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Jurjen J. Luykx [a,b,c,d,*], Antti Tanskanen [e,f,g], Markku Lähteenvuo [e,f], Peter Manu [h,i,j], Christoph U. Correll [k,l,m], Alkomiet Hasan [n,o], Johannes Lieslehto [e,f], Heidi Taipale [e,f,p], Jari Tiihonen [e,f,q]

[a] Department of Psychiatry, Amsterdam University Medical Center, Amsterdam, the Netherlands
[b] GGZ inGeest Mental Health Care, Amsterdam, the Netherlands
[c] Amsterdam Neuroscience (Mood, Anxiety, Psychosis, Stress & Sleep program) and Amsterdam Public Health (Mental Health program) research institutes, Amsterdam, the Netherlands
[d] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, the Netherlands
[e] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[f] Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland
[g] Public Health Solutions, National Institute for Health and Welfare, Helsinki, Finland
[h] Department of Psychiatry, Hofstra Northwell School of Medicine, Hempstead, NY, USA
[i] Department of Medicine, Hofstra Northwell School of Medicine, Hempstead, NY, USA
[j] South Oaks Hospital, Northwell Health System, Amityville, NY, USA
[k] The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA
[l] Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA
[m] Charité Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany
[n] Department of Psychiatry, Psychotherapy and Psychosomatics, University of Augsburg, Faculty of Medicine, Augsburg, Germany
[o] DZPG (German Center for Mental Health), partner site München, Augsburg
[p] School of Pharmacy, University of Eastern Finland, Kuopio, Finland
[q] Center for Psychiatric Research, Stockholm City Council, Stockholm, Sweden

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ABSTRACT

The risk of fatal choking for people with schizophrenia and associations with antipsychotic medication are largely unknown. Therefore, we calculated the choking-related standardized mortality ratio for schizophrenia relative to the general population ($SMR_{choking}$). We also computed adjusted hazard ratios (aHR) of choking-related mortality for antipsychotics in a nationwide cohort of patients with schizophrenia (N = 59,916). $SMR_{choking}$ was 20.5 (95 % confidence interval (CI)=17.1–23.9). The aHR was 1.74 (95 %CI=1.19–2.55) for strong dopamine 2-antagonists. For other antipsychotics, CIs included 1. Importantly, aHRs were particularly high for high dose categories of strong dopamine D2 receptor (D2R) antagonists. In conclusion, a schizophrenia diagnosis is associated with a 20-fold risk of death due to choking. This risk is elevated during use of strong D2R antagonist antipsychotics, particularly when prescribed in high dosages.

1. Introduction

Death due to choking may result from aspiration as well as a bolus of food. In schizophrenia, both scenarios may occur, with several possible underlying causes, including aberrant eating habits and antipsychotic medication use, which in turn may result in throat spasms, hypersalivation and vagal reactions.

Studies have reported varying risk estimates of death due to choking (asphyxiation) in schizophrenia across countries and treatment settings, ranging from 0.057 to 5.5. per 1000 patients annually (Funayama et al., 2019; Hussar, 1966; Hwang et al., 2010; Manu et al., 2011; Ruschena et al., 2003). Moreover, the possibly mediating role of antipsychotic medications in such increased choking-related mortality risks has remained unknown: while some studies have not detected associations between death due to choking and antipsychotics use (Hwang et al., 2010), others suggest specific compounds may be associated with an increased risk, e.g. thioridazine (Ruschena et al., 2003). Similarly, the underlying mechanisms explaining the relationships between

* Corresponding author.
E-mail address: j.j.luykx@amsterdamumc.nl (J.J. Luykx).

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antipsychotic use have not been elucidated (Cicala et al., 2019; Crouse et al., 2018).

A lack of well powered epidemiological studies may explain the inconsistent results regarding the magnitude of the risk of choking-related death in schizophrenia, as well as about associations between this risk and the use of antipsychotics. Therefore, we calculated the choking-related standardized mortality ratio for schizophrenia relative to the general population ($SMR_{choking}$) and adjusted hazard ratios (aHR) of choking-related mortality for antipsychotics by degree of dopamine D2 receptor (D2R) antagonism.

2. Methods

The study cohort was collected from a nationwide inpatient care register and included patients diagnosed with schizophrenia and schizoaffective disorder in Finland from 1997 to 2014, with follow-up for mortality until 2017 ($n = 59,916$) (Taipale et al., 2020). Death due to choking was defined as ICD-10 codes W78-W80. We performed two sets of analyses, one to examine risk of death from choking in schizophrenia relative to the general population, and one to estimate choking mortality risks per degree of D2R-antagonism.

To do so, we first examined the risk of death due to choking associated with schizophrenia using the SMR, a measure of relative excess mortality, according to established methodology for this dataset (Paljärvi et al., 2023). In brief, we calculated $SMR_{choking}$ per 1000 person-years with 95 % confidence intervals (CIs) by using as reference the entire population of Finland aged ≥15 years, so also including persons with schizophrenia, which is in line with expert opinion, also see ("StatFin database | Statistics Finland," n.d.).

We then examined the risk of death due to choking associated with the use of antipsychotics with varying strengths of dopamine D2R antagonism by running traditional between-individual Cox regression models, with no antipsychotic as a reference, using adjusted hazard ratios (aHRs), with 95 % confidence intervals. To that end, medication exposure periods of all antipsychotics were modelled using the PRE2DUP method (Tanskanen et al., 2015) and categorized into weak vs. moderate vs. strong D2R antagonism according to previous literature (Correll, 2010). Weak D2R antagonists included the weak D2R blockers and partial D2R agonists clozapine, quetiapine and aripiprazole; the only moderate D2R antagonist was olanzapine; and strong D2R-antagonistic antipsychotics included the rest, namely asenapine, chlorpromazine, chlorprothixene, dixyrazine, flupentixol, fluphenazine, haloperidol, levomepromazine, lurasidone, melperone, molindone, paliperidone, penfluridol, periciazine, perphenazine, pimozide, pipotiazine, prochlorperazine, promazine, remoxipride, risperidone, sertindole, sulpiride, thioproperazine, thioridazine, tiotixene, ziprasidone, and zuclopenthixol. For this second set of analyses, to estimate choking risk for each category of D2R antagonism strength, only outcomes occurring in outpatient care were analyzed as the register only covers outpatient medications. These analyses were adjusted for age, sex, history of stroke, substance abuse, Parkinson's disease, dementia, head injuries, time since schizophrenia diagnosis, and the use of antiepileptics. Finally, we examined whether dose was associated with risks of death due to choking by computing daily defined dosages (DDD) according to the WHO ("Defined Daily Dose (DDD)," n.d.; Taipale et al., 2022), and computing the number of choking events and aHRs for the following four dose categories, as per previously established methodology (Taipale et al., 2022): <0.6 DDDs/day; 0.6-<1.1 DDDs/day; 1.1-<1.6 DDDs/day; ≥1.6 DDDs/day.

3. Results

The study population consisted of 59,916 people with schizophrenia (mean age 46.2 years, SD 15.8 years), including $N = 29,852$ (49.8 %) women (Table 1). The mean duration of follow-up was 13.5 years (SD 6.5), and 23,205 deaths were recorded.

Table 1
Characteristics of study population at baseline and at the end of follow-up.

	At baseline% (N)	At the end of follow-up% (N)
Time since schizophrenia diagnosis, median (IQR) as years	7 (0–18)	23 (12–33)
Comorbidities		
Stroke	1.9 (1128)	6.9 (4143)
Substance use disorder	16.1 (9646)	22.7 (13,600)
Parkinson disease	0.4 (246)	1.4 (817)
Dementia	0.6 (337)	4.9 (2948)
Head trauma	7.7 (4619)	14.9 (8903)
Antiepileptic drug use	2.8 (1702)	6.0 (3573)

A total of 287 choking deaths occurred during 817,000 patient-years (corresponding to 1.2 % of all deaths being attributed to choking). $SMR_{choking}$ was 20.5 (95 % CI 17.1–23.9) in schizophrenia compared with the general population.

A total of 268 choking deaths occurred during outpatient care: 164 during use of strong D2-antagonistic antipsychotics, 30 during olanzapine use, 21 during weak D2-antagonistic antipsychotic use, and 53 during no antipsychotic use. Relative to nonuse, the corresponding adjusted hazard ratios (aHRs), in increasing order, were 1.04 (0.60–1.81) for weak D2R-antagonists, 1.59 (0.96–2.64) for the moderate D2R antagonist olanzapine, and 1.74 (95 % CI 1.19–2.55) for strong D2R-antagonists (Fig. 1).

Finally, we found evidence for dose-dependent associations as high dosages of strong D2R-blockers were found to be associated with higher risks of death due to choking than lower dosages (Table 2).

4. Discussion

Here, we found that a diagnosis of schizophrenia is associated with a 20-fold risk of death due to choking. Risks were found to be elevated only during the use of strong D2R-antagonistic antipsychotics, not during the use of weak D2-antagonistic antipsychotics. Olanzapine had an aHR of 1.59 but the confidence interval encompassed 1.

Our findings align with previous reports in different populations. Here, we extend the existing evidence in several ways. For example, Australian patients with schizophrenia were found to be up to 30 times more likely to die by choking than people in the general population (Ruschena et al., 2003). The size of our study population allowed us to calculate SMRs and increase precision in the estimates relative to previous endeavors. In addition, choking incidents (not deaths) have been found to be related to first-generation antipsychotics (Funayama et al., 2019). By computing risk estimates per each of the three D2R antagonism strength categories, we here show that the association between choking-related death and antipsychotic use is not generalizable to all antipsychotic agents.

Implications of our work mostly include raising awareness about choking risks in patients with schizophrenia in general and in relation to groups of antipsychotics. Eating habits (e.g. speed and chewing) may be monitored and information about non-fatal choking events may be elicited in outpatient and inpatient settings. The presence of bradykinetic dysphagia produced by drug-induced parkinsonism, dyskinetic dysphagia associated with tardive dyskinesia, and anticholinergic mediated xerostomia, all relatively common in patients with a long history of psychotic disorder, must be looked for (Kulkarni et al., 2017). A complete medical history must be obtained given the possibility of structural oropharyngeal abnormalities, such as surgery or radiotherapy for head and neck cancers, large goiters, and chronic reflux esophagitis complicated by a cricopharyngeal bar (Wilkinson et al., 2021). For patients with any of these conditions or with a history of aspiration pneumonia, weak to moderate D2R-antagonists may be preferable if the risk of choking is deemed high. Clearly, personalized prescribing involves balancing the risks of choking-related death against possible

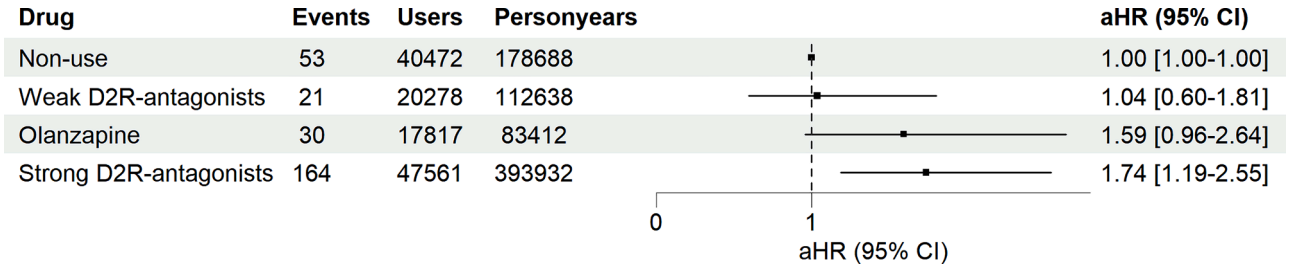

Fig. 1. Adjusted hazard ratios (aHR) for risk of death due to choking in different scenarios of antipsychotic use (nonuse as reference).

Table 2
Adjusted hazard ratios (aHR) for risk of death due to choking associated with use of strong D2R-antagonists by dose category (nonuse as reference).

Dose category	Events	aHR (95 %CI)
<0.6 DDDs/day	28	1.02 (0.63–1.65)
0.6-<1.1 DDDs/day	36	2.11 (1.35–3.31)
1.1-<1.6 DDDs/day	34	3.33 (2.11–5.26)
≥1.6 DDDs/day	66	3.05 (2.06–4.52)

DDD = daily defined dose (according to the World Health Organization).

other adverse drug reactions to weak and moderate D2R-antagonistic agents.

Strengths of our approach include the large study population and the nationwide recording of medication use and deaths due to choking, with up to 21 years of follow-up. Nonetheless, some limitations should be borne in mind when interpreting our findings. First, limitations that generally apply to the use of real-world data include the lack of generalizability to countries with healthcare systems that are different to the Finnish one, absence of medication adherence assessments, and the possibility of residual confounding impacting some of the results. The latter may apply as the between-individual analyses that were conducted to examine risk of death due to choking were corrected for possible covariates, but the possibility of confounding by indication cannot be fully ruled out. Second, we cannot dissect possible additional contributing factors to death by choking risks in schizophrenia due the lack of such data in our registries, e.g. disease severity, specific symptoms (such as disorganization), and substance use. Third, it is possible that histaminergic effects of antipsychotics, that vary by antipsychotic agent, contribute to choking risks related to the use of antipsychotics. And finally, statistical power was relatively low for a nationwide study due to the low number of fatal choking events, precluding us from stratifying by disease duration or age and from running analyses for every single antipsychotic in the dataset. Such research questions may be subjected to future projects capitalizing on larger registries that may also examine death by choking risks related to antipsychotic use in other disorders.

In conclusion, schizophrenia is associated with a 20-fold risk of death due to choking, but this risk highly varies across groups of antipsychotics, with highest risks for strong D2R-antagonistic antipsychotics, especially when prescribed in high dosages.

Author statement

The work described has not been published previously, it is not under consideration for publication elsewhere, its publication is approved by all authors and also by the responsible authorities where the work was carried out, and, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Contributions

All authors meet all four ICMJE criteria for authorship. All authors conceived and designed the study. HT performed the statistical analyses. JL and HT wrote the first draft. Study management was done by JL. All authors were involved in the writing of the final manuscript and revised the manuscript.

CRediT authorship contribution statement

Jurjen J. Luykx: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Antti Tanskanen:** Data curation, Conceptualization. **Markku Lähteenvuo:** Writing – review & editing, Data curation, Conceptualization. **Peter Manu:** Writing – review & editing, Conceptualization. **Christoph U. Correll:** Writing – review & editing, Supervision, Conceptualization. **Alkomiet Hasan:** Writing – review & editing, Supervision, Conceptualization. **Johannes Lieslehto:** Writing – review & editing, Conceptualization. **Heidi Taipale:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Jari Tiihonen:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

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