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Management of SIADH-related hyponatremia due to psychotropic medications – An expert consensus from the Association of Medicine and Psychiatry

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Abstract

Objective: Hyponatremia is the most common electrolyte imbalance encountered in clinical practice and is associated with negative healthcare outcomes and cost. SIADH is thought to account for one third of all hyponatremia cases and is typically an insidious process. Psychotropic medications are commonly implicated in the etiology of drug induced SIADH. There is limited guidance for clinicians on management of psychotropic-induced SIADH.

Methods: After an extensive review of the existing literature, clinical-educators from the Association of Medicine and Psychiatry developed expert consensus recommendations for management of psychotropic-induced SIADH. A risk score was proposed based on risk factors for SIADH to guide clinical decision-making.

Results: SSRIs, SNRIs, antipsychotics, carbamazepine, and oxcarbazepine have moderate to high level of evidence demonstrating their association with SIADH. Evaluation for an avoidance of medications that cause hyponatremia is particularly important. Substitution with medication that is less likely to cause SIADH should be considered when appropriate. We propose an algorithmic approach to monitoring hyponatremia with SIADH and corresponding treatment depending on symptom severity.

Conclusions: The proposed algorithm can help clinicians in determining whether psychotropic medication should be stopped, reduced or substituted where SIADH is suspected with recommendations for sodium (Na+) monitoring. These recommendations preserve a role for clinical judgment in the management of hyponatremia with consideration of the risks and benefits, which may be particularly relevant for complex patients that present with medical and psychiatric comorbidities. Further studies are needed to determine whether baseline and serial Na+ monitoring reduces morbidity and mortality.

Keywords

SIADH; Hyponatremia; Antidepressants; Antipsychotics; Mood stabilizers; Psychoactive medications

1. Introduction

Sodium is the principal extracellular cation responsible for fluid and electrolyte equilibrium in the body [1]. As such, it plays a predominant role in determining serum osmolality [1]. Alterations in total body water content may adversely impact serum sodium concentrations contributing to the development of hyper- or hyponatremia [1]. Hyponatremia is defined as serum sodium levels of <135 mEq/L and is the most common electrolyte imbalance encountered in clinical practice [2]. Approximately 15–30% of hospitalized patients have hyponatremia [2]. Hyponatremia is independently associated with a 55% increase in the risk of mortality, substantial hospital resource utilization, and costs [3,4]. In geriatric patients hyponatremia is demonstrated to increase fall risk and fractures [5].

Most hyponatremic patients are asymptomatic and the low serum sodium levels are incidental findings [6]. The presence and severity of any symptoms depends on the rate of onset and the magnitude of the hyponatremia. Gradual decreases in sodium levels are usually well tolerated, whereas rapid decreases can result in a potentially life-threatening condition due to the resultant edema of brain tissue [7]. Due to the impact of shifting osmolality on the brain, many of the signs and symptoms of hyponatremia are neurologic in origin. Patients with acute, but mild to moderate reductions in sodium (134–125 mEq/L) may experience dizziness, nausea, vomiting, and headache. More severe reductions (<125 mEq/L) can present with dysarthria, ataxia, lethargy, and delirium. Acute changes in mental status are more likely to occur, even at higher sodium values, in patients with risk factors for delirium. Severe acute sodium reductions may also result in seizures, coma, and death.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a condition where the body produces anti-diuretic hormone (ADH) in excess of normal physiological need or when ADH's effect on vasopressin receptors is abnormally potentiated. Unlike physiologically appropriate ADH stimulation, which can be turned off by adequate volume resuscitation or by improving the cardiac output, the ADH release is sustained despite providing fluids. SIADH is characterized by serum osmolality less than 285 mOsm/kg, urine osmolality more than 100 mOsm/kg, and a urinary sodium typically more than 20 mmol/L in the context of clinical euvolemia [8]. It is thought to account for one third of all hyponatremia cases [2]. The hyponatremia of SIADH often insidiously develops over several days or even weeks. As a result of the gradual onset, SIADH is most often asymptomatic or only mildly symptomatic [9]. SIADH was first described in patients with lung cancer in the 1950s. Since that time, many other causes of SIADH-induced hyponatremia have been identified, including many psychotropic medications (Table 1). The mechanism by which the majority of psychotropic medications cause hyponatremia is thought to be due to SIADH [10,11]. However, not all studies exploring the relationship between psychotropic medications and hyponatremia differentiate SIADH from other causes. Hence, some of the studies referenced report undifferentiated hyponatremia in the context of psychotropic medication. Antidepressants, antipsychotics, mood stabilizers, amphetamines and opioids are all described as a cause of drug-induced SIADH [4,9].

With a lack of common protocol for the management of SIADH secondary to psychotropic medications, we sought to develop recommendations from literature review and expert consensus from the Association of Medicine and Psychiatry.

2. Methods

We assembled a team of experts in internal medicine and psychiatry from the Association of Medicine and Psychiatry to develop an expert consensus on the assessment and management of SIADH from psychotropic medications. While the scope of this effort was too broad to distill into a systematic review, to minimize bias we supplemented our effort with a systematic search of the PubMed database. We conducted a literature search for the period between 1990 and 2021, employing combinations of search strings "SIADH" with "hyponatremia" and "antidepressants", "antipsychotics", "mood stabilizers" and "psychoactive medications". A total of 89 articles were identified and included in preparation for the review. For medical disorders, using search terms of "hyponatremia" and "risk factors" returned 40 articles under the category of clinical studies and 18 systematic reviews. We reviewed the latest European-based and US-based Clinical Practice guidelines and other clinical reviews and expert panel recommendations not identified within our PubMed search [12–14]. The Association of Medicine and Psychiatry writing group for the review consists of academic clinician-educators from 16 US institutions and 1 Canadian institution. Groups of 2–3 co-authors conducted additional keyword searches and generated initial drafts based on section topics. Another group of co-authors revised the combined drafts. Iterations of the drafts were completed over asynchronous electronic and live online virtual discussions. Virtual WebEx conference meetings were held to arrive at the expert consensus for the final manuscript.

3. Risk factors

Table 1 lists established risk factors and potential causes of SIADH. Patients over age 60 are at a higher risk of developing hyponatremia [11]. The increased risk in the elderly is multifactorial in etiology and likely secondary to lower total body mass and lower volume of distribution, which amplifies the impact of ADH-dysregulation, decreased glomerular filtration rate as well as increased rates of polypharmacy and medical comorbidity [11,15]. Females have a higher risk of psychotropic medication-induced SIADH than males [16]. Underweight patients as well as those with a history of hyponatremia are also at an increased risk [11]. Many non-psychotropic medications and medical conditions are associated with SIADH and may add to the risk of psychotropic-induced hyponatremia. Smoking is considered a risk factor for hyponatremia in the context of psychiatric illness and nicotine was found to stimulate ADH in humans [15]. However, we found no studies directly linking smoking with SIADH.

4. Differential diagnosis of hyponatremia

Psychotropic medication-induced SIADH is a common cause of hyponatremia [16]. However, other potential causes of hyponatremia should be ruled out before stopping psychotropic medications to avoid deterioration of patient's psychiatric status. Hypotonic

hyponatremia, of which SIADH is one etiology, is the most common cause of hyponatremia [17]. It results from excess of water in relation to sodium, due to decrease in free water excretion. In hypovolemic patients, water retention occurs in part because ADH is secreted in response to the physiologic stimulus of reduced arterial volume. In hypervolemic patients with CHF or cirrhosis, the mechanism is similar - ADH is released due to decreased *effective* arterial volume. In euvolemic patients, ADH secretion has no physiologic basis and is truly inappropriate. SIADH is the most common cause of euvolemic hypotonic hyponatremia. [17].

An algorithm for the differential diagnosis of hyponatremia is presented in Fig. 1. As an initial step, two conditions should be ruled out – pseudohyponatremia and hypertonic hyponatremia. Pseudohyponatremia develops when hyperlipidemia and hyperproteinemia cause a falsely low serum sodium due to a reduction in plasma volume and a laboratory-based erroneous reading. In those cases, no specific intervention for the observed sodium concentration is required. Hypertonic hyponatremia can be caused by hyperglycemia, due to glucose-induced hyperosmotic shifting of water into extracellular fluid compartment diluting the serum sodium concentration. It can also be caused by other hypertonic exogenous solutes which lead to movement of intracellular water to extracellular space. Examples include intravenous mannitol, immunoglobulin suspended in hypertonic solutions, surgical irrigation fluids used after prostatectomy or hysteroscopy (e.g., sorbitol, glycine). These cases are artifactual to the presence of hypertonic osmoles, and it will resolve in parallel to resolution of hypertonicity.

Once above causes are ruled out, hyponatremia from polydipsia should be excluded by evaluating the urine osmolality. In primary polydipsia, hyponatremia develops from excessive water intake which exceeds the kidneys' maximum water elimination capacity, in the absence of ADH release. Here, urine osmolality will be maximally dilute, often less than 100 mOsm/L. The aging process, as well as use of thiazide diuretics can prevent maximal urine dilution to less than 100 mOsm/L, so careful history taking is essential. Excessive water intake will lower the serum ratio of sodium to water, leading to hyponatremia. Primary (psychogenic) polydipsia is a common cause of hyponatremia in psychiatric patients [18]. Once the patient ceases excessive water intake, the serum sodium concentration normalizes as the kidney's ability to maintain fluid balance returns. One must be aware of possible overly rapid self-correction of hyponatremia in psychogenic polydipsia as discussed in the management section.

Hyponatremia may often occur due to true volume depletion from renal or extrarenal losses [8]. Hypervolemic hyponatremia occurs due to reduced effective circulatory volume despite excess total body fluid as classically observed in chronic heart failure and liver cirrhosis. Presence of peripheral edema, pulmonary congestion, jugular venous distention, and ascites serve as clues to their presence. Urine osmolality is >100 mOsm/L in these conditions. Since clinical exams can be insensitive to assessment of volume depletion, in cases that are poorly responsive to management, clinicians should consider a specialty consultation to rule out alternative etiologies of hyponatremia, such as salt wasting, adrenal insufficiency, hypothyroidism and hypopituitarism. Less frequent but important to be aware of is beer potomania. Hyponatremia can occur in patients with a very low intake of dietary solutes

when coupled with relatively large liquid volume intake. Due to the low content of protein and salt in beer, this can be seen in poorly nourished patients with excessive beer intake, also known as beer potomania syndrome. Hyponatremia seen in a “tea and toast diet” is similar in concept, reflecting the low solute intake combined with relatively high liquid intake. Finally, diuretic abuse should be considered in hyponatremia, especially in patients with eating disorders, factitious disorders and malingering.

5. SIADH due to psychotropic medications

Patients with SIADH from psychotropic medications will have normal volume status, low serum osmolality (<285 mOsm/kg), and urine osmolality >100 mOsm/kg. Frequently, hyponatremia is multifactorial and patients on long-term psychotropic mediations develop low sodium only when other risk factors are added to the picture. Psychotropic-induced hyponatremia should be suspected if found within the first two to four weeks after initiation of medication or a significant dose increase, particularly in the absence of other clinical causes [11].

5.1. Antidepressants

Antidepressants are one of the three most commonly used therapeutic drug classes in the United States [19]. According to the latest Centers for Disease Control and Prevention (CDC) data, 8.6% of males and 16.5% of females over age 12 take antidepressants [19]. There have been multiple case reports and studies implicating antidepressants as a direct cause of hyponatremia [20–33]. Selective serotonin reuptake inhibitors (SSRIs) are associated with the highest number of case reports of hyponatremia compared to other psychotropic medications. In 2019, a 10-year prospective study Ramirez et al. found that antidepressants were the second most frequent cause of drug-induced SIADH, following thiazide diuretics [32]. In 2002, Movig et al. reported that SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) were associated with a higher risk (aOR = 3.9, 95% C.I. 1.2–13.1) of precipitating hyponatremia compared to other antidepressants [29]. De Picker et al. conducted an antidepressant class-by-class literature review in 2014 that affirmed these findings. In their review of more than 100 case reports and 21 case control or retrospective studies, they found that the incidence of hyponatremia associated with SSRIs were consistently higher (OR 1.5–21.6) than tricyclic antidepressants (OR 1.1–4.9) [30]. In 2016, Viramontes et al. found that SSRIs represented 77% of reported drug induced SIADH cases.

There is very little literature and no conclusive evidence on the association of hyponatremia with monoamine oxidase inhibitors (MAOIs). Theoretically, due to its mechanism of action and the association of serotonin levels with hyponatremia, MAOIs could cause hyponatremia. Furthermore, for newer antidepressant agents such as vortioxetine, vilazodone and levomilnacipran there is limited data on the risk of hyponatremia. Although there is little conclusive evidence available to guide management of depression in patients with a history of hyponatremia, there have been studies that have found that mirtazapine or bupropion may be a safer alternative agent regarding hyponatremia risk in patients who

have developed hyponatremia with an SSRI or SNRI, due to the lower incidence of SIADH associated with these two antidepressant classes [25,34].

5.2. Antipsychotics

Antipsychotics have been hypothesized to promote ADH release through inducing hypersensitivity of the D_2 receptor, hypotension-related baroreflex stimulation, and serotonin-mediated effects (involving the 5-HT_{1A} and 5-HT_2 receptors) [35,36]. Polydipsia is commonly seen in psychiatric disorders, reportedly affecting 7% of patients with schizophrenia. In addition to the underlying psychiatric condition causing excessive water intake (often in response to a delusion commanding that the patient drink excess water), the anticholinergic side effect of psychotropic medications causing dry mouth may be a contributing factor [37]. A higher urine osmolality suggests antipsychotic-induced SIADH, while polydipsia typically presents with dilute urine [38]. Complicating the picture, serotonergic antidepressants are commonly co-prescribed with antipsychotics, including those with a primary psychotic disorder accompanied by anxiety or depression [39].

In addition to the anecdotal evidence from case series, pharmacovigilance data has also shown hyponatremia to be associated with antipsychotic use (OR 1.58, 95% CI 1.46–1.70) [40,41]. Two rigorous observational studies provide the strongest support for this assertion, although they cannot readily distinguish between hyponatremia due to SIADH versus polydipsia. A large, population-based case-control study in Sweden found admissions for hyponatremia or SIADH were strongly associated with prior antipsychotic use. The unadjusted association (OR 3.08, 95% CI 2.83–3.35) was substantially reduced (aOR 1.67, 95% CI 1.50–1.86) after extensive statistical adjustment for confounding [42]. The association was stronger for first-generation antipsychotics (aOR 2.12, 95% CI 1.83–2.46) compared to second-generation antipsychotics (aOR 1.32, 95% CI 1.15–1.51). Each of these broad groupings, however, had some notable variability by specific agent. For instance, the risk associated with the commonly-prescribed first-generation antipsychotic haloperidol had a lower, non-significant estimated risk (aOR 1.26, 95% CI 0.98–1.62) while clozapine appeared to be higher risk among the second-generation antipsychotics (aOR 5.42, 95% CI 2.97–9.99), although traditionally clozapine is generally reserved for more severe, treatment-refractory cases [43]. While clozapine is highly associated with SIADH, it was found useful in treatment of psychogenic polydipsia in a small case series [44].

5.3. Mood stabilizers

As noted with the antipsychotics, patients who are prescribed mood stabilizers are also frequently simultaneously prescribed antidepressants, which complicates the clinical assessment of the potential SIADH attribution. Carbamazepine is the mood stabilizer most commonly associated with hyponatremia [45]. In addition to inducing SIADH, carbamazepine also stimulates renal vasopressin V2 receptors in the collecting duct to promote water resorption [46]. Using propensity scores based on comparative analysis of Ontario administrative data, Gandhi et al. demonstrated that carbamazepine was associated with a significantly higher risk of hospitalization for hyponatremia (RR 8.20, 95% CI 5.40–12.46) independent of dose [47]. Valproic acid, phenytoin, and topiramate were also associated with a significantly elevated risk (RR 2.62, 95% CI 1.57–4.36) with no

significant differences reported among the three anticonvulsant medications. Carbamazepine was, however, associated with a significantly greater risk than the more commonly-used mood stabilizer valproic acid (RR 4.22, 95% CI 2.33–7.64) [47]. Evidence for valproic acid's association with SIADH is otherwise limited to case reports [48–51]. There are more limited case reports of SIADH with lamotrigine [52,53]. Unlike carbamazepine, the mechanism of any hyponatremia induced by these agents has not been elucidated. Lithium more typically presents with hypernatremia due to nephrogenic diabetes insipidus, although cases of paradoxical hyponatremia have been reported [54].

5.4. Anxiolytics and hypnotics

We found 335 cases of benzodiazepine associated SIADH reported by the FDA Adverse Events Reporting System (FAERS) as part of larger medication regimen. However, only 24 of those were associated with benzodiazepine monotherapy [55]. In the literature, a single case report was found that confirmed SIADH in an 81-year-old woman treated with benzodiazepine monotherapy [56]. All other case reports and series have too many confounding factors to support any evidence of a causal relationship. A single case report of zolpidem-associated hyponatremia described in a 62-year-old man was confounded by both supra-therapeutic dose (20 mg) and the presence of sulfonylurea in the patient's medication regimen [57]. Although $5HT_{1A}$ receptor binding affinity suggests buspirone as a potential SIADH-inducing agent, we found no published literature on buspirone alone causing SIADH. In summary, the relationship between SIADH and benzodiazepines, non-benzodiazepine hypnotics and buspirone is supported by only low-level evidence.

5.5. Central nervous system stimulants and other medications used in treatment of attention deficit hyperactive disorder (ADHD)

Medications commonly used to treat ADHD span several classes of psychoactive substances including amphetamine and methylphenidate stimulants, selective norepinephrine reuptake inhibitors (e.g., atomoxetine) and alpha-2 adrenergic agonists. There are no published systematic reviews or studies conducted exploring SIADH and hyponatremia among patients treated for ADHD. Since 1969, of 11 reports of hyponatremia by FDAER, only 1 report of ADHD treatment-related SIADH is listed [55].

Stimulants primarily exert their therapeutic action by inhibiting the reuptake of dopamine and norepinephrine into presynaptic cells, but they can also have a small effect on serotonin. The 11 cases of hyponatremia related to ADHD treatment reported in the FDAER included seven suspected methylphenidate related cases and 1 suspected amphetamine salt related case. Amphetamine-derived drugs such as MDMA ("Ecstasy"), have been reported to cause hyponatremia, which may be induced by both enhanced ADH secretion and polydipsia [58–61]. Despite this, although amphetamine and methylphenidate stimulants are widely used for the treatment of ADHD, the sparse reporting of SIADH suggests that this is a rare complication. Atomoxetine is a selective norepinephrine reuptake inhibitor used for the treatment of ADHD. Only one published report of a 32-year-old male developing hyponatremia while treated with atomoxetine monotherapy exists, with resolution of hyponatremia after discontinuing treatment [62]. There were no reported cases of hyponatremia due to alpha-2 adrenergic agonists.

5.6. Dementia medications

There is inadequate evidence linking acetylcholinesterase inhibitors and NMDA receptor antagonist memantine with SIADH. The two case reports linking dementia medications with hyponatremia have confounding factors weakening possible correlation [63,64]. Initial dementia work-up routinely includes assessment of electrolytes as the cognitive impairment in major neurocognitive disorder/dementia (including attention and memory deficits) may overlap with the CNS effects of hyponatremia [65].

5.7. Opioids and opioid use disorders treatment medications

Studies, both animal and human, have found that opioids can both stimulate and inhibit ADH [66]. Hyponatremia is a very rare complication of opioid therapy [67]. Most cases of opioid-associated hyponatremia have been reported in the presence of other risk factors for SIADH. Tramadol and codeine were associated with hyponatremia, especially in those who were newly initiated on these drugs. However, the effect of pain, nausea and underlying disease could not be excluded [66]. Reports of buprenorphine, methadone, and opioid-antagonists (naloxone, naltrexone) associated SIADH are in the zero to single published case range [32,66].

5.8. Other psychotropic agents

Dextromethorphan, a component of the pharmacologic agent dextromethorphan/quinidine used to treat pseudobulbar affect, has one report of being associated with drug induced SIADH. Acamprosate, FDA-approved for alcohol use disorder, has no reported association with SIADH [32]. Oxcarbazepine, which is used off-label in a variety of neuropsychiatric conditions, has been strongly associated with hyponatremia. Hyponatremia has been estimated to occur in 30–46% of those taking oxcarbazepine, compared to 14–26% with carbamazepine [68,69]. In an analysis of 560 hospitalized patients, oxcarbazepine was the anticonvulsant most frequently associated with hyponatremia [70]. A register-based case-control study in Sweden also reported the highest adjusted odds ratio estimate for oxcarbazepine for hospitalization due to hyponatremia with ongoing treatment (aOR 8.0, 95% CI 3.7–18.5) [71].

6. Management of hyponatremia in drug-induced SIADH

Once SIADH is confirmed, treatment involves managing the underlying cause and correcting serum sodium [12,72]. If a temporally associated causative medication(s) is identified, cessation of the suspected drug should be considered, and sodium normalization is expected between 2 and 28 days after discontinuation [28,73]. Restriction of water intake is critical in correcting the serum sodium while waiting for SIADH to resolve.

In some instances, the offending agent cannot be stopped, especially when the risk of psychiatric decompensation (e.g., worsening depression, mania, psychosis) is very high. In addition, risk of withdrawal symptoms, rebound symptoms, and persistent post-withdrawal disorders should be considered [6,74]. The severity of the hyponatremia and the properties of the offending medication often guides the process of discontinuation. In cases of moderate, severe, and/or symptomatic hyponatremia the offending agent should be stopped

immediately. In mild and asymptomatic cases (e.g., serum sodium level of ≥130 mEq/L), the offending medication dose should be reduced or gradually tapered off if clinically appropriate. [6]

After the offending agent is stopped, there are several ways in which the serum sodium can be raised. The standard method, especially for asymptomatic chronic hyponatremia, is restricting water intake to 500–1000 mL/day [75]. Water restriction can be difficult for many due to poor adherence and this can be complicated by acute mental health issues. Another method for raising the serum sodium involves administration of hypertonic saline (3%) in a general hospital setting. The efficacy and safety of utilizing hypertonic saline (3%) has been clearly established in the literature [76–80]. This is often necessary in acute, severe hyponatremia, where consultation with a critical care intensivist and/or nephrologist is paramount to prevent severe complications such as seizures and respiratory failure.

A guiding estimation of 1 ml/h of 3% hypertonic saline per kg of patient's weight, (e.g., 70 kg patient having 70 ml/h of 3%) can be considered as an initial starting point for a sodium correction rate of 1 meq/h. In some instances, a carefully dosed bolus of 3% saline is needed to safeguard the patient from acute risks of hyponatremia. A safe correction goal of 6 to 8 mEq/L in 24 h, 12 to 14 mEq/L in 48 h, and 14 to 16 mEq/L in 72 h is recommended [81]. Sodium levels should be corrected into a safe range rather than normal levels, and emphasis should be placed on monitoring the patient's change in serum sodium, rather than the estimated infusion rate. Sodium levels should be monitored frequently in an acute care setting, as often as every 1–2 h, to avoid osmotic demyelination (formerly central pontine myelinolysis), "locked in syndrome" or other permanent brain damage. The deleterious effects of osmotic demyelination might not be immediately apparent and typically occurs up to 5–6 days after rapid sodium correction. [82].

We recommend seeking nephrology guidance when possible to manage patients with a serum sodium <120 mEq/L. Oral salt tablets at 6–9 g per day in two to three divided doses is typically used to correct this level of hyponatremia [83]. Previous literature suggests adding Furosemide 20 mg twice a day to promote free water excretion in those with highly concentrated urine (e.g., >500 mosmol/kg, or Uosm/Sosm ≥2). However, a recent study suggest furosemide does more harm than good and oral salt repletion is of little benefit in SIADH patients [84]. Potassium should be monitored and supplemented as necessary [85]. Correction calculations using salt tablets can be made knowing that a 1 g oral salt tablet is the equivalent to about 35 ml of a 3% saline solution.

Vasopressors antagonists can be used judiciously to cause water diuresis without sodium excretion by blocking receptors to ADH. Conivaptan, a V2 and V1a receptor antagonist, is approved in the US for IV use and considered safe [86]. Tolvaptan is a selective V2 antagonist, but caution is advised due to potential for overly rapid correction of hyponatremia, and high cost [87,88]. Desmopressin can be used to prevent or reverse an inadvertent overcorrection of severe hyponatremia, especially in cases of psychogenic polydipsia where strict water restriction may cause rapid loss of free water [12].

Demeclocycline reduces urine osmolality and increases serum sodium levels, but the risk of nephrotoxicity and variable efficacy makes its use undesirable [88]. Urea is more effective in increasing urine production by acting as an osmotic diuretic and is now available in a more palatable formulation [89].

7. AMP consensus recommendations

Overall, psychotropic medication induced SIADH is most commonly associated with SSRIs and SNRIs, although oxcarbazepine is more likely to cause SIADH. This may be due to SSRIs and SNRIs being more widely prescribed. Although, there is little evidence available to guide management of depressive disorder in patients with a history of hyponatremia, in view of sparsity of case reports there have been multiple studies that have found that mirtazapine or bupropion may be safer alternative agents [27,28].

However, the case reports do bring to light the importance of consistently completing medication list review and screening for symptoms that may be associated with hyponatremia. This is especially important when serotonergic medications are added to an already extensive medication regimen or delivered at a high dose. It is important to consider the risk of SIADH in every patient and take a meticulous approach when initiating a new psychotropic medication to decrease the risk of side effects and drug-drug interactions. Once hyponatremia is confirmed by laboratory studies, temporal determination of possible causative medications should be established.

The risk factors and proposed management algorithm for psychotropic medication induced SIADH were developed based on the literature cited in the review and collective consensus of the authors (Fig. 2). While there is currently a lack of prospective studies examining the utility of baseline [Na+] monitoring, it is our opinion that a baseline measurement is prudent in patients who are at a high risk for hyponatremia to identify those who already have some degree of hyponatremia before adding a medication that could further lower sodium. A risk score of ≥2 should prompt baseline [Na+] measurement and clinical management depends on severity of symptoms. Patients with acute, but mild to moderate reductions in sodium (135–125 mEq/L) may experience dizziness, nausea, vomiting, and headache. More severe reductions (<125 mEq/L) can present with dysarthria, ataxia, lethargy, and delirium. In patients with severe symptomatic hyponatremia, or mild to moderate symptoms with [Na+] < 130 mEq/L, the medication should be discontinued and inpatient work up and monitoring should be considered. For those with mild to moderate symptoms with the [Na+] 130–135 mEq/L, the medication may be reduced by 50% and sodium rechecked within 1 week. In psychiatrically stable patients with asymptomatic hyponatremia and [Na+] 130–135 mEq/L, the dose may be lowered by 25–50% with subsequent monitoring of [Na+] within 2 to 4 weeks or within 1 to 2 weeks in similar patients with [Na+] 125–130 mEq/L. For patient with no symptoms of hyponatremia but [Na+] < 125 mEq/L medical admission and/or re-checking [Na+] within 1 week should be considered. In addition, 50% dose reduction or if possible, discontinuation of the offending psychiatric medication should be considered. For patients with asymptomatic hyponatremia who are psychiatrically unstable, benefits vs risks of medications should be considered and if continued, [Na+] should be checked every 3 months until normalization. It is important to address medical co-morbidities along

with the review and adjustment of other medications that may contribute to hyponatremia drop of less than 125 mEq/L. Consultation with primary care, cardiology (in patients with congestive heart failure), nephrology (in patients where multiple etiologies of hyponatremia are plausible), and other relevant specialists should be considered.

Primary prevention of drug induced SIADH should be kept in mind, especially those in higher risk populations; e.g., the elderly or those who have had brain injury or stroke. Evaluation for and avoidance of medications that cause hyponatremia (e.g., diuretics, angiotensin-converting enzyme (ACE) inhibitors, antidepressants, antipsychotics) particularly important for those at risk for developing or has a history of SIADH [13]. Caution should be taken when re-starting psychotropic medications in patients who have experienced SIADH from any cause. Unless alternative treatment options are not available, re-challenge with offending medications should be avoided. Further research is warranted to optimize an evidence-based approach to the management of SIADH induced by psychotropic medications.

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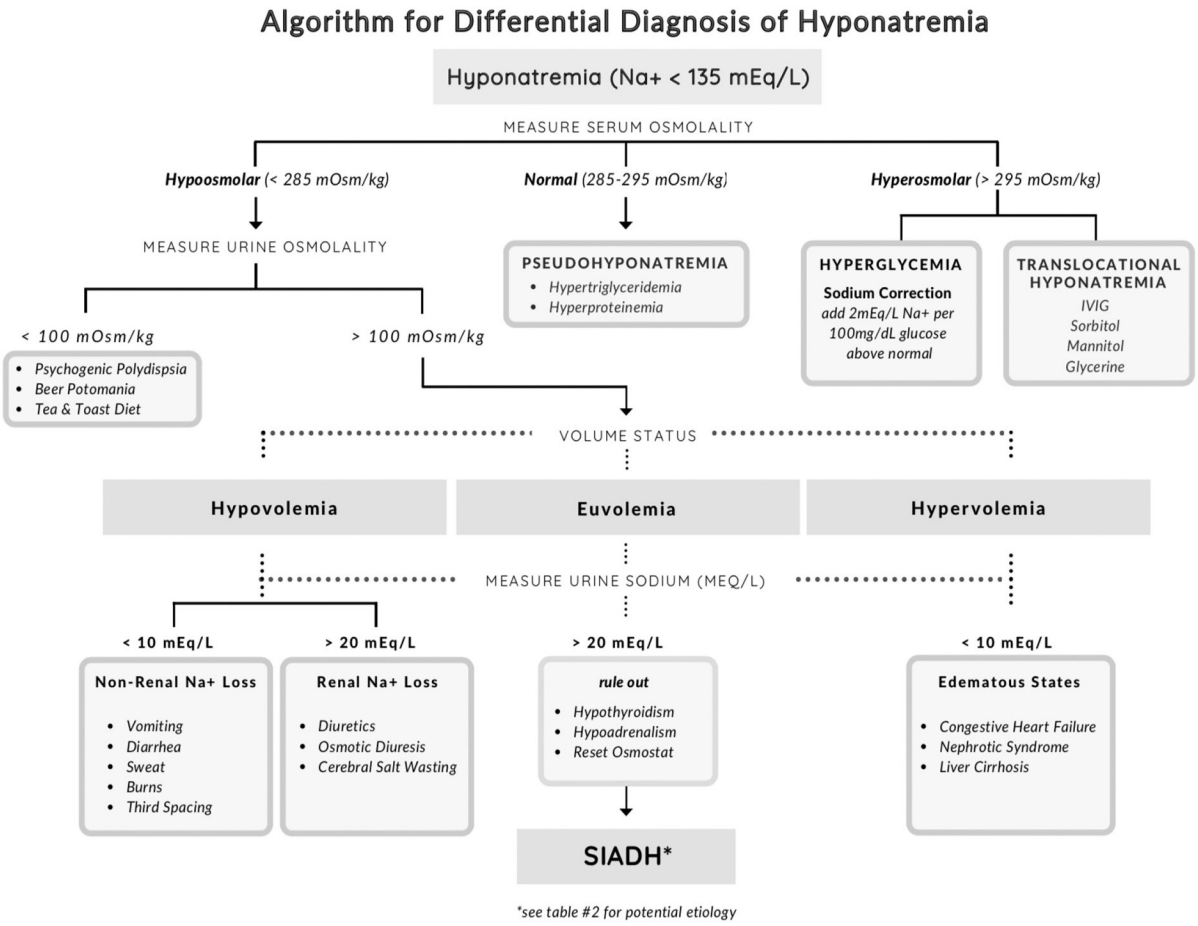

Fig. 1.

Algorithm for the differential diagnosis of hyponatremia: Differential diagnosis of hyponatremia. The above algorithm outlines a clinical approach to the differential diagnosis of hyponatremia. BP = blood pressure; Na = sodium; Osm = osmolality; SIADH = syndrome of inappropriate anti-diuretic hormone. Modified from Maxine A. Papadakis, Stephen J. McPhee, Michael W. Rabow, Current Medical Diagnosis and Treatment 2021, McGraw Hill.

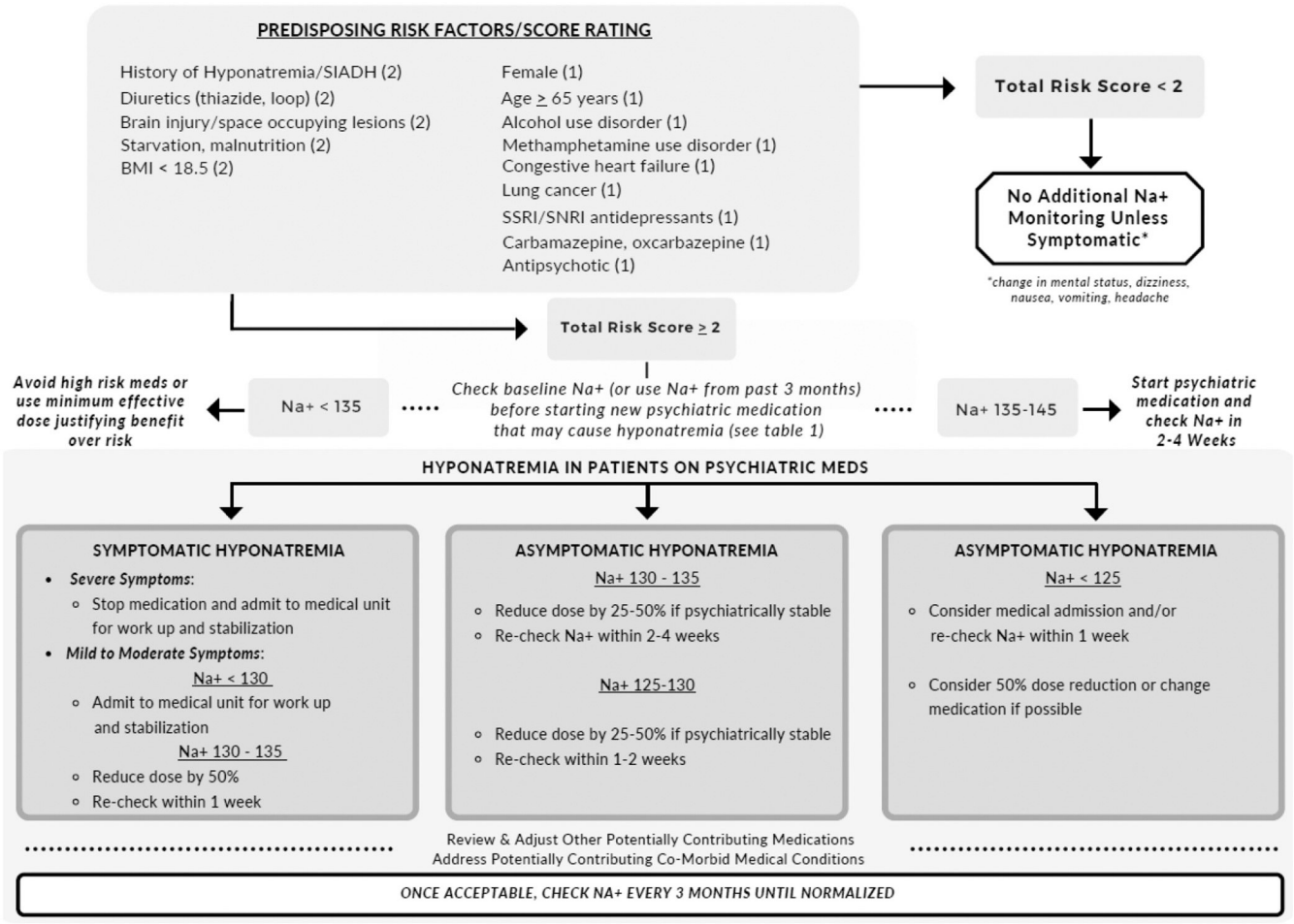

Fig. 2.

Proposed risk scoring & management algorithm of psychotropic medication induced SIADH*.

***** BMI = body mass index, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin norepinephrine reuptake inhibitor.

Disclaimer: The proposed risk scoring and algorithm is not validated by randomized control studies and is based on the compilation of the available clinical data and expert consensus.

Table 1

Risk factors and potential causes of SIADH.

Age	≥60 years old	
Sex	Female gender	
Nutritional status	Low Body Weight (BMI <18.5 kg/m^2)	
Baseline Na	History of hyponatremia ([Na+] <135 mEq/L)	
Medications	*CNS Active Drugs*	Antipsychotics, Antidepressants, Amphetamines, Carbamazepine, Oxcarbazepine, Valproate, Opiates, Barbiturates, Nicotine, Bromocriptine
	Other Drugs	Amiodarone, Ciprofloxacin, Vincristine, Vinorelbine, Vinblastine, Cisplatin, Cyclophosphamide, Ifosfamide, Sulfonylureas, Interferons-alpha/gamma, NSAIDs, Methotrexate
CNS disorders	CVA, infection, TBI, hemorrhage[a], MS, lupus cerebritis, epilepsy, hydrocephalus, encephalitis, meningitis	
Malignancies	Lung (especially small cell carcinoma), gastrointestinal, head & neck, genitourinary, sarcomas, lymphomas and neuroblastomas	
Pulmonary Disorders	Bacterial/viral infection, bronchial asthma, atelectasis, acute respiratory failure, pneumothorax, positive pressure ventilation, tuberculosis, aspergillosis, COPD, pulmonary fibrosis, sarcoidosis	
Major surgery	Abdominal, thoracic, brain	
Hormone administration or deficiency	Vasopressin, desmopressin, oxytocin	
Other	AIDS[a], Malaria, Rocky Mountain Fever, Hereditary SIADH, smoking	

[a]These and other conditions may be associated with salt or volume depletion. Further discussion is beyond the scope of this article. Nephrology consultation is indicated in such conditions where hyponatremia is life threatening.