# TECHNICAL COMMENTARY

## Relapse

### Introduction

People with bipolar disorder may relapse with manic, mixed, or depressive episodes, regardless of what their previous episode involved. The chance of relapse is complicated by differential response to treatments and other factors associated with the disorder. Preventing the development of rapid cycling symptoms is particularly paramount to good outcomes.

### Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent or comprehensive review was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCT) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

### Results

We found eight reviews that met inclusion criteria[3-10].

- Moderate to high quality evidence suggests a medium-sized effect of more major life events occurring just prior to a mood episode than just prior to an euthymic phase. There were no differences in major life events between people with bipolar disorder prior to a mood episode and people with unipolar depression, physical illness, or schizophrenia.
- Moderate quality evidence suggests the risk of any subsequent mood episode after any first mood episode in people diagnosed with bipolar disorder is around 44% in the first year, reducing to around 20% in the second and third years. Adolescents show consistent rates over three years of around 20%. The median time to any subsequent mood episode after any first mood episode is around 1.5 years. Time is longer in people with bipolar I than bipolar II disorder, in adolescents than adults, in people tested in



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the euthymia than mood phase, and in people with ongoing subsyndromal symptoms.

- Moderate to low quality evidence suggests a small effect of greater risk of any subsequent mood episode after an index episode of depression rather than mania or mixed. The risk of a depressive subsequent mood episode was higher in people with bipolar II than bipolar I disorder. The polarity of the index episode predicted the polarity of the subsequent episode.
- Moderate quality evidence finds a small effect that children and adolescents with bipolar disorder were more likely to be readmitted to a psychiatric hospital than children and adolescents with other psychiatric disorders.
- For people with a first episode of mania, but not necessarily a diagnosis of bipolar disorder, moderate quality evidence suggests rates of relapse are around 26% at 6 months and up to 48% at 4 years. Older age at first episode was associated with lower relapse rates.
- For people with a first episode of mania or mixed symptoms, moderate to low quality evidence suggests rates of relapse are around 35% at 12 months up to 58% at 4 years.
- For pregnant women, moderate to low quality evidence suggests the median rate of mood episodes during pregnancy is around 24%, with most episodes being depressive.
- For women in the postpartum period, moderate to low quality evidence suggests mood relapse rates are around 37%, which is similar to psychotic relapse rates in women with a history of postpartum psychosis, however severe relapses are greater in women with a history of postpartum psychosis.
- Women taking prophylactic medications during pregnancy or during the postpartum period had a lower relapse rate than those who were medication free.
- Low quality evidence is unsure of the risk of relapse following discontinuation of mood stabilisers during pregnancy. Review authors conclude that for severe conditions of bipolar disorder, close monitoring, support and prophylactic medication during pregnancy and the postpartum period is recommended. For women with stable bipolar disorder, a well-planned and slow discontinuation of mood stabilisers before pregnancy could be commenced. For unplanned pregnancies, a slow discontinuation is particularly important. Medication should be re-started soon after delivery, as the risk of postpartum relapse is high.



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*Edgcomb JB, Sorter M, Lorberg B, Zima BT*

## Psychiatric Readmission of Children and Adolescents: A Systematic Review and Meta-analysis

**Psychiatric services 2020; 71: 269-79**

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| **Comparison** | **Rates of psychiatric readmissions in children and adolescents with bipolar disorder vs. other psychiatric disorders.** |
| **Summary of evidence** | **Moderate quality evidence (large sample, inconsistent, imprecise, direct) finds a small effect that children and adolescents with bipolar disorder were more likely to be readmitted than children and adolescents with other psychiatric disorders.** |
| **Psychiatric readmissions** | |
| *A small effect showed children and adolescents with bipolar disorder were more likely to be readmitted than children and adolescents with other psychiatric disorders;*<br>5 studies, N = 55,330, OR = 1.44, 95%CI 1.23 to 1.68, $I^2$ = 35% | |
| **Consistency in results‡** | Inconsistent |
| **Precision in results§** | Imprecise |
| **Directness of results‖** | Direct |

*Gignac A, McGirr A, Lam RW, Yatham LN*

## Recovery and recurrence following a first episode of mania: a systematic review and meta-analysis of prospectively characterized cohorts

**Journal of Clinical Psychiatry 2015; 76: 1241-8**

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| **Comparison** | **Relapse rates in people with bipolar disorder after a first-episode of mania.** |
| **Summary of evidence** | **Moderate quality evidence (medium sample sizes, inconsistent,** |

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| | **precise, direct) suggests rates of relapse after a first episode of mania are around 26% at 6 months and up to 48% at 4 years. Older age at first-episode was associated with lower relapse rates.** |
| **Relapse** | |
| 6 months: 4 studies, N = 374, relapse rate = 26%, 95%CI 16% to 38%, $I^2$ = 78%<br>1 year: 7 studies, N = 526, relapse rate = 41%, 95%CI 33% to 50%, $I^2$ = 69%<br>2 years: 2 studies, N = 226, relapse rate = 48%, 95%CI 42% to 55%, $I^2$ not reported<br>4 years: 3 studies, N = 159, relapse rate = 48%, 95%CI 44% to 52%, $I^2$ = 0%<br>Older age at first-episode was associated with lower relapse rates; 49% for 20-year olds, 40% for 25-year olds and 33% for 30 year-olds.<br>There were no associations with substance use or the presence of psychotic symptoms. | |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Precise |
| **Directness of results** | Direct |

*Kessing LV, Andersen PK, Vinberg M*

## Risk of recurrence after a single manic or mixed episode - a systematic review and meta-analysis

**Bipolar Disorders 2018; 20: 9-17**

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| **Comparison** | **Relapse rates in adults or children with bipolar disorder after a first-episode of mania or mixed episode.** |
| **Summary of evidence** | **Moderate to low quality evidence (small to medium sample sizes, precise, direct, unable to assess consistency) suggests rates of relapse in adults after a first episode of mania or mixed episode are around 35% at 12 months up to 58% at 4 years. Similar rates are observed in children with bipolar disorder, with 48% relapsing within 1 year, up to 65% at 5 years.** |
| **Relapse** | |
| In adults<br>1 year: 3 studies, N = 293, relapse rate = 35%, 95%CI 30% to 41%, $I^2$ not reported | |

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| 2 years: 1 study, N = 166, relapse rate = 59%, 95%CI not reported<br>4 years: 1 study, N = 24, relapse rate = 58%, 95%CI not reported<br>In children<br>1 year: 2 studies, N = 90, relapse rate = 48%, 95%CI 38% to 58%, $I^2$ not reported<br>2 years: 2 studies, N = 55, relapse rate = 46%, 95%CI 33% to 60%, $I^2$ not reported<br>5 years: 2 studies, N = 55, relapse rate = 65%, 95%CI 52% to 77%, $I^2$ not reported |

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| **Consistency in results** | Unable to assess; no measure of consistency is reported. |
| **Precision in results** | Precise |
| **Directness of results** | Direct |

*Larsen ER, Saric K*

**Pregnancy and bipolar disorder: the risk of recurrence when discontinuing treatment with mood stabilisers: a systematic review**

**Acta Neuropsychiatrica 2017; 29: 259-66**

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| **Comparison** | **Risk of relapse after discontinuation of mood stabilisers during pregnancy in women with bipolar disorders (I or II).** |
| **Summary of evidence** | **Low quality evidence (appears inconsistent, imprecise, small samples, direct) is unsure of the risk of relapse following discontinuation of mood stabilisers during pregnancy.**<br>**Review authors conclude that for severe conditions of bipolar disorder, close monitoring, support and prophylactic medication during pregnancy and the postpartum period is recommended. For women with stable bipolar disorder, a well-planned and slow discontinuation of mood stabilisers before pregnancy could be commenced. For unplanned pregnancies, a slow discontinuation is particularly important. Medication should be re-started soon after delivery, as the risk of postpartum relapse is high.** |

| **Risk of relapse** |
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| 1 study (N = 36) found a large, increased risk of relapse during pregnancy in previously stable women with bipolar disorder after rapid discontinuation of lamotrigine, lithium or divalproex (over 1-13 days), compared to pregnant women with bipolar disorder who continued on lamotrigine (OR = |

23.2, 95%CI 1.5 to 366, $p < 0.0001$). Note that the women who discontinued medication had more unplanned pregnancies than those continuing on medication (81.3% vs. 20%, $p = 0.005$).

1 study (N = 83) found increased risk of relapse during pregnancy and postpartum among women with bipolar disorder who discontinued medication (not specified) compared to those remaining on medication (76.9% vs. 45.2%, $p < 0.05$).

1 study (N = 89) found lower rates of relapse in women with bipolar disorder I or II who continued mood stabiliser treatment during pregnancy, than in women who discontinued mood stabilisers proximate to conception (37% vs. 85.5%; RR = 2.30, 95%CI 1.40 to 3.80, $p < 0.001$). In women who relapsed, the duration of illness was longer with discontinuation (43.3% vs. 8.8% of the pregnancy, $p < 0.001$), and the time to relapse was shorter (9 weeks vs. >40 weeks), particularly with abrupt discontinuation (discontinuation over 1-14 days = 2 weeks time to relapse). Note that unplanned pregnancies were associated with greater likelihood of rapid discontinuation (95.8% vs. 20.3% for planned pregnancies, $p < 0.0001$). The majority of first relapses were depressive or mixed episodes after discontinuing mood stabilisers (88.7% vs. 18.5% when treated). The use of antidepressants was also an independent risk factor for relapse.

1 study (N = 101) found no significant differences in relapse rates between pregnant women with bipolar disorder who discontinued lithium within 6 weeks of conception, and non-pregnant women with bipolar disorder who discontinued lithium due to mood stabilization or adverse events (52.4% vs. 57.6%, $p > 0.05$). However, after 40 weeks of discontinuation, relapse rates were significantly higher in the previously-pregnant group (70% vs. 24%, $p = 0.0002$). The time to relapse was significantly shorter after abruptly discontinuing lithium compared to gradually discontinuation (8 weeks vs. 20 weeks, $p = 0.006$). Women with more than 3 prior mood episodes had a greater risk of relapse after discontinuation than women with 1 to 3 prior mood episodes (66.1% vs. 38.5%, $p = 0.006$). Note that pregnant women discontinued lithium more rapidly than non-pregnant women (1-14 days vs. 15-30 days), and pregnant women more often had depressive/mixed-dysphoric episodes than non-pregnant women (63% vs. 38%, $p = 0.02$).

2 studies with no comparison groups (N = 61 and 41) reported women with typical, lithium responsive bipolar I disorder experience fewer abnormal moods during pregnancy, in terms of both frequency and duration of recurrence, if lithium is maintained.

1 study (N = 70) found lower rates of relapse in non-medicated woman with bipolar disorder who were not experiencing mood episodes during pregnancy, but who were at high risk for postpartum psychosis, than in women medicated with lithium who were experiencing mood episodes during pregnancy, and who were also at high risk for postpartum psychosis (0% vs. 60.0% during pregnancy; 13.8% vs. 27.7% post-pregnancy).

1 study (N = 37) of pregnant women with bipolar disorder II found lower rates of relapse in the non-medicated group than in the medicated group during pregnancy (65% vs. 40%), but higher rates of



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| relapse in the non-medicated group post-pregnancy (90% vs. 47%). | |
| **Consistency in results** | Appears inconsistent |
| **Precision in results** | Imprecise where CIs are reported |
| **Directness of results** | Direct |

*Lex C, Bazner E, Meyer TD*

**Does stress play a significant role in bipolar disorder? A meta-analysis**

**Journal of Affective Disorders 2017; 208: 298-308**

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| **Comparison 1** | **Prior major life events in people with bipolar disorder in a mood episode vs. people with bipolar disorder in the euthymic phase.**<br>**Life events were events that related to transitions in life (e.g., first job), significant life changes (e.g., birth of a child), and major individual experiences (e.g., death of spouse).** |
| **Summary of evidence** | **Moderate to high quality evidence (large sample, some inconsistency, precise, direct) suggests a medium-sized effect of more major life events occurring just prior to any mood episode than just prior to an euthymic phase.** |
| **Major life events** | |
| *Medium-sized effect of increased life events prior to any mood episode;*<br>9 studies, N ~800, $g$ = 0.51, 95%CI 0.26 to 0.76, $p < 0.01$, $I^2$ $p$ = 0.07<br>Publication year and quality of studies did not influence the results. | |
| **Consistency in results** | Some inconsistency |
| **Precision in results** | Precise |
| **Directness of results** | Direct |
| **Comparison 2** | **Prior major life events in people with bipolar disorder in a mood episode vs. controls.** |
| **Summary of evidence** | **Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a medium-sized effect of increased life events prior to a mood episode in people with bipolar disorder** |

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| | **compared to controls.** |
| **Major life events** | |
| *Medium-sized effect of increased life events prior to a mood episode;*<br>13 studies, N ~36,000, $g$ = 0.57, 95%CI 0.33 to 0.81, $p < 0.01$, $I^2$ $p < 0.001$<br>Publication year and quality of studies did not influence the results. | |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Precise |
| **Directness of results** | Direct |
| **Comparison 3** | **Prior major life events in people with bipolar disorder in a mood episode vs. people with schizophrenia.** |
| **Summary of evidence** | **Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests no differences in prior major life events between people with bipolar disorder in a mood episode and people with schizophrenia.** |
| **Major life events** | |
| *No significant differences between groups;*<br>7 studies, N ~800, $g$ = 0.19, 95%CI -0.13 to 0.50, $p$ = 0.24, $I^2$ $p$ = 0.01<br>Publication year and quality of studies did not influence the results. | |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Precise |
| **Directness of results** | Direct |
| **Comparison 4** | **Prior major life events in people with bipolar disorder in a mood episode vs. people with unipolar depression.** |
| **Summary of evidence** | **Moderate to high quality evidence (large sample, inconsistent or imprecise, direct) suggests no differences in prior major life events between people with bipolar disorder in a mood episode and people with unipolar depression. Childbirth in particular may be indicative of more prior life events in people with bipolar disorder.** |
| **Major life events** | |

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| *No significant differences between groups;*<br>18 studies, N = 4,493, *g* = 0.05, 95%CI -0.17 to 0.07, *p* = 0.39, $I^2$ *p* < 0.01<br>*Subgroup analysis of studies assessing mood episodes after childbirth found a medium-sized effect of increased life events prior to a mood episode in people with bipolar disorder;*<br>3 studies, N = 515, *g* = 0.47, 95%CI 0.02 to 1.87, *p* < 0.05, $I^2$ *p* = 0.09<br>Publication year and quality of studies did not influence the results. There were also no significant differences in the number of stressful events prior to onset of bipolar or unipolar depression. | |
| **Consistency in results** | Inconsistent, apart from the subgroup analysis. |
| **Precision in results** | Precise, apart from the subgroup analysis. |
| **Directness of results** | Direct |
| **Comparison 5** | **Prior major life events in people with bipolar disorder in a mood episode vs. people with a physical illness.** |
| **Summary of evidence** | **Moderate to low quality evidence (medium-sized sample, inconsistent, imprecise, direct) suggests no differences in prior major life events between people with bipolar disorder in a mood episode and people with a physical illness.** |
| **Major life events** | |
| *No significant differences between groups;*<br>4 studies, N = 291, *g* = 0.72, 95%CI -0.06 to 1.50, *p* = 0.07, $I^2$ *p* < 0.001<br>*Deleting one outlier increased the effect size, and decreased heterogeneity;*<br>3 studies, N = 267, *g* = 1.06, 95%CI 0.43 to 1.68, *p* = 0.07, $I^2$ *p* = 0.06 | |
| **Consistency in results** | Inconsistent, apart from the sensitivity analysis. |
| **Precision in results** | Imprecise |
| **Directness of results** | Direct |

*Radua J, Grunze H, Amann BL*

**Meta-Analysis of the Risk of Subsequent Mood Episodes in Bipolar Disorder**

**Psychotherapy & Psychosomatics 2017; 86: 90-8**

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| **Comparison 1** | **Rates of any subsequent mood episodes after a first mood episode in people with bipolar disorder, diagnosed at the first episode.** |
| **Summary of evidence** | **Moderate quality evidence (large sample, appears precise, direct, unable to assess consistency) suggests the risk of any subsequent mood episode after a first mood episode is around 44% in the first year, reducing to around 20% in the second and third year. Adolescents show consistent rates over three years of around 20%.** |
| **Risk of any subsequent mood episode** | |
| *Risk of any subsequent mood episode reduced from the first to second or third year in adults with bipolar disorder;*<br>4 studies, N = 4,149<br>Rates of any subsequent mood episode in the first year = 44%, 95%CI 42% to 46%<br>Rates of any subsequent mood episode in the second year = 19%, 95%CI 15% to 22%<br>Rates of any subsequent mood episode in the third year = 21%, 95%CI 15% to 26%<br><br>*Adolescent patients showed consistent rates of subsequent mood episode over time;*<br>2 studies, N = 4,312<br>Rates of any subsequent mood episode in the first year = 21%, 95%CI 14% to 27%<br>Rates of any subsequent mood episode in the second year = 24%, 95%CI 16% to 31%<br>Rates of any subsequent mood episode in the third year = 15%, 95%CI 7% to 22% | |
| **Consistency in results** | Unable to assess; no measure of heterogeneity is reported. |
| **Precision in results** | Appears precise |
| **Directness of results** | Direct |
| **Comparison 2** | **Time to any subsequent mood episodes after a first mood episode in people with bipolar disorder, diagnosed at the first episode.** |
| **Summary of evidence** | **Moderate quality evidence (large sample, appears precise, direct, unable to assess consistency) suggests the median time to any subsequent mood episode after a first mood episode is around 1.5 years.**<br>**Small effects show that time to any subsequent mood episode is longer in people with bipolar I than bipolar II disorder, in adolescents than adults, in people tested in the euthymia than mood phase, and in people with ongoing subsyndromal** |

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| | **symptoms.** |
| **Time to any subsequent mood episode** | |
| *Median time to subsequent mood episode after an index episode in adults with bipolar disorder;*<br>4 studies, N = 4,149, 1.44 years, 95%CI 1.32 to 1.78 years<br><br>*Small effect suggests time to subsequent mood episode was significantly longer in people with bipolar disorder I than in people with bipolar disorder II;*<br>4 studies, N = 3,936, 0.81 vs. 1.63 years, HR = 1.49, 95%CI 1.21 to 1.84, $p < 0.001$<br><br>*Small effect suggests time to subsequent mood episode was significantly longer in adolescents than in adults with bipolar disorder;*<br>2 studies, N = 4,312, 3.01 vs. 1.44 years, HR = 0.67, 95%CI 0.54 to 0.83, $p < 0.001$<br>This was observed when the analysis was restricted to people with bipolar disorder I, and in subgroup analyses of people recruited during a manic, mixed, or depressive episode.<br><br>*Small effect suggests time to subsequent mood episode was significantly longer in people recruited during euthymia rather than during an index episode;*<br>5 studies, N = 5,684, 2.76 vs. 1.44 years, HR = 0.63, 95%CI 0.58 to 0.70, $p < 0.001$<br>This was observed when the analysis was restricted to either bipolar disorder I or bipolar disorder II.<br><br>*Medium-sized effect suggests time to subsequent mood episode was significantly shorter in people with ongoing subsyndromal vs. no ongoing subsyndromal symptoms;*<br>4 studies, N = 986, 2.30 vs. 0.75 years, HR = 2.17, 95%CI 1.77 to 2.65, $p < 0.001$<br>This was observed when the analysis was restricted to patients recruited during an index episode or during euthymia, and in outpatients. | |
| **Consistency in results** | Unable to assess; no measure of heterogeneity is reported. |
| **Precision in results** | Appears precise |
| **Directness of results** | Direct |
| **Comparison 3** | **Type of subsequent mood episodes after a first mood episode in people with bipolar disorder, diagnosed at the first episode.** |
| **Summary of evidence** | **Moderate to low quality evidence (large sample, direct, appears imprecise, unable to assess consistency) suggests a small effect of greater increased risk of a subsequent mood episode after an index episode of depression rather than mania or mixed.** |

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| | **The polarity of the index episode predicted the polarity of the subsequent episode. The risk of a depressive subsequent mood episode was higher in people with bipolar II than bipolar I disorder.** |
| **Type of subsequent mood episode** | |
| 3 studies, N = 3,800<br>*Small effects suggest the risk of any subsequent mood episode was significantly higher after an index episode of depression rather than an index episode of manic or mixed;*<br>Depressive vs. manic: HR = 1.41, 95%CI 1.16 to 1.71, $p < 0.001$<br>Depressive vs. mixed: HR = 1.33, 95%CI 1.08 to 1.65, $p = 0.009$<br>No differences were found when the analysis was restricted to people with bipolar disorder I.<br><br>*Medium-sized effects suggest depressive index episodes were mostly followed by depressive episodes;*<br>Depressive vs. manic: HR = 2.45, 95%CI 1.50 to 4.03, $p < 0.001$<br>Depressive vs. mixed: HR = 2.40, 95%CI 1.44 to 4.00, $p < 0.001$).<br><br>*Small effect suggests manic index episodes were mostly followed by manic rather than mixed episodes;*<br>Manic vs. mixed: HR = 1.89, 95%CI 1.46 to 2.45, $p < 0.001$<br>No significant differences were reported between subsequent manic vs. depression episodes following an index manic episode.<br><br>*Large effects suggest mixed episodes were mostly followed by mixed episodes;*<br>Mixed vs. manic: HR = 4.26, 95%CI 3.23 to 5.63, $p < 0.001$<br>Mixed vs. depressive: HR = 5.14, 95%CI 1.27 to 20.85, $p = 0.022$<br><br>*Large effect suggests the risk of a depressive subsequent mood episode was significantly higher in people with bipolar disorder II than in people with bipolar disorder I;*<br>HR = 4.73, 95%CI 3.65 to 6.13, $p < 0.001$ | |
| **Consistency in results** | Unable to assess; no measure of heterogeneity |
| **Precision in results** | Appears mostly imprecise |
| **Directness of results** | Direct |

*Salim M, Sharma V, Anderson KK*

## Recurrence of bipolar disorder during pregnancy: a systematic review

**Archives of Women's Mental Health 2018; 21: 475-9**

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| **Comparison** | **Rates of mood episodes in pregnant women with bipolar disorder.** |
| **Summary of evidence** | **Moderate to low quality evidence (large sample, inconsistent, imprecise, direct) suggests the median rate of mood episodes (mostly depression) during pregnancy is around 24%, however the rates vary greatly between studies.** |
| **Mood episodes** | |
| 11 studies, N = 3,525, median prevalence = 24%, range = 4% to 73%, $I^2$ = 97%<br>The majority of episodes were depressive or mixed episodes. | |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Imprecise |
| **Directness of results** | Direct |

*Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJ, Kushner SA, Bergink V*

## Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A Systematic Review and Meta-Analysis

**American Journal of Psychiatry 2016; 173: 117-27**

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| **Comparison** | **Relapse rates postpartum in women with bipolar disorder vs. women with a history of postpartum psychosis.** |
| **Summary of evidence** | **Moderate to low quality evidence (large samples, inconsistent, imprecise, direct) suggests mood relapse rates are around 37%, which is not significantly different to psychotic relapse rates in women with a history of postpartum psychosis. Women taking prophylactic medications during pregnancy or over the postpartum period had a lower relapse rate than those who were** |

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| | **medication free. Severe relapses are greater in women with a history of postpartum psychosis.** |
| **Relapse to mood or psychosis** | |
| *There were no significant differences in relapse rates;*<br>Bipolar disorder: 25 studies, N = 5,105, relapse risk = 37%, 95%CI 29% to 45%, $I^2$ = 95%<br>Postpartum psychosis: 14 studies, N = 595, relapse risk = 31%, 95%CI 22% to 42%, $I^2$ = 78%<br>Subgroup analysis revealed the risk of severe postpartum episode was greater in women with a history of postpartum psychosis than in women with bipolar disorder.<br>Women with bipolar disorder using prophylactic medications during pregnancy or postpartum had a lower relapse rate than those who were medication free.<br>There were no differences in relapse rates between people with bipolar disorder I or II. | |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Imprecise |
| **Directness of results** | Direct |

## Explanation of acronyms

CI = confidence interval, Hedges' *g* = standardised mean differences, HR = hazard ratio, $I^2$ = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus

## Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[11].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[11].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[12]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. $I^2$ is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. $I^2$ can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[11];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[13].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.



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