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Atypical Antipsychotic Induced Weight Gain: Pathophysiology and Management

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There is compelling evidence that patients with schizophrenia are prone to gain weight. In addition, atypical antipsychotic (AAP) drugs also induce weight gain. All antipsychotic drugs produce weight gain but the potential varies. Many studies overwhelmingly confirm that AAP drugs produce substantially more weight gain in comparison to conventional antipsychotic drugs. Clozapine and olanzapine have the most weight inducing potential. Even ziprasidone, which is considered to be weight neutral, and aripiprazole a dopamine modulator produce weight gain in some. The pathophysiology of weight gain is complicated. Many neurohormones, neuropeptides, gut hormones, as well as adipose tissue and hair root derived hormones interact with environmental factors to produce weight gain. Management of weight gain is a difficult problem. Basic to treatment is an understanding of the etiology. Drug induced obesity provides a unique opportunity to psychiatrists to understand this clinically important problem. In the absence of this knowledge, prevention is the best hope. Education, diet control and simple behavioral measures may prevent excessive weight gain. In those with weight gain, treatment can be attempted with pharmacotherapy with careful monitoring of the side effects.

Keywords   Atypical antipsychotic induced weight gain; Weight gain and drugs; Management of drug-induced weight gain; Pathophysiology of weight gain; Schizophrenia and weight gain.

INTRODUCTION

Overweight (BMI $> 27\,\mathrm{kg/m^2}$ and obesity (BMI $> 30\,\mathrm{kg/m^2}$) are the most easily recognized, the most rapidly increasing, and the most difficult to treat medical conditions affecting almost all parts of the world. Over the past 10 years, the prevalence of obesity in the general population worldwide has been increasing significantly (1). One half of US adults are currently overweight and 22% are obese (2,3). Obesity is multi-factorial with the interaction of cultural, environmental and genetic factors. Obese individuals have an increased risk of death from all causes compared to normal weight individuals.

People with psychiatric disorders have shown a greater predisposition for obesity than the general population (4). There is compelling evidence that obesity and obesity related conditions (5–7) are frequent in schizophrenia. This may be related to schizophrenia itself or to the antipsychotic medication treatment. Support for the possibility that the disease itself promotes obesity comes from studies, which have shown that both schizophrenic patients treated with or without antipsychotic drugs developed equal weight gain (5,6). Recently, a number of publications have focused on the ability of atypical antipsychotic (AAP) drugs to induce obesity, and its consequences such as hypertension, diabetes (8), and others including discontinuation of treatment and relapse (9,10). This paper will review the conventional and AAP drug induced obesity as well as its mechanisms, and treatment.

REVIEW

Conventional Antipsychotic (CAP) Agents and Obesity

Reports of weight gain induced by CAP drugs began to appear soon after these drugs became available (11,12). A 12-week study (11) indicated that the administration of phenothiazines produced weight gain, and that those patients switched from phenothiazines to phenobarbital or placebo tended to return to their previous weight. A double blind study (13) indicated that thioridazine induced more weight than fluphenazine and long acting fluphenazine enanthate produced four times more weight gain than that found in the general population (14). A comparative 6-week random assignment study (15) indicated that haloperidol and thioridazine, but not molindone, increased weight. Another investigator (16) noted a weight loss with thioridazine and loxapine, and weight gain with haloperidol, thiothixene, and fluphenazine. In this study, weight gain seemed to plateau by the 36th week with haloperidol, but not with thiothixene or fluphenazine. Weight gain is a common cause of noncompliance to, and discontinuation of, CAP drugs (14,17–19). Most of the abovementioned studies suggest that all CAP drugs increase weight, but each drug's ability to do so varies. The associations speculated between a particular drug and its dose, clinical improvement and weight gain are currently unproven.

Weight Gain with Atypical Antipsychotic (AAP) Agents

Many studies overwhelmingly confirm that AAP drugs produce substantially more weight gain in comparison to CAP drugs. In a study designed to evaluate the prevalence, severity, and burden of side effects associated with the use of antipsychotic agents, the effects of six antipsychotic agents (divided into four potency groups) were evaluated in 64 psychotic outpatients from a veteran population (20). These agents were chlorpromazine and thioridazine (low potency), perphenazine (mid-potency), fluphenazine and haloperidol (high potency), and clozapine (atypical). Weight gain was reported in all groups, but patients in the high-potency group had the lowest weight gain. Weight gain was more frequent and severe in the atypical group. The published reports indicate that all AAP drugs produce a weight gain of 0.9–3.6 kgs in 8 weeks, and that it is most significant with clozapine (21). Long-term weight gain is higher by several more kg before it stabilizes with clozapine (22).

Clozapine

Rate of weight gain among patients treated with clozapine has been thoroughly investigated. In a review of over 13,000 patients treated with clozapine worldwide, Lieberman et al. (23) reported weight gain in 0.73% of patients. Naber and Hippius (24) noted weight gain in only three patients treated with clozapine in a retrospective review of 503 inpatient medical charts. In contrast to these earlier findings, a recent retrospective study of 216 inpatients treated with a mean daily dose of 317 mg/day of clozapine for up to 12 years, noted a weight gain frequency of 11.6% (25). Hummer et al. (26) prospectively followed 81 ambulatory patients on clozapine and found that 36% of patients gained more than 10% of their body weight with an average of 3.5 kg. Wirshing et al. (27) analyzed weight gain in 92 males with schizophrenia and noted that their weight gain plateaued at 20 weeks, which is similar to the findings of others (28–30). Together these reports indicate that weight gain occurs frequently during clozapine treatment.

In addition to weight gain, increases in body mass index (BMI) has been documented with AAP treatment. Frankenburg et al. (31) found the average body mass index (BMI) increase for men to be 3.3 kg/m^2 and for women to be 5.9 kg/m^2. Furthermore, since it has been shown that patients treated with other psychotropic agents have elevated BMIs, and many of the patients in this study were taking multiple psychotropic drugs including clozapine, it cannot be conclusively stated that clozapine was the exclusive factor, or even a factor at all, in the BMI increase.

Another aspect in clozapine induced weight gain is the finding that clozapine may be associated with a decrease in smoking (32). The association between smoking cessation and weight gain has been well established (33), and a modest but significant amount of variance in BMI in patients treated with clozapine is associated with decreases in cigarette consumption (31). Some authors imply that the weight gain associated with clozapine correlates with a good clinical response (34,35). Leadbetter et al. (36) suggested that weight gain might relate to the efficacy of clozapine and/or to its unique pharmacological effects. Bai et al. (37) found that among patients taking clozapine, a greater weight gain was related to a significant clinical response among female patients, but not among male patients. On the other hand, Lamberti et al. (38) and Umbricht et al. (39) did not find any relationship between clozapine induced weight gain and clinical improvement. Zhang et al. (40) noted a negative relationship between weight gain and improvement. Therefore, the relationship between clinical improvement or gender and weight gain remains conjectural at this time.

Risperidone

Eighteen percent of patients on risperidone, compared with 9% of patients on placebo, gained more than 7% of their total body weight (41). In a 52-week comparison of risperidone and haloperidol for the prevention of relapse in

patients with schizophrenia, there was a mean increase in body weight of 2.2 kgs with risperidone and a mean decrease in body weight of 0.7 kgs with haloperidol (42). The weight gain with risperidone at 8 weeks was the same as that in 52 weeks (43). Peuskens et al. (44), in an 8-week study involving 1362 patients, noted a weight gain in risperidone treated patients significantly higher than that of haloperidol. Another study (45) reported that 39% of patients in the risperidone group, compared to 20% of patients in the perphenazine group, gained weight. In a 52 weeks clinical trial, Csernansky and Okamoto (46) noted that patients in the risperidone group gained a mean weight of 2.27 kg compared to 0.74 with haloperidol. While all the above mentioned studies indicate that weight gain with risperidone is moderate, Cohen et al. (47) noted that 37 of 39 adult mentally retarded psychotic patients developed a mean weight gain of 8.5 kgs over 2 years. The weight gain reported in this population is higher than that noted by others. It is possible that the mentally retarded gain more weight than non-mentally retarded psychotic patients.

Quetiapine

In a 6-week study, patients in the quetiapine group had a mean weight gain of 2.3 kg, compared to 0.3 kg in the haloperidol group (48). Peuskens et al. (49) noted a mean weight gain of 1.8 kg, compared to 1.3 kg with chlorpromazine over a 6-week duration. Another study found a weight gain of 2 kg compared to 0.1 kg with placebo at the sixth week (50). Similarly, 25% of quetiapine treated patients, compared with 4% of placebo treated patients, and 9.8% of ziprasidone treated patients, compared with 4% of placebo treated patients, developed an increase of more than 7% of total body weight (51).

Ziprasidone

Many investigators have noted no weight change with this drug in both 4- and 6-week studies (52–55). Of the AAP drugs, ziprasidone produces the least amount of weight gain. In a 52-week study with chronic schizophrenic patients, ziprasidone treated patients lost 2.65 kg, and the placebo group lost 3.77 kg (56). The weight loss may be due to the withdrawal of the weight inducing AAP drugs. As the drug is relatively new in the market the long tem effects and the potential to increase weight in the unselected population is yet to be established.

Olanzapine

Patients receiving 15 mg/day of olanzapine experienced a mean weight gain of 11.8 kg at the end of a one-year clinical trial (57). The most significant weight increases occurred in patients who were the most underweight at baseline. Pre-marketing data (58) also showed that during long-term trials, 56% of the olanzapine-treated patients reported a weight gain of greater than or equal to 7% of their body weight. In a recent large (N = 377) 8-week comparison study of olanzapine and risperidone (42), olanzapine-treated patients had significantly greater increases in mean body weight and BMI than risperidone-treated patients. When weight gain between olanzapine and risperidone was compared in a group of patients with bipolar disorder, the average increase at week 12 was 4.8 kgs for the olanzapine-treated patients and 1.7 kgs for the risperidone-treated patients (59,60). Gupta et al (61) found that 93.75% of patients treated with olanzapine experienced weight gain. We compared the weight gain of patients receiving olanzapine, risperidone, ziprasidone, and haloperidol monotherapy with behavioral measures. Patients in the olanzapine group gained about 1.6 kgs, in the risperidone group 0.6 kgs, and in the ziprasidone group 0.45 kg, while those in the haloperidol group lost 0.05 kg at the end of 52 weeks. The weight gains in all the groups are muted in contrast to published data. For example, Allison and Casey (21), in a meta-analysis, indicated that weight increase at the end of 10 weeks with olanzapine was 4.15 kg, risperidone 2.10 kg, ziprasidone 0.04 kg, and clozapine 4.15 kg. In a one-year study, weight increase with olanzapine was reported to be over 10 kg (57). The behavioral measures have a significant effect in limiting weight gain.

Dose

Robinson and colleagues (62) found that the appetite and body weight change in 18 schizophrenic outpatients was significantly higher in those treated with high doses of chlorpromazine (>1500 mg/day) than in those receiving a low-dose schedule (<800 mg/day). The results of this study appear to be clear-cut. However, the sample was too small and the reported dose-range too wide to allow for a more precise discrimination. Along the same lines, a significant dose-response relationship was observed only at the highest—above 400 mg daily and lowest doses of chlorpromazine—50 mg daily (63) or depot AP (64). The relationship between dose and increase in body mass makes intuitive sense, however, many studies (26,31,65) did not find a relationship between dose and weight increase.

WEIGHT GAIN: PLATEAU OR EXPONENTIAL

Weight gain is usually the most rapid in the acute phase of treatment. Clozapine associated weight gain is the highest in the first few weeks (36). Ultimately it reaches a plateau in every patient after one or two years (66). During long-term

treatment, no significant differences in mean weight change were seen with olanzapine treatment at any of the time points between 1 and 3 years (67), indicating a plateau at one year. Henderson et al (68) in a five-year naturalistic study of 82 patients treated with clozapine found that weight significantly increased over time. Patients in this study gained the highest amount of weight gain within the first 12 months of clozapine therapy. The daily dose of clozapine did not correlate with weight change. Further analysis of the data indicated that the patients continued to gain weight until approximately month 46, when it appeared to level off. Johnson and Breen (64) indicated that weight gain continued even after more than 2 years on depot AP drugs. Wirshing and associates (27) noted that weight gain plateaued around 20 weeks with olanzapine and clozapine and at 10 weeks with risperidone and sertindole. In our study weight gain plateaued with olanzapine around 30 weeks and with risperidone around 20 weeks. All these results indicate that weight gain should be frequently monitored during the first six months, as the gain during this period is rapid. In addition, the weight gain continues at a slower pace until the end of one or two years and eventually tapers, reaching a plateau, rather than continuing to exponentially rise throughout the duration of treatment.

MECHANISM OF WEIGHT GAIN

Obesity is multifactorial and is determined by the interplay of numerous polypeptides and neurohormones with environmental factors such as dietary habits and affluence. Neuropeptides and neurohormones known to stimulate feeding are neuropeptide Y, galanin, dynorphin, β-endorphin, growth hormone, releasing hormone, norepinephrine, anandamide, GABA, and grhrelin. Those that inhibit feeding are serotonin, insulin, neurotensin, corticotropic releasing factor, dopamine, cholecystokinin, leptin, thyroid releasing hormone, melanocyte stimulatin hormone, glucagon, and somatostatin (69). The role of each of these is difficult to predict as they work harmoniously together and the weight gain may be related to their delicate balance or multiple abnormalities at different levels (70,71).

The mechanisms of weight gain induced by psychiatric drugs are unclear and therefore diverse mechanisms have been implicated. As the prevalence of clinically relevant obesity has also been reported to be four times higher in patients receiving typical or atypical antipsychotic drugs than in general population (6,14) dopaminergic blockade, the putative common mode of action for all antipsychotic drugs may have a role to play. Animal pharmacological studies in rats with olanzapine (72) and with chlorpromazine, haloperidol, risperidone, sulpiride, olanzapine and clozapine (73) produced an increase in feeding behavior through suppression of satiety and weight gain. Further the propensity

to gain weight in rats has been reported to be higher in females (74,75) probably related hyperprolactinemia and its effect of gonadal-adrenal steroids and insulin sensitivity (75). A study in schizophrenic patients indicated a relationship between heterozygous CYP2D6 and percentage of increase in BMI during olanzapine treatment (76). As olanzapine is metabolized by CYP2D6, heterozygous cytochrome only increases the level of olanzapine by decreasing its metabolism and thereby produces weight gain.

The serotoninergic system has been extensively implicated in the control of feeding behavior. Increase in central serotonin transmission reduces food intake in man and animals (77,78) and conversely low cerebrospinal 5-HT levels have been reported in obese women (79). Serotoninergic agents like fenfluramine have been widely used for the treatment of obesity (80). Fluoxetine, a selective serotonin reuptake inhibitor has been reported to reduce hunger and food intake in humans and to cause hypophagia in animals (78,81,82). These findings suggest that a decrease in serotoninergic transmission may cause weight gain. AAP agents block the 5 HT2 serotonin receptors thereby causing obesity.

Clozapine besides being a D_2 dopamine receptor blocker significantly blocks D_1, D_4, $5HT_{1a}$, $5HT_2$ and $\alpha 1$ and $\alpha 2$ adrenoreceptors. Risperidone on the other hand exhibits strong D_2, $5HT_2$, $\alpha 1$- and $\alpha 2$-adrenoreceptors antagonism (83). Affinities to D_2 dopamine, H_1 histamine and $5HT_2$ receptor action appear to have robust correlation with body weight gain.

Administration of a dopamine D_1 receptor antagonist produced an initial decrease in food intake and thereafter increased hyperphagia (84). An interaction study revealed that quinpirole, a dopamine D_1 receptor agonist, suppress feeding during a 40-minute food access period in both food deprived and nondeprived rats (85). Kaur et al. (73) showed that clozapine induced hyperphagia was reversed by quinperole indicating the role of D_1 receptors in AAP drug induced weight gain.

Increased Appetite

Increaed appetite is considered to be partly responsible for weight gain, and is probably related to the interaction of AAP drugs with dopamine, serotonin, and histamine neuronal receptors (9). Inactivity and sedation can indirectly contribute to weight gain. Particularly, the blockade of $5-HT_2$ receptors may lead to appetite deregulation causing weight gain (86). $5-HT_{2c}$ gene knockout produced obese rats (87) indicating that the blockade of these receptors can cause obesity. Weight gain induced by olanzapine may in part be related to $5HT_{2c}$ receptor blockade. Topiramate, a $5HT_{2c}$ receptor agonist, has been found to be useful in treating olanzapine induced obesity. Intraperitoneal injections of chlorpromazine or haloperidol increase feeding behavior

in animals (74,88). Thus increased dopamine blocking and consequent increased appetite is the major factor in antipsychotic drug induced obesity. Increased appetite has been probably related to the interaction of antipsychotics with dopamine (D_2) serotonin ($5HT_{1b}$, $5HT_{2c}$) and histamine (H_1 and H_2) receptors in the perifornical lateral hypothalamus (89).

Increased Leptin

The role of leptin in drug induced obesity is an important issue. Mice and humans deficient in leptin are obese (90). In healthy overweight subjects, a correlation between weight gain and leptin levels has been observed, however, the role of leptin in producing obesity in humans is controversial. Only 10% and not the remaining 90% of healthy obese subjects studied had normal leptin levels (91). The fact that haloperidol does not and olanzapine does increase leptin and only olanzapine and not haloperidol is associated with weight gain has been of interest attesting that increased leptin can be the cause of obesity. No increase in leptin was observed in patients without an increase in body weight after the administration of haloperidol (92) sulpiride (93) or lithium (94). In patients receiving clozapine or olanzapine, significant increases in body weight, BMI, and leptin levels have been noted. Independent of elevated BMI, 57% of patients treated with olanzapine had high leptin levels (95). On the other hand, in patients receiving haloperidol or no medication, these measures remained stable (92). Unlike in healthy obese persons, in patients treated with olanzapine or clozapine, no correlation between weight gain and leptin levels has been noted (96). The above mentioned studies indicate that leptin may have a primary or secondary role in obesity. A recent review provides compelling evidence that increased leptin levels are secondary to increased weight in drug free patients and in patients receiving antipsychotic medications (97). Therefore, the relationship is complicated by the fact that increases in leptin may be a primary cause of obesity, or secondary as a result of leptin receptor insensitivity, thereby producing a complex picture.

The complexity of the role of leptin has been enlightened by some of the recent findings. A hormone produced by fat cells may be the link between obesity and insulin resistance. Expression of this protein, called adiponectin, is reduced in obese mice and humans. Adiponectin injections improved both obesity and blood glucose in mice (98). This indicates an intricate communication between adipose tissue, leptin, blood glucose, and insulin resistance. Leptin happens to be one player in this elaborate multifactorial relationship. Leptin and cytokine changes are secondary to weight gain and may not be the primary pathophysiological cause (97).

Cytokines

Clozapine treatment increases systemic levels of various cytokines and soluble cytokine receptors, particularly those of tumor necrosis factor, TNF-1alpha, and leptin (92,99,100). Cytokines are pivotal mediators of cell-to-cell interactions within the immune system and between immune and other physiological systems. The same cytokine receptors, together with leptin, are involved in body weight regulation (101,102). Therefore, it is suggested that the production and secretion of cytokines and soluble receptors may in turn be responsible for clozapine induced fever, sedation, and weight gain. SSRI and AAP combinations have been reported to improve negative symptoms and possibly decrease weight gain (100).

COMPLICATIONS OF WEIGHT GAIN

Do those psychiatric patients who gain weight suffer from the normal complications of obesity such as hypertension and heart disease? Study results indicate that the magnitude of weight gain associated with several AAP drugs can be expected to produce increases in 10-year mortality rates hypertension and impaired glucose tolerance (103). No data is available to substantiate the claim that psychiatric patients with AAP drug induced obesity, develop complications similar to those seen in the general obese population. The only pertinent finding is the incidence of diabetes, which is know to occur frequently amongst AAP treated patients (10). However, as diabetes has been known to occur in patients who are not obese, it is difficult to conclude that obesity causes diabetes in this particular group of patients.

MANAGEMENT

From the data it is evident that there is truly no one, single mechanism by which AAP agents may increase body weight. There is a low recognition rate (20% of cases) of considerable weight gain in patients treated with antipsychotic medications. Obesity is the most important cause of type 2 diabetes today (104). An excess of body weight is associated with a deterioration of glucose utilization and promotes the development of type 2 diabetes, particularly in those with a genetic predisposition. This is a serious problem, as the proclivity of a single patient to gain weight cannot be predicted. Obesity, male gender, and chronic antipsychotic drug administration are all risk factors for sleep apnea (105); a serious often unrecognized problem increasing the morbidity in patients.

Treatment of drug induced weight gain has three components including (a) understanding its pathophysiology, (b) prevention and (c) treatment.

UNDERSTAND PATHOPHYSIOLOGY

Genetics play a part in the mechanism of weight gain. Currently, 25 Mendelian disorders exhibiting obesity and 165 quantitative trait loci have been identified. Fifty-seven loci most of whom are on chromosome Y have been linked to obesity disorders (106). Obesity is polygenic with each gene having a relatively small effect (susceptibility) and work in combination with environmental factors (107). Multiple neurohormones such as leptin and resistin (108) from fat cells, intracellular hormones such as cellular gamma peroxisome activating receptor (109) and hypothalamic pituitary factors as well as dopamine, serotonin and norepineprine all play a part. These biological factors interact with cultural and environmental factors to produce weight gain. Therefore, drug induced weight gain provides a unique opportunity for research, may yield valuable insight into the pathophysiological factors and thereby lead to etiologically oriented treatment of antipsychotic drug induced obesity. In addition, future antipsychotic drugs without obesity potential can be manufactured. The interaction between cultural, environmental and biological factors modifying, augmenting or changing multitudes of neuropeptides, neurohormones and energy maintenance factors, along with their interplay, will be a harvest of opportunity for understanding the role of AAP drugs in this puzzle, and in improving psychosis as well. While it is a dream that one single factor can be isolated to understand the drug related obesity, any understanding will provide a clue to furthering strategies to help these patients.

PREVENTION

Behavior and lifestyle are an important part of weight maintenance amongst psychiatric patients. Most patients can attain a loss of 10% of their baseline weight at a rate of 0.5 to 1 kg per week if they are willing to establish an energy deficit of 300 to 500 calories per day through a combination of dietary changes and increased physical activity. Physical activity is an important component to weight. Exercise should be initiated slowly and increased gradually. Approximately 45 minutes of intense walking at least five days per week is a predictor for successful weight maintenance. Mere dietary changes without exercise, or diet without a negative energy balance does not reduce weight. Cohen et al. (47) noted that dietary restriction alone produced a weight loss of merely 0.05 kg per month in only 3 of 20 patients; the remaining seven patients, gained weight. Dietary restriction must be such that there should be a negative energy balance. Additional exercise to spend energy is also necessary. Generally, after discontinuation of the psychiatric medications, the patient's weight frequently stabilizes, and actually decreases in some instances (52,55). It has been reported that calorie intake reduction is not of much use within psychotic populations in decreasing weight (47,62,69).

One method of reversing weight gain is to substitute the incriminating drug with another agent reported to have a lower potential for weight gain. This strategy may not always work, as the individual's susceptibility to gain weight and their lifestyle, or other independent variables affecting weight gain, continue to operate. However, in some instances the results can be gratifying. For example, Reinstein et al (110) reported a decrease in weight with lowering the dose of clozapine and adding quetiapine in schizophrenic patient on clozapine who had diabetes and/or weight. Further studies are necessary to evaluate whether the substitution strategy has a clinically significant effect on reducing weight.

TREATMENT

In an attempt to decrease weight, or to control further weight gain, anti-obesity drugs can be added to the antipsychotic drug regimen. The goal of anti-obesity drugs is to maintain a negative energy balance until the desired weight loss is reached (111–116). A number of drugs with diverse action mechanims (117) have been used to treat obesity.

Sympathomimetics/appetite suppressants have been approved for short-term use for weight reduction. They include phentermine, phenmetrazine, mazindol, diethylepropion, dextroamphetamine, and sibutramine. Sibutramine, a noradrenaline reuptake inhibitor, has been found to be as effective as d-fenfluramine in achieving weight loss of 8 kg in a year in doses of 5 to 15 mg daily (118). Such an action subsequently leads to improved glycemic control.

Orlistat, a fat absorption blocker, in doses of 120 mg taken with each meal, has been used to reduce AAP drug induced weight gain (119,120). Although effective as weight reducing agents, orlistat and phentermine may decrease the absorption of antipsychotic drugs.

Metformin is known to lower blood sugar by inhibiting hepatic glucose production and increasing insulin sensitivity in peripheral tissues. Other effects include delayed intestinal glucose absorption and a decrease in lipids. As an increase in free fatty acids may be responsible for weight gain, metformin 500 mg three times a day, was used adjunctively in 7 adolescents who experienced weight gain (121). A statistically significant weight decrease was noted in 4–12 weeks. However, the potential of metformin in reducing weight is limited and its administration warrant further investigation (122).

Due to its weight reducing property, the anticonvulsant topiramate, may be useful in the treatment of weight gain (123,124). A 29-year-old male taking clozapine lost 29 kg of body weight in five months with 125 mg/daily of topiramate (125).

Table I Effects and Side Effects of Drugs Used for Weight Gain

Drug	Effect on obesity	Side effects	References
Sibutramine	Improved compliance with restricted energy intake More useful for prevention	Insomnia, dry mouth, headache, tachycardia, hypertension (5%)	113
Orlistat	Useful if dieting has produced a weight loss of 2.5 kg over 4 consecutive weeks Low fat diet is needed.	Flatulance Fecal incontinence Diarrhea Depression	115
Prozac	Some weight reduction along with dietary control Lipid and glycemic control transient	Sexual side effects	
Topiramate	Dose related weight loss. Randomized study needed.	Acute glaucoma Cognitive difficulties Extreme sedation	119
Amantadine	Limited clinical data	Depression, delirium agitation psychosis rashes up to 30%	123
Nizatidine	Decrease weight Improve glycemic control and lipid profile Effect dose related.	Hyperprolactinemia delirium, confusion, depression, blood dyscrasia and atrioventricular block	101 117
Metformin	Improves serum glucose and lipids Weight reducing capacity weak	Lactic acidosis, decreased B12 and folate absorption	117

Amantadine, is suggested as an adjunctive treatment for weight gain. Its dopaminergic activity and consequent decrease of antipsychotic induced high prolactin levels may be responsible for weight reduction. An open-label study by Correa et al (126) reported that all the 10 patients on chlorpromazine experienced weight loss of 1.3 to 5.9 kgs when prescribed amantadine 200–300 mg/day. Similar results have been noted in patients treated with olanzapine (127). However, amantadine has a risk of worsening psychotic symptoms, as it is a dopamine agonist (128).

Nizatidine, an H-2 receptor blocker, has been reported to reduce weight gain during olanzapine therapy for up to 16 weeks in doses of 600 mg/daily (129). This effect may be related to a decreased appetite, which is a consequence of increased cholecystokinin or to suppression of gastric acid (130). Cimetidine, another H-2 receptor blocker, has also been reported to reduce weight (131).

CONCLUSIONS

Antipsychotic drugs produce weight gain and some more than the other. However these drugs are clinically very useful making a vast difference in the life of the chronically mental ill patients. Therefore their use is justified but the consequences of weight gain can not be taken lightly. In this dilemma, the psychiatrist should use the AAP drugs with caution and appropriate monitoring. While there are a number of pharmacological agents available there are two problems with these drugs: 1) The loss of weight is minimal. Most of the drugs available curb the appetite. As eating is a habit, patients can overeat even without hunger; and 2) They all produce a number of side effects, which may affect the quality of life (Table I). These side effects preclude their use routinely in psychotic patients who have gained weight. Prevention and education at the beginning of antipsychotic drug treatment is the best measure we have now. As some drugs have a higher propensity to produce weight gain, neutral antipsychotic drugs can be substituted in patients who have gained weight. Theoretically we need to understand what the new drugs do so that pharmaceutical companies will try to produce future drugs, which lack this troublesome side effect.

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