TECHNICAL COMMENTARY

Treatments during pregnancy and breastfeeding

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Introduction

Medication use during pregnancy requires careful consideration of the mother's risk of illness relapse, against the risk of harm or complications for the developing infant if medication is to be continued. However, there is currently very little evidence regarding the use of medications for bipolar disorder during pregnancy and the postpartum period.

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 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 and/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, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked 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 (RCTs) 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are 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 four systematic reviews that met inclusion criteria[3-6]. Most of these reviews included people with bipolar disorder as well as other psychiatric disorders.

- Moderate to low quality evidence suggests a small increased risk of heart defect or lower birth weight in infants exposed to antipsychotics in utero, and a small increased risk of preterm delivery. Review authors report that the studies did not routinely adjust for potential confounding factors, such as other medications.
- Moderate to low quality evidence suggests small effects of increased risk of neuromotor deficits in early childhood with exposure to antipsychotics in utero. Again, studies did not allow correction for other medications, genetic predisposition or parental psychiatric illness.
- Moderate to low quality evidence suggests no differences in the odds of autism

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spectrum disorders in the offspring of mothers with SSRI antidepressant exposure during pregnancy compared with mothers with no antidepressant exposure during pregnancy.

- 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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Coughlin CG, Blackwell KA, Bartley C, Hay M, Yonkers KA, Bloch MH

Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy

Obstetrics and gynecology 2015; 125: 1224-35

View review abstract online

Comparison	**Adverse effects of antipsychotic use during pregnancy vs. no antipsychotic use during pregnancy.** **This review included women taking antipsychotics regardless of disorder.**
Summary of evidence	**Moderate to low quality evidence (consistent, large samples, indirect, imprecise, possible confounding factors) suggests a small increased risk of heart defect or lower birth weight in infants, and a small increased risk of preterm delivery, but not stillbirth, with exposure to antipsychotics (first or second generation).** **Low quality evidence (inconsistent, imprecise, indirect, possible confounding factors) is unsure about risk of termination or spontaneous abortion, and size and malformation in infants with exposure to antipsychotics.** **Authors report that the studies did not routinely adjust for potential confounding factors, such as other medications.**
Prenatal factors	
Elective termination *A large, significant effect of increased risk of elective termination in women on antipsychotics;* 4 cohort studies, N = 3,788, OR = 5.98, 95%CI 2.94 to 12.14, $p < 0.001$, $I^2 = 73\%$, $p = 0.01$ Spontaneous abortion *No significant difference between groups;* 4 cohort studies, N = 3,788, OR = 1.05, 95%CI 0.61 to 1.81, $p = 0.86$, $I^2 = 70\%$, $p = 0.02$	
Perinatal factors	
Preterm delivery *A small, significant effect of increased risk of preterm delivery in women on antipsychotics;* 7 cohort studies, N = 1,534,350, OR = 1.86, 95%CI 1.45 to 2.39, $p < 0.00001$, $I^2 = 46\%$, $p = 0.08$ Stillbirth	

No significant differences between groups; 3 cohort studies, N = 1,018,795, OR = 1.18, 95%CI 0.88 to 1.57, $p = 0.27$, $I^2 = 0\%$, $p = 0.47$
Postnatal factors
Small for gestational age at birth *A small, significant effect of increased risk of being small for gestational age at birth in infants exposed to antipsychotics;* 4 cohort studies, N = 1,578,906, OR = 2.44, 95%CI 1.22 to 4.86, $p = 0.01$, $I^2 = 81\%$, $p = 0.001$ Large for gestational age at birth; *No significant differences between groups;* 4 cohort studies, N = 1,578,906, OR = 2.50, 95%CI 0.77 to 8.16, $p = 0.13$, $I^2 = 91\%$, $p < 0.001$ Low birth weight *A small, significant effect of lower birth weight in infants exposed to antipsychotics;* 3 cohort studies, N = 358,677, WMD = -0.57.89g, 95%CI -103.69 to -12.10g, $p = 0.01$, $I^2 = 0\%$, $p = 0.37$ Any malformation *A small, significant increased risk of any major malformation in infants exposed to antipsychotics;* 7 cohort studies, N = 1,640,660, OR = 2.12, 95%CI 1.25 to 3.57, $p = 0.005$, $I^2 = 84\%$, $p < 0.001$ Meta-regression showed a significant association between better study quality and larger effect sizes. Heart defect *A small, significant increased risk of any heart defect in infants exposed to antipsychotics;* 4 cohort studies, N = 1,628,021, OR = 2.09, 95%CI 1.50 to 2.91, $p < 0.001$, $I^2 = 0\%$, $p = 0.48$ Authors report no differences in results when comparing first to second generation antipsychotics.

Consistency in results‡	Consistent for heart defect, low birth weight, stillbirth, and preterm delivery. Inconsistent for elective termination, spontaneous abortion, gestational age, and any malformation.
Precision in results§	Imprecise
Directness of results‖	Indirect for bipolar disorder (mixed psychiatric samples).

Kobayashi T, Matsuyama T, Takeuchi M, Ito S

Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis

Reproductive Toxicology 2016; 65: 170-8 View review abstract online	
Comparison	**Relationship between selective serotonin reuptake inhibitor (SSRI) use during pregnancy and risk of autism spectrum disorders in the offspring.** **This review included women taking SSRIs regardless of disorder.**
Summary of evidence	**Moderate to low quality evidence (consistent, large sample, indirect, imprecise) suggests no differences in the odds of autism spectrum disorders in the offspring of mothers with a psychiatric disorder (including bipolar disorder) and SSRI exposure during pregnancy vs. mothers with no antidepressant exposure during pregnancy.**
Autism spectrum disorders	
A significant, very small effect of increased odds of autism spectrum disorders in the offspring of mothers with any SSRI exposure during pregnancy vs. mothers with no antidepressant exposure during pregnancy; 8 studies, N = 988,245, OR = 1.45, 95%CI 1.15 to1.82, $p < 0.05$, $I^2 = 31\%$, $p = 0.19$ Study design (case-control vs. cohort) did not moderate this effect.	
Subgroup analysis showed no differences in the odds of autism spectrum disorders in the offspring of mothers with a psychiatric disorder (including bipolar disorder) and SSRI exposure during pregnancy vs. mothers with no antidepressant exposure during pregnancy; 3 studies, OR = 0.96, 95%CI 0.57 to 1.63, $p > 0.05$, $I^2 = 35\%$, $p = 0.22$	
Subgroup analysis showed no differences in the odds of autism spectrum disorders in the offspring of mothers with SSRI exposure during pregnancy vs. mothers with other antidepressant exposure during pregnancy; 3 studies, N = 703,799, OR = 1.14, 95%CI 0.67 to 1.96, $p > 0.05$, $I^2 = 0\%$, $p = 0.74$	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Indirect for bipolar disorder (mixed psychiatric and subclinical samples).

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

Acta Neuropsychiatrica 2017; 29: 259-66

View review abstract online

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.** **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

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 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

Poels EMP, Schrijver L, Kamperman AM, Hillegers MHJ, Hoogendijk WJG, Kushner SA, Roza SJ

Long-term neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics: a systematic review and meta-analysis

European Child and Adolescent Psychiatry 2018; 1-22

View review abstract online

Comparison	**Adverse effects of mood stabilisers or antipsychotics during pregnancy on child development.** **Note that the samples included people with various disorders.**
Summary of evidence	**Moderate to low quality evidence (large sample, consistent, imprecise, indirect) suggests small effects of increased risk of neuromotor deficits in childhood with exposure to antipsychotics in utero. However, there is a lack of high-quality studies, as studies did not allow correction for genetic predisposition or parental psychiatric illness.** **Low quality evidence (small samples) is unable to determine the effects of exposure to lithium in utero and child development outcomes.**
Neuromotor outcomes	
Small effect of increased neuromotor deficits with exposure to antipsychotics in utero; 2-24 month follow-up: 3 studies, N = 32,624, RR = 1.97, 95%CI 1.47 to 2.62, $p < 0.001$, $I^2 = 0\%$	
Other child development outcomes	
3 cohort studies assessed the long-term effects (up to 15 years) of lithium use during pregnancy. 2 studies (N = 139+) reported no differences in child developmental outcomes between those exposed to lithium and those not exposed to lithium. 1 study (N = 15) reported 1 child showed low IQ, 2 showed subclinical anxiety problems, and 1 showed subclinical oppositional behaviour.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Indirect for neuromotor outcomes (mixed samples). Direct for lithium.

Explanation of acronyms

CI = confidence interval, 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), RR = relative risk, vs. = versus

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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[7].

† 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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[7].

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[8]. 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 can provide an

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indirect 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) which 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[7];

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

§ 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[9].

‖ 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 which 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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