If antidepressant-induced hyponatraemia has been diagnosed, how should the depression be treated?

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Date prepared: 16/05/2019

Background

In May 1994, the Committee on Safety of Medicines (CSM) issued a warning, stating they had received a number of reports of hyponatraemia in patients receiving serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCADs). The CSM said that all types of antidepressants had been associated with hyponatraemia. Any patient taking an antidepressant who reports drowsiness, confusion or convulsions should be investigated for hyponatraemia. The CSM advised that sodium levels would normally respond promptly to discontinuation of the antidepressant (1).

Answer

Risk factors and monitoring

Antidepressant-induced hyponatraemia occurs particularly frequently in elderly patients, and is predominantly recognised in female elderly patients (2 - 7). One study has stated a prevalence of 9% in patients over 60 years old (8). It has been suggested that age alone is not an independent risk factor, but that the increased incidence of hyponatraemia seen in the elderly can be explained by higher rates of co-morbidities and co-prescribed medicines (5, 9).

Hyponatraemia is more commonly found when patients have co-morbidities or risk factors such as low body mass index, previous hyponatraemia, circulating volume depletion, bleeding, urinary loss, malignancies, pulmonary disorders, congestive heart failure, cirrhosis, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, adrenal insufficiency, hypothyroidism, major surgery, pregnancy, or co-therapy with other drugs associated with hyponatraemia (2, 10, 11). Some psychiatric diseases may also be associated with hyponatraemia, such as psychosis (8).

Although not a recommendation in the antidepressant Summaries of Product Characteristics (SPCs) or the British National Formulary (BNF), the Maudsley Prescribing Guidelines in Psychiatry and the Psychotropic Drug Directory suggest monitoring serum sodium levels in patients at high risk of developing hyponatraemia (2, 3, 12 - 39).

All patients who have been newly prescribed an antidepressant should be monitored for signs of hyponatraemia (e.g. dizziness, nausea, lethargy, confusion, cramps, and seizures). For patients who are at a high risk of developing hyponatraemia, serum sodium levels should be monitored closely (levels should be taken at baseline, 2 and 4 weeks after starting therapy, and then 3 monthly thereafter). (2)

Antidepressants associated with hyponatraemia

Most antidepressants are associated with hyponatraemia and no antidepressant has been reported not to be associated with hyponatraemia (2).

A retrospective cohort study of the safety and harms of antidepressant drugs in patients aged 65 years and over diagnosed with depression in primary care showed that there was an increased risk of hyponatraemia for all classes of antidepressant in the first 28 days after starting the drugs. The risk of hyponatraemia was significantly associated with use of SSRIs overall, particularly citalopram, escitalopram and fluoxetine, and the risk tended to decrease as dose increased (40).

Another retrospective cohort study also investigated the risk of hyponatraemia secondary to antidepressant use. This analysis included 638,352 individuals, of which 72,509 developed

hyponatraemia. 6,476 of these events happened during treatment with antidepressants. The authors concluded that all antidepressants except mianserin are associated with hyponatremia. The association is strongest with citalopram and lowest with duloxetine, venlafaxine and mirtazapine. However, one limitation was that not all antidepressants (e.g. MAOIs) were evaluated (41).

A third retrospective study, published in 2018, investigated the association between antidepressant use and risk of hospitalisation due to hyponatraemia (42). A total of 14,359 individuals were identified as being admitted to hospital with a main diagnosis of hyponatraemia, of which 4,134 were taking an antidepressant (newly initiated in 1,559 patients). The authors found that there was a strong association between newly initiated treatment with SSRIs or venlafaxine and hospitalisation due to hyponatremia. The association for TCADs and mirtazapine was small to moderate. They also concluded that there was no evidence that ongoing treatment with antidepressants increases the risk for hospitalization due to hyponatremia.

Other sources state that there are very few reported cases of hyponatraemia associated with mirtazapine. There have also been no cases of agomelatine-induced hyponatraemia documented in literature (2, 3).

A summary of the risk of hyponatraemia with antidepressants as follows (2):

Antidepressant	Risk of hyponatraemia	Level of evidence
SSRI	High	Strong
SNRI	High	Strong
TCAD	Moderate	Strong
MAOI	Low	Weak
NaSSA (mirtazapine, mianserin)	Low	Strong
Bupropion	Low	Moderate
Agomelatine	Low	Weak

SNRI = Serotonin–norepinephrine reuptake inhibitor; MAOI = Monoamine oxidase inhibitor; NaSSA = Noradrenergic and specific serotonergic antidepressants

Onset of hyponatraemia

Hyponatraemia normally occurs within 30 days of starting an antidepressant (2, 6), but occasionally it may take many months (43). A case report from 2006 indicates that hyponatraemia occurred 5 months after starting mirtazapine (44). There are also cases of rapid onset hyponatraemia occurring within the first few days of antidepressant therapy (45 – 47). The problem may be transient and improve with time and no treatment but it can also be persistent and recurrent (48).

Treatment of hyponataemia

If hyponatraemia is diagnosed and no other cause can be identified, then the antidepressant should be stopped immediately and plasma sodium levels measured daily until normal levels are achieved (2, 49). Usually sodium levels will normalise within a week or two of discontinuation of the antidepressant (50-52). If sodium levels are below 125mmol/l, the patient should be referred for urgent specialist medical care. Antidepressant withdrawal symptoms should be anticipated, but are unlikely to occur if the hyponatraemia occurs soon after initiation of antidepressant treatment (2, 49). If the antidepressant has a long half-life (e.g. fluoxetine) then the appearance of any withdrawal symptoms may be delayed and the hyponatraemia may take longer to subside.

Tolvaptan is an oral vasopressin receptor antagonist licensed for treatment of hyponatraemia secondary to SIADH. The pivotal studies with tolvaptan (SALT 1 and SALT 2) excluded patients with hyponatraemic conditions associated with the use of medication. Therefore use of tolvaptan to treat antidepressant induced hyponatraemia cannot be recommended (53, 54).

Treatment of depression

Little evidence is available to guide antidepressant selection in a patient with a history of hyponatraemia (55). Once sodium levels have normalised, a replacement antidepressant must be chosen. Generally re-challenge with the same antidepressant is not worthwhile. In one paper, hyponatraemia re-occurred on re-challenge in 18 out of 27 patients who had developed hyponatraemia on initiation of an SSRI (6). Some studies have shown the incidence of hyponatraemia to be about four times higher in patients taking SSRIs compared to other antidepressants (mainly TCADs) but the confidence limits are very wide and the studies were retrospective controlled studies, with small numbers of patients. Therefore patients who have developed hyponatraemia while receiving an SSRI or venlafaxine may benefit from a trial of a TCAD or even a monoamine oxidase inhibitor (MAOI), after considering the adverse effects, risk in overdose and drug interaction profile of individual drugs (4, 9, 56, 57). Mirtazapine may also be considered in patients who have developed hyponatremia secondary to other antidepressants.

There is limited evidence involving 19 elderly patients started on paroxetine or fluoxetine, that sodium levels can return to normal even if the antidepressant is continued (50, 51). Some authors have suggested that hyponatraemia may be controlled by continuing the antidepressant alongside stringent fluid restriction and/or careful use of demeclocycline (5, 50). In a study of 58 patients aged over 65 years started on venlafaxine, 10 developed hyponatraemia. Fluid restriction (800ml/day) successfully raised the plasma sodium to normal range within 2 weeks, after which fluid restriction was relaxed without relapse occurring (58).

If none of these options are appropriate, or the patient still remains hyponatraemic while on antidepressant therapy, electroconvulsive therapy (ECT) may be considered (2). Although ECT can cause SIADH, there are few case reports of this actually occurring – however, ECT may also induce or contribute to a hyponatraemically induced seizure (5, 59).

Summary

- Most antidepressants are associated with hyponatraemia, with the highest risk being with SSRIs.
- If the hyponatraemia is mild (125-134mmol/litre serum sodium) and there is no other cause for the hyponatraemia, discontinue the antidepressant and monitor serum sodium levels daily until they are within normal range or if asymptomatic, consider fluid restriction.
- If the patient has serum sodium below 125mmol/litre, discontinue the antidepressant immediately and treat medically for hyponatraemia.
- After serum sodium levels have normalised, choose another appropriate antidepressant.
- If the patient developed hyponatraemia whilst on an SSRI or venlafaxine, consider changing to a TCAD or a MAOI or mirtazapine. The increased risk of overdose, adverse effects, and drug interactions of these antidepressants must be considered before prescribing. Agomelatine may also be considered. Monitor serum sodium levels weekly initially.
- Consider ECT if none of these options are appropriate, or the patient still remains hyponatraemic while on antidepressant therapy.

Limitations

This review has looked at adult patients only. Special consideration will need to be given to patients with disorders likely to cause electrolyte disturbance. If the antidepressant is being used for other indications such as pain or anxiety, then the substitutions suggested above may not be appropriate.

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Quality Assurance

Prepared by
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Date Prepared
16/05/2019

Checked by
Abigail Scott, East Anglia Medicines Information Service

Date of check
10/06/2019

Search strategy
- BNF online, SPCs, Martindale, NICE, CKS, NHS Evidence.
- Maudsley Prescribing Guidelines 13th Ed, 2018 & Psychotropic Drug Directory 2018
- Embase: HYPONATREMIA/ AND exp ANTIDEPRESSANT AGENTS/ae [ae=Adverse Effects] Limited to years 2017-2019
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