Antipsychotics and severe hyponatremia: A Swedish population–based case–control study

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ABSTRACT

Background: Antipsychotics have been claimed to cause hyponatremia. The risk associated with individual antipsychotics, or groups (first-generation [FGAs] or second-generation [SGAs] antipsychotics), is not well-documented. The objective of this study was to investigate the association between antipsychotics and hospitalization due to hyponatremia.

Methods: The general Swedish population was the base of this register–based case–control study. Comparisons were made between patients hospitalized with a principal diagnosis of hyponatremia ($n = 14,359$) and matched controls ($n = 57,383$). Multivariable logistic regression adjusting for concomitant drugs, medical conditions, previous hospitalizations and socioeconomic factors was performed to investigate the association between hyponatremia and antipsychotic use. In addition newly initiated (≤ 90 days) or ongoing use was analysed separately.

Results: Compared to controls, the adjusted OR (95%CI) for hospitalization due to hyponatremia was for any antipsychotic 1.67(1.5–1.86). Individuals on FGA were more likely to experience severe hyponatremia (2.12[1.83–2.46]) than those on any SGA (1.32[1.15–1.51]). No increased risks, neither as newly initiated nor ongoing therapy, were found for risperidone (0.86[0.56–1.31] and 0.83[0.67–1.02]) and aripiprazole (1.16[0.30–4.46] and 0.62[0.27–1.34]), respectively.

Conclusions: There was an association between antipsychotic therapy and hospitalization due to hyponatremia. The association was stronger for FGAs than SGAs. Risperidone was not associated with an increased risk.

1. Background

Hyponatremia is the most common electrolyte disturbance affecting 15–30% of hospitalized patients [1]. Symptoms range from mild, non-specific symptoms such as lethargy, agitation and confusion to severe life-threatening symptoms such as seizures, coma and ultimately death due to brain oedema [2–4]. Medications are often the cause of hyponatremia resulting in hospitalization. Thiazide diuretics, anti-depressants and antiepileptic drugs are the most frequent culprits [5–7]. In addition, antipsychotics can occasionally lead to severe hyponatremia [5,8–10]. Since decreased sodium values can result in symptoms resembling those seen in psychiatric conditions, including dementia, hyponatremia may be difficult to recognise [8].

First-generation (typical) antipsychotics (FGAs) have been available for over 60 years and produce a combination of strong D2-antagonism together with anticholinergic and antihistaminergic effects [11]. Due to adverse reactions, second-generation (atypical) antipsychotics (SGAs) were developed with lower affinity to D2-receptors in combination with potent 5-HT$_{2A}$ receptor action in addition to variable affinity to other receptors. Antipsychotic drugs have been associated with hyponatremia in schizophrenia and other severe mental illnesses [9]. Most reports on antipsychotic-induced hyponatremia have been case report/series [8,12–14], with only a few exceptions [9,10,15]. Hence, quantitative data on the risk of drug-induced hyponatremia, comparing different antipsychotics, is utterly scare [11]. We believe it is of clinical importance to fill this knowledge gap.

The aim of this study was primarily to investigate the association between treatment with antipsychotic drugs and hospitalization due to

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Table 1

Included variables in the multiple logistic regression analysis and their definition.

Variables	Codes
	ATC codes beginning with
Antipsychotics	N05A (excluding lithium N05AN)
FGA	N05AA01- N05AL03
Chlorpromazine	N05AA01
Levomepromazine	N05AA02
Acepromazine	N05AA04
Cyamemazine	N05AA06
Dixyrazine	N05AB01
Fluphenazine	N05AB02
Perphenazine	N05AB03
Prochlorperazine	N05AB04
Trifluoperazine	N05AB06
Periciazine	N05 AC01
Thioridazine	N05 AC02
Haloperidol	N05 AD01
Melperone	N05 AD03
Pipamperone	N05 AD05
Droperidol	N05 AD08
Flupentixol	N05AF01
Chlorprotixene	N05AF03
Zuclopenthixole	N05AF05
Fluspirilene	N05AG01
Pimozide	N05AG02
Loxapine	N05AH01
Tiapride	N05AL03
SGA	N05AE03- N05AX16
Sertindole	N05AE03
Ziprasidone	N05AE04
Lurasidone	N05AE05
Clozapine	N05AH02
Olanzapine	N05AH03
Quetiapine	N05AH04
Sulpiride	N05AL01
Amisulpride	N05AL05
Risperidone	N05AX08
Aripiprazole	N05AX12
Paliperidone	N05AX13
Brexpiprazole	N05AX16
Other drugs	
Carbamazepine	N03AF01
Oxcarbazepine	N03AF02
Phenytoin	N03AB02
Valproate	N03AG01
Lamotrigine	N03AX09
Levetiracetam	N03AX14
Gabapentin	N03AX12
Furosemide	C03C
Thiazides	C03A, C09BA, C09DA
Agents acting on the renin-angiotensin system	C09
Fluoroquinolones	J01MA
Macrolides	J01FA
Trimethoprim sulfamethoxazole	J01EE
SSRIs	N06AB
Other antidepressants	N06AX
Amiodarone	C01BD01
Tramadol	N02AX02
Desmopressin	H01BA02
Proton pump inhibitors	A02BC, A02BD06
Diagnosis	ICD10 codes beginning with
Renal diseases	N17–19, procedure codes DR016, DR024, KAS00, KAS10, KAS20
Sepsis	A41
Pneumonia	J18
Meningitis	G00-G07
Ischemic heart disease	I20–25
Malignant disease	C
Congestive heart failure	I50
Pancreatic disease	K85, K860–1
Inflammatory bowel disease	K50–51
Liver diseases	K70–77 Procedure codes JJB, JJC
Cerebrovascular diseases	I60–64, I69

Table 1 (*continued*)

Variables	Codes
	ATC codes beginning with
Hypothyroidism	E03, E06.3
Malnutrition	E43.9, E41.9
Chronic obstructive pulmonary disease	J44
Pulmonary embolism	I26
	Combination of ATC- and ICD-10 codes, each beginning with
Alcoholism	ATC: N07BB03, N07BB04, N07BB01, N07BB05, N07BB
	ICD10: E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90–91, Z502, Z714
Adrenal insufficiency	ATC: N07BB03, N07BB04, N07BB01, N07BB05, N07BB
	ICD10: E27
Diabetes mellitus	ATC: A10A, A10AB
	ICD10: E10-E14
Other factors	
Education	Increasing levels of education from 1 to 6, continuous variable
Income	Income in Swedish crowns during 1 year, continuous variable
Unemployment	Number of days, continuous variable
Drug use	Number of dispensed drugs 90 days prior to index date, categorised into < 4, 4–7, 8–12 and > 12 drugs
Duration of hospitalization	≥3 days

FGA, first-generation antipsychotics. SGA, second-generation antipsychotics. SSRIs, selective serotonin reuptake inhibitors.

hyponatremia. Secondly, we aimed to compare different antipsychotic drugs with respect to the risk of hyponatremia-caused hospitalization.

2. Methods

This was a retrospective case–control study of the Swedish general population. To capture the most reliable cause of the admission in each patient, the principal diagnosis was used. The attending physicians code all hospitalizations and outpatient visits in Sweden with *International Classification of Diseases* codes, 10th Revision (ICD10) [16]. Cases were defined as all adult patients (18 years or older) hospitalized between 1 October 2005 and 31 December 2014 with a first-ever (defined as not occurring since 1 January 1997) principal ICD10 code of E87.1 (hyponatremia) or E22.2 (syndrome of inappropriate ADH secretion [SIADH]) in The National Patient Register (NPR) (see below). From the Total Population Register four controls (age-, sex- and municipality-matched with no previous diagnosis of hyponatremia since 1 January 1997) per each case were randomly identified. Details on this study population have recently been published elsewhere [6,7,17].

Table 1 presents all variables used in the multiple logistic regression analysis. ICD10 codes, Anatomical Therapeutic Chemical (ATC) codes, and parameters from the Longitudinal integration database for health insurance and labor market studies (LISA)-register were used to identify potential confounders. Which drugs that were defined as a FGA or a SGA can be seen in Table 1. Antipsychotic drug exposure was defined as a documented dispensation within 90 days prior to the index date, i.e., the date of admission due to hyponatremia (in controls, the index date was the admission date of their matched case). In Sweden, almost all drug–dispensation is done every 90 days for ongoing treatment. Concomitant diseases were controlled for since 1 January 1997 to the index date, except infectious diseases, which were controlled for within 90 days before the index date (Table 1). Newly commenced antipsychotic therapy was defined as treatment initiated within 90 days before the index date. The definition of ongoing antipsychotic therapy also required one or more dispensations in the period 91 to 454 days

prior to the index date.

The Swedish personal identification number was used for linkage between the three population-based registers NPR, The Swedish Prescribed Drug Register (SPDR) and the LISA-register, which encompasses socioeconomic data [16,18,19]. Since 1997, all admissions in Sweden have been coded with ICD10 and stored in the NPR. In addition, the SPDR has stored all prescriptions dispensed in Sweden since 1 July 2005. The LISA register was used to adjust for socioeconomic factors. The study and study protocol were approved by the Regional Ethical Review Board in Stockholm.

2.1. Statistical analysis

Logistic regression, univariable and multivariable, was used to analyze associations between hospitalization due to hyponatremia and antipsychotics. Individuals not exposed to any of the drugs or diagnosed with any of the diseases (since 1 January 1997) included in the model (see Table 1) were considered the reference group. The relationships between antipsychotics and severe hyponatremia in cases and controls were reported as crude and adjusted (for potential confounders) odds ratios (OR), with 95% confidence intervals (95%CI). A P-value < .05 was considered significant. R version 3.3.2 was used for all calculations [20].

3. Results

A principal diagnosis of hyponatremia was found on the admission of 14,359 individuals, 18 years or older, over the nine-year study period. In addition, 57,382 matched controls were identified. The great majority were females (72%) and the median age was 76 years (range 18–103). Table 2 presents a selection of medical conditions and the different antipsychotics used in the study population at the index date. Hypertension, malignancy, ischemic heart disease, diabetes and alcoholism were the most common concomitant medical conditions, while the most regularly prescribed antipsychotics were risperidone, olanzapine, levomepromazine, haloperidol and quetiapine. In total, 7.0% of the cases had recently been dispensed an antipsychotic compared to only 2.4% of the controls.

Fig. 1 illustrates the association between exposure to different antipsychotics and hospitalization due to hyponatremia. Compared to controls, the adjusted OR (95%CI) for hospitalization due to hyponatremia was for any antipsychotic 1.67 (1.5–1.86). Adjusted ORs ranged from 0.72 (0.36–1.41) for aripiprazole to 5.96 (2.41–16.01) for prochlorperazine. Patients using any FGA were more likely to experience hospitalization with hyponatremia (adjusted OR 2.12 [1.83–2.46]) than those on any SGA (adjusted OR 1.32 [1.15–1.51]). However, the associations varied between the individual drugs with neither aripiprazole (adjusted OR 0.72 [0.36–1.41]) nor risperidone (adjusted OR 0.85 [0.70–1.02]) showing any association with severe hyponatremia.

In Fig. 2, newly initiated antipsychotic therapy is separated from ongoing therapy (all adjusted ORs). Newly initiated treatment with dixyrazine, haloperidol, perphenazine, prochlorperazine and zuclopenthixole (all FGAs) showed a significant association, while none of the SGAs showed a significant association. However, for ongoing treatment the adjusted ORs decreased for the FGAs while it increased slightly for the SGAs. Being newly initiated on any antipsychotic increased the risk with an adjusted OR of 1.80 (1.38–2.34) while ongoing therapy had a slightly lower adjusted OR of 1.65 (1.47–1.85). Thus, no association between SGAs and hospitalization for hyponatremia could be demonstrated when the SGAs had been commenced (1.05 [0.75–1.47]) but there was a weak, albeit significant, association if they had been used for more than three months (1.37 [1.18–1.59]). In contrast, FGAs exhibited an increased risk of severe hyponatremia both when newly commenced and during ongoing treatment (2.94 [2.09–4.13] and 1.98 [1.68–2.33], respectively). No increased risks, neither as newly initiated nor ongoing therapy, were found for

Table 2
Medical characteristics (selection of items from Table 1) and antipsychotics among cases (hospitalized with a principal diagnosis of hyponatremia) and controls at index date.

	Number of total cases (n = 14,359)	Number of total controls (n = 57,382)
Diagnosis		
Hypertension	8818 (61.4%)	15,336 (26.7%)
Malignancy	3826 (26.6%)	11,231 (19.6%)
Ischemic heart disease	2808 (19.6%)	7880 (13.7%)
Diabetes mellitus	2423 (16.9%)	6581 (11.5%)
Alcoholism	2285 (15.9%)	1028 (1.8%)
Congestive heart failure	1900 (13.2%)	4493 (7.8%)
Cerebrovascular diseases	1884 (13.1%)	4540 (7.9%)
Chronic obstructive pulmonary disease	1477 (10.3%)	1958 (3.4%)
Adrenal insufficiency	821 (5.7%)	405 (0.7%)
Renal diseases	631 (4.4%)	1098 (1.9%)
Liver diseases	553 (3.9%)	417 (0.7%)
Pancreatic disease	327 (2.3%)	513 (0.9%)
Antipsychotics, total		
FGA		
Chlorpromazine	3 (0.02%)	1 (0.001%)
Chlorprotixene	15 (0.1%)	4 (0.07%)
Dixyrazine	23 (0.2%)	12 (0.02%)
Flupentixol	50 (0.3%)	70 (0.1%)
Fluphenazine	4 (0.03%)	3 (0.005%)
Haloperidol	155 (1.1%)	223 (0.4%)
Levomepromazine	170 (1.2%)	125 (0.2%)
Melperone	26 (0.2%)	31 (0.05%)
Perphenazine	62 (0.4%)	43 (0.07%)
Prochlorperazine	19 (0.1%)	8 (0.01%)
Thioridazine	11 (0.08%)	7 (0.01%)
Zuclopenthixole	93 (0.6%)	54 (0.09%)
SGA		
Aripiprazole	27 (0.2%)	31 (0.05%)
Clozapine	44 (0.3%)	25 (0.04%)
Olanzapine	210 (1.5%)	177 (0.3%)
Paliperidone	4 (0.03%)	4 (0.007%)
Quetiapine	100 (0.7%)	94 (0.2%)
Risperidone	233 (1.6%)	587 (1.0%)
Ziprasidone	11 (0.08%)	7 (0.01%)
Any FGA	546 (3.8%)	558 (1.0%)
Any SGA	576 (4.0%)	895 (1.6%)
Any antipsychotic	1008 (7.0%)	1373 (2.4%)
Antipsychotics newly initiated treatment		
FGA		
Chlorpromazine	1 (0.007%)	1 (0.002%)
Chlorprotixene	4 (0.03%)	1 (0.002%)
Dixyrazine	14 (0.1%)	1 (0.002%)
Flupentixol	5 (0.03%)	8 (0.01%)
Fluphenazine	1(0.007%)	1 (0.002%)
Haloperidol	46 (0.3%)	44 (0.08%)
Levomepromazine	16 (0.1%)	12 (0.02%)
Melperone	5 (0.03%)	7 (0.01%)
Perphenazine	6 (0.04%)	2 (0.003%)
Prochlorperazine	13 (0.09%)	2 (0.003%)
Thioridazine	1 (0.007%)	0 (0%)
Ziprasidone	2 (0.01%)	0 (0%)
Zuclopenthixole	10 (0.07%)	6 (0.01%)
SGA		
Aripiprazole	9 (0.06%)	6 (0.01%)
Clozapine	5 (0.03%)	2 (0.003%)
Olanzapine	27 (0.2%)	20 (0.03%)
Paliperidone	1 (0.007%)	0 (0%)
Quetiapine	21 (0.1%)	18 (0.03%)
Risperidone	46 (0.3%)	100 (0.2%)
Any FGA	110 (0.8%)	81 (0.1%)
Any SGA	89 (0.6%)	133 (0.2%)
Any antipsychotic	148 (1.0%)	169 (0.3%)

Antipsychotics with no case or control using are not shown in the table (acepromazine, cyamemazine, trifluoperazine, periciazine, pipamperone, droperidol, sertindole, lurasidone, fluspirilene, pimozide, loxapine, sulpiride, tiapride, amisulpride and brexpiprazole). FGA, first-generation antipsychotics. SGA, second-generation antipsychotics.
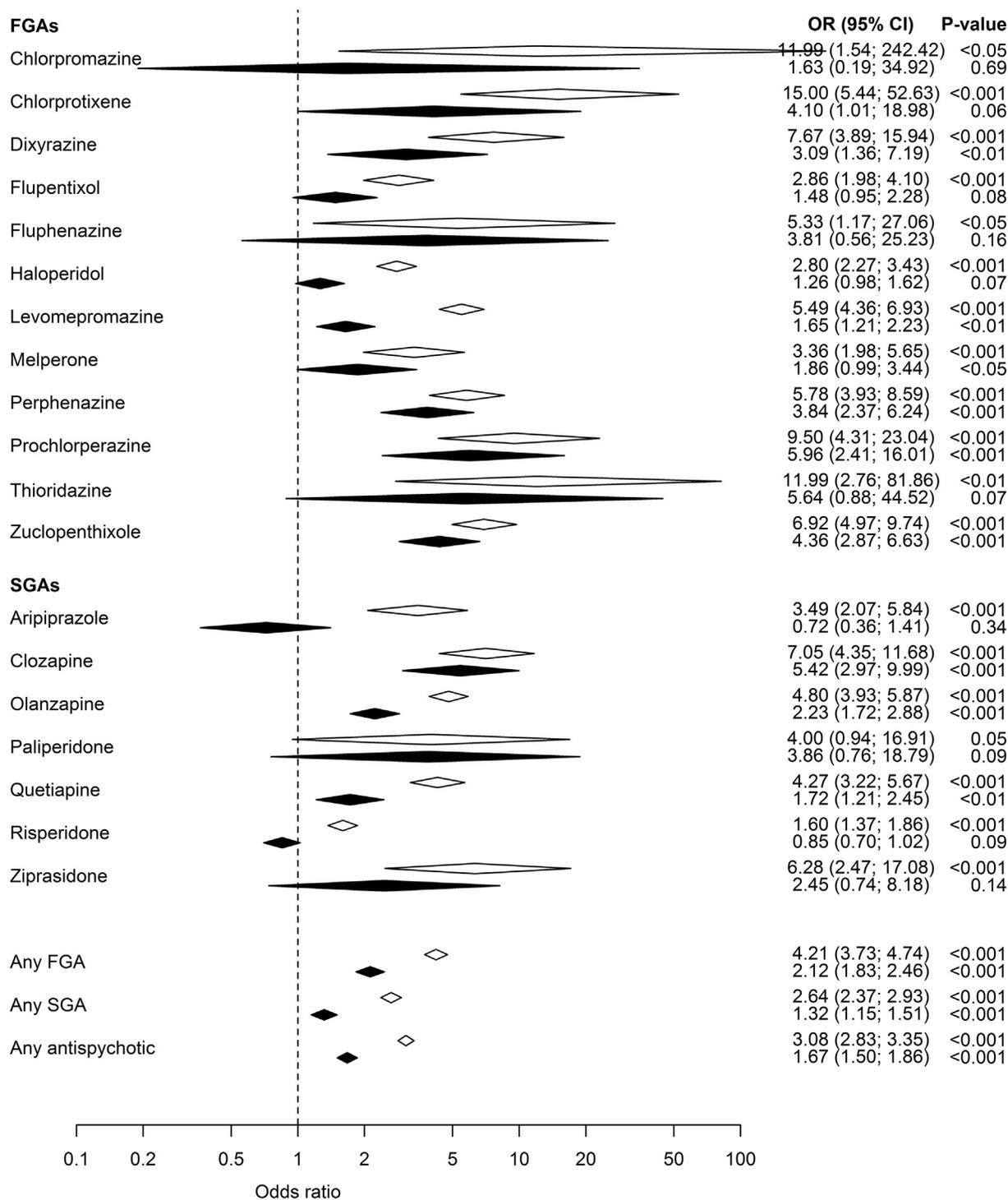
Fig. 1. The crude (white) and adjusted (black, all variables in Table 1) odds ratio (OR), including 95% confidence intervals (95% CI) for hospitalization due to hyponatremia in patients on different antipsychotics (newly/ongoing). FGA, first-generation antipsychotics. SGA, second-generation antipsychotics.

risperidone (0.86 [0.56–1.31] and 0.83 [0.67–1.02]) and aripiprazole (1.16 [0.30–4.46] and 0.62 [0.27–1.34]), respectively.

4. Discussion

This is the first population-based study reporting on the risk for hospitalization due to antipsychotic-related hyponatremia with a large number of individual antipsychotics. Individuals on any FGA were more likely to experience severe hyponatremia than those on any SGA (adjusted OR 2.12 vs. 1.32). For risperidone we found no increased risk.

The mechanism of antipsychotic-induced hyponatremia is uncertain. The main cause, similar to other psychotropic drugs, is believed to be SIADH [5,8]. Both FGAs and SGAs have been suggested to stimulate ADH secretion from the posterior pituitary gland [21]. However, increased activity of ADH on the kidney has also been suggested [9]. Haloperidol has been shown to reduce free water excretion and urinary dilution [22]. Severe polydipsia may be induced by both FGAs and SGAs via thirst center simulation in the CNS [9]. This effect may be less pronounced for SGAs, but the reports are mixed and controversial [9,23].
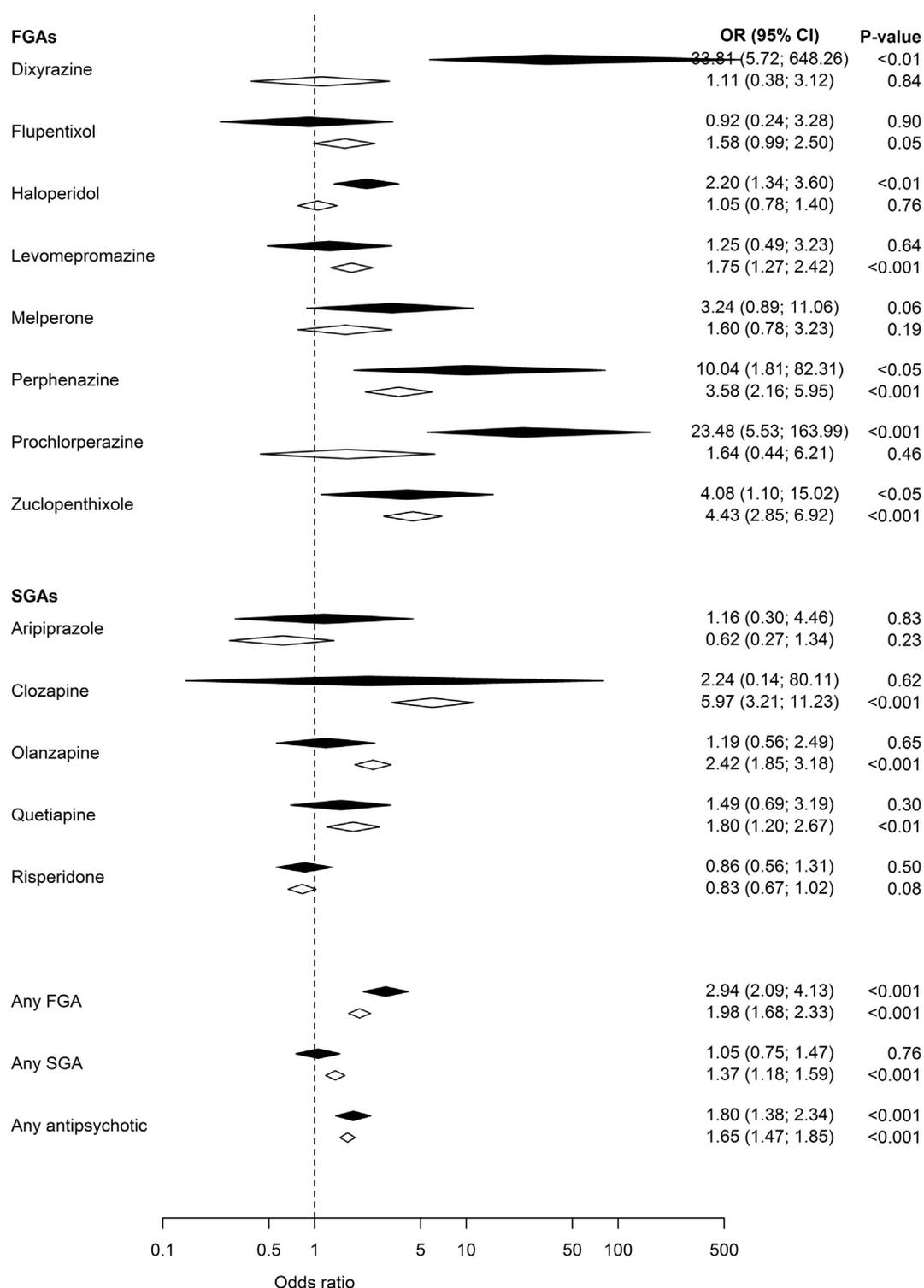
Fig. 2. The odds ratio (OR), including 95% confidence intervals (95% CI) for hospitalization due to hyponatremia in patients with ongoing (white) and newly initiated antipsychotics (black). All ORs have been adjusted for the confounding factors in Table 1. FGA, first-generation antipsychotics. SGA, second-generation antipsychotics.

In the present study, we found that the risk of hospitalization in individuals on any FGA were clearly higher than in those treated with any SGA. Most previous evidence on hyponatremia associated with antipsychotics is based on case reports or case series [8,12–14], with a few exceptions [9,10,15]. There is very limited number of comparisons between SGAs and FGAs [11]. Mannesse et al. compared antipsychotic use in 15,728 cases with reported hyponatremia with 129,525 controls

using the WHO global individual case safety report database (VigiBase) [9]. Adjusted reported odds ratios for hyponatremia for FGAs and SGAs antipsychotics were similar (1.66 vs 1.55). Being based on spontaneous reporting of adverse reactions, the study population may be biased and the results should be interpreted with caution. Gandhi et al. who reported on a population-based cohort from Ontario, Canada, comprising 58,008 older adult antipsychotic users matched with 58,008 controls

unexposed to antipsychotics [10]. The relative risk for individuals with one of three different SGAs within the last 30 days, namely risperidone, olanzapine or quetiapine was 1.62. However, the study did not include data on the risk associated with FGAs. Although SGAs were associated with a lower risk of hyponatremia compared to FGAs (OR 1.32 vs. 2.12) in the current study, exposure to SGAs was no less common than exposure to FGAs among patients hospitalized for hyponatremia (4.0% vs 3.8%). Since SGA use is much more common compared to FGA use in the general population (as reflected in the control group), the seemingly balanced exposure among cases represents an overrepresentation of FGAs, explaining the higher odds ratio for FGAs.

In our study, the risk associated with individual antipsychotics varied from no significant association to odds ratios around 6. Interestingly, no increased risks, neither as newly initiated or ongoing therapy, were found for risperidone and aripiprazole. The result contrast against the studies by Mannesse et al. and Gandhi et al. who found that treatment with risperidone was associated with hyponatremia (reported OR 1.52 (95%CI 1.30–1.77) [9] and RR 1.83 (95% CI 1.10–3.04) [10], respectively). The population-based approach of the present study, involving a large number of patients indicates that risperidone is relatively safe with regard to severe hyponatremia. Aripiprazole also did not demonstrate any association with severe hyponatremia in our study which is similar to others [9]. However, the drug was not widely used and the confidence intervals were wide. Hence, the lack of association should be interpreted with caution.

In contrast to our previous findings concerning antidepressants [6], antiepileptic drugs [7], and proton pump inhibitors [17], we could not find a clear temporal association between initiation of antipsychotics and clinically significant hyponatremia. Antipsychotic treatment is often initiated during hospitalization but we only captured outpatient prescriptions, hence we may have misclassified some of the ongoing treatments as newly initiated. Primary polydipsia, which is characterized by excessive fluid intake [23], could not be controlled for, since we used national databases. This may have played a role on the timing of hyponatremia. Polydipsia-induced hyponatremia may occur intermittently, especially in patients with schizophrenia [24]. However, antipsychotics may improve the psychiatric condition with subsequent decrease of the polydipsia [25]. A systemic review of mainly case reports found that 10% of antipsychotic-induced hyponatremia had concurrent polydipsia [8]. Moreover, the same study could, similar to us, not find a clear correlation between treatment duration and the onset of hyponatremia [8].

Our study has several important clinical implications. In a patient requiring antipsychotics with a history of hyponatremia or increased risk of hyponatremia, a SGA, especially risperidone may be preferable. Hyponatremia resulting in hospitalization can occur at any time after commencing treatment with an antipsychotic drug. Consequently, vigilance of hyponatremia symptoms are important but systematic sodium monitoring has generally not been recommended [11]. However, in those with deteriorated psychiatric or somatic condition while on antipsychotics, sodium testing could be advocated [9]. The benefit/risk of withdrawing or switching the antipsychotic should be considered carefully since this may result in worsening of the psychosis and behavioral issues. Moreover, the current study also demonstrates the importance of post marketing surveillance to detect previously unrecognized effects that may be associated with a drug and to evaluate the real world effectiveness and safety of the drug [26,27].

There are some additional strength and limitations that deserve attention. The major strength is the population-based approach that enabled the inclusion of all patients hospitalized due to hyponatremia in the entire country during more than nine years. Consequently, it was possible to analyze an extensive collection of different antipsychotics individually. We adjusted for a broad range of potential confounders such as concomitant treatment, comorbidities and socioeconomic factors. However, the results may still be influenced by residual confounding. Confounding by indication, with the underlying disease

predisposing to hyponatremia rather than the therapy, is also possible. This could in part explain the low difference in risk of hyponatremia with newly initiated vs. ongoing therapy. However, it cannot explain the differences in risk with different drugs. The absence of plasma sodium levels is a limitation of the current study. Instead, we took advantage of the Swedish physicians' mandatory selection of principal diagnosis, i.e., which clinical conditions that best motivated inpatient care. Focusing exclusively on the principal diagnosis may therefore, from a clinical point of view, be more relevant as compared to investigations also including individuals with hyponatremia as a secondary diagnosis, diagnoses made in the secondary care [28], or patients with a mild or moderate hyponatremia regardless of symptoms [29]. Moreover, our previous validation study showed that 89% with a principal diagnosis of hyponatremia had been hospitalized primarily due to symptoms of hyponatremia in a population with mean plasma sodium level of 121 mmol/L and 77% of the population was exposed to levels below < 125 mmol/L (moderate to severe hyponatremia), further emphasizing the clinical relevance of the outcome used [6]. Usually, case-control studies are not suitable for the evaluation of multiple outcomes and the temporality of the exposure and outcome may not be clearly defined. Therefore, starting from that assumption, we suggest the possibility to evaluate in the future further adverse outcomes related to antipsychotic treatment using the same study design as the present study.

In conclusion, we found a clear association between antipsychotics and hospitalization due to hyponatremia. The association was stronger for FGAs than SGAs. Risperidone did not seem to increase the risk.

Conflicts of interest

Drs. Jakob Skov and Buster Mannheimer report consultancy fees from Otsuka Pharma Scandinavia AB, outside the submitted work. No other authors had any conflicts of interest.

Financial disclosure

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