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Olanzapine-induced thrombocytopenia in association with idiopathic thrombocytopenic purpura

Sir: Thrombocytopenia is one of the common side-effects of pharmacological therapy, but it is rarely induced by psychotropic drugs. We would like to draw attention to a case where the conditions of both an idiopathic and a neuroleptic-induced thrombocytopenia occurred.

A 30-year-old woman had a four-year history of paranoid schizophrenia. She was hospitalised because of a grand-mal seizure and persistent delusions while receiving clozapine. She presented with psychomotor retardation, affective blunting and delusions of reference. Routine examinations were unremarkable, except a platelet count of 137/nl. Medical records on previous hospitalisations elsewhere report low platelet counts of 107/nl and 117/nl prior to receiving medication; and she had a history of petechia. However, 11 years ago platelets had been within normal range. She made a good recovery on benperidol. To meet psychomotor side-effects, we then prescribed olanzapine (20 mg). While checking laboratory values regularly we discovered a decrease in platelets to 10/nl on the 17th day of treatment with olanzapine. This decrease had occurred in three days. The patient was transferred to a general medical ward. Platelets returned to normal after discontinuation of olanzapine and administration of human gamma globulins and prednisolone. The patient was discharged on 300 mg sulpiride and a maintenance dose of prednisolone.

We assumed that olanzapine had worsened a pre-existing idiopathic thrombocytopenic purpura (ITP) on an autoimmune

basis. To confirm this diagnosis, we repeatedly attempted to document the presence of autoantibodies directed against the complex formed by the drug binding to the thrombocyte membrane. This is possible in about 40% of all presumed cases of drug-induced thrombocytopenia (Greinacher *et al*, 1994). Since we failed, the attribution of thrombocytopenia to autoimmune drug-dependent destruction was not proved definitively, and relies on the time-dependence of the abnormal blood count on the administration of olanzapine. Thrombocytopenia usually occurs 5–15 days after starting a drug therapy (Handin, 1998).

Previous reports support the hypothesis that psychiatric medication can worsen the condition of a pre-existing ITP (König *et al*, 1995) or induce an immune-mediated thrombocytopenia (Balon *et al*, 1987; Durst *et al*, 1993; Mahmood *et al*, 1996). Therefore, this case raises the issue of a coincidence or a possible interdependence between an idiopathic tendency to thrombocytopenia as in ITP, and drug effects of olanzapine.

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Platelet dysfunction association with clozapine therapy. *Southern Medical Journal*, **86**, 1170–1172.

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Heparin-associated thrombocytopenia: isolation of the antibody and characterization of a multimolecular PF4-heparin complex as the major antigen. *Thrombosis and Haemostasis*, **71**, 247–251.

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Salinophagia in anorexia nervosa

Sir: We report a case of pathological salt ingestion as a feature of anorexia nervosa.

The patient is a single woman in her thirties with a 15-year history of anorexia nervosa (World Health Organization, 1992), of sufficient severity to necessitate in-patient treatment on a specialist unit. While engaged in our standardised treatment programme, combining weight gain with psychotherapy, she admitted to intermittent pathological ingestion of table salt over the preceding two years in the form of up to 20 packets (approximately 80 g) of salt per day, which she would consume with bread or potatoes. Her impulses towards salt ingestion existed in negative reciprocity with her body mass index, and came to light as her weight reached the mean matched population weight. Despite this history her electrolyte levels were normal, with adequate renal compensation of hypernatraemia.

The phenomenology of her behaviour appeared to be a form of deliberate self-harm, ego-syntonic but self-punitive in nature. In particular, her salt ingestion lacked salient features of an obsessive-compulsive disorder or pica. Notably, another patient on the unit appeared to adopt similar behaviour in imitation, which reflects the tendency for some symptoms of anorexia nervosa to run in trends.

We addressed her salt ingestion as a form of learned maladaptive behaviour, combining both cognitive-behavioural and psychodynamic techniques, and the patient remains in treatment.

Compulsive eating of unusual substances has been described in a variety of psychiatric disorders, including schizophrenia, learning disability (Jawed *et al*, 1993) and anorexia nervosa (McLoughlin & Hassanyeh, 1990). The latter description linked pagophagia (the compulsive eating of ice) with iron and zinc deficiency. However, our patient's behaviour was not compulsive in nature and, to our knowledge, is the first published description of pathological salt ingestion, or 'salinophagia', as a symptom of anorexia nervosa. Although rare, we feel it should be added to the list of maladaptive behaviours associated with anorexia nervosa and bulimia nervosa. In addition, physicians should consider salinophagia among their differential diagnoses when faced with unexplained compensated or uncompensated hypernatraemia.

Jawed, S. H., Krishnan, V. H., Prasher, V. P., et al (1993)
Worsening pica as a symptom of depressive illness in a person with severe mental handicap. *British Journal of Psychiatry*, **162**, 835–837.

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Fluoxetine and graded exercise in chronic fatigue syndrome

Sir: First, may we congratulate Wearden *et al* (1998) on completing such an important and technically difficult study of chronic fatigue syndrome (CFS). We wondered whether the authors were able to give further data which might explain the relatively modest results with fluoxetine and which are also relevant to the commentary on this study (Deale *et al*, 1998).

Many patients in such studies may have long illness durations and in this case the median duration of fatigue symptoms for all patients was over two years. It was unclear how long the duration of mood symptoms was, bearing in mind that major depression and dysthymia were important components of the psychiatric comorbidity in 46% of patients.

These issues are important as, in our experience at a multi-disciplinary CFS clinic, most patients will have been offered a range of antidepressants before referral to tertiary care and it is possible that these mood symptoms may have become refractory to treatment (Scott, 1988). This might partly explain the very modest response to fluoxetine seen and is an alternative explanation to that suggested by Deale *et al* (1998). The neuroendocrine hypothesis of CFS is indeed of great interest but not all of these findings have been consistently replicated (Yatham *et al*, 1995), which may point to heterogeneity in this patient group.

Deale, A., Chalder, T. & Wessely, S. (1998)

Commentary on: Randomised, double-blind, placebo-controlled trial of fluoxetine and graded exercise for chronic fatigue syndrome. *British Journal of Psychiatry*, **172**, 491–492.

Scott, J. (1988) Chronic depression. *British Journal of Psychiatry*, **153**, 287–297.

Wearden, A. J., Morriss, R. K., Mullis, R., et al (1998) Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *British Journal of Psychiatry*, **172**, 485–490.

Yatham, L. N., Morehouse, R. L., Chisholm, B. T., et al (1995) Neuroendocrine assessment of serotonin (5-HT) function in chronic fatigue syndrome. *Canadian Journal of Psychiatry*, **40**, 93–96.

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Author's reply: Drs Lynch and Fraser raise an important question concerning the duration of symptoms of depression in our trial of fluoxetine in patients with CFS (Wearden *et al*, 1998) and in other CFS trials. Unfortunately, we do not have data on the duration of depressive symptoms, although symptoms of depressive or anxiety disorder preceded symptoms of fatigue in only nine (7%) of the 136 patients with CFS. In our paper we showed that patients with depressive disorders at baseline randomly allocated to fluoxetine or placebo tended to improve over the six-month period, which does not support the assertion that there was a substantial proportion of patients in our sample with difficult-to-treat chronic depression.

Possibly one reason why fluoxetine was shown overall to have a modest effect over six months is because there was a differential effect of fluoxetine on CFS patients with or without any depressive diagnosis at baseline. The 26 patients with any DSM-III-R depressive disorder randomly allocated to fluoxetine showed a mean improvement between baseline and six months of 3.2 (95% CI 1.6–4.8) on the Hospital Anxiety and Depression (HAD) scale depression score and 3.5 mlO₂/kg per min (95% CI 1.3–5.7) on the Functional Work Capacity (FWC) measure. The 20 patients with any DSM-III-R depressive disorder randomly allocated to placebo showed a mean improvement over the same time scale on the HAD depression scale of 1.7 (95% CI 0–3.3) and FWC measure of 0.3 mlO₂/kg per min (95% CI –1.9–2.4). The 42 patients without DSM-III-R depressive disorder randomly allocated to fluoxetine showed a mean improvement of 0.9 (95% CI –0.1–1.9) on the HAD depression scale and 0.2 mlO₂/kg per min (95% CI –1.1–1.5) on the FWC measure. The 48 patients without DSM-III-R depressive disorder randomly allocated to placebo showed a mean improvement of 0.9 (95% CI 0.04–1.9) on the HAD depression scale and 1.4 mlO₂/kg

per min (95% CI –0.1–3.0) on the FWC measure. Although this is a *post-hoc* analysis which must be treated with great caution, it suggests that fluoxetine has a modest effect on depression and functional work capacity in depressed CFS patients only. Fluoxetine provides no benefit over placebo in the treatment of CFS patients with no depression.

As we suggested in the discussion section of our paper, the overall effect of fluoxetine on depression in the whole sample is dependent on the proportion of patients in the sample with a diagnosis of depression.

Wearden A. J., Morriss, R. K., Mullis, R., et al (1998) Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *British Journal of Psychiatry*, **172**, 485–490.

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Chromosome 22q11 deletions and aggressive behaviour

Sir: We thank Lachman & Papolos (1998) for their interest in our paper on the prevalence of velo-cardio-facial syndrome (VCFS) in a population of subjects with idiopathic learning disability (Murphy *et al*, 1998) and agree that aggressive behaviour was a feature of the clinical presentation of both patients reported. Lachman & Papolos (1998) suggest that, as the low-activity catechol-O-methyltransferase (COMT) allele is associated with violence in schizophrenia, hemizyosity for this allele may be the common denominator that leads to aggression in individuals with VCFS and schizophrenia.

To test this hypothesis, we genotyped the COMT codon 158 polymorphism in both individuals with VCFS and schizophrenia reported in our study (Murphy *et al*, 1998). Both individuals were found to be hemizygous for the low-activity COMT allele. Consequently, our results lend support to the hypothesis proposed by Lachman & Papolos (1998) that hemizyosity for the low-activity COMT allele may be a determinant for aggressive behaviour in individuals with schizophrenia with or without VCFS.

Lachman, H. M. & Papolos, D. F. (1998) Chromosome 22q11 deletions and aggressive behaviour (letter). *British Journal of Psychiatry*, **172**, 540.

Murphy, K. C., Jones, R. G., Griffiths, E., et al (1998) Chromosome 22q11 deletions. An under-recognised