 10–12, and >12 years), country of birth (Sweden, other), the Charlson comorbidity index (0, 1, 2, and ≥3 comorbidities), alcohol abuse (no, yes), and psychiatric disease (none, psychosis, and bipolar or unipolar depression). All estimates were mutually adjusted for the use of first- and second-generation antipsychotic drugs (no use, current use, past use).

The positive association between first-generation antipsychotic drugs and acute pancreatitis in our study (1667 cases exposed) is supported by some, but not all, of the previous pharmacoepidemiological studies. In the study by Gasse et al., there was a positive association with current and past use of first-generation agents (128 cases exposed), especially for agents with a low potency to block dopamine receptors<sup>12</sup>; and in the study by Bodén et al. (213 cases exposed), there was a positive association with past use of first-generation agents with intermediate potency to block dopamine receptors.<sup>13</sup> Finally, in an older Swedish study (462 cases), there was no association with first-generation phenothiazines after adjustment for potential confounders (17 cases exposed).<sup>11</sup>

A causative role of antipsychotic drugs in the development of acute pancreatitis is theoretically plausible, either via direct hypersensitivity reactions or via indirect obesogenic, diabetogenic, and lipidogenic effects.<sup>27,28</sup> The latter explanation model bodes well with our finding that the strongest association was observed for first-generation agents with low potency to block dopamine receptors, as these agents have stronger effects on weight gain, hyperlipidemia, and hyperglycemia than agents with intermediate or high potency to block dopamine receptors.<sup>27</sup> However, the same explanation model does not bode well with the overall null association for second-generation agents, as these agents are even more obesogenic, diabetogenic, and lipidogenic than first-generation agents.<sup>28</sup>

In general, the observed association between first-generation antipsychotic drugs and acute pancreatitis should

be interpreted with caution, especially in the light of the small magnitude of the point estimates (ORs ranging from 1.18 to 1.33) and the high probability of unmeasured and residual confounding. With respect to unmeasured confounding, we had no data on diet<sup>29,30</sup> and did not account for polypharmacy according to pharmacological mechanisms or by potential risk of drug–drug interactions.<sup>2–4</sup> With respect to residual confounding, and using alcohol as an example (but the same reasoning can be applied to cigarettes and obesity), the utilization of diagnosis codes to create a proxy variable for alcohol consumption will, so to say, only reveal the “tip of the iceberg”. In our data, consistent with the available literature,<sup>31,32</sup> subjects with a diagnosis of psychosis and/or bipolar or unipolar depression had a markedly higher burden of alcohol-related diseases. While adjustment for that proxy variable largely attenuated the ORs in our model, one can still assume that the alcohol intake is higher and that the drinking behavior is riskier in most patients on antipsychotic drug treatment, even if they have not developed consequences of such alcohol exposure yet—a fact that is unaccounted for in our analyses. Further highlighting the potential of residual confounding-by-alcohol was the interaction by age in our study (similar to the observation by Gasse et al.<sup>12</sup>). The ORs for both first-generation and second-generation agents were markedly higher in younger subjects, for which there is no apparent biological rationale, but among whom the alcohol pattern is more often characterized by high-quantity and high-risk drinking.<sup>33</sup> In extension to that reasoning, it is quite noteworthy that second-generation agents had an inverse association with acute pancreatitis in older subjects.

In addition to unmeasured and residual confounding, first-generation phenothiazines are sometimes used as non-addictive alternatives to treat symptoms in patients with alcohol dependence,<sup>23</sup> introducing the possibility of confounding-by-indication. In fact, in the subgroup analyses by underlying psychiatric disease, we observed indications for that type of bias, given that use of first-generation agents did not lead to higher risk of acute pancreatitis in subjects with psychosis and/or bipolar or unipolar depression; but it did so in subjects without such diagnoses. No similar observation was observed for second-generation agents.

Two additional limitations of the present study must be mentioned. First, despite that the diagnosis of acute pancreatitis has been validated in the National Patient Register, a small degree of outcome misclassification is always expected in a register-based setting. In theory, if a physician is aware of the case reports on antipsychotic drugs and acute pancreatitis, such outcome misclassification could be differential with respect to exposure status. However, since the bulk of the case reports has detailed second-generation agents, for which we observed a null association (except for past use of the highly publicized agents Clozapine and Olanzapine<sup>5-9</sup>), the practical implications were most likely negligible. Second, we could not control whether the study subjects had taken their dispensed prescriptions (reducing the specificity of the exposure) and had no access to in-hospital use of antipsychotic drugs (reducing the sensitivity of the exposure). However, we do not expect that such misclassification should have differed with respect to case status.

The strengths of the present study were the large sample size (with more than nine times the number of cases than in any previous study), allowing for precise estimations and multiple subgroup and sensitivity analyses; and the use of register-based data with a nationwide coverage (both with respect to exposure and outcome), limiting selection and recall bias.

To conclude, in this nationwide study of 52,006 cases of acute pancreatitis, which aimed to study the exposure-outcome association with use of antipsychotic drugs and by different disease subtypes (i.e., gallstone-related and non-gallstone-related), there was no overall association between second-generation antipsychotic drugs and risk of acute pancreatitis after adjustment for potential confounders. In contrast, first-generation antipsychotic drugs (especially agents with a low potency to block dopamine receptors) were associated with a slightly increased disease risk (particularly for non-gallstone-related cases). Given the small magnitude of the point estimates and the high probability of confounding, the causality of this association is highly questionable.

#### AUTHOR CONTRIBUTIONS

Omid Sadr-Azodi: Handled the data collection, the ethical permissions, the data management, the creation of working

data sets and the statistical analyses. Viktor Oskarsson: Drafted the manuscript; and Omid Sadr-Azodi, Rickard Ljung, Mats Lindblad, and Viktor Oskarsson: Revised the manuscript for important intellectual content, including interpretation of presented data, approved the final version, and were responsible for the final version of the manuscript.

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#### CONFLICT OF INTEREST STATEMENT

Rickard Ljung is employed at the Swedish Medical Products Agency, Uppsala, Sweden. The views expressed in this paper do not necessarily represent the views of this Government agency. The other authors have no conflicts of interest to declare.

#### PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13561>.


#### DATA AVAILABILITY STATEMENT

Data may be obtained from a third party and are not publicly available. According to Swedish legislation, the research data need to be held by the authorities and are protected under statistical secrecy. The data are stored on servers of the regional authority and individual data cannot be shared with people who are not directly associated to the record-holding authority.

#### ETHICS STATEMENT


Ethical approval for the current study was granted by the Central Ethics Review Board in Stockholm, Sweden (2010/920-31/4; 2015/0090-32).

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## SUPPORTING INFORMATION

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

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