Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials

Correll C U

CRD summary
The author concluded that data on the effects of mood stabilisers and antipsychotics on weight change and metabolism in paediatric patients with bipolar disorder are limited. The evidence appeared to support these conclusions, but the limited search and other limitations of the review mean that they may not be reliable.

Authors’ objectives
To evaluate the effects of mood stabilisers and antipsychotic medications on weight gain and metabolism in paediatric patients with bipolar disorders.

Searching
MEDLINE/PubMed was searched to July 2006 using the reported search terms. In addition, the reference lists of identified studies were screened.

Study selection

Chart reviews, case series, naturalistic trials, open trials and randomised controlled trials (RCTs) with at least 9 patients were eligible for inclusion.

Specific interventions included in the review
Studies that evaluated mood stabilisers, antiepileptics, antipsychotics or combinations of these medications were eligible for inclusion. The included studies evaluated mood-stabiliser monotherapy (divalproex (DVPX), lithium, lamotrigine, oxcarbazepine and topirimate), mood-stabiliser combination therapy (DVPX plus lithium), antipsychotic monotherapy (olanzapine, quetiapine, risperidone, aripiprazole and clozapine) and antipsychotics plus mood-stabiliser combination therapy (quetiapine plus DVPX, risperidone plus lithium, and risperidone plus DVPX). Most studies were short term (4 to 8 weeks); other studies were medium term (18 to 28 weeks) and only one was long term (up to 1 year).

Participants included in the review
Studies of paediatric patients who had been diagnosed with a bipolar spectrum disorder were eligible for inclusion. In the included studies, the mean age of the patients was 12.3 years; most studies included patients aged 4 to 20 years but some only included adolescents or pre-school-aged children. In most studies patients had manic or mixed symptomatology.

Outcomes assessed in the review
Studies that assessed changes in body composition, glucose or lipid values were eligible for inclusion. Studies had to report numeric values for their measure of ‘weight gain’.

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The author did not report any formal assessment of validity. However, aspects of methodological quality such as drop-out rates, concomitant medications, measures used for weight-change outcomes, reporting of statistical significance and sample size were noted in the text.

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, where possible, the weight gain plus a measure of variance and the p-value for the statistical
significance of the treatment effect of the drug of interest compared with the control were tabulated.

**Methods of synthesis**

**How were the studies combined?**

The number of studies which reported statistically significant or clinically relevant changes in weight was reported; where possible, effect sizes were pooled across similar studies. Cohen’s ‘d’ effect size was calculated for each subgroup. Pooled changes in weight were also apparently calculated for each subgroup. Other studies were combined in a narrative. ‘Clinically relevant’ was not defined in the review.

**How were differences between studies investigated?**

Differences between the studies were described in the narrative summary. The studies were grouped by intervention and duration of treatment. Differences between different drug groups were tested statistically using the F test, and pairwise comparisons were undertaken using Student’s t-test.

**Results of the review**

Nineteen studies involving 24 individual drug trials were included (n=684): 4 RCTs (n=174), 11 open-label studies (n=458) and 4 chart reviews (n=52).

The drop-out rates ranged from 0 to 59% (mean 21). Only 5 studies prohibited or restricted concomitant medications. Twelve studies only reported absolute weight change. Nine studies did not report the results of tests of statistical significance.

Eighteen of the 24 individual trials reported a statistically significant or clinically relevant increase in weight. One study of lamotrigine (n=20) and one study of lithium (n=17) and lithium plus risperidone (n=21) reported no significant weight change at 8 weeks and 1 year, respectively. Three trials reported weight loss: two involved topirimate (n=9, and n=29 in an RCT) and one involved aripiprazole (n=14).

For short-term studies (mean duration 12 weeks or less), pairwise comparison showed significantly greater weight gain in patients receiving one second-generation antipsychotic plus mood stabiliser compared with those receiving one mood stabiliser (5.5 kg based on 32 patients in 2 trials versus 1.2 kg based on 171 patients in 6 trials, p<0.05; Cohen’s d =2.32) or two mood stabilisers (2.1 kg based on 128 patients in 2 trials, p<0.05; Cohen’s d = 2.17). The results were similar after excluding a study on topirimate. There were no significant differences for other pairwise comparisons.

The author stated that there were too few patients to pool weight change data for medium- and long-term trials.

Only two 8-week open-label trials systematically assessed changes in glucose and lipid levels. Neither reported any significant change in non-fasting glucose or lipid (n=31 treated with risperidone or olanzapine and n=30 treated with risperidone). The levels appeared to be non-fasting.

**Authors’ conclusions**

Data on the effects of mood stabilisers and antipsychotics on weight change and metabolism in paediatric patients with bipolar disorder are limited. Weight gain appeared greater with antipsychotics plus mood stabilisers than with one or two mood stabilisers.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention and outcomes. Inclusion criteria for the study design were broad but this seems appropriate in view of the limited number of clinical trials identified. Only one database and references were searched and no attempts to minimise publication or language bias were reported. This might have resulted in the omission of other relevant studies and raises the potential for publication bias. Although some methodological flaws were mentioned, there was no formal assessment of validity, thus the results from these studies and any synthesis may not be reliable. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Pooled weight change data from similar studies were apparently calculated, but the methods used were not reported and it is not clear if the results were sufficiently similar for pooling to be appropriate. Comparisons between different drug...
treatments were based on indirect comparisons and cannot be considered definitive. As the author concluded, the data do, indeed, appear limited but a more extensive search might have identified additional data. In view of the limited search, lack of reporting of review methods, unclear methods of analysis and indirect comparisons, the author’s conclusions may not be reliable.

Implications of the review for practice and research

Practice: The author stated that clinicians need to select treatment carefully for individual patients, taking into account the potential risk of adverse effects. Counselling on healthy lifestyle should be given, and body composition and metabolic measures should be routinely monitored.

Research: The author stated the need for further research in paediatric patients to evaluate the effects of individual drugs, combinations of drugs and drug classes on weight gain and metabolic adverse effects. Studies should use gender- and age-adjusted measures of weight and body composition and measure fasting blood levels and blood-pressure, and follow patients long term. Research should also be conducted to evaluate behavioural and pharmacological interventions.

Funding
Zucker Hillside Hospital NIMH Advanced Centre for Intervention and Services Research for the Study of Schizophrenia, grant number MH 074543-01); NSLIJ Research Institute NIH General Clinical Research Center, grant number MO1RR018535.

Bibliographic details

PubMedID
17513981

DOI
10.1097/chi.0b013e318040b25f

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Anticonvulsants /adverse effects; Antimanic Agents /adverse effects; Antipsychotic Agents /adverse effects; Bipolar Disorder /drug therapy; Child; Drug Therapy, Combination; Glucose Metabolism Disorders /chemically induced /prevention & control; Humans; Lipid Metabolism Disorders /chemically induced /prevention & control; Lithium Compounds /adverse effects; Weight Gain

AccessionNumber
12007001925

Date bibliographic record published
01/04/2008

Date abstract record published
30/09/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.