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Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis

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Abstract

Introduction: Antipsychotics (AP) induce weight gain. However, reviews and meta-analyses generally are restricted to second generation antipsychotics (SGA) and do not stratify for duration of AP use. It is hypothesised that patients gain more weight if duration of AP use is longer.

Method: A meta-analysis was conducted of clinical trials of AP that reported weight change. Outcome measures were body weight change, change in BMI and clinically relevant weight change (7% weight gain or loss). Duration of AP-use was stratified as follows: ≤6 weeks, 6–16 weeks, 16–38 weeks and >38 weeks. Forest plots stratified by AP as well as by duration of use were generated and results were summarised in figures.

Results: 307 articles met inclusion criteria. The majority were AP switch studies. Almost all AP showed a degree of weight gain after prolonged use, except for amisulpride, aripiprazole and ziprasidone, for which prolonged exposure resulted in negligible weight change. The level of weight gain per AP varied from discrete to severe. Contrary to expectations, switch of AP did not result in weight loss for amisulpride, aripiprazole or ziprasidone. In AP-naive patients, weight gain was much more pronounced for all AP.

Conclusion: Given prolonged exposure, virtually all AP are associated with weight gain. The rational of switching AP to achieve weight reduction may be overrated. In AP-naive patients, weight gain is more pronounced.

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Introduction

Weight gain resulting in overweight and more particularly obesity is a growing problem worldwide. Overweight and particularly obesity predicts cardiovascular risk, metabolic syndrome (MS) and diabetes mellitus type 2 (DM-II) [1–5] as well as an increased risk for cancer [6,7].

In general, the life expectancy of patients with Severe Mental Illness (SMI) is reduced compared with the general population [8]. In SMI patients, overweight and obesity are more prevalent compared to the general population [9], whilst risk of developing cardiovascular diseases is substantially increased [9,10]. People with a diagnosis of schizophrenia have a 2–3 times increased standard mortality ratio, for all causes of death [11–13]. Compared to the general population, the risk of developing cardiovascular illness is doubled and more than five times higher for endocrine disease [12,14]. For people with bipolar disorder, the standard mortality rate (SMR) due to cardiovascular disease is 2, and for unipolar depression the SMR is 1.5 in men and 1.6 in women [15]. Long term use of antipsychotics (AP) is associated with increased mortality risk in people with SMI [16,17]. In general, it is concluded that AP add to the increased mortality risk of people with SMI either through direct cardio toxic effects or by impacting on weight gain [8,18].

In 1999, Allison [19] showed that most AP are associated with an increase in body weight and this was the starting point for the present meta-analysis, given that after this date, systematic attention to weight gain in trials became the norm. In addition, Allison [19] suggested to study clinically significant weight gain and weight loss and provided a definition. Subsequent meta-analyses confirmed the finding that most AP contributes to weight gain [20–26]. Particularly clozapine and olanzapine were associated with severe weight gain, whereas aripiprazole and ziprasidone appeared almost weight neutral [5,20,23,24,26–31]. The meta-analysis by Tarricone and colleagues is of special interest as this study showed that in AP naive patients, BMI increases with duration of AP use [26].

Duration of AP use was studied in only two meta-analyses [24,26]. The study by Parsons and colleagues contrasted a short duration (4–12 weeks) with a long duration (around 52 weeks). The study by Tarricone and colleagues included 11 studies in AP-naive patients who were prescribed an AP, defining three periods of AP exposure (4–8 wks, 10–12 wks and 24–48 wks). Both studies showed that long term use of AP was associated with more weight

gain compared with short term use. These studies did not differentiate individual AP.

Several factors explain weight gain due to AP and the impact of duration of AP use on bodyweight. AP medication induces changes in appetite and food intake, most likely because of interaction with serotonergic [32], histaminergic [33] and dopaminergic [34] neurotransmitter systems inducing increase in appetite and food intake. Therefore, the effects on weight and Body Mass Index (BMI) likely will progress with time. Duration of AP use thus is thought to constitute an important factor contributing to weight gain [24,26]. In addition, certain diagnoses like schizophrenia and to lesser extent bipolar disorder have been associated with a higher level of metabolic dysregulation [32] and weight gain may be more substantial in this group of patients.

The study by Allison [19] recalculated the data towards a 10 weeks period and in the study by Leucht and colleagues [35] only studies shorter than 12 weeks were included. These studies ignore the importance of duration of AP use. Changes in body weight are usually more prominent after prolonged exposure to an AP. So, there is an urgent need to summarise studies stratified by duration of exposure.

Studies in drug-naive patients are more informative than switch studies, as weight outcomes are not influenced by the level of overweight due to a previous AP, thus allowing for assessment of an effect that can be attributed to a specific AP. Two previous meta-analyses have published data in AP-naive patients. In first-episode schizophrenia patients, weight gain was more prominent compared to chronic patients [24]. Second, BMI increases after first exposure to AP from more than 1 BMI point after 4–8 weeks, to almost 4 BMI points after 24–48 weeks [26]. However, because studies in drug-naive patients starting an AP are rare, the present meta-analysis examines both the total group and the subgroup of studies in restricted to drug-naive patients. When drawing conclusions, it should be considered that results pertaining to drug-naive patients are more likely to reflect the true extent impact of weight change induced by AP than results from a meta-analysis combining switch studies and studies in AP-naive patients.

The various systematic reviews and meta-analyses described above addressed the association between a selection of antipsychotics and weight gain. However, none of the previous reviews intended to include all randomised controlled trials, irrespective of diagnosis or dosage of all antipsychotics including data on weight change across all durations of treatment. Meta-analyses almost exclusively focused on schizophrenia and related psychoses or bipolar disorder, whereas AP are used in many patients with other diagnostic categories such as anxiety disorders, depression, dementia, personality disorders or Tourette's Syndrome. Therefore, a more comprehensive approach is required. A complete overview of all AP will enhance the understanding of the clinical impact of weight change for each AP separately. Additionally, AP are generally used long-time and, therefore, duration of AP exposure is a factor of interest associated with potential weight gain over time. Only two previous meta-analyses included this factor [24,26]. Finally, as already mentioned above, meta-analyses on AP naive patients are very rare. Therefore, the present meta-analysis aims to assess crude weight changes after the start of an antipsychotic or after the switch to another antipsychotic, including all antipsychotics ever examined in a randomised controlled trial (RCT).

The study by Allison [19] launched the interest in weight change and metabolic problems as important side effects of antipsychotics. After this study, interest in metabolic changes due to AP gradually increased, leading to presentation of data on metabolic changes, including changes of body weight, in medication studies. The present meta-analysis additionally included proportion of clinically relevant weight gain and weight loss as well as durations of follow-up exceeding one year. The search in the present paper was limited to articles published after January 1999. Before 1999, there was no systematic consensus to assess body weight, BMI or 7% weight gain or loss.

Whether all AP result in weight gain remains unclear, as the majority of the studies are restricted to the most prescribed SGAs or haloperidol as comparator [19–21,24–26,34]. Previous meta-analyses and reviews did not focus on FGA with the exception of haloperidol, or treated FGA as a single homogenous group. Generally, it is suggested that FGA are weight neutral, but at the time these drugs were launched studies did not include weight change as an outcome. Another problem is that outcome of studies and meta-analyses are contaminated by two factors: (i) mix of study duration (short and long term studies) whereas effects on weight are delayed and (ii) no distinction is made between first episode of drug naive patients and chronic patients [20].

The recent meta-analysis by Leucht et al [35] included 15 AP of which only haloperidol was a FGA compound. A refined statistical method (network analysis) allowed for mutual comparison between AP and shows that haloperidol has the least impact weight gain. Leucht and colleagues only included weight change as an outcome, not BMI change or 7% weight gain of 7% weight loss. The result showed that olanzapine was associated with the most gain in weight. However the authors did not control for duration of AP use effects. In addition, the meta-analyses did not include variables BMI change nor the proportion of subjects with 7% weight increase or 7% weight loss [35]. Finally, as mentioned above previous meta-analyses studied predominantly schizophrenia and related psychoses and bipolar disorders. This emphasizes the need for comprehensive analyses including all data on weight change per AP available.

Hypothesis/study goals

The present study assessed absolute changes in body weight and BMI as well as the proportion of subjects with more than seven per cent increase or decrease in body weight after the start of a specific AP. Second, body weight change, change in BMI and change in $>$ 7% weight increase (or clinically relevant weight gain) or $>$7% weight loss (or clinically relevant weight loss) in AP-naive patients were examined as a function of duration of AP exposure, allowing for assessment of possible progress with duration of AP exposure.

Method

Data sources

The meta-analysis was conducted and reported according to recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [36]. A review protocol was construed following the MOOSE guidelines. This was not published but only for internal use of this study.

A PubMed and Embase search was conducted for articles on metabolic side effect profiles of antipsychotic medication. The search term used was: ((“weight gain” OR “BMI” OR “7% weight”) AND (chlorpromazine OR haloperidol OR bromperidol OR fluphenazine OR zuclopenthixol OR pentixol OR flupentixol OR levopromazine OR perphenazine OR pimozide OR penfluridol OR sulpiride OR amisulpride OR amoxapine OR asenapine OR aripiprazole OR blonanserine OR clozapine OR iloperidone OR melperone OR olanzapine OR risperidone OR paliperidone OR quetiapine OR sertindole OR lurasidone OR ziprasidone)) NOT (addition OR additive OR adjunctive OR augmentation OR lithium OR valproate OR carbamazepine OR metformin OR

topiramate OR ramelteon OR rimonabant OR modafinil OR sibutramine OR genetics OR pharmacokinetics OR vomiting OR nausea OR review OR "cognitive behavioural therapy" OR "cognitive behavioral therapy" OR delirium OR steroids OR ropinirole OR sleep OR "brain volume")

Limits Activated: Humans, Clinical Trial, Randomized Controlled Trial, Clinical Trial, Phase IV, Controlled Clinical Trial, English, German, All Adult: 18+ years, Publication Date from 1999/01/01 to 2011/12/31.

Inclusion criteria and study evaluation

The aim of the search was to identify randomised controlled studies (RCT) or controlled clinical trials where subjects were randomised into various AP intervention groups. The identified outcome was absolute change in weight, BMI (continuous) or 7% weight loss or 7% weight increase. Studies were included if they compared two or more AP or AP versus placebo. There were no restrictions with regard to diagnosis, age, dosage of AP or duration of AP exposure.

The inclusion criteria were:

1. Weight gain (continuous), BMI (continuous) or 7% weight loss or 7% weight increase.
2. Age 18 years or older
3. Minimum follow-up of one week
4. Data available for AP treatment and weight change
5. Randomised controlled trial, controlled clinical trial or clinical trial or phase IV clinical trial with adequate control group with intention to treat.
6. 01-01-1999/12-31-2011

Excluded were studies designed to influence weight gain in patients with eating disorders such as anorexia or bulimia nervosa and studies involving somatic causes of weight change irrespective of the medication (e.g. delirium). Very short term or acute antipsychotic interventions, rapid tranquilisation, or brain imaging studies used for assessing AP impact on brain morphology or brain function were excluded. In these studies, antipsychotic interventions were very brief (ranging from a single dose to a 7-day regimen). These studies are excluded as they are not expected to show a clear change on body weight. Additionally, evaluation of weight change in short term interventions is often evaluated in case of treatment of transient confusion or delirium which is complicated by underlying somatic illness that may explain body weight change directly and therefore represents a biased assessment of AP-impact on weight change. Also excluded were studies on specific (non-) pharmacologic interventions to reduce weight such as medication augmentation strategies, dietary programs, psycho-education or cognitive behavioural therapy (CBT). Systematic reviews, meta-analyses, case reports and poster presentations are also excluded.

Quality assessment was based on items given in the MOOSE checklist, which summarises recommendations of an expert panel for reporting meta-analyses and systematic reviews of observational studies [36]. Methodological issues evaluated with the checklist were the presence of a clearly focused study question, an appropriate study type, an adequate recruitment of patients and controls, an unbiased measurement of outcomes, the identification of and statistical control of important confounding factors, the completeness of follow-up and the precision of estimates.

All papers were reviewed by two independent researchers (MB and AF or JJ), who studied the papers closely on methodology and outcome measures based on the MOOSE checklist criteria. In case of doubt, papers were discussed and consensus was reached.

The search strategy initially was limited to PubMed. After this search was completed, including the screening of papers and data entry, the same strategy was applied to EMBASE. First authors were contacted in case of missing information. Pharmaceutical companies were contacted for unpublished data or papers not cited in Pubmed or Embase. In case of papers that were not present in the University Library, authors were contacted to provide the requested article.

Search strategy

The PubMed search yielded 1088 citations. The Embase search yielded 1423 citations. After removing duplicates between Pubmed en Embase 2374 papers remained. Screening papers resulted in exclusion of papers if the study did not meet the inclusion criteria despite the limits activated, e.g. rapid tranquillisation studies, reviews or meta-analyses, case reports, weight intervention studies, studies with duration of one week or brain morphology studies examining the effect of a single dose of medication, and left 1380 articles. Of the studies eligible for more detailed evaluation. Full text article screening resulted in rejection of papers because of incomplete data, absence of crude data, study or data redundancy or failure to provide data per antipsychotic (an exception was made for articles presenting data as FGA or SGA, rather than the specific AP) overviews, risk assessment studies, case reports or cross-sectional studies and resulted in 519 papers. After qualitative assessment 307 papers were selected and used for data extraction (See Figure 1 Prisma Checklist flow diagram). One paper was treated as two separate studies, as it presented two separate data sets in a single paper [37].

Data extraction

Data from RCT's were extracted if based on intention-to-treat analysis. Before data entry, lbs units were converted to kg.

Duration of exposure categories

In order to calculate the association between duration of antipsychotic use and gain in body weight, four exposure categories were defined: short term ($\leq$6 weeks), medium short term (6–16 weeks), medium term (16–38 weeks) and long term ($>$ 38 weeks).

Outcomes

Four outcome measures were defined: (i) body weight gain in kilogram's (kg), (ii) BMI, and (iii) 7% proportion of weight gain or (iv) weight loss after starting an AP. The 7% weight gain or weight loss represents the cut-off for clinically relevant weight change. The association between an AP and any of the four outcomes (weight change, change in BMI, proportion $>$7% weight gain, and $>$7% weight loss) was only presented if data of more than one study was available. Rates were transformed [ln(proportion/(1-proportion))], in order to avoid negative numbers in the confidence intervals (CI) (0 is lowest valid value in rates).

In case weight change or BMI change were not presented in the original paper, weight change or BMI change were calculated by subtracting end of study body weight or BMI post-baseline study body weight or BMI (body weight baseline - end body weight or baseline BMI - end BMI). As in this instance standard errors were not available, these were estimated using the formulas below:

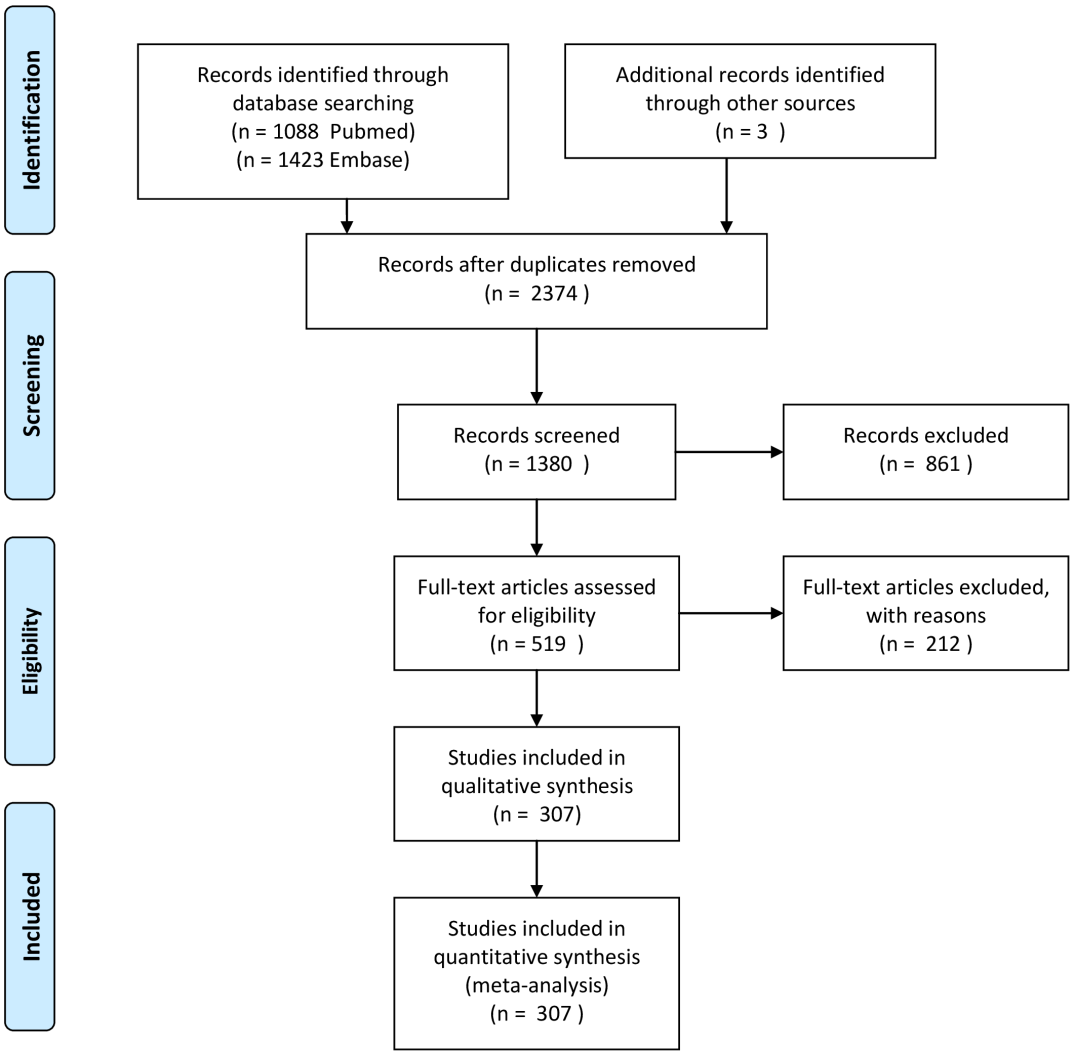

Figure 1. Prisma Checklist flow diagram.
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$$sd\_change = sqrt\left(sd\_baseline^2 + sd\_endp^2 - 2 \times r \times (sd\_baseline) \times (sd\_endp)\right)$$

$$se\_change = \left(sd\_change / sqrt(n)\right)$$

in which:

r = correlation between weight at baseline and weight at follow up

sd_change = estimated standard deviation of weight change scores

sd_baseline = standard deviation of baseline weight

sd_endp = standard deviation of endpoint weights

se_change = estimated standard error of weight change

n = number of subjects per study.

r was estimated using data from a local longitudinal register of medication use in relation to somatic parameters [38] (data available July 2006–September 2012) as follows: weight change →6–16 weeks: 0.96 (n = 220); 16–38 weeks: 0.95 (n = 241); 38–260 weeks 0.93 (n = 961); BMI change →6–16 weeks: 0.96 (n = 212); 16–38 weeks (n = 240): 0.96; 38–260 weeks: 0.92 (n = 936). The r for duration of ≤6 weeks was also conservatively set at 0.96, as the longitudinal register had relatively few observations for this duration (n = 11) and in theory r increases when duration decreases.

Statistical analysis

All analyses were performed using Stata 12 [39]. In order to examine the four outcomes per antipsychotic for each duration of exposure category, the Stata command *metan* [40] generated forest plots including pooled estimates (absolute changes) with their corresponding 95% confidence interval (95% CI). This was repeated including only studies with drug-naive patients. This same procedure was performed for the rates, but because of the transformation of the rates before analyses, the R-program was used to make forest plots of the back-transformed results [41].

The computation of summary effects was carried out under the random-effects model, in which Tau was estimated using the DerSimonian-Laird method. Heterogeneity analyses were carried out using the chi-square, I-square, and Tau-square statistics. Tau-square estimates the total amount of variability (heterogeneity)

among the effect sizes, but does not differentiate between sources. Heterogeneity may be due to random or systematic differences between the estimated effect sizes. I-square estimates the proportion of the total variability in the effect size estimates that is due to heterogeneity among the true effects.

The present analyses aim to test whether changes in weight, BMI or the proportion of 7% weight gain and weight loss are statistically significant. The present paper also presents figures per AP for each outcome measure. These figures are for descriptive purposes only. Using the present methods of analysis, comparisons between interventions (including placebo) or between exposure durations ignores clustering in the data (given more than one intervention group extracted per article and given the fact that intervention groups are clustered because of the randomisation).

In addition, in a subset of antipsychotic compounds with sufficient data available, a meta-regression analysis was performed to test whether duration of AP use was a modifier.

Results

Weight change per type of antipsychotic for each duration of exposure category

Of the 307 included studies, a total of 257 studies reported results on weight change (603 records in the meta-analysis data). In table S1 the number of reporting papers per AP are given for the outcomes weight change, BMI change, percentage >7% weight gain, percentage >7% weight loss. Figure 2 shows the mean change per antipsychotic per duration of exposure category. More details are presented in see table S2 and forest plots S1–S16 in File S1 and File S2. For some AP, only 1 study was available, or data could not be used (sd or se could not be calculated) – these were therefore not included in the meta-analyses. The excluded AP and their weight change are amoxapine 1.05 kg (<6 wk, n = 22) [42], blonanserine 1.29 kg, sd = 3.48 (6–16 wk, n = 92) [43], fluphenazine −2.6 (16–38 wk, n = 9) [44], iloperidone 2.6, sd = 3.7 (< 6 wk, n = 1239) [45], levomepromazine 4.1 (16–38 wk, n = 19) [46], lurasidone 0.9 kg (<6 wk, n = 90) [47], pimozide 2.9 (6–16 wk, n = 24) [48] and zuclopentixol 0.6 (6–16 wk, n = 19) [49]. The I-square of the included studies varied strongly, ranging from 10.3%–99.8% (in case 4 or more studies were included in the analysis), indicating little heterogeneity to very strong heterogeneity.

Most AP showed a statistically significant change in weight post-baseline, with the exception of amisulpride, aripiprazole, asenapine, sertindole, ziprasidone and placebo which showed no statistically significant weight change. However, these results are crude outcomes regarding weight change and therefore merely suggestive for differences in the magnitude of weight change per AP. Although comparison between APs is not tested, the crude data suggest that clozapine and olanzapine show the most severe weight gain post-baseline, while FGA, for example haloperidol, are also associated with significant weight gain. Even over the shortest exposure period of ≤6 weeks, an increase in body weight post-baseline was evident for most AP (Table 1).

The increase in weight was significantly greater in exposure period 4 (>38 weeks) then in exposure period 1 (0–6 weeks) for FGA and olanzapine (see table S2) and forest plots S1–S16 in File S1 and File S2). For example, in the analysis of olanzapine, subjects gained 1.74 kilogram more weight (95% CI 0.50–2.99, p = 0.006) in exposure period 4 (>38 weeks) than in exposure period 1 (≤6 weeks). On the other hand, in the placebo group, patients lost weight in exposure period 4 and this was significantly different from the weight change in exposure period 1. Other AP did not show statistically significant changes in body weight over the consecutive exposure periods compared with exposure period 1.

Weight change in AP-naive patients for each duration of exposure category

Weight change post-baseline in AP-naive patients was limited to 39 studies, yielding 90 records. Data were available only for aripiprazole, chlorpromazine, clozapine, FGA, haloperidol, olanzapine, perphenazine, quetiapine, risperidone, SGA, sulpiride, ziprasidone and the placebo group. Figure 3 shows the weight change of the various AP within the group of AP-naive patients. Most associations between AP and weight gain were statistically significant at all exposure periods. For sulpiride, only 1 record was available (1.86, se 0.45; >38 wk, n = 162) and therefore not presented in the figure (Figure 3) [50]. For more detailed information see Table S3 and Forest plots S17–S24 in File S3). The short term period (≤6 weeks) showed substantial and statistically significant weight gain, olanzapine 3.42 kg, quetiapine 1.91 kg, risperidone 2.68 kg. I-square varied between 63.9% and 98.6% for meta-analysis. Weight was increased over time. Studies with 4 or more studies are presented.

For exposure period 4 (>38 weeks), patients receiving olanzapine gained significantly more weight than in exposure period 1 (See Table 2 and Table S3).

BMI change per duration of exposure category

Ninety-one studies reported results on BMI change (227 records in the meta-analysis data). BMI increased over time after the start of a specific AP (Figure 4). Not all changes were statistically significant, likely due to the relatively low number of studies for each separate antipsychotic (Table S4 and Forest plots S25–S35 in File S4).

BMI changes in AP-naive patients per duration of exposure category

The number of studies reporting data on BMI change in AP-naive patients was limited to 18 studies with 51 records. All included AP showed a statistically significant increase in BMI (Figure 5). For quetiapine (6–16 weeks) and ziprasidone (<6 weeks), only a single exposure period was available in the data. Placebo did not result in increase of BMI over consecutive periods (Table S5 and Forest plots S36–S44 in File S5).

7% weight gain per duration of exposure category

There were 126 studies reporting on proportional weight gain (319 records in the meta-analysis data). The proportion of patients gaining more than 7% weight expanded with duration of AP use for each AP (Figure 6). The exception is the placebo group proportional weight increase remained constant at 4% during all exposure periods (Table S6 and Forest plots S44a–S58d in File S6 and File S7).

7% weight gain in AP-naive patients per duration of exposure category

The number of papers that presented data of 7% weight gain in antipsychotic naive patients is limited (11 studies with 32 records). For almost all included AP the proportion of subjects with clinically relevant weight gain is statistically significant (Figure 7). Apart from the short-term exposure period (≤6 weeks) treatment with aripiprazole resulted in an elevated number of subjects with clinically relevant weight gain at each duration of exposure category. The proportion of subjects gaining weight is also statistically significant in the placebo group after >38 weeks. For

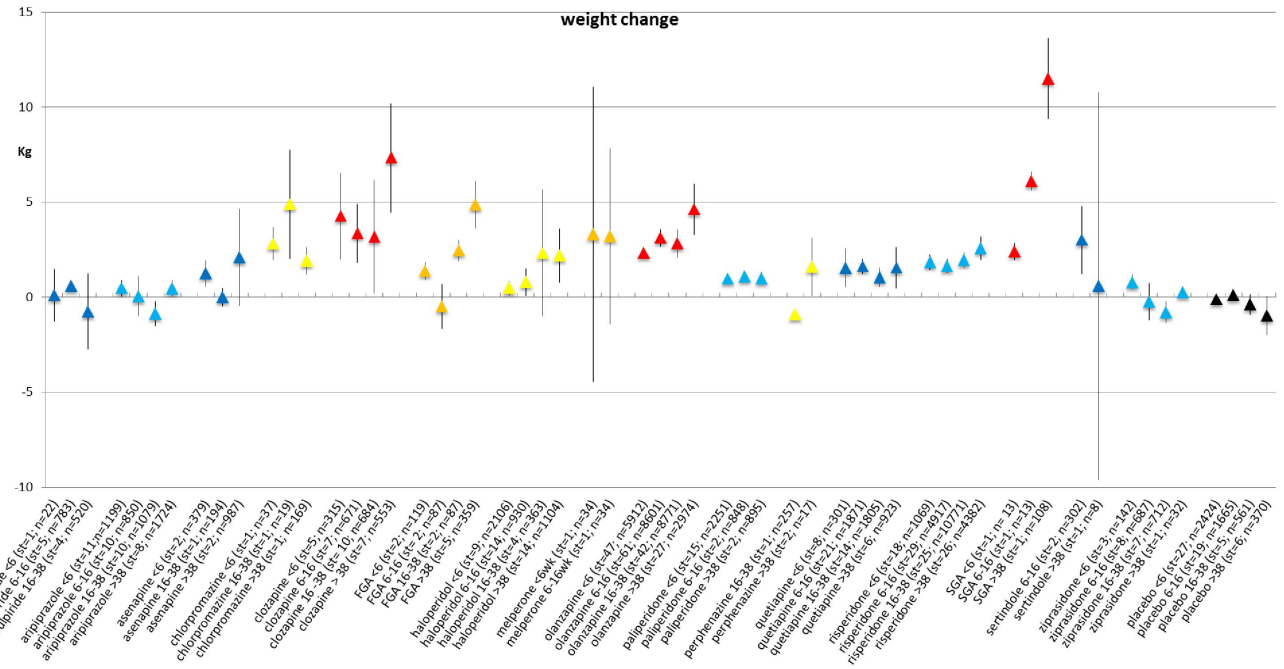

Figure 2. Weight change (in kg) per period per antipsychotic medication.
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more detailed information see Table S7 Forest plots S59a–S64c in File S8.

7% weight loss per duration of exposure category

Twenty-four studies (representing 53 records) reported on proportional weight loss. Only data for amisulpride, aripiprazole, asenapine, olanzapine, paliperidone, ziprasidone and placebo were available (for 1 or more exposure periods, see Figure 8). Results showed that a statistically significant proportion of the patients had clinically relevant weight loss after the start of any of these AP, but visual inspection did not show a duration-response pattern (Table S8 and Forest plots S65–S72 in File S9).

Discussion

Main findings

This meta-analysis presents four outcome measures: (i) body weight change, (ii) BMI change, (iii) proportion of clinically relevant weight gain and (iv) proportion of clinically relevant weight loss for an extensive number of AP and within a subgroup of AP naive patients as well, simultaneously in one paper, The main result was that almost all AP showed a mean increase in body weight, BMI and a clinically relevant proportion of weight gain with increased duration of AP use, except for amisulpride, aripiprazole and ziprasidone which were weight neutral with duration of AP use. The AP-naive subgroup showed more robust increases of mean weight gain and BMI with duration of AP use. The proportion clinically of weight gain in the AP naive was at least 20% for all AP. In contrast, the outcome measure 'proportion of clinically relevant weight loss' showed a modest weight loss of around 10% for all AP studies, except aripiprazole showed clinically relevant weight loss in excess of 15%. Unfortunately, in the subgroup of AP-naive patients the proportion of clinically relevant weight loss could not be analysed because of lack of data. In conclusion, the present results add to the existing knowledge, showing that (i) duration of AP use is a modifying factor; (ii) that there are also AP users who lose weight; (iii) that AP switch to metabolically more neutral compounds may not result in weight loss in all cases; and (iv) that AP naive patients are more vulnerable to weight gain. This meets the criticism of Alvares-Jimemez that AP naive patients or first episode patients need to be studied separately from chronic patients [20].

The meta-regression analyses suggested that increased exposure to AP over time is associated with increased weight gain. Indicating that duration of AP exposure may be regarded as a causal factor, contributing to weight gain. Inspection of figure 1 to 8 suggests that other AP also display duration-response associations with weight gain.

Perspectives

Although studies in AP-naive patients are more informative on weight gain induced by a specific AP, only one previous meta-analysis addressed the issue of weight change after start of an AP in AP-naive patients [26]. An increase in body weight and BMI for the combined group of all AP in AP-naive patients with schizophrenia over three duration categories of AP use was reported: 4–8 weeks, 10–12 weeks and 24–48 weeks [26]. This is in agreement with the present meta-analysis that showed that duration of AP use in AP naive patients resulted in weight gain. This result confirms also the direct impact of AP on weight gain.

Switching to an AP like amisulpride, aripiprazole or ziprasidone may not result in weight loss in all cases, as the mean weight change post-baseline according to this meta-analysis is neutral. On the other hand, the outcome "proportion of patients with weight loss" suggests that a considerable proportion of patients on aripiprazole, amisulpride or ziprasidone show significant weight loss after switching AP medication. However, this needs to be put into perspective: (i) the fact that the mean body weight change is neutral for these AP indicates that a comparable proportion will show weight gain, as shown in the outcome "proportion of clinically relevant weight gain" and (ii) this is based on the crude

Table 1. Metaregression of weight changes per period.

Period	aripiprazole	asenapine	clozapine	FGA	haloperidol	olanzapine	quetiapine	risperidone	ziprasidone	placebo
≤6 wk*	0	0	0	0	0	0	0	0	0	0
6–16 wk	−0.46 *−1.78–0.85*		−2.37 *−6.93–2.19*	−2.19 *−6.63–2.25*	−0.25 *−2.50–1.99*	0.472 *−0.16–1.60*	0.05 *−1.26–1.36*	−0.58 *−1.57–0.72*	−0.97 *−3.08–1.13*	0.25 *−0.14–0.64*
16–38 wk	**−1.43** ***−2.75–−0.12***	−1.25 *−5.98–3.48*	−3.81 *−8.18–0.55*		2.75 *−0.58–6.08*	0.26 *−0.68–1.20*	−0.54 *−1.94–0.86*	−0.03 −1.03–0.96	−1.68 *−3.78–0.41*	−0.26 *−0.81–0.28*
>38 wk	−0.20 *−1.64–1.24*	0.74 *−3.24–4.72*	1.09 *−3.47–5.66*	2.79 *−1.12–6.70*	1.81 *−0.53–4.15*	**1.74** ***0.50–2.99***	−0.85 *−2.56–0.87*	0.37 −0.63–1.38	−0.50 *−3.67–2.68*	**−1.08** ***−1.88–−0.29***

The coeffecient indicates the changes of weight compared with the constant (period 1).
* period 1 (≤6 wk) is the reference category.
Data in italics indicate 95% confidence interval.
The data in **bold** indicate significant difference in weight change of reference category.
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data, which are only suggestive, and may not be used for a direct comparison of AP's.

The consequence is that switching to another AP should be planned with care involving monitoring and evaluation of at least body weight and BMI, among other metabolic parameters [51]. Of interest is the outcome of proportion of clinically relevant weight loss (7% weight loss). It sheds light on the mean changes in body weight, as treatment with amisulpride, aripiprazole or ziprasidone resulted in a higher proportion of patients with clinically relevant weight loss, compared to other AP. Combining mean weight change, the proportion of clinically relevant weight gain and weight loss, offers a more precise impact of AP on body weight. The fact that treatment with aripiprazole resulted in only marginal mean weight loss after a switch, but occasioned a high percentage of patients losing >7% of their body weight indicates that a comparable proportion must experience >7% weight gain. The same is seen for olanzapine. Olanzapine shows a mean increase in body weight over the various duration categories, but even for this AP, a small proportion of patients showed clinically relevant weight loss.

Previous systematic reviews and meta-analyses reported that clozapine and olanzapine induce most severe weight gain [19,20,24,26]. Amisulpride, aripiprazole and ziprasidone were weight neutral and may even result in some weight reduction [52]. A direct comparison between AP to calculate differences between the various AP was only presented by Rummel-Kluge, performing a head-to-head comparison [25] Leucht and colleagues [35] also showed that (i) all AP are associated with at least some weight gain compared with placebo and (ii) that olanzapine and clozapine have the most profound impact on weight gain. These two studies uniquely allow for a direct comparison between AP. However, it should be kept in mind that the study by Leucht and colleagues was restricted to patients with a diagnosis of schizophrenia, with a follow-up time of 4–12 weeks, and only presenting a single weight related outcome (measure mean body weight change). The short period of AP use and the diagnostic restrictions may explain some of the differences found between this study and the study by Leucht and colleagues [35].

The weight gain post-baseline for most AP in this study may not seem severe. Several factors may explain this finding. First, all diagnostic categories were included in the analyses. In most of the earlier meta-analyses, inclusion was restricted to severe mental illness, schizophrenia or bipolar disorders. Patients with SMI have an increased risk for metabolic problems like obesity [9,53,54]. Within the group of SMI, the risk for weight gain is more enhanced for schizophrenia than for bipolar disorder [55,56]. Additionally, the level of weight change is predicted by baseline BMI. A low baseline BMI (≤27.5) results in a greater weight increase compared to high baseline BMI (>27.5) levels [57]. As most studies presented in the current study are switch studies, and the reason for a switch often is AP-related obesity, this would explain the relatively low impact by AP on weight change in the current study, most patient groups having a BMI>27.5. On the other hand, a continuous increase in body weight was observed over time, implying that switching from one AP to another AP has limited effect on body weight, even for AP like aripiprazole or amisulpride. Only ziprasidone may result in some weight loss. This issues needs to be addressed in more detail given its clinical importance.

A previous meta-analysis suggested that switching from higher to lower metabolic risk AP as a way of managing metabolic side should be conducted with care, considering the effect on psychopathology and other side effects [51]. Our findings also shed light on the effect of switching from so-called high to low metabolic risk AP. A proportion of patients may indeed benefit

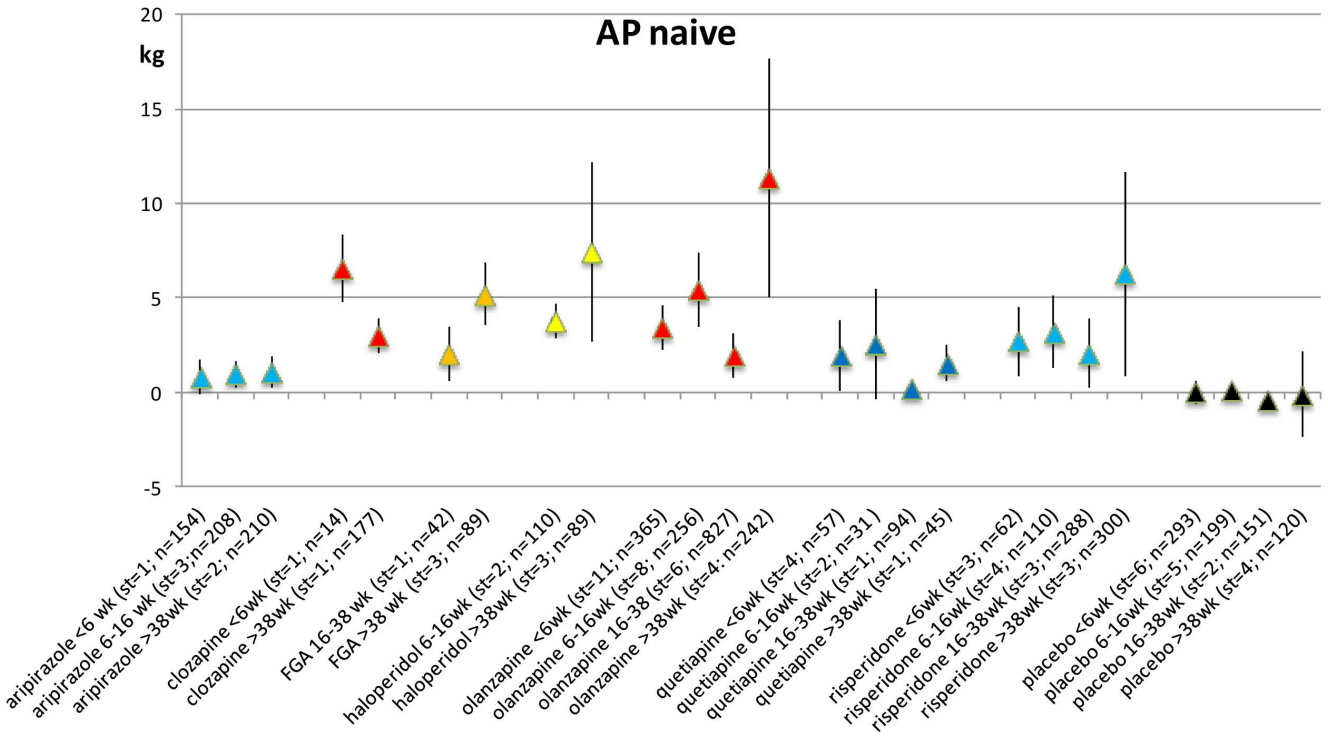

Figure 3. Weight change (kg) per period only including AP-naive samples.
doi:10.1371/journal.pone.0094112.g003

and lose weight. However, prolonged duration of AP use, the mean weight did not change. The principal message is that switching to an AP with a different metabolic risk profile does not always result in losing body weight. Psychiatrists should keep in mind that switching antipsychotics requires monitoring and evaluation [51] and may benefit from concurrent non-pharmacological interventions [58,59].

Methodological issues

In the present systematic review, only RCTs were included. In our view this is a legitimate choice because the RCT study design is generally accepted as gold standard [60]. However, some AP were not, or only once examined in an RCT. In addition, the RCT design also has its drawbacks. The patient group in an RCT is kept artificially homogeneous; all patients with comorbidity, using other medications or presenting with substance use problems tend to be excluded. Drop-out due to probable weight problems may also bias the results. Therefore, only ITT analyses were included, as a best possible correction procedure in the analyses. These factors impact on the generalizability of the results. In real life clinical practice therapeutic effects of the tested medications may be different and side-effects like weight changes may also be different because of co-medication and other factors. For these two reasons, future meta-analyses on various antipsychotics including and comparing, both RCTs and observational studies would be a welcome addition to the present meta-analysis. In addition, a follow-up meta-analysis, using the present data set, need to address direct comparison of weight change between AP and modifying factors, using modern analysis techniques like network analysis.

Despite the fact that various systematic reviews have been published before, this systematic review is the only meta-analysis that did not exclude any AP *a priori*. In addition, a clinically intuitive exposure period was used to assess the association between duration of AP intake and weight change. In spite of these advantages, several limitations apply.

Table 2. Metaregression of weight changes per period in drug-naive patients.

Period	aripiprazole	olanzapine	Quetiapine	risperidone	placebo
≤6 wk*	0	0	0	0	0
6–16 wk	0.15 (*−1.55–1.27*)	1.30 (*−2.34–4.93*)	0.09 (*−6.47–6.65*)	−1.26 (*−6.83–4.32*)	0.24 (*−0.69–1.17*)
16–38 wk		−1.19 (*−5.00–2.63*)	−2.34 (*−9.95–5.27*)	−1.30 (−6.83–−4.23)	−0.38(*−1.48–0.71*)
>38 wk		**5.41 (*0.17–6.13*)**	−0.98 (*−8.70–6.74*)	2.31 (*−3.38–7.91*)	−0.36 (*−2.0–1.29*)

The coeffecient indicates the changes of weight compared with the constant (period 1).
*constant is period 1 that serves as reference in change.
Data in italics indicate 95% confidence interval.
The outcome in **bold** indicate significant difference in weight change of reference category.
doi:10.1371/journal.pone.0094112.t002

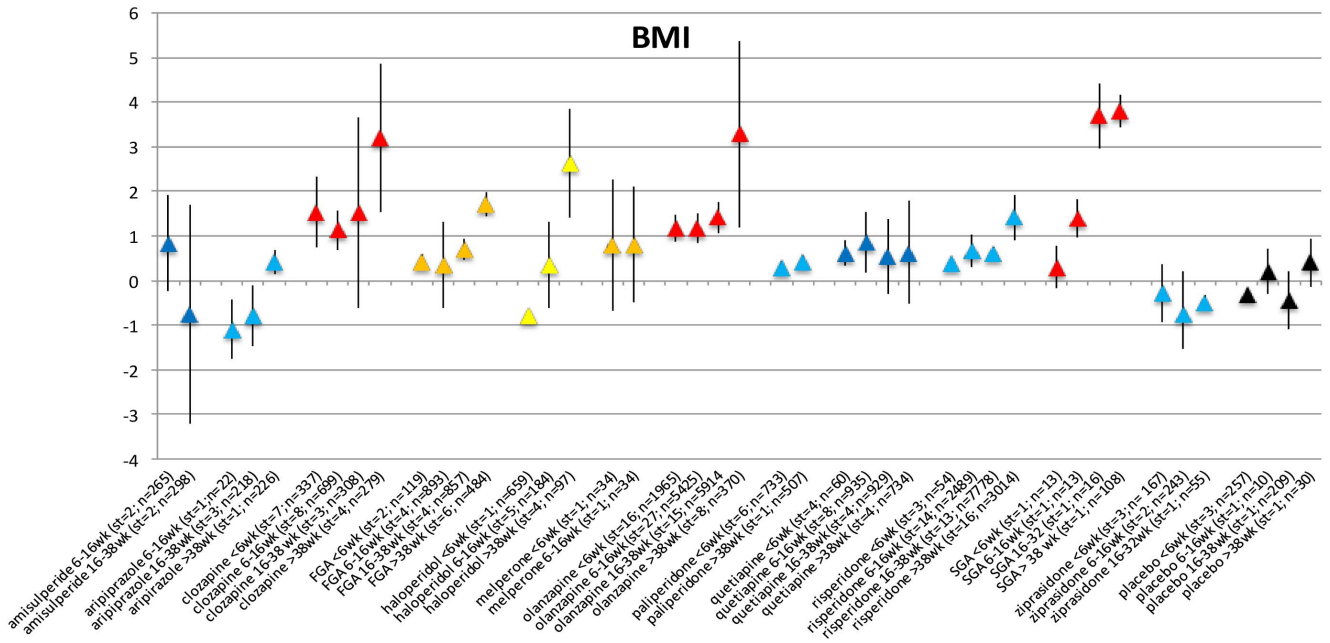

Figure 4. BMI change per period.
doi:10.1371/journal.pone.0094112.g004

First, despite the inclusion of 307 articles, the results for each AP separately were often based on very limited numbers of articles - one to three. This was occasioned by grouping length of AP use in 4 exposure periods. Data thus were particularly sparse for AP-naive groups. This calls for a careful interpretation of results. On the other hand, the results of various outcome measures all point in the same direction.

Second, the aim of the present meta-analysis was to test whether weight changes are significantly different from the null for each AP across the 4 exposure periods. For the purpose of analysis, in case of multiple outcomes per study, the last outcome assessment per exposure period (≤6 weeks, 6–16 weeks, 16–38 weeks, >38 weeks) per AP was selected, to avoid clustering in the data (also see statistical analysis).

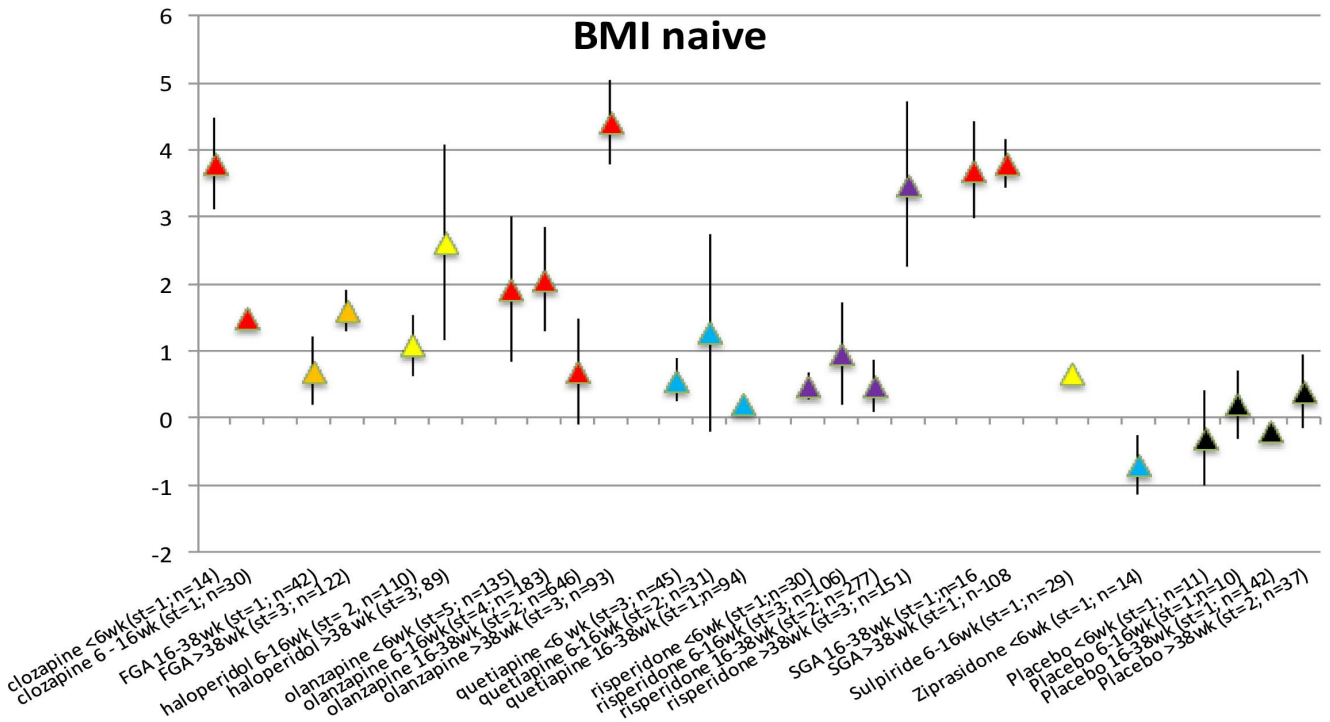

Figure 5. BMI change in AP naive patients per time period.
doi:10.1371/journal.pone.0094112.g005

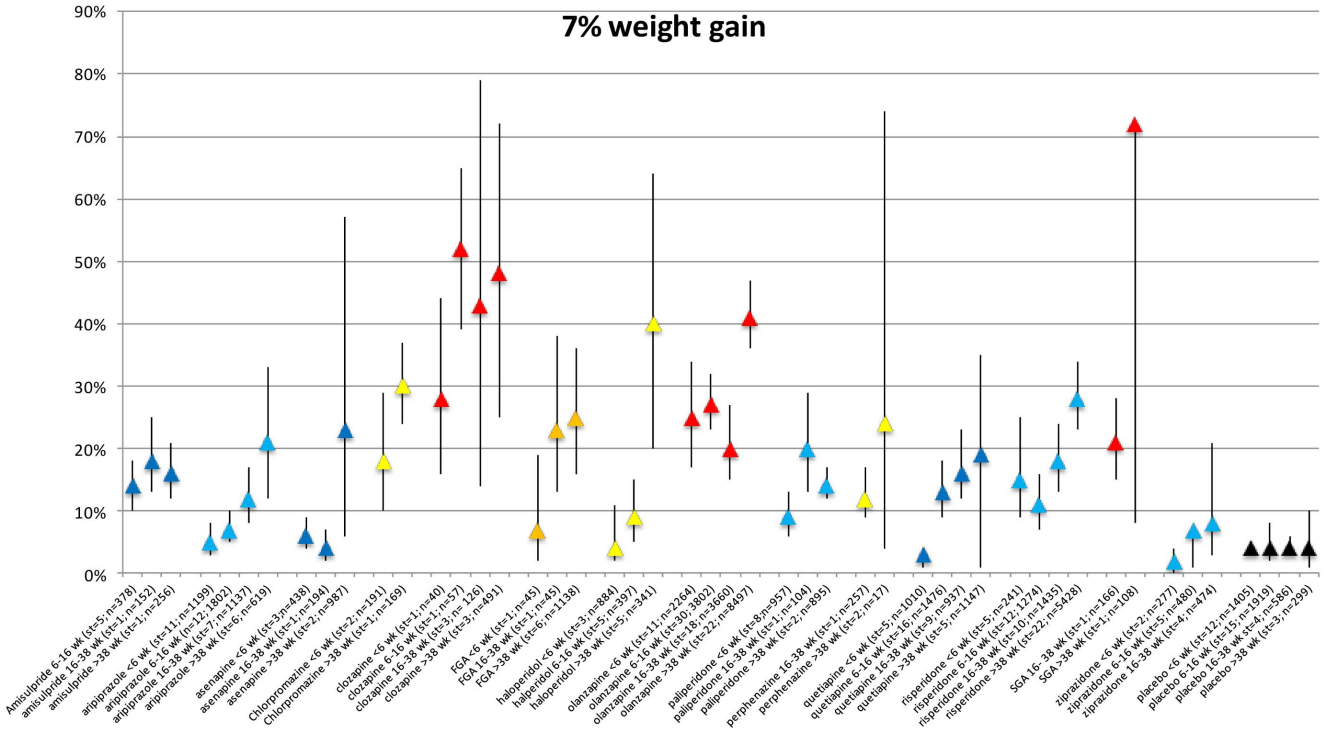

Figure 6. Proportion of weight increase per antipsychotic per time period.
doi:10.1371/journal.pone.0094112.g006

Third, the definition of the 4 exposure categories is based on the average duration of exposure of the studies in the meta-analysis. Although the periods are chosen around the most common time frames presented in the studies, the demarcation is arbitrary. Most studies have fixed periods, however a substantial number of publications used average duration of study. This may have resulted in some measure of regression to the mean.

Fourth, weight gain in groups treated with AP could be the result of other medications like antidepressants or mood stabilisers. This problem is not present, as in studies that entered this meta-analysis, all other medications did not change during the study period, except the AP studied and control medication. Studies on weight change intervention were excluded.

Fifth, not all AP were included. Publications on older AP rarely describe data on the adverse event of weight change. Further, AP with a single reference, blonanserine, fluphenazine, levopromethazine, lurasidone, melperone, pimozide and zuclopentixol, similarly could not be included. Only papers published since 1999 were included, the year the meta-analysis by Allison [19] was published. This paper represented the start of a growing interest in metabolic side effects of AP, particularly weight gain. The current meta-analysis was originally designed as an extension of the Allison paper

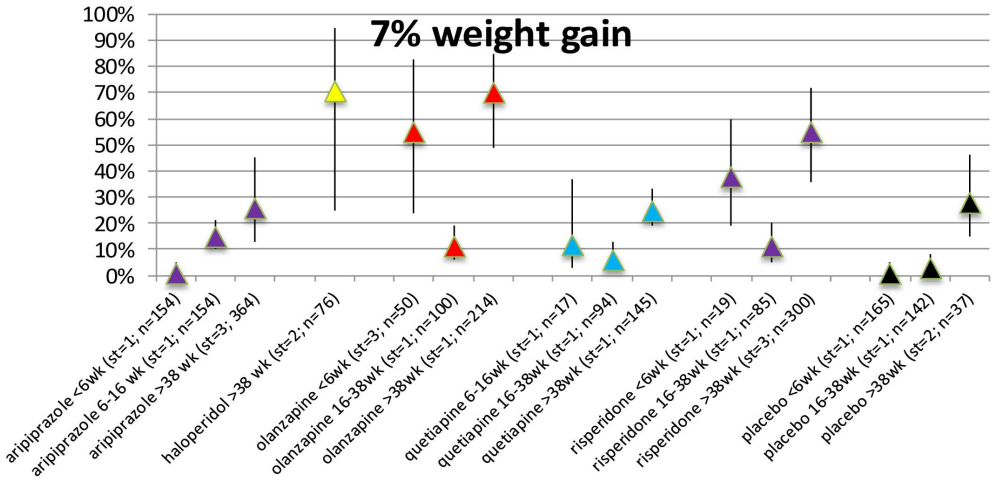

Figure 7. Proportion of weight increase in AP naïve.
doi:10.1371/journal.pone.0094112.g007

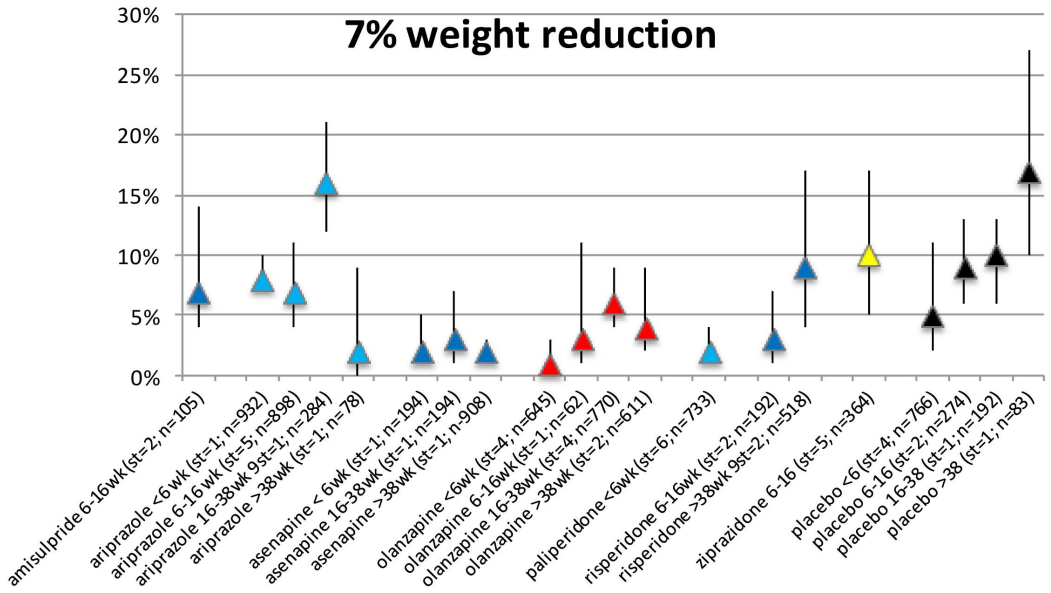

Figure 8. Proportion of weight reduction.
doi:10.1371/journal.pone.0094112.g008

[19]. Unfortunately, first generation AP were mainly studied before 1999 and, therefore, information on weight is scarcer for some FGA.

Furthermore, in a large number of studies neither standard deviation nor standard errors of the continuous outcomes (weight change, BMI change) were available and standard error, therefore, was estimated using a formula (see methods section). Sensitivity analyses were performed to assess the impact of this on the final results (weight change and BMI change), assuming a worst case scenario (using the present data, it was possible to calculate the correlation between pre and post assessment if a study presented variances of both pre and post assessment as well as change score; in these studies the lowest correlation was 0.85 and this correlation was entered in the worst case scenario). Results of these sensitivity analyses were very similar to the original results (results available upon request). Sensitivity analyses removing all estimated standard errors were not informative because too few studies remained (results available upon request).

Sixth, although only RCTs using the intention-to-treat principle were included, some of the included studies had a long-term follow-up after ending the study. Because these long-term results were very important for the research question, we did include these data, despite the fact that they were not per analysed intention-to-treat. This means that for the long-term results bias, due to drop-out after weight gain is largest. In spite of this, weight gain in the long-term studies was largest. Therefore, contrary to the expected direction of results with bias, we found that AP were associated with weight gain and that weight gain was larger over time.

Finally, this study did not address the issue of differences in weight change across various diagnostic groups. Indeed some reviews address this issue although restricted to only schizophrenia and bipolar disorder [27,61]. As mentioned in the introduction section, AP are more widely used and studied for various diagnoses other than schizophrenia of bipolar disorder. In this meta-analysis, the number of studies that only include either schizophrenia or bipolar disorder is limited. The diagnostic categories included in studies mostly pertain to combinations of various psychiatric diagnoses of schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, or depression. Given the complexity of the current study and the importance of the modifying factor diagnosis, a separate study to address this issue is required, but beyond the scope of the current analysis. Results reported in the present study provide a comprehensive overview of weight changes in all studies, but the reader has to keep in mind that associations may be stronger in specific diagnoses and weaker in others this meta-analysis. Therefore, interpretation might be done with caution considering the potential influence of diagnosis or AP doses on weight change.

Conclusion

All AP show weight gain over time. The increase in weight varies per AP and per duration of exposure category, both in switch studies and in studies of AP-naive patients. The initial weight increase at ≤6 weeks is most important, as patients will not lose weight afterwards. The vast majority of the studies included are switch studies. This analysis does not suggest that switching AP is likely to result in weight reduction in the long term. Additionally, in AP-naive patients the short term weight gain is substantial for all AP, although the number of studies with AP-naive patients was limited. More work in AP-naive patients is of interest, particularly in FGA. Apart from haloperidol and chlorpromazine, FGA are poorly studied with respect to their metabolic effects. Lastly, given that haloperidol is not weight neutral, it is questionable whether it can serve as a good comparator AP in studies.

List of studies per year of publication

1999 [62–68]; 2000 [69–73]; 2001 [74–90]; 2002 [37,91–106]; 2003 [107–132]; 2004 [133–157]; 2005 [158–191]; 2006 [46,192–218]; 2007 [219–254]; 2008 [45,49,255–286]; 2009 [287–317]; 2010 [43,318–338]; 2011 [50,339–359]

Supporting Information

Checklist S1 Prisma Checklist Meta-analysis.
(DOC)

File S1 Forest Plots S1–S8 Weight changes per exposure category.
(ZIP)

File S2 Forets Plots S9–S16 Weight changes per exposure category.
(ZIP)

File S3 Forest plots S17–S24. Weight changes in AP naives per exposure category.
(ZIP)

File S4 Forest Plots S25–S35. Change of BMI per exposure category.
(ZIP)

File S5 Forest Plots S36–S43. Changes of BMI in AP naives per exposure category.
(ZIP)

File S6 Forest Plots S44–S51d - Proportion (7%) of weight gain per exposure category.
(ZIP)

File S7 Forest Plots S52–S58 - Proportion (7%) of weight gain per exposure category.
(ZIP)

File S8 Forest plots S59a–S64c. Proportion (7%) of weight increase in AP naives per exposure category.
(ZIP)

File S9 Forest Plots S65–S72d. Proportion of 7% weight loss per exposure category.
(ZIP)

Table S1 Number of studies reporting on each of the antipsychotics (switch studies and drug naive separately).
(DOCX)

Table S2 Weight changes per exposure category.
(DOCX)

Table S3 Weight changes in AP naives per exposure category.
(DOCX)

Table S4 Change of BMI per exposure category.
(DOCX)

Table S5 Change of BMI in AP naives per exposure category.
(DOCX)

Table S6 Proportion (7%) of weight gain per exposure category.
(DOCX)

Table S7 Proportion (7%) of weight increase in AP naives per exposure category.
(DOCX)

Table S8 Proportion of 7% weight loss per exposure category.
(DOCX)

Author Contributions

Conceived and designed the experiments: MB JvO. Analyzed the data: MD JvO MB. Wrote the paper: MB AF JJ JvO MD. Performed the article search: MB AF JJ. Computed the data base: MB AF MD. Performed the statistical analysis of this paper: MB JvO MD. Supervised the process: JvO.

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