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

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).

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 (2-31).

Answer
Risk factors and monitoring
Antidepressant-induced hyponatraemia occurs particularly frequently in elderly patients, and is predominantly recognised in female elderly patients (30-35). One study has stated a prevalence of 9% in patients over 60 years old (36). 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 (33, 37).

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 or pregnancy (38, 39). Some psychiatric diseases may also be associated with hyponatraemia, such as psychosis (36).

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). (30)

Antidepressants associated with hyponatraemia
Most antidepressants are associated with hyponatraemia and no antidepressant has been reported not to be associated with hyponatraemia (30).

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 published in 2016 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).

Other sources also state that mirtazapine appears to have the lowest risk based on current evidence and case reports, although case reports have been described. There have also been no cases of agomelatine induced hyponatraemia documented in literature (30, 31).

**Onset of hyponatraemia**

Hyponatraemia normally occurs within 14 days of starting an antidepressant (30, 34), but occasionally it may take many months (42). A case report from 2006 indicates that hyponatraemia occurred 5 months after starting mirtazapine (43). The problem may be transient and improve with time and no treatment but it can also be persistent and recurrent (44).

**Treatment of hyponatremia**

If hyponatremia 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 (30, 45). Usually sodium levels will normalise within a week or two of discontinuation of the antidepressant (46, 47, 48). 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 hyponatremia occurs soon after initiation of antidepressant treatment (30, 45). If the antidepressant has a long half-life (e.g. fluoxetine) then the appearance of any withdrawal symptoms may be delayed and the hyponatremia 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 hyponatremic conditions associated with the use of medication. Therefore use of tolvaptan to treat antidepressant induced hyponatraemia cannot be recommended (49, 50).

**Treatment of depression**

Little evidence is available to guide antidepressant selection in a patient with a history of hyponatremia (51). Once sodium levels have normalised, a replacement antidepressant must be chosen. Generally re-challenge with the same antidepressant is not worthwhile. In one paper, hyponatremia re-occurred on re-challenge in 18 out of 27 patients who had developed hyponatremia on initiation of an SSRI (34). Some studies have shown the incidence of hyponatremia 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 hyponatremia 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 (32, 37, 52, 53). Due to its low incidence mirtazapine may also be considered in patients who have developed hyponatremia secondary to other antidepressants. A case report from 2007 discusses a patient who had hyponatremia with citalopram then duloxetine but not with nortriptyline (54). A patient who developed hyponatremia with duloxetine was switched to moclobemide and no recurrence of the hyponatremia occurred (55).

There is limited evidence involving 19 elderly patients started on paroxetine or fluoxetine, that sodium levels can return to normal even if the antidepressant it continued (46, 47). Some authors have suggested that hyponatremia may be controlled by continuing the antidepressant alongside stringent fluid restriction and/or careful use of demeclocycline or fludrocortisone (33, 46, 56). In a study of 58 patients aged over 65 years started on venlafaxine, 10 developed hyponatremia. Fluid restriction (800ml/day) successfully raised the plasma sodium to normal range within 2 weeks, after which fluid restriction was relaxed without relapse occurring (57).
If none of these options are appropriate, or the patient still remains hyponatraemic while on antidepressant therapy, electroconvulsive therapy (ECT) may be considered (30). 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 (33, 58).

**Summary**
- Most antidepressants are associated with hyponatraemia, with the highest risk being with SSRIs and lowest risk being with mirtazapine.
- 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 an MAOI. The increased risk of overdose, adverse effects, and drug interactions of these antidepressants must be considered before prescribing. Mirtazapine may also be considered due to low incidence of hyponatraemia. 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.

**References**
All SPCs accessed via [http://emc.medicines.org.uk](http://emc.medicines.org.uk) and [http://www.mhra.gov.uk/spc-pil/](http://www.mhra.gov.uk/spc-pil/) on 19/04/17

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Search strategy
♦ BNF online, SPCs, Martindale, NICE, CKS, NHS Evidence, MHRA Drug Analysis Prints.
♦ Embase: HYPONATREMIA/ AND exp ANTIDEPRESSANT AGENTS/ae [ae=Adverse Effects] Limited to years 2015-2017
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