Bulimia Nervosa

Bulimia Nervosa (BN) is a type of eating disorder characterized by eating a large amount of food in a discrete time (a binge), feeling a lack of control during this episode, and then compensating with a behaviour such as self-induced vomiting or laxative use to prevent weight gain (a purge). Updated Diagnostic and Statistical Manual (DSM-5) criteria require the binge and purge behaviour to occur at least once a week for three months in order for a patient to be diagnosed with BN (1). Symptoms of BN cause significant distress and shame for the patient. Additionally, mortality rates for bulimia are stated to be approximately 4 percent (2), with suicide being a large contributor to this figure. Functional MRI studies have demonstrated altered brain structures (specifically medial orbitofrontal cortex, insula, and striatum) in female patients with BN (3). It is still unclear if this represents a premorbid condition indicating a tendency toward the disease, or if the structural changes are secondary effects of the disease process itself.

Treatment goals

Goals of treatment for BN include enhancing the patient’s motivation in restoring healthy eating patterns, and treating deficits in mood, impulse regulation, self-esteem, and behavioural problems (4). These goals are achieved by the combined usage of nutritional rehabilitation, cognitive behavioural therapy, family support/counselling, and pharmacotherapy. This review will be limited to the use of Selective Serotonin Reuptake Inhibitors (SSRIs), specifically sertraline, in the treatment of binge eating behaviours.

Drug treatment with SSRIs

Fluoxetine was the first SSRI released into the Canadian market, and thus was the first tested for use in BN. Sertraline, its sister compound, was shown to be effective for the treatment of BN (5). APA guidelines suggest that high doses of SSRI (60mg
fluoxetine or 200mg sertraline) may be required for an extended period of time (9 to 12 months minimum) in order to achieve treatment goals (4). Tricyclic Antidepressants (TCAs) including imipramine, desipramine, and amitriptyline, and Monoamine Oxidase Inhibitors (MAOIs) such as phenylzine were also studied, but found to be less effective. SSRIs are considered to have a favourable safety and side effect profile compared to TCAs and MAOIs, especially in patients with chaotic eating habits or potential electrolyte imbalances due to purging.

Role of serotonin
Serotonin is postulated to play a significant role in binge eating behaviours. We know from studies of depression that sertraline is known to primarily inhibit the 5-HT (serotonin) transporter and thus prevent reuptake of serotonin into neurons (6). Researchers have compared cerebrospinal fluid (CSF) of bulimic and control patients to determine the quantities of 5-hydroxyindolacetic acid, the primary metabolite of serotonin (7). BN patients indeed had higher levels than control patients, thus implicating the serotonin system as being integral to the disease. It remains unknown if these elevated serotonin metabolite levels indicate biological vulnerability to BN or are a result of binge and purge behaviours. Of interest, it should be noted that testing of CSF in this study was completed during the follicular phase of the menstrual cycle for both active and control patients. Freeman et al demonstrated that serotonin pathways play a role in Premenstrual Syndrome/Premenstrual Dysphoric Disorder (PMS/PMDD) (8), so consistent testing should avoid any possible variation in metabolite levels due to differences in menstrual cycle phases.

Binge Eating Disorder
Binge Eating Disorder (BED) shares some of the same symptomology as BN, but without the purging behaviours. Symptoms include eating a large amount of food in a discrete time (a binge) and experiencing a sense of lack of control during this episode. DSM-5 requires that a patient must exhibit these symptoms at least once a week for three months in order to be diagnosed with BED (1). Treatment consists of nutritional rehabilitation, psychotherapy, and pharmacotherapy.

Drug treatment with SSRIs
Sertraline was found to be effective in the treatment of BED in a double-blind, placebo-controlled clinical trial (9). This trial, however, was only six weeks in length and had a high withdrawal rate. Further long-term studies showed that both sertraline and fluoxetine are effective in reducing the frequency of binge eating behaviours in obese patients (10). Within eight weeks, patients experienced significant improvement in symptoms and reduction in weight. These responders were able to maintain these changes over six months, the duration of the study. It was suggested that patients who do not respond to SSRIs within the first eight weeks be considered for alternate treatment such as cognitive behavioural therapy. It should be noted that this particular study lacked a control group, so this design flaw limits our application of the study results. It would be interesting to see if a placebo effect was noted with BED patients. A significant placebo effect has been noted in other studies involving patients with eating disorders.
Sibutramine is a serotonin (and norepinephrine) reuptake inhibitor used for weight loss. It was shown to be effective in treating obese patients with BED (11). Unfortunately, it was pulled from the Canadian market in 2010 after safety concerns, including excessive cardiovascular risk.

Patient considerations
When treating a patient with BN or BED, it is necessary to consider comorbidities. It is common for patients to have issues with mood disorders, anxiety disorders, diabetes, or substance abuse (4) in addition to the eating disorder. This could potentially complicate or simplify treatment regimens. Additionally, since many patients with eating disorders happen to be female, it is important to re-evaluate the treatment during pregnancy. Metabolism of SSRIs can be accelerated during the second half of pregnancy, resulting in lower serum levels of drug and requiring an increased dosage (12). As patients with BN or BED may already be on high-dose SSRI, this could result in reluctance by some practitioners to proceed with a dose adjustment.

Sertraline is highly metabolized in the liver by the cytochrome P450 system. This system consists of multiple types of isoenzymes which can be affected by drug interactions, if two drugs are competing for the same isoenzyme. As well, some drugs are known to inhibit or accelerate the function of these isoenzymes, which can alter serum levels of concurrent medications. Sertraline and fluoxetine differ in the variation of isoenzymes required for drug metabolism. Sertraline is metabolized by at least five different isoenzymes (13), whereas fluoxetine is mainly metabolized by only one – the 2D6 isoenzyme. Sertraline may be less likely to be affected by drug interactions due to the numerous pathways available, while fluoxetine may remain more vulnerable (14).

Anorexia Nervosa
Reviews on the use of SSRIs in Anorexia Nervosa (AN) have been completed. To date, there have not been positive results (15). AN has the highest mortality rate of any psychiatric disorder (16), with death due to suicide and starvation-related effects. The severe restrictive-eating patterns of the patient with AN do not seem to be affected by serotonergic drugs. Instead, the brain’s “reward centres” are altered by endogenous opioids and dopamine (17). Literature reviews are unable to determine the risk/benefit ratio of using SSRIs for anorexia, and it is suggested that underweight patients may be lacking the necessary nutrients required for the body to manufacture serotonin. Therefore, medications which modulate serotonin will not be effective (18). Second-generation antipsychotics such as olanzapine, risperidone, and quetiapine preferentially target dopamine receptors. These agents may be used for AN patients who demonstrate delusional or obsessional thinking about food (4), however patients may be reluctant to continue with therapy as potential side effects of increased appetite and weight gain are undesirable in this population. A recent report on identical twin adolescent girls with AN, one treated with fluoxetine and the other with olanzapine, showed that the antipsychotic appeared more effective in achieving and maintaining a normalized weight than the SSRI (19). The twins were only twelve years old, so compliance was likely not an issue as parents would be closely monitoring the
administration of medication. It is probable that in an adult population with AN, compliance with olanzapine would be poor.

Summary

In conclusion, it has been demonstrated that sertraline and other SSRIs are effective in reducing binge-type eating behaviours, including those found in Bulimia Nervosa and Binge Eating Disorder. The same cannot be said for the restrictive type of eating behaviours seen in Anorexia Nervosa. Investigations into alternate neurotransmitters such as dopamine may ultimately lead to standardized pharmacotherapy for anorexia, however much research needs to be completed. Eating disorders have historically been very difficult to overcome and so the availability of drug treatment options remains so vital to improving the quality of life for these patients.

References:

11. Appolinario J et al, A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of BED. Arch Gen Psychiatry 2003; 60(11): 1109-1116
13. Kobayashi K et al, Sertraline N-Demethylation is Catalyzed by Multiple Isoforms of Human Cytochrome P450 In Vitro. Drug Metabolism and Disposition 1999; 27(7): 763-766