LETTERS TO THE EDITOR

Medical restrictions to driving: the awareness of patients and doctors

EDITOR—Kelly *et al*'s study of knowledge of medical restrictions on driving reveals worrying deficits in doctors' knowledge.[1] This accords with results of previous studies[2] concerning knowledge of psychiatrists, but contrasts with a comparable study of knowledge[3] after dissemination of the Driving Vehicle Licence Authority's (DVLA) "at a glance guidelines".[4] For example, 93% of the sample of 89 psychiatrists were aware of DVLA regulations on late dementia, suggesting that ignorance can be countered by educational campaigns. However, even this study revealed inadequate knowledge of General Medical Council (GMC) guidelines on confidentiality, in which the trend was to underestimate the need for doctors to break confidentiality and to inform the medical adviser at the DVLA. For example, only 32% of respondents were aware that the DVLA should be informed when a patient continues to drive against medical advice. Information concerning the breaking of confidentiality is not explicit in the "at a glance guidelines", but is described with clarity by the GMC in *Duties of a doctor*.[5]

It seems likely that legal precedent will establish medical negligence when doctors fail to provide appropriate advice on driving regulations. The study of Morgan showed that junior trainees have least knowledge of guidelines,[3] and it would seem appropriate to make driving regulations a clearly defined topic for examination in Membership curricula. However, other doctors may require the threat of litigation to focus their minds.

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1 Kelly R, Warke T, Steele I. Medical restrictions to driving: the awareness of patients and doctors. *Postgrad Med J* 1999;**75**:537–9.
2 Thompson P, Nelson D. DVLA regulations concerning driving and psychiatric disorders. *Psychiatr Bull* 1996;**20**:323–5.
3 Morgan JF. DVLA and GMC guidelines on "fitness to drive" and psychiatric disorders: knowledge following an educational campaign. *Med Sci Law* 1998;**38**:28–33.
4 Medical Advisory Branch of the DVLA. *At a glance guide to the current medical standards of fitness to drive*. Swansea: DVLA, 1993.
5 General Medical Council. *Duties of a doctor (confidentiality)*. London: GMC, 1995: 11–12.

The authors respond:

The paper of J F Morgan[1] shows some improvement in psychiatrists' knowledge of driving restrictions after dissemination of the DVLA's "at a glance guidelines"[2] compared with the findings of Thompson and Nelson.[3] Even with these improvements the majority of respondents were incorrect for some of the clinical situations questioned (for example heroin, methadone, and cannabis use/dependence). Both studies used postal questionnaires and it may be that there was an increased awareness of where information could be obtained from, rather than an increase in working knowledge. Not knowing where to obtain the necessary information was apparent in our own study.[4] Our experience has been that attempts to increase the ability of doctors to consider fitness to drive has been difficult. We recently used an educational programme incorporating slide presentations and the display of relevant posters on the wards to try and increase awareness of driving restrictions. This produced only small improvements in the ability of doctors to record in the medical notes that they had considered a patient's driving status and had advised them appropriately.[5]

We would agree with Dr Morgan that making driving regulations a specific topic for examination in Membership curricula may increase doctors' awareness. However, undergraduate education should be the main priority. That way all doctors will learn to ask about driving as part of the routine social history and will hopefully, as a result, consider whether any of the patient's medical conditions impact on their fitness to drive.

1 Morgan JF. DVLA and GMC guidelines on "fitness to drive" and psychiatric disorders: knowledge following an educational campaign. *Med Sci Law* 1998;**38**:28–33.
2 Medical Advisory Branch of the DVLA. *At a glance guide to the current medical standards of fitness to drive*. Swansea: DVLA, 1993.
3 Thompson P, Nelson D. DVLA regulations concerning driving and psychiatric disorders. *Psychiatr Bull* 1996;**20**:323–5.
4 Kelly R, Warke T, Steele I. Medical restrictions to driving: the awareness of patients and doctors. *Postgrad Med J* 1999;**75**:537–9.
5 Kelly R, Warke T, Steele IC. Documentation of driving in case notes by medical staff. *Age Ageing* 1999;**28**(suppl 2):47.

Fish odour syndrome

EDITOR—We read with interest the excellent review article on fish odour syndrome (trimethylaminuria) by Rehman.[1] However the author does not address the clinical relevance of trimethylaminuria (TMA-uria) well beyond the intermittent unpleasant body odour. TMA-uria is caused by the deficiency of the flavin-containing monooxygenase isoform 3 (FMO3).[2 3] The *FMO3* gene has been described, and disease causing mutations have been reported.[2 3] In addition to TMA this enzyme is required for detoxification of many substances including endogenous amines, tyramine, nicotine, and drugs (for example, tricyclic antidepressants, ranitidine).[4] Zschocke *et al* have followed up patients with mild TMA-uria, and have examined the *FMO3* gene in them.[5] The molecular analyses revealed compound heterozygosity for mis-sense mutations on one chromosome and a variant allele with two amino acid polymorphisms (E158K, E308G) on the other chromosome. E158K (allele frequency 48% and 43% in German (n=230) and Turkish (n=68) control chromosomes, respectively) has been reported to reduce enzyme activity in an in vitro assay, whereas E308G, which is apparently always linked to E158K, has been reported without functional data. The variant allele (E158K, E308G) is very common in the white population, with reported frequencies of 20% and 6% in German and Turkish controls respectively.[5] Studies have shown that the variant allele is associated with markedly reduced FMO3 enzyme activity in vivo. Individuals homozygous for the wildtype sequence or compound heterozygous for wildtype/E158K showed normal TMAO (trimethylamine N-oxide)/total ratios in the same range as under physiological conditions (>94%). Individuals with mild TMA-uria showed very low TMAO/total ratios of about 30%. Homozygosity for (E158K, E308G), as found in 4% of controls, resulted in decreased TMA oxidation capacity (<50%), also indicative of mild TMA-uria.[5]

Thus FMO3 deficiency is not merely a rare recessive disorder but rather a spectrum of phenotypes of transient or mild malodour depending on environmental exposures. In view of its other physiological functions mild FMO3 deficiency may lead to an abnormal metabolism of drugs, hypertension, or increased cardiovascular risk. Two adults with mild TMA-uria (one homozygous for (E158K, E308G), one compound heterozygous for a severe mutation and the variant allele (E158K, E308G) presented with hypertension.[5] Population studies are required to analyse the spectrum of molecular variation at the *FMO3* locus, and to evaluate the clinical relevance of mild, normally unrecognised FMO3 deficiency.

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1 Rehman HU. Fish odour syndrome. *Postgrad Med J* 1999;**75**:451–2.
2 Dolphin CT, Janmohamed A, Smith RL, *et al*. Mis-sense mutation in flavin-containing monooxygenase 3 gene, FMO3, underlies fish-odour syndrome. *Nat Genet* 1997;**17**:491–4.
3 Treacy EP, Akerman BR, Chow LML, *et al*. Mutations of the flavin-containing monooxygenase gene (FMO3) cause trimethylaminuria, a defect in detoxication. *Hum Mol Genet* 1998;7:839–45.
4 Cashman J. Structural and catalytic properties of the mammalian flavin-containing monooxygenase. *Chem Res Toxicol* 1995;**8**:166–81.
5 Zschocke J, Kohlmueller D, Quak E, *et al*. Mild trimethylaminuria caused by common variants in FMO3 gene. *Lancet* 1999;**354**:834–5.

The author responds:

I agree with Kashyap and Kashyap that TMA is required for detoxification of many substances including the ones mentioned by them in addition to TMA, amphetamine, metamphetamine,[1] clozapine,[2] chlorpromazine, and methimazole. The FMO gene family has been localised to chromosome 1q and various mutations have been described to cause the metabolic defect. Individuals with these *FMO3* gene mutations may have defective metabolic activity for many clinically used drugs. The human flavin-containing mono-oxygenase (FMO) gene family comprises at least five distinct members (*FMO1* to *FMO5*) that code for enzymes responsible for the oxidation of a wide variety of soft nucleophilic substrates, including drugs and environmental pollutants.

Apart from the two adults with mild TMA-uria and hypertension described by Zschocke *et al*,[3] I am not aware of any other related literature either to this particular

association or with other cardiovascular risk factors. It could prove to be a chance association but I agree with Kashyap and Kashyap that population studies are required to evaluate the clinical of mild, unrecognised FMO3 deficiency.

1 Cashman JR, Xiong YN, Xu L, *et al.* N-oxygenation of amphetamine and methamphetamine by human flavin-containing monooxygenase (form 3): role in bioactivation and detoxification. *J Pharmacol Exp Ther* 1999;**288**:1251–60.
2 Fang J, Coutts RT, McKenna KF, *et al.* Elucidation of individual cytochrome P450 enzymes involved in the metabolism of clozapine. *Naunyn-Schmiedebergs Arch Pharmacol* 1998; **358**:592–9.
3 Zschocke J, Kohlmueller D, Quak E, *et al.* Mild trimethylaminuria caused by common variants in FMO3 gene. *Lancet* 1999;**354**:834–5.

Drug induced syndrome of inappropriate antidiuretic hormone secretion

EDITOR—We read with interest the excellent adverse drug reaction report by Belton and Thomas.[1] They state "Treatment of severe or persistent hyponatremia is controversial" and highlight the danger of central pontine myelinolysis due to sodium infusion, particularly in patients with chronic hyponatraemia. In the learning points they mention "Sodium infusion is controversial and should only be considered in severe cases".

We do not agree. Earlier it has been suggested that much of the brain damage associated with chronic hyponatraemia may be a consequence of improper treatment rather than hyponatraemic encephalopathy.[2] In general, studies of patients suffering from chronic hyponatraemia lack information regarding whether the patients were symptomatic.[3]

Recent studies have demonstrated that the major criterion for use of intravenous sodium chloride treatment in patients with acute symptomatic hyponatraemia is the presence of central nervous system symptoms, regardless of the concentration of plasma sodium.[4] It has been suggested that treatment with sodium chloride might be appropriate in patients with chronic symptomatic hyponatraemia.[4] When pondering treatment options in patients with hyponatraemia, the pivotal issue is to determine if the patient displays encephalopathic symptoms of hyponatraemia. Ayus and Arieff have reported 53 postmenopausal women with chronic hyponatraemia who were all encephalopathic.[4] Seventeen of these patients were seen before evidence of hypoxia or respiratory failure supervened. The remainder had already become hypoxic and required intubation and ventilatory assistance. The 17 patients without respiratory failure and 22 of the 36 patients with hypoxia were treated with saline or hypertonic saline to increase their plasma sodium concentration by no more than 0.8 mmol/l per hour but not greater than an end point of 133 mmol/l. The average absolute change in plasma sodium concentration was 22 and 30 mmol/l in patients with and without hypoxia respectively. Patients with seizures were given sufficient hypertonic sodium chloride to increase serum sodium concentration by 8 mmol/l during the first hour. The remaining 14 hypoxic patients who were treated conservatively with water deprivation showed an average increase of plasma concentration of 3 mmol/l during the entire course of their treatment. All patients without hypoxia recovered completely. None of the patients available for magnetic resonance imaging one year later showed cerebral abnormalities. Six of the 11 patients treated with saline who had imaging studies performed before treatment showed evidence of cerebral oedema.

Of the saline treated patients who were hypoxic, two recovered completely, six recovered partially, and the remainder either developed irreversible disabling brain damage or died. In contrast, each hypoxic patient treated with simple water deprivation either died or experienced permanently disabling brain damage. None of the 18 patients treated with saline examined with imaging techniques after treatment showed demyelination. This finding suggests that hypertonic saline, if used appropriately, does not impose that risk.

The presence of cerebral oedema on cerebral imaging before treatment in six of 11 patients treated with saline implies that cerebral adaptation to hypotonicity does not always occur, and further strengthens the justification for using hypertonic saline solution. The outcome was universally tragic in patients treated with simple water deprivation and indicates that this treatment should be abandoned in patients with symptomatic hyponatraemia. Thus, central nervous system symptoms would appear to be an indicator of the need for initiation of treatment with hypertonic sodium chloride in chronic hyponatraemia.[5]

Elderly patients with chronic hyponatraemia have a very high mortality rate: among 295 such patients, the mortality rate was 25%. Of these, neither the percentage of those with encephalopathy or who died of hyponatraemia can be ascertained, but at least part of this total appears to be associated with reluctance to treat chronic hyponatraemic patients with intravenous sodium chloride.[4]

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1 Belton K, Thomas SHL. Drug-induced syndrome of inappropriate antidiuretic hormone secretion. *Postgrad Med J* 1999;**75**:509–10.
2 Ellis SJ. Severe hyponatremia: complications and treatment. *Q J Med* 1995;**88**:905–9.
3 Hirshberg B, Ben-Yehuda A. The syndrome of inappropriate antidiuretic hormone secretion in the elderly. *Am J Med* 1997;**103**: 270–3.
4 Ayus JC, Arrief AI. Chronic hyponatremic encephalopathy in postmenopausal women. Association of therapies with morbidity and mortality. *JAMA* 1999;**281**:2299–304.
5 Knochel JP. Hypoxia is the cause of brain damage in hyponatremia (editorial). *JAMA* 1999; **281**:2342–3.

The authors respond:

We are grateful to Kashyap and Kashyap for their remarks on our paper and for allowing us to comment on the report of Ayus and Arieff ,which was published after our adverse drug reaction report was accepted for publication.[1]

This study compared outcomes in postmenopausal hyponatraemic women treated in three different ways. Hyponatraemia was of mixed aetiology and only five of the 53 patients had inappropriate antidiuretic hormone secretion. Other causes were polydipsia (21), thiazide diuretics (17), and being postoperative (15). Group 1 (17 patients) were treated with intravenous sodium chloride before the onset of respiratory insufficiency. Group 2 (n = 22) received intravenous sodium chloride after the onset of respiratory insufficiency and group 3 (14 patients) were treated with fluid restriction only. All patients had neurological features. Outcome in group 1 was good for the nine patients successfully followed up but eight patients were lost to follow up. For group 2, two patients recovered completely, six recovered partially and were able to live independently, but 14 either died or developed neurological impairment severe enough to require institutionalisation. For group 3 all 14 patients either died or experienced permanent neurological damage and 10 died within 24 hours.

As Drs A and S Kashyap suggest, cerebral oedema was commonly present on cranial imaging before saline infusion was given, and no evidence of central pontine myelinolysis was found in the 18 patients who were evaluated at least four months after recovery.

At face value these results do suggest a very poor outcome for patients treated with fluid restriction alone. However, outcome was also poor in group 2 with only two of 22 patients recovering completely in spite of saline infusion. Furthermore, it is important to appreciate that this was not a randomised comparison. Group 3 were preselected as patients who had not responded to conservative treatment and were referred to a specialist team by the general physician. We do not know how many patients who would meet entry criteria for group 3 actually recovered with simple fluid replacement and as a result were not referred for more intensive treatment. It is also important to note that there was no relationship between the rate of correction of plasma sodium and the outcome. Furthermore, as Ayus and Arieff point out, over-rapid correction of plasma sodium also contributes to brain injury.

We accept that the data of Ayus and Arieff indicate that in severe hyponatraemia associated with neurological symptoms the benefits of sodium infusion at an appropriate rate are likely to outweigh the potential risks. However, as we suggested in our original paper, sodium infusion should only be advocated for patients with severe symptoms associated with hyponatraemia. All patients with neurological features would fall into this category. Drs A and S Kashyap's implication that sodium infusion should be considered in non-severe cases in not something that we would agree with. Under these circumstances the risks of sodium infusion are likely to outweigh benefits in this group of patients who often do well with conservative treatment.[2]

1 Ayus JC, Arrief AI. Chronic hyponatremic encephalopathy in postmenopausal women. Association of therapies with morbidity and mortality. *JAMA* 1999;**281**:2299–304.
2 Knochel JP. Hypoxia is the cause of brain damage in hyponatremia (editorial). *JAMA* 1999; **291**:2342–3.

DIARY

3rd European Conference on Psychosomatic Research

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Details: Falk Foundation eV, Congress Division, Leinenweberstr 5, PO Box 6529, D-79041 Freiburg, Germany (tel: +49 (0) 761 130340, fax: +49 (0) 761 1303459, e-mail: symposia@falkfoundation.de).

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