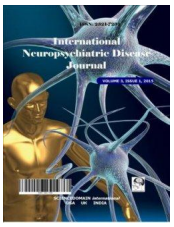

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Antipsychotic Medications and Weight Gain: Etiologies, Predictors and Adverse Clinical Consequences

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Authors' contributions

This work was carried out in collaboration between all authors. Authors NAQ, DSAD and SOS designed the study. All authors contributed to the writing of the protocol as well as the first draft of the manuscript. Authors NAQ, DSAD, SOS, FKA and OAA managed the analyses of the study. All authors managed the literature searches. Authors NAQ and SOS revised the manuscript a number of times. All authors read and approved the final manuscript.

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ABSTRACT

Background: First and second-generation antipsychotic medications are commonly prescribed to millions of psychiatric patients with psychosis around the world. Antipsychotic medications are associated with a variety of adverse effects including weight gain. Objective: This review aimed to describe etiologies, predictors and morbidity and mortality associated with weight gain induced by antipsychotics in a psychiatric population.
Methods: Electronic searches (2000-2018) of PubMed, Medline, and Google Scholar were conducted using Boolean operators and keywords. Of all articles retrieved (n=37,987), two

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independent reviewers identified 105 relevant articles published in English peer-reviewed journals.
Results: In conjunction with other biopsychosocial and cultural risk factors, first and second generation antipsychotic medications are associated with weight gain in psychiatric population having a spectrum of severe mental illnesses. The weight gain linked with multiple predictors was differentially more common during initial intake of all antipsychotics but remained stable or decreased during the longer timeline. The most weight gain associated with a variety of adverse consequences affecting safety of patients was reported with clozapine and olanzapine and the least weight gain was seen with aripiprazole and amisulpiride, and no weight gain with the use of newer drugs especially ziprasidone, lurasidone and paliperidone.
Conclusion: Most antipsychotic medications commonly increase weight gain in patients with psychotic conditions around the world. Consequently, weight gained induced and predicted by multiple paradigms causes a variety of additional potentially adverse effects including medical and psychological conditions and premature deaths in psychiatric vulnerable patients who need close monitoring and appropriate management across antipsychotic treatment trajectories.

Keywords: Antipsychotics; clozapine; olanzapine; weight gain; obesity; biopsychosocial.

1. INTRODUCTION

There is no health without public mental health [1]. Mental health is as important as physical health for a variety of functions and daily activities. However millions of people suffer from mental and physical health problems due to multiple biopsychosocial factors [2,3]. Therefore psychotropic medications including antipsychotic drugs, psychosocial modalities and spiritual and religious therapies are developed to benefit millions of psychiatric patients across the world mainly for the last seven decades or so. First and second generations of antipsychotic medications are relatively safe but associated with problematic extrapyramidal symptoms and weight gain and metabolic syndrome, respectively. Multimodal integrated approaches globally tend to better improve their mental health conditions, reduce disabilities, enhance well-being and happiness and promote their mental health [4,5]. Despite continuous advancements in psychopharmacology, psychotherapies, integrated health approaches and other mental health services, a proportion of psychiatric patients (less than 50%) do not have access to standard psychiatric care. This trend is attributed to sociodemographic variables, under-recognition of mental conditions, severity and comorbidities of mental disorders, stigma, exclusion, shame, ethnicity, cost, mental health literacy and lack of services in rural areas [6-8].

Psychotropic drugs are the mainstay of treatment for mentally ill patients and these include antipsychotics, antidepressants, anxiolytics, mood stabilizers, sedatives and hypnotics, psychostimulants, anti-dementia drugs, opioid and their derivatives, and other anti-addictive drugs compatible with ATC system (A = anatomical site of action, T= therapeutic indication and C= chemical class of the drug) developed by WHO [9]. The alternative newer classification of psychotropic drugs to ATC system includes neuroscience-based nomenclature [10,11]. However, none of the nomenclatures of psychotropic drugs is seamless [11] and their detailed description is beyond this paper. These psychiatric medications including antipsychotics associated with overweight are used in all age groups from child to elderly population having a variety of mental disorders and they act on eleven domains of receptors including serotonin 2C receptor [11,12] and dopaminergic reward and endogenous opioid pain systems. SGAs knock down reward system making it insensitive to hedonic impact of foods and in turn increase appetite and, hence, causing overweight and obesity in psychiatric patients with schizophrenia [13]. Mental disorders tend to co-occur with psychiatric as well as physical disorders and both mental and physical disorders have etiological bidirectional relationship with greater disease burden [14] including human, social and economic. In such scenarios, weight gain and its management further add to the burden of mental disorders treated by psychotropic drugs especially antipsychotic medications around the world. Notably mental health professionals face many challenges especially balancing the treatment of psychosis with SGAs, developed in 1990s, and concurrently preventing weight gain and metabolic syndrome in mentally ill patients. Researchers recognized the weight gain and its negative consequences including premature death attributed to FG and SG antipsychotics soon after their use in patients with severe mental illnesses worldwide.

This review critically describes the etiologies, predictive factors and adverse clinical consequences of antipsychotic-induced weight gain in patients with severe mental illnesses. The relevance of this review is that this potentially important research avenue with a wide variety of adverse consequences is not given adequate consideration in Arabian Gulf countries. The significance of this review underlies the fact that it will bridge the information gap of mental health professionals and physicians concerning weight gain caused by first and second generations of antipsychotic drugs, and possibly by extension patient population and public at large will also benefit considerably.

2. METHODS

2.1 Search

Boolean operators were used to search specific data (from 2000 to 2018) on antipsychotic medications linked or not to weight gain and obesity. Electronic searches of three databases and three open access publishing houses (Google Scholar, MEDLINE/PubMed, OvidSP and Dovepress.com, Hindawi.com & Sciencedomian.org) were conducted using Boolean operators and keywords such as antipsychotic medications AND weight gain OR overweight OR obesity OR psychiatric disorders. Additional searches were made using keywords such as antipsychotic (FG and SGA) medications AND weight gain OR obesity adverse effects OR Case reports OR observational studies OR randomized clinical trials (RCTs) OR systematic reviews OR meta-analysis for retrieving pertinent articles published in English literature. Boolean operators are words such as AND, OR, NOT or AND NOT used as conjunctions to combine or exclude keywords in web searches that result in more focused and productive results, and ultimately save time and effort by eliminating inappropriate hits.

The searches were modified whenever needed and compatible with databases.

3. RESULTS

A large number of articles (n=37,987) were retrieved. A quick screening by a single author excluded 32721 articles that did not focus on weight gain associated with typical and atypical antipsychotics. Then two authors (NAQ and DSD) independently reviewed the available data (n= 5266) for extracting relevant articles. Consequently, unrelated articles (n=2052), inaccessible papers because of high price tag (n=360), articles cited in systematic reviews and meta-analysis (n=86, no exclusive focus on antipsychotic medications), no abstract available (n=63), duplications (n=2492), and irrelevant information (n=98) were excluded from this study. The remaining were 115, which were screened further for eligibility, and those articles which did not focus on antipsychotic (typical or atypical) medications concerning weight gain, overweight, obesity and types of antipsychotic medications were excluded (n=10). Thus, the total articles included in this narrative review were 105 (Fig.1).

3.1 Definition of Weight Gain

The prevalence and definitions of weight gain and obesity tend to guide researchers to precisely assess and monitor the weight in healthy and ill population. Weight gain mainly measured in kilograms is an increase in body weight involving muscle mass, fat deposits, and excess fluids including water. The average body weight is a minimum of 57.7 kg to a maximum of 87.7 kg. Adult population of Asia is 2.82 billion and overweight population constitutes 24.2%.The adult population of North America is 263 million and overweight population is 73.9%. The adult population globally is 4.63 billion with an average weight of 62 kg and overweight population constitutes 34.7 % of the total population [15]. Overweight and obesity are linked to cardiovascular diseases, diabetes, musculoskeletal disorders, cancers, neurological diseases, disabilities and impairment of social functioning. Body mass index (BMI, formula = weight in kg/square of height in meters), a simple weight measurement tool for male and female adults is commonly used to classify overweight (BMI ≥25) and obesity (BMI≥30). Abdominal obesity is defined as waist circumference >102 cm in men or >88 cm in women [16]. The weight gain is defined as a mean weight gain of 1.9kg to 20.1 kg. A normal BMI is between 18.5 and 24.9, a BMI between 25 and 29.9 is classified as overweight, and 30 to 39.9 denotes obesity. Patients with a BMI above 40 are considered extremely obese [17]. In sum, the normal weight, weight gain, overweight and obesity are well defined concepts in obesity research including antipsychotic medications paradigm.

3.2 Prevalence of Mental Disorders

Mental illnesses are commonly occurring disorders around the world. Most people tend to

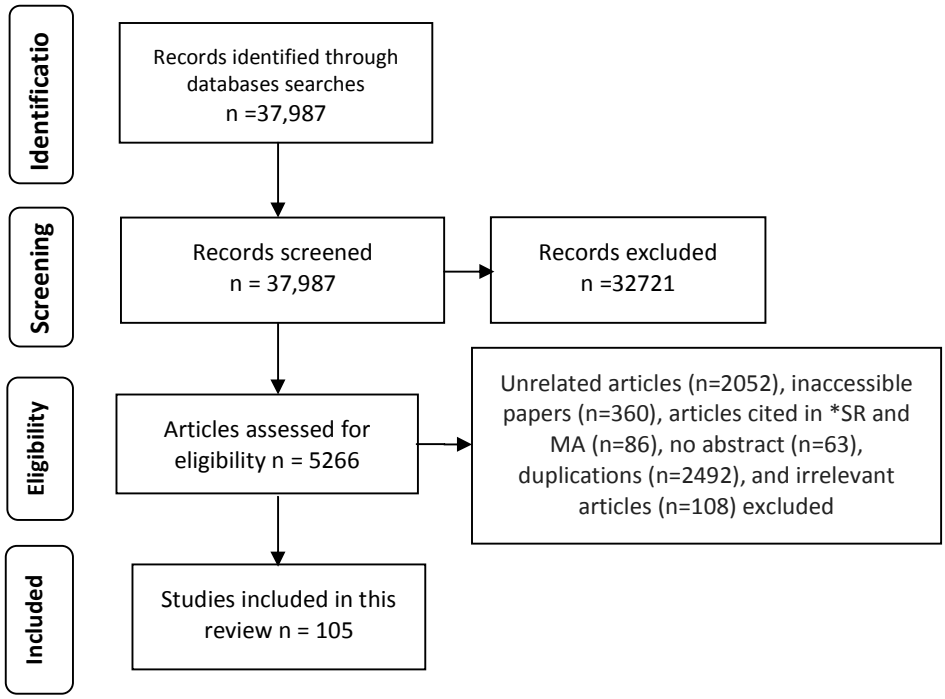

Fig. 1. Prisma diagram summarizing the flow of search results
*(*SR=systematic review & MA=meta-analysis)*

develop a diagnosable psychiatric disorder during lifetime, a variable proportion of them are prescribed antipsychotic drugs leading to weight gain and other adverse health consequences which are preventable conditions. Antipsychotic medication induced weight gain overweight and obesity are also linked with diabetes, cardiovascular diseases, metabolic syndrome and premature death. Psychiatric disorders such as depression and anxiety are also important comorbidities of overweight and obesity. In other words, overweight and obesity may relate to psychiatric disorders, physical diseases and antipsychotic medications, the latter are prescribed to about 20% to 25% of world population suffering from moderate to severe mental illness (SMI) [18]. Furthermore, each year about 38% of European population suffers from depression, dementias, alcohol use disorders and stroke [19] and possibly many of them manifesting psychotic features would be prescribed off-label first or second generation of antipsychotics (F&SGA). In an interesting cohort study, Schaefer and colleagues reported the prevalence of enduring mental health, a psychological phenotype (means persons never diagnosed with a mental disorder) to be only 17% (n=171, cohort mode=409) [20]. Instead 83% of people tend to develop non-enduring mental health echoing the fact that most people will develop a diagnosable mental disorder during life time. Currently the global trend is the study of prevalence of specific mental disorder and its psychiatric and physical comorbidities along with adverse consequences rather than a group of psychiatric disorders in different age groups [21-24]. However, this is not the platform to describe the prevalence rate of each psychiatric disorder. Overall, the prevalence of mental disorders is variable across the world and is determined by sociodemographic variables, biological factors including genetics, environment and cultural paradigm.

3.3 Causes of Weight Gain

3.3.1 Antipsychotic medications

First and second-generation antipsychotics (FGA & SGA) but not all tend to cause iatrogenic weight gain in mentally ill patients around the world [25,26]. Notably FGA were problematic in regard to causing severe extrapyramidal syndromes whereas SGA are known to produce equally challenging metabolic syndrome, both are associated with multiple adverse consequences. Besides additional contribution by antipsychotic drugs, overweight and obesity

are global commonplace complex problems with multiple etiologies and diverse negative health consequences having negative impact on patient safety worldwide.

There are many important contributing factors to weight gain or obesity in psychiatric population. Genetic vulnerability is one of them, and at least 50% of individual difference in BMI is due to genetic factors. However, increasing obesity rate over the recent years illustrates significantly the impact of environmental factors on body weight [27]. Thus, genetic-environment interaction paradigm also may underlie the weight gain and obesity in psychiatric as well as general population along with associated adverse events. Another indicator of genes involvement is that males and females are differentially susceptible to weight gain. Gender differences are apparent concerning how and where body fat is stored, and consequently men accumulate more fat in the intra-abdominal area than pre-menopausal women. This relatively increases males' risk of developing cardiovascular diseases, T2DM, cancers and stroke and metabolic changes including hyperglycemia [28] and early death compared to women.

The increased appetite and other mechanisms linked with weight-gain and psychosis resulting from cannabis use has been documented in the literature. However most studies have focused on short-term outcomes but the long-term effects of cannabis use are not well defined [29]. This study suggested that cannabis use in patients with psychosis may cause increased body weight and other health-related problems [29] including respiratory and cardiovascular diseases, and cancer. It is also documented that people with cannabis use have poor outcomes in those with pre-existing psychotic disorders [30,31]. Besides antipsychotic drugs, other biopsychosocial factors globally contribute to overweight and obesity including reduced sleep and overeating [17,32-38]. Weight gain linked with reduction in sleep hours (≤5) might be attributed, interalia, to increased caloric intake and reduced activity (lethargy), alteration in serum leptin and ghrelin levels, and menopause hormone changes and nocturnal eating and stress related cortisol. Other factors such as sedentary lifestyle, relative lack of healthcare clinics concerning overweight and obesity, neuroinflammation, alteration in neurometabolism and oxidative stress may contribute to obesity and psychiatric and medical conditions [39]. When patients are on antipsychotic medications, then it becomes challenging to know the contribution of these biopsychosocial and cultural factors to overweight and obesity. Obesity is reported to comorbid with physical and psychiatric conditions, increased human, social and economic burden of diseases and premature deaths [40-43]. Overall antipsychotic medications and biopsychosocial factors in tandem tend to increase weight gain in clinical populations (Table 1). A full paper on biological mechanisms underlying weight gain induced by psychotropic drugs including antipsychotic medications is forthcoming soon [under review].

Table 1. Etiologies of weight gain, overweight and obesity

Factors	Remarks
Psychiatric disorders	People with schizophrenia and other psychotic disorders, anxiety, PTSD, and severe depression
Genetic	Multiple genes are involved in drug-induced obesity, Prader-Willy syndrome
Physical disorders	Thyroid disease, Cushing disease
Biological	Neuroinflammation, alteration in neurometabolism and oxidative stress, hormones in the brain, GIT and fat cells, gut microbiota-brain-axis, Modulation of mitochondria
Body constitutions	Genetic endowment and impact on behavior
Dietary habits	Overeating with craving to different foods
Insomnia	sleep less than 5 to 6 hours,
Lifestyle	Sedentary, i.e., lack of exercise
Geographic region	Influenced the type of psychiatric medication prescribed and the psychiatric diagnoses.
Environment	Fast food outlets, violence – infested neighbor and pesticides, lack of recreational centers and parks, lack of safe walking and biking routes [44]
Cultural	Breast feeding (initial one year) protects children from obesity and allergic diseases [45,46] and African-American women gain weight associated with cumulative socioeconomic position [47].

Evidently most antipsychotics - FGA-thioridazine, chlorpromazine, and haloperidol and SGA - risperidone, ziprasidone, iloperidone and amisulpiride increase weight gain in psychiatric patients possibly through increasing insulin resistance [48]. In a well conducted study, Kim et al. (2010) found that BMI contributes to the variance in insulin resistance (25% to 33%) among patients on SGA similar to the reference population but olanzapine showed an independent effect on insulin resistance without any connectivity to obesity [49]. Ziprasidone has both sides of the coin, i.e., reported to increase or decrease weight [42]. Recently antipsychotics are reported to disturb gut microbiome resulting in weight gain in patients with schizophrenia [50]. In another study, mitochondrial (mtDNA, nuclear-encoded mitochondrial genes) functions in terms of energy homeostasis were disturbed by antipsychotic medications resulting in weight gain in psychiatric patients [51]. Conversely paliperidone is not reported to cause weight gain among patients with schizophrenia [52]. Like ziprasidone, aripiprazole is found to uncommonly cause weight loss as well as gain in patients with psychoses. Lurasidone either monotherapy or adjunctive with mood stabilizers such as lithium, approved for the treatment of bipolar depression and schizophrenia is reported to cause sleepiness and weight gain, which are milder compared to quetiapine [42,53]. Importantly, schizophrenic patients on lurasidone tend to think better cognitively and take part in everyday life compared to placebo or extended-release quetiapine [53]. According to one study, the antipsychotic medications that cause the greatest weight gain in psychiatric patients are olanzapine and clozapine, moderate weight gain due to quetiapine, risperidone, paliperidone and the least weight gain attributed to aripiprazole and ziprasidone [54], and typical antipsychotic molindone, not available in USA, does not increase weight gain in patients with schizophrenia [55]. In light of variable results, the longterm exposure to newer antipsychotic medications like paliperidone and lurasidone in patients with psychosis will ultimately clarify whether or not they contribute to overweight. Asenapine a relatively newer antipsychotic causes up to 0.9 kg weight gain in patients with bipolar disorder and schizophrenia in the first three weeks of treatment. Conversely, Food and Drug Administration (FDA) USA Package Insert reported a 52-week regulatory trial causing negligible weight gain. Thus, asenapine may be less problematic drug concerning metabolic effects [56,57]. Furthermore 19% of patients with mania treated with asenapine reported weight gain compared to 31% treated with olanzapine [58]. Asenapine targeting multiple receptors in the brain and having good tolerability is reported to reduce weight by 6.6% (ideal should be 7%) in a patient with schizophrenia previously treated with olanzapine [59]. However, asenapine require further rigor studies. Olanzapine (craving 48.9%) and clozapine (23.3%) are also reported to link with binge eating (16.7% vs. 8.9%) and, hence, induce the largest weight gain in patients with schizophrenia and related disorders [60].Using 3-year observational data concerning amisulpride, clozapine, olanzapine, quetiapine, risperidone, and oral and depot FGAs, Bushe and colleagues (2012) reported that the mean weight gain was lowest with amisulpride (SGA, 1.8 kg) and highest with olanzapine (4.2 kg). The weight change by all antipsychotics was variable but most rapid was during the first 6 months, and then very slow over three years period without plateau. The proportion of patients losing ≥7% of their baseline bodyweight was highest with quetiapine (10%) and lowest with depot FGAs (5%). Furthermore, between 7% and 15% of patients moved into an overweight or obese BMI category (≥25). In summary, all antipsychotics were associated with significant (≥7%) weight gain and loss from baseline [61]. (Table 2).

FGA used in men were reported to reduce BMI, lower waist/height ratio, android fat mass index, and peripheral insulin resistance. Conversely, SGAs were associated with increased BMI and lowering of insulin resistance [62]. A meta-analysis results support that prolonged exposure (> 38 weeks) to all antipsychotics except amisulpride, aripiprazole and ziprasidone are associated with weight gain. Interestingly, antipsychotic-naive patients showed pronounced weight gain [63,64]. Overall the weight gain and loss attributed to FGA and SGAs is inconsistent in the literature may be due to methodological differences including settings, sampling, definitions of weight gain, several risk factors and predictors, and antipsychotic related properties.

3.4 Strength of Causal Relationship

A causal link between weight gain and use of antipsychotic drugs is certainly evidence-based finding and its strength needs to be further studied in details. The strength of the causal relationship between antipsychotic drug exposure and weight-gain can be assessed by a drug trial conducted with antipsychotic-naive patients. Tarricone and colleagues [65] reviewed

11 studies reporting the effects of antipsychotic drugs on body weight among patients naïve to antipsychotic drugs. The mean values of weight-gain in patients exposed to antipsychotics were highly significant during the first few weeks of treatment. The sample averaged around 3.8 kg in gained weight and an increase of 1.2 in BMI. Weight-gain associated with antipsychotic drug treatment appears to occur rapidly in the first few weeks and minimal weight gain during the following months [65]. As reported, younger patients and initial low BMI were significantly associated with weight gain [66]. Thus, first three to six months of treatment by antipsychotics are crucial for monitoring and minimizing the weight gain in psychiatric patients on FGA and SGA. Early weight gain predicts obesity development in patients with schizophrenia (62%) and bipolar disorder (50%) on long followup of 20 years [67]. Overall, there is a strong relationship between antipsychotic use and weight gain in patients with psychosis, major depression, and anxiety and autistic disorders [65-68] and all classes of antipsychotic medications tend to produce variable amount of (high to medium to low) weight gain (Table 3).

Table 2. Second generation of antipsychotics (SGAs) and weight changes in clinical population

Medications	Wt. gain	Wt. loss	Remarks
Olanzapine	4.2–7.4 kg, average gain of 12 kg, average weight gain 2.3 kg/month,	No	Up to 90% of patients
Quetiapine	4.1 to 5.6 kg, 1.8kg/month	+/-	
Risperidone	0.3–2.6 kg, average weight gain 1.0 kg/ month	No	
Asenapine	0.9 kg weight gain	No	In first three months
Ziprasidone	0.8 kg/month	+/-	Its role in weight gain needs longtime exposure
Lurasidone		No	
Iloperidone	1.5–2.1 kg	No	Similar to Risperidone
Paliperidone	+/-	No	Its role in weight gain needs longtime exposure
Aripiprazole	0.5–0.9 kg	+/-	Compared to placebo
Clozapine	2.4 to 31.3 kg, 1.7 kg/month	No	10 percent gain over baseline
Amisulpride	1.8 kg		Like amisulpiride, + weight gain with brexpiprazole and cariprazine,
FGAs	First Generation of Antipsychotics - chlorpromazine, thioridazine, haloperidol, loxapine, molindone, perphenazine and others now used rarely; however they slightly decrease or increase weight in psychiatric population compared to most SGAs linked to moderate to severe wt. gain.		

Table 3. Antipsychotic class and weight gain risk

Psychiatric medications	Risk of weight gain
Olanzapine and Clozapine	High – risk (obesity)
Amisulpride, asenapine, iloperidone, quetiapine, risperidone and sertindole	Medium – risk (overweight)
Aripiprazole, lurasidone, paliperidone and ziprasidone	Low – risk (weight gain)
First-generation antipsychotics (FGAs)	Low - risk
Younger patients with initial low BMI highly vulnerable to gain weight with all antipsychotic medications. FGAs mostly cause extrapyramidal symptoms but SGAs are associated with weight gain and metabolic syndrome. High-, medium- and low-risk, standard terms, used in classifying drug risk profile [69].	

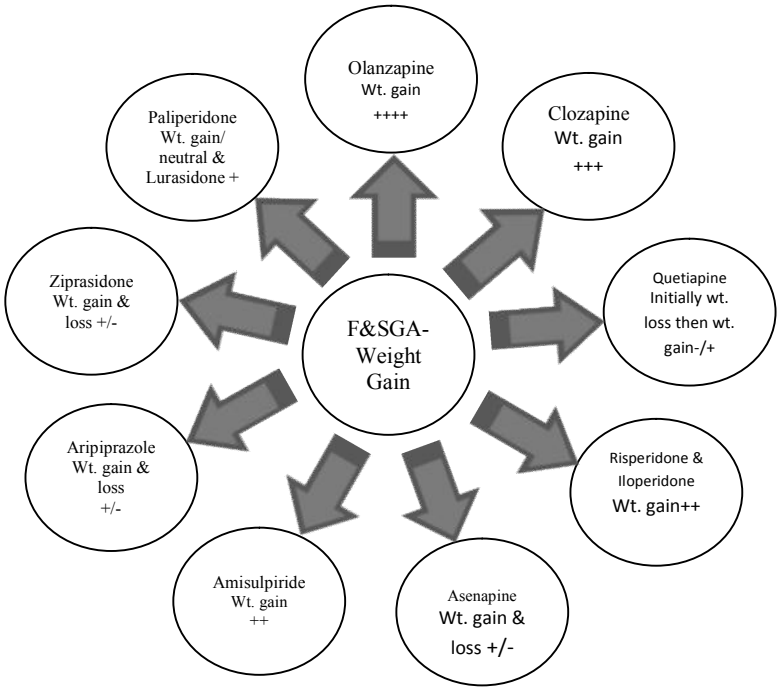

Fig. 2. Highest wt. gain (olanzapine and clozapine, ++++) to lowest wt. gain or loss (aripiprazole and ziprasidone +/-) and wt. loss from baseline then wt. gain (quetiapine -/+) and neutral or wt. gain (paliperidone and lurasidone)

3.5 Predictors of Antipsychotic-Induced Weight Gain

This is extremely important to know the predictors of weight gain in mentally ill patients on antipsychotic medications. Research indicates that antipsychotic-induced weight-gain is predicted by higher parental BMI, patients' pre-morbid BMI, the female gender, younger age, and non-smoking status [66,70]. These findings suggest that there is a strong impact of pre-dispositional factors on weight-gain, which may interact with antipsychotic medications or may be beyond treatment factors. Additionally, Gebhardt, et al. [70] reported that the diagnosis of a schizophrenia spectrum disorder was related to an increased BMI and suggested that this weight gain may result from a longer duration of SGAs. Similarly, Saddichha, et al. [71] examined a group of patients diagnosed with first-episode schizophrenia and found that waist circumference and weight at baseline, as well as antipsychotic use, were related to greater weight-gain. When looking at the impact of different medications on weight-gain, olanzapine linked with greater weight-gain compared to risperidone and haloperidol. Some predictors of long-term weight-gain include an initial lower BMI, a rapid initial increase in weight and increased appetite. Weight-gain also seems to be greater in first onset patients with schizophrenia naïve to antipsychotic treatment. However, the weight-gain results in reducing patients' self-esteem, quality of life, and adherence to given medications, and also causes patients' re-hospitalization and increased morbidity and mortality [54]. Weight gain in first month may predict longterm weight gain among adolescents on SGAs [72]. Lower cognitive functioning is another factor that increases in BMI in bipolar patients even after clinical and treatment variables were adjusted [73]. Schizoaffective disorder but not schizophrenia and bipolar disorder predict the development of metabolic syndrome, and this effect is mediated by genetic vulnerability and initial BMI [74]. It is wise to know that prolonged exposure to any antipsychotics produces weight gain and switching antipsychotics does not result in weight reduction [63]. In a longitudinal study involving French people, Godin et al. [75] reported co-occurring depressive symptoms were significantly associated with a rapid weight gain in patients with schizophrenia receiving antipsychotic medications and even the frequency of metabolic syndrome increased after

one year (26.6%; baseline, 21.0%) of exposure. Furthermore, lack of cognitive self-control along with increased appetite and overeating predicted weight gain (> or 1 kg) in patients (with schizophrenia and bipolar disorder) receiving olanzapine and weight controlling medications (nizatidine, sibutramine or amantadine). Conversely, predictors of weight loss ≥2 kg were several including high baseline BMI and cravings for carbohydrates [76]. Overall, there are many predictors including antipsychotics use mediating the weight gain in mentally ill patients.

The prevalence of obesity is increasing globally at an alarming rate [77]. This has advanced extensive research into the causes, co-morbidities, adverse consequences, and treatment of obesity in recent years. Clinical studies indicate that a high prevalence of metabolic syndrome exists in individuals afflicted with serious mental illnesses, particularly those with schizophrenia, schizoaffective disorder, and other psychotic disorders. In addition, psychotropic agents including antipsychotic medications have been definitely found to be associated with substantial weight-gain among those exposed to such drugs [41,78]. The weight gain associated with antipsychotic use has further aggravated the status of overweight and obesity worldwide. This weight-gain is problematic from many perspectives including individuals' risk for developing various diseases with poor quality of life and burden of disease [54,78]. Research examining the differential effects of various antipsychotics has shown that both the frequency as well as the amount of weight gained is high in patients treated with olanzapine (average gain of 2.3 kg/month), clozapine (1.7 kg/month), quetiapine (1.8 kg/month), and zotepine (2.3 kg/month) [79]. Additional findings suggest the weight gain linkage with risperidone (average gain of 1.0 kg/month) and ziprasidone (0.8 kg/month) [73]. However, the largest body of research exists to support an association between weight-gain and treatment with olanzapine and clozapine [70]. Overall converging evidence supports that most FG and SG antipsychotics produce weight gain in severely mentally ill patients; however, the shared role of other biopsychosocial and cultural factors should never be underestimated.

3.6 Antipsychotics Associated Weight Gain and Public Health

The weight-gain associated with antipsychotic medications represents a liability to the public health system around the world. A variety of factors including psychotropic drugs make schizophrenia and other psychotic disorders (mood disorders, drug-induced psychosis, psychosis co-morbid other physical and psychiatric disorders and pervasive development disorders) an economic burden on humanity, society and public healthcare system. Patients with psychotic disorders are often unemployed, incarcerated, have multiple admissions, poor drug adherence, homelessness, and associated with considerable morbidity and mortality and healthcare utilization [80]. Despite aforesaid research findings, our intention is never to stigmatized patients with severe mental illnesses including drug addictions, rather to remind globally all stakeholders to scale up required clinical services, research, and new drug development with safe clinical profile devoid of weight gain supported by appropriate funds. Obesity and overweight induced by FGAs and SGAs and biosociocultural dimension contribute globally to the huge economic and humanistic burden concerning schizophrenia [81,82] and other related severe and persistent disorders. It may be more difficult to treat obesity in individuals who have gained weight as a result of antipsychotic interventions. Most antipsychotic drugs increase appetite together with fatigue in mentally ill patients. In addition, the psychotic disorders also decrease motivation and social activities including exercise, all these factors relate to weight gain and obesity [83]. However, those patients who were initially overweight and continuing with SGAs tend to lose weight on longterm timeline [83]. Thus, the individuals who have gained weight as a result of their psychiatric treatment and associated multiple adverse consequences are an additional cost (humanistic and economic) to the public healthcare system [81-83]. Furthermore, the medical and health risks associated with obesity result in a cost to society beyond that of psychiatric care alone [81,82]. Overall, preceding obesity and additional weight gain due to antipsychotic medications prescribed to a larger number of patients with schizophrenia, major depression and other psychoses considerably contribute to a pool of public health problems.

3.7 Timeline of Weight Gain

Weight gain linked with psychotropic drugs including antipsychotics tends to occur in early part of the treatment rapidly. In bipolar patients, Fagiolini and colleagues found that most weight-gain occurred during acute treatment with mood

stabilizers and antipsychotic medications [84]. This research emphasized the benefit of maintenance treatment as minimal weight is gained during this phase, whereas acute depressive episodes (post-manic) were related to weight-gain. Also, stabilization on maintenance medication facilitates participation by patients in interventions directed specifically at weight loss [84] which include psychosocial approaches, life style strategies and dietary modifications and other CAM therapies [5,83,84]. In patients treated with clozapine, Umbricht, et al. (1994) found that significant weight-gain occurred primarily during the first six to 22 months, and continued into the third year of treatment with minimal additional weigh gain. Further report suggested that being underweight at baseline was correlated with a greater amount of weight-gained [71,84]. Conversely, overweight status at baseline was associated with little weight gain but above ideal weight following treatment compared to those who had normal weight at baseline [85]. Several long-term naturalistic studies found that weight-gain is less marked in the longterm as revealed in drug controlled trials [54,84-86]. With the use of other antipsychotics, weight gain may stabilize early but it continues beyond the first year especially with clozapine [54]. Fortunately, it does seem that weight-gain resulting from antipsychotics occurs primarily during the first two years of treatment and then levels off [86] however, this study needs replication to prove or refute this premature finding. In a nutshell, weight gain associated with psychotropic drugs especially SGAs tend to occur mostly during early part of treatment; therefore, an antipsychotic with a minimal weight induction, good tolerability and effectiveness should be used in mentally ill patients with severe psychoses.

3.8 Weight Gain and Doses

Weight gain associated with antipsychotic medications may relate to their prescribed dosages. A comprehensive review attempted to answer the question; whether or not weight-gain and associated metabolic changes is dose-dependent [87]. A relationship appears to exist between the administered dose of clozapine and olanzapine and metabolic outcomes including weight gain. With regard to risperidone and other antipsychotic medications, further research is required to make an accurate assessment of a possible dose-weight-gain dimension. However, the relationship between clozapine and olanzapine plasma concentrations and metabolic disturbances including weight gain provides a cause-effect relationship [87]. In a study that used body weight-related data from clinical trials found that lower doses of antipsychotic drugs were not associated with lower weight gain. However, all factors including outcome, olanzapine doses, lower BMI, ethnicity (non-white race), younger age, male gender, and increased appetite tend to affect acute weight gain in schizophrenia and related disorders [88]. Haloperidol and risperidone doses were not significantly associated with weight gain in patients with schizophrenia. Clearly olanzapine higher doses are associated with weight gain in patients with severe mental illnesses [88].

3.9 Weight Gain, Morbidity and Mortality

Weight gain resulting from antipsychotics use in patients with a variety of mental conditions is linked with adverse health consequences, which are largely preventable. Research suggests that individuals with SMIs have significantly worse health outcomes and premature mortality than the general population. People with SMI suffer from a 20-year shortfall in life expectancy [89]. Individuals with schizophrenia have up to a 20% shorter lifespan compared to the general population, and the cardiovascular diseases being the most common cause of death [78]. Many factors are implicated concerning the poor health of individuals with schizophrenia or psychoses; increased prevalence of smoking, poverty and unemployment, poor nutrition, homelessness, dietary habits, and adverse metabolic effects of antipsychotic medications including weight-gain [80,90-92]. The study suggested that an important aspect of dealing with serious mental illness is to carefully manage the side effects of antipsychotics using a multidimensional approach supporting administrative, behavioral and medical intervention [91]. Additional clinical perspectives to be addressed concurrently are overweight and obesity related numerous psychological and physical problems, such as depression, anxiety disorders, eating disorders, stroke, disabilities, diabetes, musculoskeletal diseases and metabolic syndrome [93]. Hence, mental health professionals need to take special care in the case of patients with obesity exposed to antipsychotic medications, and to watch for and treat these additional health concerns in collaboration with physicians if they should arise. Evidence suggests that mentally ill patients often do not receive adequate psychiatric and medical care for their medical illnesses, highlighting the

need for increased awareness of and attention to the physical health problems of individuals with mental illness [78]. In particular, the metabolic and weight gain issues resulting from psychotropic drugs including antipsychotics require appropriate management. In addition, non-adherence, relapse and repeated hospitalization related to weight gain and obesity which in turn cause additional physical and psychiatric co-morbidities [39,58] need integrated special care.

Antipsychotic medication polypharmacy, a common clinical practice in psychiatric population is also linked with weight gain in patients with schizophrenia [94]. Sadly the premature mortality of those with serious mental disorder [95,96] is coupled with under-recognition and under-treatment of the physical conditions including overweight [97,98], requiring proactive preventive and appropriate early recognition and treatment approaches. Ultimately this perspective reinforces the need to prioritize this area for research and globally scaling up the mental healthcare services to patients with severe mental illness complicated by physical and psychiatric comorbidities but more to be done in developing eastern world [99]. In summary, the morbidity and mortality emerging in the shadow of induced weight gain and schizophrenia and other psychoses including major depression and bipolar disorders are preventable with appropriate multidimensional treatment interventions (a related paper is forthcoming soon).

4. DISCUSSION

This narrative review describes the etiological factors, clinical consequences and predictors of weight gain related to antipsychotic use in psychiatric population. Schizophrenia, a severe mental illness affects 1% world population [81]. The lifetime prevalence of schizophrenia is reported to be 0.4% concerning the Netherlands population between the age of 18-64 years [100]. The psychiatric disorders in which antipsychotics are used include schizophrenia and schizophrenic spectrum disorders, affective psychosis, major depression and psychosis occurring in patients with dementia, alcohol and drug addictions [65-68,101]. Multiple antecedent risk factors individually or collectively determine the etiopathogenesis of these severe psychotic disorders [102]. Whether or not their roles has something to do with weight gain when patients with SMI are prescribed antipsychotic drugs need exploration.

Overweight and obesity is caused by multiple risk factors including antipsychotic medications, their doses, duration of use and diagnoses [63,72-74]. The other etiological factors include genetics, sociodemographic (gender, poverty, stresses), psychological (psychological disorders including depression, anxiety and personality disorders), cultural factors (dietary habits & sedentary life) and others such as ethnicity and environment (gut microbiota) [26-28,50,70,88,92]. When mentally ill patients especially having any type of psychosis, i.e., schizophrenia, affective and schizoaffective disorders and major depression and others such as drug-induced psychosis and dementia-related psychosis are exposed to antipsychotic drugs, all above factors in one way or the other tend to contribute to the burden of weight gain along with risks of morbidity and mortality [54,103]. This review reported psychotropic treatment-related diseases including nutritional and metabolic diseases, cardiovascular diseases, viral diseases, respiratory tract diseases, musculoskeletal diseases, sexual dysfunction, pregnancy complications, stomatognathic (an anatomic system comprising teeth, jaws and associated soft tissues) diseases, and possibly obesity-related cancers in a patient with SMI [103]. In sum, overweight and obesity caused by antipsychotic drugs and concurrent factors is a multidimensional problem and needs to be looked from different perspectives including genetic-environment interaction model in patients with severe mental disorders [104].

There are many predictors of antipsychotics induced weight gain among patients with severe mental illnesses. These parameters include higher parental BMI, patients' pre-morbid BMI, the female gender, younger age, diagnosis of schizophrenia and schizoaffective disorder and non-smoking status [66,70,74]. These results guide towards pre-dispositional factors and, hence, weight gain may be beyond antipsychotic treatment factors [70]. Saddichha, et al. (2008) also examined a group of patients diagnosed with first-episode schizophrenia and found that waist circumference and weight at baseline, as well as antipsychotic use, were significant predictors of a greater weight-gain. Exploring the impact of different medications on weight-gain, olanzapine predicted significant weight-gain compared to risperidone and haloperidol [71]. The predictors of long-term weight-gain included an initial lower BMI, the rapid increase in weight, voracious appetite, and schizophrenia naïve to antipsychotic treatment [54]. In addition, early

weight gain predicts longterm obesity among adolescents receiving SGAs [72]. Cognitive impairment predicted higher BMI in bipolar patients after confounding variables were adjusted [73]. It is wise to know that prolonged exposure to any antipsychotics produces weight gain and switching antipsychotics does not result in weight reduction [63]. In a longitudinal study involving French people, Godin et al. reported co-occurring depressive symptoms predicted a rapid weight gain in patients with schizophrenia receiving antipsychotic medications [75]. Furthermore, lack of cognitive self-control along with increased appetite and overeating predicted weight gain (> or1 kg) in patients with schizophrenia and bipolar disorder receiving olanzapine and weight controlling medications including nizatidine, sibutramine and amantadine. Conversely, predictors of weight loss ≥2 kg were several including high baseline BMI and cravings for carbohydrates [76]. Overall, there are many predictors including antipsychotics use mediating the weight gain or loss in severely mentally ill patients.

Patients with SMIs are mostly prescribed typical and atypical antipsychotic medications that produce overweight and obesity and other adverse consequences. For example, antipsychotic medications are reported to cause premature deaths when given to patients with dementia [105]. When children and adolescents with autistic spectrum disorders with irritability and hyperactivity are exposed to atypical (aripiprazole, lurasidone, ziprasidone, paliperidone, risperidone, olanzapine, quetiapine, and typical antipsychotics (haloperidol), the improvement rate was variable and almost all of them produced minimal (aripiprazole, quetiapine, lurasidone, ziprasidone) to maximum weight gain (olanzapine, haloperidol), high level of prolactin and other adverse effects [63,106]. Conflicting reports exist regarding weight gain among patients with schizophrenia by paliperidone [52,54]. In several studies, heavy cannabis users tend to develop psychosis, weight gain (including due to antipsychotic drugs) and other similar diseases produced by nicotine addiction. There is a possible link between cannabis use and increased mortality [29,107]. Overall the use of antipsychotic medications is linked to overweight and obesity, which in addition to SMIs may cause metabolic syndrome, diabetes, cardiovascular conditions, stroke, cancers, and musculoskeletal disorders and a variety of psychological conditions, social adversities and premature death [16,18,19,28,54,78,93,108]. Consequently, therapeutic approaches should address simultaneously antipsychotic-associated weight gain and related social problems, psychiatric and physical conditions [109-113].

This review has two main limitations. This is not systematic and comprehensive review because of selection and publishing biases. The strength of this pilot review is that it encompasses important information on antipsychotic-induced weight gain among patients with SMIs and related adverse psychological and physical consequences. Ultimately mental health professionals and allied personnel who prescribe antipsychotic medications to a larger clinical population will definitely benefit from this narrative review. There are other important topics on weight gain caused by other psychotropic drugs, underlying mechanisms and effects, and therapeutic challenges which will be forthcoming soon.

5. CONCLUSION

In summary, first and second generations of antipsychotics mostly produce variable weight gain among patients with severe mental illnesses along with potentially adverse physical and psychological consequences including death. Several identified risk factors and predictors of weight gain may guide mental health professionals to choose most appropriate antipsychotic medication when consulting patients with SMIs. This review calls for rigor studies that would analyze the individual contribution of biological, psychological and sociocultural risk factors to overweight among patients with severe mental illnesses managed by antipsychotic medications.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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