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Antipsychotic-associated hyponatraemia

186 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Antipsychotic-associated hyponatraemia Hyponatraemia can occur in the context of: ■ ■Water intoxication, where water consumption exceeds the maximal renal clearance capacity. Serum and urine osmolality are low. Cross-sectional studies of chronically ill, hospitalised, psychiatric patients have found the prevalence of water intoxication to be 6–17%.1,2 A longitudinal study found that 10% of severely ill patients with a diagnosis of schizophrenia had episodic hyponatraemia secondary to fluid overload.3 The primary aetiology is poorly understood. It may be driven, at least in part, by an extreme compensatory response to the anticholinergic adverse effects of some antipsychotic drugs.4 An alternative theory is that postsynaptic dopamine receptor antagonism results in receptor supersensitivity, increased presynaptic dopamine release, and elevated dopamine in the hypothalamus, driving thirst and polydipsia.5 The fact that many reported cases occur in patients with long illness histories and treatment with antipsychotics with high D2 receptor affinity (and that clozapine can improve polydipsia independent of improvement in psychosis) appears to support this suggestion.5 ■ ■Drug-induced syndrome of inappropriate antidiuretic hormone (SIADH), where the kidney retains an excessive quantity of solute-free water. Serum osmolality is low and urine osmolality relatively high. The prevalence of SIADH may be as high as 11% in acutely ill psychiatric patients.6 Risk factors for antidepressant-induced SIADH (increasing age, female gender, medical comorbidity and polypharmacy) seem to be less relevant to the population of patients treated with antipsychotic drugs.7 SIADH usually develops in the first few weeks of treatment with the offending drug8 but can appear at a later time.8 Case reports/series7,9–30 implicate various phenothiazines, haloperidol, pimozide, risperidone, paliperidone, quetiapine, -olanzapine, aripiprazole, cariprazine and clozapine. Systematic review31 and case–control studies32,33 suggest a clear increase in risk of hyponatraemia with antipsychotics. One large Swedish study found a stronger association for first- generation antipsychotics than for SGAs.33 Analysis of pharmacovigilance reports appears to support this.34 Another review35 confirmed that drug-induced hyponatraemia is associated with concentrated urine and suggested that antipsychotic treatment was five times more likely than water intoxication to be the cause of hyponatraemia. Overall prevalence of antipsychotic-induced hyponatraemia has been estimated at

0.004%36 and 26.1%.37 It is assumed that the true figure is somewhere between these two widely different extremes. Desmopressin, when used for clozapine-induced enuresis, can also result in hyponatraemia.38 Other drugs, including antidepressants and anticonvulsants (especially carbamazepine),39 valbenazine40 and many drugs for physical health conditions (diuretics, angiotensin- converting-enzyme [ACE] inhibitors, angiotensin II receptor blockers, proton pump inhibitors), have also been implicated.41 The risk of hyponatraemia is probably additive with concomitant prescriptions.42–44 ■ ■Severe hyperlipidaemia and/or hyperglycaemia lead to secondary increases in plasma volume and ‘pseudohyponatraemia’.4 Both are more common in people treated with antipsychotic drugs than in the general population and should be excluded as causes.

Schizophrenia and related psychoses CHAPTER 1 Mild to moderate hyponatraemia presents as confusion, nausea, headache and lethargy. As the plasma sodium falls, these symptoms become increasingly severe, and seizures and coma can develop. Monitoring of plasma sodium is desirable for all those receiving antipsychotics, particularly if several risk factors for hyponatraemia are present. A risk-scoring algorithm has been proposed.45 Signs of confusion or lethargy should provoke thorough diagnostic analysis, including plasma sodium determination and urine osmolality (Table 1.42). Tolvaptan,46 a so-called vaptan (non-peptide arginine-vasopressin antagonist, also known as aquaretics because they induce a highly hypotonic diuresis),47 shows promise in the treatment of hyponatraemia of various aetiologies, including that caused by drug-related SIADH and psychogenic polydipsia.48 Table 1.42 Treatment of hyponatraemia associated with antipsychotic treatment.4,6 Cause of hyponatraemia Antipsychotic drugs implicated Treatment Water intoxication (serum and urine osmolality low) Only very speculative evidence to support drugs as a cause. ■ ■Fluid restriction with careful monitoring of serum sodium, particularly diurnal variation (Na drops as the day progresses). Refer urgently to specialist medical care if Na <125 mmol/L. Note that over-rapid correction of sodium levels can cause irreversible osmotic demyelination syndrome.49 ■ ■Consider treatment with clozapine, which has been shown to increase plasma osmolality into the normal range and increase urine osmolality.50,51 These effects are consistent with reduced fluid intake but are not clearly related to improvements in mental state.52 ■ ■There are both7 positive and negative reports for olanzapine53 and risperidone54 and one positive case report for quetiapine.55 Compared with clozapine, the evidence base is weak. ■ ■There is no evidence that either reducing or increasing the dose of an antipsychotic results in improvements in serum sodium in water-intoxicated patients56 although reducing the number and dose of antipsychotics prescribed may decrease dopamine receptor supersensitivity and drug adverse effects5 ■ ■Demeclocyline may be used57,58 and it is included in some practice guidelines for psychogenic polydipsia.59 However, it exerts its effect by interfering with alcohol dehydrogenase and increasing water excretion, which is already at capacity in these patients. Any rationale for its use in the absence of SIADH is therefore debatable (and some cases in the literature may have been complicated by undiagnosed SIADH).60 A single small RCT showed no benefit.61 ■ ■Many other drugs have been used (naloxone, enalapril, clonidine, naltrexone, acetazolamide, captopril, propranolol, losartan, carbamazepine, fluoxetine, bupropion, trazodone, mianserin) but data are limited.62 Successful use of the carbonic anhydrase inhibitor acetazolamide has also been reported.63,64 Core part of illness in a minority of patients (e.g. psychotic polydipsia) (Continued)

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