

Dr Aitchison explained that, for example, the new approach to rating scales may differentiate psychopharmacological effects more finely than current methods. Indeed, the approach facilitated the first clinical study to show a quantifiable difference in efficacy between an SSRI and a tricyclic antidepressant.

GENDEP (see <http://gendep.iop.kcl.ac.uk/results.php>), an 18-centre Integrated Project funded by the European Commission (2004-2008), aimed to use pharmacogenomics to inform clinicians' decisions about antidepressant prescribing. GENDEP also aimed to enhance our understanding of the molecular mechanisms that underlie the effects of antidepressants. For a review in this field, see Gupta *et al.*, in press.<sup>1</sup> The project encompassed several elements including rodent studies, integrative analysis (ultimately aiming to identify predictive biomarkers) and ethical, legal, and social policy issue (ELSI) research. In this presentation, Dr Aitchison focused on how data analysis from the clinical pharmacogenomics study points to novel ways of measuring anxiety in depression, and how this changes over time.

Dr Aitchison noted that clinicians and researchers use several clinical rating scales to measure symptoms of depression and anxiety. However, numerous factors potentially influence results from these rating scales, including differences between self-reporting and clinician-rating, and differential weighting of individual symptoms in summed scores. Therefore, GENDEP took a novel approach, including item response theory (IRT) and factor analysis, integrating data from three different rating scales for depression administered at multiple time points, to generate dimensions representing different symptom

# Improving the measurement of anxiety and depression

**Current rating scales for depression differ in internal consistency, their applicability to outpatients and the aspects of the condition that they capture. A new approach – suggested by Dr Katherine Aitchison, Senior Lecturer at the Institute of Psychiatry at King's College London, on behalf of the GENDEP Consortium – appears more rigorous and informative than traditional rating scales. She was speaking at the Latest Advances in Psychiatry Symposium, held in London, in April 2008. Mark Greener reports.**

domains, including mood and neurovegetative (somatic) symptoms. This approach was shown to be much more powerful for the detection of change in symptomatology.

The clinical pharmacogenomics component of GENDEP comprised nine centres across Europe, who recruited approximately 900 depressed patients over a period of about four years, and followed them up for six months. Escitalopram or nortriptyline was offered to subjects, in a potential crossover design. The three measures of depression were the 17-item Hamilton Depression Rating Scale (HDRS-17); the Montgomery-Åsberg Depression Rating Scale (MADRS); and the Beck Depression Inventory (BDI). These were administered at weekly intervals for 12 weeks. A further rating was performed at 26 weeks.

Escitalopram is an SSRI with the highest affinity of any clinically available antidepressant for the serotonin transporter (5-HTT). Nortriptyline is a tricyclic antidepressant that shows greater affinity for the noradrenaline transporter than the 5-HTT. The metabolic routes also differ: cytochrome P450 enzymes CYP2C19 and CYP2D6 are the primary drug metabolising enzymes for escitalopram and nortriptyline respectively.

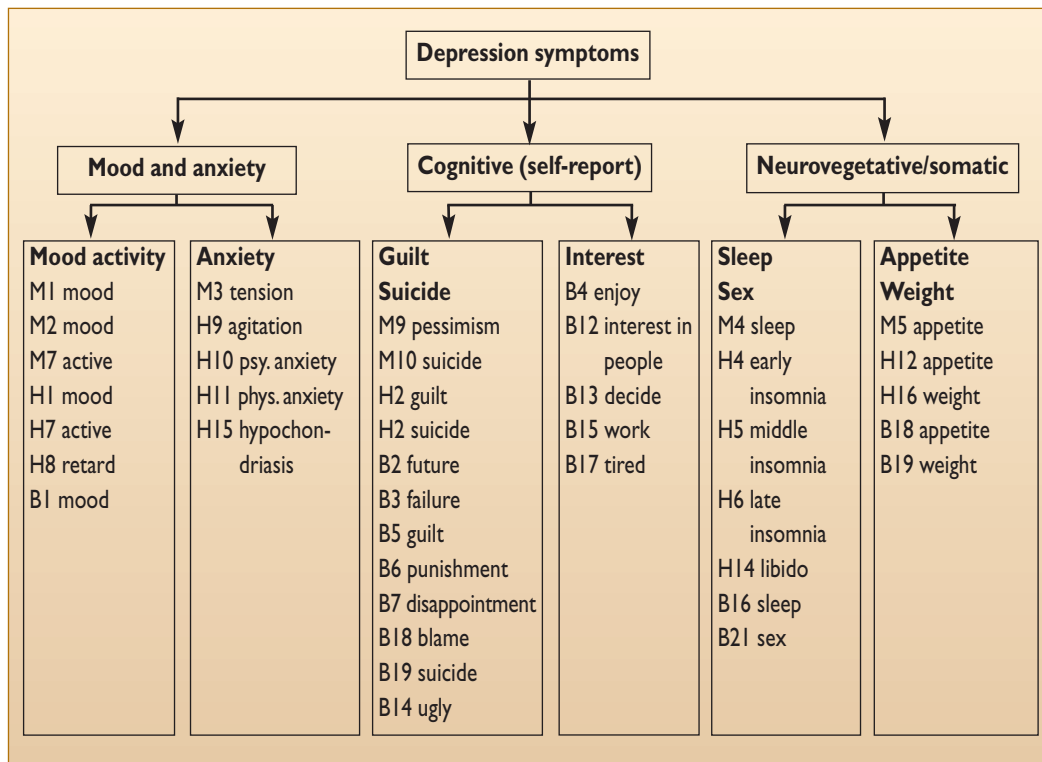
## Findings from GENDEP

In Uher *et al.* (2008),<sup>2</sup> data from 660 patients recruited for GENDEP, with depressive disorder according to ICD-10 or DSM-IV, were analysed. The centres enrolled an ethnically homogenous group (Caucasians) to limit genetic variability. The researchers excluded patients with a history of bipolar disorder or schizophrenia either personally or in a first-degree relative. They also excluded patients with a personal history of mood incongruent psychotic symptoms, primary substance misuse or primary organic disease.

Patients were randomly allocated to either escitalopram or nortriptyline, and those who were refractory or intolerant to the first antidepressant were offered a switch to the other study medication. Clinicians could also override randomisation. The original study design for GENDEP was double-blind. This was found to be impossible to maintain in practice, as treatment emergent adverse drug reactions in combination with the patient information sheet meant that the study participants were usually able to guess which medication they were taking. It was then attempted to maintain a single-blind approach, *ie* that the

# Latest Advances in Psychiatry

## Depression and anxiety rating scales



**Figure 1.** Depression resolves into several symptom domains. 'M' = MADRS, 'H' = HDRS-17, 'B' = BDI, the numbers corresponding to items in these clinical rating scales

researchers performing the ratings would be blind to allocation; however, in practice, in most centres, even this was not possible, and hence an essentially open design resulted. Dr Aitchison also noted that a placebo arm was viewed as being unethical in the participating centres.

In IRT, the data analysis is robust to missing values, and hence no methods of imputation (such as last observation carried forward) are necessary. All of the items in each rating scale over all the time points for all available data may be included. In this study, only one item, the insight on the HDRS-17, was excluded, as it was not informative (not surprisingly, patients consenting to a treatment study in depression have insight, and hence there was little variability in this item). Ninety-two per cent of patients

scored zero on this item, *ie* had insight, and in addition, insight showed little correlation with other items. Therefore, the insight item showed negligible discriminatory power, and was dropped from the analysis.

MADRS and BDI performed better than HDRS-17 on the IRT analysis, *ie* the items showed greater variability across the random sample, indicating that they were more sensitive to change. Furthermore, the MADRS was the most internally consistent. Dr Aitchison commented that this might be expected, as the HDRS was developed for use in inpatients. The BDI was also relatively internally consistent, but different from the MADRS in the symptoms of depression covered. The MADRS and BDI therefore provide mutually distinct estimates of depression severity.

Following the IRT, factor analysis was undertaken on a random sample of the data set (both exploratory and confirmatory factor analysis). The most parsimonious (least complex) model comprised three symptom dimensions: 'observed mood and anxiety'; 'cognitive'; and 'somatic' or 'neurovegetative'. Each of these differentiated into two further dimensions (see Figure 1). Specifically, anxiety was a subfactor within the mood and anxiety dimension. Dr Aitchison showed the statistics for the items from the HDRS-17 and MADRS comprising this subfactor.

Factor analysis can also be used to see how the different symptom dimensions change over time and by drug. In a further paper since published investigating the change in factor scores over time by drug (Uher *et al.*, 2009),<sup>3</sup> the discriminatory ability of the original clinical rating scales is compared to that of the factors.

The longitudinal analysis revealed no difference in the efficacy of escitalopram and nortriptyline using any of the three rating scales on its own. However, longitudinal analysis of change in the factor scores revealed that the 'observed mood and anxiety' and 'cognitive' dimensions improved more with escitalopram than nortriptyline. The difference in 'observed mood and anxiety' among patients taking escitalopram differed significantly from nortriptyline. The 'somatic' dimension, including disturbances in sleep and appetite, improved more with nortriptyline compared with escitalopram.

### Conclusion

'This approach may therefore differentiate psychopharmacological effects, such as those on depres-

sion and anxiety, more finely between drugs and potentially between active agents and placebo than has been revealed by the types of analyses, *eg* clinical response at a certain time point defined by a percentage change in one rating scale, typically conducted in clinical trials to date,' Dr Aitchison concluded.

Psychiatrists have recognised differences between SSRIs and tricyclic antidepressants intuitively for some time. We know, for example, that nortriptyline may have a sedative effect and may stimulate appetite. However,

this is the first clinical trial that has shown a significant and quantifiable difference in profile of efficacy on symptom domains between two antidepressants in current clinical use. Moreover, these two medications are representative examples of the two biggest classes of antidepressants currently available, *ie* SSRIs and tricyclic antidepressants.

### Acknowledgements

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