Rapid-cycling bipolar disorder: effects of long-term treatments

Tondo L, Hennen J, Baldessarini R J

CRD summary
This review assessed the overall effect of rapid-cycling (RC) bipolar disorder status on treatment response, and the relative effectiveness of various treatments. Patients with RC bipolar disorder showed a less favorable treatment response than non-RC patients across all treatments. However, the findings should be interpreted with caution due to limited evidence and poor study quality.

Authors' objectives
The authors assessed the overall effect of rapid-cycling (RC) bipolar disorder status on treatment response, and the relative effectiveness of various treatments.

Searching
MEDLINE, Current Contents, and PubMed were searched until September 2002; the search terms were listed. The references in identified studies were also checked.

Study selection
Study designs of evaluations included in the review
The authors did not specify whether any particular study designs were eligible for inclusion. Studies were eligible for inclusion if they involved at least 10 patients.

Specific interventions included in the review
No particular drugs were specified as being eligible for inclusion. The drugs identified by the review were valproate, cabamazepine, lithium, lamotrigine and topiramate.

Participants included in the review
Studies of patients that had experienced at least four recurrences of depression or mania within a year, and had been treated for at least 4 months, were eligible for inclusion.

Outcomes assessed in the review
Outcomes that could be calculated as rates from proportions of patients with recurrences or with no substantial improvement from treatment, per average exposure time, were eligible for inclusion. Treatment effects were assessed in two ways: as the proportion of patients with at least one recurrent episode of mania or depression, and as the proportion lacking clinical improvement. Clinical improvement was rated as reduction of morbidity, use of Clinical Global Impression (CGI) or Global Assessment Scale (GAS) scores, reduction of illness severity or recurrence rate by at least 50%, or being euthymic for at least 30% of time during treatment.

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

Assessment of study quality
The authors rated the studies on a number of criteria: studies comparing RC and non-RC patients (2 points); studies directly comparing an active treatment with placebo or at least two active treatments randomly assigned (2 points); treatment investigated as a monotherapy (1 point); studies at least 12 months in duration (1 point), including at least 30 patients (1 point), with blinded design (1 point). The total scores out of 8 were calculated as percentages. Validity was assessed using the authors’ own criteria. It was unclear how many reviewers performed the validity assessment.
Data extraction
Data were extracted into tables under the following headings; study type, treatment, outcome and calculated failure rate. The authors did not state how many reviewers performed the data extraction. The outcome data was extracted as failure rate per month.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis. The main analysis was RC patients versus non-RC patients. The studies that compared the responses of RC patients with non-RC patients were pooled using a random-effects model. Relative risks (RRs) were calculated by dividing the failure rates of RC patients by the failure rates of non-RC patients. Standard errors were also estimated, along with the pooled RR and a 95% confidence interval (CI).

For studies that provided data on both recurrence and non-response outcomes, each outcome was considered separately. A Poisson distribution was used to estimate failure rates and 95% CIs; a random-effects model was used, with weighting based on the inverse variance plus a between-studies variance factor.

The effectiveness of carbamazepine and lithium was compared in a meta-analysis using a random-effects model to calculate a pooled RR and 95% CI. Risk estimates were calculated with an adjustment for estimated drug exposure time.

A 5% significance level was used in each of the analyses

How were differences between studies investigated?
The authors used the chi-squared test to assess heterogeneity between treatment effects.

Results of the review
Sixteen studies (1,856 patients) were included in the review. There were 905 RC patients and 951 non-RC patients.

The average quality rating score was 42.2% plus or minus 21.4%. There were no significant differences among specific drugs.

Nine studies included both RC and non-RC patients. For treatment effects, recurrence (Q=90.2, d.f.=8) and non-improvement (Q=111.5, d.f.=10) were heterogeneous across studies (both P<0.0001).

At least one recurrence was experienced in 384 out of 505 (76%) RC patients receiving any active treatment, compared with 70 out of 93 (75.3%) RC patients randomised to placebo (9 studies with 15 treatment arms). At least one recurrence was experienced in 287 out of 452 (63.5%) non-RC patients receiving any active treatment, compared with 9 out of 10 (90%) non-RC patients randomised to placebo. The crude rate-estimate of recurrence was 2.31%/month for RC patients and 1.25%/month for non-RC patients.

Risk estimates were also calculated without adjusting for exposure times. This resulted in substantial changes in the magnitude of study-specific risk estimates, with small changes in the relative sizes of risk estimates. Both methods of estimating the risk found a greater risk of treatment failure with RC patients.

Non-improvement was experienced in 264 out of 524 (50.4%) RC patients receiving any active treatment, compared with 309 out of 878 (35.2%) RC patients (11 studies). The crude rate-estimate of recurrence was 1.57%/month for RC patients and 0.48%/month for non-RC patients.

Risk estimates were also calculated without adjusting for exposure times. This resulted in minor differences between treatments in RC cases. Both methods of estimating the risk found a greater risk of treatment failure with RC patients.

The summary statistics indicated a significantly higher rate of treatment failure in RC patients compared with non-RC patients.
The pooled recurrence rate for RC and non-RC patients in studies providing a direct comparison was 1.40 (95% CI: 1.26, 1.56, P<0.0001). The pooled non-improvement rate for the same comparison was 1.45 (95% CI: 1.21, 1.74, P<0.0001).

The one direct treatment comparison possible found no statistically significant difference. In studies that compared carbamazepine with lithium, the pooled recurrence rate for RC patients was 0.93 (95% CI: 0.74, 1.18, P=0.54) and the pooled non-improvement rate for RC patients was 0.94 (95% CI: 0.81, 1.08, P=0.37).

Authors' conclusions
Patients with RC bipolar disorder showed a less favourable treatment response than non-RC patients across all treatments. The authors also concluded that their findings should be interpreted with caution due to the limited evidence and poor study quality.

CRD commentary
The review provided a clear question with specifications for study inclusion. The search for relevant literature was limited and no attempt to identify unpublished literature was made; this may introduce publication bias into the results. Study quality was assessed on the basis of specific aspects of study design, but was not used to influence the findings of the review. The designs of the individual studies were unclear: only two randomised controlled trials with blind assessment appear to have been included.

The meta-analyses of RC versus non-RC patients were subject to substantial clinical heterogeneity caused by treatment, patient numbers, study duration, potential use of concomitant therapy, length of treatment exposure, and definition of clinical improvement. This degree of clinical heterogeneity calls into doubt the validity of pooling all the studies, and is demonstrated by the high level of statistical heterogeneity identified. The results of heterogeneity tests for the by treatment comparison of RC versus non-RC were not reported, making it difficult to assess the reliability of these comparisons also. The authors stated that the findings must be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future trials should make direct comparisons of RC and non-RC patients randomised to monotherapies and, later, drug combinations for periods longer than the recurrence cycles found in untreated bipolar disorder. Symptomatic and functional status should be assessed as outcomes rather than recurrence rates.

Bibliographic details

PubMedID
12807371

Indexing Status
Subject indexing assigned by NLM

MeSH
Bipolar Disorder /classification /drug therapy; Humans; Long-Term Care /statistics & numerical data; Treatment Outcome

AccessionNumber
12003001377
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.