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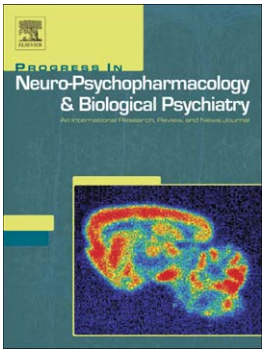

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Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment

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Abstract

Rates of obesity are higher than normal across a range of psychiatric disorders, including major depressive disorder, bipolar disorder, schizophrenia and anxiety disorders. While the problem of obesity is generally acknowledged in mental health research and treatment, an understanding of their bi-directional relationship is still developing. In this review the association between obesity and psychiatric disorders is summarised, with a specific emphasis on similarities in their disturbed biological pathways; namely neurotransmitter imbalances, hypothalamus–pituitary–adrenal axis disturbances, dysregulated inflammatory pathways, increased oxidative and nitrosative stress, mitochondrial disturbances, and neuroprogression. The applicability and effectiveness of weight-loss interventions in psychiatric populations is reviewed along with their potential efficacy in ameliorating disturbed biological pathways, particularly those mediating inflammation and oxidative stress. It is proposed that weight loss may not only be an effective intervention to enhance physical health but may also improve mental health outcomes and slow the rate of neuroprogressive disturbances in psychiatric disorders. Areas of future research to help expand our understanding of the relationship between obesity and psychiatric disorders are also outlined.

Keywords: psychiatric disorders; obesity; weight loss; inflammation; oxidative stress; neuroprogression

List of Abbreviations: BMI, body mass index; BDNF, brain-derived neurotrophic factor; CBT, cognitive behaviour therapy; COX, cyclooxygenase; CNS, central nervous system; CRP, C-reactive protein; HPA, hypothalamus-pituitary-adrenal; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; PTSD, post-traumatic stress disorder; TNF, tumour necrosis factor.

Investigations into the biological mechanisms associated with psychiatric disorders such as major depressive disorder, bipolar disorder, schizophrenia and anxiety disorders have identified several mechanisms specific to each disorder. For example, dysregulation of the neurotransmitter serotonin is associated with major depressive disorder and, to a lesser extent, with several anxiety disorders (Cowen, 2008, Dantzer et al., 2011). Recently, increased attention into the kynurenine pathway has revealed that it is upregulated in major depressive disorder, and interest in its role in other psychiatric disorders such as schizophrenia is underway (Maes et al., 2011b, Myint, 2012, Myint et al., 2011). Other neurotransmitters such as glutamate are linked primarily with schizophrenia, and dopamine with bipolar and psychotic disorders (Abi-Dargham, 2004, Cousins et al., 2009, Seeman, 2009, Steele et al., 2012). Several genetic polymorphisms are also uniquely associated with different psychiatric disorders, such as polymorphisms in the serotonin transporter gene with depression (Kuzelova et al., 2010), and catechol-O-methyl transferase gene polymorphisms with schizophrenia and bipolar disorder (Sagud et al., 2010).

Despite the unique characteristics of each disorder, they share several common dysregulated biological pathways. As illustrated in Figure 1, these include neurotransmitter imbalances; hypothalamus–pituitary–adrenal (HPA) axis disturbances; dysregulated inflammatory pathways; increased oxidative and nitrosative stress and reduced antioxidant defences; neuroprogression resulting in neurodegeneration, apoptosis, reduced neurogenesis and neuronal plasticity; and mitochondrial disturbances (Altamura et al., 2013, Anderson et al., 2013a, Anderson et al., 2013b, Berk et al., 2011, Moylan et al., 2013, Moylan et al., 2012, Salim et al., 2012, Vieta et al., 2013). These dysregulated pathways interact significantly with each other, and their translation into specific psychiatric disorders is influenced by other biological mechanisms, environmental factors and genetic polymorphisms.

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While it is acknowledged that these disturbances are influenced by genetic and environmental factors, psychological, lifestyle and social influences are also important (Anderson and Maes, 2013, Leonard and Maes, 2012, Lopresti et al., 2013, Maes et al., 2011a). One often overlooked influence concerns obesity. This review provides an overview of the relationship between obesity and psychiatric disorders, similarities in their disturbed biological pathways, and the

potential of weight loss interventions not only to improve general health but also to enhance mental health outcomes in psychiatric patients.

Is there an association between obesity and psychiatry disorders?

Rates of obesity are greater than normal in psychiatric populations, particularly in women (Allison et al., 2009, McElroy, 2009). For example, Daumit et al. (2003) reported that 29% of men and 60% of women with severe and persistent mental illness were obese, compared to 17.7% of men and 28.5% of women in the general population. Dickerson et al. (2006) found that 50% of a female, and 41% of a male psychiatric sample were obese, compared to 27% of women and 20% of men in a non-psychiatric matched comparison group. In a meta-analysis of 15 longitudinal studies, Luppino et al. (2010) concluded that depression was associated with increased rates of obesity. More specifically, a bidirectional association was found between depression and obesity with obesity increasing the risk of depression and prior depression increasing the likelihood of obesity. Several studies have found that abdominal obesity in particular may be characteristic of depression (Carpiniello et al., 2012, Rivenes et al., 2009, van Reedt Dortland et al., 2013).

After controlling for several demographic influences, Petry et al. (2008) concluded that obesity increased the odds of any mood, anxiety, and alcohol use disorder significantly, as well as any personality disorder, with odds ratios ranging from 1.21 to 2.08. In a large, nationally representative sample, Goldstein et al. (2011) found a nearly two-fold age-, race-, and sex-adjusted increased risk of obesity among adults with bipolar disorder versus controls. Obese participants with bipolar disorder also had greater comorbidity with anxiety disorders, longer depressive episodes, and significantly poorer physical and mental health functioning compared to non-obese people with bipolar disorder.

Possible mediators of the relationship between obesity and psychiatric disorders

Current and past unhealthy dietary patterns are associated both with obesity (Hsiao et al., 2011, Rosenheck, 2008, Schroder et al., 2007) and psychiatric disorders (Jeffery et al., 2009, Sanchez-Villegas et al., 2009, Sanchez-Villegas et al., 2012) . Lower rates of physical activity and increased sedentary behaviours are also commonly observed in currently obese (Bailey et al., 2007, Tucker and Tucker, 2011) and psychiatric patients (Azevedo Da Silva et al., 2012, Song et al., 2012) and are also risk factors for the future development of both these conditions. Rates of sleep disorders such as insomnia and sleep apnoea are also increased in obesity and psychiatric disorders (Costa

e Silva, 2006, Kalucy et al., 2013, Krystal et al., 2008, Leger et al., 2000), and both obesity and psychiatric disorders are associated with a greater prevalence of cardiovascular diseases (Stanley and Laugharne, 2012), metabolic disorders (Leonard et al., 2012, Rotella and Mannucci, 2013, Yau et al., 2012) and autoimmune conditions (Aballay et al., 2013). Early life trauma, including sexual and physical abuse, has also been identified as a risk factor for the development of obesity (Boynton-Jarrett et al., 2012, D'Argenio et al., 2009, Gunstad et al., 2006) and psychiatric disorders (Breslau, 2002, Chou, 2012).

Can psychiatric medications account for the increased rates of obesity in psychiatric populations?

Weight gain is a commonly reported side effect of many psychiatric medications. In a recent meta-analysis, the antidepressants amitriptyline, mirtazapine, and paroxetine were associated with the greatest risk of weight gain, with other investigated antidepressants having only transient or negligible effects on body weight in the short term (Serretti and Mandelli, 2010). However, the effect of each antidepressant may be influenced by several individual characteristics (e.g., sex, BMI, previous medication history, genetic polymorphisms) and generally becomes more evident over the long term (Dent et al., 2012). Weight gain is also a common problem associated with many atypical antipsychotics such as clozapine and olanzapine, and also increases the risk of metabolic disorders such as diabetes mellitus and dyslipidaemia (Dent et al., 2012, Gautam and Meena, 2011, Newcomer, 2005, Rummel-Kluge et al., 2010).

Increasing evidence suggests that genetic factors may be particularly important in medication-induced weight gain. This is supported by monozygotic twin and sibling studies (Wehmeier et al., 2005), and several genetic polymorphisms have also been identified as risk factors for weight gain (Muller et al., 2013). Serotonin and histamine receptors have received most attention as they seem to play important roles in eating behaviour and may contribute to weight gain via their influence on lipolytic activity (Deng et al., 2010). For example, at least 17 studies have reported an association between the 759 T/C SNP in the 5HT2C gene and antipsychotic medication-induced weight gain. This effect was particularly strong in patients treated with clozapine and olanzapine, both of which have high affinity to 5HT2C receptor (De Luca et al., 2007). The 2548 A/G variant of the leptin gene has also been associated with long-term (but not short term) weight gain (Ellingrod et al., 2007, Templeman et al., 2005).

Although medication-induced weight gain may partly account for the increased prevalence of obesity in psychiatric populations, it seems unlikely to totally explain this relationship. For example, in a systematic review and meta-analysis, Luppino et al. (2010) confirmed that obesity at baseline increased the risk of onset of depression at follow-up. This finding was also supported in a review by Berkowtiz and Fabricatore (2011). Childhood overweight and obesity is associated with an increased risk of mood disorder in adulthood (Sanderson et al., 2011), and higher rates of overweight and obesity have been observed in medication-naïve patients with bipolar disorder (Maina et al., 2008).

Thus, the increased risk of psychiatric disorder in obese individuals is likely caused by a combination of psychological, social, lifestyle, genetic and biological factors, with the latter cause being the primarily focus of this review.

What effect does obesity have on treatment outcomes?

Surprisingly little research has investigated the effects of obesity on treatment resistance in psychiatric disorders; however, studies conducted to date have shown that obesity is associated with an increased likelihood of treatment failure. Studies on antidepressant therapies have found that higher body weight, but not obesity, was associated with a poorer response to fluoxetine (Papakostas et al., 2005), a higher body mass index (BMI) and obesity predicted poorer response to nortripitlyine but had no influence on the response to escitalopram (Uher et al., 2009), and individuals with higher BMI experienced a slower clinical response to general antidepressant treatment (Kloiber et al., 2007). Khan et al. (2007) also found that depressed, obese men experienced little or no therapeutic benefit from antidepressant treatment. An investigation on patients with rapid-cycling bipolar disorder also showed that obesity was associated with a poorer treatment response to lithium and valproate (Kemp et al., 2010). Inflammation and increased pro-inflammatory cytokine production, commonly observed in obesity, are also associated with a poor antidepressant treatment response (Eller et al., 2008, O'Brien et al., 2007, Yoshimura et al., 2009). No studies have been identified investigating the effect of obesity on psychological and other non-drug treatments for psychiatric disorders.

How obesity influences biological pathways associated with psychiatric disorders

As summarised in Figure 2, studies over the past two decades have confirmed that obesity is associated with increased inflammation, oxidative stress, HPA disturbances, neurotransmitter imbalances, mitochondrial disturbances and neuroprogression.

White adipose tissue, the main site for long-term fat storage in the body, contains adipocytes that secrete a variety of hormones and inflammatory cytokines (referred to as adipocytokines or adipokines). These include leptin, resistin, vistfatin, interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and chemokines (Shelton and Miller, 2010). These are all consistently elevated in obesity, as are acute phase proteins such as c-reactive protein (CRP) (Das, 2001, Gregor and Hotamisligil, 2011, Shelton and Miller, 2010). Obesity is also associated with upregulation of the kynurenine pathway, evidenced by reduced concentrations of plasma tryptophan (Breum et al., 2003) and an increased kynurenine/tryptophan ratio (Brandacher et al., 2007). Upregulation in the kynurenine pathway influences neurotransmitter production (particularly serotonin) and is associated with increased oxidative stress and neurodegeneration. This pathway is dysregulated in major depressive disorder, and may also be important in schizophrenia and bipolar disorder (Myint, 2012).

Fat accumulation is also associated with systemic oxidative stress, demonstrated by elevations in lipid and protein peroxidation (Furukawa et al., 2004, Vincent et al., 2007). An altered mitochondrial energy production, particularly in skeletal muscles (Rogge, 2009), and dysregulation in the HPA axis are also observed in obese people (Duclos et al., 2001, Salehi et al., 2005). Support for neurotransmitter disturbances in obesity is obtained by findings of decreased availability of dopamine D2 receptors in the CNS of obese individuals (Wang et al., 2001, Wang et al., 2009). Animal studies have shown that serotonin transporter mRNA levels are significantly down-regulated in neurons in the dorsal raphe nucleus of obese mice (Collin et al., 2000), while overeating has been associated with decreased release of serotonin in the hypothalamus (Svec et al., 2002). Obesity is also associated with unhealthy diets, excess calorie intake and inactivity, which can influence pathways associated with depression and other psychiatric disorders (Lopresti et al., 2013).

Investigations into structural brain changes has largely confirmed that obese and overweight individuals have a smaller hippocampal size compared to healthy individuals (Fotuhi et al., 2012, Mueller et al., 2012, Raji et al., 2010, Taki et al., 2008). A higher mid-life BMI also increases the rate of hippocampal atrophy in late life (Jagust et al., 2005, Taki et al., 2008). Low total brain

volumes are also observed in overweight individuals and in those who have a normal BMI but a large abdominal diameter (Kurth et al., 2012). Brain derived neurotrophic factor (BDNF), which has a key role in regulating neuronal development and synaptic function, also plays a part in the control of energy balance by the central nervous system. BDNF deficiency is associated with increased weight in mice and humans (Noble et al., 2011, Schwartz and Mobbs, 2012).

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Does weight loss improve dysregulated pathways associated with psychiatric disorders?

Weight loss interventions are regularly associated with lower markers of inflammation such as CRP, IL-6 and TNF-α (Bougoulia et al., 2006, Illan-Gomez et al., 2012, Nicklas et al., 2004, Pakiz et al., 2011). These effects are often enhanced when interventions include an exercise component (Pakiz et al., 2011), although this is not always found (Church et al., 2010). Many studies have demonstrated that anti-inflammatory effects of weight loss may not be observed for up to 6 months (Snel et al., 2011), but then continue despite participants gaining weight and returning to baseline weight levels (Olszanecka-Glinianowicz et al., 2012, Snel et al., 2011). After a 5 year follow-up, significant decreases in TNF-α and IL-6 obtained after initial weight loss treatment were maintained. This even occurred in women who regained all their weight (Olszanecka-Glinianowicz et al., 2012). Reductions in inflammatory markers such as CRP and IL-6 have even been observed after weight loss as little as 5% (Imayama et al., 2012), although Madsen et al. (2008) found that over a 3-year period weight loss needed to exceed 10% to induce a significant improvement in inflammatory markers. Weight loss is also associated with reduced markers of oxidative stress such isoprostane, thiobarbituric acid reactive substances and malondialdehyde (Boesing et al., 2010, Bougoulia et al., 2006, Ozcelik et al., 2005, Wycherley et al., 2008), and increased antioxidant enzymes such as glutathione peroxidase and catalase (Boesing et al., 2010, Bougoulia et al., 2006).

Is weight loss possible in psychiatric patients?

Investigations into weight loss programs on psychiatric populations have confirmed that weight loss is an achievable goal. In a study by Faulconbridge et al. (2012), overweight patients suffering from depression and type 2 diabetes lost 8.6% of their initial weight after a one year intensive

lifestyle intervention. Severity of depressive symptoms at baseline did not influence the magnitude of weight lost (Faulconbridge et al., 2012). Obese females diagnosed with major depressive disorder receiving weekly group behavioural weight management for 16 weeks, combined with cognitive behaviour therapy (CBT) for depression, lost 11.4% of their initial weight (Faulconbridge et al., 2011) and, compared to a non-depressed sample, depressed, obese individuals achieved similar weight loss following participation in a behavioural weight loss treatment (Linde et al., 2011). Significant weight loss can also be achieved in depressed and bipolar patients following gastric bypass surgery (Deliopoulou et al., 2013, Malone et al., 2011, Steinmann et al., 2011). Furthermore, taking antidepressant medication prior to surgery did not affect weight loss outcomes at 12 months (Malone et al., 2011).

In patients with schizophrenia and psychotic disorders, weight loss and weight maintenance is also an achievable goal (Daumit et al., 2011, Pendlebury et al., 2007). In a meta-analysis on randomised, controlled, cognitive-behavioural weight loss trials, Bonfioli et al (2012) concluded that in patients with psychosis, a weight loss of 0.98 points in BMI (corresponding to a loss of 3.12% of initial weight) was demonstrated from pooled data. Weight loss programs can also prevent weight gain associated with antipsychotic use and even promote weight loss (Chen et al., 2009, Gabriele et al., 2009, Menza et al., 2004, Vreeland et al., 2003). In a study by Zhang et al. (2012), patients with psychotic spectrum disorders experienced a greater percent baseline weight loss at 12 months, and greater percent BMI loss at 9 and 12 months than people suffering from other psychiatric disorders and no psychiatric disorder. Furthermore, weight loss of 5% or more occurred in 42.6% of patients with psychotic spectrum disorders compared to 18.4% and 23.0% in patients suffering from other psychiatric disorders and no psychiatric disorders, respectively.

Does weight loss improve mental health?

Investigations into the effect of weight loss on mental health outcomes have primarily investigated its effect on depressive symptoms. In a meta-analysis of 31 studies, Fabricatore et al. (2011) concluded that lifestyle modification was superior to control and non-dieting interventions in reducing symptoms of depression, and was marginally better than dietary counselling and exercise-alone programs. Bariatric surgery in obese individuals also improved symptoms of depression and lowered rates of antidepressant use, but had no effect on anxiolytic use (Rutledge et al., 2012). Intragastric balloon insertion was also effective in lowering depressive symptoms in a subsample of depressed adults (Deliopoulou et al., 2013). Using a depressed population of obese women, participation in a behavioural weight loss program or a combined

weight loss and depression program led to a reduction in depressive symptoms and modest weight loss in both groups. Interestingly, there were no differences in outcomes between the two treatment groups (Linde et al., 2011). Little is known about the effect of weight loss programs on mental health outcomes in other psychiatric disorders such as schizophrenia, bipolar and anxiety disorders. However, in a study by Chen et al. (2009) on patients with schizophrenia and antipsychotic-related obesity, participation in a 10-week multimodal weight control program led to weight loss that was mostly maintained at 12-months follow up. Completers also reported significant improvements in measures of quality of life, general health, bodily pain, depression and other emotional subscales. Significant improvements were also reported in positive and negative symptoms as measured by the positive and negative symptom scale. In a study on obese participants suffering from post-traumatic stress disorder (PTSD), weight loss after a 16-week weight loss intervention was associated with a significant decline in PTSD and depressive symptoms (Deliopoulou et al., 2013).

Conclusion and directions for future research

Psychiatric disorders are common in obese and overweight people, with both disorders sharing several common dysregulated physiological pathways. These include heightened inflammation and oxidative stress, HPA imbalances, mitochondrial disturbances and neurotransmitter imbalances. Both disorders are also associated with neuroprogression as evidenced by decreased neurogenesis and changes in brain structure, particularly in the hypothalamus. Several studies have also confirmed that obesity is associated with increased treatment resistance, although weight loss is achievable in psychiatric patients and is often associated with improvements in mental health symptoms. Weight loss also leads to improvements in a number of physiological pathways that are disturbed in mental health disorders.

It is generally accepted that obesity is caused by an array of genetic, biological, environmental and psychological factors that influence each other. While this review has been limited to the discussion of a few key biological pathways, it is acknowledged that a range of other factors are important in the development and maintenance of the obesity-psychiatric disorder relationship (Grimm and Steinle, 2011, Karasu, 2012, Power et al., 2007, Soczynska et al., 2011). This genetic-biological-environmental-psychological interaction will significantly influence food choices, activity patterns, hunger and satiety cues, self-regulation around food and exercise, lifestyle habits, belief systems, and numerous physiological processes associated with both obesity and psychiatric disorders. Other hormones which are important but have not been the focus of this

review includes leptin, insulin, adiponectin, ghrelin, cholecystokinin, and neuropeptide Y (Grimm and Steinle, 2011, Soczynska et al., 2011).

While our understanding of the relationship and psychiatric disorders is increasing, there remain an array of unanswered questions that require further investigation. These include the following:

1. *Is there a bi-directional relationship between obesity and psychiatric disorders?*

   Research to date, particularly in the area of depression, suggests a bi-directional relationship between obesity and psychiatric disorders (Luppino et al., 2010). Longitudinal studies will help further elucidate this relationship. Does suffering from obesity increase the likelihood of suffering from a psychiatric disorder and, if so, what are the important mechanisms that underlie this? Alternatively, does suffering from a psychiatric disorder increase the likelihood of experiencing future obesity and is this due to medication use or are other biological and lifestyle factors involved? Understanding other mediators involved in the relationship between obesity and psychiatric disorders such as dietary and lifestyle factors will also be important areas of investigation.

2. *If weight loss is an important treatment goal in psychiatric populations, what is the most appropriate form of intervention?*

   Sustained weight loss remains an elusive goal for the general population; however, studies do show positive health benefits associated with modest weight losses of 5 to 10 percent (Imayama et al., 2012, Madsen et al., 2008). What is most promising is that many markers of inflammation and oxidative stress remain low even after all weight lost has been regained (Olszanecka-Glinianowicz et al., 2012, Snel et al., 2011). However, the question remains as to the most appropriate weight loss intervention for psychiatric populations. A range of options are available including behavioural weight loss programs (with or without an exercise component), individual and/or group formats, inpatient or outpatient programs, weight loss medications, and bariatric surgeries. The length and intensity of treatment to achieve optimal results in psychiatric populations also requires investigation.

3. *Does weight loss have positive effects for all psychiatric disorders and symptoms?*

   Investigations into the mental health benefits of weight loss have primarily investigated its effect on depressive symptoms. Given the positive influence of weight loss on a number of physiological pathways found to be disturbed in a range of psychiatric disorders, weight loss may also have positive benefits on manic, psychotic, anxiety and other affective and behavioural symptoms. However, this is an area that has received very little attention.

4. *Are mental health benefits from weight loss short-lived or long standing?*

The durability of positive changes in psychiatric symptoms following weight loss requires investigation. Most studies have assessed changes immediately following a weight loss intervention. However, long-term follow-up studies are required to determine whether these changes persist.

5. *Are improvements in psychiatric symptoms the result of changes in physiological, psychological, or environmental processes, or a combination?*

   If mental health improvements occur following weight loss treatments, an understanding into the specific mechanisms that underlie change would be useful. Are positive changes the result of changes in inflammatory, neurogenic and oxidative stress pathways or are they mediated by changes in diet, physical activity, belief systems, social acceptance, or other lifestyle factors? For example, exercise is an effective treatment for moderate depression and anxiety, and healthier diets, particularly adherence to a mediterranean diet, is associated with improvements in mental health (Lopresti et al., 2013, Moylan et al., 2013). Changes in these areas are major components of weight- loss programs. To answer this question, ongoing measurement of psychological, social, lifestyle, and behavioural changes, and measurement of relevant biomarkers over time will be required.

6. *How much weight loss is required for mental health benefits to be achieved?*

   This will assist practitioners to develop appropriate treatment goals with patients. Given the increasing awareness of lifestyle factors such as diet, exercise and sleep in mental health problems (Jacka et al., 2012, Lopresti et al., 2013), it may be that weight loss is not an essential outcome for mental health benefits, but rather the crucial component is lifestyle changes.

7. *Are there dangers associated with weight loss interventions undertaken in psychiatric populations?*

   Developing appropriate guidelines for inclusion in weight loss programs will be important. Are there particular psychiatric disorders where weight loss interventions are not appropriate? Are there specific characteristics that would increase the likelihood of harm associated with participation in a weight loss program, or should participation be open to anyone who is motivated to attend?

8. *What inflammatory and oxidative stress changes occur in psychiatric populations after weight loss?*

   Most research into the effects of weight loss on inflammatory and oxidative stress biomarkers has been undertaken in non-psychiatric populations. Resolving this is important as there is substantial evidence of increased inflammation and oxidative stress in psychiatric disorders. The relationship between changes in these biomarkers and mental health symptoms will also provide valuable information for researchers and clinicians.

9. *Do obese and overweight psychiatric populations require specialised or additional interventions to enhance treatment gains?*

   This issue is particularly pertinent given the increasing awareness of neuroprogression in both psychiatric disorders and obesity. Potentially, suffering from both conditions may increase neuroprogressive pathways and lead to worsening treatment outcomes, relapse or treatment resistance. Adjunct interventions that may be considered include the addition of anti-inflammatory drugs such as COX-2 inhibitors (Muller and Schwarz, 2008) and the TNF antagonist, infliximab (Raison et al., 2013), medications with neuroprotective properties (e.g., antidepressants, mood stabilisers) (Dodd et al., 2013, Lee et al., 2012, Malhi et al., 2012), herbs and nutrients with anti-inflammatory and antioxidant properties (e.g., curcumin, resveratrol, omega-3 fatty acids, green tea, n-acetyl cysteine, CoQ10, selenium, zinc, alpha lipoic acid and vitamins such as A, C and E) (Alappat and Awad, 2010, Floyd, 1999, Kim et al., 2008, Lopresti et al., 2012, Magalhaes et al., 2011, Scapagnini et al., 2012) and lifestyle changes known to enhance neurogenesis (e.g., sleep hygiene interventions, meditation, yoga, relaxation therapies and exercise) (Doraiswamy and Xiong, 2007, Kiecolt-Glaser et al., 2010, Lopresti et al., 2013).

10. *What effect do psychotropic medications have on weight gain, overall health status and relevant biomarker changes in psychiatric patients?*

    As discussed previously, a significant problem associated with many psychiatric medications is weight gain. This is a serious issue for many patients who often cite this as a major reason for their discontinued drug use (Serretti and Mandelli, 2010). As proposed in Figure 3, drug-induced weight gain may potentially contribute to worsening mental health through both physiological and psychological effects associated with increased adiposity. Weight loss interventions and the prevention of weight gain may therefore be especially germane for such patients as it could lead to enhanced medication compliance and improved treatment outcomes.

    Although weight gain is linked with several psychiatric medications, part of this weight gain may also be due to the psychiatric illness. This overlooked area requires consideration in future studies on weight gain, obesity and psychiatric disorders.

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While only preliminary, alpha lipoic acid (a potent antioxidant) holds some promise as an effective agent in preventing antipsychotic-induced weight gain in patients with

schizophrenia (Kim et al., 2008, Ratliff et al., 2013). The medications metformin, d-fenfluramine, sibutramine, topiramate, and reboxetine were also confirmed in a recent meta-analysis to attenuate antipsychotic-related weight gain (Maayan et al., 2010). While these findings are positive, the effects of these medications on mental health outcomes and inflammatory and metabolic parameters in psychiatric patients require further investigation.

While our understanding of the relationship between obesity and psychiatric disorders is expanding, it is evident from this review that there are significant gaps in research. The dangers of obesity and the importance of weight loss are often discussed in relation to chronic illnesses such as diabetes and cardiovascular disease. However, their importance in mental health prevention and treatment should also be recognised.

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Adrian Lopresti conducted a literature search and wrote the first draft of this manuscript. Peter Drummond reviewed the manuscript and provided feedback, corrections and recommendations on further drafts of this manuscript. All authors contributed to and have approved the final manuscript.

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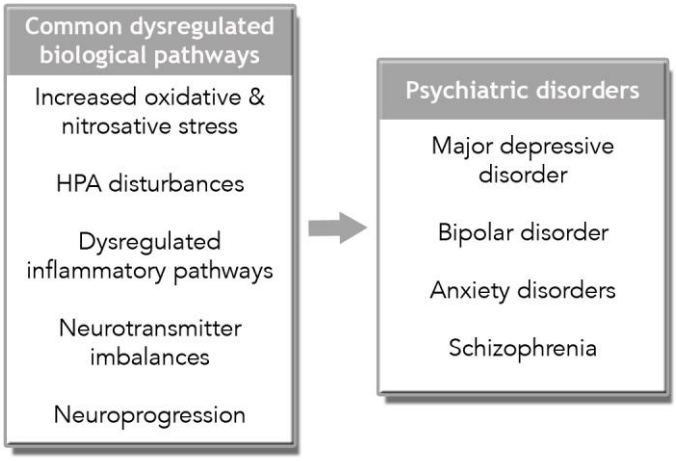

Figure 1. Common dysregulated biological pathways associated with psychiatric disorders

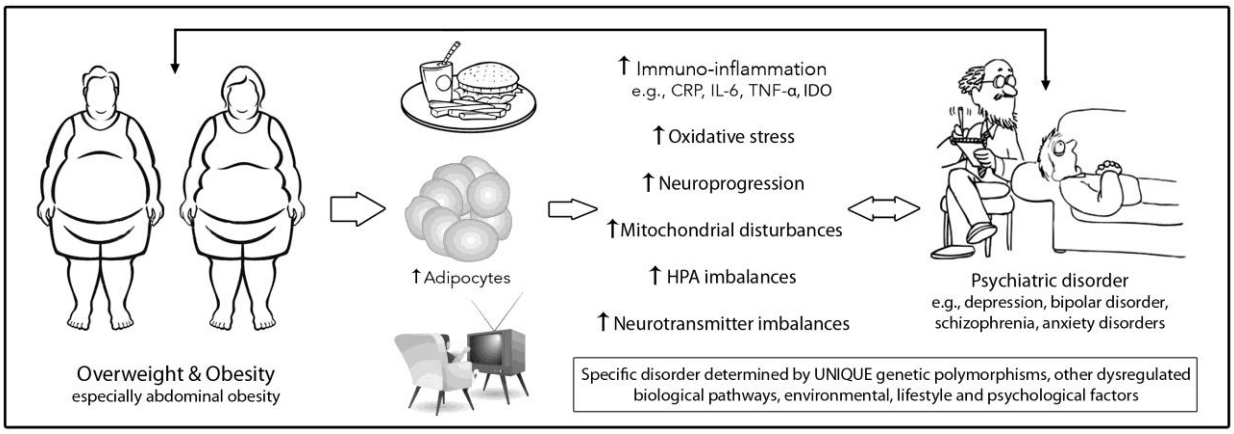

Figure 2. Obesity and its influence on pathways associated with psychiatric disorders. Obesity influences several biological pathways associated with psychiatric disorders including immuno-inflammatory processes, oxidative stress, neuroprogression, mitochondrial disturbances, HPA axis imbalances and neurotransmitter imbalances. A bi-directional relationship likely exists (represented by the bidirectional arrow) between obesity and psychiatric disorders, as obesity increases the risk of psychiatric disorders, and suffering from a psychiatric disorder increases the likelihood of obesity. Suffering from both these conditions is likely to have an additive influence on these pathways. While psychiatric disorders share many commonalities in dysregulated pathways, genetic, environmental, lifestyle and psychological factors will determine the specific disorder(s) suffered [c-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), indoleamine 2,3 dioxygenase (IDO)]

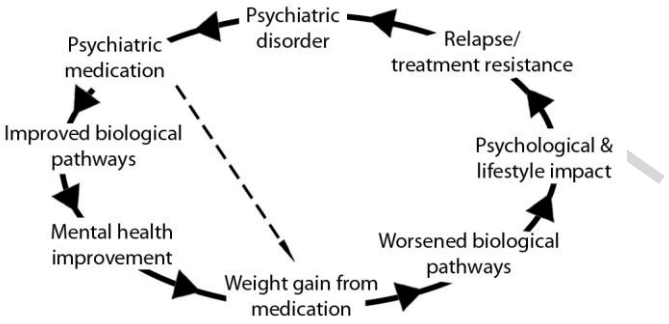

Figure 3. The problem of medication-induced weight gain in psychiatric disorders.

A significant problem associated with many psychiatric medications is weight gain. While medications may lead to mental health improvements for some patients, weight gain can have detrimental effects on several biological pathways (e.g., inflammation, oxidative stress, HPA imbalances, neuroprogression, HPA axis imbalances, mitochondrial disturbances). Weight gain may also contribute to changes in lifestyle, self-concept and other psychological processes that can further compound problems associated with psychiatric disorders. The end result is relapse or treatment resistance. (The dotted arrow represents patients who do not benefit from psychiatric medication)

Research Highlights

- The prevalence of obesity is greater in patients suffering from psychiatric disorders
- Psychiatric patients who are obese have greater treatment resistance and higher psychiatric/medical comorbidity
- Obesity and psychiatric disorders share several common dysregulated biological pathways e.g., inflammation, oxidative stress, mitochondrial disturbances, HPA imbalances, neurotransmitter imbalances and neuroprogression
- Weight loss is associated with improvements in a number of biological pathways that are dysregulated in psychiatric disorders such as inflammation and oxidative stress
- Weight loss interventions may enhance both mental and physical health in psychiatric patients