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Antipsychotic-Induced Hyponatraemia
A Systematic Review of the Published Evidence

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Abstract

Hyponatraemia is known to occur as a rare but clinically important adverse reaction to treatment with different psychotropic drugs, including selective serotonin reuptake inhibitors and antiepileptic drugs. In past decades, reports have been published that describe the development of hyponatraemia in association with antipsychotic drug treatment. Our objective was to systematically review the available evidence on antipsychotic-induced hyponatraemia, focussing on patient characteristics, drug dosage, polydipsia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

A search was carried out in the MEDLINE and EMBASE databases from January 1966 to 11 April 2009. Inclusion criteria were (i) hyponatraemia (serum sodium level <136 mmol/L) occurring after the start of treatment with an antipsychotic drug; and (ii) that the hyponatraemia potentially occurred as an adverse reaction to antipsychotic drug treatment in accordance with the WHO definition. Articles in languages other than English, Dutch, German,

French and Spanish were excluded. Information on patient characteristics, medical and diagnostic data, pharmacological treatment, drug dechallenge and drug rechallenge were extracted from the publications whenever available. A causality assessment was performed on all case reports using Naranjo's adverse drug reaction probability scale. Correlational analysis was performed to assess correlations between antipsychotic drug dosage and both serum sodium level and time to onset of hyponatraemia.

We included four studies and 91 publications containing case reports and case series; no randomized controlled studies were identified. Data from the identified case reports were further analysed. The mean age of the patients was 46 years; 57% were male. The diagnosis was schizophrenia in 70% of the cases. A history of polydipsia was diagnosed as positive in 67% of the cases and negative in 23% of the cases. Polydipsia occurred in the remaining 10% of cases, although it was reported to be drug-induced (i.e. a severe increase in water intake was observed in relation to treatment with the suspected drug). Analysis of the case reports using the adverse drug reaction probability scale indicated possible causality in most cases (80%), probable causality in a significant amount of cases (19%) and unlikely causality in one case (1%). Overall correlational analysis yielded no significant correlations between defined daily dose-equivalent dosages and serum sodium or time to onset of hyponatraemia.

The incidence of hyponatraemia induced by antipsychotics may be much higher than is currently thought. Both the newer atypical antipsychotics and the older drugs have been associated with the development of hyponatraemia. Physicians, psychiatrists and other healthcare workers should be aware of the possibility of hyponatraemia associated with the use of antipsychotics. Further studies are required to establish the risks of and risk factors associated with antipsychotic-induced hyponatraemia.

Hyponatraemia is seen in about 4% of patients with chronic schizophrenia[1,2] and occasionally in patients with other psychiatric disorders, including manic depressive psychosis, psychotic depression and mental retardation.[3] Hyponatraemia is a state of imbalance in water-electrolyte homeostasis, generally defined as a lowered serum sodium level of <136 mmol/L (normal: 136–144 mmol/L),[4] although different definitions such as <130 mmol/L are also used.[5,6] Dilutional hyponatraemia, caused by inappropriate retention of water and excretion of sodium, can occur as an adverse effect of treatment with different psychotropic medications, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, benzodiazepines, antiepileptic drugs and antipsychotics.[7] It is a complication that is usually either asymptomatic or accompanied by mild symptoms, such as nausea and general malaise. In more severe cases (serum sodium <125 mmol/L or when sodium levels drop quickly) it is of clinical importance, with predominantly neurological symptoms, including headache, muscle cramps, lethargy, confusion, delirium and agitation. Many of these symptoms can also occur in association with mental disease, implying that it may be difficult to recognize hyponatraemia as an adverse drug reaction and to dissociate drug and disease as underlying causes. Severe or rapidly developing hyponatraemia can cause convulsions, coma and even death. Furthermore, hyponatraemia has been associated with the development of rhabdomyolysis.[8,9] Although hyponatraemia as an adverse effect of treatment with antidepressants, particularly SSRIs, is well established,[10] the role of antipsychotics is far less conclusive.

In the 1970s, it was recognized that antipsychotics such as tiotixene (a thioxanthene derivative) and haloperidol (a butyrophenone derivative) could impair the ability of patients to excrete a free water load.[11,12] Later, it was shown that elderly patients treated with phenothiazines (including chlorpromazine, thioridazine and fluphenazine) had significantly lower serum sodium levels than patients not treated with phenothiazines.[13] Furthermore, it was shown that a greater portion of patients treated with haloperidol had impaired free water excretion and urinary dilution than healthy controls.[14] No such data have been reported for the newer atypical agents, although case reports of drug-induced hyponatraemia in patients using atypical drugs suggest that these probably also affect water balance and can induce hyponatraemia in some cases.[15,16]

We systematically reviewed the available published evidence on antipsychotic-induced hyponatraemia, focussing on the role that patient characteristics, drug dosage, duration of treatment, polydipsia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) have in its occurrence. In addition, we were interested in the association between treatment with the newer atypical antipsychotics and the development of drug-induced hyponatraemia.

1. Literature Search Methodology

1.1 Data Sources

A search was conducted in the MEDLINE and EMBASE databases between January 1966 and 11 April 2009. For the search, which was based on keywords from the systematic catalogue or alphabetic index, the following terms were used: 'antipsychotic agents', 'neuroleptic agent', 'hyponatremia', 'inappropriate ADH syndrome', 'sodium blood level', 'sodium deficiency', 'sodium depletion', 'water-electrolyte balance', and 'polydipsia'. The only limit on the search was time.

1.2 Study Selection

The search results were then screened by title and abstract. All potentially relevant publications were retrieved in full text and evaluated in detail. Furthermore, these full-text publications were manually searched for additional relevant references, which were also retrieved and evaluated. To be eligible for inclusion, publications had to meet the following criteria: (i) hyponatraemia (defined as serum sodium levels <136 mmol/L) occurred after the start of treatment with one or more antipsychotic drugs; (ii) hyponatraemia occurred as a potential adverse reaction of antipsychotic treatment, in accordance with the WHO definition for adverse drug reaction: "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".[17] This criterion excluded intentional intoxications. Publications in which serum sodium levels had not been measured or mentioned, or which did not specify which antipsychotic drug was involved, were excluded. Publications in languages other than English, German, Dutch, French and Spanish were also excluded.

1.3 Data Extraction

The identified studies were described. Based on the guidelines for adverse event reporting,[18] the following parameters were extracted from the case reports: patient characteristics (age, sex); medical data (diagnosis, history of disease, history of polydipsia); diagnostic data (serum sodium level, SIADH diagnosis); pharmacological treatment (antipsychotic drugs, other drugs potentially responsible for hyponatraemia; defined daily dose [DDD]-equivalent dosage of antipsychotic[s]); time to onset of hyponatraemia; drug dechallenge; and drug rechallenge. The diagnosis of SIADH was based on reported diagnosis and laboratory measures, which were assessed using the criteria initially proposed by Bartter and Schwartz,[19] combined with more recently proposed diagnostic criteria.[20] The concomitant use of diuretics was considered to be an exclusion criterion for SIADH. To evaluate the role of antipsychotic drug dosage in the development of hyponatraemia, DDD-equivalent dosages, which were previously suggested to be more suitable

than chlorpromazine equivalents when comparing typical and atypical agents,[21] were calculated based on the 2008 WHO anatomical and therapeutic classification (ATC)/DDD index.

1.4 Causality Assessment

Two researchers (DM and CM) independently performed a causality assessment on all included case reports, using the adverse drug reaction probability scale as proposed by Naranjo et al.[22] The scale is composed of ten questions, which are to be answered with 'yes', 'no' or 'not known', which, depending on the answer, results in addition or subtraction of points. The final score expresses the probability that the adverse drug reaction (i.e. hyponatraemia) was caused by the drug. Scores range from −4 to +13 and are categorized as 'unlikely' (−4 to 0), 'possible' (1 to 4), 'probable' (5 to 8) and 'certain' (9 to 13). A consensus panel (DM, CM and PJ) was used to reach consensus on conflicting results from the initial independent assessments. Scoring was done conservatively, i.e. in cases of ambiguous reporting that were open to multiple interpretations, no points were assigned. Where patients were using more than one antipsychotic drug and the assessment would yield different results for each drug, these drugs were independently assessed.

1.5 Data Analysis

Descriptive data analysis was used to summarize the data that were extracted from the included publications. Pearson's correlation coefficient (r) was used to analyse the relationship between DDD-equivalent dosage and both serum sodium levels and time to onset of hyponatraemia. For these statistical tests, the criterion for significance was $p < 0.05$. All statistical analyses were carried out using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

2. Data Synthesis

2.1 Selected Studies

As is shown in figure 1, the search resulted in 1161 unique titles. All titles were screened, after which 169 full-text articles were retrieved for further evaluation. The large decrease in the number of titles in this first stage was due to the fact that we chose to include all subterms and derivatives of the search terms, which made the search more sensitive to loss of specificity. Many titles were related to bipolar disorder, without any mention of antipsychotics (which may be explained by the fact that lithium is assigned an ATC code in the antipsychotics group, N05A). Other titles were excluded because they were animal studies, cases related to hypernatraemia or pharmacokinetic studies related to renal metabolism of antipsychotics. Of the retrieved full-text articles, two case reports of antipsychotic overdose with accompanied hyponatraemia were not included because they did not comply with the WHO definition of adverse drug reaction.[23,24] Twelve other publications were excluded for the following reasons: language;[25-30] no serum sodium levels mentioned;[31] the temporal relationship between treatment and hyponatraemia was doubtful, or too little information was present.[32-36] The remaining titles were off topic and therefore not included. After detailed evaluation of the remaining titles and manual search, 94 publications were included. Of these, four described studies related to antipsychotic drug treatment and hyponatraemia,[13,37-39] and 91 described case

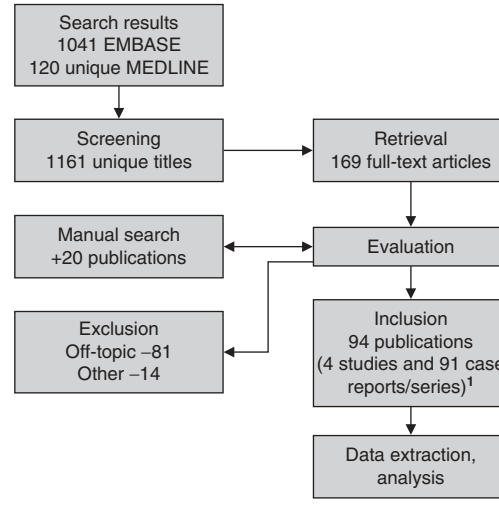

Fig. 1. Study selection. **1** One publication described both a case report and a study.

reports and case series of hyponatraemia in patients treated with antipsychotics[8,9,11-13,15,16,40-122] (one publication described a case report as well as a study[13]).

2.2 Data Description

Three observational studies[13,38,39] and one interventional study[37] were included in our review. Kimelman and Albert[13] reported in a preliminary study of a small population of elderly patients that serum sodium levels were significantly lower in patients taking phenothiazines compared with patients not taking phenothiazines. The authors controlled for age and use of diuretics. Jos et al.[38] performed a retrospective case-control study comparing psychiatric patients with self-induced water intoxication (sodium ≤130 mmol/L) with matched controls without self-induced water intoxication. They compared psychotropic drug use (including antipsychotics) in the month before admission and found no differences between groups. Spigset and Hedenmalm[39] analysed the correlation between antipsychotic drug dosage and serum electrolyte levels. They analysed serum sodium levels of patients with schizophrenia or other psychotic disorders who were using perphenazine (n = 112) or clozapine (n = 59). In these groups, they found a prevalence of hyponatraemia (serum sodium <135 mmol/L) of 25.9% and 13.6%, respectively. They did not find significant correlations between perphenazine or clozapine dosage and serum sodium levels. However, they observed a trend for a negative correlation between perphenazine dosage and sodium level in the age group older than 60 years ($r = -0.12$, $p = 0.12$) and, interestingly, a trend for a positive correlation between clozapine dosage and serum sodium level ($r = 0.24$, $p = 0.07$). Canuso and Goldman[37] studied the effect of lowering antipsychotic drug dosage on serum sodium levels in schizophrenic hyponatraemic patients (n = 5). These patients were observed to be hyponatraemic (125–134 mmol/L) during treatment with either fluphenazine, haloperidol, tiotixene or perphenazine. They found that lowering the antipsychotic drug dosage down to 1–33% of baseline dosage did not significantly affect serum sodium levels.

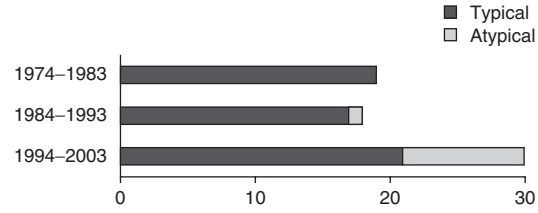

Fig. 2. The number of published articles reporting on cases of hyponatraemia associated with antipsychotic treatment between 1974 and 2003.

The 91 published case reports and case series described a total of 120 patients with one or more hyponatraemia events. The year of publication ranged between 1974 and 2008. Figure 2 shows the number of case reports of hyponatraemia involving typical and atypical antipsychotics between 1974 and 2003.

The data that were extracted from all case reports are shown in the supplementary table (Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A20). For each case, the table shows patient characteristics (including age, history of disease, diagnosis, history of polydipsia), antipsychotic drug use (type of drug, daily dose), diagnostic characteristics (including serum sodium levels, diagnosis of SIADH, time to onset of hyponatraemia, results of dechallenge/rechallenge tests) and the result of the causality assessment. These data were further analysed, the results of which are summarized in table I. Although some case reports described a near-fatal outcome, almost all patients fully recovered within days after adequate treatment, which included discontinuation of the causative drug, fluid restriction, (hypertonic) saline infusion and, occasionally, the administration of furosemide. One patient, receiving extreme polypharmacy treatment, did not survive despite hospitalization and treatment.[73]

2.3 Causality Assessment

A total of 123 assessments were performed on 120 case reports of hyponatraemia (some patients were using multiple antipsychotic drugs). Twenty-three assessments (19%) suggested a 'probable' relationship between antipsychotic treatment and hyponatraemia, 99 assessments

Table I. Summary of data extracted from case reports

Patient characteristics and diagnostic criteria	Value	No. of reports in which data was reported (%)
Patient characteristics		
Age (years ± SD)	46 ± 15	116 (97)
Sex (%)		120 (100)
male	57	
female	43	
Diagnosis (%)		111 (93)
schizophrenia	70	
other	29	
healthy	1	
History of disease (years ± SD)[a]	15 ± 7	29 (37)
History of polydipsia[b] (%)		91 (76)
yes	67	
no	23	
drug-induced	10	
Diagnostic criteria		
DDD-equivalent dosage (mean ± SD)	2.1 ± 2.3	83 (67)
Serum sodium level (mmol/L ± SD)	117 ± 7	123 (100)
Time to onset (median, days)	19 (range 0.25–3287)	47 (38)
Diagnosis of SIADH (%)		74 (60)
yes	78	
no	22	
Dechallenge (%)		64 (52)
yes	94	
no	6	
Rechallenge (%)		
yes	11	
no/not reported	89	
Water-loading test[c]	4	

a These figures are based only on patients diagnosed with schizophrenia, since only in these reports was the history of disease reported in a substantial number of cases.

b When available, information on a history of polydipsia was scored as follows: having occurred in the past (yes); not having occurred in the past (no); or reportedly being induced by the antipsychotic drug (drug-induced).

c Under baseline and treatment conditions.

DDD = defined daily dose; **SIADH** = syndrome of inappropriate secretion of antidiuretic hormone.

(80%) indicated 'possible' causality and one assessment suggested that causality was 'unlikely' (1%).

The most important findings with regard to the causality assessment will be discussed briefly. In nearly half of the cases, hyponatraemia improved after cessation of the antipsychotic drug (47%), 2% showed no improvement and in 51% of the cases this information was not available. Reappearance of hyponatraemia after rechallenge with the suspected drug occurred in 7%, while in 8% rechallenge was uneventful (85% not known). With regard to the possibility of other causes for the occurrence of hyponatraemia, the answer 'yes' according to the questions on the Naranjo scale was assigned in 69% of the cases and 'no' in 3% (28% not known). The high percentage of the answer 'yes' for this question is because SIADH/hyponatraemia theoretically may have many causes, including some that are closely associated with psychiatric disease (i.e. psychosis). Lastly, it was found that 25% of the cases that were described had a similar previous event of hyponatraemia associated with antipsychotic drug use (not known in 75% of cases).

2.4 Correlational Analysis

To analyse the correlation between drug dosage and serum sodium levels and between drug dosage and time to onset of hyponatraemia, Pearson's correlation coefficient was used. Because not all reports clearly mentioned time to onset, only the available unambiguous data were used in the analysis (n = 83 for serum sodium levels, n = 47 for time to onset). If ranges were given, the middle of the depicted range was calculated and used in the correlational analysis. DDD-equivalent dosages were not significantly correlated with serum sodium levels (r [n = 83] = 0.02, not significant).Typical and atypical agents were analysed separately. Patients taking both types of drugs were excluded from this analysis. A trend towards a positive correlation between DDD-equivalent dosage and serum sodium was observed for typical antipsychotics (r [n = 56] = 0.25, p = 0.061), and a non-significant negative correlation between DDD-equivalent dosage and serum sodium levels was observed for atypical antipsychotics (r [n = 22] = –0.16, not significant). No significant correlations were observed between

DDD-equivalent dosage and time to onset, either when analysing all drugs (r [n = 47] = 0.07, not significant) or typical and atypical drugs separately (r [n = 28] = 0.04, not significant and r [n = 18] = 0.15, not significant, respectively).

3. Discussion

The aim of this review was to evaluate the evidence on antipsychotic-induced hyponatraemia. We identified no clinical studies that have investigated hyponatraemia as an adverse reaction associated with antipsychotic treatment. Although several preliminary studies found no association between antipsychotic treatment and hyponatraemia, a great deal of evidence is available in the form of case reports. Reports that associate both typical and atypical antipsychotics with the occurrence of hyponatraemia have been published, indicating that the newer agents can also induce antipsychotic-induced hyponatremia. A study we recently performed using the WHO global individual case safety report database system (Vigibase, maintained by the the Uppsala Monitoring Centre) showed a significant association between antipsychotic treatment and hyponatraemia.[123] Furthermore, the US FDA spontaneous reporting system describes over 300 reports of hyponatraemia associated with antipsychotic treatment between 1966 and 1999.[7] These findings may indicate that hyponatraemia as an adverse reaction to antipsychotic treatment is more common than currently thought.

We analysed several factors that are potentially associated with antipsychotic-induced hyponatraemia. In contrast to antidepressants,[124] the mean age and distribution that were observed in this study, which are similar to those for acute hyponatraemia of various aetiology,[62] indicate that age is probably not a risk factor for antipsychotic-induced hyponatraemia. In addition, our results indicate that antipsychotic-induced hyponatraemia does not preferentially occur in either men or women, which also contrasts with the suggestion that female sex is a risk factor for antidepressant-induced hyponatraemia.[124,125] Furthermore, our observation that dosage was not significantly correlated with severity of hyponatraemia is in line with the findings of Canuso and Goldman,[37] who found that lowering antipsychotic dosage did not improve serum sodium levels in hyponatraemic patients. For other psychotropic drugs, such as SSRIs, the development of hyponatraemia has been shown to be dose-dependent.[126] Our finding of a trend towards a protective effect of high-dose typical antipsychotics may be related to the improvement of mental disease. It should be mentioned that, to date, no reliable system is available for the comparison of antipsychotic drug dosages, and it has been shown that there is great discrepancy between DDDs and chlorpromazine equivalents.[21] Therefore, dose comparison, especially when typical and atypical agents are involved, remains rather problematic. We chose to use DDDs because they are based on the whole spectrum of receptor binding rather than solely on dopamine D_2 receptor antagonism. Furthermore, data on chlorpromazine equivalents reported in the literature vary widely. Clearly, more research is needed to establish the relationship between antipsychotic drug dosage and the development of hyponatraemia. Importantly, it could be concluded from our results that hyponatraemia does not always develop within the first weeks of treatment, but that it can occur even after long-term treatment. As expected, our data suggest that antipsychotic-induced hyponatraemia is most likely a result of SIADH and, in the majority of cases, a diagnosis of SIADH was made. It has been suggested that tobacco smoking increases the risk of developing SIADH in psychiatric patients, among which there is an excess of smokers.[127] In the included case reports, there was little information available on smoking habits. For this reason, we did not include smoking as a parameter in the dataset. We used an adverse drug reaction probability scale to assess the evidence for causality in the case reports. We found that the majority of the published reports indicate 'possible' causality, and 19% indicate 'probable' causality. However, some reports that describe rechallenge with the suspected drug and subsequent reappearance of hyponatraemia[11,12,67,71,91,92,112,128] indicate

strong causality between drug treatment and the development of hyponatraemia. However, in the majority of these cases, it was not possible to reliably exclude other possible causes for SIADH/hyponatraemia (such as psychosis), which led to significantly lower scores. A significant number of cases were associated with (possible) neuroleptic malignant syndrome,[45,58,64,74,84,90,92,94,115,128,129] and two cases were associated with hyperglycaemia.[113,114]

It has previously been demonstrated that schizophrenia itself is related to the development of hyponatraemia.[3,99] A subset of schizophrenic patients are known to have a condition that has been called the syndrome of psychosis, intermittent hyponatraemia and polydipsia (PIP syndrome).[130,131] These chronically hyponatraemic and polydipsic patients exhibit an increase in antidiuretic hormone (ADH) secretion,[132,133] which was recently suggested to be related to hippocampal dysfunction.[134] It was shown that the anterior hippocampal formation within the medial temporal lobe in polydipsic-hyponatraemic patients is smaller than in polydipsic-normonatremic patients and non-polydipsic patients.[135] Interestingly, these patients are able to excrete maximally dilute urine following a water load. Their condition has been termed 'reset osmostat',[136] and the relationship between plasma osmolality and ADH is shifted to the left in these patients.[133] Thus, although urinary dilution is maximal at sufficiently low plasma osmolality, urinary osmolality becomes hypertonic to plasma prematurely when plasma osmolality increases. It is not clear whether these abnormalities in some patients contribute to the development of antipsychotic-induced hyponatraemia. The fact that almost three of four of the reported cases we identified were patients with schizophrenia, and that probably less than half of patients treated with antipsychotic medications are diagnosed with schizophrenia,[137,138] may indicate that schizophrenia pathology indeed contributes to the development of antipsychotic-induced hyponatraemia. However, the high proportion of patients with schizophrenia may also result from publication bias, since for other groups of patients using antipsychotics (such as elderly demented patients), hyponatraemia may be more likely to be ascribed to other medications or co-morbidity.

Another potentially contributing factor is polydipsia,[139] which is a significant cause of the morbidity and mortality[140] that is frequently encountered in psychiatric patients.[141,142] It has been suggested that polydipsia *per se* does not induce hyponatraemia.[143] However, chronic polydipsia could induce renal changes that result in the impaired ability of the kidney to concentrate urine.[144] The relationship between polydipsia and antipsychotic treatment is complicated by the fact that increasing the dosage of antipsychotics in some patients reduces polydipsic behaviour.[145] The observed number of cases involving patients with a history of polydipsia (67%) is probably higher than in the psychiatric population, although 20% and higher has been reported.[1,146] Therefore, it may be speculated that patients with polydipsia are at higher risk for antipsychotic-induced hyponatraemia. Interestingly, we found that in some cases, antipsychotic treatment induces severe polydipsia and consequent hyponatraemia.[40,86,100,102,105,106,108,110] In all of these cases, typical antipsychotics were involved, which is in line with the suggestion that these drugs increase the likelihood of polydipsia.[59] A recent report suggests that the atypical agent risperidone can also induce excessive water intake,[31] which indicates that antipsychotic-induced polydipsia is not solely due to anticholinergic xerostomia (dry mouth). Polydipsia is probably underdiagnosed by physicians and psychiatrists because polydipsic behaviour is often denied, and its clinical manifestation may often be incorrectly diagnosed because of the similarity between its presentation and symptoms of underlying psychiatric disease.

It is not clear in what way antipsychotic treatment causes neuroendocrine abnormalities, but SIADH has most frequently been mentioned as the underlying mechanism. SIADH is characterized by excessive secretion of ADH. High levels of ADH lead to volume expansion and consequent natriuresis, which is probably mediated by atrial natriuretic peptide secretion.[147]

Pharmacodynamic hypotheses for SIADH are that antipsychotic drugs act as a non-osmolar stimulus for ADH release, resulting in SIADH in at least some schizophrenic patients[148,149] and/or enhancing the activity of ADH on the kidney.[150] Long-term D_2 receptor blockade in long-term antipsychotic drug use may lead to supersensitivity of D_2 receptors, resulting in elevation of ADH levels.[32,151] Also, it has been suggested that long term D_2 receptor blockade induces increased peripheral response to angiotensin II (and thereby dipsinogenic activity) in humans, and increases angiotensin II-induced thirst in animals.[152] However, a recent post-mortem study[153] investigating the activity of ADH neurons in the hypothalamus of schizophrenic patients under antipsychotic treatment (without history of polydipsia-hyponatraemia) and controls, showed no differences between treated patients and controls in a wide variety of activity markers. Raskind and Barnes[149] have suggested that antipsychotics do not directly stimulate ADH release, but may indirectly stimulate its release by baroreceptor reflex mechanisms if hypotension occurs. In a recent report on aripiprazole-induced hyponatraemia, the authors suggest that antipsychotic-induced hyponatraemia may be (partially) serotonin-mediated through increased ADH release, augmentation of the effects of endogenous ADH on the kidney and lowering of the threshold for ADH release by influencing the osmostat. However, since typical antipsychotics do not exert their effects through serotonin, this may not be a completely satisfactory explanation of the mechanism of antipsychotic-induced hyponatraemia. The mechanism underlying antipsychotic-induced hyponatraemia might be better understood by studying the differential pharmacology of clozapine, which has recently been proposed to have beneficial or salutary effects on polydipsic behaviour and the development of hyponatraemia in psychiatric patients (reviewed by Bersani et al.[154]). The exception of clozapine could be explained by its lower binding affinity at D_2 receptors, thereby normalizing or avoiding supersensitivity of D_2 receptors and improving polydipsia and hyponatraemia. Another suggestion by Wilke[155] is based on the finding of sigma receptors in rodents in the posterior pituitary. It was suggested that these receptors can bind sigma receptor ligands, including haloperidol and chlorpromazine, resulting in the inhibition of potassium-channel function and possibly increased release of ADH. Clozapine, which is not a sigma receptor ligand, could therefore have a salutary or improving effect.

This study has several limitations. It seems likely that only the more severe cases of hyponatraemia are published, which may have led to publication bias. In addition, the fact that hyponatraemia as an adverse reaction of antipsychotic drugs is not as established as it is for other psychotropic drugs may have caused antipsychotic-induced hyponatraemia to be ascribed to other drug treatments or factors such as high age or disease pathology (for instance psychosis). Moreover, the atypical presentation of hyponatraemia, which can mimic psychiatric symptoms, may cause antipsychotic-induced hyponatraemia to go unrecognized. These factors have most likely affected the characteristics of the available evidence and, therefore, the cases we described and analysed may not be a representative sample of cases of antipsychotic-induced hyponatraemia. Furthermore, our methodology has limitations that are intrinsic to case reports, which are regarded as low-quality evidence. However, they are the only evidence available for an adverse reaction that, in our view, is currently underrecognized. We used the Naranjo algorithm to analyse the available case reports and, to minimize interpretation bias, we used a panel of investigators with clinical experience. Finally, it may be argued that we used a rather high cut-off sodium level (<136 mmol/L) as an inclusion criterion. However, in our view, this did not lead to the inclusion of clinically irrelevant cases. In fact, only five of the cases we described concerned sodium levels >130 mmol/L.

4. Conclusions

More studies are highly warranted to establish the risks of and risk factors associated with antipsychotic-induced hyponatraemia. The incidence

of hyponatraemia induced by antipsychotics may be much higher than is currently thought. Antipsychotic-induced hyponatraemia is probably due to SIADH, and occurs in schizophrenic patients as well as patients with other disorders. It probably occurs equally among men and women. The newer atypical antipsychotics, like the older drugs, have been associated with the development of hyponatraemia. Drug dosage does not seem to be a significant determinant in its occurrence and other, unidentified aetiological factors are probably involved. The role of polydipsia is unclear, and antipsychotic-induced hyponatraemia occurs both in patients with and without a history of polydipsia. Furthermore, we found that drug-induced polydipsia may occur in some cases, and subsequently lead to the development of hyponatraemia. Physicians, psychiatrists and other healthcare workers should be aware of the possibility of antipsychotic-induced hyponatraemia.

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