

Obesity in Schizophrenia

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Abstract

Over the last three decades, an epidemic of obesity has markedly affected patients suffering from mental illnesses such as schizophrenia. Antipsychotic medications used to treat schizophrenia are considered as major culprits. The aim of this review is to first consider risk factors, to then outline negative sequelae of obesity for this population, and finally to address timing and content of recommended clinical interventions. Medical databases were searched with the terms "weight," "obesity," and "schizophrenia." Selection of articles was guided by date of publication; recent papers are preferentially cited. The main findings were that, in addition to antipsychotic medications, socio-economics, lifestyle, immune factors, and circadian rhythms also contribute to obesity risk. A barrier to effective health promotion within psychiatry has been the concern that fears about gaining weight might stop individuals with schizophrenia from taking needed antipsychotic medication. Recommendations, therefore, are to keep the dose of antipsychotic medication as low as possible, avoid polypharmacy, encourage healthy eating and physical activity, address sleep problems and substance use, monitor weight, blood pressure, and metabolic parameters regularly, utilize motivational interviewing techniques and peer support, pay special attention to special needs such as those of women during pregnancy, and include bariatric surgery as a potential intervention. Conclusion: Besides careful attention to medication regimens, the literature supports the active encouragement and support of patient self-management strategies to both prevent and manage obesity in schizophrenia.

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Introduction

Historically, schizophrenia, the diagnostic term for a severe, but treatable, brain disorder that affects 1% of the world's population and is characterized by hallucinations, delusions, disordered thinking, apathy, and cognitive deterioration, has always been linked to an asthenic (slender) body build (1). As a recent example, in a population-based cohort study of men born in Sweden between 1952 and 1982, those who subsequently developed schizophrenia had an initially lower body mass index than their peers. In fact, the men who were underweight (under 18.5 BMI) had a 30% increased risk of developing schizophrenia compared to their peers (2). And yet, today, in developed countries, schizophrenia has become closely associated with obesity, most markedly so since the 1990s, the time at which second-generation antipsychotic drugs became available (3). When I began my psychiatric residency in 1960 (chlorpromazine, the first 1st generation antipsychotic, coming on the market in 1952 in Europe) (4), essentially all my patients were thin. Today, most are portly. What has happened in the interim is greater availability and affordability of high calorie food as well as the advent of second generation antipsychotics to treat schizophrenia. While both first and second generations of antipsychotic agents exert their antipsychotic effect through dopamine D2 receptors, second generation drugs have a relatively stronger effect on insulin resistance and body weight because of their more potent actions on histamine and serotonin receptors, as well as on the muscarinic acetylcholine receptor and the adrenoreceptor (5).

This narrative review of the recent literature is intended as a brief consideration of drug and other risk factors for obesity in the schizophrenia population, illustrated with case examples, and ending with recommendations for prevention and comprehensive clinical management.

Method

The multidisciplinary Google Scholar database was searched with the terms "weight," "obesity," and "schizophrenia." The literature on this topic is voluminous. Selection of articles was guided by date of publication; recent papers are preferentially cited.

Prevalence

Individuals diagnosed with schizophrenia have a 2.8 to 3.5 increased likelihood over that of the general population of being obese (body mass index of 30 or higher) (6). Both women and men with schizophrenia develop a central form of obesity with enlarged waist circumferences (7).

Obesity Risk Factors in Schizophrenia

Lifestyle

Because the spike in obesity in this population correlates in time with the introduction of second-generation antipsychotic drugs, these agents are rightly considered to be major causal contributors to the phenomenon. During the same time period, however, obesity rates also rose in the general population not because of drugs but because of the proliferation and ready availability of calorie-rich foods and an increasingly sedentary urban lifestyle (8,9). The Noncommunicable Disease (10) Risk Factor Collaboration of the World Health Organization pooled 1698 population-based studies consisting of more than 19 million participants and found that, from 1975 to 2014, the age-corrected mean body mass index (BMI) rose from 21.7 to 24.2 in men, with a slightly lesser rise in women. There are approximately 8% more obese individuals in the world today than there were 40 years ago (10). Although many of the very poor across the world continue to be undernourished, obesity is prevalent even among this demographic because healthy foods cost more than calorie-rich food. This is

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very relevant to individuals with schizophrenia who are among the poorest poor – due to several well-known factors such as the severity and chronicity of the symptoms (false perceptions, false beliefs, lack of motivation, cognitive defects) associated with this illness, the unemployment that results from both illness and interrupted schooling, and the direct costs of the illness, its treatment, and its long years of rehabilitation (11). Over the years of illness, people with schizophrenia drift downwards in socioeconomic class (12) and end up living in disadvantaged neighborhoods where high calorie food is more affordable than low calorie food and where there are few opportunities for physical activity and energy expenditure. The neighborhoods in which people with schizophrenia live are crowded, violent, and dangerous (13), discouraging residents from even stepping outside the home, never mind walking or jogging (14). In addition, 'negative' symptoms such as apathy and asociality are characteristic of approximately 60% of individuals with schizophrenia, which means that people with this diagnosis prefer lonely, sedentary activity such as napping or watching TV to engaging in more vigorous weight-losing activities, especially when these involve other people (15-17). One study found that 81% of time spent by people with schizophrenia was sedentary time (17).

Twenty-five percent of people with schizophrenia are said to be depressed (18), which makes a passive, isolated, obesity-prone lifestyle even more likely. In order, perhaps, to stay away as much as possible from other people, patients with schizophrenia may reverse day and night, sleep during the day and, at night, have little to do but eat (19).

Another factor is alcohol. Forty percent of men with schizophrenia and 23% of women patients are addicted to alcohol, usually in the form of beer, which is particularly calorigenic (20). More than 60% smoke heavily (21) and when they stop (smoking cessation

programs are part of comprehensive care for patients with schizophrenia), they gain weight (22).

Although nutrition guidance is also part of comprehensive treatment, the low calorie diets recommended by dieticians are not only unaffordable but, in addition, require more preparation than ready-made food – a culinary effort that is difficult for people with severe psychotic symptoms to undertake. Despite guidance, patients with schizophrenia continue to eat fatty foods, few fruit and little fiber (23-25).

Genetic Risk Factors

In recent years, it has been recognized that the same genes may confer risk to different diseases. For instance, for most gene regions that have been linked to schizophrenia, overlapping regions of linkage have also been obtained in type 2 diabetes (26). Understanding copy number variations (CNVs) in the genome has opened up new mechanisms by which a genetic variation can affect more than one phenotype. In the last 5 years, an increasing number of studies have found that individuals who have micro-duplications at the 600-kilobase break points 4 and 5 near the middle of chromosome 16, at a location designated p11.2, have an increased risk of psychotic disorders (27). A meta-analysis reports a fourteen fold-increased risk of psychosis and a sixteen fold increased risk of schizophrenia in individuals with micro-duplication at proximal 16p11.2 (28). These same CNVs are associated with decreased body mass while microdeletions in this region are associated with obesity (29).

This is an interesting association between schizophrenia and asthenic build and suggests that it is probably not genetics that makes individuals with schizophrenia tend toward obesity but, rather, lifestyle and the medication they take.

Many attempts have been made to look for genes that predispose to antipsychotic-associated weight gain (30), and that work continues.

Treatment Risk Factors

There is little doubt that antipsychotic drugs are critical factors in the current widespread tendency to obesity of schizophrenia patients. A study of 51 patients with chronic schizophrenia who had never received antipsychotic drug treatment and 51 healthy comparison subjects showed that, despite the lifestyle issues referred to above, the drug-naive patients in the study had a significantly *lower* BMI (19.4) than the controls (22.7) (31). The authors of this study concluded that schizophrenia in the absence of antipsychotic drug treatment is not associated with obesity. The fact remains that almost all individuals diagnosed with schizophrenia do need to be treated with antipsychotic medication and essentially all antipsychotic medications increase weight (32), although some of the many available drugs have been more implicated than others (33-36). Large appetite increases are sometimes described.

Example

The symptoms of a young male patient with severe schizophrenia improved remarkably when he was changed from a first generation depot antipsychotic to olanzapine 20 mg HS. He had been extremely emaciated (weighing 110 pounds) and apathetic, but, in two months, lost many of his psychotic symptoms, gained twenty pounds and become more active, riding his bicycle everyday. A few months after starting olanzapine, he missed his psychiatric appointment, calling in to explain from a surgical ward of a nearby hospital that he had broken his leg falling off his bike. "I get so terribly hungry," he said, "that I fell off because I was rushing

home – I just couldn't wait to get something to eat."

Antipsychotics are not the only psychotropic medications that induce weight gain. As mentioned earlier, many people with schizophrenia suffer from co-morbid depression (18) for which they are commonly treated with antidepressants and mood stabilizers, which also have weight-inducing potential (37).

Other Potential Risks for Obesity in Schizophrenia

Circadian Rhythm Impairment

Circadian rhythms are responsible for daily food intake, hunger and satiety being under the control of a central pacemaker in the anterior hypothalamus. The core clock mechanism is linked to lipogenic and adipogenic pathways so that disruption of circadian physiology can lead to obesity by shifting food intake schedules (38,39). Meal times are potent synchronizers of biological clocks and the disrupted food intake of people with schizophrenia can be a cause (or a result) of disturbed rhythms (38,39).

Recent studies have shown that significant sleep/circadian disruption occurs in many if not most patients with schizophrenia (40-43). The disturbed sleep and lack of routines in eating predispose individuals with schizophrenia to disrupted lipid control that can lead to weight gain and obesity.

Immune Factors

Immune mechanisms can lead to disturbances in glucose metabolism and in inflammatory response that can result in obesity, and this is of potential significance in schizophrenia (44,45) because the most consistent association in genome-wide association studies (GWAS) of schizophrenia has been with the major histocompatibility complex (MHC) region of the genome, which contains hundreds of genes involved in immunity (46,47). There may be an active connection in schizophrenia patients between obesity and altered

immunity.

Sequelae of Obesity

The negative health consequences of high BMI are mediated by raised blood pressure, disturbances in glucose metabolism, and adverse lipid profiles (48).

Obesity constitutes a major risk factor for type 2 diabetes, to which people with schizophrenia seem particularly prone (see genetic factors above). It has been found that, even in first-episode, drug-naïve patients with schizophrenia, 15% show impaired fasting glucose tolerance, are more insulin resistant and have higher levels of plasma glucose, insulin, and cortisol than healthy comparison subjects. This may be due to shared predisposing genes between schizophrenia and diabetes, or to the stress inherent in this illness (49).

Obesity is a major factor in the metabolic syndrome (50,51) and in cardiovascular problems (52), which considerably shorten the lives of people with schizophrenia (53). Besides medical problems such as diabetes and metabolic syndrome and cardiovascular problems, obesity poses a risk for sleep apnea and impairs the quality of sleep (54,55). Obesity increases the risk of respiratory difficulties and, in women, leads to difficult pregnancy and labor. Obesity lowers the threshold for the development of many cancers through the secretion of estrogens, adipokines and cytokines by adipose tissue (56).

There are also psychosocial sequelae of obesity in this population, for instance non-adherence to antipsychotic medication (in an attempt to prevent more weight gain), which can lead to symptomatic relapse and rehospitalization (57). There also appears to be an unexplained positive correlation between obesity and impairment of neurocognitive function in schizophrenia (58,59). Obesity further impairs quality of life through increased physical and psychological problems as well as increased perceived stigma (60-62).

Example

One young woman with schizophrenia lived with a boyfriend who came from a well-to-do family. Because she herself was alienated from her family and had essentially no close friends other than her partner, she especially looked forward to holidays when she was invited to her boyfriend's family's lavish parties. Her illness symptoms were stable, but, over time, she put on increasing amounts of weight. Her weight soared to 300 pounds and her boyfriend's family, who had previously been very fond of her, stopped inviting her to parties – they told her boyfriend that they were ashamed for their other guests to see her.

Management of Obesity in Schizophrenia

The management of weight gain and obesity in patients with schizophrenia requires regular and frequent monitoring, early recognition, and multidisciplinary treatment (63).

The strategies are essentially the same as they are in the general population (64), with the added provisos that attempts at health promotion often do not reach this socially isolated population, that psychiatric patients may not regularly see a primary care provider for health screening and monitoring, that the motivation to change is low in this population, and that control of psychotic symptoms usually takes precedence, for both doctor and patient, over the need to keep weight down (65-67).

Health Promotion

There needs to be an emphasis on prevention through health promotion programs that focus on weight gain and its sequelae and on the urgency of tackling these issues early before metabolic changes ensue. This needs to be started in early intervention for psychosis programs (68) although clinicians are loath to do so for

fear of turning patients away from much needed medications. Health promotion for this population needs to be targeted and tailored (69), embedded in healthy life style education that includes diet, exercise, and discontinuation of use of cigarettes and street drugs (70). Despite the significant weight gain that comes after successful smoking cessation and the increase in diabetes and hypertension that comes with it, it remains of primary importance for patients with schizophrenia to stop smoking as this significantly decreases cardiovascular risk, the major factor in the high mortality rate in this population (71).

Screening and Monitoring

Screening and monitoring (waist circumference measures, weight, blood pressure, hemoglobin A1C) have to be conducted regularly and frequently (69,72), starting with first contact with psychiatric services.

Motivational Interviewing

Motivational interviewing to help motivate patients to change their behavior has been shown to be successful in schizophrenia with respect to weight reduction (73,74). It is a method that uses open-ended questioning and reflective statements that establish an empathic relationship between patient and counselor. Ambivalences and barriers to change are explored, personal feelings and opinions are solicited, up-to-date information is offered and, as a result, the motivation for change is facilitated. The approach is personalized so that preferences in foods and activities are emphasized (65,75,76).

Example

The patient referred to above who was disinclined from her boyfriend's family's parties, refused to attend exercise programs because they were "too much work." She loved dancing, however, and was happy to join a salsa class, which she attended regularly.

Personalized Behavioral Interventions

Behavioral interventions targeting calorie restriction (avoidance of high carbohydrate and high fat foods) and energy output (walking 20-30 minutes a day) work (77-79), but they need to be personalized, with frequent face-to-face contact. And the providers need to be well trained (80).

Sleep Hygiene

Because disrupted sleep contributes to weight gain, assuring sound sleep helps to combat obesity. Through its effects on circadian rhythms, or perhaps through other means of action, melatonin not only attenuates weight gain but also protects against metabolic syndrome in schizophrenia (81-83).

Somewhat paradoxically, the weight-inducing drugs used to treat schizophrenia also tend to induce sedation, so that the results of drug switching are never certain.

Example

A young man with a schizophrenia diagnosis had been treated with olanzapine and had put on weight. For this reason, he was switched to aripiprazole, an antipsychotic drug that is a partial agonist and purported to help patients lose weight (84,85) Unexpectedly, the patient gained even more weight. At the same time, his psychotic symptoms worsened so he was eventually placed on clozapine, a drug for non-responders, which is known to add weight. Paradoxically, he not only stopped gaining weight, but dropped thirty pounds in the ensuing six months. Apparently, while on aripiprazole, the patient had been up in the night eating whereas clozapine, which is sedative, made him sleep through the night.

Medication Changes

Switching from a weight-inducing antipsychotic to one that is relatively weight-sparing is a common clinical strategy, but it is of uncertain benefit (86,87). Perhaps more important is to keep doses as low as possible and to avoid using more than one antipsychotic medication at a time. Adding metformin is another potentially useful strategy (63,88,89).

Prenatal Care

Good prenatal care is critical in schizophrenia because of the potential effects of pregnancy on a genetically-at-risk fetus. Obesity during pregnancy is not uncommon in this population for all the reasons addressed earlier in this paper. Obesity during pregnancy leads to increased rates of gestational diabetes, pre-eclampsia, and difficult labors. Infants are at relatively high risk for congenital malformation and stillbirth. Mothers may experience post-partum hemorrhage. Children of obese mothers may, in later years, develop obesity and metabolic problems (90,91). Specific dietary advice is, therefore, required, during prenatal care and efforts made to ensure motivation to curb appetite and increase activity levels.

Surgery

For gross obesity, bariatric surgery is a possibility. It was initially withheld from patients with schizophrenia because it was not known if these patients would be able to manage postsurgical protocols. More recently, it has been found that the success rate of bariatric surgery for people with schizophrenia is the same as it is in the general population (92,93).

Peer to Peer Support

Peer support and counseling have become part of standard care for schizophrenia on the assumption that individuals are most likely to change behavior if they identify with the counselor. Advice from peers who

have gone through similar experiences can sound more credible than advice coming from health care providers. Peers who have experienced and overcome weight gain while maintained on the same medication as the person they are advising can be very powerful role models (94-97).

Self-Management Programs

Whoever is providing advice, support, and encouragement, in the end, patients must be engaged in their own health care and learn to manage their own weight (98). This holds true for patients with schizophrenia, but this population faces barriers to self-management that are greater than the difficulties faced by patients with other diagnoses. Certain symptoms of schizophrenia – apathy, social isolation, paranoia for example - make it difficult to engage patients in self-care. Schizophrenia patients also have knowledge barriers that can be attributed not only to isolation but also to cognitive deficits. They may be addicted to alcohol or drugs, which cloud consciousness and diminish motivation. The obesity may be of such magnitude that it poses functional barriers to activity of all sorts. Patients with schizophrenia often lack the support of friends and family and they may not be able to sustain good relationships with health care providers (99). Nevertheless, it is possible for patients with schizophrenia to be motivated to take charge of both their physical and their mental health (100).

Technology (Internet programs, email messaging, smart phones, use of pedometers) has proven very useful in the field of self-management (101-104). And people with schizophrenia have shown that they are not averse to using technology (105,106).

In many ways, it is more comfortable for many people with this diagnosis to interact with an appliance than with a person (107,108). Miller et al. (109) found that, at the time their survey was done, 56% of their study participants, all diagnosed with schizophrenia,

were using text messaging; 48% had an email account. Twenty seven percent used social media sites daily (Facebook being the most popular) and most of those who used the technology claimed that it increased their ability to socialize.

Treating Obesity in Schizophrenia

- Start early to promote health
- Use motivational interview techniques
- Help with budget, meal planning
- Promote abstinence from alcohol, drugs, cigarettes
- Offer personalized choices of activity
- Provide peer support
- Screen and monitor regularly – weight, waist circumference, blood pressure
- Address sleep problems
- Keep antipsychotic dose low
- Consider switching antipsychotics
- Avoid polypharmacy
- Consider adjunctive metformin
- Promote self-management skills
- Use technology where appropriate
- Target pregnancy in women
- Consider surgery for severe obesity

Conclusion

This brief review of the recent literature on obesity and its management in the context of schizophrenic illness has considered risk factors, sequelae, and intervention strategies. A barrier to prevention has been the concern that fears about gaining weight might stop individuals with schizophrenia from taking their antipsychotic medication, a major risk

factor for obesity. A holistic approach keeps the dose of antipsychotic medication as low as possible, avoids polypharmacy, encourages healthy eating and physical activity, addresses sleep problems and substance use, monitors weight, blood pressure, and metabolic parameters, makes use of motivational interviewing techniques and peer support, takes special care with reproductive age women and their pregnancies, and seriously considers bariatric surgery for severe obesity. Most importantly, a holistic approach encourages and supports self-management of both physical and mental health.

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