Management of clozapine-induced weight gain

Kerry Stott and Fiona Cassells review the literature on the subject of weight gain from a biopsychosocial perspective. They describe the physiological changes that occur in the hypothalamus of patients taking clozapine affecting appetite and look at the behavioural factors that can influence food choice.

The purpose of this review was to explore whether the weight gain caused by clozapine was purely pharmacodynamic or whether there other factors were involved. Issues such as why people make specific food choices were explored, as well as whether there are any reasons other than food consumption that may affect weight gain.

There are many benefits to administering atypical antipsychotics, including improvement in, and management of, symptoms and better quality of life (Luft and Taylor 2006). However, some of the new generation of antipsychotic medications has distinct side effect profiles that are the modern-day equivalent of tardive dyskinesia (Gray et al 2005). Weight gain as a side effect of taking clozapine is an important issue, not only for patients but also for nurses and other healthcare professionals involved in a person’s care. Weight gain affects not only patients’ physical health but also their self-confidence and feelings of self-worth.

Twenty per cent of the population is classed as obese—the obesity is categorised as having a body mass index (BMI) of over 30; a BMI of between 25 and 30 is classed as overweight—and the cost of obesity to the public is likely to rise to £3.6 billion by 2010 (Ali 2002). As a nation, we are making poor food choices and exercising less (Carvel 2006).

Van de Weyer (2005) undertook a comprehensive review of how food can affect our mental health and in the context of schizophrenia, she suggested that health could be enhanced greatly by considering what food an individual eats.

Regulation of hunger and satiety

The side effect profile, wanted and unwanted, of administering clozapine, must be within an acceptable range and level. While the drug is effective at reducing both positive and negative symptoms of condition (National Institute for Health and Clinical Excellence 2002), one of its main shortcomings is the weight gain people taking it can experience. On average, a patient prescribed clozapine gains about 6kg over two years (Covell et al 2004).

Clozapine directly affects the systems in the hypothalamus that moderate our eating, controlling our sensations of satiety and hunger (Tortora and Grabowski 2000). Casey and Zorn (2001) suggest that the 5-HT2A receptor, when exposed to an antagonist, can cause an increase in food consumption and consequently body weight. The 5-HT2A receptor has also been implicated in the regulation of leptin secretion. Histamine is also understood to have some impact on weight gain. Some antipsychotic drugs have a high affinity with the histamine H1 receptor and weight gain is listed among their side effects. (Affinity is the interaction between the drug and the binding site the better the interaction the higher the affinity thus increasing the efficacy of the drug.) These drugs include clozapine (Müller et al 2004).

Alpha1 adrenoreceptors are also implicated in weight gain. Drugs that have a high affinity for alpha1 or alpha2 adreno-receptors, such as tricyclic antidepressants, are associated with weight gain. However, selective serotonin reuptake inhibitor medications have a low affinity and are not reputed to have increased weight as a side effect, according to the British National Formulary.

Dopamine and monoamine reuptake sites are both implicated in weight gain, however. The weight increase profile of such a complex drug as clozapine is likely to be the result of multiple receptor reactions and interactions. Casey and Zorn (2001) conclude that antipsychotic medication with an affinity to the D2 receptors—and that have an equal or greater affinity with H1, alpha1, 5-HT1A, and 5-HT2A in the hypothalamus—are likely to trigger weight gain in patients.

Leptin

There are many mechanisms that control feelings of hunger and satiety. One of these is linked to the hormone leptin—secreted by the body’s fat cells—that crosses the blood-brain barrier to instruct the hypothalamus whether the body requires food (Tortora and Grabowski 2000). When levels of leptin are low, the hypothalamus interprets this as a need to replenish its energy stores (Montague et al 1997, Friedman and Halaas 1998). Thus, the fluctuations in body fat that occur when people diet or overeat are associated with similar changes in blood leptin levels.

As stated, serotonin neuroreceptors are implicated in the regulation of leptin. In an individual taking clozapine, the secretion of the hormone can be disrupted or even stopped as a result of polymorphism in one of the genes in the 5-HT2c receptor, causing the person to feel hungry. This is a direct side effect of clozapine and other antipsychotic medication (Baasle et al 2001, Casey and Zorn 2001). This genetic information could, in future, determine the suitability of specific antipsychotic medication prescribed to patients (Ramos et al 2005).

Appetite

The body is not ruled by brain function alone. The homeostatic systems in our gastrointestinal tract...
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affect hunger/satiety. There are mechanical (stretch and pressure) and chemical receptors in the stomach that signal to the brain that the stomach is full and increase feelings of satiety (Elmqquist 2001). Ghrelin, galanin and protein YY are peptides that are synthesised in the stomach, and blood levels of these peptides rise and fall in relation to recent food intake; lower levels indicate a diminished appetite (Kaplan 2003). Although synthesised in the stomach, ghrelin and protein YY interact with neurons in the arcuate nucleus of the hypothalamus and are thus affected by antipsychotic medication (Schwartz and Morton 2002, Leibowitz and Wortley 2004).

The above indicates that clozapine can affect the physiological functions of the hypothalamus, the stomach and certain neuroreceptors in the brain, which results in the impairment of an individual's ability to know if they are sated. However, this cannot be the only reasons for an increased appetite and therefore an increased BMI in patients who are being treated for schizophrenia.

Food choice models

However, increased appetite is not the only factor for weight gain in people prescribed clozapine. The type of diet they eat is also a key factor and the reasons underlying an individual's choice of food are incredibly complex.

Three models can help explain why we choose the food we eat. The first is the developmental model, whereby the child is exposed to food. It shows the relationship between familiar foods, unfamiliar foods and what the child learns is socially acceptable, initially by way of parental influence. The developmental model extends to social eating, eating with friends, school dinners and other people's influences on individual food choices (Ogden 2003).

Within this model, reward and food are examined – whether parents use some type of behavioural reward, such as 'If you eat this, I will be pleased with you', or more direct rewards, such as 'If you do that, you can have some sweets'. This direct approach can have long-term consequences. If used as a form of bribery, it will induce the child to eat the unwanted food in the short term. However, it will enforce the notion that the sweets are more desirable than vegetables, thus increasing desire for the sweets (Birch 1999). Using the reward system encourages a connective link between doing something 'good' and nutritionally inappropriate food, which can be set as a cognitive schema (Sanders and Willis 2005). Unfortunately, the developmental model does not cover cognitive aspects of food choice and is therefore limited. It does not explore the different reasons children are exposed to food, such as food as power, love, sexuality, religion or culture.

Second is the cognitive model of food choice. This model explores the beliefs and attitudes involved in why people choose particular food: beliefs such as butter makes you fat and chocolate makes you feel good. These beliefs derive from the socialisation of food and food choices within an individual's upbringing (McCabe and Ricciardelli 2005). However, they also incorporate experience: for example, an unpleasant experience with fish such as a bone stuck in the throat may be the initiation of the avoidance of fish and fish products for that individual because of the fear of pain. This is especially important in certain behavioural aspects. If a person is brought up to finish what is on their plate regardless of satiety, they are more likely to do this throughout their adult life. They may display behaviours such as finishing what is on their own child's plate when they too become a parent, thus increasing their risk of becoming obese and teaching their offspring maladaptive eating habits (Faith et al 2004). The cognitive link between behavioural incentives set by the parent and a cognitive feeling of guilt if the child leaves any food is set (Orrell-Valente et al 2006). Although the cognitive model does incorporate behavioural and developmental aspects of food choice, it does not include a distinction between desire and action: 'I can eat fish' and 'I am going to eat fish'. However, it is not always easy for researchers to discriminate between these two as people find it difficult to separate them.

The third model is the psychophysiological model of food choice. This centres on feelings of satiety and hunger – the physiological causes and sensations that occur when one is hungry and full. Much of this is set out above. It covers the concepts of stress and eating; some people are unable to eat at times of stress due to the physiological responses during the general adaptation syndrome (Tortora and Grabovski 2000). Other people overeat at times of stress and this is called emotional or comfort eating (Timmerman and Acton 2001). This model does not extend to cover the social, developmental, cognitive or...
**References**


**Carbohydrates**

There are common foods that people eat too much of when in a heightened emotional state. They include sweet, fatty and carbohydrate-rich foods (Ogden 2003). Wurtman and Wurtman (1989) put forward a theory that a craving for carbohydrates is due to a serotonin deficiency. They hypothesised that when carbohydrates are ingested and enter the bloodstream, the result is an increase in amounts of tryptophan. This rise in tryptophan levels is proportionally greater than with other amino acids, thus more crosses the blood-brain barrier where it is converted to serotonin and mood level is therefore raised.

However, Benton and Donahoe (1999) reviewed 30 studies of amino acid profiles after food had been consumed. They found that only if the protein element of the meal was less than 2 per cent did the resulting amino acid levels rise to the extent that serotonin levels correspondingly increased to a detectable level. Wurtman and Wurtman (1989) found that people with depression who craved carbohydrates were significantly less depressed after eating carbohydrates. It would therefore appear that although eating carbohydrates may increase an individual’s reported mood, this is not the physiological mechanism that causes its elevation, but the perceived pleasure or relief (Benton 2002).

**Cravings for sweet substances, such as chocolate, were associated with altered endogenous peptide levels in the nucleus accumbens in the brain**

**Choclate**

Chocolate is a popular choice of food for comfort eating. Parker et al (2006) wrote a comprehensive review of the properties of chocolate. It was discovered that cravings for sweet substances, such as chocolate, were associated with altered endogenous peptide levels in the nucleus accumbens in the brain. When chocolate was ingested, not only were endogenous opioids released in this part of the brain, but there was also a stimulating effect on the release of beta-endorphins in the hypothalamus, giving the eater a sensation physiologically not dissimilar to the effect of opioids (Blass 1986, Levine and Billington 2004). With this in mind, it is not unreasonable for people to want to eat chocolate when feeling low in mood. However, eating sugary food can cause a sharp rise and fall in blood sugar that can have a direct influence on mood (DesMaisons 1998).

But this is not the only reason for the popularity of chocolate; there is also the pleasure principle. Chocolate has a high hedonic value, and therefore the smell and sight of it can be enough to start cravings (Rogers 1990). The fact that it melts at just below body temperature adds to its sensory appeal. This, coupled with the implied decadence element fostered by manufacturers, enhances its appeal. And eating foods that are palatable to us will enhance our mood regardless of what they are (Ottley 2000).

**Fat and sugar**

Not everyone reaches for a bar of chocolate to self-soothe. Foods with a high fat and sugar content such as ice cream, sweets and crisps are also high on many people’s list. The combination of fat and sugar has a similar physiological effect to chocolate. These foods are often described as moreish and manufacturers have capitalised on this by marketing them as such (Rogers and Smit 2000). ‘Once you pop you can’t stop’ – a promotional tag line from Pringle crisps – is a classic example of the manufacturer giving the consumer permission to overeat a food the consumer knows is not nutritionally beneficial. Therefore, through marketing and advertising, this style of food consumption becomes socially acceptable.

The most common mood states in which people comfort-
eat are anxiety, depression, boredom, loneliness and stress. These can be internally or externally initiated. Timmerman and Acton (2001) suggest that these moods illustrate our basic need satisfaction. They propose that if there is a deficit in our psychological need satisfaction we may try to replace this loss physically with food. Lindeman and Stark (2001) concur, suggesting that emotional dieters suffer more from feelings of inadequacy, depression and ineffectiveness. This supports the perspective that eating as a form of self-medicating, alleviates feelings of low mood, albeit temporarily (Rogers and Smit 2000, Benton 2002, Parker et al 2006). However, it appears that people who comfort eat have little control over their actions and that this behavioural pattern recurs with any stressor (Oliver et al 2000).

Metabolic syndrome

There are two consequences of this in relation to clozapine-related weight gain. The first is the physiological outcome, which is called metabolic syndrome. This consists of abdominal obesity, insulin resistance, hypertension and disturbances in lipid metabolism. All these can greatly increase the risk factors for cardiovascular disease, some types of cancer and type 2 diabetes (Fenton and Chavez 2006, Bloomgarden 2006), which in turn increase the mortality rate in patients with schizophrenia who take clozapine (Lamberti et al 2006).

Interestingly, Morgan Spurlock, in the 2004 film Super Size Me, describes this syndrome in obese Americans who do not take any antipsychotic medication. He claims that the high fat, high sugar and high carbohydrate diet to which most Americans are exposed creates a ‘toxic’ food environment that has a negative impact on people’s physical and mental health. This supports the evidence that the prevalence of metabolic syndrome in patients who take clozapine is significant.

A point of interest is that in countries with westernised diets that are low in omega-3 a higher number of people are diagnosed with schizophrenia than in countries where the diets include more fish and essential fatty acids (Stoll 2001, Peet 2004).

Fenton and Chavez (2006) discovered that metabolic syndrome was 33.1 per cent more likely in patients taking clozapine than in a control group. However, it was not clear whether the control group had schizophrenia, which reduced slightly the quality of the results.

Metabolic syndrome is a concern in any individual. Unfortunately, having a diagnosis of schizophrenia is linked with a higher mortality rate compared with those who do not have this illness among the general population (Brown 1997, Brown et al 2000). Lifestyle factors such as smoking, substance misuse, poor diet and lack of exercise are all contributing factors, and people with schizophrenia are at increased risk of using these maladaptive techniques (Brown et al 1999). There are also the sedative effects of other types of neuroleptic medication, as well as periods of hospitalisation, which may compound any poor lifestyle choices. This, coupled with the side effects of clozapine, should give clinicians cause for concern.

The implication of metabolic syndrome is that there will be more calls for medication to ease physical complaints, putting a greater strain on already tight budgets (Bagust et al 2002, Ralittha and Smith 2004). Nonetheless, Duggan et al (2003) suggest that clozapine not only increases patients’ quality of life but saves money by reducing the number of periods of hospitalisation. This view is mirrored by Guest and Cookson (1999) and Hu (2006) who believe that early intervention and proactive care can reduce the cost of this illness, as well as allowing people to be more active and productive in their social environments.

Concordance

The second issue with clozapine is concordance. The patient must take the medication regularly and be subject to regular blood screening. However, the main reasons for non-concordance are sedation, sexual dysfunction, weight gain and diabetes (Toren et al 2004). The fear of weight gain with any medication, real or implied, is a barrier between the patient and better health.

Other reasons for not taking medication relate to the patient’s own beliefs in the perceived pharmacokinetic and pharmacodynamic effect of...
the drug (Lambert et al. 2003). On the other hand, patients are also influenced by the attitudes of their family, carers and healthcare professionals. Concordance is greatly improved when all the people surrounding the patient are in favour of antipsychotic medication to the extent that they would take it if they had schizophrenia (Rettenbacher et al. 2004). Gray et al. (2002) suggest that education about schizophrenia does not in itself improve concordance but that cognitive behavioural interventions around the patient's belief structures do.

**Psychological impact**

There are psychological issues related to gaining weight. The patient's self-image is altered because of the physical changes. This can also have a detrimental impact on self-esteem. There is evidence regarding the stigmatisation of patients with schizophrenia who are overweight (Puhl and Brownell 2006). This prevents them from being socially included and can exacerbate feelings of exclusion (Perkins and Sayce 2000).

A study of 300 Dutch patients found that those who had gained weight while taking antipsychotic medication had a reduced ability to make psychosocial adjustments, had lower self-esteem and a poor self-image (De Hert et al. 2006). The value of these psychological changes cannot be underestimated in patients who are already feeling vulnerable and stigmatised. It could be hypothesised that it would add to their emotional distress, thus increasing the risk of further psychiatric relapses or increased depressive symptoms.

**Ethics**

There are ethical consequences to the actions of healthcare professionals. The ethical principles of beneficence and non-malefice are stretched in this context. Is it ethically knowingly to give patients a treatment that may cause them to feel more isolated due to weight gain (Dennis 2000)? There should be some type of support for patients that takes into account how physical changes to the body can affect the patient's self-perception. If weight gain is significant enough, the patient may have physical difficulty in moving, making them unable to do what they want. For example, if the case of an inpatient, it could prevent them from absconding from the ward, and in this instance it could be argued that healthcare professionals are restraining the patient illegally by prescribing clozapine. In future, this form of detention could result in hospitals being sued or made liable under the Human Rights Act (Dimond 2005).

Although the physiological changes outlined in this article may not outweigh the psychological benefits of prescribing clozapine to patients, ethical consideration should play an active part in the prescription and maintenance of individuals on this drug. Patients should, as far as possible, be at the centre of their care and have a full awareness of the implications of taking clozapine (Gamble 2000). In cases where this is not possible, there should be family or advocacy involvement. This may benefit the patient, because it could help them to feel that someone is ‘on their side’ (Mind 2000).

Compliance with the medication regime may be increased and further relapse prevented.

**Conclusion**

Clozapine is a very effective atypical antipsychotic medication. Like all medicine it has unwanted side effects. There is a definite physiological change that occurs in the hypothalamus and which prevents the patient from experiencing feelings of satiety. This, combined with individual approaches to food intake, the profile of the illness and how weight gain is managed, all interact to determine how each patient should be helped with regard to the weight-increasing properties of this drug.

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**Those who had gained weight while taking medication had lower self-esteem and a poor self-image**

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