Bulimia nervosa

Over the years, psychiatrists tried numerous pharmacotherapies for bulimia nervosa. Tricyclic antidepressants and SSRIs seem rational given bulimia’s clinical similarity with depression and evidence that serotonergic dysfunction contributes to both disorders. Trials of brofaromine (an anti-emetic), topiramate (an anti-convulsant, reflecting a view that a bulimic episode may be epileptic in nature), and ondansetron (a 5HT2 antagonist used for vertigo and nausea) have been undertaken but with limited success.

Fluoxetine has been shown to be effective in alleviating the episodes of bulimia and reducing relapse risk. Patients who showed a decrease of at least 50 per cent in the frequency of vomiting episodes with fluoxetine were allocated to either 60mg daily of the SSRI or placebo for up to 52 weeks. Fluoxetine prolonged time to relapse and reduced the frequency of vomiting and binge eating episodes. Fluoxetine also improved scores on several indices of eating disorders scales, compared with placebo. However, attrition was high, especially in the first three months following randomisation.

Nevertheless, drugs are not a panacea for bulimia nervosa and other interventions can improve outcomes. Cognitive behavioural therapy (CBT) and interpersonal therapy (IPT), for instance, reduce binge eating and vomiting more effectively than behaviour psychotherapy. But it is more effective to combine CBT with fluoxetine: CBT plus medication was superior to fluoxetine alone, whereas supportive psychotherapy did not augment the SSRI’s efficacy. Indeed, self-help manuals also have a place in the treatment of bulimia nervosa: they can produce a modest improvement for some patients, a minority of whom enter a lasting remission.

Anorexia nervosa

Pharmacotherapy is less successful against anorexia nervosa. In 1960, Peter Dally and William Sargant reported that chlorpromazine plus modified insulin increased appetite, reduced anxiety and resistance to eating, and normalised ‘quasi-delusional’ body perceptions. However, over the next six years Dally realised that modified insulin was redundant. By 1979, further observations had revealed that only a third of inpatients required chlorpromazine. Weight monitoring, ‘routine’ behavioural approaches and the close support of nursing staff seemed to account for most of the benefit.

Since then, various researchers tried diverse agents, with generally discouraging results. Currently, there is no convincing evidence that any drug modifies the acute or chronic phase of anorexia nervosa. As a recent review remarks, anorexia nervosa is one of the few psychiatric disorders where drugs appear to be ineffective.

Two examples illustrate this. In the first study, outpatients who had their weight restored by inpatient treatment received fluoxetine or placebo for up to one year in combination with individual CBT. No statistically significant difference emerged in the proportion that maintained a body mass index (BMI) of at least 18.5 and remained in the study for 52 weeks: 26.5 per cent with fluoxetine and 31.5 per cent with placebo. Similarly, no significant difference emerged in time-to-relapse. The authors remarked that prescribing antidepressants, although widespread, ‘is unlikely to provide substantial benefit for most patients with anorexia nervosa, either when they are underweight or immediately upon weight restoration’.

In the second study, olanzapine showed disappointing clinical results, despite inducing weight gain in experimental animals and humans. Olanzapine did not produce any additional increase in BMI when added to a three-month course of CBT and programmed nutritional rehabilitation, compared with the improvement seen with non-pharmacological approaches alone. Levels of leptin and ghrelin did not correlate with the increase in BMI in either arm of the trial.

The Keynote Lecture at the eighth Latest Advances in Psychiatry Symposium, held in London in March, was given by Professor Gerald Russell, Emeritus Professor of Psychiatry at the Institute of Psychiatry in London. He noted that eating disorders are sometimes associated with a markedly excess mortality. A high crude mortality rate (2.2 per cent per annum) was recorded in a UK series of compulsorily treated anorexia patients, in keeping with these patients’ dogged resistance to treatment. While bulimia nervosa may respond to fluoxetine, there is no effective pharmacological treatment for anorexia nervosa. Nevertheless, psychological treatments may improve outcomes in both anorexia and bulimia nervosa, although NICE has only grudgingly recognised their efficacy. Medical writer, Mark Greener, reports.
Historically, several factors militated against the discovery of drugs for anorexia nervosa. First, anorexia nervosa is a chronic disease requiring long-term follow-up, compliance is often poor and attrition rates are high, which complicates study design and analysis. Secondly, nutritional deficits associated with anorexia nervosa may compromise synaptic production of key neurotransmitters, even after weight restoration. Thirdly, clinicians may have placed undue emphasis on BMI as an outcome measure. An emerging consensus suggests that trials also need to quantify cognitive outcomes, in a similar manner to schizophrenia research. In anorexia nervosa such a powerful outcome measure would be the appearance of a willingness to accept treatment and a change in behaviour. Finally, pharmaceutical companies need to become more interested in eating disorders other than obesity.

Nevertheless, drug treatment seems rational. Anorexia nervosa is conceptualised as a quasi-depressive illness, a delusional state or both, suggesting that antidepressants and antipsychotics may be appropriate. Furthermore, several lines of evidence suggest that eating behaviour responds to pharmacological manipulation. Antagonising H1 and 5HT2C receptors (for example using olanzapine) increases appetite. Conversely, SSRIs are 5HT2C agonists and decrease appetite. Moreover, certain agents alleviate specific symptoms: chlorpromazine and olanzapine increase weight; olanzapine and benzodiazepines are anxiolytic; while clomipramine reduces obsessiosity. Finally, polymorphisms associated with anorexia nervosa may produce phenotypically distinct receptors and biochemical differences that are amenable to pharmacological manipulation.

However, evaluating innovative pharmacotherapies in clinical studies may prove problematic. For example, intervention studies need to avoid using monotherapy, which appears to be associated with a high attrition rate. There are ethical and clinical objections to trials that enrol wasted patients. A ‘relapse prevention’ design minimises such concerns. All patients need painstaking, precise follow-up, which increases the cost of performing the study. Finally, trials also need to include measures, such as the Anorexia Nervosa Stages of Change Questionnaire (ANSOCQ), that ascertain whether pharmacotherapy engendered a greater acceptance among patients that they needed to change their behaviour.

**Current treatments work in anorexia nervosa**

It is likely to be several years before new drugs for anorexia nervosa reach the clinic. In the meantime, psychiatrists can offer psychotherapies that seem to improve outcomes. Unfortunately, randomised controlled trials (RCTs) – which NICE regards as providing the most compelling clinical evidence – are unsuitable to assess many important aspects of anorexia nervosa management, including severe weight loss and treatment refusal. The lack of RCTs sometimes provokes criticism regarding the rigour of the evidence-base supporting the management of anorexia nervosa. However, this neglects sound clinical evidence.

For example, Ramsay and colleagues evaluated compulsory treatment of anorexia nervosa: a pre-eminent example of an important management issue that RCTs cannot assess. In this case, the comparison group consisted of voluntary patients admitted the same year and whose name was closest in alphabetical order to each proband. Detained and voluntary patients gained, on average, 12.1 and 11.0 kg respectively. This difference was not statistically significant. On the negative side, 12.7 per cent of the detained patients died during a 5.7-year follow up compared with 2.6 per cent of the voluntary group, a difference that was statistically significant.

In the Maudsley RCT of family therapy, 40 outpatients with anorexia nervosa, aged 18 years or younger, received either conjoint or separated family therapy. After a year, the weight gain was 6.4kg and 9.8kg respectively, which was not significantly different. Both therapies continued to improve outcomes over the next five years. The mean BMI was 15.4 before treatment, which increased to 18.5 and 19.8 after one and five years respectively. After a year, 39 per cent showed no eating disorder symptoms, which rose to 76 per cent after five years. The proportion with normal menses increased from 37 per cent after a year to 86 per cent after five years. Only 8 per cent of those who achieved a healthy weight relapsed.

Discordance can arise between clinical impressions and the results of RCTs. Most specialist centres regard CBT as helpful in anorexia management. However, in RCTs CBT is superior to nutritional counselling in relapse prevention, but inferior to non-specific supportive clinical management. However, methodological problems – specifically poor acceptance and high dropout rates (around 46 per cent) – defeated one potentially valuable study assessing CBT. The authors suggested that it is premature to conduct RCTs of CBT for adults with anorexia nervosa until further research identifies and resolves the reasons underlying the poor acceptance and high dropout rates.
Concluding remarks
In conclusion, psychiatrists can employ several strategies to reduce the morbidity and mortality associated with anorexia and bulimia nervosa. In bulimia nervosa, fluoxetine is moderately successful and psychiatrists should consider offering treatment for up to one year. CBT and interpersonal therapy are effective alone. The benefits of CBT are enhanced when combined with medication. Even self-help manuals may be a reasonable first step especially in primary care, although the benefits are modest.

On the other hand, there is no effective pharmacological treatment for anorexia nervosa. Several factors contribute to this regrettable situation including major practical difficulties in performing rigorous RCTs, poor efficacy in underweight patients and the need for studies that employ a comprehensive battery of long-term outcomes. Nevertheless, inpatient care, family therapy in the young, and possibly CBT can produce worthwhile clinical improvements. Furthermore, several receptors appear to modify appetite and polymorphic phenotypes could yield new modifiable targets. Such observations raise the prospect of innovative pharmacological treatments for this potentially fatal eating disorder. After all, it seems unlikely that anorexia nervosa will be the only serious psychiatric disorder that does not respond to drug treatment.  

References

Yttrium-90 implantation
We read with interest the Case notes article by Drs Malik and Al-Dhahir ‘Carotid aneurysm after yttrium-90 implantation’ (Progress 2008;12(7): 15-6). Younger readers may be unaware that yttrium-90 (Y90) implants were once used as a treatment for psychiatric disorders such as refractory depression, bipolar affective disorder and obsessive-compulsive disorders. One series reported over 1300 such operations, and at one time Y90 stereotactic subcaudate tractotomy (Y90-SST) was recommended as a form of psychsurgery. Early uncontrolled studies were reported as favourable, but the long-term sequelae have not, to our knowledge, been reported.

We recently saw a patient referred to the neurology clinic with excessive daytime somnolence, approximately 30 years after Y90-SST performed for chronic depression with obsessional personality. Although there had apparently been an early benefit in terms of mood improvement, there was a gradual re-emergence of psychotic/paranoid depression and obsessive-compulsive behaviours about 10 years later. Moreover, there were episodes of right-sided facial twitching, thought to reflect partial seizures and treated with sodium valproate. Delusions and auditory hallucinations also became apparent, for which she was on multiple medications. CT brain scanning showed the burr holes and implants, but no evidence of leuкоencephalopathy. Her multiple medications were thought the most likely cause of her daytime somnolence.

Further long-term follow up data on both Y90-SST for psychiatric disorders and Y90 implants for pituitary disorders would be of interest.

References