REVIEW ARTICLE

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Long-Term Treatment with Atypical Antipsychotics and the Risk of Weight Gain

A Literature Analysis

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Abstract

The aim of this review is to analyse and summarise the literature data about the incidence of weight gain in patients exposed to atypical antipsychotics during long-term (≥1 year) treatment regimens. Despite the clinical relevance of the topic, the vast majority of reviewed studies showed methodological limitations. Some trials had retrospective analysis, and concomitant medications also associated with an increased risk of weight gain, such as antidepressants and mood stabilisers, were often prescribed. Results were obtained from clinical trials conducted using flexible dosages; thus, the relationship between dosage and weight change was not explored adequately. Also, in a large number of studies, the average antipsychotic daily dose was lower than the usual dosage in clinical practice. Moreover, weight gain was evaluated by different measures, such as mean weight gain in the enrolled population, percentage of patients who gained >7% of basal weight or body mass index (BMI) variations from baseline.

In short-term studies, a definite rank order of weight-gain potential among atypical antipsychotics has been demonstrated: clozapine is related to the highest risk of weight gain, followed in decreasing order of magnitude by olanzapine, quetiapine, risperidone, amisulpride, aripiprazole and ziprasidone. However, in long-term studies, except for clozapine at one end of the scale and ziprasidone at

the other, the differences in weight-gain liability showed by the other atypical antipsychotics became less intense. Differences between short-term and long-term treatment could be due to a complex overlapping of different factors, both drug-specific (relative receptorial affinity; timing of weight change plateau; and drug-specific/dose-dependent weight gain), and patient-specific (genetic vulnerability; sex; age; BMI; weight before starting antipsychotic treatment; type of psychiatric disorder; and individual lifestyle). There is an urgent need for well designed, randomised controlled trials to assess firmly both the differential effects of atypical antipsychotics on weight and the role of other factors in contributing to iatrogenic unwanted weight changes. Meanwhile, the well known benefits shown by some atypical antipsychotics in reducing akathisia and other extrapyramidal adverse effects and improving cognition should be carefully balanced with the problems of weight gain, other metabolic complications and higher healthcare costs.

Atypical antipsychotics represent an important advance in the treatment of schizophrenia and related disorders. In recent years, these agents have also been increasingly utilised in treating bipolar disorder.[1] In the US, atypical antipsychotics have captured approximately 90% of the pharmaceutical market share, resulting in burgeoning costs.[2,3] Compared with conventional antipsychotics, atypical antipsychotics are less likely to induce extrapyramidal adverse effects, although dose-related extrapyramidal adverse effects do occur with some of these agents.[4-6] Atypical antipsychotics do, however, present unique safety and tolerability issues, including metabolic effects such as an increased risk of diabetes mellitus, dyslipidaemia and weight gain.[7] These complications have been associated with increased mortality from hypertension, coronary heart disease and stroke.[8]

Weight gain is one of the most stressful undesired consequences, especially to women, of treatment with atypical antipsychotics.[9] An increase in weight may negatively impact self-esteem and translate into a deterioration in social and interpersonal relationships.[10] Additionally, compliance with treatment may be poor, which inevitably leads to disease relapse and worse long-term outcomes.[11]

The specific mechanisms determining weight changes in patients treated with atypical antipsychotics are still unclear, although antagonism of various neurotransmitter systems has been suggested, including: the serotoninergic (5-HT_{2C} and 5-HT_{2A} receptors), histaminergic (H_1), adrenergic (α_1), muscarinic (M_1 and M_4), and dopaminergic (D_2) systems.[12,13] For example, the hyperprolactinaemia associated with dopamine D_2 receptor blockade may contribute to weight gain as a result of increased food intake.[14] Additionally, antagonism of the serotonin 5-HT_{2C} receptor has been associated with peripheral dysregulation of leptin and ghrelin pathways and impaired neural processing of leptin-mediated signaling of fatty deposits.[15,16]

Individual genetic predictors have also been proposed for antipsychotic-associated weight gain. To date, significant findings have been demonstrated for regulatory variants of the genes encoding leptin and the 5-HT_{2C} receptor;[17] specifically, patients with -759C/T polymorphism of the *HTR2C* gene or -2458 leptin polymorphism may have a higher risk of developing antipsychotic-induced weight gain.[18,19]

Surprisingly, although treatment with novel antipsychotics is generally a long-term treatment, because it is utilised in patients with chronic disorders, the vast majority of data about associated weight gain is generated from short-term studies. This situation potentially represents a significant bias in identifying the true incidence of this effect and its impact on the general psychiatric population. In fact, during treatment with some of these agents, weight has been shown to increase constantly into at least the third year of treatment.[20,21]

The aim of this review, therefore, is to analyse and summarise the literature data on the incidence of weight gain in patients exposed to atypical antipsy-

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chotics during long-term treatment regimens (≥1 year).

1. Data Sources, Study Selection and Data Extraction

A literature search of MEDLINE (1966–December 2005), EMBASE (1998–December 2005) and the Cochrane Library was conducted using various combinations of the following terms: 'weight gain', 'atypical antipsychotics', 'schizophrenia and related disorders', 'bipolar disorder', 'amisulpride', 'aripiprazole', 'clozapine', 'olanzapine', 'quetiapine', 'risperidone', 'ziprasidone', 'long-acting/depot injectable preparations'. Bibliographies of relevant articles were hand-searched for additional references. Supplementary sources included manufacturer's information, relevant textbooks and institutions active in the field. Sources sought and reviewed, without language or methodology limitation, and which evaluated the incidence of weight gain after ≥1 year of treatment included: critical analyses; comprehensive reviews; meta-analyses; retrospective and prospective studies; randomised, double-blind, controlled trials; uncontrolled open-label studies; case-reports; and naturalistic studies.

2. Data Synthesis

2.1 Clozapine

Clozapine treatment is commonly thought to result in the greatest amount of antipsychotic drug-associated weight gain.[22] However, one study suggested that the magnitude of this event is not statistically significant between clozapine and conventional agents such as chlorpromazine.[23] A large amount of clinical data on weight gain were documented for clozapine (table I); the vast majority showed that such an event was related both to the duration of treatment and to patients not being overweight at baseline.[21,24,25] Furthermore, reviewed studies reported no correlation between the degree of weight gain with long-term clozapine treatment and improvement in positive or negative symptoms.[26,27] Frankenburg et al.[28] also found clinically significant mean increases in body mass index (BMI) [>7% of basal BMI] in 42 patients treated with clozapine over a 3-year period. A study conducted on bipolar or schizoaffective patients, however, showed no statistically significant differences in the incidences of somatic complications in those receiving clozapine treatment compared with those in the control group.[29]

2.2 Olanzapine

Some relevant details of reviewed trials are summarised in table II. It has been reported that olanzapine treatment is associated with weight gain to a similar extent as with clozapine.[38] Data from four clinical trials assessing the safety of olanzapine were reviewed by Nemeroff.[39] A large population of patients (n ≈ 2500) was also evaluated by Beasley et al.[40] Olanzapine showed a clear tendency to induce weight gain, and this effect was most severe in patients who were underweight at baseline. In contrast, no correlation between BMI at baseline and weight gain was reported by Wirshing et al.[24]

The risk for olanzapine-induced weight gain was also confirmed in five studies conducted by Kinon et al.,[46] Sheitman et al.,[54] Hennen et al.,[44] Tohen et al.,[56] and Sanger et al.[53] The Kinon et al.[46] study showed that patients with high BMI value at baseline (>27.6) had lower weight gain than patients with low-to-medium BMI; however, the study did not confirm that weight gain during olanzapine treatment was dose related. The study by Sheitman et al.[54] was limited by a small sample size, while the controlled trial by Hennen et al.,[44] which showed no correlation between baseline BMI values and risk of weight gain, also had some limitations, such as non-blind observations and only 39% of patients completing the first year of treatment. Furthermore, in some of these trials,[56] patients also received adjunctive pharmacological treatments, most often mood stabilisers. Preliminary data emerging from a retrospective longitudinal analysis also showed that weight gain represents a frequent complication during long-term olanzapine treatment.[42] Concomitant treatment with selective serotonin receptor inhibitors, lithium or carbamazepine was also common in a case series by Haberfellner and Rittmansberger.[43] The authors reported that olanzapine-induced weight gain per month was statistically significantly higher in patients with lower baseline BMI, yet the highest weight gain was found in the most obese patient.

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Table I. Weight gain during long-term clozapine treatment[a]

Study	Design	No. of pts	Duration	Dosage (mg/day) ± SD	Incidence and degree of weight gain	Comparator
Bustillo et al.[27]	op	33	>1y	410.5	58% of pts ≥10% overweight	Haloperidol
Briffa and Meehan[30]	op	51	1y	NR	70% of male pts	No
Covell et al.[25]	Switch to op	138	2y	NR	5.9kg	Typical antipsychotics
Henderson et al.[31]	Naturalistic	82	5y	NR	[b]	No
Hummer et al.[26]	op	31	64wk	241 ± 138	36% of pts ≥10% of basal weight	Haloperidol
Jalenques and Coudert[32]	op	20	1y	206 ± 44	45% of pts ≥5kg	No
Leppig et al.[33]	Retrospective	121	128wk	131 ± 99	23% of pts	No
Lieberman et al.[34]	op	84	1y	441 ± 120	53.3% of pts	No
Lieberman et al.[23]	r, db	81	1y	300–400	9.9kg	Chlorpromazine
Juul Povlsen et al.[35]	Retrospective	216	26–300wk	317	Up to 13% of pts	No
Suppes et al.[29]	r, op with clozapine add-on	19	1y	355 ± 248	No differences between olanzapine and control group	Lithium, valproate or carbamazepine monotherapy
Spivak et al.[36]	Retrospective	96	88wk	440 ± 180	4.7kg	Typical antipsychotics
Umbricht et al.[37]	Retrospective	82	90mo	500–600	50% of pts ≥20% overweight	No
Wehmeir et al.[21]	Prospective	2	5.5y	225 and 400	48.2 and 53.1kg	No
Wirshing et al.[24]	Retrospective analysis of clinical records	13	73.1 ± 9.9wk	NR	>45% of pts ≥10% of basal weight	Olanzapine, risperidone, sertindole, haloperidol

a Dosage and absolute weight gain values are means.

b Significant linear coefficient: 0.15 kg/mo weight gain from 12 to 60mo. Pts continued to gain weight for 46mo, when weight gain appeared to level off.

db= double-blind; **NR** = not reported; **op** = open-label; **pts** = patients; **r** = randomised.

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Table II. Weight gain during long-term olanzapine treatment[a]

Study	Design	No. of pts	Duration	Dosage (mg/day)	Incidence and degree of weight gain	Comparator
Beasley et al.[40]	db	2418	175wk	1.0–15.0 ± 5.0	40% of pts >7% of basal weight[b]	Haloperidol, placebo
Farwell et al.[41]	Retro cs	438	≥1y	NR	39.8% of pts	Risperidone, typical antipsychotics
Gentile[42]	Retro, long	19	≥1y	13.15 ± 10.02	31.5% of pts >7% of basal weight; 2.95kg	No
Haberfellner and Rittmansberger[43]	Pros case series	27	6–42mo	8.52–8.70	66.7% of pts >7% of basal weight; 9.2kg	No
Hennen et al.[44]	op	113	1y	5–20	≥12% change from BMI baseline[c] 33.9% of patients experienced an increase of BMI of at ≥10%	Placebo for the first 3wk
Jones et al.[45]	Data on file	>400	1y	NR	66% of pts <10kg; 7% of pts >20kg[c]	No
Kinon et al.[46]	Retro	573	>2y	5–20	6.26kg[c]	Haloperidol
Lee et al.[47]	Retro	34	21–255wk	12.4 ± 6.7	8.34 ± 5.97kg[c]	Risperidone
Lieberman et al.[48]	db	336	Up to 18mo	7.5–30	30% of pts ≥7% of basal weight; 5.1 ± 0.49kg	Perphenazine, quetiapine, risperidone, ziprasidone
McKee et al.[49]	Retro, long	35	2y	~2.5	No significant weight gain from baseline to endpoint	No
Meyer[50]	Retro	47	1y	16.7	≈8kg	Risperidone
Nemeroff[39]	Meta-analysis	Nearly 3000	1y	1.0–17.5	12kg with 12.5–17.5 mg/day; 3kg with 1mg/day	Haloperidol
Pancheri et al.[51]	Pros	802	1y	NR	37% of pts 3–9 kg; 10% of pts ≥9 kg	Risperidone, quetiapine
Rosenheck et al.[52]	r, db	159	1y	5–20	4.7% of pts	Haloperidol
Sanger et al.[53]	op continuation phase study	113[d]	1y	5–20	36.3% of pts	No
Sheitman et al.[54]	Pros	9	16mo	10–30	10 kg	No
Sprague et al.[55]	Literature review	532	NR	≥2.5	29% of pts ≥7% of basal weight	Placebo
Tohen et al.[56]	db, relapse prevention study	51[e]	18mo	5–20	19.6% of pts; 5–6kg	Olanzapine plus lithium/valproate vs placebo plus lithium/valproate
Tohen et al.[57]	r, db	217	1y	11.9 ± 4.4	29.8% of pts ≥7% of basal weight; 4.54kg	Lithium
Wirshing et al.[24]	Retro analysis of clinical records	13	73.1 ± 9.9wk	NR	>30% of pts ≥10% of basal weight	Clozapine, risperidone, sertindole, haloperidol
Zipurski et al.[58]	r, db	131	2y	5–20	10.2 ± 10.1kg	Haloperidol

a Dosage and absolute weight gain values are means.

b Correlation between dosage and degree of weight gain reported.

c No correlation between dosage and degree of weight gain reported.

d Only 45 of 113 pts who entered the op phase completed the phase.

e Pts were in combination therapy with other psychotropic agents.

BMI = body mass index; **CS** = cohort study; **db** = double-blind; **long** = longitudinal analysis; **NR** = not reported; **op** = open-label; **pros** = prospective; **pts** = patients; **r** = randomised; **retro** = retrospective.

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Table III. Weight gain during long-term treatment with risperidone[a]

Study	Design	No. of pts	Duration	Dosage (mg/day)	Incidence and degree of weight gain	Comparator
Barak[64]	op	97	1y	3.7	No significant weight gain[b]	None
Buitelaar[65]	op	26	1y	0.5–4	8% of pts 8–10kg[c]	None
Cohen et al.[66]	Retro chart review	37	2y	4–6	8.3kg[b]	None
Csernansky et al.[63]	db, pros	177[d]	364d	4.9 ± 1.9	2.3kg[b]	Haloperidol
Farwell et al.[41]	Retro cs	482	≥1y	NR	37.0% of pts	Olanzapine, typical antipsychotics
Fleischhacker et al.[67]	op	615[e]	1y	Depot 25, 50 or 75mg q2wk	1.7, 2.6 and 1.9kg in the 25, 50 and 75mg groups[b]	None
Hellings et al.[68]	Controlled	11[f]	1y	1–3	8.2kg in children; 8.4kg in adolescents[c]	Placebo
Lee et al.[47]	Retro	49	93.2 ± 50.6wk	4.5 ± 2.8	2.74 ± 8.09kg[b]	Olanzapine
Lieberman et al.[48]	db	341	Up to 18mo	1.5–6	14% of pts ≥7% of basal weight; 0.43 ± 0.49kg	Perphenazine, quetiapine, olanzapine, ziprasidone
McIntyre et al.[69]	Pros, naturalistic, cs	111	280 ± 312d	3.5 ± 2.4	23.7% of pts ≥7% of basal weight	Olanzapine, quetiapine
McKee et al.[49]	Retro, longitudinal analysis	6	2y	~1	No significant weight gain from baseline	None
Meyer[50]	Retro	47	1y	4.5	≈8kg	Olanzapine
Pancheri et al.[51]	Pros	280	1y	NR	31% of pts gained 3–9kg; 5% of pts ≥9kg	Olanzapine, quetiapine
Penn et al.[70]	Case report	1	1y	6[g]	46.4kg from admission weight	None
Schooler et al.[71]	r, db	211	2y	3.3	7.5 ± 9.29kg	Haloperidol
Sprague et al.[55]	Literature review	324	NR	10	18% of pts ≥7% of basal weight	Placebo
Wirshing et al.[24]	Retro analysis of clinical records	13	73.1 ± 9.9wk	NR	≈10% of pts ≥10% of basal weight	Clozapine, risperidone, sertindole, haloperidol

a Dosage and absolute weight gain values are means.

b No correlation between dosage and degree of weight gain reported.

c Correlation between dosage and degree of weight gain reported.

d Of 177 pts assigned to risperidone group, 44.1% discontinued treatment for reason other than disease relapse.

e Of 615 enrolled pts, 65% completed the study.

f Children and adolescents.

g The patient also took fluoxetine and benztropine.

cs = cohort study; **db** = double-blind; **NR** = not reported; **op** = open-label; **pros** = prospective; **pts** = patients; **q2wk** = every 2 weeks; **r** = randomised; **retro** = retrospective.

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The well designed study by Rosenheck et al.[52] concluded that olanzapine was associated with more frequent reports of weight gain compared with haloperidol. However, in a recent pan-European study, the incidence of severe weight gain during long-term olanzapine treatment was substantially reconsidered;[51] in this trial, olanzapine was compared with risperidone and quetiapine. In the study extension period (up to 24 months), the severity of weight gain during olanzapine treatment was not different to that during treatment with risperidone or other atypical antipsychotics.[59] This study, however, had some severe limitations, such as a non-randomised design and small numbers of patients in the other treatment groups; in addition, the main daily dose of atypical antipsychotics was not reported. On the other hand, Sprague et al.[55] estimated the cumulative risks for clinically significant weight gain (≥7% of baseline weight) in patients receiving olanzapine treatment to be 29%.

One of the largest studies on the risk of olanzapine-induced weight gain was conducted by Jones et al.,[45] who collected and analysed Eli Lilly data on file.[60] Additionally, another study demonstrated that the risk of weight gain complaints was 4.3-fold higher in children and 3.2-fold higher in adolescents compared with adults.[61] In an open-label, uncontrolled trial conducted in patients with bipolar disorder, Vieta et al.[62] found that long-term treatment with olanzapine plus topiramate (mean modal dosages: 13.1 ± 5.6 mg/day [olanzapine] and 319.8 ± 142.1 mg/day [topiramate] for manic patients; and 7.4 ± 2.8 mg/day [olanzapine] and 240.1 ± 100.2 mg/day [topiramate] for hypomanic patients) was not associated with weight gain. However, the risk of changes in weight was higher in olanzapine-treated patients than in lithium-treated patients and this difference reached statistical significance (13.4 [95% CI 0.5, 26.2]).[57] Furthermore, olanzapine was associated with greater weight gain and higher discontinuation rates for this event and other metabolic effects compared with either atypical or conventional antipsychotic agents.[48,58] In contrast, a 2-year evaluation suggested that patients under dietary-control regimens are unlikely to develop severe weight gain, even if treated with atypical antipsychotics such as olanzapine and risperidone.[49] However, two potential flaws of the study were that it was conducted in a residential patient population and that a low daily dosage was used for both drugs.

2.3 Risperidone

Contradictory data are available about the risk of weight gain during long-term risperidone treatment (table III). A modest increase in weight, unrelated to dose, was reported by Csernansky et al.[63] However, a severe limitation of this study was that the second weight measurement was missed in 80 patients who withdrew from the trial; it is possible, therefore, that those who withdrew experienced more weight gain than those who remained in the trial (n = 96). In another long-term study conducted in elderly patients (55 to 89 years), risperidone showed no effects on weight.[64] To determine the differences in weight changes in a specific ethnicity treated with olanzapine (table II) or risperidone (table III), Lee et al.[47] evaluated a large number of outpatients. Some of most relevant limitations of the study, however, were that the clinical data was retrieved from case records; the wide variation in the treatment duration; and the absence of weight information during the early phase of treatment. Nonetheless, the study confirmed that lower weight and BMI at baseline are associated with greater risk of weight gain.

Direct comparisons between olanzapine (table II) and risperidone (table III) were also performed in the studies by Farwell et al.[41] and Meyer.[50] One of the most severe limitations of the Meyer[50] study was that 35 of 94 patients received concomitant medications (lithium or valproate) for ≥2 months during the first year of treatment. Furthermore, the mean dosage of risperidone was relatively low compared with that of olanzapine. In contrast to the results of the study by Wirshing et al.,[24] Farwell et al.[41] concluded that olanzapine and risperidone have comparable likelihood of inducing weight gain in the first year of treatment. Conversely, other authors have confirmed that weight gain represents a troublesome adverse effect of risperidone treatment even in children and adolescents.[65,68] The estimated risk of clinically significant weight gain with risperidone 10 mg/day was 18% in a population of 324 psychiatric patients,[55] whereas devastating weight increase was reported in a sporadic case report.[70] According to the literature and to the manufacturer's

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Table IV. Weight gain during long-term treatment with quetiapine[a]

Study	Design	No. of pts	Duration	Dosage (mg/day)	Incidence and degree of weight gain	Comparator
Brecher et al.[76]	op extension phase of controlled and uncontrolled trial	178	80wk	>475	0.41kg[b]	None
Brecher et al.[77]	Retro	661	17.8mo	467	2.3kg[b]	None
Emsley et al.[78]	r, sb, pg	22[c]	1y	400–800	No significant change from baseline in BMI	Haloperidol
Jones et al.[75]	Critical analysis	NR	1y	>675	2.13kg[b]	
Kasper and Muller-Spahn[79]	Literature review	455	1y	>475	>2.0kg	
Kasper et al.[80]	op, mc, nc	18 741	1y, 208wk	Up to 800	3.4 ± 8.6kg at 1y; 4.9 ± 11.89kg at 208wk	
Lieberman et al.[48]	db	337	Up to 18mo	200–800	16% of pts ≥7% of basal weight; 0.6 ± 0.49kg	Perphenazine, risperidone, olanzapine, ziprasidone
McConville et al.[81]	op extension trial	10[d]	64wk	600	6.8kg	None
McIntyre et al.[69]	Pros, naturalistic, cs	23	324 ± 226d	324.0 ± 226.0	55.6% of pts ≥7% of basal weight	Olanzapine, risperidone
Nagy[82]	op	35	15mo	481.25	<1kg	None
Pancheri et al.[51]	Pros	94	1y	NR	16% of pts 3–9kg; 12% of pts ≥9kg	Olanzapine, risperidone
Rak et al.[74]	Critical analysis	360	1y	428	2.77kg[b]	None
Sprague et al.[55]	Literature review	510	NR	75–750	23% of pts ≥7% of basal weight	Placebo
Tariot et al.[83]	op, mc	89	1y	137.5	23% of pts ≥7% of basal weight	None

a Dosage and absolute weight gain values are means.

b No correlation between dosage and degree of weight gain reported. Of 22 patients, 10 from the quetiapine group failed to complete the study.

c Median.

d Children and adolescents.

BMI = body mass index; **cs** = cohort study; **db** = double-blind; **mc** = multicentre; **nc** = noncomparative; **NR** = not reported; **op** = open-label; **pg** = parallel group; **pros** = prospective; **pts** = patients; **r** = randomised; **retro** = retrospective; **sb** = single-blind.

prescribing information, weight gain may be dose-related,[47,72] although this finding was not replicated in a long-term study conducted on inpatients with mental retardation.[66]

A recent, well designed study compared the long-term safety and efficacy of risperidone with haloperidol.[71] Statistically significant weight gain was observed in the risperidone group at the beginning of treatment; however, at the endpoint, the difference in weight gain between the treatment groups was no longer statistically significant. Furthermore, no statistically significant difference in BMI changes was found between patients treated with olanzapine or risperidone enrolled in a 12-month randomised, multicentre trial.[7]

A long-acting injectable risperidone formulation has recently become available in several countries.[73] A multicentre international trial examined the long-term safety of this compound in a relatively large number of patients;[8,9] patients with schizophrenia or schizoaffective disorders who were symptomatically stable and who had been receiving a stable dose of oral risperidone for ≥4 weeks were eligible for the study. However, the trial provided no information about eventual weight modifications before starting depot treatment.

2.4 Quetiapine

Some relevant details of reviewed trials are summarised in table IV. A large number of patients who

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had participated in controlled, uncontrolled and open-label extension trials were included in two analyses of weight changes during long-term quetiapine treatment. In both studies, the risk for quetiapine-induced weight gain did not appear dose related.[74,75] The absence of dose-related weight changes is consistent with a report by Brecher et al.[76]

Data from three recent analyses of a relatively large number of patients who received open-label quetiapine monotherapy for up to 1 year also showed modest weight changes.[77,79,82] In contrast, in 510 patients who received 75–750 mg/day of quetiapine, 23% experienced a weight increase >7% of basal weight.[55] Clinically relevant weight gain induced by quetiapine was also reported in children and adolescents with schizoaffective disorders or bipolar disorders with psychotic features.[81] Moreover, a relationship between long-term quetiapine treatment and severe weight gain was demonstrated in a prospective, longitudinal, naturalistic study by McIntyre et al.[69] Some of the overarching objectives of this investigation were to compare safety and tolerability in patients receiving different atypical antipsychotics.

Emsley et al.[78] concluded that switching treatment from haloperidol to quetiapine is not associated with a remarkable BMI increase; this study, however, was limited in terms of sample size. Kasper et al.[80] evaluated the safety of quetiapine in patients from Europe, Canada and South Africa who had been included in four quetiapine phase IIIa trials. An increase in weight was observed; however, a limitation of this study was the high percentage of patients who received concomitant medications. In addition, the correlations between weight gain, medication dosage, and/or weight at baseline was not investigated.

Tariot et al.[83] examined the long-term tolerability of low-dose quetiapine in elderly patients (aged ≥65 years). Clinically relevant weight gain was observed in a relatively high percentage of patients affected by different typologies of psychiatric disorders, such as schizophrenia or psychotic disorders due to Alzheimer's or Parkinson's disease.

2.5 Ziprasidone

Reviewed studies on ziprasidone are summarised in table V. Two well conducted studies on the long-term effect of ziprasidone on weight both found that it did not appear to be associated with an increased risk of weight gain.[48] However, it was reported that the incidence of clinically relevant weight gain during ziprasidone treatment may be as high as 10%.[55]

2.6 Aripiprazole

Some relevant details of reviewed trials are summarised in table V. The manufacturer's information and literature reviews report that approximately 8–11% of patients gain >7% of basal weight after 4 weeks' treatment.[55,90] Although few long-term studies are available, weight gain represented a relatively frequent complication of aripiprazole.[84] In a short-term study, aripiprazole-induced weight changes were more severe than those induced by conventional antipsychotics.[91] These results were partially offset by studies reported by Kasper et al.[86] and Kujawa et al.,[85] who stated that weight modifications were not different between haloperidol-treated patients and aripiprazole-treated patients. In the Kasper study,[86] the patients were also stratified by mean BMI at baseline; in the aripiprazole group, only the patients with low BMI at baseline experienced greater weight gain than patients in haloperidol-group. However, the main limitation of the study was that only 397 of 861 patients completed the double-blind, 52-week treatment. Surprisingly, data on weight gain were collected from 859 patients; thus, because the endpoints of the study were planned at week 4, 8, 26 and 52, it is possible that this specific aspect was also recorded in patients who prematurely discontinued the trial. In a very short-term study, however, aripiprazole showed an incidence of clinically significant weight gain of 9% and 13% at daily doses of 30 and 20mg, respectively.[92]

2.7 Amisulpride

Some relevant details of reviewed trials are summarised in table V. Amisulpride has been available in different European countries since 1997. However, limited published information on the possible association between long-term amisulpride treat-

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Table V. Weight gain during long-term treatment with aripiprazole (ARI), ziprasidone (ZIP), and amisulpride (AMI)[a]

Study	Design	No. of pts	Duration	Drug and dosage (mg/day)	Incidence and degree of weight gain	Comparator
Argo et al.[84]	Comprehensive review of short and long-term studies	NR	1y	ARI 30	20% of pts[b]	Haloperidol
Kasper et al.[86]	db controlled	859	1y	ARI 30	1.05 ± 0.20kg	Haloperidol
Sprague et al.[55]	Literature review	926	NR	ARI 2–30	8% of pts >7% of basal weight	Placebo
Arato et al.[87]	r, db, pg, pc	207	1y	ZIP 40, 80, and 160	Decrease of 2.7, 3.2 and 2.9kg with ZIP 40, 80 and 160mg	Placebo
Lieberman et al.[48]	db	185	Up to 18mo	ZIP 200–800	7% of pts ≥7% of basal weight. 0.6 ± 0.49kg decrease	Perphenazine risperidone, olanzapine, quetiapine
Sprague et al.[55]	Literature review	702	NR	ZIP 10–200	10% of pts >7% of basal weight	Placebo
Colonna et al.[88]	op	488	1y	AMI 200–800	10.8% of pts	Haloperidol
Leucht et al.[89]	Sensitivity analysis of pros randomised studies	311	364d	AMI 568	2.15kg[c]	None

a Dosage and absolute weight gain values are means.

b Calculated in the population enrolled in the preliminary analysis by Kujawa et al.[85] Subsequently, the same population was also investigated by Kasper et al.[86]

c No correlation between dosage and degree of weight gain reported. The exclusion of pts with mean dosage of AMI <400 mg/day did not change the results to any substantial degree.

db = double-blind; **NR** = not reported; **op** = open-label; **pc** = placebo-controlled; **pg** = parallel group; **pros** = prospective; **pts** = patients; **r** = randomised.

ment and weight gain is available. Leucht et al.[89] analysed a pooled database of randomised amisulpride studies, whereas Colonna et al.[88] evaluated the long-term safety of the compound.

3. Discussion

Excess weight and obesity are increasing problems in the Western world. In fact, the prevalence of obesity had risen to 34% in the US and to 20–25% in European countries.[93,94] The progressive increase in fast-food industries is also contributing to obesity reaching epidemic proportions.[95]

Although data on the prevalence of obesity and other metabolic dysfunctions in schizophrenia prior to the 'neuroleptic age' or in drug-naive patients are scarce,[96] in medicated schizophrenic patients, it may be as high as 60%.[97-99] Female schizophrenic patients seem to be at particular risk for obesity and metabolic syndrome.[100] Also, the prevalence of obesity is higher in bipolar patients than in the general population.[101,102] Patients with major psychiatric disorders are more likely to be socioeconomically disadvantaged and the necessity of accessing inexpensive food is common in such contexts. Unfortunately, low-cost meals are usually characterised by high-caloric properties but low nutritional values.[103]

Furthermore, schizophrenic patients evidence a high rate of smoking and alcohol/street drug abuse;[104] thus, it is not surprising that they have a 20% shorter life-expectancy than the general population.[105] The shorter life-expectancy in the schizophrenic population seems mainly to be a result of increased cardiac mortality;[106] such data, however, remain controversial.[107]

On the other hand, weight gain is the most frequent adverse event associated with atypical antipsychotics. The magnitude of this effect has been associated with important deleterious repercussions on mortality and health (table VI).[108]

Unfortunately, the vast majority of interventions focused on preventing or reducing antipsychotic-associated weight gain are often ineffective or achieve the highest degree of efficacy merely in

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controlled settings.[109-111] In fact, excess weight and obesity are extremely hard to manage in outpatient psychiatric patients because of poor socioeconomic status and difficulty in changing lifestyle habits.[9,12]

In addition, studies demonstrating the effectiveness of different drugs (such as metformin, fenfluramine, sibutramine, amantadine, nizatidine, reboxetine, topiramate and orlistat) in reducing antipsychotic-related weight gain have shown inconclusive and contradictory findings.[1,112-122]

Despite the clinical relevance of this event, however, the vast majority of reviewed studies showed severe limitations. Numerous trials were represented by retrospective analysis, and concomitant medications also associated with an increased risk of weight gain, such as antidepressants and mood stabilisers, were often prescribed. Results were obtained from clinical trials using flexible dosages of medication. In a large number of studies, the average antipsychotic daily doses were lower than those commonly utilised in clinical practice; thus, the relationship between dosage and weight change has been not explored adequately. Nonetheless, drug dosage does not represent the best variable to evaluate because patients metabolise medication differently; thus, monitoring of drug blood concentration should be preferred.[123,124] In addition, weight gain was evaluated by non-homogenous methodologies, such as (i) mean weight gain in the enrolled population; (ii) percentage of patients who gained >7% of basal weight; and (iii) BMI changes from baseline. Thus, the fact that weight gain data vary considerably between studies makes a comparison with findings from other trials complicated.

Finally, amongst newer atypical antipsychotics, data on long-term treatments are quite robust for olanzapine (>8500 patients), quetiapine (<3000 patients), risperidone (<2500 patients including those treated with long-acting formulation), clozapine (>1000 patients), and aripiprazole (<1500 patients). By contrast, <800 and <400 patients have been selected for studies evaluating the long-term effects of amisulpride and ziprasidone, respectively. Hence, it is not surprising that a number of very relevant clinical concerns need further investigation. Few data appear, however, to be strongly consistent and potentially useful in helping clinicians to develop a balanced approach for long-term treatment with atypical antipsychotics.

Table VI. Estimated additional[a] deaths and incident cases of impaired glucose intolerance and hypertension over 10 years, as estimated in a population of 4 million patients with drug-induced weight gain of 4kg[108]

Event	No. of events
Death	24 560
Impaired glucose intolerance	92 720
Hypertension	120 760

a Compared with what would occur with a drug associated with neutral effects on weight.

4. Relative Risks of Atypical Antipsychotic-Induced Weight Gain

Short-term data (10 weeks' treatment with 'standard' dosage) recently reviewed by Newcomer[125] and Haddad[126] suggest a definite rank order of weight-gain potential among atypical antipsychotics. Clozapine was associated with the highest risk of weight gain, followed, in decreasing order of magnitude, by olanzapine, quetiapine, risperidone, amisulpride, aripiprazole and ziprasidone. Although short-term data must not be underestimated, the following points open new and unanswered questions about weight gain during long-term treatment with atypical antipsychotics:

1. A recent, well designed, randomised, prospective, analysis suggests that amisulpride may have limited effects on weight;[89] however, a previous report does not exclude the fact that the effect of basal weight may be substantial.[88]
2. Data on quetiapine are contradictory. Six reviewed studies showed that quetiapine has a moderate-to-high potential for inducing weight gain.[51,55,69,71,80,83] In addition, studies demonstrating the absence of a clinically relevant impact on weight are limited in terms of sample size and/or conducted using relatively low dosages. Furthermore, one review suggested that quetiapine-induced weight gain may continue during the first year of treatment.[127] Thus, further observations are needed in order to definitively estimate the magnitude of quetiapine-associated weight gain during long-term treatment.[128]
3. The interpretation of data on risperidone is not straightforward. Indeed, studies conducted with similar methodologies show opposing results. Thus,

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the possibility that risperidone-induced weight gain may be of concern in long-term treatment of severe psychiatric disorders should carefully be taken into consideration.

4. Conflicting data are also available on aripiprazole; all reviewed studies suffered from numerous and severe limitations. Hence, definitive conclusions about the long-term metabolic safety of aripiprazole are also unfeasible at this stage.

5. In two well designed studies, although very limited in terms of sample size, ziprasidone showed no effect on weight during long-term treatment.[48,87] However, some limitations of the CATIE (Clinical Antipsychotic Trials in Intervention Effectiveness) study,[48] such as the fact that drug dosages were not equivalent, were highlighted in a recent editorial by DeLisi and Nasrallah.[129]

5. Factors Influencing Weight Gain in Patients Treated With Atypical Antipsychotics

In two very short-term studies, it has been suggested that weight gain induced by some typical and atypical antipsychotics (olanzapine, clozapine and haloperidol, but not risperidone) correlates positively with the clinical response. The activity of atypical antipsychotics on serotoninergic receptors could determine better clinical outcomes, changes in food intake and, consequently, in weight.[130,131] Additionally, in a 6-week study, a better clinical outcome appeared to be associated with the degree of weight gain induced by risperidone and haloperidol.[132] However, all long-term reviewed studies that examined such a correlation failed to confirm that a relationship exists between weight gain and improvement of positive and negative symptoms during antipsychotic treatment.[26,27,44] Surprisingly, a correlation also seems to exist between weight gain and therapeutic improvement in patients with schizophrenia treated with placebo;[133] however, the clinical significance of this remains unclear. It has also been hypothesised that a correlation could exist between dyslipidaemia and acute-phase schizophrenia, as well as between dyslipidaemia and response to atypical antipsychotic treatment.[134]

Rapid weight gain during the early phases of treatment seems to be associated with further weight increase in long-term treatment.[135]

Despite the growing need for a gender-focused approach to mental disorders, few studies have evaluated the influence of gender on the development of antipsychotic-associated weight gain; moreover, their results provide conflicting conclusions.[26,30,45,47,132,136,137]

The vast majority of reviewed studies seem to confirm that weight gain is less severe in elderly patients compared with younger patients. By contrast, children and adolescents seem to be populations at particular risk of developing antipsychotic-induced weight gain.[45,50,61,64,68,81,138-140] However, one study demonstrated that quetiapine may induce clinically relevant weight gain in elderly patients with a relatively high frequency, even if administered at low dosages.[83]

Important clinical concerns, such as the correlation between weight and BMI at baseline and the risk of weight gain, the possibility that weight gain may reach a plateau when a patient is receiving long-term treatment, and the timing of this plateau for each single agent are still controversial and require further investigation.[24,47,69,91,141] However, preliminary reports suggest that weight gain reaches a plateau after 1 year of olanzapine treatment,[48] whereas clozapine-treated patients progressively gain weight during the entire duration of treatment.[21]

Patients with bipolar or other affective disorders seem more likely to gain weight than patients with psychosis because of the additive metabolic effect of mood stabilisers.[1,44,56,142] Such a suggestion, however, remains controversial.[143]

The correlation between dosage and weight gain is still uncertain; a correlation has been observed in one long-term study for olanzapine,[40] but excluded in others.[44-47] Some studies on risperidone also suggested that weight changes and dosage were unrelated.[47,63,64,66,67] By contrast, two reports (one conducted in children) suggested that such a correlation could exist during long-term risperidone treatment.[65,68] To date, no reports have suggested that a possible association exists between quetiapine, amisulpride, aripiprazole and ziprasidone dosage and weight gain in long-term treatments.

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Hence, given the number of inconclusive findings, the relative risks of weight gain for the different antipsychotic medications should be a consideration in drug selection, not only for patients with a BMI at baseline of ≥25,[104] but for all younger patients without gender distinction, especially if affected by affective disorders. For the same reasons, nutritional counselling and advice on physical activity should be provided, not only to younger patients who are overweight or obese,[144] but also to normal-weight younger patients who are starting any atypical antipsychotic treatment (with the possible exception of ziprasidone). Nutritional counselling, however, should be integrated with long-term multimodal weight-control programmes.[145] In outpatient psychiatric populations, these programmes should also be combined with specific psychological and social interventions to offer better support to both the patients and their relatives and to facilitate healthy lifestyle changes.[146-148] However, further research is needed in order to assess the impact of lifestyle interventions in preventing or reversing this iatrogenic metabolic syndrome in patients with severe psychiatric disorders.[149]

6. Conclusion

The differences in effect between short- and long-term treatments with atypical antipsychotics on weight gain may be due to a complex overlapping of different factors, both drug-specific (relative receptorial affinity; timing of weight-change plateaus; and drug-specific/dose-dependent weight gain) and patient-specific (genetic vulnerability; sex; age; BMI and weight before starting antipsychotic treatment; type of psychiatric disorder; individual health and lifestyle; and concomitant need for other medications). Hence, there is an urgent and growing need for well designed, randomised, controlled trials to assess both the differential effects of atypical antipsychotics on weight[150,151] and the role of all other factors in contributing to iatrogenic unwanted weight changes. Because of the difficulties, however, of maintaining optimal study conditions over long-term follow-up (such as blinded observation, fixed-dose treatment, and no concomitant treatment), prospective longitudinal studies may also be greatly useful in adding conclusive information about the risk of long-term atypical antipsychotic-induced weight gain. The assessment of the different impact of all these factors on weight will represent one the most significant challenges of psychopharmacological research in the coming years.

Meanwhile, the well known benefits shown by some atypical antipsychotics in reducing akathisia and other extrapyramidal adverse effects and improving cognition should be carefully balanced with the problems of weight gain, other metabolic complications and higher healthcare costs.[52]

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