

Review Articles

Antidepressants and the Risk of Hyponatremia: A Class-by-Class Review of Literature

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Background: Antidepressant-induced hyponatremia can cause significant morbidity and mortality. It is mostly associated with the use of selective serotonin reuptake inhibitors (SSRIs), but its frequency and class specificity are uncertain. **Objectives:** To determine the relationship between hyponatremia and antidepressants and to define the incidence and odds ratios for antidepressant classes. **Methods:** A review of the literature prior to March 2013 was performed using Web of Science and PubMed by employing combinations of search strings “antidepressants” and antidepressant class and generic drug names with “hyponatremia,” “SIADH,” or “inappropriate ADH.”

Results: Overall, 21 effect studies and more than 100 case reports were considered, most concerning SSRIs. Because of variations in study designs, populations, and cutoff values, incidence rates diverged between 0.06% and 40% for SSRIs and 0.08% and 70% for venlafaxine. Although based on less solid evidence,

incidence figures for mirtazapine and tricyclic antidepressants were lower. Regarding classes, odds ratios for SSRIs (1.5–21.6) were consistently higher than for tricyclic antidepressants (TCAs) (1.1–4.9). The risks associated with monoamine oxidase inhibitors, reboxetine, and bupropion could not be established owing to insufficient information. Patient risk factors included older age (odds ratios = 6.3) and concomitant use of (thiazide) diuretics (odds ratios = 11.2–13.5). **Conclusion:** Hyponatremia is a potentially dangerous side effect of antidepressants and is not exclusive to SSRIs. Current evidence suggests a relatively higher risk of hyponatremia with SSRIs and venlafaxine, especially when combined with patient risk factors, warranting clinicians to be aware of this complication. The risks associated with mirtazapine are moderate, supporting this antidepressant as an alternative treatment for patients with (an increased risk of) hyponatremia.

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INTRODUCTION

Hyponatremia, defined as a serum sodium level <135 mmol/L, is the most frequently encountered electrolyte disorder in clinical practice. Its clinical spectrum includes subclinical or aspecific general symptoms such as nausea, fatigue, muscle cramps, and headache in addition to serious neuropsychiatric symptoms of cerebral edema, causing confusion, restlessness, gait abnormality, lethargy, seizures, and coma. Considerable variability exists in the

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relationship between serum sodium concentration and clinical symptoms, which is affected by both the magnitude and the rate of hyponatremia that develops. Although asymptomatic hyponatremia is often self-limiting, symptomatic disease comes with substantial morbidity and mortality. Especially in the event of a sudden and large decrease in serum sodium levels, cerebral osmotic adaptation may fail to compensate sufficiently, resulting in metabolic encephalopathy and a high risk of severe complications and even death.^{1,2} In addition, by increasing the duration of hospital stays and likelihood of treatment in an intensive care unit, both the economic and clinical burden are considerable.

With their excellent diluting capacity, excreting up to 12 L of water per day, the kidneys keep serum osmolarity within a tightly controlled range by carefully regulating body fluid and sodium levels, thus normally preventing hyponatremia. Fluid balance is controlled by the hypothalamic production of the antidiuretic hormone (ADH), promoting thirst and water retention by binding to the kidneys' V2 receptors, upregulating reabsorption of water and sodium ions in the distal tubule. Except in severe primary polydipsia or kidney failure, hyponatremia always involves an increased ADH secretion, either as an adequate response to the decreased effective circulatory volume (liver cirrhosis and heart failure) or due to a (drug-induced) syndrome of inappropriate ADH secretion (SIADH), characterized by the sustained release of ADH from the posterior pituitary or an ectopic source.²

In SIADH, a patient's ability to excrete diluted urine is reduced and ingested fluids are retained, thereby causing extracellular fluid to increase and become hypo-osmolar. Key signs are euvoletic hyponatremia, serum hypo-osmolarity ($S_{\text{osm}} < 275 \text{ mOsm}$) and a less than maximally diluted urine ($U_{\text{osm}} > 300 \text{ mOsm}$, $U_{\text{Na}} > 40 \text{ mEq/L}$). As depicted in [Figure 1](#), a differential diagnosis requires determination of both serum and urinary osmolarity and urinary sodium levels. Because ADH levels that fall within the normal range do not exclude a diagnosis of SIADH, analysis of serum ADH is less useful in clinical settings. Causes of this syndrome include central nervous system pathology (including craniocerebral trauma and psychosis), malignancy (especially small cell lung cancer), lung diseases, major surgery, and pharmacologic substances.

Frequently, hyponatremia is caused by use of medications. As it can occur with many different drug classes, the possibility of a drug-related adverse event should always be considered. A relationship between antidepressants and changes in serum sodium concentrations was first described in 1974 with amitriptyline and has received increased attention since the 1990s with the arrival of selective serotonin reuptake inhibitors (SSRIs), a new class of antidepressants that exert their effect by selectively inhibiting serotonergic reuptake.^{3,4} Although antidepressant-induced hyponatremia has been described in previous reviews, none has systematically reviewed the evidence for individual classes of antidepressants. In addition, several larger-scale and highly relevant effect studies have been published in recent years, meriting an update on the topic.

Because the bulk of scientific publications focus on SSRI-induced hyponatremia, we wondered whether this complication is indeed class specific and at which frequency the different classes of antidepressants provoke the adverse event. A better awareness and knowledge of the risks of hyponatremia associated with specific (classes of) antidepressants could guide clinicians in their choice of drug, promoting safer treatments for at-risk patients, such as those with a history of SIADH or those presenting with the first signs of hyponatremia associated with the current antidepressant.

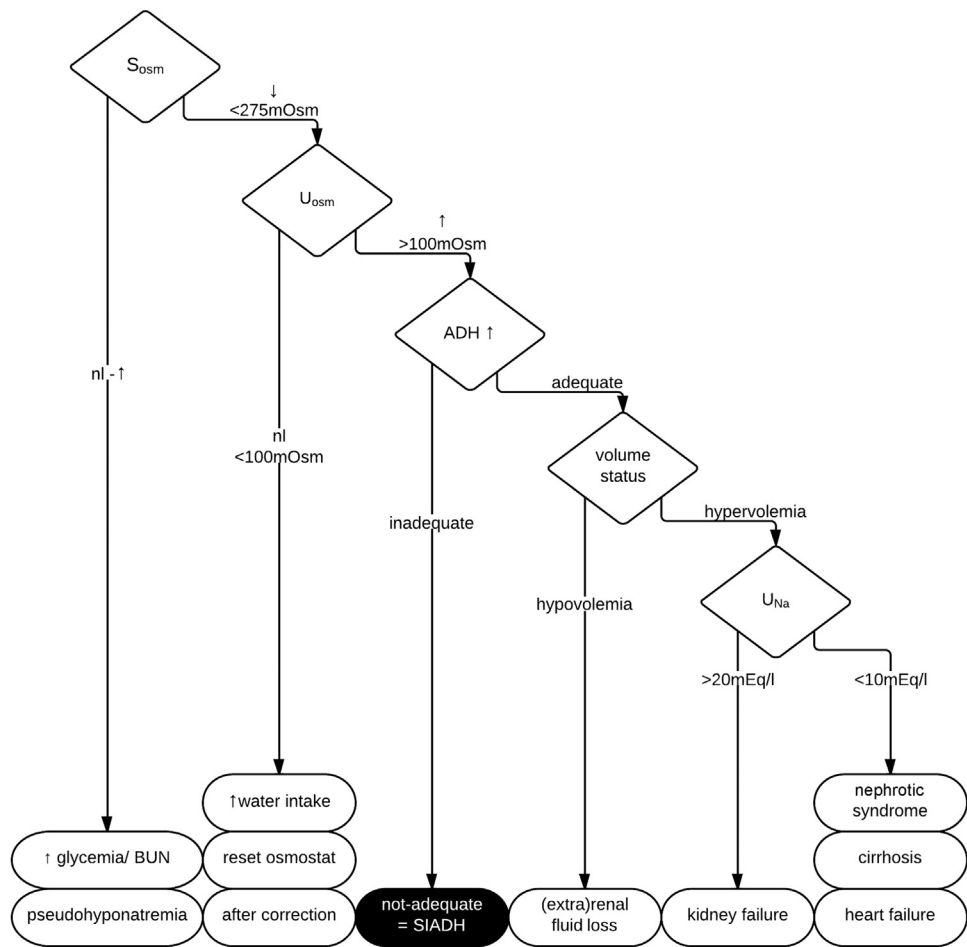
METHODS

We performed a review of the scientific literature for evidence of hyponatremia caused by different antidepressant classes, as described in cohort and case-control studies and case reports. Outcome measures were incidence rates and the odds or hazard ratios (OR/HR) of hyponatremia in both inpatients and outpatients treated with antidepressant agents.

Search Strategy

The literature published before March 2013 was searched without restrictions of language in PubMed (MESH terms “Hyponatr(a)emia,” “Inappropriate ADH Syndrome,” and “Antidepressive agents”) and in Web of Knowledge, using combinations of search strings “antidepressant,” “SSRI,” “reuptake inhibitor,”

FIGURE 1. Hyponatremia Diagnostic Flow Chart. ADH = Antidiuretic Hormone; BUN = Blood Urea Nitrogen; S_{osm} = Serum Osmolarity; U_{osm} = Urinary Osmolarity; UNa = Urinary Sodium level; SIADH = Syndrome of Inappropriate Antidiuretic Hormone Secretion.



“SNRI,” “TCA,” “tricyclic,” “MAO,” “mono-amine oxidase” with “hyponatr(a)emia,” “SIADH,” or “inappropriate ADH.”

An additional manual search was conducted based on the reference lists of all relevant articles. Efforts were made to include all available studies by contacting the corresponding authors for a full-text copy of their study.

Data Selection

After duplicate removal, the relevance of the resultant studies was verified by assessment of their titles and abstracts. Papers for which no English abstract was available were dismissed. The remaining studies were screened and included in the review when they concerned original articles and included descriptions

of study design and population(s) and case definitions of hyponatremia.

Because of our broad inclusion criteria, we anticipated considerable heterogeneity, which is why we assessed and compared effect studies for study design, sample size, study population (in/outpatients, age, and source), cutoff values, definition of hyponatremia, adjustment for confounders, and outcomes. Case reports of antidepressant-induced hyponatremia were included in the database and sorted by antidepressant class to assess the number of case reports per drug. We individually reviewed the case reports of those antidepressant drugs for which fewer than 5 effect studies were identified. Data from effect studies were abstracted into an evidence table (Tables 1 and 2), whereas evidence from case reports were not included in this table but discussed in the text. Table 3 offers a case report count.

TABLE 1. Observational Cohort Studies on Incidence of Hyponatremia With SSRI, SNRI, and TCA

References	Year	Sample size (cases/study sample)	Cutoff S _{Na} ⁺ (mmol/l)	Mean age	Study design			Patients		Incidence (%)						
					Study type	Control group (no AD)	S _{Na} ⁺ active monitoring			SSRI			SNRI		TCA	
										F	P	S	V	C	A	
Letmaier et al. ⁷	2011	(14y) 93/ 263.864	130	49	MDSP	No	ADR	in	Ψ	0.06				0.08	0.005	0.01
Coupland et al. ^{8,9}	2011	1.114/60.405	ICD-10	75 ^G	P	Yes	No	out	GP	0.44*	0.49*	0.30*	0.29*	0.44*	0.30*	0.33*
Wilkinson et al. ⁴⁹	1999	14/845	130	80 ^G	R	No	No	in/out	Ger	0.47*	0.63*	0.35*				
Pillans et al. ⁵	1994	(4y) 7/?	130	> 68 ^G	MDSP	No	No	in/out	?	0.85	0.85					
Huyse et al. ⁵²	1994	1/37	ICD-10	60	P	No	Yes	in	C-L	2.6	2.6					
Oslin et al. ⁵³	2003	2/52	?	83	P	No	ADR	in	Ger	4			4	4		
Jung et al. ¹⁴	2011	11/240	135	51	R	No	No	in	Ψ	8.6				4.2		
Fabian et al. ⁵⁰	2004	9/75	135	75 ^G	P	No	Yes	out	Ψ	12		12				
Spigset et al. ²³	1996	18/197	135	44	P	Yes	Yes	in	TDM						16.7	16.7
Wee et al. ⁵⁴	2004	23/103	135	80 ^G	R	No	No	in	Ger	22						
Roxanas et al. ¹³	2007	10/58	130	75 ^G	P	No	Yes	in/out	Ψ				17			
Strachan et al. ⁵⁵	1998	13/55	135	76 ^G	R	No	No	in	Ψ	24	28	22				
Bouman et al. ⁵¹	1998	8/32	135	77	R	No	No	in	Ψ	25						
Kirby et al. ¹¹	2002	29/199	135	74 ^G	R	Yes	No	in	Ψ	32		32	29	71		
Fabian et al. ⁵⁶	2003	6/15	135	75 ^G	P	No	Yes	out	Ψ	40		40				

Age: ^G = geriatric only.

Study design: R = retrospective; P = prospective; MDSP = observational multidrug surveillance program/ADR = adverse drug reaction monitoring.

Patients: in = inpatient; out = outpatient; ad = hospital admission for hyponatremia/Ψ = psychiatric care facility; C = community; C-L = consultation-liaison psychiatry; GP = general practices; Ger = rehabilitation or geriatric care facility; TDM = therapeutic drug monitoring sample.

Antidepressants (AD): SSRI: F = fluoxetine; P = paroxetine; S = sertraline/SNRI: V = venlafaxine/TCA: A = amitriptyline; C = clomipramine.

Outcome: HR = hazard ratio; OR = odds ratio/nonadj = nonadjusted for confounders; adj = adjusted for confounders.

* Absolute risk over 1 year of treatment (%). The non-italic % relate to the overall incidence for that antidepressant class (SSRI, SNRI, TCA), whereas the italic figures are incidences for individual drugs in that class (eg F, P, S in SSRIs).

TABLE 2. Observational Cohort and Case-Control Studies on Relative Risk and Odds Ratio of Hyponatremia With SSRI and TCA

References	Year	Sample size (cases/study sample)	Cutoff S _{Na} ⁺ (mmol/l)	Mean age	Study design		Patients		Outcome					
					Study Type	S _{Na} ⁺ monitoring			Measure	Drug	Vs no AD		Vs other AD	
							nonadj	adj			nonadj	adj		
Coupland et al. ^{8,9}	2011	1.114/60.405	ICD-10	75 ^G	P Cohort	No	out	GP	HR	SSRI	1.62	1.52	vs. TCA	1.44
Kirby et al. ¹¹	2002	29/199	135	74 ^G	R Cohort	No	in	Ψ	OR	SSRI		2.7		
Siegler et al. ¹⁰	1995	64/256	130	62	R Case-Control	No	in	Ψ	OR	SSRI (F)	6.1	21.4		
Movig et al. ⁴⁵	2002	29/107	130	68	R Case-Control	No	ad	C	OR	SSRI			vs. other AD	3.3 3.9
Kirby et al. ¹¹	2002	29/199	135	74 ^G	R Cohort	No	in	Ψ	OR	SSRI+V	5.6	3.5	vs. nonsero-tonergic AD	3.96 1.87
Movig et al. ⁴⁶	2001	10/203	ICD-10	71	R Case-Control	No	ad	C	OR	SSRI+V+C				
Coupland et al. ^{8,9}	2011	1.114/60.405	ICD-10	75 ^G	P Cohort	No	out	GP	HR	TCA	0.99	1.05		
Siegler et al. ¹⁰	1995	64/256	130	62	R Case-Control	No	in	Ψ	OR	TCA	1.9	4.9		

Age: ^G = geriatric only
Study Design: R = retrospective; P = prospective; MDSP = observational multidrug surveillance program/ADR = adverse drug reaction monitoring.
Patients: in = inpatient; out = outpatient; ad = hospital admission for hyponatremia/Ψ = psychiatric care facility; C = community; C-L = consultation-liaison psychiatry; GP = general practices; Ger = rehabilitation or geriatric care facility; TDM = therapeutic drug monitoring sample.
Antidepressants (AD): SSRI: F = fluoxetine; P = paroxetine; S = sertraline/SNRI: V = venlafaxine/TCA: A = amitriptyline; C = clomipramine.
Outcome: HR = hazard ratio; OR = odds ratio/nonadj = nonadjusted for confounders; adj = adjusted for confounders.

TABLE 3. Number of Studies and Case Reports (CR), Incidences, and Odds Ratios (OR) per Antidepressant Drug (class)

	SSRI	Venlafaxine	TCA	Mirtazapine	Duloxetine	Bupropion	MAOI	Reboxetine
Number of studies	15	6	3	2	1	0	0	0
and case reports	> 90 CR	9 CR	21 CR	7 CR	12 CR	4 CR	3 CR	2 CR
Incidence	0.06–40%	0.08–71%	0.005%–16.7%	0%–0.004%	0.11%	–	–	–
OR	1.5–21.6	–	1.0–4.9	–	–	–	–	–
Risk group	{Higher risk}		{Moderate risk}		{Insufficient evidence}			

Note: Some case reports involve more than 1 case; all cases are counted separately in this table.

CR = case report; OR = odds ratio.

RESULTS

The procedure and results of the literature search are illustrated in [Figure 2](#).

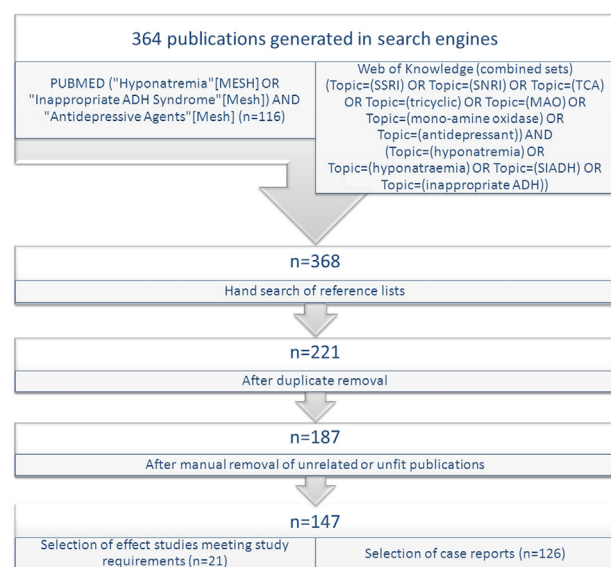
No randomized controlled trials studying hyponatremia related to antidepressant use were found. Among the 15 observational cohort studies of hyponatremia incidence we included ([Table 1](#)), 7 were prospective studies (of which 5 involved systematic monitoring of serum sodium levels, referred to as “active monitoring” in this article), 6 were retrospective case-note studies, and 2 were reports from drug-surveillance programs, relying either on clinicians' spontaneous reports⁵ or on a system of enhanced monitoring of drug-related adverse events (e.g., Arzneimittelsicherheit in der Psychiatrie; AMSP).^{6,7} The

hazard or odds ratio (HR/OR) associated with antidepressant medication state was calculated for the 2 cohort studies that had included an unmedicated control group, as well as in 3 case-control studies, comparing hyponatremia cases with nonhyponatremia controls for their relative exposure to antidepressant medication ([Table 2](#)). The 2 most recently published large-scale studies evaluated hyponatremia covering different antidepressant classes as part of a larger study of antidepressant safety in either a large primary care database (Qcare, Coupland *et al.*^{8,9}) or in a drug-surveillance program of psychiatric inpatients (AMSP; Degner *et al.*⁶; Letmaier *et al.*⁷).

Selective Serotonin Reuptake Inhibitor

A total of 13 observational cohort studies, listed in [Table 1](#), examined the occurrence of hyponatremia in patients using SSRIs. Because of variations in study designs, populations (inpatient or outpatient or both; specific psychiatric or geriatric populations) and sodium threshold values ($S_{Na^+} < 130$ vs. < 135 mmol/L), incidence rates varied greatly, with the recent large-scale studies and studies without active monitoring of serum sodium levels resulting in more modest rates. Studies with a cutoff $S_{Na^+} < 135$ mmol/L resulted in incidence figures between 9% and 40%, whereas in studies using a case definition of $S_{Na^+} < 130$ mmol/L or ICD-10 diagnosis, incidences between 0.06% and 2.6% were reported. The OR or HR associated with SSRI medication state was determined in 3 studies, listed in [Table 2](#). The lowest risk was found in the larger community-based study (adjusted HR = 1.5; Coupland *et al.*^{8,9}), whereas a very elevated risk was reported for fluoxetine use in inpatients treated in a psychiatric tertiary care facility (adjusted OR = 21.6; Siegler *et al.*¹⁰).

Several studies exclusively looked at the occurrence of SSRI-related hyponatremia in geriatric

FIGURE 2. Literature Search Strategy in Pubmed and Web of Knowledge. (Color Version of Figure is Available Online.)

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populations. Elderly patients were found to be at higher risk ($OR = 1.5\text{--}6.3$), especially with concomitant use of (thiazide) diuretics, which synergistically increased the risk for hyponatremia combined with SSRIs ($OR = 11.2$ for SSRIs with thiazides vs. 2.5 for thiazides alone, $p = 0.002$).¹¹

No conclusive evidence was found for differences between individual SSRI drugs in their potential for eliciting SIADH.¹² In most studies, sample sizes were simply too small to differentiate between the risks associated with distinct SSRIs. Although their findings need to be replicated in other large-scale samples, it is interesting to note that the large population-based cohort study by Coupland et al.^{8,9} found 3 SSRIs (i.e., fluoxetine, citalopram, and escitalopram) to be associated with significantly increased risks of hyponatremia, whereas paroxetine and sertraline were not. The same distribution was found in the AMSP study, with paroxetine and sertraline yielding lower incidences (0.033% and 0.053% , respectively) of the SSRIs studied, whereas slightly higher incidences were found for (es)citalopram (0.078% – 0.085%).^{6,7}

Serotonin-Norepinephrine Reuptake Inhibitor

Of the 6 studies investigating the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (Table 1), the larger-scale studies without active monitoring reported a hyponatremia incidence between 0.08% and 4% using a cutoff of 130 mmol/L . In the only prospective study with active monitoring, Roxanas et al.¹³ reported hyponatremia developing in 10 of 58 patients (17.2%) older than 65 years in whom venlafaxine was initiated ($<130\text{ mmol/L}$) in the first few days of treatment. Studies using a threshold of 135 mmol/L yielded incidence figures of 4% and even as high as 71% in elderly psychiatric inpatients.^{11,14} When comparing SSRIs to venlafaxine, 4 of 5 studies examining both classes found hyponatremia incidence with venlafaxine to be equal to or higher than recorded for the various SSRIs. Hyponatremia incidence for the SNRI duloxetine is less well defined. Duloxetine was formally investigated in just one prospective observational surveillance study (AMSP).^{6,7} The authors cautiously reported an incidence of 11% and a ranking above venlafaxine and SSRIs. However, their duloxetine group was quite small owing to the low frequency of duloxetine prescriptions in their study population (1% of monitored patients). Importantly, there are at least 12 case reports mentioning the occurrence of hyponatremia with duloxetine.^{15–22}

Tricyclic Antidepressants

Although the first reports of antidepressant-induced hyponatremia concerned the tricyclic antidepressant class, few studies compare the occurrence of the adverse event in this older class to the newer agents (Table 1). Incidence rates of 0.01% – 0.33% were found in the 2011 larger-scale studies,^{7–9} contrasting the 16.7% incidence for hyponatremia with clomipramine in an older study of therapeutic drug monitoring samples,²³ which had used active monitoring and a higher hyponatremia threshold. Overall, the risk of developing hyponatremia on TCAs is consistently found to be lower than for SSRIs (Table 3) and this was recently confirmed in a head-to-head comparison of the 2 classes in the large population-based Coupland cohort study, reporting significant differences in hyponatremia HR between the classes ($p = 0.002$) and an adjusted HR of 1.44 with the use of SSRIs vs. TCAs.^{8,9}

Mirtazapine

The tetracyclic antidepressant mirtazapine mostly acts as an antagonist of postsynaptic serotonin receptors. The AMSP drug-surveillance program in psychiatric inpatients could not detect a single case of hyponatremia due to mirtazapine alone and found only 1 case with mirtazapine and another medication in a total of 28,172 patients prescribed this drug (11% of the study sample). Unfortunately, in the Coupland study, mirtazapine was grouped in the “other antidepressants” category, preventing evidence from being derived for mirtazapine. Jung et al.¹⁴ also studied mirtazapine in addition to SSRI and venlafaxine in their retrospective case-note study; hyponatremia did not develop in any of the 76 patients on mirtazapine ($<135\text{ mmol/L}$), as compared with 8% on SSRIs and 4% on venlafaxine. A total of 7 case reports of mirtazapine-associated hyponatremia were published, all in patients older than 60 years.^{24–29} It is noteworthy that 2 case reports describe the successful use of mirtazapine in patients in whom hyponatremia developed previously while on an SSRI.^{30,31}

Noradrenergic Reuptake Inhibitor

The selective noradrenergic reuptake inhibitor (NRI) reboxetine was associated with the development of hyponatremia in 4 case reports, all of which

described elderly patients. In one of these cases, the pharmacologic etiology of the complication was confirmed by rechallenge.^{32–34} Reboxetine was not evaluated separately in any of the observational studies.

Bupropion

A total of 4 case reports described hyponatremia associated with the selective noradrenergic and dopaminergic reuptake inhibitor, bupropion, one of which was confirmed by rechallenge.^{35–38} Conversely, 2 case reports illustrated subsequent tolerability of bupropion in patients in whom hyponatremia developed while on sertraline and paroxetine, respectively.^{39,40}

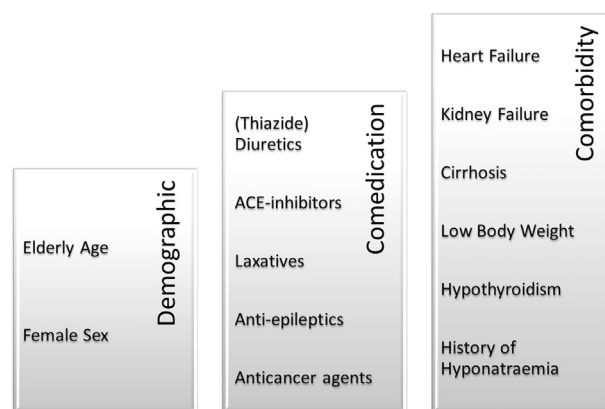
Monoamine Oxidase Inhibitors (MAOIs)

We found no cohort studies investigating the occurrence of hyponatremia with MAOIs. One case-control study evaluating risk factors for hyponatremia in a psychiatric inpatient population recorded a nonsignificant OR of 1.5 for hyponatremia with MAOIs (3/94 cases with $S_{Na^+} < 130$ mmol/L vs. 4/192 controls with $S_{Na^+} > 135$ mmol.¹⁰ The selective MAO-A inhibitor moclobemide was deemed causative of hyponatremia in 1 case report, whereas another case report mentioned its successful use in a patient with a history of hyponatremia due to duloxetine.^{17,41} There is little evidence, even in the shape of case reports, for most of the older, nonselective and irreversible MAOIs. We found 1 negative case report each for isocarboxazide and tranlycypromine. Search strings of “phenelzine”/“nardelzine” and “SIADH”/“hyponatremia” yielded no results.^{42,43}

Patient Risk Factors

At-risk groups for hyponatremia were fairly comparable throughout the studies reviewed and are summarized in Figure 3. Older age appears to be the major risk factor for SSRIs; incidences and ORs were found to be markedly increased in elderly patients, especially with concomitant use of other hyponatremia-eliciting drugs such as (thiazide) diuretics, ACE inhibitors, or laxatives¹¹ (refer to Liamis *et al.*² for a full list of hyponatremia-eliciting drugs). Apparently, this risk of hyponatremia with another medication is not limited to the elderly, as the AMSP study found the combinations of SSRI or venlafaxine with ACE inhibitors or diuretics to result in about 10-fold higher incidences ($p < 0.001$) compared with

FIGURE 3. Risk Factors for Hyponatremia, Related to Demographic Variables, Comedication, or Comorbidity



SSRI/SNRI alone.⁷ Gender is also known to be a risk factor, with higher incidence rates for women predominating the incidence figures for hyponatremia, independent of its cause. A low body weight and severe physical illness, especially when associated with altered body fluid balance (cirrhosis, heart, or kidney failure), are also associated with an increased risk.^{44,45} Obviously, a history of hyponatremia or SIADH warrants extra caution, although the condition does not necessarily recur.⁴⁴

DISCUSSION

Frequency and Class Specificity of Antidepressant-Induced Hyponatremia

The available literature suggests that the risk of hyponatremia is highest with SSRIs and venlafaxine but not confined to these antidepressant agents. The adverse event can also occur with tricyclic agents and other antidepressants, albeit less frequently. As the available evidence mostly concerns SSRIs and because the comparison of the clinical studies we identified was complicated by differences in study designs, populations, and sodium cutoff values, any conclusions about the frequency of hyponatremia with different antidepressant classes or agents need to be drawn carefully.

Rather than pure class specificity, some authors argue that the proneness to hyponatremia is defined by the antidepressant's potency to inhibit the reuptake of serotonin, in accordance with the hypothesis of a serotonin-induced increase in ADH, mediated by

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hypothalamic serotonin receptors.⁶ To substantiate this claim, a study calculated the ORs for the “serotonergic” antidepressants (SSRIs, venlafaxine, and clomipramine combined) and found these to be significantly higher than for other antidepressants (OR = 3.96 vs. 1.78, respectively).⁴⁶

Alternatively, the limited evidence of reboxetine and bupropion as causative agents of hyponatremia suggests that the mechanisms by which antidepressants can provoke hyponatremia may not be purely related to their potential to inhibit serotonergic reuptake. Animal studies have shown that both serotonin and noradrenaline can increase ADH secretion by stimulating serotonergic and α -adrenergic receptors.^{47,48} The high incidence of hyponatremia with venlafaxine may then be explained by its dual action, increasing synaptic levels of both serotonin and noradrenaline.⁴⁴

Methodologic Variance

The heterogeneity of the reported results suggests that study methodologies greatly affected outcomes, most particularly, the choice (or lack) of control groups or the presence/absence of active monitoring for hyponatremia. Systematic laboratory testing in the retrospective studies varied, and the timing of and clinical indication for sodium level checks often remained unclear, introducing an ascertainment bias: hyponatremia incidence may have been lower in studies not monitoring levels (regularly). Then again, in retrospective studies and drug-surveillance programs relying on voluntary reporting, many asymptomatic cases of hyponatremia or cases with vague, nonspecific symptoms or symptoms mimicking a worsening of the depression may have gone unrecognized, thereby underestimating the incidence of the event.

Additionally, inconsistencies in hyponatremia case definitions compromised comparison. Although the generally accepted definition is that of a serum sodium level lower than the arbitrarily defined threshold of 135 mmol/L, some studies preferred a 130 mmol/L threshold, which may in fact be more relevant to the clinical practice, considering that symptoms seldom occur at higher values. However, rather than the cutoff value, the rapidity of the decrease in serum sodium levels is a more important predictor of symptom development, as are certain

patient factors—most notably age, given that symptoms are found to be more likely to develop in elderly patients.

Studies also differed in the way they dealt with patient-related confounding factors possibly causing or contributing to hyponatremia; some studies chose to exclude such cases,⁴⁹ whereas others included them but performed multivariate regressions for statistical correction,¹¹ for instance, finding that the increased risk in elderly patients might (largely) be attributable to polypharmacy and comorbid physical illness common in this population.¹⁰ It is noteworthy that the background prevalence of hyponatremia in the general elderly population is estimated at 5%–10% and 3.4%–11% in psychiatric inpatients.⁴⁴ To avoid selection bias, careful description of the source population and the controls (age, psychiatric diagnosis, comorbidity, and concomitant medication) is indispensable. Therefore, future studies investigating the incidence and odds ratios of drug-induced hyponatremia need to detail and consider all relevant patient characteristics.

Clinical Relevance

In view of our review of the current literature, we have delineated 3 groups of antidepressants, corresponding to different degrees of risk for hyponatremia (Table 3). SSRIs are usually considered safer than older antidepressant agents and therefore are often recommended as first-choice drugs in the treatment of depression and anxiety disorders. However, the documented relatively higher hyponatremia risk profiles of SSRIs and venlafaxine imply that this recommendation might not necessarily be appropriate for specific patients. As the potential for specific adverse events varies for the different antidepressant classes, class- or drug-specific side-effect profiles should be considered together with patient-specific risk factors when deciding on the optimal treatment for individual patients.

Based on the few but relatively large-scale studies published to date, mirtazapine and tricyclic antidepressants have a more attenuated risk profile for hyponatremia.

We were unable to draw conclusions as to the risks associated with duloxetine, reboxetine, bupropion, and MAOIs owing to insufficient information. Prospective controlled studies are needed that assess the risk of hyponatremia for both SSRIs and other

antidepressant classes more systematically in well-defined, larger-scale populations.

As to the clinical recommendations as reflected in the literature, clinicians' awareness of the higher risk and signs of hyponatremia associated with certain antidepressants should be raised, as particularly in psychiatric populations, clinical symptoms of hyponatremia can be misinterpreted as a worsening of the primary illness. Sodium levels should be checked in all elderly patients exhibiting abrupt or unexplained changes in mental status (e.g., lethargy or confusion) at any time during treatment with an SSRI or venlafaxine.⁵⁰ Some authors recommend a routine serum sodium analysis within the first 2 weeks after initiating such treatment in patients with additional risk factors for hyponatremia, such as older age, female sex, diuretic use, low BMI, and a baseline plasma sodium level < 138 mmol/L.^{6,50,51} A thorough cost-benefit analysis seems warranted to validate the latter recommendation.

Follow-up and treatment of hyponatremia may not necessarily require discontinuation of the antidepressant, contingent upon a strict serum sodium monitoring regimen, where rapidly declining sodium levels or symptomatic hyponatremia usually do necessitate discontinuation or a switch to another class or

agent. Because of their more attenuated risk profiles, mirtazapine or TCAs may be used as alternative antidepressive treatment for patients with (an increased risk of) hyponatremia.^{30,31} Alternatively, in selected cases, good results may be achieved by carefully controlled fluid restriction until serum sodium levels have normalized while continuing the antidepressant.^{13,44}

CONCLUSION

Hyponatremia is a potentially dangerous side effect of antidepressants that is not exclusive to SSRIs. The current evidence suggests a higher risk of hyponatremia with SSRIs and venlafaxine, especially combined with specific patient risk factors (e.g., older age and diuretic use), underscoring the need for increased awareness of and attention to signs of the complication in such at-risk patients. The reported risks for mirtazapine and TCAs are lower, supporting these agents as an alternative treatment for patients with (an increased risk of) hyponatremia.

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