Hyponatremia in Elderly Patients Treated for Depression With Selective Serotonin Reuptake Inhibitors Versus Tricyclic Antidepressants

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Hyponatremia in Elderly Patients Treated for Depression With Selective Serotonin Reuptake Inhibitors Versus Tricyclic Antidepressants

Abstract

Background: Hyponatremia has been associated with antidepressant use in the elderly. It is prompted by multiple classes of medications, and rates of hyponatremia are higher in elderly patients. As the elderly population grows worldwide, the potential for significant rates of otherwise avoidable morbidity and mortality due to the antidepressant-related hyponatremia experiences commensurate growth. This review focuses on the relative risk of hyponatremia in elderly patients with depression using selective serotonin reuptake inhibitors (SSRIs) vs those treated with tricyclic antidepressants (TCAs).

Method: An exhaustive search of available medical literature was conducted in MEDLINE, CINAHL, and EBMR Multifile for records which referenced: hyponatremia or inappropriate antidiuretic hormone (ADH) syndrome; depression, “antidepressant agents, tricyclic”, or serotonin reuptake inhibitors; and an aged population. Results were limited to English-language studies on humans published since 2002.

Results: Three eligible studies were identified, 2 cohort and 1 case-control, based on the criteria identified in the method section. All studies considered hyponatremia in the context of elderly patients taking SSRI antidepressant medications. One study explicitly considered the relative incidence of hyponatremia in patients taking SSRIs and TCAs for depression. Each study shows increased odds or hazard ratios for hyponatremia in the setting of SSRI use by elderly patients, and the one study that examines TCA use by the elderly finds no significant increase in hyponatremia.

Conclusion: SSRIs appear to have more potential for antidepressant-associated hyponatremia in elderly patients than do TCAs. Further research is needed to quantify the relative harms, so that clinicians and patients can make informed decisions about the relative risks and benefits of these two antidepressant classes. This objective would be most readily accomplished by randomized controlled trials comparing both drug classes in elderly patients with depression. Clinicians should remain vigilant for hyponatremia in elderly patients recently started on SSRIs.

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hyponatremia; elderly; selective serotonin reuptake inhibitors (SSRIs); tricyclic antidepressants (TCAs); depression.

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Hyponatremia in Elderly Patients Treated for Depression With Selective Serotonin Reuptake Inhibitors Versus Tricyclic Antidepressants

Jonathan P. Clemens

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Information redacted for privacy]
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Keywords: hyponatremia; elderly; selective serotonin reuptake inhibitors (SSRIs); tricyclic antidepressants (TCAs); depression.
Acknowledgements

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List of Abbreviations

ADH................................................................................................................ antidiuretic hormone
ADR........................................................................................................... adverse drug reaction
CI................................................................................................................ confidence interval
DDD................................................................................................................ defined daily dose
HR...................................................................................................................... hazard ratio
IRR.................................................................................................................. incident rate ratio
OR...................................................................................................................... odds ratio
SNRI...............................................................serotonin norepinephrine reuptake inhibitors
SSRI...............................................................selective serotonin reuptake inhibitors
TCA.................................................................................................................. tricyclic antidepressant
Hyponatremia in Elderly Patients Treated for Depression With Selective Serotonin Reuptake Inhibitors Versus Tricyclic Antidepressants

BACKGROUND

Hyponatremia is a disturbance in normal electrolyte concentrations, defined specifically as serum sodium below 136 mmol/l. It is prevalent in approximately 2.5% of the general hospital inpatient population, but can approach 11% prevalence among elderly patients. Symptoms of hyponatremia vary by severity and rapidity of onset. They involve central nervous system disturbances, but can mimic gastrointestinal problems and depression.1 If untreated, hyponatremia can lead to seizure, coma, and respiratory arrest when serum sodium levels fall below 120 mmol/l.2

Worldwide, the population is aging, with more prominent demographic shifts occurring in developed nations with the best access to health care. Aged persons are susceptible to depression at a rate that exceeds that of their younger peers.3 Depression in the elderly is treated with many types of pharmaceutical interventions, but selective serotonin reuptake inhibitors (SSRIs) are the most popular class of antidepressants, having dethroned the previously most popular class, tricyclic antidepressants (TCAs), in the late 1990's, as illustrated in Figure II.4

Complicating this cycle of increasing SSRI demand in an expanding population segment is the potential adverse drug reactions (ADRs) of the SSRIs which are more pronounced in the elderly than in the general population. Hyponatremia was identified as a potential side effect of SSRIs, but its relatively increased prevalence among elderly patients was only established in the literature after the popularity of SSRIs had already
eclipsed that of the TCAs. This delay in ADR recognition may be in part because elderly patients are often underrepresented in clinical trials due to comorbidity-based exclusion.\(^5\)

Elderly patients are particularly at risk for hyponatremia in general, since many are taking diuretics for hypertension control, which some studies have shown to increase the risk of SSRI-associated hyponatremia.\(^6\) Loss of renal function, polypharmacy, dementia, and other conditions of advanced age can either exacerbate the severity of hyponatremia or mask its onset. While hyponatremia can often be readily reversed once diagnosed, slow correction is necessary to rebalance sodium without triggering side effects such as central pontine myelinosis.\(^7\)

TCAs have long been reviled for their anticholinergic side effects, such as xerostomia, which are not tolerated well by patients.\(^8\) TCAs are now prescribed for some of these ADRs, such as hypnotics or decongestants.\(^4\) Likewise, TCAs have been criticized for being more deadly in overdose, a problem for both intentional overdoses in attempted suicide and unintentional overdoses associated with poor medication compliance. Yet, for all the evidence, both formal and anecdotal, which supported the rush away from TCAs to SSRIs, formal studies of the relative harms of each antidepressant class in the elderly seem to have been infrequent and of limited scope.

This systematic review addresses the most recent evidence on the prevalence of hyponatremia in elderly patients treated for depression without co-morbid severe mental illness, focusing specifically on the relative rates of hyponatremia in such a population with SSRIs and TCAs as pharmacological interventions. It also provides recommendations for both clinical practice and future research.
METHODS

An exhaustive literature search was conducted using three online databases available through the Pacific University library: MEDLINE (via Ovid), CINAHL, and EBMR Multifile. The search examined three facets of the clinical question, each of which must have been present for a record to be selected. Using the appropriate structured vocabulary for each tool, the three criteria were that a record referenced: hyponatremia or inappropriate antidiuretic hormone (ADH) syndrome; depression, “antidepressant agents, tricyclic”, or serotonin reuptake inhibitors; and an aged population. When supported by the query interface, the search results were limited to English-language entries published since 2002 applicable to human subjects. The Web of Science's citation finding tools were also used to find relevant studies citing these resultant articles.

For a selected record to be included, it must have been a randomized controlled trial, cohort study, or case-control study, published since 2002 in English on human subjects; case studies were excluded as too anecdotal to support any evidence based process. Studies were assessed for evidence quality using the GRADE criteria.9 These criteria place studies into four categories: high, medium, low, and very low.
RESULTS

The initial search yielded 348 records, which were winnowed to 302 after duplicates were removed. These 302 records were examined for relevance against the selection criteria described in the previous section, and 73 were identified as potentially meeting those criteria through title or abstract. Of those 73, 35 were eliminated as case studies or letters to the editor, 25 as having a focus which would not bear on the clinical question, 5 as review articles rather than studies, 3 as non-English, 1 as a previously unidentified duplicate, and 1 as older than the 10-year horizon. These literature search results are graphically represented in Figure I.

This refinement yielded three cohort or case-control studies, with Coupland, Kirby, and Movig as their respective primary authors. Each was focused on the potential harms of antidepressant medications and considered the elderly as either the primary focus of the study or a defined subgroup. Of these studies, one was placed into each of the medium, low, and very low GRADE categories. No randomized controlled trials were found in the review of literature.

Coupland et al

Of the three studies included in this review, the most recent is A Study of the Safety and Harms of Antidepressant Drugs for Older People: a Cohort Study Using a Large Primary Care Database, by Coupland et al. As primarily a retrospective cohort study it covered data in the QResearch database, which compiles patient data on 60,746 patients from 570 different general practices in the United Kingdom. The second of its five stated objectives is “to directly compare the risk of adverse events for SSRIs with TCAs,” and among the measured outcomes are both hyponatremia and all-cause mortality. The
study's criteria excluded patients who already had depression, had more serious psychiatric diagnoses, were over 100 years of age, or had joined their practices within the past year. The study limited itself to persons with diagnoses of depression, such that the control group against which hazard ratios are assessed was not non-depressed elderly patients, but rather the group of patients who obtained a diagnosis of depression during the study period, yet were not currently receiving any antidepressants—TCAs, SSRIs, or others—for that condition.  

The study does not compare TCAs to SSRIs directly in either outcome of interest, but in each case compares the hazard ratios to a third class of patient: elderly people between the ages of 65 and 99, neither new to their medical practices nor with a recently prescribed antidepressant, who are diagnosed with depression but not given a pharmaceutical intervention. With all-cause mortality, the hazard ratio is elevated slightly in elderly patients using TCAs for depression compared to elderly patients with no prescription for their diagnosed depression: a 1.16 (95% CI 1.10-1.22) hazard ratio. It is elevated, but with similarly tight confidence intervals, for elderly patients using SSRIs for depression compared to elderly patients without pharmaceutical treatment for their diagnosed depression: a 1.54 (95% CI 1.48-1.59) hazard ratio.

The picture of relative hyponatremia incidence painted by the study is somewhat different. The hazard ratio between hyponatremia in elderly patients diagnosed with depression and treated with TCAs and those treated without medication is not statistically significant: a 1.05 (95% CI 0.87-1.27) hazard ratio. In elderly patients diagnosed with depression and treated with SSRIs compared to those not receiving antidepressants, the hazard ratio is 1.52 (95% CI 1.33-1.75). In this study, only SSRIs are found to have a
significant adjusted hazard ratio for hyponatremia compared to unmedicated controls, which was significant at $P < 0.001$. No other patients, regardless of medication, show a statistically significant difference in hyponatremia from patients receiving no antidepressant medication at the $P < 0.05$ level. These findings are summarized in Table II.\textsuperscript{10}

This study also tested for a defined daily dose (DDD) response curve. Elderly patients taking SSRIs at less than half of the DDD are more likely to experience hyponatremia (an HR of 1.95, with 95% CI 1.53-2.48) than those patients taking between 0.5 and 1.0 DDD (an HR of 1.46, with 95% CI 1.25-1.71) who are in turn more likely to experience hyponatremia than those taking greater than 1.0 DDD of SSRIs, whose hyponatremia rate did not differ significantly from the baseline, at HR 1.07 (95% CI 0.71-1.61).\textsuperscript{10}

Finally, using self-controlled case-series analyses, where individual patients experiencing events of interest are compared over time, the study assessed incident rate ratios for hyponatremia relative to periods of time since starting or stopping antidepressants. Of note is that in each antidepressant class there was an increase in the incident rate ratio (IRR) of hyponatremia to the $P < 0.001$ level in the first 28 days after antidepressant medications were started. In TCAs the IRR was 3.19 (95% CI 2.12-.4.81), in SSRIs it was 13.14 (95% CI 10.59-16.29), and in other antidepressants it was 3.63 (95% CI 2.03-6.51). A smaller effect is evident in increased IRR of hyponatremia in the first 28 days after antidepressant medications were stopped. In TCAs the IRR was 2.16 (95% CI 1.37-3.39), in SSRIs 3.88 (95% CI 2.71-5.57), and in other antidepressants 2.64 (95% CI 1.29-5.43).\textsuperscript{10}
Kirby et al

The Kirby et al\textsuperscript{11} study, \textit{Hyponatraemia in Elderly Psychiatric Patients Treated With Selective Serotonin Reuptake Inhibitors and Venlafaxine: a Retrospective Controlled Study in an Inpatient Unit}, does not consider tricyclic antidepressants, focusing its attentions on the differences in hyponatremia in elderly patients taking SSRIs or Venlafaxine, the first serotonin-norepinephrine reuptake inhibitor (SNRI) and the one marketed at the time of the study,\textsuperscript{12} from those not treated with either class of drug in the past three months.\textsuperscript{11}

The authors characterize their study as a “retrospective case note review” of inpatients treated at an Australian psychogeriatric unit in 1997—98. While the ward was designated for treatment of patients 65 years of age or older, the study actually considered patients as young as 60, with a mean age of 74.2 years. Identified in the study were 199 patients, the primary criterion being that at least one serum sodium level was recorded during admission. Of those 199 patients, 107 had depression as their main diagnosis.\textsuperscript{11}

The study found an adjusted odds ratio of 3.5 (95\% CI 1.4-8.9) for hyponatremia among all study participants taking SSRIs or Venlafaxine compared to controls, after controlling for other factors including mental illness severity, depression, and thiazide status. Limited to patients with depression alone and adjusted for the same factors, the study found an odds ratio of 3.1 (95\% CI 1.1-8.6) for hyponatremia in patients treated with SSRIs or Venlafaxine vs. those treated with other interventions.\textsuperscript{11}
Movig et al

The third study, *Association between antidepressant drug use and hyponatraemia: a case-control study*, by Movig et al\textsuperscript{13} in The Netherlands, examined hyponatremia in psychiatric patients. This study used laboratory and pharmacy records to identify the overlap between adult patients with a serum sodium equal to or less than 130 mmol/l and those receiving antidepressant medication at the time the low serum sodium was measured. For each of the 29 identified subjects, three matched controls were selected from those patients with serum sodium measurements between 136 and 144 mmol/l, yielding 78 total controls. The medical records of these case subjects and their associated controls were obtained to provide information on comorbidities.

Odds ratios for the cases were calculated, and adjusted for potentially confounding medications and comorbidities. In the entire study population, the adjusted odds ratio for hyponatremia in patients taking SSRI antidepressants vs. other antidepressant medications was 3.9 (95% CI 1.2-13.1). Considering only patients 65 years of age or older, the adjusted odds ratio for hyponatremia in patients taking SSRI antidepressants vs. other antidepressant medications was 6.3 (95% CI 1.0-41).\textsuperscript{13}

Another conclusion of this study was a synergistic effect of diuretics and SSRIs in observed hyponatremia. This was especially marked in the elderly where the combination yielded an adjusted odds ratio of 13.5 (95% CI 1.8-101).\textsuperscript{13}

**DISCUSSION**

The lack of studies revealed by the literature search between the Kirby et al\textsuperscript{11} and Movig et al\textsuperscript{13} studies, both of which were published in 2002, and the study by Coupland
et al\textsuperscript{10} published in 2011 is perplexing. Both 2002 studies\textsuperscript{11,13} are of modest methodological quality per GRADE evaluation (see Table I), which is entirely excusable in that each builds on a body of previous topical literature primarily comprising case studies. Indeed, just under half of the references identified for detailed scrutiny in the literature search (35 of 73) were eliminated because they were case studies. Of those 35, roughly two-thirds (23) were published between 2003 and 2011, so the publication of such case studies clearly did not end with the Kirby et al\textsuperscript{11} and Movig et al\textsuperscript{13} study publications. The dearth of published studies using incrementally improving levels of evidence for the association between SSRIs and hyponatremia is accompanied by a broadening of the literature in which articles providing such modest levels of evidence are found: general geriatric and nursing journals are replete with such case studies. One explanation for the lack of progression is that the evidence was considered adequate to prompt surveillance, but not sufficiently actionable to modify clinical practice. SSRIs, as a class, have many things to commend them over TCAs for the treatment of depression. Hyponatremia is not an infrequent problem in an elderly population, even in the absence of SSRIs, and as such focusing on SSRI-associated hyponatremia may simply not have been deemed worthy of further investigation. That is, the association may have entered clinical consciousness without a rigorous investigation of the causal relationship, potential etiologies, or overall public health impacts. Likewise, it is possible that clinicians are currently finding hyponatremia as the literature would suggest, and either treating it appropriately, or monitoring it without intervention when the intervention would be deemed riskier than stable, asymptomatic hyponatremia.
While literature searches looked for inappropriate ADH syndrome as well as hyponatremia, there was no consensus among the literature that this syndrome was the only etiology of hyponatremia in elderly persons using antidepressant medication. As such, inappropriate ADH syndrome was not further considered in the analysis of these studies.

Coupland et al

It is fair to say that, absent the Coupland et al\textsuperscript{10} study, there would be little point to this systematic review, as it stands alone in providing recent, methodologically superior data with which to directly compare the respective association between SSRI and TCA antidepressant classes and hyponatremia. Hyponatremia was the last of the 13 outcomes assessed in the study, which is implicitly ordered by severity. Nine years after the older two studies were published, the Coupland et al\textsuperscript{10} study provided an impressive retrospective study, orders of magnitude larger than any other identified in this systematic review. In the application of GRADE criteria (see Table I), this study was promoted one level to medium since it demonstrated a dose-response curve and lacked any significantly negative issues.

With up to 13 years of data, covering the years during which TCA prescriptions waned and were supplanted by SSRI prescriptions, the Coupland et al\textsuperscript{10} study is in a unique position to judge both classes of antidepressants, and what it finds is problematic. Indeed, if worldwide SSRI and TCA use follows trends documented by this study (see Figure II, reproduced from Coupland et al\textsuperscript{10}) by the time the 2002 studies were published using data from the latter third of the 1990’s, SSRIs had decisively overtaken TCAs as the dominant pharmacological intervention for depression in the elderly.
This study also covers many other differences in antidepressant-related outcomes. It is sufficiently large that subgroup analyses are readily performed and not lacking in statistical significance. One clinically-relevant pearl identified in the Coupland et al study is the time course of antidepressant-associated hyponatremia, which is substantially more likely to occur within the 28 days following starting or stopping any antidepressant, with the IRR of new onset hyponatremia in elderly patients starting an SSRI well more than double any other measured IRR.

The dose-response curve illustrated that lower doses of SSRIs were more likely to be associated with hyponatremia, but provided no explanation for the observation. It is possible that patients on the lowest dosages were those with the highest prevalence of factors prompting hyponatremia, such as polypharmacy or renal function. The study found no dose-response curve for hyponatremia among any other antidepressant class.

**Kirby et al**

The findings of the Kirby et al study demonstrate a much more profound effect than those of the Coupland et al study. The patient population of the Kirby et al study, however, is inpatient psychiatric patients, and the relevant subgroup for comparison purposes is inpatient psychiatric patients with a diagnosis of depression without more severe mental illness comorbidities. When evaluated against GRADE criteria (see Table I), the study was neither promoted nor demoted, despite minor issues with indirectness and sample size.

The study authors found a significant association between medical illness severity rating and hyponatremia, independent of the severity of patient mental illness. While the
study attempted to correct for this association, it remains possible that the larger observed
effect of SSRI s on hyponatremia is biased by the relatively more severe medical
comorbidities of the depression patients. The study\textsuperscript{11} does not specify their relative
severity of medical comorbidity, but patients with simple depression, absent other mental
illness diagnoses, admitted to an inpatient psychiatric ward were likely admitted to
mange significant medical comorbidities in that inpatient setting.

Another confounder in the Kirby et al\textsuperscript{11} study is the inclusion of Venlafaxine with the
SSRI class. As an SNRI, Venlafaxine is included in the “other antidepressant” class in
the Coupland et al\textsuperscript{10} study. A brief note in the Kirby et al\textsuperscript{11} study states that with
Venlafaxine reclassified as an “other” drug, the odds ratio for hyponatremia in the
reduced population drops to 2.7 (presumably from 3.5, but the exact comparison is not
specified).

\textbf{Movig et al}

Of the three studies, the Movig et al\textsuperscript{13} study is the least relevant to the clinical
question, because it does not account for borderline hyponatremia (serum sodium 131-
135 mmol/dl), it is not focused exclusively on elderly patients even though two-thirds of
the cases (19 of 29) are over age 65, and does not examine tricyclic antidepressants as a
separate class. By omitting mild hyponatremia, the study risks underreporting actual
hyponatremia incidence while exaggerating the severity of associated medical
complications. Applying GRADE criteria (see Table I) to Movig et al,\textsuperscript{13} the study was
demoted one level to very low for issues involving indirectness, methodology, and
sample size.
Movig et al\textsuperscript{13} report an adjusted odds ratio of 6.3 (95\% CI 1.0-41) for hyponatremia in elderly patients treated with SSRIs vs. those treated with other antidepressants, which borders on lack of significance due to the small sample size. Since the study includes both inpatients and outpatients, the discerning reader might wonder if the severity of mental illnesses reflected would be lower in comparison to the Kirby et al\textsuperscript{11} study, but this is mere conjecture since no mention is made of the indications for which antidepressant medications were prescribed. Since no diagnosis was required for the association, it is possible that both patients taking SSRIs for diagnoses more complicated that depression and those taking other antidepressants, such as TCAs, for non-depression diagnoses were included.

The study\textsuperscript{13} failed to find any increased rate of hyponatremia among patients concurrently taking diuretics and SSRIs. Likewise, while the time course of hyponatremia is discussed, the study does not assess the time-to-detection of the hyponatremia for the cases considered.

**CONCLUSION**

This review leaves clinicians with a question of which class of antidepressant medication should be preferred for treating elderly patients in light of these findings. The relative harms of SSRIs and TCAs are not well understood, and this systematic review has illustrated that our understanding of the relative prevalence of hyponatremia in elderly patients taking antidepressant medication has room for improvement. Both older studies' odds ratios for hyponatremia in elderly patients suffering from depression overlap with the narrower Coupland et al results at approximately 1.5 for SSRIs vs no pharmaceutical intervention (see Table II), and the Coupland et al study supports no statistical association between TCAs and hyponatremia in similar patients.

Clinical practice should be informed by the incident rate ratios presented in Coupland et al"s self-controlled case series analyses, which demonstrate that the time periods with the strongest associations with hyponatremia in elderly patients are within the first month after starting or
stopping any antidepressant, but most especially SSRIs. Precautionary checking of serum sodium may be indicated in elderly patients. The public health implications of routine checking for SSRI-associated hyponatremia are beyond the scope of this review, but at the very least, clinicians can weigh hyponatremia appropriately in a differential diagnosis involving any new onset of relevant symptoms.

Future research should focus on randomized clinical trial testing of SSRIs vs. TCAs in elderly patients with depression uncomplicated by more serious mental illnesses. The Coupland et al study illustrates a number of potential harms where a methodologically sound study has found a greater association between SSRIs and negative outcomes, then those between TCAs and negative outcomes in a similar patient population. Likewise, the relative rates of all-cause mortality among TCA- and SSRI-using elderly patients suggests that SSRIs may prompt relatively more mortality than TCAs, a somewhat counterintuitive finding given the relatively higher patient tolerance of SSRIs. The next logical step, then, is to assess both the relative efficacy and harms between the two classes in a study designed to answer the question with a sufficient patient population to confidently derive practice recommendations.
References


Table I. Characteristics of Reviewed Studies

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<tr>
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<th>Year</th>
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<th>Inconsistency</th>
<th>Indirectness</th>
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<td>2011</td>
<td>Retrospective cohort</td>
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<td>Does not consider TCA</td>
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<td>Retrospective Case-Control</td>
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<td>All-cause mortality in TCA-users vs. no antidepressant use</td>
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<td>All-cause mortality in SSRI-users vs. no antidepressant use</td>
<td>HR 1.54</td>
<td>1.48-1.59</td>
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<td>Hyponatremia in TCA users vs. no antidepressant use</td>
<td>HR 1.05</td>
<td>0.87-1.27**</td>
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<td></td>
<td>Hyponatremia in SSRI users vs. no antidepressant use</td>
<td>HR 1.52</td>
<td>1.33-1.75</td>
<td></td>
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<tr>
<td>Kirby et al(^{11})</td>
<td>2002</td>
<td>Retrospective cohort</td>
<td>199</td>
<td>60-100</td>
<td>46% (92/199)</td>
<td>Hyponatremia in SSRI/Venlafaxine vs. other antidepressants</td>
<td>OR 3.5</td>
<td>1.4-8.9</td>
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<td></td>
<td></td>
<td>(mean 74.2)</td>
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<td></td>
<td></td>
<td></td>
<td>107</td>
<td>unspecified</td>
<td>0%</td>
<td>Hyponatremia in SSRI/Venlafaxine vs. other antidepressants, restricted to patients with depression alone</td>
<td>OR 3.1</td>
<td>1.1-8.6</td>
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<tr>
<td>Movig et al(^{13})</td>
<td>2002</td>
<td>Retrospective case-control</td>
<td>107</td>
<td>&gt;18 years (mean 68)</td>
<td>unspecified</td>
<td>Hyponatremia in SSRI vs. other antidepressants</td>
<td>OR 3.9</td>
<td>1.2-13.1</td>
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<tr>
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<td></td>
<td></td>
<td>49</td>
<td>&gt;= 65 years</td>
<td>unspecified</td>
<td>Hyponatremia in SSRI vs. other antidepressants, restricted to age 65 or older</td>
<td>OR 6.3</td>
<td>1.0-41</td>
<td></td>
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</tr>
</tbody>
</table>

* All results listed as adjusted by the methodologies of their respective studies.
** Not significant.
Figure I: Literature Search Results

Identification

Records identified through MEDLINE/Ovid, CINAHL, and EBMR Multifile (n = 328)

Records after duplicates removed (n = 286)

Additional unique records identified through Web of Science (n = 20)

Screening

Records screened (n = 306)

Records excluded (n = 233)

Eligibility

Abstracts or full-text articles assessed for eligibility (n = 73)

Articles excluded, with rationales (n = 70)

Inclusion

Studies included in systematic review (n = 3)
Figure II: Percentages of Prescription for Each Antidepressant Class by Year of Prescription