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~~Antipsychotics~~ Antidopaminergic drugs and acute pancreatitis – a population based study

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Abstract

Objectives: To evaluate the suggested association between ~~antipsychotics~~antidopaminergic drugs and acute pancreatitis.

Design: A large population-based nested case-control study.

Setting: Swedish. Nationwide. During 2006-2008.

Participants: The Patient Register was used to identify 6,161 cases of acute pancreatitis. The 61,637 control subjects were randomly selected from the Register of the Total Population by frequency-based density sampling, matched for age, sex, and calendar year.

Exposure: Exposure data were~~as~~ extracted from the Prescribed Drug Register. ~~Antipsychotics~~Antidopaminergic drugs were grouped into antiemetic/anxiolytic and other antipsychotics. Current use of ~~antipsychotics~~antidopaminergic drugs was defined as filling a prescription 1-114 days before index date, while previous use was 115 days-3½ years before index date.

Main outcome measures: Cases were defined as being diagnosed with acute pancreatitis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression.

Results: The unadjusted OR indicated an increased risk of acute pancreatitis among current users of antiemetic/anxiolytics ~~antipsychotics~~ (OR 1.9, 95% CI 1.4-2.6), but not in the multivariable model adjusting for alcohol related co-morbidity, chronic obstructive lung disease, ischemic heart disease, obesity, diabetes, opioid use, gallstone disease, educational level, marital status, and number of concomitant medications (OR 0.9, 95% CI 0.6-1.2). Similarly, among current users of other antipsychotics, the unadjusted OR was 1.4 (95% CI 1.1-1.6), while the adjusted OR was 0.8 (95% CI 0.6-0.9). Results regarding previous use of ~~antipsychotics~~antidopaminergic drugs followed a similar risk pattern as for current use.

Conclusions: The lack of association between ~~antipsychotics~~antidopaminergic drugs and acute pancreatitis after adjustment for confounding factors in this study suggests that the previously reported positive associations might be explained by confounding.

Article Summary

Article focus:

- Case-reports and case-series have suggested a link between use of antidopaminergic drugs and acute pancreatitis.
- The aim of this study was to clarify the relationship between use of antidopaminergic drugs and the risk of acute pancreatitis
- We hypothesized that antidopaminergic drug use increases the risk of acute pancreatitis.

Key messages:

- Our paper suggests that there is no association between antidopaminergic drug treatment and acute pancreatitis.
- Further, our findings suggest that the previously reported positive association might be explained by confounding.

Strengths and limitations:

- Major strengths of the study are the population-based design, utilizing a nationwide register, counteracting recall and selection bias.
- One limitation is that drug exposure is somewhat uncertain as it is defined as filling a prescription of the drug, which might not imply actually taking the drug

Introduction

The incidence of acute pancreatitis is increasing for reasons that are not well understood.[1] The main risk factors, i.e. gallstones and excessive alcohol consumption, are present in approximately 40% and 30% of cases, respectively, while about 25% are of idiopathic (unknown) origin.[1] There have been several case reports of acute pancreatitis during use of ~~antipsychotic~~ antidopaminergic medication.[2-18] Typically, the reported cases had initiated their medication within the 6 months before the onset of acute pancreatitis,[5 7 9 12 15-19] and had recovered after withdrawing or switching ~~antipsychotic~~antidopaminergic drug.[5 11 12 15-19] Some case reports have also reported recurrent pancreatitis after re-challenge of the suspected drug.[8 18] Two possible biological mechanisms have been suggested. First, a hypersensitivity reaction might be occurring, an explanation which fits well with the observation that some cases have experienced recurrent pancreatitis at a much lower dose and much earlier at re-challenge, and is in line with the well-described hypersensitivity reactions, mainly for clozapine with subsequent agranulocytosis or myocarditis.[18 20] Second, hypertriglyceridemia might be induced by the ~~antipsychotic~~ antidopaminergic drug, resulting in an accumulation of chylomicrons.[17] However, the sparse epidemiological data available have~~s~~ not shown any clear positive association between ~~antipsychotic medication~~antidopaminergic medication ~~use~~ and the risk of acute pancreatitis.[21 22] Larger epidemiological studies elucidating this possible association are warranted before any association can be established or excluded. The aim of this study was therefore to clarify the relationship between use of ~~antipsychotics~~antidopaminergic drugs and the risk of acute pancreatitis in a large and population-based study, including adjustment for potential confounders. We hypothesized that antidopaminergic drug~~antipsychotic~~ use increases the risk of acute pancreatitis.

Method

Study design

A Swedish nationwide, population-based case-control study was performed in the period from January 1, 2006 to December 31, 2008. The source population was defined as all Swedish residents aged between 40 and 84 years. The Patient Register was used to identify cases with a first episode of acute pancreatitis. The Register of the Total Population was used to randomly select control subjects from the general population. Individual data on drug exposure among cases and control subjects were~~as~~ collected from the Prescribed Drug Register. Information on the highest achieved formal educational level was obtained from the Education Register. In order to censor for person-time no longer at risk of being diagnosed with acute pancreatitis in the Patient Register, data regarding emigration and death were~~as~~ obtained from the Register of the Total Population, and the Causes of Death Register, respectively. Additionally, censoring for any cancer was conducted through the Cancer Register. The unique personal identity number assigned to all Swedish residents was used to link individual information between the registers.[23] The study has been approved by the Regional Ethical Review Board in Stockholm.

Sources of data

The Patient Register comprises information on all in-hospital care and outpatient specialist care in Sweden, including codes for diagnoses (according to the "International Classification of Diagnoses" [ICD]) and surgical procedures (according to the "Nordic Classification of Surgical Procedures"). It has complete nationwide coverage of inpatient data since 1987, and complete outpatient specialist care data since 2001.[24]

The Prescribed Drug Register records all medications dispensed to individual patients since July 1st 2005, capturing the entire Swedish population of approximately 9 million inhabitants [25]. This register contains data on drugs, including names of drug substances according to the Anatomical Therapeutic Chemical (ATC) classification.[26] Additionally, it includes information about amount, dosage, and date of expenditure and reimbursement, as well as patient data, including age, sex, and place of residence. The register lacks information regarding indication for treatment, ~~and~~ over-the-counter drugs and drugs administered at hospitals during inpatient treatment.

The Cancer Register was set up in 1958, and since then every clinician, pathologist and cytologist in Sweden has been required to notify the National Board of Health and Welfare of every person diagnosed with a new primary malignancy. The Cancer Register includes primary malignancies, and certain benign tumors and precancerous lesions classified according to the ICD system.[27]

The Causes of Death Register contains information on the dates and causes of all deaths of Swedish residents since 1952, with 100% coverage of death dates.[28]

The Register of the Total Population contains individual characteristics of all Swedish residents since 1968 (100% coverage), including sex, age, country of birth, marital status, and place of residence.[29]

The Education Register was established by Statistics Sweden in 1985, and is annually updated with information on the highest formal education attained by each individual, from elementary to post-graduate level.[30]

Case and control identification

Cases were defined as individuals in the study cohort with a first time registered discharge diagnosis in the Patient Register of acute pancreatitis between 2006 and 2008. The code K85 in the 10th version of the ICD represented acute pancreatitis. Control subjects were randomly selected according to the principle of frequency-based density sampling, matched for age, sex, and calendar year. Exposure was considered in relation to an index date assigned to each case and control participant. For case subjects, the index date was set to the date of admission for acute pancreatitis. For control subjects, the index date was a randomly assigned date within the study period. All potential case and control subjects with a previous cancer (apart from non-melanoma cancers of the skin) or any pancreatic disease (defined by the diagnosis codes K85, K86, K87 [ICD-10], and 577 [ICD-9]) recorded in the Patient Register before the study started, were excluded.

Exposure to ~~antipsychotic~~antidopaminergic drugs

Dispensed drug prescriptions of ~~antipsychotic~~antidopaminergic drugs were identified by their specific ATC code [N05A] in the Prescribed Drug Register. Only exposure prior to the index date was considered. As drugs for longer-term use typically are dispensed for 3-month periods in Sweden, we assumed that a prescription normally comprised 100 days of drug use, and added a margin of 14 days. Thus, a single prescription of ~~antipsychotics~~antidopaminergic drugs was assumed to last 114 days. ~~Antipsychotic~~Antidopaminergic drug use was defined as "current", "recent", "past", or "former", if the drug had been dispensed 1-114 days, 115-180 days, 181-365 days, or 1-3½ years before the index date, respectively. Previous use was categorized to enable us to study short-term effects, and better evaluate potential confounding effects of concomitant diseases. Depot formulations were recalculated to fit the above categorization. The absence of any prescription for ~~antipsychotics~~antidopaminergic drugs was classified as "non-use". Two groups of ~~antipsychotic~~antidopaminergic drugs ~~drugs~~ were studied separately: 1) *antiemetic/anxiolytic~~s antipsychotics~~*, including dixyrazine, levomepromazine, melperone, and proklorperazine, and 2) *other antipsychotics*, including fluphenazine, perphenazine, flupenthixole, thioridazine, chlorpromazine, haloperidol, pimozide, ziprasidone, aripiprazole, quetiapine, risperidone, paliperidone, clozapine and olanzapine. A separate analysis of the two most metabolically adverse antipsychotic drugs, clozapine and olanzapine, was also conducted. To facilitate comparison with previous studies we also performed secondary analyses grouping the antidopaminergic drugs into atypical/ typical antipsychotics and subdividing typical into high-, medium-, and low potency antipsychotics. Finally, to maximize power we made an analysis including any antidopaminergic drug use in one group.

Statistical analysis

The relative risk of acute pancreatitis was estimated by unconditional logistic regression, which was used to calculate odds ratios (OR) with 95% confidence intervals (CI). Adjustments were made in three models: 1) A crude model was based on the matching variables only, i.e. sex, age (in 5-year age groups) and the three calendar years, 2) A multivariable model added *i*) history of excessive alcohol consumption or disease related to alcohol, defined by the diagnosis codes E244, F10, G312, G621, G721, I426, K292, K70, O354, T51 in ICD-10 or 291, 303, 305A, 357F, 425F, 535D, 571A, 571B, 571C, 571D, 980 in ICD-9, or use of anti-alcohol drugs defined by the ATC code N07BB, and 3) A full multivariable model further added ii) chronic obstructive lung disease, defined by the diagnosis codes J41, J42, J42, J44 in ICD10 or 491, 492, 496 in ICD-9, *iii*) ischemic heart disease, defined by the diagnosis codes I20 to I25 in ICD-10 or 410 to 413, 414A, 414W in ICD-9, *iv*) obesity, defined by the diagnosis codes E66 in ICD-10 or 278A in ICD9 or anti-obesity drugs defined by the ATC code A08A, *v*) diabetes, defined by the diagnosis codes E10-E14 in ICD10 or 250 in ICD-9 or anti-diabetic medication, defined by the ATC code A10, *vi*) opioid drug use, defined by the ATC code N02A, *vii*) gallstone disease, defined by the diagnosis codes 574, 575A, or 575B in ICD9 or K80, K81 in ICD10, *viii*) educational level (divided into three categories of highest attained education: elementary school, secondary school, university, and one category for missing data [2.3% among cases and 1.6 % among controls]), *ix*) marital status (categorized as married or not), *x*) a co-morbidity score based on number of distinct medications. The co-morbidity score was defined as the sum of unique 7-digit ATC codes dispensed during the 6 months prior to the index date, and was categorized as 0-4, 5-9, 10-14, or ≥15 drugs. Presence of the listed diseases or conditions was determined by a recorded hospitalization or outpatient visit according to the Patient Register since 1987, or a dispensed prescription between July 1, 2005 and the index date. In a sub

analysis, the study period was restricted to 2007 and 2008 to account for the fact that the study participants, depending on their index date, had different follow-up times from the start of the Prescribed Drug Register on July 1, 2005. Hence, for some participants included throughout the entire study period, we could assess drug exposure only 1-180 days before the index date. In addition, the association between ~~antipsychotic~~antidopaminergic medication and acute pancreatitis was studied among those with and without a previous hospital record of psychosis, defined by the diagnosis codes F20-F29 in ICD10 or 295, 296, 297, 298 in ICD9. The SAS statistical software package EG 4.2 (SAS Institute, Cary, N.C., USA) was used for the analyses.

Results

Study participants

The study included 6,161 cases of acute pancreatitis and 61,637 control subjects. Characteristics of the study participants are presented in Table 1. The frequency-based sampling produced a similar age and sex (and calendar year) distribution among cases and control subjects. Among the cases, 194 had used antiemetic/anxiolytic antidopaminergic drugs and 78 had used other antipsychotics. Current and previous use of antiemetic/anxiolytics ~~antipsychotics~~, as well as other antipsychotics, was more common among cases than controls (Table 1). All covariates presented in the methods section were overrepresented among the case subjects compared to the control participants. This was especially evident for factors representing lifestyle. Diseases related to alcohol overconsumption were, for example, four times more common in cases than controls (Table 1).

Antiemetic/anxiolytics ~~antipsychotics~~ and risk of acute pancreatitis

Table 2 presents the ORs for the association between antiemetic/anxiolytics ~~antipsychotic~~ use, and other antipsychotic medication, and the risk of developing acute pancreatitis. The ORs in the crude model, adjusting for the matching variables, indicated an increased risk among current users of antiemetic/anxiolytic ~~antipsychotics~~s (OR=1.9, 96% CI 1.4-2.6) as well as for each of the categories representing previous use of antiemetic/anxiolytics ~~antipsychotics~~ (Table 2). In the multivariable model, adjusting for alcohol related co-morbidity, the risk among current users of antiemetic/anxiolytics ~~antipsychotics~~ was attenuated (OR=1.4, 95% CI 1.0-1.9), and in the full multivariable model, no increased risk for acute pancreatitis was observed for current use of antiemetic/anxiolytic ~~antipsychotics~~ (OR=0.9, 95% CI 0.6-1.2).

Other antipsychotic medication and risk of acute pancreatitis

Correspondingly, current use of other antipsychotics was associated with an increased risk of acute pancreatitis in the crude model (OR=1.4, 95% CI 1.1-1.6). However, this risk increase disappeared after adjusting for confounding by alcohol related co-morbidity (OR=1.1, 95% CI 0.9-1.4). Each of the categories representing previous use of other antipsychotics showed a similar decrease in the ORs from the crude model to the fully adjusted model (Table 2).

For current use of clozapine or olanzapine, the OR in the crude model was 1.6 (95% CI 1.1-2.3), and decreased to 0.9 (95% CI 0.6-1.4) in the full multivariable model.

Stratifying by sex did not reveal any major differences between the sexes (data not shown). When stratifying by age, the results for the group younger than 65 were similar to those of the main analysis, but among those 65 and older, the OR for current use was close to unity in both the crude and the fully adjusted model (data not shown). Among participants younger than 65 years, the group with a previous history of alcohol overconsumption had no increased risk of acute pancreatitis associated with current use of other antipsychotics, in either the crude or the full multivariable model (OR 0.8, 95% CI 0.5-1.3 and OR 0.8, 95% CI 0.5-1.2, respectively). However, participants without such history of alcohol overconsumption rendered similar results as in the main analysis (data not shown). Individuals with a previous hospital record of psychosis had no increased risk for current use of other antipsychotics in the crude or full multivariable model (data not shown). However, participants with a previous hospital record of psychosis who had stopped other antipsychotic medication within the last 3 months were at an increased risk of acute pancreatitis after adjustment in the multivariable model (OR 4.0 95% 1.4 -11.2). Stratifying by calendar year (2006 and 2007-08) rendered similar results as in the main analysis (data not shown).

The secondary analyses of atypical antipsychotics and three potency groups of typical antipsychotics showed low or no risk increase except for former use of medium potency antipsychotics and a non-significant increased risk for recent use of low potency antipsychotics (Supplemental Table I). Use of any antidopaminergic drug was not associated with increased risk of acute pancreatitis.

Discussion

This population-based study found no association between current use of ~~antipsychotic~~antidopaminergic medication and acute pancreatitis after adjustment for potential confounding factors.

Among strengths of the study is the population-based design, utilizing a nationwide register, counteracting recall and selection bias. Other advantages include the large sample size, the complete nationwide coverage of the exposure (~~antipsychotics~~antidopaminergic drugs ~~drugs~~) and the outcome (acute pancreatitis), and the adjustment for several potential confounding factors. Misclassification of the outcome in the Patient Register is a possible concern, but the high validity of the diagnosis of acute pancreatitis in this register has recently been shown by our group to have a positive predictive value of 98%.[31] There are, however, also several weaknesses. We regarded a dispensed prescription of ~~antipsychotics~~antidopaminergic drugs as an exposure, but there was no information on whether the patients had actually taken their medication. This potential misclassification of the exposure would, however, most likely be non-differential, i.e. not associated with risk for future acute pancreatitis, and thus only dilute the risk estimates towards null results. Additionally, there was no information on drugs administered during in-hospital care, and no information on indication for treatment. This

might lead to a misclassification resulting in some of the patients with probably the highest doses of ~~antipsychotics~~antidopaminergic drugs (being inpatient treated) being classified as not having been exposed to ~~antipsychotics~~antidopaminergic drugs. We could not investigate any potential dose-response relation due to the lack of detailed information on drug dosages. Moreover, detailed patient information is not available in registers, particularly regarding some potential confounding factors. It could, for instance, be possible that substantial alcohol consumption, smoking or obesity could not be captured with the variables retrieved from the national registers. Nevertheless, several potential confounding variables were adjusted for, and the results clearly show that confounding by these factors did occur, and were seemingly sufficiently adjusted for. There is no reason to believe that misclassification of alcohol exposure would be a greater concern among the controls than the cases.

Use of ~~antipsychotics~~antidopaminergic drugs in our study was associated with an increased risk of acute pancreatitis in the crude models, but after adjustment for known risk factors for acute pancreatitis this association disappeared. The principal confounding effect seemed to be through alcohol, as the major decrease of the elevated risk of acute pancreatitis among users of ~~antipsychotics~~antidopaminergic drugs was attenuated when adjusting for alcohol related diagnoses and drug treatments for alcohol dependence. This confounding may be for two different reasons. First, ~~antipsychotics~~antidopaminergic drugs are used as a non-addictive alternative to treat withdrawal, agitation and anxiety among patients with alcohol dependence.[32] Second, alcohol dependence is overrepresented among patients with severe mental illnesses, where ~~antipsychotics~~antidopaminergic drugs often are the first-line treatment.[33] Not all of the increased risk disappeared after adjusting for alcohol; instead, the effect entirely disappeared only after further adjustment for additional known risk factors for

acute pancreatitis, i.e. chronic medical conditions, sociodemographic factors, obesity and gallstone related diseases.

This study revealed no association between clozapine and olanzapine and the risk of acute pancreatitis. These two antipsychotic drugs are known to be particularly obesogenic, diabetogenic, and with high liability of inducing lipid abnormalities.[34-36] Yet, other studies have shown that obesity, as well as diabetes, might increase the risk of acute pancreatitis.[37 38]

Further, in our study, patients with a previous hospital record of psychosis who had stopped using other antipsychotic medication within the previous 3 months had an increased risk of acute pancreatitis which remained after full adjustment. One possible explanation of this delay in the effect is that patients with a psychotic disorder are more non-adherent to pharmacotherapy when suffering from a comorbid alcohol abuse disorder.[39] Thus, patients might have stopped their antipsychotic medication following a period of excessive alcohol intake, which subsequently may have led to an acute pancreatitis.

Before the analyses, we chose to divide ~~antipsychotics~~antidopaminergic drugs into two groups according to the main clinical usage pattern. The ~~antipsychotics~~antidopaminergic drugs in the group antiemetic/anxiolytics are typically used intermittently and in lower doses than other groups of ~~antipsychotic~~antidopaminergic drugs. Notably, users of antiemetic/anxiolytic ~~antipsychotics~~ had a higher crude risk of acute pancreatitis than users of other antipsychotics in our study, although they probably received lower total doses. However, one might speculate that if the ~~antipsychotics~~antidopaminergic drugs in the antiemetic/anxiolytic group are used more often for treatment of withdrawal and anxiety in the post detoxification phase from alcohol, than other antipsychotics, it would explain this discrepancy. Other studies have

chosen to divide ~~antipsychotics~~antidopaminergic drugs into conventional and atypical antipsychotics,[13 22] but the rationale behind such categorization has been criticized, and recently has been proposed to be abandoned due to the great overall heterogeneity within these groups.[40] However, for the sake of comparison with a recent Danish case-control study,[22] we performed secondary analyses with the same categorization of the antidopaminergic drugs. Former use of medium potency antipsychotics was associated with increased risk of pancreatitis, as was recent use of low potency antipsychotics, even though non-significant. Nevertheless, none of the other time exposure categories were associated with a risk increase and thus we consider those two observations as probably being chance findings.

The case reports and case series indicating an association between ~~antipsychotics~~antidopaminergic drugs and acute pancreatitis concerned the following compounds previously attributed as atypicals: clozapine,[2 10 13 18] olanzapine,[3 4 8 11-13 17] quetiapine,[7 16] risperidone,[5 6 9 13] aripiprazole,[15] ziprasidone,[19] but also reported on the conventional antipsychotics haloperidol and chlorpromazine.[13 14] However, relying simply on adverse reaction reports would probably exaggerate the possible risk of acute pancreatitis, as case reports have a limited capability to establish causality between drug use and disease outcome in the absence of re-exposure confirmation. There are few epidemiological studies available. A Swedish case-control study observed an overall increased risk for all phenothiazines.[21] However, it included clomethiazole among the phenothiazines, a hypnotic compound which has been one of the first-line treatments for alcohol withdrawal, and adjustments for alcohol co-morbidity were not made. A recent Danish pharmacoepidemiological study found an increased risk for acute pancreatitis among current users of low-potency conventional antipsychotics (mainly levomepromazine) even after

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having adjusted for alcohol related diagnoses, whereas former users of atypicals displayed a decreased risk.[22] The contrasting findings to our study can probably be attributed to different methodology, where we might have reduced residual confounding by alcohol more completely, but it might still be present in the Danish study. This was accomplished in our study, as we used a much broader definition and inclusion of alcohol related diagnoses, and we also included prescription of medications used to treat alcohol dependence.

In conclusion, this large population-based study with complete data on the exposures and outcome indicates that use of ~~antipsychotic~~antidopaminergic drugs is not associated with any increased risk of acute pancreatitis after proper adjustment for confounding by known risk factors for pancreatitis. Therefore, any acute pancreatitis among ~~antipsychotic~~antidopaminergic treated patients might not be attributed to the ~~antipsychotic~~antidopaminergic pharmacotherapy *per se*, but instead to the classical risk factors of acute pancreatitis such as excessive alcohol intake, gallstones and obesity.

Disclosures: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) None of the authors have support from any company for the submitted work; (2) None of the authors have any relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none of the authors have non-financial interests that may be relevant to the submitted work."

Competing interest statement: None.

Contributors: RL came up with the idea for the study. All authors participated in designing the study protocol. FM constructed and maintained the database. RL conducted the statistical analyses. RB and RL drafted the manuscript. All authors revised the manuscript. RL is the guarantor for the study.

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Access to data: All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: No additional data available.

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Table 1. Characteristics of cases with acute pancreatitis and frequency matched population control subjects in Sweden during the period 2006-2008. Generic name for antidopaminergic drugs used time before index date.

	Cases		*Controls*	
	Number	*%*	*Number*	*%*
Total	6161	100.0	61637	100.0
Sex				
Women	2774	45.0	27745	45.0
Men	3387	55.0	33892	55.0
Age group				
40-44 years	522	8.5	5226	8.5
45-49 years	533	8.7	5336	8.7
50-54 years	648	10.5	6480	10.5
55-59 years	749	12.2	7498	12.2
60-64 years	883	14.3	8830	14.3
65-69 years	776	12.6	7760	12.6
70-74 years	702	11.4	7019	11.4
75-79 years	689	11.2	6889	11.2
80-84 years	659	10.7	6599	10.7
Use of other antidopaminergic drugs*				
No use	5967	96.9	60415	98.0
Current (0-114 days)	108	1.8	807	1.3
Recent (115-180 days)	14	0.2	79	0.1
Past (6-12 months)	21	0.3	129	0.2
Former (>12 months)	51	0.8	207	0.3
***Use of* antiemetic/anxiolytic antidopaminergic drugs†**				
No use	6083	98.7	61315	99.5
Current (0-114 days)	36	0.6	201	0.3
Recent (115-180 days)	10	0.2	22	0.0
Past (6-12 months)	13	0.2	40	0.1
Former (>12 months)	19	0.3	59	0.1
Alcohol related diagnoses or drugs for alcoholism‡				
No	5565	90.3	60030	97.4
Yes	596	9.7	1607	2.6
Gallstone related diagnoses§				
No	5086	82.6	59102	95.9
Yes	1075	17.4	2535	4.1

* fluphenazine, perphenazine, flupenthixole, thioridazine, chlorpromazine, haloperidol, pimozide, ziprasidone, aripiprazole, quetipaine, risperidone, paliperidone, clozapine & olanzapine

† dixyrazine, levomepromazine, melperone, proklorperazine

‡ International Classification of disease ICD: E244, F10, G312, G621, G721, I426, K292, K70, O354, or T51 in ICD10 or 291, 303, 305A, 357F, 425F, 535D, 571A, 571B, 571C, 571D, or 980 in ICD9, or drugs used for treatment of alcohol addiction

§ International Classification of disease ICD: K80, or K81 in ICD10,or 574, 575A, or 575B

Table 2. Use of antidopaminergic drugs and acute pancreatitis among 6,161 cases and 61,637 control subjects from 2006-2008 in Sweden. Odds ratios (OR) and 95 % confidence intervals (95% CI). No use of antidopaminergic drugs is the reference category.

	Antiemetic/anxiolytic antidopaminergic drugs*			**Other antidopaminergic drugs†**		
Antidopaminergic drug use. Timebefore index date	Crude‡ OR (95% CI)	Model 1§ OR (95% CI)	Model 2□ OR (95% CI)	Crude‡ OR (95% CI)	Model 1§ OR (95% CI)	Model 2□ OR (95% CI)
No use	1	1	1	1	1	1
Current (0-114 days)	1.9 (1.4-2.6)	1.4 (1.0-1.9)	0.9 (0.6-1.2)	1.4 (1.1-1.6)	1.1 (0.9-1.4)	0.8 (0.6-0.9)
Recent (115-180 days)	3.1 (1.6-5.7)	2.5 (1.3-4.9)	1.6 (0.8-3.0)	1.8 (0.9-3.4)	1.4 (0.7-2.8)	1.2 (0.6-2.4)
Past (6-12 months)	2.3 (1.4-3.9)	1.8 (1.0-3.0)	1.1 (0.6-1.9)	2.3 (1.5-3.7)	1.9 (1.2-3.1)	1.5 (0.9-2.4)
Former (>12 months)	3.2 (2.3-4.5)	2.1 (1.5-3.0)	1.5 (1.0-2.1)	1.5 (0.9-2.4)	1.1 (0.7-1.8)	1.0 (0.6-1.6)

* dixyrazine, levomepromazine, melperone, proklorperazine

† fluphenazine, perphenazine, flupenthixole, thioridazine, chlorpromazine, haloperidol, pimozide, ziprasidone, aripiprazole, quetiapine, risperidone, paliperidone, clozapine & olanzapine

‡Adjusted for age and sex

§Adjusted for history of alcohol related co-morbidity

□Adjusted for history of alcohol related diagnoses or drugs for alcoholism, chronic obstructive lung disease, ischemic heart disease, obesity, diabetes, opioid use, gall stone disease, educational level, marital status, and number of concomitant medications

Supplemental Table 1. Use of antidopaminergic drugs in different classes and acute pancreatitis among 6,161 cases and 61,637 control subjects from 2006-2008 in Sweden. Adjusted odds ratios (OR) and 95 % confidence intervals (95% CI)*. No use of antidopaminergic drugs is the reference category.

Antidopaminergic drug use.	Any		Atypicals		High potency		Medium potency		Low potency	
Timebefore index date	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
No use	1		1		1		1		1	
Current (0-114 days)	0.8	(0.7-0.9)	0.8	(0.6-1.0)	0.9	(0.6-1.3)	0.7	(0.5-1.0)	0.7	(0.5-1.1)
Recent (115-180 days)	1.3	(0.8-2.1)	1.0	(0.3-2.8)	1.5	(0.6-3.8)	0.6	(0.3-1.6)	2.2	(0.9-5.4)
Past (6-12 months)	1.2	(0.8-1.7)	1.0	(0.5-2.0)	1.1	(0.5-2.4)	0.9	(0.5-1.8)	1.1	(0.5-2.2)
Former (>12 months)	1.2	(0.9-1.7)	0.8	(0.4-1.5)	1.1	(0.6-2.3)	1.5	(1.0-2.2)	1.2	(0.6-2.2)

*Adjusted for history of alcohol related diagnoses or drugs for alcoholism, chronic obstructive lung disease, ischemic heart disease, obesity, diabetes, opioid use, gall stone disease, educational level, marital status, and number of concomitant medications

-We would like to start this response letter by thanking both reviewers for their time and effort to improve this manuscript!

Reviewer: 1
This is a very well written manuscript with an important subject. Patients with schizophrenia/users of antipsychotics have been associated with an increased mortality and since the use of antipsychotics has widened we urge more data on the safety of atypical antipsychotics. Especially, nationwide register studies like this.
I only have minor comments:

1) Why were the data not analyzed using a conditional logistic regression? The cases were matched on sex and age, so what was reason for analyzing the data unconditionally? There might be a reason, but please explain.
-Control subjects were randomly selected according to the principle of frequency-based density sampling, matched for age, sex, and calendar year. This control subject sampling method does not directly sample controls to a specific case, but should rather reflect the underlying source population (in the age-sex-calendar year-strata). Hence, conditional logistic regression should not be used. Also see answer to query 4 below.

2) page 4: "experienced recurrent pancreatitis at a much lower doser at re-challenge" What about duration of treatment? did pancreatitis occur earlier the second time?
-Yes. This has been added to the sentence referred to above

3) In addition to number 2: Please add few lines in the introduction about the duration og treatment before pancreatitis develops.

-This is mentioned in the third sentence of the introduction that most cases have a shorter duration than six month of medication.

4) A few years ago we investigated whether clozapine was associated with an increased risk for acute myeloid leucemia. For this analyses we used a minimum exposure based on the Defined Daily Doses. Does it make any sense to use this approach in the current manuscript?

-As the only information we have is DDD, and not Prescribed Daily Doses, we prefer not to use DDD. The DDD is a rather blunt measure, especially when trying to evaluate dose from depot injections.

5) page 7, line 41: Why did you choose a randomly assigned date for controls? Why not use the same date for the controls as for the cases (this in line with number 1 regarding the conditional logistical regression).
-As the controls were not matched to a specific case, but rather should reflect the source population the controls were assigned a random index date. If that index date is within the start- and endpoints of the possible subject that control is eligible as a control. If the control is finally sampled depends on the random sampling.

Reviewer: 2

Comments:
This is a Swedish register study assessing the relationship between antidopaminergic agents and pancreatitis in a large total sample, finding no significant associations after adjustment for relevant covariates.

The study uses straight forward methodology and analyses. The manuscript is very well written and accessible, the limitations are well described. Further strengths include the large and complete overall data base and careful adjustment of the analyses using known risk factors for pancreatitis as relevant covariates.

Overall, I believe that the topic and the "negative" finding are of potential interest and relevance. However, a number of issues reduce the enthusiasm for this manuscript in its current form, which should be addressed in a major revision:

Main Issues:
1. The actual number of pancreatitis cases on current antipsychotic and of antiemetic/anxiolytic treatment is still quite small (n=108 and n=36), with even less patients being in the recent (n=14 and n=10), past (n=21 and n=13) and former (n=51 and n=19) "antipsychotic" use groups. This calls into question whether the study had sufficient power, especially when starting to adjust for this many (relevant) covariates. Thus, I strongly believe that this study can only be useful if the N is increased. The authors should add the data from years 2009 and 2010, which should double their number of cases (and controls) to eliminate the possibility of a type II error in the presented results.
-We agree that adding additional years (2009 and 2010) to foremost increase the number of exposed cases among recent and past users could be valuable. Though, at present we have no possibility to do this. However, we plan to initiate an updated data application also including year 2011, but this cannot be possible until then end of 2012. Despite the possible low power for recent and past users we feel that the findings regarding present users are valid and of great interest and should thus be published as soon as possible. Regarding number of potential confounders in the model we find no extreme difference in the estimates when adding additional covariates. However, we agree that the "fully" adjusted model could be presented with only adding number of concomitant drugs, as this variable seems to be a good proxy for co-morbidity.

2. The second main problem besides the small N of cases includes the occurrence of pancreatitis during hospitalization for which no medication treatment data seem to be available in the Swedish registry (as indicated in the discussion section). This was not clearly noted in the methods section (see #4).
-This has been added to the last sentence in the paragraph "Sources of data" in the Methods section.

3. The authors did not analyze all antidopaminergics together as a secondary analysis, providing additional power, and they did not analyze separately the risk for phenothiazines and low potency, which have been implicated with a higher risk for pancreatitis in one prior epidemiological data set

each (see also #6). Again, to conduct these meaningful and relevant analyses, more data are needed from additional years of observation (see #1).
-These additional analyses have now been performed and these text amendments are added to the very end of the methods and results sections and the numbers as a supplemental table.

Additional points are outlined below:

General comment:
4. Please use the term dopamine blocking medications or antidopaminergics instead of "antipsychotics" if you refer to all D2 blockers that include antiemetics and anxiolytics, which are not "antipsychotics".
-Great idea to increase clarity! This has been changed throughout the manuscript.

Abstract:
5. Accordingly, please revise "Antipsychotics were grouped into antiemetics/anxiolytics and other antipsychotics" to something like "Antidopaminergic agents were grouped into antiemetics/anxiolytics and antipsychotics". (Also: data are plural).
-This has been changed accordingly.

6. Please specify the number of cases in the antiemetic/anxiolytics and in the antipsychotic group.
-Theses numbers are given in table 1.
Methods:
7. It is unclear whether pts with pancreatitis during hospitalization for which no antipsychotic prescription data are available were treated. Were they excluded? How many such cases were there in relationship to the analyzed outpatient cases? Were the inpatient cases counted as "unexposed", as alluded to in the discussion?! This would be a serious problem/confound.
-Exposure is measured from filled prescriptions only. Hence, we have no information on drugs given during hospitalization. A potential misclassification of exposure would be that we miss patients exposed to antipsychotics administered during hospitalization (without any record of a filled prescription), i.e. we do not know what drugs they were given during hospital stay. However, this misclassification would be non-differential, i.e. unrelated to later pancreatitis or not. Thus, this misclassification would dilute the risk estimates towards null results. This could be of a concern as we report no association of antipsychotic use and acute pancreatitis. However, the apparent confounding by foremost disease related to high alcohol consumption speaks against that we miss a true increased risk of pancreatitis.

8. Why were no formal analyses of a dose relationship conducted/presented using DDDs? The lack of a dose response relationship is alluded to in the discussion. DDDs should be available in the prescription data base.
-As the only information we have is DDD, and not Prescribed Daily Doses, we prefer not to use DDD. The DDD is a rather blunt measure, especially when trying to evaluate dose from depot injections.

9. The analyses should also be conducted combining all antidopaminergic agents together and – for comparison sake with the study by Gasse et al (Pharmacotherapy 2008) also separately for low

potency, medium potency and high potency FGAs, as well as SGAs.
-These additional analyses have now been performed and these text amendments are added to the very end of the methods and results sections and the numbers as a supplemental table.

Results:
10. In the texr, please specify the number of cases in the antiemetic/anxiolytics and in the antipsychotic group that the analyses and results are each based on.
-This has been added as a third sentence in the results section

11. Table 1: Please specify the N per each antipsychotic and class.
-The numbers of each class of antidopiminergic drugs are already given in table 1. Giving the numbers of each antipsychotic drug is in our opinion unnecessarily detailed while the calculations are based on composite groups.

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Antidopaminergic drugs and acute pancreatitis – a population based study

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Antidopaminergic drugs and acute pancreatitis – a population based study

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Abstract

Objectives: To evaluate the suggested association between antidopaminergic drugs and acute pancreatitis.

Design: A large population-based nested case-control study.

Setting: Swedish. Nationwide. During 2006-2008.

Participants: The Patient Register was used to identify 6,161 cases of acute pancreatitis. The 61,637 control subjects were randomly selected from the Register of the Total Population by frequency-based density sampling, matched for age, sex, and calendar year.

Exposure: Exposure data were extracted from the Prescribed Drug Register. Antidopaminergic drugs were grouped into antiemetic/anxiolytic and other antipsychotics. Current use of antidopaminergic drugs was defined as filling a prescription 1-114 days before index date, while previous use was 115 days-3½ years before index date.

Main outcome measures: Cases were defined as being diagnosed with acute pancreatitis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression.

Results: The unadjusted OR indicated an increased risk of acute pancreatitis among current users of antiemetic/anxiolytics (OR 1.9, 95% CI 1.4-2.6), but not in the multivariable model adjusting for alcohol related co-morbidity, chronic obstructive lung disease, ischemic heart disease, obesity, diabetes, opioid use, gallstone disease, educational level, marital status, and number of concomitant medications (OR 0.9, 95% CI 0.6-1.2). Similarly, among current users of other antipsychotics, the unadjusted OR was 1.4 (95% CI 1.1-1.6), while the adjusted OR was 0.8 (95% CI 0.6-0.9). Results regarding previous use of antidopaminergic drugs followed a similar risk pattern as for current use.

Conclusions: The lack of association between antidopaminergic drugs and acute pancreatitis after adjustment for confounding factors in this study suggests that the previously reported positive associations might be explained by confounding.

Article Summary

Article focus:

- Case-reports and case-series have suggested a link between use of antidopaminergic drugs and acute pancreatitis.
- The aim of this study was to clarify the relationship between use of antidopaminergic drugs and the risk of acute pancreatitis
- We hypothesized that antidopaminergic drug use increases the risk of acute pancreatitis.

Key messages:

- Our paper suggests that there is no association between antidopaminergic drug treatment and acute pancreatitis when adjusting for potentially confounding variables.
- Further, our findings suggest that the previously reported positive association might be explained by confounding.

Strengths and limitations:

- Major strengths of the study are the population-based design, utilizing a nationwide register, counteracting recall and selection bias.
- Limitations include the relatively small number of acute pancreatitis cases during antidopaminergic exposure, lack of information on medication treatment during hospitalization and lack of information about adherence to the prescribed medications.

~~One limitation is that drug exposure is somewhat uncertain as it is defined as filling a prescription of the drug, which might not imply actually taking the drug~~

Introduction

The incidence of acute pancreatitis is increasing for reasons that are not well understood.[1] The main risk factors, i.e. gallstones and excessive alcohol consumption, are present in approximately 40% and 30% of cases, respectively, while about 25% are of idiopathic (unknown) origin.[1] There have been several case reports of acute pancreatitis during use of antidopaminergic medication.[2-18] Typically, the reported cases had initiated their medication within the 6 months before the onset of acute pancreatitis,[5 7 9 12 15-19] and had recovered after withdrawing or switching antidopaminergic drug.[5 11 12 15-19] Some case reports have also reported recurrent pancreatitis after re-challenge of the suspected drug.[8 18] Two possible biological mechanisms have been suggested. First, a hypersensitivity reaction might be occurring, an explanation which fits well with the observation that some cases have experienced recurrent pancreatitis at a much lower dose and much earlier at re-challenge, and is in line with the well-described hypersensitivity reactions, mainly for clozapine with subsequent agranulocytosis or myocarditis.[18 20] Second, hypertriglyceridemia might be induced by the antidopaminergic drug, resulting in an accumulation of chylomicrons.[17] However, the sparse epidemiological data available have not shown any clear positive association between antidopaminergic medication and the risk of acute pancreatitis.[21 22] Larger epidemiological studies elucidating this possible association are warranted before any association can be established or excluded. The aim of this study was therefore to clarify the relationship between use of antidopaminergic drugs and the risk of acute pancreatitis in a large and population-based study, including adjustment for potential confounders. We hypothesized that antidopaminergic drug use increases the risk of acute pancreatitis.

Method

Study design

A Swedish nationwide, population-based case-control study was performed in the period from January 1, 2006 to December 31, 2008. The source population was defined as all Swedish residents aged between 40 and 84 years. The Patient Register was used to identify cases with a first episode of acute pancreatitis. The Register of the Total Population was used to randomly select control subjects from the general population. Individual data on drug exposure among cases and control subjects were collected from the Prescribed Drug Register. Information on the highest achieved formal educational level was obtained from the Education Register. In order to censor for person-time no longer at risk of being diagnosed with acute pancreatitis in the Patient Register, data regarding emigration and death were obtained from the Register of the Total Population, and the Causes of Death Register, respectively. Additionally, censoring for any cancer was conducted through the Cancer Register. The unique personal identity number assigned to all Swedish residents was used to link individual information between the registers.[23] The study has been approved by the Regional Ethical Review Board in Stockholm.

Sources of data

The Patient Register comprises information on all in-hospital care and outpatient specialist care in Sweden, including codes for diagnoses (according to the "International Classification of Diagnoses" [ICD]) and surgical procedures (according to the "Nordic Classification of Surgical Procedures"). It has complete nationwide coverage of inpatient data since 1987, and complete outpatient specialist care data since 2001.[24]

The Prescribed Drug Register records all medications dispensed to individual patients since July 1st 2005, capturing the entire Swedish population of approximately 9 million inhabitants [25]. This register contains data on drugs, including names of drug substances according to the Anatomical Therapeutic Chemical (ATC) classification.[26] Additionally, it includes information about amount, dosage, and date of expenditure and reimbursement, as well as patient data, including age, sex, and place of residence. The register lacks information regarding indication for treatment, over-the-counter drugs and drugs administered at hospitals during inpatient treatment.

The Cancer Register was set up in 1958, and since then every clinician, pathologist and cytologist in Sweden has been required to notify the National Board of Health and Welfare of every person diagnosed with a new primary malignancy. The Cancer Register includes primary malignancies, and certain benign tumors and precancerous lesions classified according to the ICD system.[27]

The Causes of Death Register contains information on the dates and causes of all deaths of Swedish residents since 1952, with 100% coverage of death dates.[28]

The Register of the Total Population contains individual characteristics of all Swedish residents since 1968 (100% coverage), including sex, age, country of birth, marital status, and place of residence.[29]

The Education Register was established by Statistics Sweden in 1985, and is annually updated with information on the highest formal education attained by each individual, from elementary to post-graduate level.[30]

Case and control identification

Cases were defined as individuals in the study cohort with a first time registered discharge diagnosis in the Patient Register of acute pancreatitis between 2006 and 2008. The code K85 in the 10th version of the ICD represented acute pancreatitis. Control subjects were randomly selected according to the principle of frequency-based density sampling, matched for age, sex, and calendar year. Exposure was considered in relation to an index date assigned to each case and control participant. For case subjects, the index date was set to the date of admission for acute pancreatitis. For control subjects, the index date was a randomly assigned date within the study period. All potential case and control subjects with a previous cancer (apart from non-melanoma cancers of the skin) or any pancreatic disease (defined by the diagnosis codes K85, K86, K87 [ICD-10], and 577 [ICD-9]) recorded in the Patient Register before the study started, were excluded.

Exposure to antidopaminergic drugs

Dispensed drug prescriptions of antidopaminergic drugs were identified by their specific ATC code [N05A] in the Prescribed Drug Register. Only exposure prior to the index date was considered. As drugs for longer-term use typically are dispensed for 3-month periods in Sweden, we assumed that a prescription normally comprised 100 days of drug use, and added a margin of 14 days. Thus, a single prescription of antidopaminergic drugs was assumed to last 114 days. Antidopaminergic drug use was defined as "current", "recent", "past", or "former", if the drug had been dispensed 1-114 days, 115-180 days, 181-365 days, or 1-3½ years before the index date, respectively. Previous use was categorized to enable us to study short-term effects, and better evaluate potential confounding effects of concomitant diseases. Depot formulations were recalculated to fit the above categorization. The absence of any prescription for antidopaminergic drugs was classified as "non-use". Two groups of antidopaminergic drugs were studied separately: 1) *antiemetic/anxiolytics*, including dixyrazine, levomepromazine, melperone, and proklorperazine, and 2) *other antipsychotics*, including fluphenazine, perphenazine, flupenthixole, thioridazine, chlorpromazine, haloperidol, pimozide, ziprasidone, aripiprazole, quetiapine, risperidone, paliperidone, clozapine and olanzapine. A separate analysis of the two most metabolically adverse antipsychotic drugs, clozapine and olanzapine, was also conducted. To facilitate comparison with previous studies we also performed secondary analyses grouping the antidopaminergic drugs into atypical/ typical antipsychotics and subdividing typical into high-, medium-, and low potency antipsychotics. Finally, to maximize power we made an analysis including any antidopaminergic drug use in one group.

Statistical analysis

The relative risk of acute pancreatitis was estimated by unconditional logistic regression, which was used to calculate odds ratios (OR) with 95% confidence intervals (CI). Adjustments were made in three models: 1) A crude model was based on the matching variables only, i.e. sex, age (in 5-year age groups) and the three calendar years, 2) A multivariable model added *i*) history of excessive alcohol consumption or disease related to alcohol, defined by the diagnosis codes E244, F10, G312, G621, G721, I426, K292, K70, O354, T51 in ICD-10 or 291, 303, 305A, 357F, 425F, 535D, 571A, 571B, 571C, 571D, 980 in ICD-9, or use of anti-alcohol drugs defined by the ATC code N07BB, and 3) A full multivariable model further added ii) chronic obstructive lung disease, defined by the diagnosis codes J41, J42, J42, J44 in ICD10 or 491, 492, 496 in ICD-9, *iii*) ischemic heart disease, defined by the diagnosis codes I20 to I25 in ICD-10 or 410 to 413, 414A, 414W in ICD-9, *iv*) obesity, defined by the diagnosis codes E66 in ICD-10 or 278A in ICD9 or anti-obesity drugs defined by the ATC code A08A, *v*) diabetes, defined by the diagnosis codes E10-E14 in ICD10 or 250 in ICD-9 or anti-diabetic medication, defined by the ATC code A10, *vi*) opioid drug use, defined by the ATC code N02A, *vii*) gallstone disease, defined by the diagnosis codes 574, 575A, or 575B in ICD9 or K80, K81 in ICD10, *viii*) educational level (divided into three categories of highest attained education: elementary school, secondary school, university, and one category for missing data [2.3% among cases and 1.6 % among controls]), *ix*) marital status (categorized as married or not), *x*) a co-morbidity score based on number of distinct medications. The co-morbidity score was defined as the sum of unique 7-digit ATC codes dispensed during the 6 months prior to the index date, and was categorized as 0-4, 5-9, 10-14, or ≥15 drugs. Presence of the listed diseases or conditions was determined by a recorded hospitalization or outpatient visit according to the Patient Register since 1987, or a dispensed prescription between July 1, 2005 and the index date. In a sub

analysis, the study period was restricted to 2007 and 2008 to account for the fact that the study participants, depending on their index date, had different follow-up times from the start of the Prescribed Drug Register on July 1, 2005. Hence, for some participants included throughout the entire study period, we could assess drug exposure only 1-180 days before the index date. In addition, the association between antidopaminergic medication and acute pancreatitis was studied among those with and without a previous hospital record of psychosis, defined by the diagnosis codes F20-F29 in ICD10 or 295, 296, 297, 298 in ICD9. The SAS statistical software package EG 4.2 (SAS Institute, Cary, N.C., USA) was used for the analyses.

Results

Study participants

The study included 6,161 cases of acute pancreatitis and 61,637 control subjects. Characteristics of the study participants are presented in Table 1. The frequency-based sampling produced a similar age and sex (and calendar year) distribution among cases and control subjects. Among the cases, 194 had used antiemetic/anxiolytic antidopaminergic drugs and 78 had used other antipsychotics. Current and previous use of antiemetic/anxiolytics, as well as other antipsychotics, was more common among cases than controls (Table 1). All covariates presented in the methods section were overrepresented among the case subjects compared to the control participants. This was especially evident for factors representing lifestyle. Diseases related to alcohol overconsumption were, for example, four times more common in cases than controls (Table 1).

Antiemetic/anxiolytics and risk of acute pancreatitis

Table 2 presents the ORs for the association between antiemetic/anxiolytics use, and other antipsychotic medication, and the risk of developing acute pancreatitis. The ORs in the crude model, adjusting for the matching variables, indicated an increased risk among current users of antiemetic/anxiolytics (OR=1.9, 96% CI 1.4-2.6) as well as for each of the categories representing previous use of antiemetic/anxiolytics (Table 2). In the multivariable model, adjusting for alcohol related co-morbidity, the risk among current users of antiemetic/anxiolytics was attenuated (OR=1.4, 95% CI 1.0-1.9), and in the full multivariable model, no increased risk for acute pancreatitis was observed for current use of antiemetic/anxiolytic (OR=0.9, 95% CI 0.6-1.2).

Other antipsychotic medication and risk of acute pancreatitis

Correspondingly, current use of other antipsychotics was associated with an increased risk of acute pancreatitis in the crude model (OR=1.4, 95% CI 1.1-1.6). However, this risk increase disappeared after adjusting for confounding by alcohol related co-morbidity (OR=1.1, 95% CI 0.9-1.4). Each of the categories representing previous use of other antipsychotics showed a similar decrease in the ORs from the crude model to the fully adjusted model (Table 2).

For current use of clozapine or olanzapine, the OR in the crude model was 1.6 (95% CI 1.1-2.3), and decreased to 0.9 (95% CI 0.6-1.4) in the full multivariable model.

Stratifying by sex did not reveal any major differences between the sexes (data not shown). When stratifying by age, the results for the group younger than 65 were similar to those of the main analysis, but among those 65 and older, the OR for current use was close to unity in both the crude and the fully adjusted model (data not shown). Among participants younger than 65 years, the group with a previous history of alcohol overconsumption had no increased risk of acute pancreatitis associated with current use of other antipsychotics, in either the crude or the full multivariable model (OR 0.8, 95% CI 0.5-1.3 and OR 0.8, 95% CI 0.5-1.2, respectively). However, participants without such history of alcohol overconsumption rendered similar results as in the main analysis (data not shown). Individuals with a previous hospital record of psychosis had no increased risk for current use of other antipsychotics in the crude or full multivariable model (data not shown). However, participants with a previous hospital record of psychosis who had stopped other antipsychotic medication within the last 3 months were at an increased risk of acute pancreatitis after adjustment in the multivariable model (OR 4.0 95% 1.4 -11.2). Stratifying by calendar year (2006 and 2007-08) rendered similar results as in the main analysis (data not shown).

Analyzing cumulative dose of antidopaminergic drugs since start of the Drug Register in 1st July, 2005 and risk of acute pancreatitis yielded the highest OR for the lowest quartiles of total amount of Daily Defined Dose (DDD) (OR 2.0, 95% CI 1.58-2.51) and the lowest OR for the 10% with the highest amount of DDD (OR=0.93, 95% CI 0.72-1.21) in the crude model. Adjustment for alcohol related diseases attenuated the association for all categories of cumulative dose (data not shown).

Within 114 days of pancreatitis 1098 (18%) of cases were hospitalized at least once, for within 60 days before and 30 days before the corresponding hospitalized cases were, 850 (14%) and 608 (9.9%), respectively. The corresponding figures for hospitalization in a psychiatric ward was, 78 (1.3%), 43 (0.7%), and 26 (0.4%), respectively. The median length of stay for somatic hospitalizations was 4.3, and 3 days for the three time intervals respectively and for psychiatric hospitalizations 4.3, and 2 days.

The secondary analyses of atypical antipsychotics and three potency groups of typical antipsychotics showed low or no risk increase except for former use of medium potency antipsychotics and a non-significant increased risk for recent use of low potency antipsychotics (Supplemental Table I and II). Use of any antidopaminergic drug was not associated with increased risk of acute pancreatitis.

Discussion

This population-based study found no association between current use of antidopaminergic medication and acute pancreatitis after adjustment for potential confounding factors.

Among strengths of the study is the population-based design, utilizing a nationwide register, counteracting recall and selection bias. Other advantages include the large sample size, the complete nationwide coverage of the exposure (antidopaminergic drugs) and the outcome (acute pancreatitis), and the adjustment for several potential confounding factors. Misclassification of the outcome in the Patient Register is a possible concern, but the high validity of the diagnosis of acute pancreatitis in this register has recently been shown by our group to have a positive predictive value of 98%.[31] There are, however, also several weaknesses. We regarded a dispensed prescription of antidopaminergic drugs as an exposure, but there was no information on whether the patients had actually taken their medication. This potential misclassification of the exposure would~~, however,~~ most likely be non-differential, i.e. not associated with risk for future acute pancreatitis, and thus ~~only~~ dilute the risk estimates towards null results. Additionally, there was no information on drugs administered during in-hospital care, and no information on indication for treatment. This might lead to a misclassification resulting in some of the patients with probably the highest doses of antidopaminergic drugs (being inpatient treated) being classified as not having been exposed to antidopaminergic drugs. However, as other hospitalizations prior to index hospitalization for acute pancreatitis were not common and were of short duration we consider this potential misclassification negligible. ~~We could not investigate any potential dose-response relation due to the lack of detailed information on drug dosages.~~ Moreover, detailed patient information is not available in registers, particularly regarding some potential confounding factors. It could,

for instance, be possible that substantial alcohol consumption, smoking or obesity could not be captured with the variables retrieved from the national registers. Nevertheless, several potential confounding variables were adjusted for, and the results clearly show that confounding by these factors did occur, and were seemingly sufficiently adjusted for. There is no reason to believe that misclassification of alcohol exposure would be a greater concern among the controls than the cases.

Use of antidopaminergic drugs in our study was associated with an increased risk of acute pancreatitis in the crude models, but after adjustment for known risk factors for acute pancreatitis this association disappeared. The principal confounding effect seemed to be through alcohol, as the major decrease of the elevated risk of acute pancreatitis among users of antidopaminergic drugs was attenuated when adjusting for alcohol related diagnoses and drug treatments for alcohol dependence. This confounding may be for two different reasons. First, antidopaminergic drugs are used as a non-addictive alternative to treat withdrawal, agitation and anxiety among patients with alcohol dependence.[32] Second, alcohol dependence is overrepresented among patients with severe mental illnesses, where antidopaminergic drugs often are the first-line treatment.[33] Not all of the increased risk disappeared after adjusting for alcohol; instead, the effect entirely disappeared only after further adjustment for additional known risk factors for acute pancreatitis, i.e. chronic medical conditions, sociodemographic factors, obesity and gallstone related diseases.

This study revealed no association between clozapine and olanzapine and the risk of acute pancreatitis. These two antipsychotic drugs are known to be particularly obesogenic, diabetogenic, and with high liability of inducing lipid abnormalities.[34-36] Yet, other studies have shown that obesity, as well as diabetes, might increase the risk of acute pancreatitis.[37 38]

Further, in our study, patients with a previous hospital record of psychosis who had stopped using other antipsychotic medication within the previous 3 months had an increased risk of acute pancreatitis which remained after full adjustment. One possible explanation of this delay in the effect is that patients with a psychotic disorder are more non-adherent to pharmacotherapy when suffering from a comorbid alcohol abuse disorder.[39] Thus, patients might have stopped their antipsychotic medication following a period of excessive alcohol intake, which subsequently may have led to an acute pancreatitis.

Before the analyses, we chose to divide antidopaminergic drugs into two groups according to the main clinical usage pattern. The antidopaminergic drugs in the group antiemetic/anxiolytics are typically used intermittently and in lower doses than other groups of antidopaminergic drugs. Notably, users of antiemetic/anxiolytic had a higher crude risk of acute pancreatitis than users of other antipsychotics in our study, although they probably received lower total doses. However, one might speculate that if the antidopaminergic drugs in the antiemetic/anxiolytic group are used more often for treatment of withdrawal and anxiety in the post detoxification phase from alcohol, than other antipsychotics, it would explain this discrepancy. Other studies have chosen to divide antidopaminergic drugs into conventional and atypical antipsychotics,[13 22] but the rationale behind such categorization has been criticized, and recently has been proposed to be abandoned due to the great overall heterogeneity within these groups.[40] However, for the sake of comparison with a recent Danish case-control study,[22] we performed secondary analyses with the same categorization of the antidopaminergic drugs. Former use of medium potency antipsychotics was associated with increased risk of pancreatitis, as was recent use of low potency antipsychotics, even though non-significant. Nevertheless, none of the other time exposure categories were

associated with a risk increase and thus ~~we consider~~ it is possible that those two observations ~~as probably being~~are chance findings. However, an actual effect cannot be entirely ruled out as similar results have been found previously and the confidence intervals in the present study are relatively large. However, it is reassuring that, at least, no findings in the current use group approached significance and that there was an inverse relationship between cumulative DDD and risk of pancreatitis. Nevertheless studies with larger numbers of patients exposed to these individual agents are needed to confirm our findings.

The case reports and case series indicating an association between antidopaminergic drugs and acute pancreatitis concerned the following compounds previously attributed as atypicals: clozapine,[2 10 13 18] olanzapine,[3 4 8 11-13 17] quetiapine,[7 16] risperidone,[5 6 9 13] aripiprazole,[15] ziprasidone,[19] but also reported on the conventional antipsychotics haloperidol and chlorpromazine.[13 14] However, relying simply on adverse reaction reports would probably exaggerate the possible risk of acute pancreatitis, as case reports have a limited capability to establish causality between drug use and disease outcome in the absence of re-exposure confirmation. There are few epidemiological studies available. A Swedish case-control study observed an overall increased risk for all phenothiazines.[21] However, it included clomethiazole among the phenothiazines, a hypnotic compound which has been one of the first-line treatments for alcohol withdrawal, and adjustments for alcohol co-morbidity were not made. A recent Danish pharmacoepidemiological study found an increased risk for acute pancreatitis among current users of low-potency conventional antipsychotics (mainly levomepromazine) even after having adjusted for alcohol related diagnoses, whereas former users of atypicals displayed a decreased risk.[22] The contrasting findings to our study can probably be attributed to different methodology, where we might have reduced residual

confounding by alcohol more completely, but it might still be present in the Danish study. This was accomplished in our study, as we used a much broader definition and inclusion of alcohol related diagnoses, and we also included prescription of medications used to treat alcohol dependence.

In conclusion, this large population-based study with complete data on the exposures and outcome indicates that use of antidopaminergic drugs is not associated with any increased risk of acute pancreatitis after proper adjustment for confounding by known risk factors for pancreatitis. Therefore, any acute pancreatitis among antidopaminergic treated patients might not be attributed to the antidopaminergic pharmacotherapy *per se*, but instead to the classical risk factors of acute pancreatitis such as excessive alcohol intake, gallstones and obesity.

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Data sharing: No additional data available.

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Table 1. Characteristics of cases with acute pancreatitis and frequency matched population control subjects in Sweden during the period 2006-2008. Generic name for antidopaminergic drugs used time before index date.

	Cases		*Controls*	
	Number	*%*	*Number*	*%*
Total	6161	100.0	61637	100.0
Sex				
Women	2774	45.0	27745	45.0
Men	3387	55.0	33892	55.0
Age group				
40-44 years	522	8.5	5226	8.5
45-49 years	533	8.7	5336	8.7
50-54 years	648	10.5	6480	10.5
55-59 years	749	12.2	7498	12.2
60-64 years	883	14.3	8830	14.3
65-69 years	776	12.6	7760	12.6
70-74 years	702	11.4	7019	11.4
75-79 years	689	11.2	6889	11.2
80-84 years	659	10.7	6599	10.7
Use of other antidopaminergic drugs*				
No use	5967	96.9	60415	98.0
Current (0-114 days)	108	1.8	807	1.3
Recent (115-180 days)	14	0.2	79	0.1
Past (6-12 months)	21	0.3	129	0.2
Former (>12 months)	51	0.8	207	0.3
***Use of* antiemetic/anxiolytic antidopaminergic drugs†**				
No use	6083	98.7	61315	99.5
Current (0-114 days)	36	0.6	201	0.3
Recent (115-180 days)	10	0.2	22	0.0
Past (6-12 months)	13	0.2	40	0.1
Former (>12 months)	19	0.3	59	0.1
Alcohol related diagnoses or drugs for alcoholism‡				
No	5565	90.3	60030	97.4
Yes	596	9.7	1607	2.6
Gallstone related diagnoses§				
No	5086	82.6	59102	95.9
Yes	1075	17.4	2535	4.1

* fluphenazine, perphenazine, flupenthixole, thioridazine, chlorpromazine, haloperidol, pimozide, ziprasidone, aripiprazole, quetipaine, risperidone, paliperidone, clozapine & olanzapine

† dixyrazine, levomepromazine, melperone, proklorperazine

‡ International Classification of disease ICD: E244, F10, G312, G621, G721, I426, K292, K70, O354, or T51 in ICD10 or 291, 303, 305A, 357F, 425F, 535D, 571A, 571B, 571C, 571D, or 980 in ICD9, or drugs used for treatment of alcohol addiction

§ International Classification of disease ICD: K80, or K81 in ICD10,or 574, 575A, or 575B

Table 2. Use of antidopaminergic drugs and acute pancreatitis among 6,161 cases and 61,637 control subjects from 2006-2008 in Sweden. Odds ratios (OR) and 95 % confidence intervals (95% CI). No use of antidopaminergic drugs is the reference category.

	Antiemetic/anxiolytic antidopaminergic drugs*			Other antidopaminergic drugs†		
Antidopaminergic drug use. Time before index date	Crude‡ OR (95% CI)	Model 1§ OR (95% CI)	Model 2□ OR (95% CI)	Crude‡ OR (95% CI)	Model 1§ OR (95% CI)	Model 2□ OR (95% CI)
No use	1	1	1	1	1	1
Current (0-114 days)	1.9 (1.4-2.6)	1.4 (1.0-1.9)	0.9 (0.6-1.2)	1.4 (1.1-1.6)	1.1 (0.9-1.4)	0.8 (0.6-0.9)
Recent (115-180 days)	3.1 (1.6-5.7)	2.5 (1.3-4.9)	1.6 (0.8-3.0)	1.8 (0.9-3.4)	1.4 (0.7-2.8)	1.2 (0.6-2.4)
Past (6-12 months)	2.3 (1.4-3.9)	1.8 (1.0-3.0)	1.1 (0.6-1.9)	2.3 (1.5-3.7)	1.9 (1.2-3.1)	1.5 (0.9-2.4)
Former (>12 months)	3.2 (2.3-4.5)	2.1 (1.5-3.0)	1.5 (1.0-2.1)	1.5 (0.9-2.4)	1.1 (0.7-1.8)	1.0 (0.6-1.6)

* dixyrazine, levomepromazine, melperone, prochlorperazine

† fluphenazine, perphenazine, flupenthixole, thioridazine, chlorpromazine, haloperidol, pimozide, ziprasidone, aripiprazole, quetiapine, risperidone, paliperidone, clozapine & olanzapine

‡Adjusted for age and sex

§Adjusted for history of alcohol related co-morbidity

□Adjusted for history of alcohol related diagnoses or drugs for alcoholism, chronic obstructive lung disease, ischemic heart disease, obesity, diabetes, opioid use, gall stone disease, educational level, marital status, and number of concomitant medications

Supplemental Table I. Use of antidopaminergic drugs in different classes and acute pancreatitis among 6,161 cases and 61,637 control subjects from 2006-2008 in Sweden. Adjusted odds ratios (OR) and 95 % confidence intervals (95% CI)*. No use of antidopaminergic drugs is the reference category.

Antidopaminergic drug use.	Any		Atypicals		High potency typicals		Medium potency typicals		Low potency typicals	
Time before index date	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
No use	1		1		1		1		1	
Current (0-114 days)	0.8	(0.7-0.9)	0.8	(0.6-1.0)	0.9	(0.6-1.3)	0.7	(0.5-1.0)	0.7	(0.5-1.1)
Recent (115-180 days)	1.3	(0.8-2.1)	1.0	(0.3-2.8)	1.5	(0.6-3.8)	0.6	(0.3-1.6)	2.2	(0.9-5.4)
Past (6-12 months)	1.2	(0.8-1.7)	1.0	(0.5-2.0)	1.1	(0.5-2.4)	0.9	(0.5-1.8)	1.1	(0.5-2.2)
Former (>12 months)	1.2	(0.9-1.7)	0.8	(0.4-1.5)	1.1	(0.6-2.3)	1.5	(1.0-2.2)	1.2	(0.6-2.2)

*Adjusted for history of alcohol related diagnoses or drugs for alcoholism, chronic obstructive lung disease, ischemic heart disease, obesity, diabetes, opioid use, gall stone disease, educational level, marital status, and number of concomitant medications

Supplement Table II. Characteristics of cases with acute pancreatitis and frequency matched population control subjects in Sweden during the period 2006-2008. Generic name for antipsychotic drugs used time before index date.

	Cases		*Controls*	
	Number	*%*	*Number*	*%*
Total	6161	100.0	61637	100.0
***Use of* atypicals**				
No use	6051	98.2	60877	98.8
Current (0-114 days)	81	1.3	565	0.9
Recent (115-180 days)	4	0.1	32	0.1
Past (6-12 months)	12	0.2	66	0.1
Former (>12 months)	13	0.2	97	0.2
***Use of* high potency typicals**				
No use	6107	99.1	61303	99.5
Current (0-114 days)	29	0.5	199	0.3
Recent (115-180 days)	6	0.1	28	0.0
Past (6-12 months)	8	0.1	50	0.1
Former (>12 months)	11	0.2	57	0.1
***Use of* medium potency typicals**				
No use	6067	98.5	61159	99.2
Current (0-114 days)	33	0.5	219	0.4
Recent (115-180 days)	6	0.1	44	0.1
Past (6-12 months)	12	0.2	73	0.1
Former (>12 months)	43	0.7	142	0.2
***Use of* low potency typicals**				
No use	6096	98.9	61326	99.5
Current (0-114 days)	31	0.5	205	0.3
Recent (115-180 days)	8	0.1	17	0.0
Past (6-12 months)	11	0.2	37	0.1
Former (>12 months)	15	0.2	52	0.1