Antipsychotics and Associated Risk of Out-of-Hospital Cardiac Arrest

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Antipsychotic drugs have been associated with sudden cardiac death, but differences in the risk of out-of-hospital cardiac arrest (OHCA) associated with different antipsychotic drug classes are not clear. We identified all OHCAs in Denmark (2001–2010). The risk of OHCA associated with antipsychotic drug use was evaluated by conditional logistic regression analysis in case–time–control models. In total, 2,205 (7.6%) of 28,947 OHCA patients received treatment with an antipsychotic drug at the time of the event. Overall, treatment with any antipsychotic drug was associated with OHCA (odds ratio (OR) = 1.53, 95% confidence interval (CI): 1.23–1.89), as was use with typical antipsychotics (OR = 1.66, CI: 1.27–2.17). By contrast, overall, atypical antipsychotic drug use was not (OR = 1.29, CI: 0.90–1.85). Two individual typical antipsychotic drugs, haloperidol (OR = 2.43, CI: 1.20–4.93) and levomepromazine (OR = 2.05, CI: 1.18–3.56), were associated with OHCA, as was one atypical antipsychotic drug, quetiapine (OR = 3.64, CI: 1.59–8.30).

Psychiatric diseases are disabling and are associated with increased morbidity and mortality.[1] Antipsychotic drugs are commonly used to alleviate symptoms among patients with psychiatric disorders[2] but have been associated with risk of sudden cardiac death (SCD).[3] Although SCD is one of the most important causes of death in the industrialized world, it is unknown as to what extent adverse drug reactions may contribute to the overall SCD burden.[4] Previous studies have identified adverse drug reactions as one of the leading causes of death among hospitalized patients.[5] Hence, it is likely that a considerable amount of all out-of-hospital cardiac arrests (OHCAs) could in fact be drug induced.

Antipsychotic drugs are traditionally divided into typical and atypical antipsychotics based on their mechanism of action and ability to produce extrapyramidal adverse effects.[6] Atypical antipsychotics have largely replaced typical antipsychotics in clinical practice as the drug class of choice due to their risk profile, which is considered more benign than that of typical antipsychotics, although recent data have questioned this notion.[7]

Although there is a large burden of evidence linking antipsychotics with increased risk of SCD,[8,9] in a dose-dependent manner,[7,10,11] it is unclear whether there are differences in the risks of a cardiac arrest in an out-of-hospital setting associated with typical and atypical antipsychotic drug use. It is also uncertain whether there are differences in the risks of OHCA associated with specific antipsychotics within drug classes. In the current study, we evaluated the association between the most commonly used antipsychotics and OHCA in a nationwide unselected cohort.

RESULTS

In total, 28,947 patients with an OHCA were identified from the Danish Cardiac Arrest Register (2001–2010). Of these, 2,205 (7.6%) were in treatment with a total of 2,650 antipsychotics at the time of OHCA (i.e., the case period): 1,834 patients were in treatment with one antipsychotic drug, 302 were in treatment with two antipsychotic drugs, 64 were in treatment with three antipsychotic drugs, and five were in treatment with 4 antipsychotic drugs. Among the patients in treatment with an antipsychotic drug during the case period, the median age was 66.4 years (interquartile range (IQR): 54.3–78.3), with women comprising 50.7% (n = 1,117). A total of 1,196 of 2,205 patients (54.3%) were in monotherapy with a typical antipsychotic, 766 of 2,205 (34.7%) were in monotherapy with an atypical

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antipsychotic, and 243 of 2,205 (11.0%) were in concurrent treatment with both a typical and an atypical antipsychotic drug. Although there were few statistically significant differences in clinical characteristics stratified by the type of antipsychotic used (typical antipsychotics, atypical antipsychotics, or both), patients in concurrent treatment with both typical and atypical antipsychotics at the time of OHCA were younger and more likely to have a hospital admission for a psychiatric disease compared with patients in treatment with an antipsychotic belonging to one drug class only (typical or atypical) ($P < 0.001$). No difference in ischemic heart disease, previous myocardial infarction, or heart failure was identified among OHCA patients in treatment with typical or atypical antipsychotics ($P > 0.05$ for all). Overall, 39.5% of all OHCA patients in antipsychotic treatment had been hospitalized within 5 years of the event for a psychiatric-related disorder. When we extended this definition to include outpatient visits as well, 46.6% of patients had a history of a psychiatric disorder. The clinical characteristics of patients in treatment with an antipsychotic at the time of OHCA are listed in **Table 1**. Nineteen percent ($n = 419$) of OHCA patients who were in treatment with an antipsychotic at the time of OHCA also had a history of substance abuse.

Trends in antipsychotic usage

Figure 1 depicts the proportion of OHCA patients and age- and gender-matched controls in treatment with an antipsychotic drug over time. The overall proportion of OHCA patients in treatment with an antipsychotic drug at the time of OHCA increased from 2001 to 2010 (6.7% and 7.8%, respectively, P for trend <0.001). Among OHCA patients treated with antipsychotics, use of atypical antipsychotics increased from 2001 to 2010; whereas use of typical antipsychotics decreased (P for trend <0.001 for both) (**Figure 1**).

Case–time–control analyses

Overall, treatment with any type of antipsychotic was significantly associated with risk of OHCA (OR = 1.53, CI: 1.23–1.89). Analyzing typical antipsychotics and atypical antipsychotics separately yielded the following associations with OHCA: OR = 1.66, CI: 1.27–2.17 and OR = 1.29, CI: 0.90–1.85, respectively. Among the 243 OHCA patients in treatment with both a typical and an atypical antipsychotic at the time of OHCA, no additional risk of OHCA was identified (OR = 1.10, CI: 0.39–3.09; 97 patients contributed to the analysis). In addition, 371 patients were in treatment with ≥2 different antipsychotics at the time of the event; no associated risk was identified (OR = 0.96, CI: 0.43–2.18; 144 patients contributed to the analysis).

The main results from the case–time–control analyses, including the number of OHCA patients contributing to the analysis, are depicted in **Figure 2**. In total, we identified three different antipsychotic drugs to be significantly associated with OHCA: the typical antipsychotics haloperidol (OR = 2.43, CI: 1.20–4.93) and levomepromazine (OR = 2.05, CI: 1.18–3.56), and the atypical antipsychotic quetiapine (OR = 3.64, CI: 1.59–8.30). No significant associations with OHCA were identified for flupentixol, zuclopenthixol, prochlorperazine, perphenazine, chlorprotixene, olanzapine, risperidone, or clozapine (**Figure 2**). Detailed information on who contributed to each analysis is listed in **Supplementary Table S1** online.

We also performed a dose–response analysis among patients who were in treatment in both the case and the control periods and who experienced a change in dosing between the two periods, using median doses for each drug. **Supplementary Table S2** online lists the medians and IQRs of each antipsychotic drug. **Figure 3** depicts the results from the dose–response analysis using medians to determine high and low doses.

Sensitivity analysis

We used 30-day treatment periods in our main case–time–control analyses, whereas we used 20- and 40-day treatment intervals for our sensitivity analyses. The case–time–control results using 20- and 40-day treatment intervals for the antipsychotic drug significantly correlated with OHCA from the main case–time–control analysis: levomepromazine (OR = 1.90, CI: 1.01–3.58 and OR = 2.24, CI: 1.34–3.76, respectively), haloperidol (OR = 1.66, CI: 0.76–3.58 and OR = 3.38, CI: 1.77–6.44, respectively), and quetiapine (OR = 3.62, CI: 1.39–9.43 and OR = 1.74, CI: 0.83–3.65, respectively).

Additional analyses among patients with no hospital admission within the 60 days before OHCA did not affect our findings regarding the positive correlation between OHCA and quetiapine. No significant association was identified for levomepromazine (OR = 1.43, CI: 0.75–2.75; 76 contributed to the analysis) or haloperidol (OR = 1.92, CI: 0.69–5.39, 33 contributed to the

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Although antipsychotic drugs have previously been associated with SCD, it is unclear whether there are differences in the risk of a cardiac arrest in an out-of-hospital setting that are associated with the type of antipsychotic drug being used.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ This study evaluated the possible association between antipsychotic drug use and OHCA in a nationwide cohort of Danish OHCA patients (2001–2010) using conditional logistic regression analysis in case–time–control models.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ This study found that overall, antipsychotic drug use is associated with OHCA. Moreover, overall use of typical antipsychotic drugs was associated with OHCA, whereas atypical antipsychotic drug use was not. Significant associations between OHCA and specific antipsychotic drugs were identified for haloperidol, levomepromazine, and quetiapine.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ This study adds to the existing body of literature on the associations between psychotropic drugs and risk of cardiac arrest and SCD and may help clinicians decide which antipsychotic drugs to prescribe.

Table 1 Characteristics of out-of-hospital cardiac arrest patients in treatment with an antipsychotic at the time of event

		Typical antipsychotics	Atypical antipsychotics	Both
N (%)	2,205	1,196 (54.2)	766 (34.7)	243 (11.0)
Overall age, years (IQR)	66.4 (54.3–78.3)	66.9 (56.1–77.1)	70.7 (55.9–81.2)	55.4 (42.8–65.5)
Male (%)	1,088 (49.3)	591 (49.4)	377 (49.2)	120 (49.4)
Age, years (IQR)	63.5 (50-9-76.0)	65.1 (53.9–74.8)	65.1 (50.8–78.8)	50.5 (39.3–62.2)
Women (%)	1,117 (50.7)	605 (50.6)	389 (50.8)	123 (50.6)
Age, years (IQR)	69.2 (57.9–80.4)	68.8 (58.4–79.4)	74.9 (62.6–83.5)	59.6 (47.8–67.2)
Income group (%)				
0 (lowest income quintile)	186 (8.4)	118 (9.8)	59 (7.7)	9 (3.7)
1	500 (22.7)	299 (25.0)	167 (21.8)	34 (14.0)
2	861 (39.1)	464 (38.8)	294 (38.4)	103 (42.4)
3	512 (23.2)	237 (19.8)	188 (24.5)	87 (35.8)
4 (highest income quintile)	146 (6.6)	78 (6.6)	58 (7.6)	10 (4.1)
Comorbidity (%)				
Diabetes	305 (13.8)	166 (13.9)	104 (13.8)	35 (14.4)
Peripheral vascular disease	76 (3.5)	53 (4.4)	21 (2.7)	2 (0.8)
Previous myocardial infarction	115 (5.2)	73 (6.1)	37 (4.8)	5 (2.1)
Ischemic heart disease	262 (11.9)	149 (12.5)	91 (11.9)	22 (9.1)
Heart failure	264 (12.0)	158 (13.2)	88 (11.5)	18 (7.4)
COPD	385 (17.5)	249 (20.8)	99 (12.9)	37 (15.2)
Cancer	148 (6.7)	99 (8.3)	39 (5.1)	10 (4.1)
Dementia	162 (7.4)	39 (3.3)	113 (14.8)	10 (4.1)
Psychosis	291 (13.2)	75 (6.3)	134 (17.5)	82 (33.7)
Depression	197 (8.9)	81 (6.8)	102 (13.3)	14 (5.8)
Any psychiatric disease	871 (39.5)	347 (29.0)	385 (50.3)	139 (57.2)
Charlson Score (IQR)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–1)
Concomitant pharmacotherapy (%)				
Lipid-lowering drugs	227 (10.3)	116 (9.7)	89 (11.6)	22 (9.1)
Loop diuretics	602 (27.3)	358 (29.9)	202 (26.4)	42 (17.3)
β-Blockers	292 (13.2)	163 (13.6)	103 (13.5)	26 (10.7)
ACE inhibitors	351 (15.9)	200 (16.7)	121 (15.8)	30 (12.4)
Lithium	67 (3.0)	28 (2.3)	30 (3.9)	9 (3.7)
Antidepressants	1,019 (46.2)	485 (40.6)	411 (53.7)	123 (50.6)
Anxiolytics	1,074 (48.7)	632 (52.8)	321 (41.9)	121 (49.8)

Typical antipsychotics: flupentixol, haloperidol, zuclopenthixol, perphenazine, levomepromazine, and chlorprotixene; atypical antipsychotics: olanzapine, risperidone, clozapine, and quetiapine. Dichotomous variables are given in absolute numbers and percentages. Continuous variables are given in medians and interquartile range IQRs.

ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

analysis). We also examined all patients with no cancer diagnosis during the 5 years before OHCA (including hospital admissions and outpatient clinic visits), which yielded results similar to the main case–time–control analysis: haloperidol (OR = 2.38, CI: 1.05–5.41), levomepromazine (OR = 1.89, CI: 1.07–3.35), and quetiapine (OR = 4.06, CI: 1.71–9.67). No additional positive associations were identified for other antipsychotics. Finally, excluding patients with a history of substance abuse, patients receiving nonoral antipsychotics, patients who died from a suicide, or patients <18 years old did not affect our findings.

DISCUSSION

In this nationwide cohort study, we evaluated the risk of OHCA associated with the most commonly used antipsychotic drugs from 2001 to 2010 in Denmark. Our study yielded three main findings. First, we identified that overall use of antipsychotic drugs was associated with increased risk of OHCA. Second, overall use of any typical antipsychotic drug was associated with OHCA; whereas use of atypical antipsychotic drugs was not, although the latter trended in the same direction. Third, of the antipsychotics tested, significant associations were

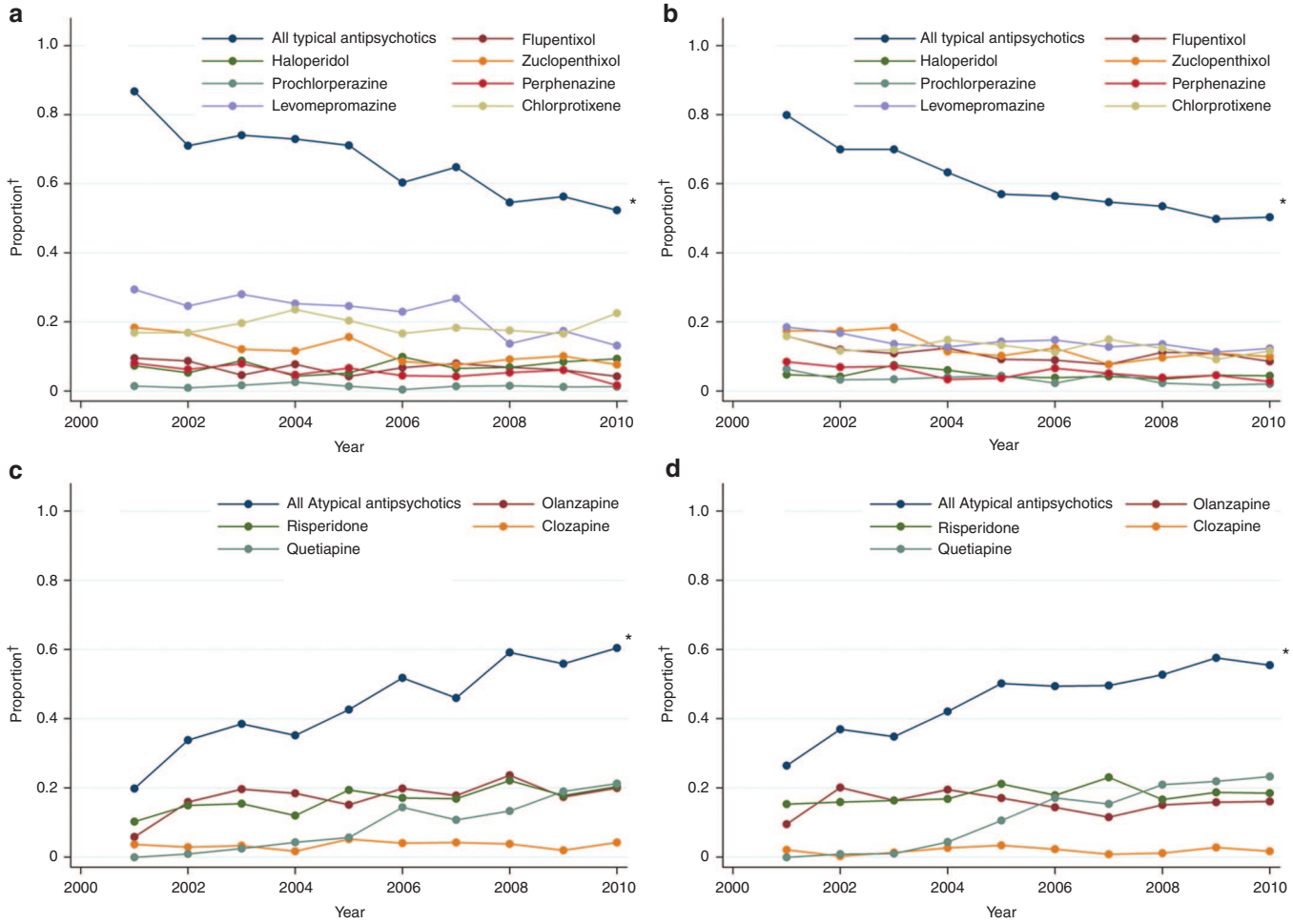

Figure 1 Trends in specific antipsychotic drug usage within 30 days before the event among antipsychotic-treated individuals who experienced an OHCA from 2001 to 2010 and age- and gender-matched controls. All typical antipsychotics: flupentixol, haloperidol, zuclopenthixol, prochlorperazine, perphenazine, levomepromazine, chlorprotixene; all atypical antipsychotics: olanzapine, quetiapine, risperidone, and clozapine. (**a**) Proportion of cases in treatment with a typical antipsychotic; (**b**) proportion of controls in treatment with a typical antipsychotic; (**c**) proportion of cases in treatment with an atypical antipsychotic; and (**d**) proportion of controls in treatment with an atypical antipsychotic. In total, 2,205 of 28,947 (7.6) OHCA cases and 2,729 of 115,788 (2.4%) age- and gender-matched controls were in treatment with an antipsychotic within 30 days before the event. OHCA, out-of-hospital cardiac arrest. **P* value for trend <0.05. †Yearly proportions: *n* in treatment with specific antipsychotic/overall *n* in treatment with an antipsychotic.

identified for haloperidol, levomepromazine, and quetiapine. A dose–response analysis was explored but was underpowered for evaluating clinically meaningful doses.

The use of atypical antipsychotics has risen dramatically in recent years due to atypical antipsychotics being associated with a more benign risk profile than that of typical antipsychotics and the fact that overall use of antipsychotics has increased in general.[12,13] This was also confirmed in the current study (**Figure 1**). Ray *et al*. have previously associated atypical antipsychotics with risk of SCD, comparing users of antipsychotic drugs with nonusers; use of atypical antipsychotics increased risk of SCD in a dose-dependent manner.[7] We did not find a statistically significant association between overall use of atypical antipsychotics and OHCA, although a trend toward risk of OHCA was observed. However, we identified associations between both specific typical and atypical antipsychotics and OHCA. Such findings could indicate that the traditional grouping of antipsychotic drugs may be inadequate to captivate all drugs within one group in terms of safety and efficacy, as previously suggested in a large meta-analysis by Leucht *et al*.[14]

Quetiapine is an atypical antipsychotic drug known for its low risk of inducing extrapyramidal symptoms, but it has been associated with a prolonged QT interval.[6,15] Case reports and large epidemiological studies have also associated quetiapine with SCD in a dose-dependent manner.[7,16,17] In addition, support for a dose–response relationship is reinforced by observations after coadministration of drugs that produce increased plasma levels of quetiapine by inhibiting its metabolism (e.g., lovastatin or ketoconazole).[18,19] Collectively, these findings have prompted the US Food and Drug Administration (FDA) to request an update on the quetiapine label warning against use of quetiapine in combination with other drugs that prolong the QT interval.[20] In the current study, quetiapine was associated with increased risk of OHCA, which is in agreement with previous reports as well as with emerging data from the World Health Organization pharmacovigilance database (VigiBase)

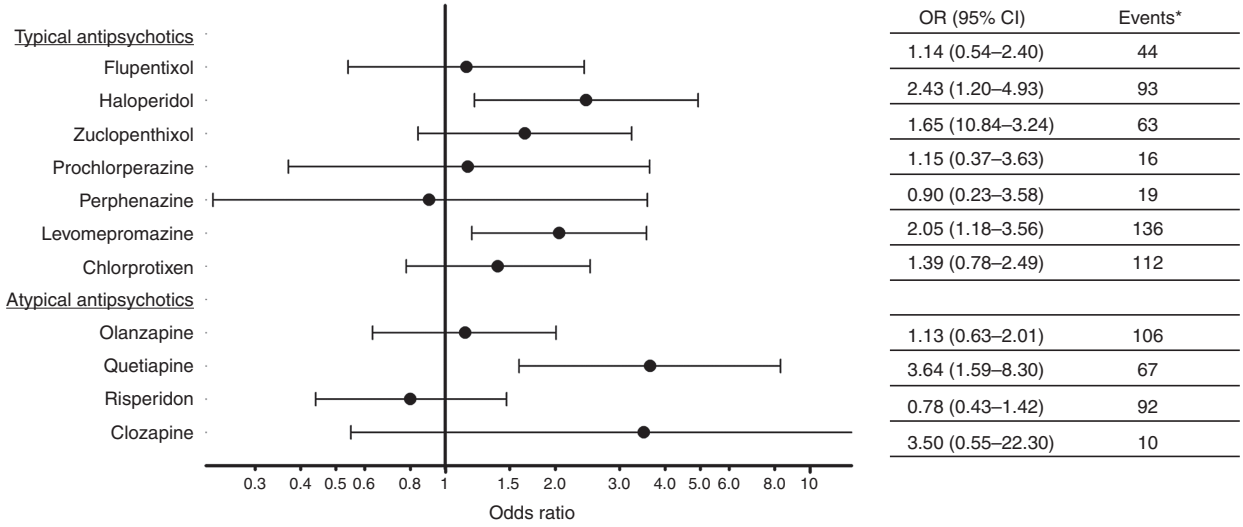

Figure 2 Antipsychotic treatment and risk of out-of-hospital cardiac arrest. Odds ratios (ORs) from the conditional logistic regression analysis in case–time–control models are presented. *OHCA cases contributing to the analysis by having a discordant drug exposure history in the case and control periods. 95% CI, 95% confidence interval; OHCA, out-of-hospital cardiac arrest.

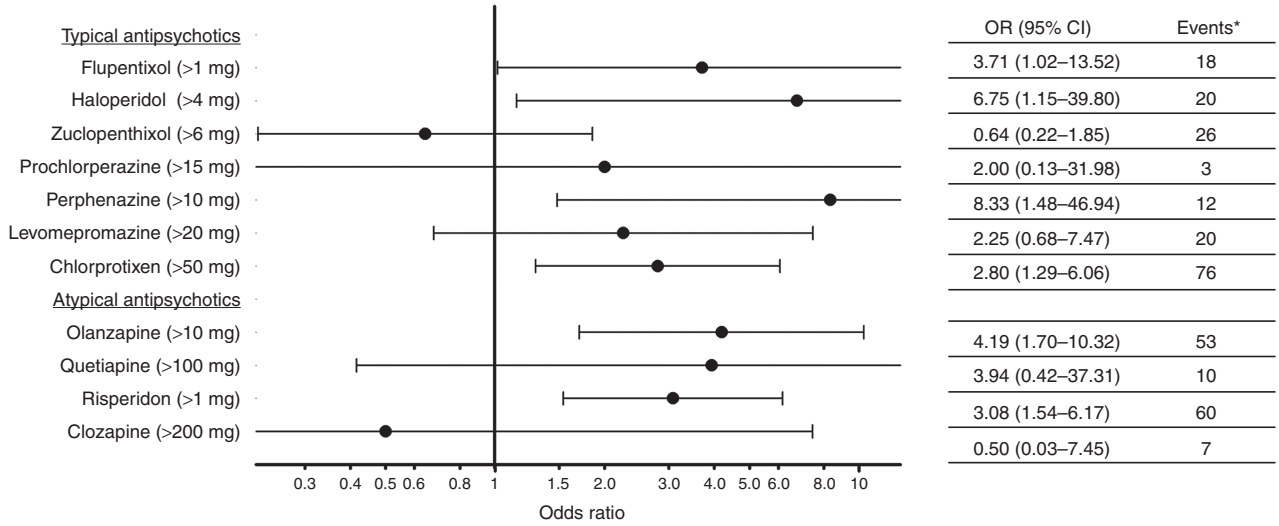

Figure 3 Dose–response analysis of antipsychotic treatment and risk of OHCA. Odds ratios (ORs) from the conditional logistic regression analysis in case–time–control models are presented. CI, confidence interval; OHCA, out-of-hospital cardiac arrest. *OHCA cases contributing to the analysis by having concordant drug exposure histories in the case and control periods but experiencing a change in drug dosing that crossed the median value between the case and control period.

and the US FDA Adverse Event Reporting System Database.[21,22] Mining of such large databases has indicated that haloperidol and quetiapine have a similar cardiac risk profile, including risk of torsade de pointes.

Haloperidol is a typical antipsychotic that targets dopamine, glutamate, and serotonin receptors, and it is used in patients with and without psychiatric disease (e.g., chemotherapy-induced nausea or control of agitation). Although haloperidol is not usually associated with clinically detrimental effects on the QT interval,[15,19,23] it has been strongly associated with drug-induced arrhythmias and SCD[15,20,24,25] in a dose-dependent manner.[26] In accordance with the existing body of evidence, haloperidol was also associated with increased risk of OHCA in the current study. However, because haloperidol is widely used for both on- and off-label indications,[2] confounding factors should be acknowledged, although results from subanalyses are in agreement with our main findings. Haloperidol was not significantly associated with OHCA in one subanalysis that was designed to eliminate potential bias associated with deterioration in patient health status leading up to the OHCA (i.e., we excluded patients with a hospital admission within 60 days before the event). It is likely that a lack of statistical power masked an otherwise significant association (i.e., only 33 individuals on haloperidol contributed to the analysis), which is highlighted by the wide confidence interval (OR = 1.92, CI: 0.69–5.39).

Levomepromazine, a typical low-potency antipsychotic with strong analgesic and antiemetic properties, was the most commonly used antipsychotic identified in the current analysis.

Levomepromazine was also associated with increased risk of OHCA in the main case–time–control analysis and most of the performed sensitivity analyses. Levomepromazine has previously been associated with prolongation of the QT interval among patients with schizophrenia, although the extent of the prolongation was not reported.[27] In addition, one identified case report potentially implicates levomepromazine in drug-induced arrhythmia in a postsurgery setting.[28] However, the overall body of evidence linking levomepromazine with drug-induced arrhythmias, and possibly SCD, is small. The statistically significant correlation between levomepromazine and OHCA in the main analysis was not replicated in one additional subset analysis designed to eliminate potential bias associated with deterioration in patient health status leading up to the OHCA. Here, a neutral correlation between levomepromazine and OHCA was identified. Hence, it is possible that the identified risk is attributable to imminent health deterioration among levomepromazine users. Other known conditions associating with levomepromazine include hyperlipidemia and metabolic syndrome, which may have affected our findings.[3]

One proposed mechanism by which most drugs (including antipsychotics) induce sudden cardiac death is by blocking the rapid component of the delayed rectifying potassium current (I_{Kr}), encoded by *KCNH2*, which in turn leads to a prolonged cardiac repolarization (measured by the QT interval on a surface electrocardiogram) and increased risk of arrhythmia.[29,30] Although the drug-induced effect on the QT interval is highly variable and imperfectly correlated with the risk of arrhythmia (i.e., long QTc interval does not always predict ventricular arrhythmias or torsade de pointes), it is currently the best available tool for risk stratification for individuals susceptible to drug-induced arrhythmia.[31] This imperfect correlation is underscored by two large randomized clinical trials evaluating the risk of various cardiovascular end points (including SCD) that are associated with ziprasidone (the atypical antipsychotic with the highest effect on the QT interval) and olanzapine (the atypical antipsychotic with the least effect on the QT interval).[15]

Limitations

Although we used a nationwide cohort of OHCA patients, the rarity of the outcome limited the final study cohort and may have influenced our findings; we also acknowledge the possibility for ascertainment bias influencing our results. Another limitation is related to patients with psychiatric disorders, who are more likely to display poor adherence to treatment. However, we assumed that patients who claimed a prescription were also likely to take the medication, as they also had an economic incentive because of the medical expenses being only partially reimbursed by the Danish government–financed health-care system. Another limitation of this study is related to the large differences in sample size for the individual antipsychotics. Within the class of atypical antipsychotics, we identified an increased risk associated with levomepromazine and haloperidol. However, the substantially smaller sample size of other typical antipsychotics does not allow the conclusion that these are necessarily safer. This limitation also applies to atypical antipsychotics and quetiapine.

The case–time–control method used cannot distinguish between the risk of starting medication and the indication for the medication, and we acknowledge the possibility of our results being influenced by this. However, we did find that a range of drugs used within a spectrum of disease yielded a range of risks, which suggests that the medication is the factor associated with risk rather than the indication. The most common indications for antipsychotic treatment carry similar standardized mortality rates (SMRs): SMR for schizophrenia: 2.8 in males and 2.5 in females; SMR for bipolar disorder: 1.9 in males and 2.1 in females; and SMR for depression: 1.6 in males and 1.5 in females.[32,33] In addition, we performed multiple sensitivity analyses while excluding other important indications (e.g., cancer), which were in accordance with our main study findings. Although we do not know the indication for starting antipsychotic treatment, 46.6% of OHCA patients were seen in an outpatient clinic or required hospital admission for a psychiatric illness within 5 years before their OHCA, which suggests that psychiatric illness could be the likely cause for antipsychotic drug treatment in these patients. By contrast, the other half of OHCA patients had no immediate history of psychotropic therapy in spite of antipsychotic treatment preceding their OHCA. These findings are in agreement with the findings by Olfson *et al.*, in which individuals treated with antidepressants became more likely to also receive treatment with antipsychotic medications and less likely to undergo psychotherapy in a hospital setting, whether in or out of the clinic.[34] Although a prolonged QT interval may have preceded the OHCA, it is important to note that the current study is strictly observational and does not lend itself to prove such causation. Hence, we are unable to determine whether each OHCA was in fact preceded by an arrhythmic event. Other potential mechanisms that may also increase susceptibility to OHCA after treatment with antipsychotic pharmacotherapy include weight gain, dyslipidemia, hypertension, disorders of the heart and blood vessels related to atherosclerosis, and impaired glucose metabolism. Although the latter mechanisms may induce risk of OHCA, their effects are more likely to be of importance among patients in more chronic treatment.

Conclusion

In the current study, we identified a significant association between OHCA and overall antipsychotic drug use. Moreover, overall typical antipsychotic drug use was also associated with OHCA, whereas atypical antipsychotic drug use was not. Two individual typical antipsychotic drugs, haloperidol and levomepromazine, were associated with OHCA, as was the atypical antipsychotic drug, quetiapine.

METHODS

Study population. OHCA was defined as a clinical condition in which a cardiac arrest resulted in resuscitative efforts by bystanders (with activation of the emergency medical services (EMS) system) or EMS personnel according to the Danish Cardiac Arrest Register (2001–2010), as it was defined in a previous study.[35] OHCA patients who on 1 January 1997 were ≥10 years were included in the current study. Patients with obvious signs of death (e.g., trauma or rigor

mortis), and for whom no resuscitative efforts were performed by bystanders or EMS personnel, were excluded from the Danish Cardiac Arrest Registry. The registry is a nearly complete record of OHCAs in Denmark because the EMS is required to complete a case report form for it for every OHCA, including information on date, time, and occurrence of the OHCA.

Databases. The assignment of a unique and permanent civil registration number to all Danish citizens enables linkage of nationwide registers at an individual level. The Danish National Patient Registry contains information on all hospital admissions to Danish hospitals since 1978, with every hospital admission and discharge being registered with one primary diagnosis and, if appropriate, two or more secondary diagnoses (International Classification of Diseases (ICD); before 1994, the 8th revision (ICD-8), and from 1994, the 10th revision (ICD-10)).[36]

The Danish Registry of Medicinal Product Statistics is a complete nationwide register that contains detailed information on all dispensed drug prescriptions from Danish pharmacies since 1995 according to the Anatomical Therapeutic Chemical (ATC) system. By law, all Danish pharmacies are obliged to register every dispensed prescription due to the partial reimbursement of drug expenses by the government-financed health-care system, making the register both valid and accurate.[37]

The primary cause of death, as well as contributing causes, is included in the National Causes of Death Register. The Database for the Danish Labour Market contains information on individual annual gross income.

Patient comorbidity and concomitant pharmacotherapy. We defined patient comorbidity through the Danish National Patient Registry using hospital discharge diagnoses (primary or secondary) for ~5 years before the date of OHCA for diseases specified in the Charlson Comorbidity Index (cerebral vascular disease, peripheral vascular disease, ischemic heart disease, myocardial infarction, heart failure, malignancy, and chronic obstructive pulmonary disease),[38] modified for use with the ICD-10.[39,40] Patients with diabetes were identified as individuals who claimed ≥1 prescription for any glucose-lowering medication (ATC: A10; oral or insulin) within 180 days before the time of event according to the Danish Register of Medicinal Product Statistics. Psychiatric illness was defined by the following discharge diagnoses: F00–F99 (ICD-10). As previously done, a history of substance abuse was defined as a claimed prescription for Antabuse (ATC: N07BB) or methadone (ATC: N07BC02) within 90 days of OHCA, or a hospital admission for cirrhosis (ICD-10: I85) or drug/alcohol-related issues (ICD-10: F10–F16, F18–F19) within 5 years before time of OHCA.[41] Depression was defined by F31.3–5, F32, and F33; psychosis: F20–F31; dementia: G30–G31; and bipolar disorder: F30–F31. Patients who committed suicide were defined by the following primary causes of death according to the National Causes of Death Register (ICD-10: X60–X84). We assessed socioeconomic status by averaging the annual patient income for the 5 years preceding the year of the event among all OHCA patients.

Concomitant pharmacotherapy was defined as a claimed prescription ≤90 days before the time of event for the following drugs (ATC codes): angiotensin-converting enzyme inhibitors (A09A), loop diuretics (C03C), β-blockers (C07), cholesterol-lowering agents (C10), epileptic drugs (N03A), lithium (N05AN), sedatives and anxiolytics (N05B, N05C), and antidepressants (N06A).

Antipsychotic pharmacotherapy: duration of treatment and treatment periods. Using the Danish National Prescription Registry, we identified the most commonly used antipsychotics from 2001 to 2010. Typical antipsychotics evaluated (ATC codes) were levomepromazine (N05AA02), perphenazine (N05AB03), prochlorperazine (N05AB04), haloperidol (N05AD01), flupentixol (N05AF01), chlorprotixene (N05AF03), and zuclopenthixol (N05AF05); atypical antipsychotics evaluated were clozapine (N05AH02), olanzapine (N05AH03), quetiapine (N05AH04), and risperidone (N05AX08).

For each drug, the daily dosage was estimated using information from up to five consecutive claimed prescriptions before the actual prescription, constituting a treatment interval, according to the Danish Register of Medicinal Product Statistics. With the current method, changes in dose and treatment duration can be accurately assessed.[42,43]

Statistical analysis. Categorical variables were compared with the Pearson's χ^2-test, and continuous variables were compared with the Kruskall–Wallis test. Time trends of antipsychotic treatment usage were evaluated using the Cochran–Armitage trend test. Risk of OHCA associated with antipsychotic use was examined using conditional logistic regression analysis in case–time–control models. The case–time–control design is an extension of the case–crossover design, in which each individual serves as his or her own control, thereby adjusting for time-invariant confounders such as chronic comorbid conditions (e.g., hypertension, smoking, overweight, and chronic psychiatric disease). In addition, the case–time–control design adjusts for time trends in the general prescribing patterns that may otherwise lead to biased results.[44,45] In brief, information from the design is driven by patients with a discordant exposure history, which means patients treated in the case period only (OR > 1), or patients treated in the control periods only (OR < 1). Patients with concordant exposure histories, which means those treated in both the control and case periods or those not treated at all, do not contribute to the case–time–control analysis. The case–time–control design is based on an assumption of conditional independence of exposure at different time points.[44–46] We tested our models for violation of this assumption using simulations and chose models with one instead of two reference periods because the latter biased the estimates (data not shown). Consequently, the case period was defined as 30–0 days before OHCA, and the control period was defined as 90–60 days before OHCA. A washout period was defined as 60–30 days before OHCA.

Dose–response analysis. A dose–response analysis was performed among patients with concordant exposure histories (i.e., in treatment in both the control and case periods) but whose dosing differed in the case and the control periods (crossed the median). Hence, patients in treatment with the same drug dose in the case and control periods did not contribute to this analysis. We determined the median dose and evaluated the risk of OHCA associated with being in treatment with the median dose or higher using conditional logistic regression analysis in case–time–control models; our study was underpowered to evaluate clinical meaningful high vs. low doses.

Other analyses. The robustness of our results was tested in additional sensitivity analyses. Although the main case–time–control analysis utilized 30-day treatment periods, we also performed additional case–time–control analyses with 20- and 40-day treatment periods. To eliminate the risk of biased results because of deterioration in patient health before OHCA, we repeated our main analysis while excluding patients who had been admitted to hospital within 60 days before the time of OHCA. We also repeated our analyses while excluding patients who had been admitted to the hospital with a diagnosis of cancer ≤5 years before the time of the event. Separate analyses using only orally administered antipsychotics to estimate drug use were performed to eliminate potential bias associated with the assessment of antipsychotics administered intramuscularly. Patients >18 years old and patients with no evidence of substance abuse were also tested separately, as were patients with no evidence of attempted suicide.

We identified an age- and gender-matched (1:4) control population that was used to adjust for the exposure development in the general population.[47] The threshold for statistical significance was a two-sided P value <0.05. We performed all analyses using SAS, version 9.2 (SAS Institute, Cary, NC) or R (http://www.R-project.org).

Ethics. This study was approved by the Danish Data Protection Agency (no. 2008-41-2685). In Denmark, deidentified retrospective register-based studies do not require ethical approval.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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AUTHOR CONTRIBUTIONS

P.W. wrote the manuscript. P.W., A.J., G.H.G., L.K., and C.T.-P. designed the research. P.W. and A.J. performed the research. P.W., A.J., F.F., G.H.G., J.B.O., E.L.F., M.W., F.K.L., E.F.C., S.L.N., E.H., J.K.K., H.E.P., L.K., and C.T.-P. analyzed the data.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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