https://doi.org/10.1192/S0007125000151499 Published online by Cambridge University Press

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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.

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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 mlO_2/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 mlO_2/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 mlO_2/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 mlO_2/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, hemizygosity 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 hemizygosity 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