Changes in Body Weight and Psychotropic Drugs: A Systematic Synthesis of the Literature

Robert Dent¹,³*, Angelique Blackmore¹, Joan Peterson², Rami Habib³, Gary Peter Kay³, Alan Gervais¹, Valerie Taylor⁴, George Wells⁵

¹Weight Management Clinic, Ottawa Hospital, Ottawa, Ontario, Canada, ²Ottawa Health Research Institute, Ottawa, Ontario, Canada, ³Department of Psychiatry, University of Ottawa, Ottawa, Ontario, Canada, ⁴University of Toronto, Toronto, Ontario, Canada, ⁵Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

Abstract: Introduction: Psychotropic medication use is associated with weight gain. While there are studies and reviews comparing weight gain for psychotropics within some classes, clinicians frequently use drugs from different classes to treat psychiatric disorders.

Objective: To undertake a systematic review of all classes of psychotropics to provide an all encompassing evidence-based tool that would allow clinicians to determine the risks of weight gain in making both intra-class and interclass choices of psychotropics.

Methodology and Results: We developed a novel hierarchical search strategy that made use of systematic reviews that were already available. When such evidence was not available we went on to evaluate randomly controlled trials, followed by cohort and other clinical trials, narrative reviews, and, where necessary, clinical opinion and anecdotal evidence. The data from the publication with the highest level of evidence based on our hierarchical classification was presented. Recommendations from an expert panel supplemented the evidence used to rank these drugs within their respective classes. Approximately 9500 articles were identified in our literature search of which 666 citations were retrieved. We were able to rank most of the psychotropics based on the available evidence and recommendations from subject matter experts. There were few discrepancies between published evidence and the expert panel in ranking these drugs.

Conclusion: Potential for weight gain is an important consideration in choice of any psychotropic. This tool will help clinicians select psychotropics on a case-by-case basis in order to minimize the impact of weight gain when making both intra-class and interclass choices.

Introduction

Weight Gain is associated with psychotropic medication use, and while particular attention has been paid to atypical antipsychotics, the typical antipsychotics, mood stabilizers, tricyclic antidepressants (TCA’s), certain serotonin selective reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) can cause weight gain as well. Because weight gain and obesity are often overlooked in patients [1], there can be a lack of follow-up to monitor for weight gain [2–7] or subsequent weight related co-morbidities [8].

Psychotropic-induced weight gain is an important cause of non-adherence to pharmacotherapy for antidepressant medications [9–14], for antipsychotic medications [15–22] and for lithium [23,24] and has been cited by an expert consensus panel on adherence problems in serious and persistent mental illness [25,26]. Non-adherence to prescribed medications places patients at a greatly increased risk of illness exacerbation and rehospitalization. These costs are high [27], and were estimated to range from $1392 million to $1826 million in 2005 in the US for antipsychotics alone [28]. These issues are balanced by the therapeutic benefit of the psychiatric medication. The CATIE trial concluded that the superior efficacy of olanzapine might prevent discontinuation due to weight gain [29,30]. This may suggest the potential for weight gain may be offset by effectiveness or lack of other adverse events.

Psychotropic-associated weight gain carries significant risk. As a consequence, the weight-related co-morbidities associated with these medications have been the most studied and we now have a plethora of evidence on glucose dysregulation [29,31–41], increases in triglycerides [29,41] and total cholesterol [29,42], and hypertension. Fontaine [43] estimated that weight gain associated with this class of drugs contributed to an increase in mortality that offset the decreased risk of suicide with their use.

The adverse effects of long term weight gain have not escaped regulatory bodies. A number of clinical practice guidelines [4,44,45] and other studies [46–50] all recommend choosing psychotropics least likely to cause weight gain, or switching to those less likely to cause weight gain [51–53] if weight gain occurs. This is because the CATIE trial data does provide some evidence that patients who stayed on medications with high propensity to induce weight gain, showed greater weight gain than those who switched from these medications to other drugs that were less likely to cause weight gain [54].

There are studies and reviews comparing weight gain for psychotropics within classes for the atypical antipsychotics [29], typical antipsychotics [36] and antidepressants [55]. But clinicians

Citation: Dent R, Blackmore A, Peterson J, Habib R, Kay GP, et al. (2012) Changes in Body Weight and Psychotropic Drugs: A Systematic Synthesis of the Literature. PLoS ONE 7(6): e36889. doi:10.1371/journal.pone.0036889

Editor: Silvia Alessi-Severini, University of Manitoba, Canada

Published: June 15, 2012

Copyright: © 2012 Dent et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The authors have no support or funding to report.

Competing Interests: The authors have the following interests to declare: Dr. Gary Kay has been a speaker for Astrozenea (makers of Seroquel). This does not alter the authors’ adherence to all the PLoS ONE policies on sharing data and materials, as detailed online in the guide for authors.

* E-mail: bdent@ottawahospital.on.ca
frequently use drugs from many different classes to treat any one psychiatric disorder. Therefore, we saw a need for an all encompassing evidence-based tool that would allow clinicians to balance efficacy against the risks of weight gain in making both intra-class and interclass choices of psychotropics [45,56–59].

Our primary objective was to consider weight change with psychotropic drugs in adults with psychiatric conditions comparing drugs to placebos or other psychotropics, more specifically, to answer the following questions:

1. Is a particular psychotropic weight-neutral or is it associated with weight gain or weight loss?
2. Can the weight gain be quantified?
3. What is the difference between the weight gain in drug-naïve patients and the weight gain in those already on psychotropics?
4. How does the psychotropic rank with respect to weight gain in its class?

Our secondary objective was to develop a clinical tool that would provide information on psychotropic-associated weight gain to allow clinicians to make informed choices with respect to this important side effect.

Methods

While a Cochrane-style review is well suited for finding the weight gain potential of a single drug or even a class of psychotropics it becomes very cumbersome when seeking evidence for all classes of psychotropics. We therefore developed a hierarchical search strategy (Table 1) that made use of systematic reviews that were already available. When such evidence was not available we went on to evaluate clinical trials that were double blind and randomly controlled, followed by cohort and other clinical trials.

Inclusion Criteria

Studies were included if they contained information about psychotropic drug use in patients with a psychiatric disease (anxiety disorder, depressive illness, psychosis) or related condition (chronic pain, fibromyalgia, chronic fatigue). The psychotropic medication must have been compared with a placebo or comparator drug, ideally for 12 or more weeks and reviews had to report on weight change.

Exclusion Criteria

We excluded children (since normal growth would be a confounder to evaluating weight gain) and patients with ADHD (since many of the studies were done in children). We also excluded subpopulations that may not be able to express drug-induced weight gain, such as the elderly with dementia, those in controlled environments where they may not have free access to food, those with anorexia nervosa, bulimia nervosa, malignancies and HIV disease. Studies were also excluded where the study drug was added to multiple other psychotropics.

The Literature Search

A medical librarian searched a number of databases (from their inception to April 2011) for articles where weight gain was designated as the outcome or key word (Ovid Medline search strategy Appendix S1, PsycINFO search strategy Appendix S2, CCTR, CDSR (coch), Dare Search Strategy Appendix S3, Embase search strategy Appendix S4). These data bases were then searched again, using the same search strategy and key words for systematic reviews where weight gain was not a key word or designated outcome. The searches were limited to English only [60].

The literature search yielded almost 9500 reports. Two of four potential reviewers (RD, AB, JP, GK) screened the reports for eligibility according to the criteria in Table 1: on the basis of title, then abstract, and then full-text reviews. At the title review stage,

Table 1. The Hierarchical strategy for selection of reports.

| Level of study | Description | Rules for selection |
|---------------|-------------|---------------------|
| I             | Systematic Review where weight change is the focus or a key word | Rate according to Amstar [97]; The minimum criteria for a systematic review would be a search in 2 electronic databases using a stated search strategy; Where such reviews exist, choose in descending order: the one with the highest rating and the most recent; if after 2 years of the chosen review, there is a study in category III, then it is reviewed to determine if it changes the outcome; If there are two reviews at level 1 or 2 of the same year, the one with the higher rating is chosen; if a systematic review contained only one randomized controlled trial (RCT) dealing with weight then it is accepted as a systematic review because it was felt that the process yielding negative results was important. |
| II            | Systematic Review where weight change is not the focus but “side effects” or “adverse events” or “tolerability” are present in the key words or abstract. | Similar to above |
| III           | RCTs where weight change is a key word | Duration ≥12 wks, n ≥50; Rate with SIGN 50 [98]; Where such studies exist as the highest level of evidence, choose the one with the highest methodological rating and the most recent and no other study; Where there is more than one RCT and there is disagreement, then chose the one with the highest rating and acknowledge that there is disagreement |
| IV            | Cross-sectional or population studies where weight change is a key word | Duration ≥12 wks, n ≥50; Rate with SIGN 50 [98]; Where such studies exist as the highest level of evidence, choose in descending order, the one with the highest methodological rating according to SIGN 50 [98] and the most recent. |
| V             | Narrative Review with weight change is a key word | Not graded; Only used if no other in levels I-IV available; If a narrative review contained only one RCT dealing with weight then that RCT would be put in category 4 and take precedence over the narrative review. |
| VI            | Other evidence/clinical experience or studies that would be IV, or V where the n<50 or duration <12 wks | Not graded; Only used if no other in levels I-V available. |
any title selected by either reviewer was included in the abstract review.

Assessment of Articles
Each study was given a number from I to VI based on the hierarchical classification of the study according to the pre-established criteria in Table 1. We used the AMSTAR scale, a reliable and valid 11-item checklist for evaluating systemic reviews to assess the methodological quality of the reviews chosen [61] and graded according to good (A), fair (B), and poor (C). The quality of each randomized controlled trial, cross-sectional or population study was assessed using the SIGN 50 assessment form and similarly graded [62]. The quality of evidence for change in weight for a particular drug in a trial was graded with a score of 1, 2, or 3 according to quality. Each study was scored independently by two out of four potential reviewers (AB, JP, RH, GK) and disagreements were resolved by consensus. The individual that did the scoring was never the same individual that did the initial reviewing of that article.

Data Extraction and Building of a Database
For each article that met inclusion/exclusion criteria, quantitative data (actual weight gain in drug-naïve and non drug-naïve patients) of the study drug and its comparators was sought wherever possible. If there was no quantitative evidence, the study with the best qualitative evidence was obtained, whether or not the drug was associated with weight gain. The sources of funding, either direct (funding from a pharmaceutical manufacturer), indirect (where authors had research funds) or unknown/unfunded, psychiatric disease and the duration of study were also extracted. Three groups of studies were collected: those giving qualitative or quantitative information on a drug, those comparing drugs within a class and those reporting weight gain in drug-naïve patients.

Ranking of Psychotropics that Reported Weight Gain
In order to rank the weight gain caused by psychotropics, we selected studies that dealt with multiple drugs. Because we were not aware of any study that included all psychotropic drugs within their respective class, we included all of the studies that qualified. The data on ranking was extracted from each article and placed in a separate table to allow a comparison of the change in weight caused by psychotropics.

The Subject Matter Expert Panel
An expert panel was formed to review the rankings and to deal with any potential discrepancies between articles. The methodology for review and the membership were formulated by an epidemiologist (G.W.). This panel consisted of 6 members: 4 psychiatrists (C.M., G.K., V.T., R.H.); 1 family physician (S.W.), whose practice was large and busy enough to include a large number of patients with psychiatric illnesses and 1 internist (J.S.). Secretarial assistance was provided by A.G. and R.D.

The mandate of this panel was to review the literature that was used in developing the ranking of the psychotropics and to provide comments on the rankings based on their clinical experience. When there was a disagreement in the rankings, or when the rankings were at variance from the clinicians’ experience, the panel was asked to re-examine the articles in detail and attempt to provide a rationale for the controversy. All controversies were noted, as was the corresponding rationale.

Classification of Psychotropics and Presentation of Data
The recommendations from the panel were subsequently used to rank the drugs within their respective classes. We have used a common and largely mechanistic classification for the psychotropics [63]. There does not seem to be a standardized classification – often the term “second generation antipsychotics” is used rather than “atypical antipsychotics” [45]. Given the results of the review and the input of the expert panel, a table of weight analysis was constructed.

Results
The screening for eligibility began by examining 3975 articles (Figure S1). They included systemic reviews, randomized controlled studies, cross-sectional or population studies, and narrative reviews where weight gain was the focus. Of these, 956 articles were requested for full text review. The second search of systemic reviews, where weight gain was not a key word or identified in the abstract, screened an additional 5500 articles. Of these, 957 were requested for full text review. A short list of 666 articles resulted.

The older classes of psychotropics yield very little information on weight gain. Ideally, the best ranking evidence for psychotropics would come from drug-naïve patients, but there was no ranking data available. We were only able to find data in drug-naïve patients for 7 antipsychotics olanzapine, chlorpromazine, clozapine, quetiapine, risperidone, aripiprazole and haloperidol. There were 14 articles that met our hierarchical search strategy to enable us to rank psychotropics. Two articles [60,61] ranked the MAOIs (Table 2). Seven articles ranked the typical and atypical antipsychotics (Table 3). Five articles were classified as level I, three with good quality of evidence [62–64] and two provided evidence that was fair. Two articles were level III with good quality of evidence [29,65].

Six articles ranked the antidepressants (excluding MAOIs) (Table 4). Three articles were classified as level I with quality of evidence that was fair [66–68]. The most comprehensive ranking data came from one article [55]. The ranking was based on the data from drug non naïve patients. This article presented the effect of each antidepressant on weight during two treatment periods, 4–
Table 3. Typical and atypical antipsychotic ranking and change in body weight (ranked from most to least weight gain).

| Antidepressant | Author | Study Level | Quality of Study | Quality of Evidence for the Drug | Funding Source | Quantitative Weight Gain | Comments | Articles used for ranking |
|----------------|--------|-------------|------------------|----------------------------------|----------------|--------------------------|----------|--------------------------|
| Clozapine      | Bitter [99] | III | B | 2 | D | 4.1 ± 5.6 kg. | Olanzapine 3.3 ± 5.3 kg over 18 wks, not significant between groups | [63–65,75] |
|                | Lieberman [29] | III | A | 2 | D | Drug Naïve 9.9 kg | Chlorpromazine mean weight gain at 52 weeks (6.5 kg). Not statistically significant. | Not ranked |
| Olanzapine     | Komossa [100] | I | A | 1 | I | 10X and 2.5X greater wt gain with olanzapine | vs amisulpride (2 studies, 26 & 24 weeks) | [29,62,63,75,76,100] |
|                | I | A | 1 | 6X greater wt gain with olanzapine | vs aripiprazole (1 study 26 weeks) |
|                | I | A | 1 | 3 studies show greater wt gain with clozapine | vs clozapine (4 studies) |
|                | I | A | 1 | 10X, 1.5X, 2X, 4X, 1.8X, 2X greater wt gain with olanzapine | vs risperidone (7 studies: 78, 52, 52, 30, 52, 28, 22 wks) |
| Alvarez-Jiminez [62] | I | A | 1 | I | Drug Naïve: 7.1–9.2 kg or 47–61% | 10–12 weeks; 3 studies, up to 4 fold greater weight gain in drug naïve. | Not ranked |
|                | I | A | 1 | 10.2–15.4 kg or 80–100% | >9 mos; 3 studies |
| Olanzapine orally dissolving | Karagianis [101] | I | C | 3 | U | Drug Naïve: first episode psychosis: 3.3 kg; First episode psychosis oral tablets: 6.4 kg in 6 weeks wt gain. | Not ranked |
| Olanzapine IM | Canas [102] | I | B | 1 | D | Mean weight gain 1.4 kg, 28%. | Long term similar to oral olanzapine | Not ranked |
| Thoridazine    | Fenton [103] | I | A | 2 | I | Wt gain >4.5 kg: 3/15 | Wt gain >4.5 kg 5/15 with Pimozide, 1/10 with Placebo. Only 1 study, 6 month duration | [65] |
| Chlorpromazine | Allison [65] | I | B | 3 | D | Mean weight gain 2.1 kg, 10 weeks | | [65] |
|                | Lieberman [104] | III | A | 2 | D | Drug Naïve: mean weight gain 6.5 kg | Clozapine mean weight gain at 52 weeks (9.9 kg). Not statistically significant. | Not ranked |
| Quetiapine     | Komossa [64] | I | A | 1 | I | Greater with quetiapine (mean weight gains and % gaining >7%) | Greater with ziprazidone (mean weight gains and % gaining >7%) | [29,63,64,75,76] |
|                | I | A | 1 | Mean weight gains 2 to 8X greater with olanzapine | vs olanzapine (4 studies >12 weeks) |
|                | I | A | 1 | 2 to 8X greater wt gain with olanzapine | vs olanzapine (2 studies >12 weeks) |
|                | I | A | 1 | Equal (mean weight gains and % gaining >7%) | vs risperidone (7 studies, >12 weeks) |
|                | I | A | 1 | Greater with quetiapine (mean weight gains vs ziprazidone and % gaining >7%) | Not ranked |
| McEvoy [105]   | III | A | 1 | Drug Naïve: M: 4.3 kg or 20%; F: 2.1 kg or 72% remained in at 12 weeks. | | Not ranked |
|                | | | | | | M: 6.9 kg or 11%; F: 2.9 kg or 4% | 33% remained in at 52 weeks. |
| Risperidone    | Alvarez-Jiminez [62] | I | A | 1 | I | 1–2.3 kg or 9–11% in 8.4–3.9 kg | 10–12 wks (>9 mos) | [29,62–65,75,76] |
|                | Alvarez-Jiminez [62] | I | A | 1 | Drug Naïve: 4.0–5.6 kg or 33–38% | 5 studies 10–12 wks up to 4 fold greater weight gain in drug naïve | Not ranked |
|                | | | | | | 6.6–8.9 kg or 59% | 3 studies >9 mos |
| Antidepressant          | Author       | Study Level | Quality of Study | Quality of Evidence for the Drug | Funding Source | Quantitative Weight Gain | Comments                                                                 |
|-------------------------|--------------|-------------|------------------|----------------------------------|----------------|--------------------------|--------------------------------------------------------------------------|
| Risperidone injectable | Canas [102]  | I           | B                | 1                                | D              | Mean 0.95 kg (range 0.4 to 1.9 kg); [mean 3–6 mos [over 1 year] of 3 kg (range 2–3.3 kg)]. | Not ranked                                                                |
| Amisulpride             | Komossa [106]| I           | A                | 1                                | I              | 14% vs risperidone: 20% (26 weeks) | [63,65,75]                                                             |
| Aripiprazole            | Komossa [107]| I           | A                | 2                                | I              | Mean loss of -1.37 kg or 13.3% vs olanzapine: +4.23 kg, or 36% (26 weeks) | [63]                                                                     |
| Haloperidol             | Alvarez-Jimenez [62]| I     | A                | 1                                | I              | Drug Naive: 35.5% gained 2.85 kg 26 weeks: 64.5% non naive patients gained 1.6 kg Not ranked | [62,63,65]                                                             |
| Depo haloperidol        | Bechelli [109]| III        | B                | 2                                | U              | Wt gain of 4.0–9.7 kg or 7% 3 studies, >9 mos | Not ranked                                                               |
| Fluphenazine            | Allison [65] | I           | B                | 3                                | D              | 0.43 kg 10 weeks | [65]                                                                     |
| Fluphenazine decanoate  | Wistedt [110]| III        | B                | 2                                | U              | Qualitative data only | 20-wk RCT: Depo Flu vs Depo Halop: > wt inc with Not ranked depo fluphenazine but NS. |
| Ziprasidone             | Komossa [111]| I           | A                | 1                                | I              | 8.3% 12 weeks vs amisulpride 17.5% | [29,63–65,75,76]                                                        |
| Molindone               | Bagnall [112]| I           | A                | 2                                | I              | Molindone: 0/14 gained >4.5 kg 12,8 weeks: Placebo: 0/15 gained >4.5 kg. Chlorpromazine: 4/15 | [65]                                                                     |
| Perphenazine            | Lieberman [29]| III        | A                | 1                                | D              | Mean weight loss: -0.9 kg, (1.2%) 78 weeks: All patients were previously on typical or[29,76] atypical antipsychotics. |                                            |

% = % gaining >7% body weight. Sources of funding: D = direct funding from a pharmaceutical manufacturer; I = indirect funding (where authors had research funds) U = unfunded or unknown funding. doi:10.1371/journal.pone.0036889.t003
## Table 4. Antidepressant Ranking and Effect on Body Weight (ranked from most weight gain to weight loss).

| Antidepressant | Author | Study Level | Quality of Study | Quality of Evidence for the Drug | Funding Source | Quantitative Weight Change in kg. >12 weeks unless indicated | Articles used for ranking |
|----------------|--------|-------------|------------------|----------------------------------|----------------|-------------------------------------------------------------|---------------------------|
| **Weight gain** |        |             |                  |                                  |                |                                                             |                           |
| Paroxetine     | Serretti [55] | I           | B                | 1                                | U              | 2.73 CI 0.78 to 4.68*                                       | [55,66–68]                |
| Mirtazapine    | Serretti [55] | I           | B                | 1                                | U              | 2.59 CI –0.23 to 5.41*                                      | [55,66–69]                |
| Doxepin        | Feighner [70] | III          | B                | 2                                | U              | 2.73                                                        | Not ranked, placement based on quantitative data |
| Amitriptyline  | Serretti [55] | I           | B                | 1                                | U              | 2.24 CI 1.82 to 2.66                                       | [55,60,69]                |
| Citalopram     | Serretti [55] | I           | B                | 1                                | U              | 1.69 CI –0.97 to 4.34                                      | [55]                      |
| Nortriptyline  | Serretti [55] | I           | B                | 1                                | U              | 1.24 CI –0.51 to 2.99                                      | [55,60]                   |
| Clomipramine   | Serretti [55] | III          | B                | 3                                | U              | 1.0 CI –0.44 to 2.43=12 weeks                              | [55]                      |
| Desipramine    | Serretti [55] | I           | B                | 3                                | U              | 0.82 CI –0.77 to 2.42=12 weeks                             | [55,64]                   |
| Imipramine     | Serretti [55] | I           | B                | 1                                | U              | -0.04 CI –1.36 to 1.28*                                    | [55] [64] Ranking based on expert panel recommendation |
| Duloxetine     | Serretti [55] | I           | B                | 1                                | U              | 0.71 CI –0.23 to 1.65                                      | [55]                      |
| Escitalopram   | Serretti [55] | I           | B                | 1                                | U              | 0.65 CI –0.16 to 1.45                                      | [55]                      |
| Tramipramine   | Harris [71] | VI           |                  | U                                |                | Qualitative data only                                      | Not ranked                |
| **Minimal effect on weight** | | | | | | | |
| Venlafaxine    | Serretti [55] | I           | B                | 3                                | U              | -0.5 CI –0.74 to -0.27≤12 weeks *                          | [55]                      |
| Fluvoxamine    | Serretti [55] | I           | B                | 3                                | U              | -0.02 CI –0.49 to 0.45≤12 weeks                            | [55]                      |
| Fluvoxamine CR | Davidson [72] | III          | B                | 1                                | D              | Qualitative data only                                      | Not ranked                |
| Moclobemide    | Serretti [55] | I           | B                | 3                                | U              | -0.21 CI –0.30 to –0.13≤12 weeks                           | [55]                      |
| Fluoxetine     | Serretti [55] | I           | B                | 1                                | U              | -0.31 CI –1.04 to 0.43                                     | [55,66,67]                |
| Desvenlafaxine | Perry [74] | III          | B                | 2                                | U              | -0.8 kg, Minimal effect on weight in both short-term and long term use (12 weeks) | Not ranked                |
| **Weight Loss** | | | | | | | |
| Bupropion      | Serretti [55] | I           | B                | 1                                | U              | -1.87 CI –2.37 to –1.37                                    | [55]                      |

Sources of funding: D = direct funding from a pharmaceutical manufacturer; U = unfunded or unknown funding *controversy in the ranking table. doi:10.1371/journal.pone.0036889.t004
Table 5. Weight gain caused by typical and atypical antipsychotics and flunarizine (drugs not ranked due to insufficient data).

| Antipsychotic          | Author          | Study Level | Quality of Study | Quality of Evidence for the Drug | Funding Source | Quantitative Weight Gain | Comments                                                                 |
|-------------------------|-----------------|-------------|------------------|----------------------------------|----------------|--------------------------|---------------------------------------------------------------------------|
| Weight gain             |                 |             |                  |                                  |                |                          |                                                                            |
| Levopromazine           | Sivaraman [113] | II          | A                | 2                                | I              | Qualitative data only    | Similar weight gain as Chlorpromazine, 30 weeks                           |
| Trifluoperazine         | Marques [114]   | I           | A                | 1                                | I              | Qualitative data only    | No difference in wt gain vs Pimozide, 6 studies only 2>12 weeks           |
| Loxapine                | Chakrabarti [115]| II          | A                | 1                                | I              | 18.6%                    | At 12 weeks vs 0% in placebo                                            |
| Depot flupenthixol decanoate | Johnson [116]   | IV          | C                | 3                                | U              | 62% gained 1.5 to >11 kg | 6 months: 16% lost 1.5 to 4.9 kg; 22% no change; Similar to fluphenazine decanoate |
| Zucloopenthixol         | Kumar [117]     | I           | A                | 3                                | I              | Qualitative data only    | Two studies 10 and 12 weeks: short duration and low N. No difference in weight gain compared to sulpiride |
| Paliperidone extended release | Chwieduk [118] | I           | C                | 2                                | U              | 1.5 kg                   | 3–6 wk trials with 52 wk extensions. Olanzapine 3.8 kg                   |
| Paliperidone injectable | Citrome [119]   | I           | B                | 2                                | U              | 0.7 kg or 12% (mild)    | Open label prior to randomization.                                       |
|                         |                 |             |                  |                                  |                |                          | I B 2 6%                                                                 |
|                         |                 |             |                  |                                  |                |                          | Open-label extension period relative to starting the extension phase. Lowest incidence among patients who received double-blind paliperidone – presumably had already gained the weight they were going to. |
| Perospirone             | Okugawa [120]   | III         | C                | 3                                | D              | Mean Weight Gain: 2.2 kg | Greater mean weight gain vs risperidone, 1.7 kg                          |
| Haloperidone            | Marino [121]    | I           | C                | 2                                | U              | 4.8 kg                   | 52 week duration: Haloperidol 3.0 kg. Weight gain may be dose related. Majority of weight gain occurs in first 6 weeks of treatment. |
|                         | Hale [122]      | I           | C                | 2                                | U              | 3.8 kg                   | Haloperidol 2.3 kg. 1 study of 52 weeks                                  |
| Flunarizine             | Bisol [123]     | III         | A                | 1                                | I              | mean wt gain 1.2 kg or 8% | 12 weeks: Haloperidol -0.8 kg or 7.4%                                  |
| Asenapine               | Citrome [124]   | I           | B                | 2                                | D              | 23%                      | vs olanzapine, 57.1% in patients with initial BMI <23                    |
|                         |                 |             |                  |                                  |                |                          | vs olanzapine, 21.9% in patients with initial BMI >27. Weight gain is not dose related. |

Unless specified, % = % gaining >7% body weight. Sources of funding: D = direct funding from a pharmaceutical manufacturer; I = indirect funding (where authors had research funds); U = unfunded or unknown funding. doi:10.1371/journal.pone.0036889.t005
Table 6. Change in weight caused by mood stabilizers (Ranked most to least weight gain).

| Mood Stabilizer               | Author                  | Study Level | Quality of Study | Quality of Evidence for the Drug | Funding Source | Quantitative Weight Change | Comments                                                                 |
|-------------------------------|-------------------------|-------------|------------------|----------------------------------|----------------|-----------------------------|--------------------------------------------------------------------------|
| Weight Gain and Ranked [77–78] |                         |             |                  |                                  |                |                             |                                                                          |
| Valproate                     | Leslie [80]             | I           | B                | 2                                | D              | 2.5 kg to 1.2 kg            | At 12 weeks and 47 weeks respectively.                                  |
| Valproate Extended Release    | Smith [125]             | I           | B                | 3                                | D              | 19/103                      | 9 studies (2–6 weeks x 5, 1–12 weeks x 4). Compared to delayed release caused less weight gain 29/103. (not ranked) |
| Lithium                       | Bowden [79]             | III         | A                | 1                                | D              | 1.1 kg in lean patients    | A randomized, double-blind, placebo-controlled study at 52 weeks. 6.1 kg in obese patients. |
| Weight Neutral                |                         |             |                  |                                  |                |                             |                                                                          |
| Carbamazepine Extended Release| Ketter [126]            | IV          | B                | 2                                | D              | Qualitative data only      | 26 weeks. Based on one study.                                            |
| Carbamazepine                 | Melvin [77]             | II          | B                | 3                                | I              | Qualitative data only      | Study duration not provided.                                             |
| Oxcarbazine                   | Reinstein [127]         | III         | C                | 2                                | D              | Qualitative data only      | 10 weeks                                                                  |
| Lamotrigine                   | Bowden [79]             | III         | A                | 1                                | D              | -0.5 kg in lean patients   | A randomized, double-blind, placebo-controlled study at 52 weeks. -4.2 kg in obese patients. |
| Weight Loss                   |                         |             |                  |                                  |                | Qualitative data only      | 3 studies all <12 weeks demonstrate weight loss vs placebo. Many studies have used topiramate for weight loss however, few were done in psychiatric illness. |

Sources of funding: D = direct funding from a pharmaceutical manufacturer; I = indirect funding (where authors had research funds).

doi:10.1371/journal.pone.0036889.t006
12 weeks and ≥4 months. Data from the 4–12 week interval was used to rank the antidepressants only when data from the longer time period was not available. The quality of the evidence for the change in weight was classified as good for the ≥4 month treatment period interval. However, when the duration of the treatment period was ≤12 weeks we assigned a poor quality rating to the evidence. One article was classified as level III with evidence that was fair [69] and the other article was level V with poor quality of evidence [60].

Controversies in the ranking were reviewed by the expert panel and they provided their recommendations which were incorporated into the above table. Three articles [55,67,68] provided controversy in the ranking between paroxetine and mirtazapine. Two articles [68] and [67] both concluded that mirtazapine caused more weight gain than paroxetine. After reviewing the evidence from the three studies, the ranking from the Serretti article was selected due to the fact that the other two studies were ranked lower on our scoring system, and were of shorter duration compared to Serretti. It was also noted that the short term data from these two articles were consistent with the short term data from Serretti. In addition, although [68] and [67] were published as two separate articles, they both obtained their data from the same references.

There was agreement with the ranking of the tricyclic antidepressants based on the Serretti article except for the ranking of imipramine. Based on the clinical experience of the panel, all tricyclic antidepressants are associated with some degree of weight gain. One article [60] used to rank the antidepressants provided evidence to support the claim that imipramine causes weight gain in the long term. As a result, imipramine was ranked with, but below, the other tricyclic antidepressants.

The data from Serretti on venlafaxine was ≤12 weeks. Based on the clinical experience of the panel and the lack of long term data on venlafaxine that met our selection criteria, the panel disagreed with Serretti's classification of venlafaxine as causing weight loss. In their experience, longer term use of venlafaxine would not result in significant weight loss and as a result it was ranked just below escitalopram as venlafaxine was observed to have minimal effect on weight in the long term.

The long term data on fluoxetine from the Serretti article would imply that fluoxetine was associated with a small weight loss. The panel considered fluoxetine as having minimal effect on weight.

Although there was no data to rank four antidepressants, doxepin, trimipramine, fluvoxamine CR and desvenlafaxine, there was quantitative and/or qualitative data available and this data was included in the ranking table 4 [70–74].

There was no controversy between the two articles that ranked the MAOIs [60,61]. In the panel’s opinion, the ranking in this table was consistent with that seen in clinical practice.

Seven articles were located that met our criteria and provided data to allow us to rank the typical and atypical antipsychotics Table 3 [29,62–65,75,76]. The ranking was based on the data from drug non naive patients. There were a few discrepancies identified that were presented to the panel for their recommendations as five articles ranked both quetiapine and risperidone. Two articles [75] and [29] ranked quetiapine as causing more weight gain than risperidone, one article [76] provided qualitative data only stating that they both caused weight gain, one article [63] placed risperidone above quetiapine and one article [64] concluded that they were similar. After reviewing the available data the panel recommended placing quetiapine ahead of risperidone acknowledging that at this time the literature indicates the difference in weight gain between the two drugs is minimal. One article [75] also stated that the weight gain caused by

Table 7. Change in weight caused by anxiolytics (Not ranked).

| Anxiolytics          | Author                  | Study Level | Quality of Study | Quality of Evidence for the Drug | Funding Source | Quantitative Weight Change | Comments            |
|----------------------|-------------------------|-------------|------------------|---------------------------------|----------------|-----------------------------|---------------------|
| Benzodiazepines –    | Oswald [129]            | III         | B                | U                               | U              | U                           | Qualitative data    |
| Weight Neutral       |                         |             |                  |                                 |                |                             | only 5 months       |
| Nitrazepam           | Bjertnaes [130]         | VI          | NA               | U                               | NA             | U                           | Qualitative data    |
| Lorazepam            | Smits [131]             | IV          | A                | U                               | U              | U                           | Qualitative data    |
| Diazepam             | Smits [131]             | IV          | A                | U                               | U              | U                           | Qualitative data    |
| Oxazepam             | Smits [131]             | IV          | A                | U                               | U              | U                           | Qualitative data    |

U = unfunded or unknown funding; NA = not able to assess.

doi:10.1371/journal.pone.0036889.t007

Changes in Body Weight and Psychotropic Drugs
olanzapine was equal to quetiapine however; the qualitative data was presented on a scale of 1–5 without providing a range for their scoring system.

We were also unable to find ranking data on drugs that were available in formulations other than oral. For the drugs that are available in formulations such as injectable that had quantitative or qualitative data, we included this data in the ranking table with the oral formulation. However, the ranking of drugs in these tables only applies to the oral formulation.

Table 5 provides the weight gain caused by typical and atypical antipsychotics and flunarizine but not ranked due to insufficient data. Among the mood stabilizers, both lithium and valproate caused weight gain (Table 6). Two studies were used to rank these two drugs. The study presented by Melvin (Level II/B) [77] described the weight gain due to both lithium and valproate as “++”. The Bowden study (Level III/B) [78] at 12 weeks ranks valproate slightly ahead of lithium (1.1 kg vs 0.2 kg). Quantitative data obtained from two different publications [79,80] and the clinical impressions of the expert panel support the ranking of valproate slightly ahead of lithium.

Anxiolytics

Qualifying papers were found for five benzodiazepines and buspirone (Table 7). All of the anxiolytics were weight neutral. Unfortunately, the highest level of evidence was III and all of the data was qualitative only. There was no information for the previous drug status of the patients included in these studies.

Discussion

In this review we used a predefined strategy to search for the available evidence on the ability of psychotropics to induce changes in body weight. The articles were selected based on a hierarchical level of evidence and were subsequently evaluated using AMSTAR for systematic reviews and SIGN 50 for controlled trials. The best evidence available was presented. We restricted our search to subjects with psychiatric disease since this review is intended as a resource to help choose psychotropics for psychiatric illness according to risk of weight gain.

Although most antipsychotics were found to be associated with weight gain, there are inherent difficulties in quantifying this weight. Many trials did not account for weight gain among the reported side-effects, some reported change in mean body weight, and some reported the percentage who gained more than 7% of their initial body weight. Many studies did not consider drug dosages or parameters for drug adherence, gender, and pharmacogenetics. Most studies had high dropout rates. There are factors that would result in significant underestimations of weight gain potential. These include studies of short duration, the use of last observation carried forward to handle data from study dropouts, previous drug use that would cause weight gain, and industry sponsorship.

Since the treatment of psychiatric illness often takes months or years, and because it takes time for weight gain to develop, we selected articles with study duration of 12 weeks or longer. Unfortunately, many of the randomized clinical trials were of short duration and thus were not able to provide sufficient information about the full impact of the drug on body weight. Kinon [81] and Tran [82] reported on the time course of weight gain with olanzapine; they showed continued weight gain up to 39 and 22 weeks.

Reciprocity from the psychiatric illness itself may influence study outcome. This may be a more important factor in the treatment of depression than of other psychiatric disorders [83]. Also, measures that patients take to offset weight gain are rarely discussed but may influence the degree to which a patient gains weight.

The effect of drug dosage on weight gain has been reviewed [84], but it is rarely discussed in reviews. We minimized this effect by verifying that all studies and reviews also had efficacy as an outcome measure.

We found only two studies that addressed the issue of drug adherence by determining plasma drug levels in the study subjects [85,86]. Genetic and gender differences may also be significant factors affecting a patient’s side-effect response to these drugs [87]. Pharmacogenetics approaches may offer the possibility of identifying patient-specific biomarkers for predicting the risk of these side effects [88]. A retrospective chart review [89] indicates that women and those with a greater initial BMI are more susceptible to weight gain [87], for example, obese patients given lithium gained more weight on lithium compared with lean patients [79]. There were high drop-out rates in many of the studies. In one study 74% of the patients discontinued the study medication within 18 months. The Last Observation Carried Forward (LOCF) method used in many studies for dealing with dropouts is likely to underestimate drug-associated weight gain [90].

Many studies have confounding variables that have contributed to the underestimation of drug-induced weight gain. Weight gain differs between those with previous psychotropic treatments and those previously unexposed to psychotropics. In patients who are not drug-naive, weight gain can be affected by the previous drug as well as the study drug. For example, studying the weight gains with long-acting risperidone in patients who had been switched from other antipsychotics, Lindenmayer [91] found an overall mean weight gain of 0.4 kg over 12 weeks. The same study found a gain of 1.4 kg in patients who had been on haloperidol and of 0.3 kg in those who had been on quetiapine, and a loss of 0.5 kg in those on olanzapine. This shows that absolute weight gain is underestimated in studies that include patients who are not drug-naive. Weight gain was three to four times greater in studies that included individuals with limited previous exposure to antipsychotic drugs [62].

Approximately one third of the studies presented in the tables were directly funded by pharmaceutical manufacturers. This number may be underestimated because many of the studies did not declare their source of funding. Two systematic reviews, Sismondo, and Ahmer conclude that pharmaceutical company sponsorship is strongly associated with results that favour the sponsors’ interests [92,93]. In studying “wish bias” in antidepressant drug trials, Barbui found that fluoxetine was favoured in clinical trials when fluoxetine was the experimental agent, and that comparator antidepressants were favoured in trials using fluoxetine as the reference agent [94]. In a report with a noteworthy title (“Why Olanzapine beats Risperidone, Risperidone beats Quetiapine and Quetiapine beats Olanzapine”) Heres et al come to the same conclusion and suggest ways in which potential sources of bias can be addressed by study initiators, peer reviewers and readers [95]. However, in a secondary analysis of a systematic review, Gartelhner found that the effect of study sponsorship on a systematically evaluated body of evidence of head-to-head trials was modest and perhaps not clinically significant [96].

We saw an urgent need for a clinical tool to allow choice of psychotropic drugs with respect to weight change. A full systematic review was beyond the scope of our resources, we therefore developed this hierarchical approach. The biggest challenge in conducting this systematic synthesis was the analysis of very heterogeneous study designs. While we have done our best to summarize the extremely large amount of published literature, we caution the user about the limitations of this analysis. These limitations include drug dosage, variation in reporting of weight changes in body weight and psychotropic drugs.


Appendix S1  Ovid Medline search strategy.  
(DOCX)

Appendix S2  PsycINFO search strategy.  
(DOCX)

Appendix S3  CCTR, CDSR (coch), Dare Search Strategy.  
(DOCX)

Appendix S4  Embase search strategy.  
(DOCX)

Acknowledgments

We would like to acknowledge the members of the expert panel, including: Rami Habib, Gary Peter Kay, Valerie Taylor, George Wells, Carlos Muiru (Psychiatrist, Royal Ottawa Health Care Group), Sonja Wickham (Family Physician, Weight Management Clinic), Judy Shiau (Internist, Weight Management Clinic), and Joan Peterson. Secretarial assistance for the expert panel was provided by Alan Gervais and Robert Dent. Special thanks to the medical library at The Ottawa Hospital, including Alexandra Davis, Medical Librarian and Megan Visinski, Library Technician. We truly appropriate the technical support with the manuscript from Jennifer Brown (Registered Dietitian, Weight Management Clinic).

Author Contributions

Conceived and designed the experiments: GW RD. Analyzed the data: AG JP AB. Contributed reagents/materials/analysis tools: GPK RH JP AG RD VT GW AB. Wrote the paper: RD GW AB JP VT.

Supporting Information

Figure S1  PRISMA 2009 Flow Diagram.  
(TIF)

References

1. Bramlage P, Wittchen HU, Pittrow D, Kirch W, Krause P, et al. (2004) Recognition and management of overweight and obesity in primary care in Germany. Int J Obes Relat Metab Disord 28: 1299–1308.

2. Mackin P, Bishop DR, Watkinson HM (2007) A prospective study of monitoring practices for metabolic disease in antipsychotic-treated community psychiatric patients. BMC Psychiatry 7: 28.

3. Suppes T, McElroy SL, Hirschfeld R (2007) Awareness of metabolic concerns and perceived impact of pharmacotherapy in patients with bipolar disorder: a survey of 500 US psychiatrists. Psychopharmacol Bull 40: 22–37; quiz 38–40.

4. Buckley PF, Miller DD, Singer B, Arena J, Styrcwalt EM (2005) Clinicians’ recognition of the metabolic adverse effects of antipsychotic medications. Schizophr Res 79: 291–292.

5. Ferney L, Mooney M (2005) Atypical antipsychotic monitoring in the Kilkenny Mental Health Services. Irish Journal of Psychological Medicine 22: 101–102.

6. Bolton M, Hamilton RJ (2005) A survey of monitoring of weight and blood glucose in inpatients. Psychiatr Bulletin 27: 424–426.

7. Nguyen D, Brakoulis V, Boyce P (2009) An evaluation of monitoring practices in patients on second generation antipsychotics. Australas Psychiatry 17: 295–299.

8. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, et al. (2009) Metabolic screening after the American Diabetes Association’s consensus statement on antipsychotic drugs and diabetes. Diabetes Care 32: 1037–1042.

9. Cash TF, Brown MA (2000) Attitudes about antidepressants: influence of information about weight-related side effects. Percept Mot Skills 90: 435–436.

10. Ashton AK, Janmerson BD, Weinstein WL, Wagoner C (2005) Antidepressant-related adverse effects impacting treatment compliance: results of a patient survey. Current Therapeutic Research - Clinical and Experimental 66: 95–106.

11. Goethe JW, Woolley SB, Cardoso AA, Woznicki BA, Piez DA (2007) Selective serotonin reuptake inhibitor discontinuation: side effects and other factors that influence medication adherence. J Clin Psychopharmacol 27: 451–458.

12. Shenton RC (2000) Medications related to adherence in the treatment of depression. Primary Psychiatry 14: 42–46.

13. Anderson IM, Nutt DJ, Deakin JF (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British Association for Psychopharmacology: Psychopharmacol 27: 252–258.

14. Masand PS (2003) Tolerability and adherence issues in antidepressant therapy. Clin Ther 25: 2289–2304.

15. Perkins DO (2002) Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 63: 1121–1128.

16. Susman N (2003) The implications of weight changes with antipsychotic treatment. J Clin Psychopharmacol 23: S21–26.

17. Allison DB, Mackell JA, McDonnell DJ (2003) The impact of weight gain on quality of life among persons with schizophrenia. Psychiatr Serv 54: 563–569.

18. Weden PJ, Mackell JA, McDonnell DD (2004) Obesity as a risk factor for antipsychotic noncompliance. Schizophr Res 66: 51–57.

19. Tham M, Jones S, Chamberlain J, Castle D (2007) The impact of psychotropic weight gain on people with psychosis-patient perspectives and attitudes. Journal of Mental Health 16: 771–779.

20. Hanner S, Haddad PM (2007) Adverse effects of antipsychotics as outcome measures. Br J Psychiatry Suppl 50: 564–70.

21. Haddad PM, Sharma SG (2007) Adverse effects of atypical antipsychotics: differential risk and clinical implications. CNS Drugs 21: 911–936.

22. Henderson DC (2007) Weight gain with atypical antipsychotics: evidence and insights. J Clin Psychiatry 68 Suppl 12: 18–26.

23. Gitlin MJ, Cochran SD, Jamison KR (1989) Maintenance lithium treatment: side effects and compliance. J Clin Psychiatry 50: 127–131.

24. Anderson T, Goldberg J, Harrow M (2004) A review of medication side effects and treatment adherence in bipolar disorder. Primary Psychiatry 11: 40–54.

25. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, Kinon BJ, Staufer V, et al. (2009) Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. J Clin Psychiatry 70: 990–996.

26. Bellack AS, Boudewin CL, Bowie CR, Byerly MJ, Carpenter WT (2009) The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. Journal of Clinical Psychiatry 70: 1–48.

27. Thirda P, Beard S, Rizley A, Kane J (2003) An economic review of compliance with medication therapy in the treatment of schizophrenia. Psychiatr Serv 54: 508–516.

28. Sun SX, Liu GG, Christensen DB, Fu AZ (2007) Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin 23: 2305–2312.

29. Laermarka J, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, et al. (2003) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353: 1209–1223.

30. Beasley CM, Jr., Staufer VL, Liu-Seifert H, Taylor CC, Dunayevich E, et al. (2007) All-cause treatment discontinuation in schizophrenia during treatment with olanzapine relative to other antipsychotics: an integrated analysis. J Clin Psychopharmacol 27: 252–258.

31. Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R (2002) Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 159: 561–566.

32. Henderson DC, Cagijero E, Gray C, Nasrallah RA, Hayden DL, et al. (2000) Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. Am J Psychiatry 157: 975–981.

33. Leslie DL, Rosenheck RA (2004) Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. Am J Psychiatry 161: 1709–1711.

34. Hedenalm K, Hagg S, Stahl M, Mortimer O, Spiagget O (2002) Glucose intolerance with atypical antipsychotics. Drug Saf 25: 1107–1116.
Changes in Body Weight and Psychotropic Drugs

35. Kurzhaler I, Fleischhacker WW (2001) The clinical implications of weight gain in schizophrenia. J Clin Psychiatry 62 Suppl 7: 32–37.
36. Allison DB, Casey DE (2001) Atypical antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry 62 Suppl 7: 22–31.
37. Aronow LJ, Krag CR (2007) Weight gain in the treatment of mood disorders. J Clin Psychiatry 68 Suppl 2: 22–29.
38. Newcomer JW (2004) Metabolic risk during antipsychotic treatment. Clin Ther 26: 1936–1946.
39. Bergman RM, Weden P, Pigott T, Murray S, Sin CO, et al. (2005) Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. Am J Psychiatry 162: 1535–1538.
40. Fontaine KR, Heo M, Harrigan EP, Shear CL, Lakshminarayanan M, et al. (2003) Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. Psychiatry Res 101: 277–288.
41. Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, et al. (2004) Physical health monitoring of patients with schizophrenia. Am J Psychiatry 161: 1334–1344.
42. American Diabetes Association APA, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity (2004) Consensus development conference on antipsychotics and obesity and diabetes. Diabetes Care 27: 596–601.
43. Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Måle R, et al. (2009) Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. Ill. Pharmacother. 39: 2046–2055.
44. Schatzberg AF (2007) Safety and tolerability of antipsychotics: weighing the impact on treatment decisions. J Clin Psychiatry 68 Suppl 8: 26–34.
45. Malone M (2005) Medications associated with weight gain. Ann Pharmacother 39: 2046–2055.
46. Perucca E, Meador KJ (2005) Adverse effects of antiepileptic drugs. Acta Neurol Scand Suppl 181: 30–35.
47. Bergman RN, Ader M (2005) Atypical antipsychotics and glucose homeostasis. Ann Intern Med 143: 620–626.
48. Gualdi-Russo E, Maione P, Piazza G, et al. (2008) Efficacy and safety of second-generation antipsychotics in the treatment of major depressive disorder. Int Clin Psychopharmacol 23: 198–204.
49. Montgomery SA, Reimitz PE, Zivkov M (1998) Mirtazapine versus haloperidol in the treatment of schizoaffective disorder. Acute and long-term therapy. Br J Psychiatry 174: 15–22.
50. Lencz T, Malhotra AK (2009) Pharmacogenetics of antipsychotic-induced side effects. Dialogues Clin Neurosci 11: 405–415.
51. Gehlhar J, Haberhausen M, Heimel-Gutenbrunner M, Gebhardt H, Remschmidt H, et al. (2009) Antipsychotic-induced weight gain: predictors and a systematic categorization of the long-term weight course. J Clin Psychopharmacol 29: 620–626.
52. Zipursky RB, Gu H, Green AI, Perkins DO, Tohen MF, et al. (2005) Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. Br J Psychiatry 186: 537–543.
53. Davidson J, Yaryura-Tobias J, DuPont R, Stallings L, Barbato LM, et al. (2004) Fluvoxamine-controlled release formulation for the treatment of generalized social anxiety disorder. J Clin Psychopharmacol 24: 118–125.
54. Westenberg HG, Steen HJ, Yang H, Li D, Barbato LM, et al. (2004) A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. J Clin Psychopharmacol 24: 49–55.
55. Perry R, Cassagnoul M (2009) Desvenlafaxine: a new serotonin-norepinephrine reuptake inhibitor for the treatment of adults with major depressive disorder. J Clin Psychopharmacol 31 Pt 1: 1374–1384.
56. Taylor DM, McAllister R (2000) Atypical antipsychotics and weight gain—a systematic review. Acta Psychiatr Scand 101: 416–432.
57. Jeste DV, Dolder CR (2004) Treatment of non-schizophrenic disorders: focus on augmentation and combination treatment. J Clin Psychiatry 65 Suppl 8: 23–25.
58. Montgomery SA, Reimitz PE, Zivkov M (1998) Mirtazapine versus haloperidol in the treatment of schizoaffective disorder. Acute and long-term therapy. Br J Psychiatry 174: 15–22.
59. Lencz T, Malhotra AK (2009) Pharmacogenetics of antipsychotic-induced side effects. Dialogues Clin Neurosci 11: 405–415.
60. Gehlhar J, Haberhausen M, Heimel-Gutenbrunner M, Gebhardt H, Remschmidt H, et al. (2009) Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. J Clin Psychopharmacol 29: 620–626.
61. Zipursky RB, Gu H, Green AI, Perkins DO, Tohen MF, et al. (2005) Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. Br J Psychiatry 186: 537–543.
62. Lencz T, Malhotra AK (2009) Pharmacogenetics of antipsychotic-induced side effects. Dialogues Clin Neurosci 11: 405–415.
63. Gehlhar J, Haberhausen M, Heimel-Gutenbrunner M, Gebhardt H, Remschmidt H, et al. (2009) Antipsychotic-induced weight gain: predictors and a systematic categorization of the long-term weight course. J Clin Psychopharmacol 29: 109–113.
64. Barbui C, Cipriani A, Brambilla P, Hotopf M (2004) “Wish bias” in antipsychotic drug trials. J Clin Psychopharmacol 24: 126–130.
65. Hemby SE, Davis J, Mamo M, Knudsen E, Kindig W, et al. (2006) Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 163: 185–194.
96. Gartlehner G, Morgan L, Thieda P, Fleg A (2010) The effect of study sponsorship on a systematically evaluated body of evidence of head-to-head trials was modest: secondary analysis of a systematic review. J Clin Epidemiol 63: 117–125.

97. Shek BJ, Grinnshaw JM, Wells GA, Boers M, Andersson N, et al. (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 7: 10.

98. SIGN 50 website. Available: http://www.sign.ac.uk/guidelines/fulltext/50/annexc.html. Accessed 2011 Apr 24.

99. Bitter I, Dossenbach MR, Brook S, Feldman PD, Metcalfe S, et al. (2004) Olanzapine versus clozapine in treatment-resistant or treatment-intolerant schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 28: 173–180.

100. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwartz S, et al. (2010) Olanzapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev: CD006634.

101. Karagiani J, Hoffmann VP, Arranz B, Treuer T, Maguire GA, et al. (2008) Orally disintegrating olanzapine and potential differences in treatment-emergent weight gain. Hum Psychopharmacol 23: 273–281.

102. Comas F, Möller H-J (2010) Long-acting atypical injectable antipsychotics in the treatment of schizophrenia: safety and tolerability review. Expert Opin Drug Saf 9: 683–697.

103. Fenton M, Rathbone J, Reilly J, Sultana A (2007) Thioridazine for schizophrenia. Cochrane Database Syst Rev: CD001944.

104. Lieberman JA, Phillips M, Guo H, Stropes S, Zhang P, et al. (2003) Atypical and conventional antipsychotic drugs in treatment-naïve first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. Neuropsychopharmacology 28: 995–1003.

105. McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, et al. (2007) Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry 164: 1050–1060.

106. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, et al. (2010) Aripiprazole versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev: CD006624.

107. Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwartz S, et al. (2009) Ziprasidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev: CD006627.

108. Kwon J, Jiang JH, Kang DH, Yoo SY, Kim YK, et al. (2009) Long-term efficacy and safety of aripiprazole in patients with schizophrenia, schizoaffective disorder, or schizotypal disorder: 26-week prospective study. Psychiatry Clin Neurosci 63: 73–81.

109. Bechelli LPC, Iecco MC, Acioli A, Pontes MC, et al. (2008) A double-blind trial of haloperidol decanoate and pipotiazine palmitate in the maintenance treatment of schizophrenia in a public outpatient clinic. Current Therapeutic Research - Clinical and Experimental: 37: 662–671.

110. Winstead B, Persson T, Hellsom E (1984) A clinical double-blind comparison between haloperidol decanoate and fluphenazine decanoate. Current Therapeutic Research - Clinical and Experimental 35: 590–614.

111. Komossa K, Rummel-Kluge C, Hunger H, Schwartz S, Bhooopathi PS, et al. (2009) Ziprasidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev: CD006627.

112. Bagnall A, Fenton M, Kleijn P, Lewis R, et al. (2007) Molindone for schizophrenia and severe mental illness. Cochrane Database Syst Rev: CD002083.

113. Sivaraman P, Rathehali RD, Jayaram MB (2010) Levomepromazine for schizophrenia. Cochrane Database Syst Rev: CD007779.

114. Marques LO, Lima MS, Soares BG (2004) Trifluoperazine for schizophrenia. Cochrane Database Syst Rev: CD000354.

115. Chakrabarti A, Ragull A, Chue P, Fenton M, Palaniswamy V, et al. (2007) Luca pinate for schizophrenia. Cochrane Database Syst Rev: CD001943.

116. Johnson DA, Beein M (1979) Weight changes with depot neuroleptic maintenance therapy. Acta Psychiatr Scand 59: 525–528.

117. Kumar A, Streech D (2009) Zuclopenthixol dihydrochloride for schizophrenia. Schizophr Bull 35: 855–856.

118. Chwieduk CM, Keating GM (2010) Paliperidone extended release: a review of its use in the management of schizophrenia. Drugs 70: 1295–1317.

119. Citrome L (2010) Paliperidone palmitate - review of the efficacy, safety and cost of a new second-generation depot antipsychotic medication. Int J Clin Pract 64: 216–239.

120. Ogugua G, Kato M, Wakeno M, Koh J, Morikawa M, et al. (2009) Randomized clinical comparison of perospirone and risperidone in patients with schizophrenia: Kansai Psychiatric Multicenter Study. Psychiatry Clin Neurosci 63: 322–329.

121. Marino J, Callabero J (2010) Iloperidone for the treatment of schizophrenia. Ann Pharmacother 44: 863–870.

122. Hale KS (2010) Iloperidone - A second-generation antipsychotic for the treatment of acute schizophrenia. The Journal of Pharmacy Technology 26: 193–202.

123. Biel LW, Brunstein MG, Ottone GL, Ramos FL, Borba DL, et al. (2008) Iloperidone - a long-acting oral atypical antipsychotic? A randomized clinical trial versus haloperidol for the treatment of schizophrenia. J Clin Psychiatry 69: 1572–1579.

124. Citrome L (2009) Aripiprazole for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. Int J Clin Pract 63: 1762–1784.

125. Smith MC, Centorrino F, Welge JA, Collins MA (2004) Clinical comparison of extended-release divalproex versus delayed-release divalproex: pooled data analyses from nine trials. Epilepsy Behav 5: 746–751.

126. Keffer TA, Kalali AH, Weider RH (2004) A 6-month, multicenter, open-label evaluation of extended-release, extended-release carbamazepine capsule monotherapy in bipolar disorder patients with manic or mixed episodes. J Clin Psychiatry 65: 668–673.

127. Reinstein MJ, Sonnenberg JG, Hedberg TG, Jones LE, Reynold P (2003) Oxcarbazepine versus Divalproex Sodium for the Continuing Treatment of Mania. Clin Drug Investig 23: 671–677.

128. Stoffers J, Vollno BA, Rucker G, Tisser T, Huband N, et al. (2010) Pharmacological interventions for borderline personality disorder. Cochrane Database Syst Rev: CD005633.

129. Oswald I, Adam K (1980) Benzodiazepines cause small loss of body weight. Br Med J 281: 1039–1040.

130. Bjorneraas A, Bock JM, Hatfield PE, Holte M, Ottesen S, et al. (1982) A multicentre placebo-controlled trial comparing the efficacy of mianserin and chloridiazepoxide in general practice patients with primary anxiety. Acta Psychiatr Scand 66: 199–207.

131. Smits JA, Rosenfield D, Mather AA, Tart CD, Giersek C, et al. (2010) Psychotropic medication use mediates the relationship between mood and anxiety disorders and obesity: findings from a nationally representative sample. J Psychiatr Res 44: 1010–1016.

132. Yuanguang CC, Xiaogang C, Chuanyue W (1998) A randomized controlled study of buspirone and valium in the treatment of general anxiety disorder. Chinese Journal of Psychiatry 31: 43–46.