



Treatment with antidepressant drugs and hyponatremia: a network meta-analysis

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Abstract

Objective To evaluate the risk of hyponatremia during therapy with antidepressant drugs, in particular by investigating whether there is a different risk profile depending on the class or single active principles.

Methods A meta-analysis was performed including all studies in which the risk of hyponatremia in subjects with or without antidepressant treatment was assessed. An extensive Medline, Embase and Cochrane search was performed, to retrieve all studies published up to February 5th 2024, using the following words: hyponatremia and antidepressant.

Results Of 409 retrieved articles, 10 studies satisfied the inclusion criteria encompassing a total of 1,026,870 patients with 89,403 hyponatremic subjects. Treatments with selective serotonin reuptake inhibitors (OR=3.31 [2.41;4.56], $p<0.01$), serotonin-noradrenaline reuptake inhibitors (OR=5.79 [1.27;26.49], $p=0.02$) and tricyclic antidepressants (OR=3.01 [1.27;7.14], $p=0.01$) were found to be significantly associated with an increased risk of hyponatremia, whereas treatment with noradrenaline and specific serotonergic antidepressants was not. A network meta-analysis indicated that treatments with venlafaxine (OR=5.99 [2.39;14.99], $p<0.01$), paroxetine (OR=4.93 [2.01;12.12], $p<0.01$), sertraline (OR=4.15 [1.98;8.70], $p<0.01$), citalopram (OR=3.49 [1.54;7.9], $p<0.01$), escitalopram (OR=3.49 [1.49;8.19], $p<0.01$), fluoxetine (OR=3.40 [1.13;10.21], $p=0.03$) and mirtazapine (OR=2.83 [1.16;6.92], $p=0.02$) were found to be significantly associated with an increased risk of hyponatremia with a progressively decreasing OR. Clomipramine (OR=4.50 [0.97;20.93], $p=0.05$) also showed a trend towards a greater risk of hyponatremia. Otherwise, treatments with fluvoxamine, imipramine, maprotiline, amitriptyline and mianserin were not associated with an increased risk of hyponatremia.

Conclusions These data appear useful on clinical grounds, in order to increase the awareness regarding the possibility that antidepressants induce hyponatremia and to encourage regular serum sodium monitoring.

Keywords Hyponatremia · Antidepressants · Network · Meta-analysis · SIAD

Introduction

Hyponatremia is the most common electrolyte disorder in clinical practice and mild forms occur in up to 30% of hospitalized patients [1, 2]. Neurological manifestations of

symptomatic hyponatremia depend on the degree of hyponatremia, but even more on its rapidity of onset. Symptomatic patients with limited manifestations, usually due to chronic hyponatremia (duration ≥ 48 h), can show clinical features such as headache, irritability, nausea, vomit,

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mental slowdown, confusion, delirium, disorientation, and gait alterations. Patients with acute hyponatremia (duration <48 h) often present with more severe symptoms, and life-threatening manifestations such as stupor, coma, seizures, and respiratory failure may occur [3, 4].

In recent years, it has been shown that hyponatremia, even when mild and apparently asymptomatic, may have deleterious effects, such as an increased risk of falls, bone fractures [5], impairment of neurocognitive and motor performance, mood disorders [6, 7] and increased risk of mortality in different clinical settings [8].

It has also been shown that alterations in different tissues, such as bone loss, skeletal muscle sarcopenia, cardiomyopathy, hypogonadism, and liver steatosis, can be induced by hyponatremia in rats [9, 10], although these findings have not been investigated systematically in humans, so far.

The Syndrome of Inappropriate Antidiuresis (SIAD) is frequently involved in the etiopathogenesis of hyponatremia [11]. There are many conditions that can cause SIAD and among these the administration of a number of drugs, including antidepressants, should be taken into account [12].

In the literature there is a relative paucity of data about hyponatremia during antidepressant treatment. The objective of this meta-analysis is to evaluate the risk of developing hyponatremia during therapy with antidepressants, in particular by investigating whether there is a different risk profile depending on the class or single active principle.

Methods

A meta-analysis was performed including all studies in which the risk of hyponatremia was assessed in subjects with or without antidepressant treatment.

An extensive Medline, Embase and Cochrane search was performed using the following words: hyponatremia and antidepressant. The search was carried out on all articles published until February 5th 2024. The inclusion criterion was original studies in which the risk of hyponatremia was assessed among patients with or without antidepressant treatment. The exclusion criteria were studies conducted on experimental animals and articles not in English. The details of the literature search process are illustrated in the flow chart (Fig. 1).

The relevant abstracts were identified, the articles were selected based on the previously described criteria and the data were subsequently extracted. Regarding the 87 articles that did not meet inclusion criteria: 62 were not in English, 14 were studies conducted on experimental animals and 11 did not have data about antidepressants.

Full-text articles and meeting abstracts were included.

The protocol of this study (CRD42024498869) was published on the website of University of York (Centre for Reviews and Dissemination), https://www.crd.york.ac.uk/protospero/display_record.php?ID=CRD42024498869.

Statistical analysis

Heterogeneity for the risk of hyponatremia in patients with or without antidepressant treatment was assessed by using I^2

Fig. 1 Trial flow diagram

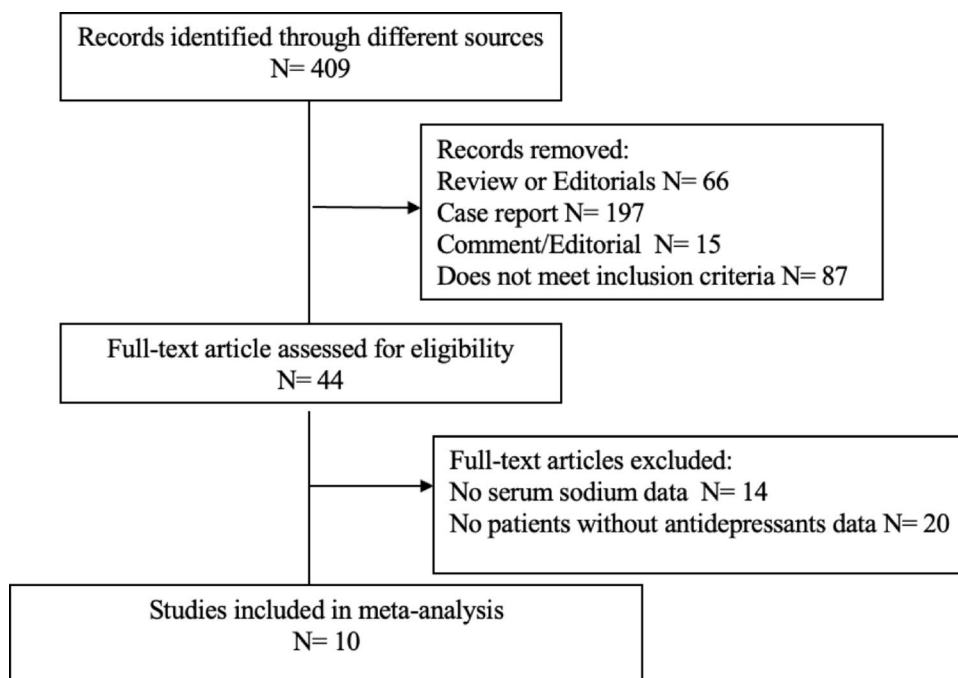


Table 1 Classification of antidepressant drugs analyzed in the study

Class	Active principle
SSRI (selective serotonin reuptake inhibitors)	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
SNRI (serotonin-noradrenaline reuptake inhibitors)	Duloxetine, venlafaxine
NASSA (noradrenaline and specific serotonergic antidepressants)	Mirtazapine, mianserin
TCA (tricyclic antidepressants)	Amitriptyline, clomipramine, dosulepin, imipramine, lofepramine, nortriptyline
TeCA (tetracyclic antidepressants)	Maprotiline
SARI (serotonin antagonists and reuptake inhibitors)	Trazodone

statistics. The risk of hyponatremia among subjects with or without antidepressant treatment was calculated using both a random and fixed effect model. For a more conservative approach, results of random effect model were presented.

The Odds Ratio (OR) with 95% Confidence Interval (CI) of the various active principles of antidepressants grouped by classes were calculated.

The active principles of antidepressants have been grouped into the following classes (Table 1): selective serotonin reuptake inhibitors (SSRI), serotonin-noradrenaline reuptake inhibitors (SNRI), noradrenaline and specific

serotonergic antidepressants (NASSA), tricyclic antidepressants (TCA), tetracyclic antidepressants (TeCA), and serotonin antagonists and reuptake inhibitors (SARI). The analysis by class was carried out if data for at least two active principles were present.

A network meta-analysis was also performed to compare the risk of hyponatremia caused by the various active principles of antidepressants (if the data were present in at least two studies) compared to the control group consisting of subjects not being treated with antidepressant drugs.

Statistical significance was considered if $p < 0.05$.

The data were calculated using the following programs: R version 4.3.1, rmeta R package version 3.0, netmeta R package version 2.8-2.

Results

Of 409 retrieved articles, 399 articles were excluded for different reasons. The flow of the meta-analysis is shown in Fig. 1 and the characteristics of the included studies are summarized in Table 2 [13–22].

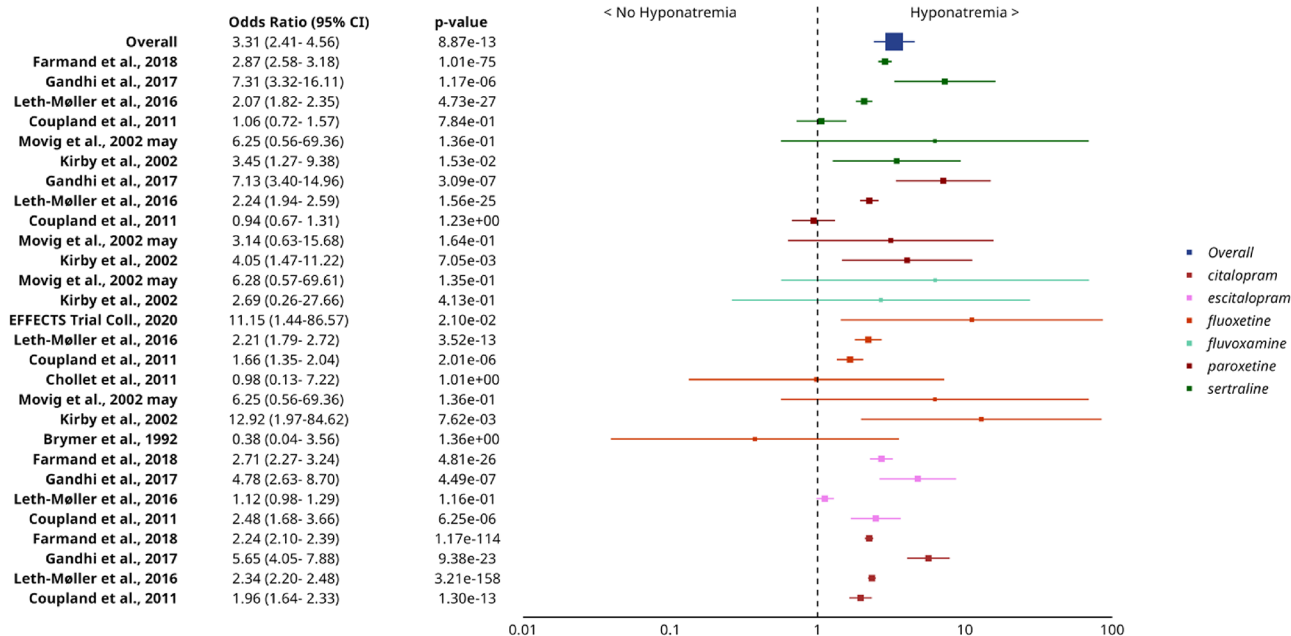
Retrieved trials included 1,026,870 patients with 89,403 hyponatremic subjects (8.7%). Seven studies included data on hospitalized patients, whereas three trials focused on non-hospitalized subjects. Hyponatremia was defined

Table 2 Characteristics of the studies included in the meta-analysis

Source	Type of setting	Age (years $\pm$ SD)	Male (%)	Na ⁺ cut-off (mEq/L)	Patients (n)	H (n)	NH (n)	Antidepressants evaluated individually
Brymer et al., 1992 ¹³	Ambulatory	78.06 $\pm$ NA	91.3	135	65	5	60	Fluoxetine
Spigset et al., 1996 ¹⁴	Ambulatory	42.12 $\pm$ NA	46.2	135	197	19	178	Clomipramine
Kirby et al., 2002 ¹⁵	Hospitalized	74.2 $\pm$ 7.5	35	135	199	42	157	Fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine
Movig et al., 2002 may ¹⁶	Hospitalized	71 $\pm$ 15	27	NA	811	203	608	Amitriptyline, clomipramine, fluoxetine, fluvoxamine, imipramine, maprotiline, mianserine, paroxetine, sertraline, venlafaxine
Chollet et al., 2011 ¹⁷	Hospitalized	64.65 $\pm$ 12.55	61	NA	113	109	4	Fluoxetine
Coupland et al., 2011 ¹⁸	Ambulatory	75 $\pm$ 7.6	33.3	NA	60,746	1114	59,632	Amitriptyline, citalopram, dosulepin, escitalopram, fluoxetine, lofepramine, mirtazapine, paroxetine, sertraline, trazodone, venlafaxine
Leth-Møller et al., 2016 ¹⁹	Hospitalized	36.32 $\pm$ NA	49.9	135	638,352	73,045	565,307	Amitriptyline, citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, mianserine, mirtazapine, nortriptyline, paroxetine, sertraline, venlafaxine
Gandhi et al., 2017 ²⁰	Hospitalized	76 $\pm$ 7.25	32.5	135	253,146	495	252,651	Citalopram, escitalopram, mirtazapine, paroxetine, sertraline
Farmand et al., 2018 ²¹	Hospitalized	74 $\pm$ 14	28	135	71,741	14,359	57,382	Citalopram, escitalopram, mirtazapine, sertraline, venlafaxine
EFFECTS Trial Collaboration, 2020 ²²	Hospitalized	70.8 $\pm$ 10.9	62	130	1500	12	1488	Fluoxetine

H: patients with hyponatremia; NH: patients without hyponatremia; SD: standard deviation; NA: not available

A



B

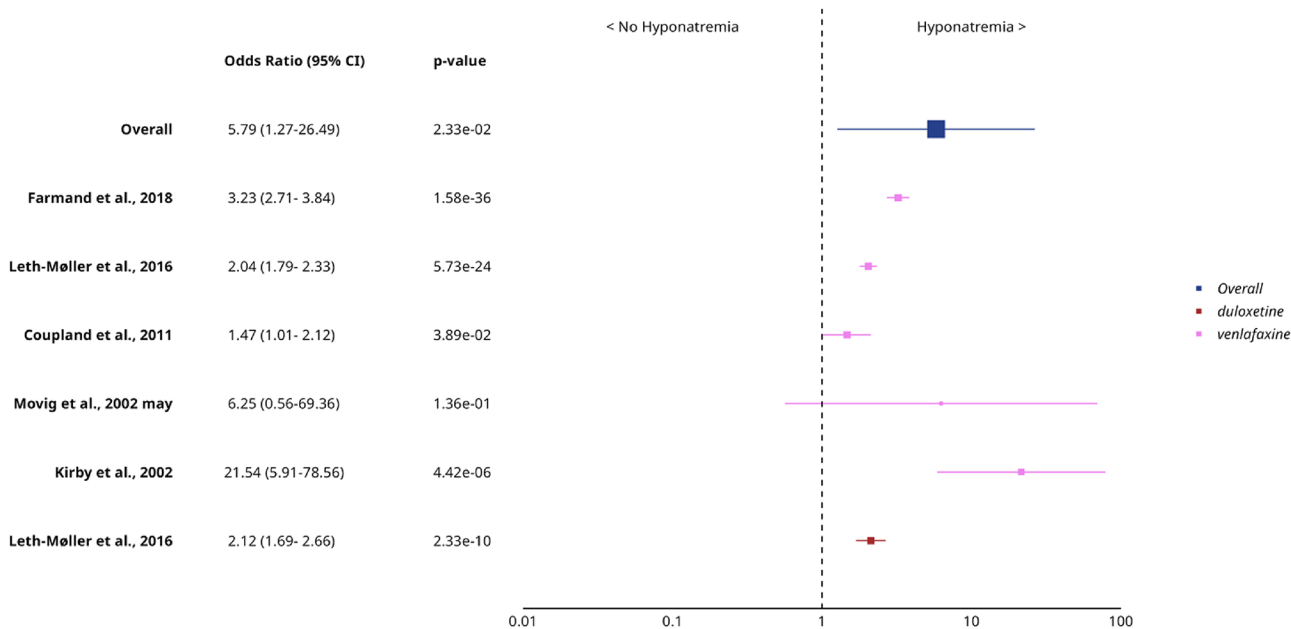


Fig. 2 Odds Ratio for hyponatremia in patients treated with SSRI (A), SNRI (B), TCA (C) and NASSA (D) compared to subjects not treated with antidepressants

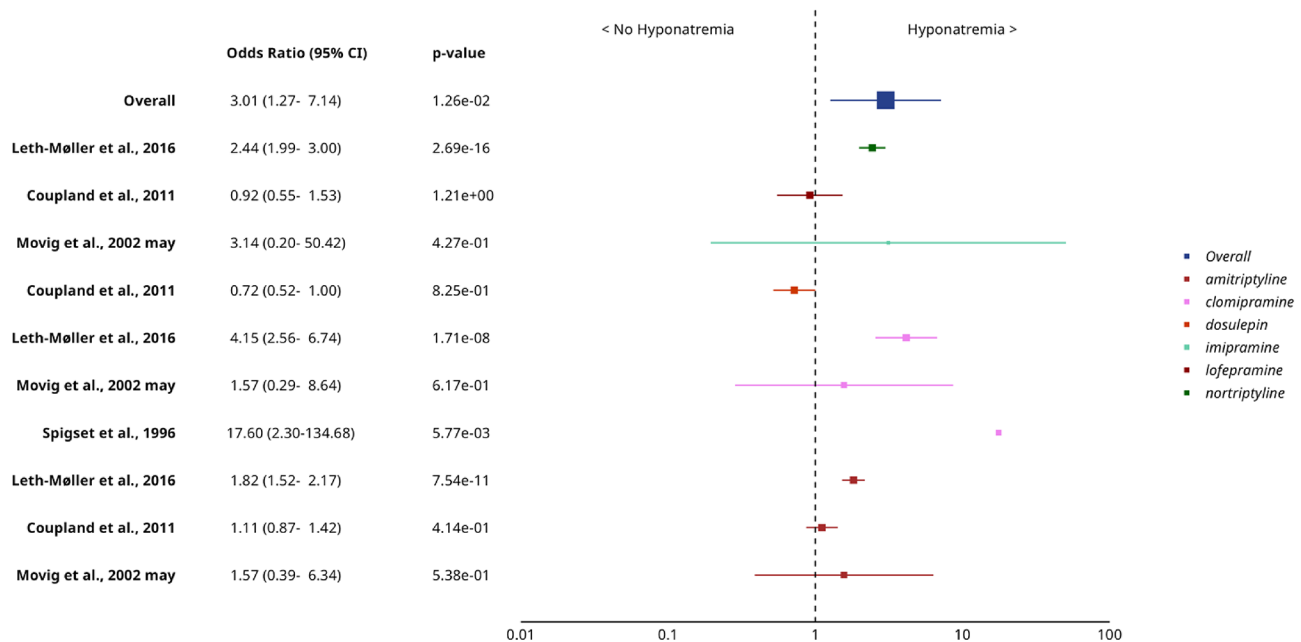
according to different cut-off definitions of the included studies (Table 2).

In the analysis of antidepressant drugs grouped by class (Table 1), treatments with SSRI (OR = 3.31 [2.41;4.56], $p < 0.01$), SNRI (OR = 5.79 [1.27;26.49], $p = 0.02$) and TCA (OR = 3.01 [1.27;7.14], $p = 0.01$) were found to be

significantly associated with an increased risk of hyponatremia, whereas treatment with NASSA was not statistically significant (Fig. 2).

A network meta-analysis was also performed, in which the risk of hyponatremia related to the various active principles of antidepressants was compared with the control

C



D

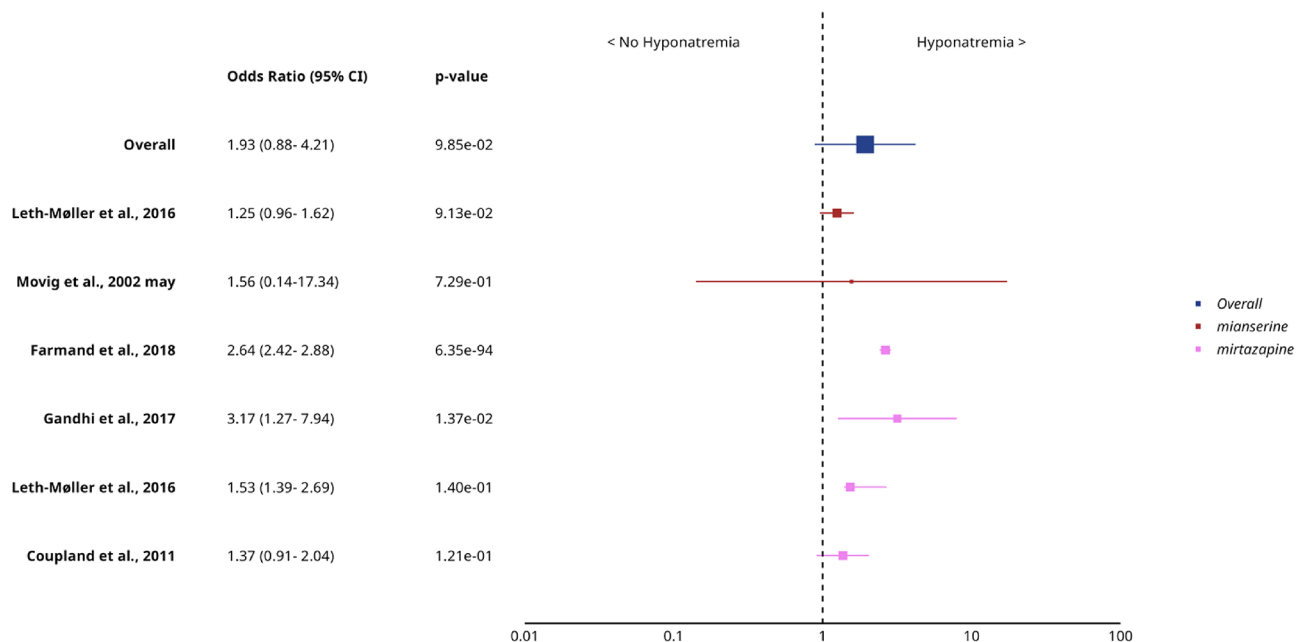


Fig. 2 (continued)

group made up of subjects not being treated with antidepressant drugs, with the aim of drawing up a ranking of the risk of hyponatremia for each molecule (Figs. 3 and 4). Treatments with venlafaxine (OR = 5.99 [2.39;14.99], $p < 0.01$), paroxetine (OR = 4.93 [2.01;12.12], $p < 0.01$), sertraline

(OR = 4.15 [1.98;8.70], $p < 0.01$), citalopram (OR = 3.49 [1.54;7.9], $p < 0.01$), escitalopram (OR = 3.49 [1.49;8.19], $p < 0.01$), fluoxetine (OR = 3.40 [1.13;10.21], $p = 0.03$) and mirtazapine (OR = 2.83 [1.16;6.92], $p = 0.02$) were found to be significantly associated with an increased risk

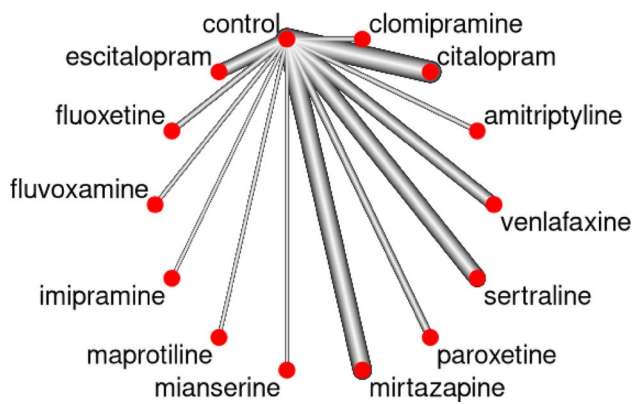


Fig. 3 Network meta-analysis graph

of hyponatremia with a progressively decreasing OR. Clomipramine (OR = 4.50 [0.97;20.93], $p = 0.05$) also showed a trend towards a greater risk of hyponatremia, although the statistical significance was not reached. Treatments with fluvoxamine, imipramine, maprotiline, amitriptyline and

mianserin were not associated with a significant increased risk of hyponatremia (Fig. 4). I^2 was 60.25 ($p < 0.01$).

Discussion and conclusions

Antidepressants are known to possibly induce hyponatremia secondary to SIAD. Among them, SSRI in particular can cause SIAD in approximately three-six people out of a thousand treated per year. According to the available literature, fluoxetine appears to be the active principle mainly associated with hyponatremia among SSRI, but cases of hyponatremia have also been reported with paroxetine, fluvoxamine and sertraline. The highest risk is in patients over sixty-five years, in whom the electrolyte disorder usually appears within two weeks from treatment initiation. Older adults might be at increased risk for antidepressant-induced SIAD possibly due to age-related physiological changes in hydrosaline balance as a reduction in total body water and/or diminished renal blood flow and glomerular filtration,

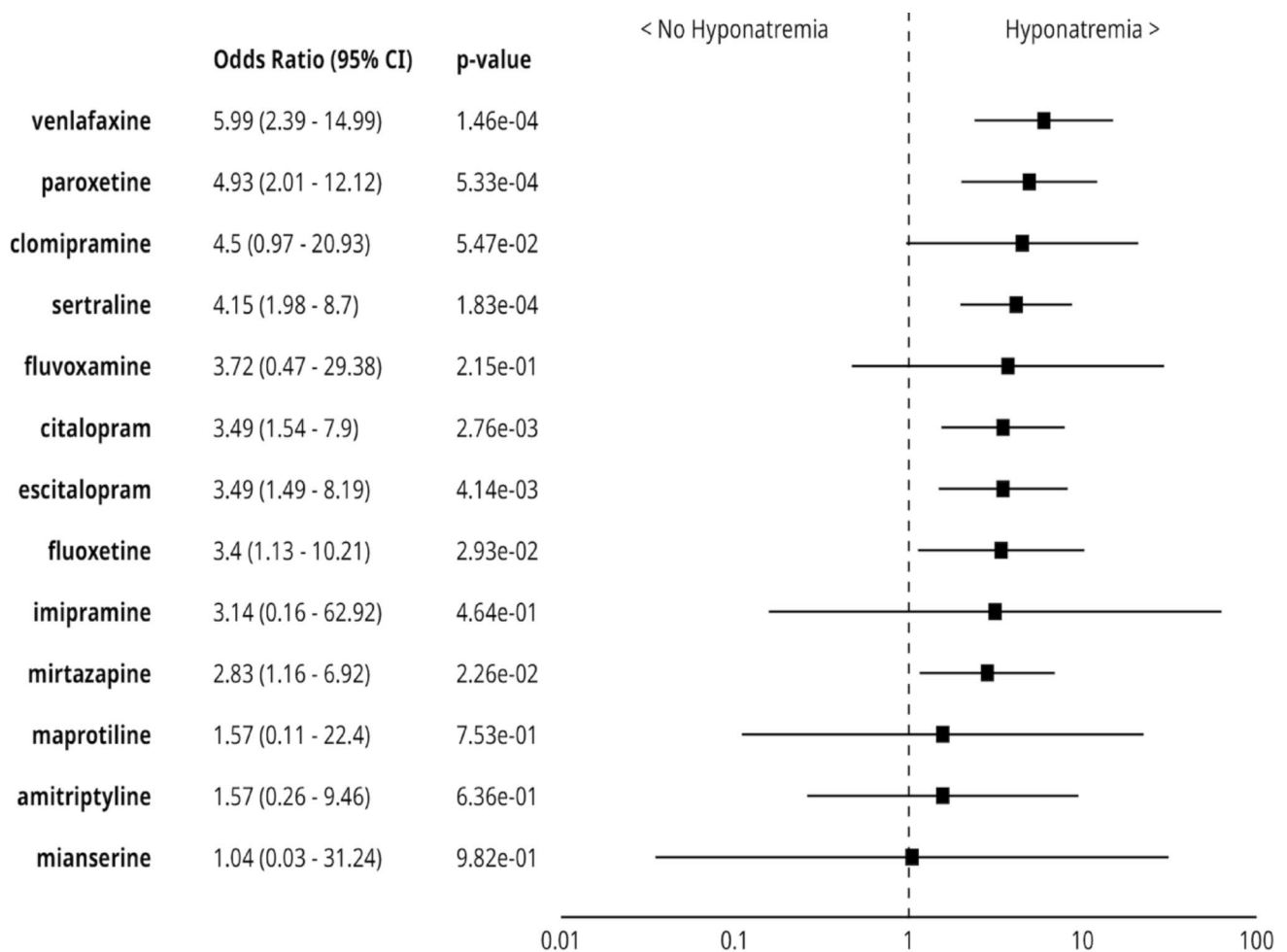


Fig. 4 Network meta-analysis with comparison of Odds Ratio for hyponatremia in patients treated with various active principles of antidepressants compared to the control group consisting of subjects not treated with antidepressants

increased arginine-vasopressin (AVP) secretion or lack of AVP suppression in response to osmolar or pharmacologic stimuli, and decreased renal response to AVP [23–25]. Indeed, in a 2004 prospective study, 12% of elderly patients treated with paroxetine developed SIAD, on average within 9 days from the beginning of therapy [26].

In the last twenty years, new antidepressants have been placed on the market, the so-called second-generation antidepressants, which include, in addition to SSRI, SNRI and NASSA. These drugs have different pharmacological mechanisms and are better tolerated than TCA and monoamine oxidase inhibitors [27]. Despite numerous population studies published in recent years, it is still controversial whether all antidepressants cause hyponatremia in the same way [28].

To better clarify the association between antidepressants use and hyponatremia we conducted a meta-analytic study.

This meta-analytic study analyzed a very large sample of patients (1,026,870 subjects, of which 8.7% were hyponatremic), evaluating various antidepressants both individually and grouped by class.

The results showed a significant increase in the risk of hyponatremia during therapy with SSRI, SNRI and TCA, whereas treatment with NASSA was not associated with hyponatremia.

Our findings confirmed the increased risk of hyponatremia during therapy with SSRI, SNRI and TCA showed by Gheysens et al. in a very recent published meta-analysis. The authors showed that compared to SSRI, SNRI were significantly more likely to be associated with hyponatremia [29].

The novelty of our study is represented by the network meta-analysis that is a useful tool for comparing more than two treatments, combining the results of direct and indirect comparisons. Present network meta-analysis allowed to compare the risk of hyponatremia caused by the various antidepressant active principles compared to the control group made up of subjects not being treated with antidepressant drugs, with the aim of drawing up a risk ranking of hyponatremia.

Our network meta-analysis showed that treatments with venlafaxine, paroxetine, sertraline, citalopram, escitalopram, fluoxetine and mirtazapine are associated with a significantly increased risk of hyponatremia with a progressively decreasing OR. Clomipramine also showed a trend towards an increased risk of hyponatremia, although the statistical significance was not reached. Conversely, treatment with fluvoxamine, imipramine, maprotiline, amitriptyline and mianserin was not associated with a higher risk to develop hyponatremia.

The antidepressants found in our study to be associated with an increased risk of hyponatremia share a common

mechanism: inhibition of serotonin and/or noradrenaline reuptake. The relationship between the inhibition of this reuptake and the onset of hyponatremia, secondary to an increase in AVP release, has been studied in clinical and preclinical studies [30–34].

Gibbs and Vale demonstrated in rats that fluoxetine caused a significant increase in AVP concentrations in peripheral plasma as well as a significant increase in AVP concentrations in hypophyseal portal plasma, suggesting an increase in the hypothalamic secretion of AVP [30]. Furthermore, it has been reported in rats that the injection of serotonin and serotonin receptors agonists into the lateral cerebral ventricle causes an increase in plasma AVP levels [31, 32].

Regarding this aspect, Vacher et al. studied monoamine oxidase-A gene knock-out mice, which present high levels of noradrenaline and serotonin in the brain, and found an increase in the amount of mRNA levels of AVP in the paraventricular and supraoptic nuclei [33].

A correlation between AVP and serotonin has also been reported in humans, since cerebrospinal fluid concentrations of AVP were increased by administration of serotonin releaser/uptake inhibitors [34].

Noteworthy, hyponatremia and depressive syndrome have a dual relationship. In fact, on one hand, antidepressants may induce SIAD-related hyponatremia, as previously discussed [11]. On the other hand, some studies have shown the presence of mood alteration in hyponatremic subjects [6, 35].

The effect of hyponatremia on mood disorders and on the risk of depression has not been investigated in depth so far, with some exceptions [6, 35, 36], perhaps due to the assumption that the mental condition of patients is likely determined by the underlying pathologies rather than by hyponatremia. The SALT trials showed a significant improvement in the mental health components of the SF-12 Health Survey in the group of patients with SIAD in which hyponatremia had been corrected by the V₂ receptor antagonist tolvaptan [35], thus suggesting a negative influence of hyponatremia on patients' mood. On the other hand, Brinkkoetter et al. [36] did not find a difference between hospitalized geriatric patients with mild-to-moderate hyponatremia and normonatremic controls, matched for age and gender, using the Geriatric Depression Scale. It has to be said that the presence of minor symptoms could easily be missed in the geriatric setting due to a high prevalence of mood disorders [36]. However, the assessment of Beck's Depression Inventory [37], a well-established and widely used instrument for detecting and classifying depressive disorders, in our previous study on 130 hospitalized patients with euvolemic hyponatremia, showed pathological results indicative of the presence of depression in more than 50% of non-geriatric patients in the

group with severe hyponatremia [6]. These findings suggest that the impact of hyponatremia on mood stability has been largely underestimated, so far.

Some limitations must be acknowledged regarding this study. Although this meta-analysis documented a close association between hyponatremia and antidepressant treatment, insufficient data were available to evaluate the contribution of different forms of hyponatremia or its confounding factors. A further limitation of this study is the incomplete data on the risk of hyponatremia during antidepressant treatments in trials designed only marginally for the evaluation of these endpoints.

In conclusion, this study analyzed in a comprehensive and updated way the risk of hyponatremia during antidepressant treatment. The network meta-analysis, in particular, allowed to highlight the differences in the risk of hyponatremia between the various active principles. This aspect is relevant, also considering the possible negative effect of hyponatremia on mood disorders. These data need confirmation in subsequent studies, but appear useful, if translated into clinical practice, in order to increase the awareness regarding the possibility that antidepressants induce hyponatremia and to encourage regular serum sodium monitoring in treated patients.

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Declarations

Conflict of interest There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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