

SSRI – Thiazide Hyponatremia In-Depth Analysis for Decision Support

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Hyponatremia is the most common electrolyte abnormality both in and out of the hospital, and can lead to both morbidity and mortality. SSRI and SNRI increase the risk of hyponatremia (Farmand 2018, Leth-Møller 2016, Jacob 2006), as do thiazide diuretics and thiazide-like diuretics such as chlorthalidone, indapamide, metolazone, and quinethazone (Nadal 2018, Liamis 2016, Ware 2017).

Combined use of SSRI/SNRI with thiazide type diuretics appears to increase the risk of hyponatremia over either drug alone. (Movig 2002) Adverse outcomes range from mild to life-threatening, and fatalities have occurred. Hyponatremia is usually defined as a serum sodium less than 135 mmol/L, although some have used a lower cutoff. The following charts are presented to facilitate the preparations of tools for clinical decision support.

Antidepressant Classes and Risk of Hyponatremia

Antidepressants	Cause of Hyponatremia?	Comments
Selective Serotonin Reuptake Inhibitors (SSRI)	Established	It is not clear if some SSRIs are more likely than others to cause hyponatremia. Some evidence suggests that fluoxetine, citalopram, and escitalopram may have higher risk than paroxetine and sertraline, but more data are needed. (De Picker) Pending more data, assume all SSRIs have roughly the same risk.
Serotonin - Norepinephrine Reuptake Inhibitors (SNRI)	Established	Available evidence suggests that the risk of hyponatremia with venlafaxine is as high as with SSRI. Duloxetine has also been shown to cause hyponatremia in case reports and case series. Clomipramine probably also increases the risk of hyponatremia. Pending additional data, assume that SNRI and SSRI have a similar risk of causing hyponatremia.
Mirtazapine	Possible	Isolated cases of possible mirtazapine-induced hyponatremia have been reported, (Ladino, Shepshelovich 2017) but evidence from clinical studies suggests that mirtazapine less likely than SSRIs or SNRIs to do so. In one case, a patient with probable citalopram hyponatremia (with positive dechallenge) was put on mirtazapine with no recurrence of hyponatremia. (Jagsch) In another case switching from citalopram to mirtazapine resulted in recurrence of hyponatremia. (Bavbek)
Tricyclic Antidepressants (TCA)	Possible	The clinical evidence suggests that tricyclics are less likely than SSRI or SNIR to result in hyponatremia. (Movig, Farmand, Shepshelovich 2017) Clomipramine and imipramine are classified as SNRIs (see above).

Bupropion	Possible	Isolated cases (including one confirmed by rechallenge) suggest that bupropion may cause hyponatremia. More evidence is needed to establish the extent to which it is less likely than SSRI/SNRI to cause hyponatremia, but in one case of hyponatremia normalized after the patient was switched from sertraline to bupropion.(Pinon)
Mianserin	Unlikely	A retrospective cohort study of 72,509 patients in Denmark with hyponatremia suggested that mianserin was not associated with hyponatremia. (Leth-Moller)
MAO Inhibitors	Unlikely	There is little information to suggest that nonselective MAOI antidepressants cause hyponatremia.

A. Evidence of the Interaction:

1. Interactive Properties	The precise mechanisms for hyponatremia following SSRI/SNRI or thiazide diuretics are not established, and the mechanisms are probably not identical. Thus the hyponatremic effects may be additive. In any case, since both SSRI/SNRI and thiazide diuretics given alone can cause hyponatremia, it is reasonable to assume that a person taking both would be at greater risk.
2. PK Studies (Healthy)	Not applicable. This is a pharmacodynamic drug interaction
3. PK Studies (Patients)	Not applicable. This is a pharmacodynamic drug interaction
4. PD Studies (Healthy)	None available.
5. PD Studies (Patients)	None available.
4. Case Reports	Many of the case reports of hyponatremia with SSRI/SNRI or thiazide-type diuretics have involved the use of the antidepressant or the diuretic alone. See Appendix 1 for case reports involving the combination of SSRI/SNRI and thiazide-type diuretics.
5. Case Series	None available.
6. Epidemiologic Studies	Thiazide-induced hyponatremia is relatively common, and thiazides probably produce a several-fold increase in the risk of hyponatremia. (Burst 2017, Rodenburg 2013, Winzeler 2016) In a case-control study of patients on antidepressants, 29 hyponatremic patients were compared with 78 controls who had normal serum sodium. (Movig) Patients on SSRIs had more than a 3-fold higher risk of hyponatremia than patients on other antidepressants. When both diuretics and SSRIs were used, the risk was 8-fold higher, and with SSRIs + diuretics + age 65 or older the risk was 13-fold higher.
7. Product Information	The product information for fluoxetine (2017) states under “Warnings and Precautions” that hyponatremia may occur, and that diuretics may increase the risk of fluoxetine-induced hyponatremia. The product information for other SSRI/SNRI such as vortioxetine (2017 label) have similar warnings. The product information for thiazides briefly mentions hyponatremia as an adverse effect, but there is no discussion of combined effects with SSRIs or SNRIs.
8. ADR Registries (eg. FDA)	Not known.
9. Summary Assessment:	Based on dozens of epidemiological studies, case series, and case reports, there is compelling evidence that both SSRI/SNRI and thiazide-type diuretics can individually increase the risk of hyponatremia. (Jacob 2006, and others) Based on epidemiological data, case reports, and theoretical considerations—it is likely that concurrent use of thiazide-type diuretics with SSRI/SNRI increases the risk of hyponatremia over SSRI/SNRI alone.

B. Clinical Characteristics of Interaction

1. Adverse Outcomes	<p>The signs and symptoms of hyponatremia are highly variable, and are not always directly related to the degree of hyponatremia. For example, one patient with marked hyponatremia (serum sodium: 107 mmol/L) did not exhibit any of the typical signs and symptoms of hyponatremia (she only had lower back pain and mild abdominal pain). (Vidyasagar 2017)</p> <ul style="list-style-type: none">▪ <i>Asymptomatic Hyponatremia.</i> Patients may have subtle deficits that are not obvious▪ <i>Mild to Moderate Outcomes.</i> Many of the adverse outcomes are nonspecific, such as confusion, lethargy, fatigue, weakness, headache, anorexia, nausea, vomiting, irritability, memory impairment. These symptoms may be attributed to other causes, especially in the elderly.▪ <i>Severe Outcomes.</i> Gait abnormalities may occur, increasing risk of falls and fractures. Seizures, tremor, rigidity, and hallucinations have also been reported.▪ <i>Fatalities.</i> Coma and respiratory arrest may lead to death.
2. Time Course	<p>The time course is variable, but it is usually within 1 to 3 weeks of starting the second drug (the SSRI/SNRI or thiazide). In some particularly predisposed people, it may occur only a day or two after the second drug is added. In some cases, a patient tolerating combined therapy with an SSRI/SNRI and thiazide may develop hyponatremia after the development or exacerbation of a disorder that predisposes to hyponatremia. (Burst 2017)</p> <p><u>SSRI Alone:</u> In a review of spontaneous reports of hyponatremia in patients started on SSRIs, the mean time to onset of hyponatremia was 13 days, but the range was 3 to 120 days. (Liu 1996) In one prospective study of paroxetine-induced hyponatremia in older adults, the onset of hyponatremia was about 9 days after starting paroxetine. (Fabian)</p> <p><u>Thiazide Alone:</u> In a systematic review, thiazide-induced hyponatremia occurred a mean of 19 days after starting the thiazide. (Barber 2014)</p>
3. Treatment of the Adverse Outcome	<p>The hyponatremia is usually treated with discontinuation of both the SSRI/SNRI and the diuretic, water restriction, loop diuretics, and in severe cases hypertonic saline. See Filippatos (2018) for comprehensive discussion of the management of hyponatremia.</p>

C. Modulating Factors DRUG: (Mitigating Factors and Risk Factors):

1. Doses of Drugs*	<ul style="list-style-type: none"> ▪ SSRI/SNRI: The evidence does not suggest that the dose of the SSRI/SNRI is an important risk factor. ▪ Diuretics: Theoretically, larger doses of diuretics may increase the risk, but too little information is available for definitive statements.
2. Duration of Drugs*	<p>Both case reports and case-control studies suggest that SSRI-induced hyponatremia usually occurs after the SSRI/SNRI is newly started. (Farmand) See also “Time Course” above (B.2)</p>
3. Overlap of Medications	<p>There are no specific studies of overlap, but one would expect that the diuretics (most of which have relatively short half-lives) would have to be given while the serum concentrations of the SSRI/SNRI are therapeutic. The half-lives of SSRI/SNRI vary dramatically, with fluoxetine and its metabolite lasting for weeks. Consider the half-lives of both SSRI/SNRI and the diuretic to estimate the risk of various lengths of overlap.</p>
4. Route of Administration	<p>Only routes of administration of SSRI/SNRI and diuretics that result in systemic effects would be likely to interact.</p>
5. Order of Administration	<p>One would not expect order of administration to affect the interaction.</p>
6. Timing of Doses	<p>Timing of doses is not known to affect outcome. Theoretically it should not affect the magnitude of the interaction.</p>
7. Dosage Form	<p>The dosage form is not known to affect outcome. Antidepressants and diuretics are almost always given orally.</p>
8. Other Medications (See Shepshelovich)	<p>Drugs that may increase risk of hyponatremia:</p> <ul style="list-style-type: none"> ▪ <i>ACE Inhibitors (ACEI), ARBs.</i> ACEIs and ARBs have been associated with an increased risk of hyponatremia in patients over age 65. (Grattagliano 2018) Some patients on SSRI/SNRI or thiazides who develop hyponatremia have been on ACEI or ARB (Soysal 2014) ▪ <i>Amiodarone.</i> Amiodarone probably increases risk (Dutta 2014, Singla2013, Nakamura 2017) ▪ <i>Anti-epileptics.</i> Carbamazepine, oxcarbazepine (most common), but also lamotrigine, levetiracetam, gabapentin, phenytoin, and valproic acid, (Lu 2017, Shepshelovich 2017, Levine 2017). Carbamazepine may have increased risk of hyponatremia with concurrent thiazide therapy (Ranta 2004). ▪ <i>Antipsychotics.</i> Risperidone, haloperidol, quetiapine, and other antipsychotics probably increase the risk of hyponatremia somewhat. (Shepshelovich 2017)

	<ul style="list-style-type: none">▪ <i>Antineoplastics</i>. Vincristine, cyclophosphamide, and cisplatin probably increase the risk of hyponatremia, and some (Moriyama, Nagappa, Shepshelovich 2017)▪ <i>NSAIDs</i>. The use of NSAIDs alone can produce hyponatremia due to effects on renal prostaglandins, but it is rare unless the patient is predisposed due to diseases or concurrent therapy with drugs such as desmopressin. (Rault 1993, Garcia 2003, Verrua 2013) It has been proposed that NSAIDs increase the risk of hyponatremia caused by thiazide-type diuretics (Liamis 2016) but the extent of the increased risk is not clear.
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D. Modulating Factors PATIENT: (Mitigating Factors and Risk Factors):

1. Renal Function	The kidneys regulate sodium homeostasis, and certain types of renal disease may increase the risk of hyponatremia, (Woodward 2018, Palmer 2003) but there is not a specific renal function test that is known to be predictive for hyponatremia.
2. Other Disease States	Heart Failure. Probable increased risk of hyponatremia. (Grattagliano 2018 , Upadhyay 2006) Cirrhosis. Probable increased risk of hyponatremia. (Greenblatt 2016 , Upadhyay 2006) Pneumonia. Probable increased risk of hyponatremia. (Upadhyay 2006) AIDS. Probable increased risk of hyponatremia. (Upadhyay 2006) Adrenal Insufficiency. (Greenblatt 2016) Malignancy. Greenblatt 2016 Hyperglycemia. (Grattagliano 2018, Liamis 2016) Hypothyroidism.
3. Indication for Drugs	Indication for the drugs is not known to affect outcome per se, but see #2 (“Other Disease States”) above.
4. Pharmacogenomics	Available evidence suggests that CYP2D6 genotype is not a risk factor for SSRI-induced hyponatremia. In 20 patients with hyponatremia from fluoxetine or paroxetine, only one was a CYP2D6 poor metabolizer (PM). (Stedman) Pharmacogenomics may be important for thiazide-induced hyponatremia (TIH), however, and one study found the <i>A396T</i> variant of <i>SLCO2A1</i> was twice as frequent in TIH cases as in controls or the general population. ¹ Also, half of all TIH patients had this variant. (Ware 2017)
5. Patient Age	Older patients appear to be at greater risk of developing hyponatremia, and one retrospective study of people with drug-induced hyponatremia found increased severity with increasing age. (Shepshelovich 2017, Ware 2017, De Picker 2014, Rodenburg 2013) A case control study of SSRI-induced hyponatremia found a 6-fold increase in risk with patients 65 and older. (Movig). In a meta-analysis of thiazide-induced hyponatremia, the mean age was 75. (Barber 2014). In a home-based primary care program, frailty was associated with an increased risk of hyponatremia (Ganguli 2015)
6. Patient Gender	Most studies indicate that women may be at greater risk, but the gender difference varied between studies. In one retrospective study of people with drug-induced hyponatremia 56% were women (Shepshelovich 2017). In a meta-analysis of thiazide-induced hyponatremia, 79% were women. (Barber 2014) Hyponatremia due to any cause appears to be higher in women, and they should assumed to be at greater risk from this interaction. (Ware 2017,

¹ They found a number of SNPs that had possible association with TIH, but they chose *SLCO2A1* due its potential role in regulating water reabsorption in the kidney. They propose that decreased *SLCO2A1* activity increases renal collecting duct water permeability, and this combines with the effect of thiazides on free water generation to increase the risk of thiazide-induced hyponatremia. (Ware 2017)

	Nadal 2018) One study of thiazide-induced hyponatremia did not find women to be at greater risk (Rodenburg 2013)
9. Body Mass Index	Body Mass Index: Low body mass index is considered a risk factor (Greenblatt 2016, Liamis 2008, Rodenburg 2013). In a meta-analysis of thiazide-induced hyponatremia, BMI was not found to influence the risk, (Barber 2014) but most evidence suggests that low BMI is a risk factor (Nadal 2018)
7. Laboratory Results	Laboratory evidence of preexisting hyponatremia (i.e., serum sodium below 135 mmol/L) suggests a higher risk. (Greenblatt)
8. Diet/Alcohol/Smoking	Patients on salt restriction are probably at higher risk of SSRI-induced hyponatremia. (Rawal 2017) Alcohol intoxication can increase the risk due to increased fluid load and lack of food intake.
9. Environmental Factors	Weather. There is epidemiological evidence to suggest that drug-induced hyponatremia is more common when the weather is warmer. (Jonsson) Possible mechanisms include increased sodium loss through sweating and increased water intake during exposure to hot weather.
10. Other	Extreme Exercise. Participants in marathons and ironman triathlons have a fairly high incidence of hyponatremia, probably related to fluid overload. (Upadhyay 2006)

E. Management Options:

1. Change Precipitant Drug* (Antidepressant)	Some antidepressants appear to be more likely to cause hyponatremia than others. See Table on Page 1 for risk with various antidepressants.
2. Change Object Drug* (Diuretic)	This generally would not be an option, since all thiazide-type diuretics seem to increase the risk of hyponatremia.
4. Pause Precipitant Drug (Antidepressant)	Since SSRI/SNRI are normally given chronically, pausing the antidepressant is not likely to be appropriate.
4. Pause Object Drug (Diuretic)	Since diuretics are normally given chronically, pausing the diuretic is not likely to be appropriate.
5. Laboratory Monitoring	Monitor serum sodium, serum osmolality, urine osmolality.
6. Symptom Monitoring	Monitor for evidence of hyponatremia (see B.1 above)
7. Change Dosing Times	Not expected to help avoid interaction.
8. Prophylactic Dose Change	This would not be expected to be helpful, since therapeutic doses of both drugs are needed.
9. Patient Education	If SSRI/SNRI are co-administered, advise the patient to watch for evidence of hyponatremia (see B.1 above)
10. Add Other Drug/Device	Loop diuretics may help reduce the risk.
11. Change diet/ habits/etc.	Low sodium diets and high fluid intake may increase the risk.

* May be another drug or other treatment; may be no treatment at all.

F. Summary of Decision Support Points

Description of DDI	<p>SSRI/SNRI and thiazide-type diuretics given alone are well-documented to cause hyponatremia, probably through different mechanisms. Concomitant use of SSRI/SNRI and thiazides increases the risk of hyponatremia over either drug alone.</p>
Risk Factors: Demographic	<ul style="list-style-type: none"> • Age over 65: Epidemiological studies and case reports indicate that the elderly are at greater risk. Frailty is probably also associated with increased risk. • Female gender: Epidemiological studies and case reports indicate that women are at greater risk, but many men also develop drug-induced hyponatremia. (Of the 11 cases in Appendix 1, nine are women)
Risk Factors: Diseases and Conditions	<ul style="list-style-type: none"> • Pharmacogenomics: Although CYP2D6 does not appear to influence SSRI-induced hyponatremia, early evidence suggests that the <i>A396T</i> variant of <i>SLCO2A1</i> increases the risk of thiazide-induced hyponatremia. • Renal Function: Although hyponatremia is more common with certain kidney diseases, there does not appear to be a relationship with GFR. • Diseases: Many diseases increase the risk of hyponatremia including heart failure, diabetes, pneumonia, various malignancies, hepatic cirrhosis, and AIDS. The extent to which these diseases increase the risk varies. • Low Body Mass Index: Most clinical evidence suggests that low BMI increases the risk, but, as with gender, there are many exceptions.
Risk Factors: Other Drug Therapy	<ul style="list-style-type: none"> • Antiepileptic Drugs: These are probably the best documented of other drugs that can cause hyponatremia. Most cases with carbamazepine and oxcarbazepine, but also lamotrigine, levetiracetam, gabapentin, phenytoin, valproic acid • ACE Inhibitors and ARBs: Appear to increase risk of hyponatremia • Amiodarone: Many case reports suggest increased risk of hyponatremia • NSAIDs: Given alone, they rarely cause hyponatremia, but may increase risk when given with other drugs that cause hyponatremia. • Antineoplastics. Probably increase risk of hyponatremia (vincristine, cyclophosphamide, and cisplatin) • Beta-adrenergic blockers. Possibly increased risk, but not well documented.
Risk Factors: Other	<ul style="list-style-type: none"> • Low Sodium Diet: Increased risk of hyponatremia • Polydipsia: Excessive free water intake (may be psychiatric issue, or to counteract dry mouth) • Extreme Exercise: Hyponatremia not uncommon • Hot Weather: Probably increases risk due to sweating and increased water intake

Appendix 1. SSRI/SNRI + Thiazide Case Reports

Patient & Ref.	SSRI/SNRI	Diuretic ^a dose	Onset ^b	Serum Na	Signs and Symptoms	Possible Risk Factors	Outcome	DIPS Rating
65F Fitzgerald	"SSRI" Drug NS	HCTZ 12.5 mg/d	3 wks	122	Anorexia, nausea, fatigue, headache, confusion	Increased fluid intake, Elderly	Resolved over 3 days	Possible
65M Amiri	Citalopram Dose NS	Indapamide Dose NS	"a few days"	105	Confusion, blurred vision, extrapyramidal symptoms	Low Na (127), Ramipril, Elderly	Resolved in 4 weeks	Probable
84F Rosner	Paroxetine 20 mg/d	HCTZ 25 mg/d	2 wks	122	Lethargy, headache, malaise	Elderly	Resolved over 3 days	Probable
63F Rosner	Sertraline 50 mg/d	HCTZ 25 mg/d	2 wks	109	Seizures, lethargy, confusion, headache	Ibuprofen, Lorazepam	Resolved	Probable
71F Strachan	Paroxetine 30 mg/d	BDFZ Dose NS	28 days	131	NS	Elderly	Resolved	Unknown
59M Diken	Escitalopram 10 mg/d	HCTZ 50 mg/d	7 days	107	Confusion, hallucinations, drowsiness	Perindopril, Diabetes	Resolved	Probable
90F Wright	Citalopram 20 mg/d	HCTZ 12.5 mg/d	Several days	112	Confusion, disorientation, a fall without fractures	ACE inhibitor, Low Na, Elderly	Resolved	Probable
63F Siegel	Duloxetine 40 mg/d	HCTZ 25 mg/d	4 days	103	Seizures, unresponsiveness,	NS	Resolved	Probable
67 F Grover	Escitalopram 15 mg/d	HCTZ 25 mg/d	1 week	127	Delirium	Diabetes, Valproic acid, Losartan, Elderly	Resolved	Probable
75F Covyeou	Escitalopram Dose NS	HCTZ Dose NS	5 days	116	NS	Alprazolam, Esomeprazole, Low Na (129)	Resolved over 5 days	Probable
81F Adiga	Escitalopram 10 mg/d	HCTZ Dose NS	3 weeks	120	Confusion	Ramipril, Elderly	Resolved over 4 days	Probable

NS = Not stated. Unk = Unknown

a. HCTZ=hydrochlorothiazide, BDFZ=Bendrofluazide, PPI=Proton Pump Inhibitor

b. Onset of symptoms (or presentation at emergency department) after starting second drug (SSRI/SNRI or diuretic)

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