Antipsychotic-induced weight gain: a comprehensive research synthesis

Authors' objectives
To estimate and compare the effects of antipsychotics - both newer ones and the conventional ones - on body weight.

Searching
MEDLINE (1966 to Nov 1996), PsycINFO (1967-Oct 1996), CINAHL (1982-Sept 1996), HealthSTAR (1975 to Oct 1996) and Dissertation Abstracts International (1861 to Jan 1997) were searched (search terms available from author). In addition the bibliographies of retrieved articles were searched for additional references. Contact was made with experts in the field, the authors of primary studies and the manufacturers of the drugs included in the review in order to locate any further published/unpublished studies. There were no restrictions on the language of publication.

Study selection
Study designs of evaluations included in the review
Any studies including data on weight change that had a sample size greater than one. Review articles were not included.

Specific interventions included in the review
Antipsychotics approved for use in the USA or that were not currently approved but were under investigation in humans for use as antipsychotics including: chlorpromazine, thioridazine/mesoridazine, fluphenazine, perphenazine, trifluoperazine, thiothixene, loxapine, clozapine, risperidone, haloperidol, molindone, pimozide, chlorprothixene, prochlorperazine, olanzapine, quetiapine, sertindole and ziprasidone (using various regimens). A list was compiled using Hyman et al. (see 'Other Publications of Related Interest' no.1), the 1997 edition of the Physicians' Desk Reference, and expert colleagues. Comparators included placebo, a non-pharmacologic non-placebo control and polypharmacy.

Participants included in the review
Patients taking antipsychotic medication. Studies including patients on weight reducing diets, patients with anorexia nervosa or Huntington's chorea and studies looking at prenatal exposure to neuroleptic drugs were excluded.

Outcomes assessed in the review
Weight change after initiation of drug treatment.

How were decisions on the relevance of primary studies made?
Studies were coded by one author and spot-checked by one of two other investigators. When a discrepancy was identified the coders met to resolve the discrepancy and reach a consensus.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Studies were coded by one author and spot-checked by one of two other investigators. When a discrepancy was identified the coders met to resolve the discrepancy and reach a consensus. Data tables included in the review reported: bibliographic details, intervention/control details, details (age, gender) and number of participants, duration of treatment, and mean and standard deviation of weight change. If articles were published in 1990 or later, authors were contacted for missing data. Missing means, standard deviations and sample sizes were also directly calculated by using other information available in the article. If this was not possible the statistical values were also estimated using maximum likelihood methods or by using a method developed by Tippett (see 'Other Publications of Related Interest', no.2). Standard deviations were estimated as the square root of the weighted average variance across all other studies where the weights used were the sample sizes in each study. If all of these methods failed the study was only included in
the narrative summary and not the meta-analysis.

**Methods of synthesis**

**How were the studies combined?**

Those studies with insufficient data for inclusion in the meta-analyses were summarised in a narrative. Those studies reporting sufficient data were combined in a meta-analysis calculating the weighted mean weight change and standard error based on both a fixed-effect model and a random-effects model. Both sets of data were presented in tables but only the data from the random-effects model were discussed in the text, given the level of heterogeneity present. For each drug, where sufficient data were available (i.e. six or more data points) the mean weight change was regressed (least squares multiple regression) on the standardised drug dosage and length of treatment. The weight-promoting effects of each drug at the midpoint of its recommended dose at 10 weeks were estimated using both a fixed-effect model and a random-effects model. Finally, pairwise comparisons for the estimated weight changes at 10 weeks at the standard dose of each compound were conducted and the statistical significance of the differences tested using the 'z statistic'. Where possible 95% confidence intervals (CI) were reported.

**How were differences between studies investigated?**

A chi-squared test was used. Sensitivity analyses were also carried out of estimated 10-week weight gains (random-effects model) based on different definitions of standard dose.

**Results of the review**

Eighty-one studies incorporating 418 estimates of weight change in an antipsychotic or control group, were included (study designs not stated, included 1823 participants). Eighteen of the studies were placebo-controlled.

Narrative overview of duration of treatment at the time weight change was measured:

It was unclear how many studies were included in this synthesis and the study designs were not reported. One poorly controlled study with follow-ups as long as 11 years was excluded as an outlier. Many of the drugs seemed to induce clinically meaningful weight gain. Perphenazine had the shortest mean duration of treatment (2.0 weeks) and loxapine the longest (43.2 weeks (range 12-104 weeks)).

**Meta-analyses:**

In total 418 estimates of weight change were identified from 81 studies with useable data. A complete list of the studies included in the meta-analysis is available from the authors, and in almost all cases the chi-squared tests for heterogeneity were highly significant, hence the discussion focused more on the random-effects data.

1. Mean weight change (in kg) (fixed-effect model):

The studies varied greatly in terms of length of treatment and dosage. The chi-squared tests in almost all cases showed highly significant heterogeneity and so the fixed-effect findings were not very informative. However, the results were reported in tabular form.

2. Mean weight change (in kg) (random-effects model):

'N' relates to the total number of means; and number of independent cohorts the means came from.

- **Chlorpromazine (N=25; 13)** 4.19 (95% CI: 2.94, 5.44).
- **Clozapine (N=14; 12)** 5.67 (95% CI: 4.34, 7.00).
- **Fluphenazine (N=11; 10)** 1.13 (95% CI: 0.09, 2.17).
- **Haloperidol (N=25; 19)** 0.51 (95% CI: 0.20, 0.82).
Loxapine (N=5; 3) 0.65 (95% CI: -2.56, 3.86).
Molindone (N=17; 10) -0.10 (95% CI: -1.39, 1.19).
Non-pharmacologic control (N=7; 4) 0.82 (95% CI: 0.08, 1.56).
Olanzapine (N=157; 7) 4.17 (95% CI: 3.70, 4.64).
Perphenazine (N=4; 4) 5.77 (95% CI: 0.44, 11.10).
Pimozide (N=2; 2) -2.69 (95% CI: -9.30, 3.92).
Placebo (N=25; 22) -0.97 (95% CI: -1.79, -0.15).
Polypharmacy (N=26; 13) 0.46 (95% CI: 0.24, 0.68).
Quetiapine (N=8; 3) 2.49 (95% CI: 1.51, 3.47).
Risperidone (N=38; 26) 1.67 (95% CI: 1.38, 1.96).
Sertindole (N=7; 4) 2.94 (95% CI: 2.70, 3.18).
Thioridazine/mesoridazine (N=16; 12) 2.81 (95% CI: 1.59, 4.03).
Thiothixene (N=4; 3) 2.89 (95% CI: 1.01, 4.77).
Trifluoperazine (N=2; 2) 0.34 (95% CI: -0.86, 1.54).
Ziprasidone (N=25; 22) 0.28 (95% CI: -0.27, 0.83).

3. Mean estimated weight change (in kg) at 10 weeks (fixed-effect model):

'N' relates to the total number of means; and number of independent cohorts the means came from.

Chlorpromazine (N=25; 13) 2.10 (95% CI: 0.85, 3.35).
Clozapine (N=14; 12) 3.99 (95% CI: 2.72, 5.26).
Fluphenazine (N=11; 10) 0.43 (95% CI: -0.65, 1.51).
Haloperidol (N=25; 19) 0.48 (95% CI: 0.07, 1.03).
Loxapine (N=5; 3) Not reported.
Molindone (N=17; 10) -0.81 (95% CI: -2.16, 0.54).
Non-pharmacologic control (N=7; 4) 1.33 (95% CI: 0.84, 1.82).
Olanzapine (N=157; 7) 3.51 (95% CI: 3.29, 3.73).
Perphenazine (N=4; 4) Not reported.
Pimozide (N=2; 2) Not reported.
Placebo (N=25; 22) -0.41 (95% CI: -1.29, 0.47).
Polypharmacy (N=26; 13) 1.22 (95% CI: 0.36, 2.08).
Quetiapine (N=8; 3) Not reported.
Risperidone (N=38; 26) 2.00 (95% CI: 1.61, 2.39).
Sertindole (N=7; 4) 2.92 (95% CI: 1.76, 4.08).
Thioridazine/mesoridazine (N=16; 12) 3.49 (95% CI: 1.75, 5.23).
Thiothixene (N=4; 3) Not reported.
Trifluoperazine (N=2; 2) Not reported.
Ziprasidone (N=25; 22) 0.04 (95% CI: -0.49, 0.57).

4. Chi-squared test for random-effects variance of 10-week estimate: 'N' relates to the total number of means; and number of independent cohorts the means came from.

Chlorpromazine (N=25; 13) 68.4, df=20, p<0.0005.
Clozapine (N=14; 12) 38.3, df=9, p<0.0005.
Fluphenazine (N=11; 10) 6.9, df=6, p=0.23.
Haloperidol (N=25; 19) 63.3, df=20, p<0.0005.
Loxapine (N=5; 3) Not reported.
Molindone (N=17; 10) 49.5, df=12, p<0.0005.
Non-pharmacologic control (N=7; 4) 1.5, df=2, p=0.69.
Olanzapine (N=157; 7) 709.5, df=152, p<0.0005.
Perphenazine (N=4; 4) Not reported.
Pimozide (N=2; 2) Not reported.
Placebo (N=25; 22) 237.1, df=20, p<0.0005.
Polypharmacy (N=26; 13) 75.3, df=21, p<0.0005.
Quetiapine (N=8; 3) Not reported.
Risperidone (N=38; 26) 161.9, df=33, p<0.0005.
Sertindole (N=7; 4) 0.2, df=2, p=0.88.
Thioridazine/mesoridazine (N=16; 12) 32.9, df=11, p=0.0003.
Thiothixene (N=4; 3) Not reported.
Trifluoperazine (N=2; 2) Not reported.
Ziprasidone (N=25; 22) 21.1, df=20, p=0.39.

5. Mean estimated weight change (in kg) at 10 weeks (random-effects model):

'N' relates to the total number of means; and number of independent cohorts the means came from.
Chlorpromazine (N=25; 13) 2.58 (95% CI: 0.91, 4.25).
Clozapine (N=14; 12) 4.45 (95% CI: 3.02, 5.88).
Fluphenazine (N=11; 10) 0.43 (95% CI: -0.65, 1.51).
Haloperidol (N=25; 19) 1.08 (95% CI: 0.35, 1.81).
Loxapine (N=5; 3) Not reported.
Molindone (N=17; 10) -0.39 (95% CI: -2.43, 1.65).
Non-pharmacologic control (N=7; 4) 1.33 (95% CI: 0.84, 1.82).
Olanzapine (N=157; 7) 4.15 (95% CI: 3.82, 4.48).
Perphenazine (N=4; 4) Not reported.
Pimozide (N=2; 2) Not reported.
Placebo (N=25; 22) -0.74 (95% CI: -1.60, 0.12).
Polypharmacy (N=26; 13) 1.82 (95% CI: 0.84, 2.80).
Quetiapine (N=8; 3) Not reported.
Risperidone (N=38; 26) 2.10 (95% CI: 1.69, 2.51).
Sertindole (N=7; 4) 2.92 (95% CI: 1.76, 4.08).
Thioridazine/mesoridazine (N=16; 12) 3.19 (95% CI: 1.39, 4.99).
Thiothixene (N=4; 3) Not reported.
Trifluoperazine (N=2; 2) Not reported.
Ziprasidone (N=25; 22) 0.04 (95% CI: -0.49, 0.57).

Authors' conclusions
Both conventional and newer antipsychotics are associated with weight gain. Among the newer agents, clozapine appears to have the greatest potential to induce weight gain, and ziprasidone the least. The differences among newer agents may affect compliance with medication and health risk.

CRD commentary
This review is based on an extensive search of the literature aimed at identifying both published and unpublished material. The risk of publication bias is therefore likely to be low. The inclusion/exclusion criteria were reasonably clear however the type of study design was not specified in detail and it is unclear what type and how many of each type of study were included in the review. It would appear that one reviewer conducted the assessment of study relevancy and the process of data extraction, with a sub sample of decisions been checked by two other reviewers. However, no assessment of study validity was performed. Little information was presented with regard to 81 individual studies although this is not surprising given the number of studies involved. It would however have been useful to have a clearly presented table and summary of the studies included in the meta-analysis. It was not very clear what study designs were included in the meta analysis or how many studies and what designs were included in the narrative summary.

A statistical test was used to assess the level of heterogeneity between studies used in the meta-analysis. However, it
would appear that the studies were pooled regardless of heterogeneity, although the authors placed more weight on the more conservative random-effects model for this reason. Great caution is required when interpreting pooled effect sizes from heterogeneous studies, regardless of the method used. Furthermore, without more details of the studies it was also not clear whether the poolings made clinical sense. Estimated weight changes were also presented using both the random-effects and fixed-effect models by regressing the mean weight change on standardised drug dosage and length of treatment. However, the robustness of the data is questionable. Some data were estimated and other data were based on studies containing only very small numbers of participants (e.g. two participants). In view of these comments, the findings of the review should be treated with caution.

Implications of the review for practice and research

Practice: The authors state that 'among the newer agents, clozapine appears to have the greatest potential to induce weight gain, and ziprasidone the least'. However, 'in the end clinical choices must be made on a case-by-case basis, with careful consideration of issues or weight, therapeutic efficacy, and other relevant factors'.

Research: The authors state that 'weight gain data (is reported) in an incomplete, idiosyncratic, and poorly defined manner' and 'this is clearly an area that would benefit from guidelines and standardisation'.

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