Hyponatraemia during psychopharmacological treatment: results of a drug surveillance programme

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Abstract

Hyponatraemia (HN) can be a life-threatening medical condition which may lead to severe neurological and psychiatric symptoms. The AMSP (Arzneimittelsicherheit in der Psychiatrie) is a multicentre drug surveillance programme that assesses severe or new adverse drug reactions during psychopharmacological treatment in psychiatric inpatients. We report on a total of 263 864 psychiatric inpatients monitored from 1993 to 2007 in 80 psychiatric hospitals in Germany, Switzerland and Austria. During this period plasma sodium levels below 130 mmol/l (severe HN according to AMSP) were reported in 93 patients (relative frequency 0.04%). On average, the plasma sodium levels of all cases were 119.7 mmol/l (±5.8 S.D.); median 121 mmol/l (range 104–129 mmol/l). Patients who showed no clinical signs (n = 65, 70%) had a mean sodium level of 121.3 mmol/l (±5.0 S.D.); median 122 mmol/l (range 114–129 mmol/l). By contrast, patients with clinical symptoms (n = 28, 30%) had a mean sodium level of 116.0 mmol/l (±6.0 S.D.); median 117 mmol/l (range 104–125 mmol/l). HN was mainly observed during treatment with selective serotonin reuptake inhibitors (SSRIs) (0.06%), Serotonin noradrenaline reuptake inhibitors (SNRIs) (0.08%), carbamazepine (0.10%) and oxcarbazepine (1.29%); the highest rate was found for oxcarbazepine. Antipsychotics, mirtazapine and tricyclic antidepressants were only rarely involved in HN (0.003–0.005%). Combinations of several drugs known to induce HN significantly increased the risk of HN, e.g. more than 10-fold for SSRI + diuretics + ACE inhibitors (0.37%) vs. SSRI given alone (0.02%). This is clinically relevant because such combinations, e.g. SSRI + diuretics may occur especially in elderly patients, who are in general at higher risk of developing HN.

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Introduction

Hyponatraemia (HN) is the most common aberrance in serum electrolytes and has an incidence of 2.5% in general hospital patients (Adrogue & Madias, 2000). In certain populations the incidence of HN is much higher. Approximately 11% of the elderly suffer from HN (Sunderam & Mankikar, 1983). This increased risk is attributed to age-correlated alterations in endocrine and renal functions (Turnheim, 2003). Concerning higher frequencies of HN in subpopulations of patients, Boumann and colleagues in a retrospective review on a psychogeriatric ward over 1 yr evaluated the prevalence of HN as 7.7% (Bouman et al. 1998). Generally, plasma sodium concentration is maintained between 135 and 145 mmol/l. This is achieved through an integrated homeostatic system that regulates water intake and urine output via changes in thirst and the secretion of antidiuretic hormone. Osmoreceptors located in the hypothalamus detect small changes in the extracellular fluid osmolality,
while baroreceptors respond to changes in effective circulating volume (Kovacs & Robertson, 1992). The aetiologies of HN can be classified into three types according to the patient’s volume status (Kirby & Ames, 2001). For this reason the evaluation of hypona-traeamic patients first requires an assessment of extracellular fluid volume, which may be elevated, low or normal, leading to hypervolaemic, hypovoltaemic or euvolaemic HN, respectively (Druckenbrod & Mulsant, 1994). Euvolaemic HN is commonly caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). In SIADH, the anti-diuretic hormone stimulates retention of water in the absence of appropriate physiological stimuli (Kirby & Ames, 2001). The diagnosis of SIADH can only be established in the absence of other potential causes of HN such as the use of diuretics, hyper- or hypo-volaemic HN, hypothyroidism or renal dysfunction (Bartter & Schwartz, 1967). A large number of different drugs like psychopharmacological and internistic drugs are held responsible for inducing HN (Douglas, 2006; Ghali, 2008; Liamis et al. 2008). The majority of patients with HN show no clinical signs, but untreated acute HN is associated with increased mortality (Gross, 2001). Decaux (2006) illustrated that chronic HN (serum sodium level around 125 mmol/l) can increase the rate of falls and may lead to impairment of attention, posture and gait mechanism. HN often starts asymptptomatically, and early symptoms are unclear and non-specific. The symptoms may also imitate those of depression and therefore may be mis-interpreted. Once the serum sodium level falls below 125 mmol/l neurological symptoms are predominate. Complications of severe and rapidly developed HN include seizures, coma, brainstem herniation, respiratory arrest, permanent brain damage, and death. Possibly fatal demyelinization can occur with an overly rapid serum sodium equalization. A moderate improvement (e.g. <12 mmol/d) can minimize this risk.

Drug surveillance programmes allow for early identification of HN, thus minimizing its consequences. An example for such a programme is the Boston Collaborative Drug Surveillance Program, which has enhanced the understanding of serious adverse drug reactions from a pharmaecoepidemiological view (Jick et al. 2003). A drug surveillance programme in psychiatry is the AMSP study (AMSP; Arzneimittelsicherheit in der Psychiatrie), a drug safety programme for the systematic evaluation of severe adverse reactions to psychotrophic drugs in psychiatric inpatients (Grohmann et al. 2004). The AMSP generates an ongoing database of severe adverse drug reactions monitored in psychiatric hospitals in Germany, Austria and Switzerland. In the present study we analysed HN reports in this database. We focused on illness-related and sociodemographic aspects, severity of clinical signs and symptoms and sodium levels as well as on combination therapies as possible risk factors (e.g. psychotropic drugs + internistic drugs such as angiotensin-converting enzyme (ACE) inhibitors, proton pump inhibitors or diuretics).

Method

The AMSP programme is a continuous pharmacovigilance programme. Severe adverse drug reactions to all psychotropic drugs are assessed during inpatient treatment at – in 2010 – 56 university, state, or municipal psychiatric hospitals or departments. A total of 80 hospitals participated at some time from 1993 to 2007. The AMSP methods have been described in detail previously (Grohmann et al. 2004). In brief, monitoring is performed by psychiatrists (‘drug monitors’), who ask their colleagues regularly (i.e. bi-weekly) if serious adverse drug reactions (ADRs) have taken place on their hospital ward. Drug monitors collect data on ADR and document cases using a standardized questionnaire. A detailed description of adverse events is given along with basic demographic patient records as well as psychiatric and somatic drug data. Possible risk factors, alternative explanations for the adverse event, measures taken, course of the ADR, and prior exposure to the drug are documented. The cases are re-examined by a senior doctor of each hospital and discussed thereafter at regional and central case conferences held three times a year. These conferences are attended by the drug monitors from all participating hospitals, representatives of the national drug regulating authorities, and drug safety experts of the pharmaceutical industry in the participating countries. When an agreement is reached and a probability rating is given to the ADR, the case questionnaires are sent to the relevant authorities and pharmaceutical companies and saved in the AMSP central database for further analysis. The probability for the severe ADR is rated as follows:

- **Grade 1**: possible (ADR unknown or alternative explanation likelier).
- **Grade 2**: probable (ADR known for drug in question and time-course and dosage in accordance with previous experience; alternative explanation less probable).
- **Grade 3**: definite (the same as grade 2 together with reappearance after re-exposure with drug in question).
• **Grade 4**: questionable or not sufficiently documented.

In cases of polypharmacy often more than one drug is imputed. In those cases in which a pharmacodynamic interaction is held responsible for an ADR, e.g. HN, each drug which is imputed is given a rating of ‘possible’, ‘probable’, or ‘definite’ according to the given facts. In addition, data evaluation takes into account that each drug was imputed in combination with others. Consequently, AMSP data on ADR rates for single drugs/groups distinguish between ‘all cases’, including cases in which the drug/group in question was imputed in combination with others as well as those in which it was imputed alone. The category ‘drug imputed alone’ includes only the latter. Data on drug use at the participating hospitals are evaluated on two reference days per year. On these reference days, all administered drugs are assessed along with basic demographic and diagnostic as well as detailed drug treatment data from all patients. Moreover, the contributing hospitals provide the number of inpatients and the mean treatment duration for all patients under surveillance per year. Data shown in this study refer only to HN cases rated as grades 2 and 3 (probable and definite). As to HN, only cases with sodium level <130 mmol/l (severe according to the definition of the AMSP programme) were assessed (Grohmann et al. 2004). The definition of severe HN as a sodium level <130 mmol/l was given by endocrinological experts. For medical conditions AMSP relies on the judgement of the relevant experts as a rule.

Our retrospective analysis was based on data obtained from the anonymized AMSP database with reference-day data from all participating institutions for each year. AMSP in its form and function as a pharmacovigilance programme received approval from the leading boards of each participating institution before its implementation. Ethical committee approval was not needed since the AMSP programme is not a clinical trial. A list of all currently participating institutions along with the statutes of the programme is available online (www.amsp.de). The evaluated data were obtained from a totally anonymized data bank, therefore informed consent was not necessary to obtain, since subjects were not traceable.

### Statistics

Incidence rates were evaluated as percent of patients (263,864 inpatients) exposed to a given compound, drug combination, drug class or subclass, respectively, and shown together with their 95% confidence intervals (CIs). With regard to the low actual HN incidence rates and the high number of individuals exposed, the CI was calculated according to the exact method and not one of the approximate methods (Vollset, 1993). For comparison of HN rates regarding gender and age and those between various drugs and combination therapies, Fisher’s exact tests were used. Significance was set at $p < 0.05$.

### Results

#### Sociodemographic and illness-related data

From 1993 to 2007 a total of 263,864 psychiatric inpatients were monitored within the AMSP programme in 80 hospitals. Severe HN (serum sodium <130 mmol/l) was attributed to 14/172 used psychotropic drugs during the observation period and documented in 93 cases, resulting in a relative frequency of 0.04%. In contrast to the total population, women prevailed in HN cases (77.4%, see overview and significance levels in Table 1) and showed a frequency of HN approximately three times higher than men. The mean ($\pm$ S.D.) age of HN patients ($60.7 \pm 15.9$ yr) was significantly ($p < 0.001$) higher than that of all monitored patients ($48.8 \pm 17.9$ yr); the frequency of HN in older patients (age $\geq 65$ yr, 0.076%) was three times higher than in patients aged <65 yr (0.025%). The highest rates of HN were observed in patients diagnosed with a substance-related disorder.

#### HN levels and clinical symptoms

The mean ($\pm$ S.D.) sodium level of the reported patients was $119.7 \pm 5.8$ mmol/l; median 121 mmol/l (range 104–129 mmol/l). Patients who showed no or only minor clinical symptoms ($n = 65$) had a mean sodium level of $121.3 \pm 5.0$ mmol/l; median 122 mmol/l (range 114–129 mmol/l). Patients with clinical symptoms (e.g. psychiatric and neurological symptoms, e.g. coma, disorientation, convulsions or agitation, $n = 28$) had a mean sodium level of $116.0 \pm 6.0$ mmol/l; median 117 mmol/l (range 104–125 mmol/l). From the group of patients with severe clinical symptoms nine patients suffered from adynamia or sedation and had a mean sodium level of $117.3 \pm 4.2$ mmol/l. Six patients had convulsions and their mean sodium level was $117.7 \pm 7.5$ mmol/l. Similarly, six patients were delirious showing a mean sodium level of $116.0 \pm 4.1$ mmol/l. Two patients went into coma, both with a serum sodium level of 104 mmol/l. In 84% ($n = 78$) of patients the ADR remitted. In 11% ($n = 10$) of all cases the ADR was in remission at the moment of evaluation. In 3% ($n = 3$) HN was still present at the
time of reporting. One patient suffered permanent brain damage due to a very severe HN leading to coma, and one patient’s clinical course remained unknown.

**Drugs involved in HN**

In 44 patients (47% of all HN cases) one single substance was held responsible for HN. In all other patients combinations of several drugs were imputed. HN rates for the different drug classes and subclasses, as well as absolute values for HN and monitored in-patients, are given in Table 2. From all drug classes the group of anticonvulsants showed a rate of 0.093% for HN, due exclusively to carbamazepine and oxcarbazepine prescribed, for instance, as mood stabilizers, seizure prophylaxis in alcohol withdrawal, or for comorbid epilepsy. No other member of the – chemically heterogeneous – group of anticonvulsants was involved in HN. In detail, patients who were treated with oxcarbazepine developed HN in 1.3% of cases followed by carbamazepine in 0.1% of cases. When oxcarbazepine was deemed responsible for HN alone (n = 16) the median time until onset of HN was 13.5 d (range 5–144 d). The most frequent diagnostic groups involved in HN during treatment with carbamazepine were schizophrenic/schizoaffective (29% of all cases) or organic (23%) disorders. Serotonin noradrenaline reuptake inhibitors (SNRIs) as a drug class, including duloxetine and venlafaxine, showed a rate of 0.081% for HN, when ‘all cases’ rates relative to all patients exposed, i.e. SNRI alone or in combination with other HN-inducing drugs (0.08%) were taken into account. Duloxetine, however, had a relatively low administration rate (n = 2823) resulting in a wide CI (95% CI 0.044–0.626). Selective serotonin reuptake inhibitor (SSRIs) caused HN in 0.06% of cases. Escitalopram (0.09%), citalopram (0.08%) and sertraline (0.05%) had HN rates above the average of all drugs attributed to HN. When a SSRI was deemed responsible for HN alone (n = 10), the median time until onset of HN was 11 d (range 6–421 d). By contrast, rates for tricyclic antidepressants (TCAs) and mirtazapine were only 0.005% and 0.004%, respectively. Not surprisingly, when venlafaxine or a SSRI were deemed responsible for HN, the most frequent diagnostic group involved was affective disorders (67% and 46%, respectively). Antipsychotics were less commonly involved in HN (Table 2). All classes of antipsychotics had HN rates below the average of other psychotropic drugs under surveillance. Only three antipsychotics [perazine (0.023%), haloperidol (0.007%), risperidone (0.004%)] were judged to be responsible for HN in rare cases. Consequently, co-prescription of antipsychotics – irrespective of probability rating – did not increase the risk of HN, e.g. the rate of HN for SSRI + antipsychotics was 0.01% (95% CI 0.003–0.04). Among the drug groups of benzodiazepines or nootropics (e.g. acetylcholinesterase inhibitors) no substance was held responsible for HN.

### Table 1. Age, sex and ICD-10 diagnosis of patients monitored during the period 1993–2007 suffering from hyponatraemia (HN), and of the total population under surveillance (263 864 patients monitored; 93 patients with HN)

<table>
<thead>
<tr>
<th>Diagnosis (ICD-10)</th>
<th>All patients monitored, n (% of all)</th>
<th>Patients with HN, n (% of 93 inpatients)</th>
<th>% of patients with HN</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic disorders (F0)</td>
<td>32 439 (12.3)</td>
<td>13 (14.0)</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>Addiction (F1)</td>
<td>9567 (03.6)</td>
<td>6 (06.5)</td>
<td>0.063</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia (F2)</td>
<td>100 910 (38.2)</td>
<td>21 (22.6)</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>Mood disorders (F3)</td>
<td>86 512 (32.8)</td>
<td>46 (49.5)</td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td>Others (F4 to F7)</td>
<td>34 436 (13.0)</td>
<td>7 (07.5)</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>&lt; 65</td>
<td>209 688 (79.5)</td>
<td>52 (54.7)</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>54 176 (20.5)</td>
<td>41 (45.3)</td>
<td>0.076</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>116 796 (44.3)</td>
<td>21 (22.6)</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>147 068 (55.7)</td>
<td>72 (77.4)</td>
<td>0.049</td>
<td></td>
</tr>
</tbody>
</table>

\[ \chi^2 = 18.28, \text{d.f.} = 4, p < 0.002 \]
Pharmacokinetic and dose-dependent aspects of involved drugs

As seen in Table 2 there was no relevant difference in the median dosages between the drugs which were seen as responsible for HN and those for all monitored patients. Only oxcarbazepine showed a higher dosage (median 1200 mg/d) compared to all monitored patients (median 900 mg/d). The mean dosage of all monitored patients (884 mg/d) using oxcarbazepine was outside the 95% CI around the mean dosage of the oxcarbazepine patients with HN (mean 1128 mg/d, 95% CI 953–1302).

Carbamazepine was deemed responsible for HN in 21 cases. In two cases carbamazepine and oxcarbazepine were used in cross-titration and both imputed for HN. Carbamazepine known as an inducer mainly of the cytochrome-P450 system and 3A4 enzyme was prescribed and imputed in one case each with escitalopram, citalopram and venlafaxine. In the other combination cases with carbamazepine internistic drugs (e.g. ACE inhibitors, diuretics, proton pump inhibitors) were involved. Carbamazepine has a strong inducing effect on the 3A4 enzyme but does not affect a major pathway of any of this drug, so that no relevant interaction has to be taken into account.

Combination treatment and HN

Table 3 compares rates of HN for drugs/drug groups given and imputed alone vs. combinations of several possibly HN-inducing drugs. For this evaluation, only the most commonly imputed drugs such as oxcarbazepine, carbamazepine, venlafaxine and the SSRIs as a group, and their combinations only if given to a minimum of 500 patients, were included, since rare events cannot be estimated with reliable accuracy from exposures of <500. They are also shown in Fig. 1 together with their CIs. Combination therapies of several possibly HN-inducing drugs showed a significantly higher rate (p < 0.001) of HN compared to patients exposed to only one HN-inducing psychotropic drug; e.g. the combinations of a SSRI together with diuretics and/or ACE inhibitors led to approximately 10-fold higher frequencies of HN (0.14–0.35% for combinations with SSRIs vs. 0.02% for SSRI alone), whereas the effect of combined treatment of SSRI and proton pump inhibitors was less pronounced.
Table 3. Frequency of hyponatraemia (HN) during treatment with combinations of HN-inducing drugs vs. treatment with only one HN-inducing psychotropic drug/group (only combinations with more than 500 prescriptions)  

<table>
<thead>
<tr>
<th>Drugs/combinations</th>
<th>Exposed patients</th>
<th>n with HN</th>
<th>% with HN</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI alone</td>
<td>41 204</td>
<td>10</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>SSRI + DIU</td>
<td>4856</td>
<td>7</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>SSRI + ACE-I</td>
<td>4510</td>
<td>12</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>SSRI + ACE-I + DIU</td>
<td>1348</td>
<td>5</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>SSRI + PPI</td>
<td>2398</td>
<td>1</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>SSRI + CARB</td>
<td>2738</td>
<td>2</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>CARB alone</td>
<td>17 883</td>
<td>12</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>OXC alone</td>
<td>1499</td>
<td>16</td>
<td>1.07</td>
<td></td>
</tr>
<tr>
<td>VEN alone</td>
<td>2331</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>VEN + DIU</td>
<td>1766</td>
<td>9</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>VEN + ACE-I</td>
<td>1694</td>
<td>6</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>VEN + ACE-I + DIU</td>
<td>607</td>
<td>5</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>VEN + PPI</td>
<td>789</td>
<td>2</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>VEN + CARB</td>
<td>662</td>
<td>1</td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>

ACE-I, Angiotensin-converting enzyme inhibitor; CARB, carbamazepine; DIU, diuretic; OXC, oxcarbazepine; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; VEN, venlafaxine.

*a ‘alone’ means SSRI without ACE-I, DIU, PPI and without CARB or OXC.
*b ‘alone’ means CARB without ACE-I, DIU, PPI and without a SSRI or OXC.
*c ‘alone’ means OXC without ACE-I, DIU, PPI and without a SSRI or CARB.
*d ‘alone’ means VEN without ACE-I, DIU, PPI and without a SSRI or CARB/OXC.

Fig. 1. Incidence rates (95% confidence intervals) of HN with imputed drugs (only combinations with more than 500 prescriptions are included). ACE-I, angiotensin-converting enzyme inhibitor; CARB, carbamazepine; DIU, diuretic; OXC, oxcarbazepine; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; VEN, venlafaxine.

Similarly, combined treatment of venlafaxine with diuretics and/or ACE inhibitors led to higher frequencies of HN (0.35–0.82%) for the combinations with venlafaxine vs. venlafaxine alone (0.00). In comparison to the frequency of all psychotropic drugs judged to be responsible for HN (0.04%), only
oxcarbazepine showed a higher frequency of HN when it alone was held responsible (1.07%); i.e. 27 times the rate of all patients. Combinations of oxcarbazepine with other HN-inducing drugs were rare and therefore not evaluated. In general, a significant higher frequency ($p < 0.001$) of HN was recorded in women compared to men (see Table 1). Regarding single drugs, when oxcarbazepine alone was deemed responsible for HN, women showed a significantly higher frequency ($p = 0.020$) of HN compared to men. By contrast, when a SSRI, venlafaxine or carbamazepine alone were held responsible for HN there was no significant difference between women and men (see Table 4). Concerning age, patients aged ≥65 years showed a significantly higher frequency ($p < 0.05$) of developing HN, especially when a SSRI was imputed alone or with an internistic drug, e.g. an ACE inhibitor or a diuretic (see Table 5). When a SSRI together with a proton pump inhibitor were imputed, there was no significant difference concerning age (Table 5). When venlafaxine and a diuretic were imputed together, there was a significantly higher frequency ($p = 0.006$).
of developing HN in the elderly. In general, the highest incidence of HN was found in female patients aged ≥65 yr compared to younger women and men.

Discussion

In the course of clinical trials ADRs are reported in a restricted and selected population, whereas unstructured reporting systems have the difficulty of incompleteness and liability. Drug surveillance programmes, by contrast, are seen as monitoring large populations of patients systematically. Up to now, research on the frequency of HN during psychopharmacological treatment consists predominantly of case reports; therefore the evaluation of the frequency of this serious ADR has been limited so far. This methodological lack of accuracy can be reduced with systematic pharmacovigilance programmes. Different drug safety surveillance studies have revealed correlations between ADRs and different psychotropic drugs (Jick et al. 2003; Madhusoodanan et al. 2002; Mannesse et al. 2010; Meulendijks et al. 2010). Compared to the frequencies of other ADRs during psychopharmacological treatment, such as severe cutaneous adverse reactions, which in one study, for example, showed a frequency of 0.10% (Lange-Asschenfeldt et al. 2009), HN showed a moderate frequency of 0.04% in the large AMSP patient sample. In contrast to our study, other epidemiological studies showed higher rates of HN (Adrogué & Madias, 2000). One interpretation of this issue is a probable underreporting of ADR in the AMSP pharmacovigilance system. In addition, HN with serum sodium levels of around 130 mmol/l shows only minor clinical signs. When blood levels are not monitored regularly in the hospital, patients experiencing asymptomatic HN will not be detected. Despite the fact that HN is a clinically relevant adverse event with psychopharmacological drugs in daily practice, the question arises as to whether the awareness of physicians for moderate HN, which can lead to severe complications, might be underdeveloped in the course of treatment. Finally, in the AMSP programme which focuses only on severe ADRs (Großmann et al. 2004), HN is assessed only if the serum sodium level is below 130 mmol/l, in contrast to other studies in which HN is reported when serum sodium levels are lower than 135 mmol/l (e.g. Adrogué & Madias, 2000; Bouman et al. 1998; Douglas, 2006; Kirby & Ames, 2001; Meulendijks et al. 2010). This probably led to a lower rate of HN in our patient sample because patients with serum sodium levels between 134 mmol/l and 131 mmol/l were not registered.

Quite a few changes in the mechanisms that adjust water and sodium balance take place as a normal part of the ageing process, such as decreased glomerular filtration rate and impaired water excretion. These physiological changes effect an increased possibility of developing hyponatraemia in the elderly (Douglas, 2006; Smith, 2010). These physiological aspects of age were reflected in our evaluation. Our data showed that older patients, especially women, had a substantially higher risk of developing HN. Even extensive literature research failed to bring any explanation for this issue, i.e. why women are at a higher risk to develop HN.

In agreement with the results of a study by Kirby & Ames (2001) risk factors for developing HN during treatment with SSRIs were also detected in our patient sample. The risk of developing HN with SSRIs seems to increase with age and the concomitant use of other medications known to be responsible for HN. Although HN has been reported for treatment with SSRI or venlafaxine, most studies had small sample sizes, were retrospective and limited by confounding variables, or were individual case reports (Kirby et al. 2002). Therefore, the results of our evaluation are strengthened by the fact that a large number of patients were monitored (263 864 inpatients). When administered as the only drug deemed responsible for HN, SSRIs showed an overall incidence for HN that was half of that for all drugs (0.02% vs. 0.04%). By comparison, our data show that combined treatment of a SSRI with internistic drugs, i.e. diuretics or ACE inhibitors, increases the risk for HN significantly. Similar data were reported by Rosner (2004). It can be concluded that there is an additive effect of different drugs known to be responsible for the development of HN. Among internistic drugs, especially thiazide diuretics are reported to enhance the risk of HN. Taking into account the high co-morbidity of depression and arterial hypertension in the elderly and the higher prescribing rates of SSRIs in this group of patients, it seems obvious that these patients have a higher risk of developing HN (Egger et al. 2006; Liu et al. 1996; Smith, 2010).

Carbamazepine is an inducer of the cytochrome-P450 system, mainly of the 3A4 enzyme. Therefore it might be argued that co-medication with carbamazepine can reduce HN risk due to lowering of plasma levels of other HN-inducing drugs. However, concerning SSRIs and dual antidepressants, the main other drug group involved in HN in our data, carbamazepine, leads to no changes of major pathways. Thus, additive pharmacodynamic effects are more relevant in combinations with carbamazepine.
In addition, there were no significant differences in median dosages of SSRIs and dual antidepressants in the group of patients with HN compared to all monitored patients. When a SSRI was imputed alone as the cause of HN in our patient sample, the median time until onset of HN during treatment with SSRIs was 11 d (range 6–421 d). In other clinical studies, most cases of HN were detected within a range of 1–3 wk after the start of treatment with an antidepressant (Kirchner et al. 1998). In the study by Kirby & Ames (2001) about 75% of the patients who were likely to develop HN developed it within the first 30 d of therapy with a SSRI (Kirby & Ames, 2001).

In contrast to the results of Meulendijks and colleagues our data did not detect antipsychotics as agents that are frequently involved in the appearance of HN (Meulendijks et al. 2010). Even the antipsychotics which were held responsible for HN (see Table 2), had a lower incidence than all other psychopharmacological drugs imputed for HN, and co-prescription of antipsychotics did not increase the HN risk. Factors such as low body weight are also suggested in the literature as risk factors for developing HN (Kirby & Ames, 2001). Uncompleted evaluation of the body-weight value in our data did not allow an assessment of weight as a relevant factor.

In summary, it can be stated that patients who suffer from a substance-related disorder are at a higher risk of developing HN under treatment with psychopharmacological drugs. Similarly, patients who received internistic drugs such as diuretics or ACE inhibitors in addition to their treatment with SSRI or venlafaxine were at the highest risk of developing HN. By contrast, low rates of HN were found in patients who were treated with tricyclic antidepressants or antipsychotics, regardless of their classification as conventional or atypical. No substances from the drug group of benzodiazepines or nootropics were deemed responsible for HN. Focusing on the higher incidence of HN and its potential dangers, older female patients, in particular, should be informed about clinical symptoms of HN when being treated with SSRIs or venlafaxine in addition to other HN-inducing drugs. Clinicians must be aware of this possible risk situation and, upon occurrence of such combinations in the elderly, should carefully monitor the serum sodium level within this population. They should also balance the benefits of such combinations with the potential risk of possible side-effects (Chali, 2008). Signs of cognitive impairment, falls or dizziness should lead to immediate drug discontinuation. To our knowledge, no other study has reviewed the effects of HN in such a large psychiatric patient sample thus highlighting the possible adverse effects of common augmentation and combination strategies and the risk of developing HN.

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