

What is the role of mood stabilisers in the management of bipolar mood disorder in pregnancy?

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SUMMARY STATEMENT:

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REQUEST:

What is the role of mood stabilisers in the management of bipolar mood disorder in pregnancy?

REQUESTED BY:

Dr. Spiri Katsenos, Senior Psychiatric Registrar, Department of Psychiatry, MMC, Clayton

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defined the 'best available evidence' as that research we can identify that is least susceptible to bias.

First we search for systematic reviews, evidence-based clinical practice guidelines, or health technology assessments. Then we identify diagnostic studies with independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalizable, or have other methodologic difficulties. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Some studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request:

Patient/condition: Pregnant women with bipolar mood disorder
Intervention: Lithium or sodium valproate
Comparisons: Placebo, all other treatments.
Outcome: Clinical outcomes, foetal development, adverse events

Search terms:

The following search terms were used to scour electronic databases and websites:

Table 1. Search terms used in the retrieval of articles from electronic databases and websites

| Field of focus | Search term |
|----------------------|--|
| Condition-related | Bipolar Disorder, bipolar mood disorder, depressive disorder, depression postpartum, postnatal depression, antenatal depression, maternal distress, maternal depression, pregnancy complications/psychiatry, manic depression. |
| Intervention-related | Lithium, Sodium valproate, valproic acid |
| Outcome-related | Fetal/fetus/foetal development, side effects, clinical outcome, adverse events, treatment outcomes |
| Other | Management, patient care management, case management, |

Resources Searched

We searched the following databases and Internet websites:

Cochrane Library CD-ROM- Issue 1, 2001

Medline (OVID)- 1966 to February 2001

Best Evidence (OVID)- 1991 to January/February 2001

CINAHL (OVID) – 1982 to March 2001

PreMedline (OVID)- April 2, 2001

PsycINFO (OVID)- 1984 to April week 3 2001

Refinements, Searching & Reporting Constraints:

We included items of evidence that were available to us on 27 April 2001. Having identified a systematic review of Psychotropic medications in pregnant women from the Cochrane database (Issue 1, 2001), a restriction period of 2000-2001 was applied while searching the other databases. The search was restricted to humans, females, and articles published in English.

RESULTS:

From our sources we identified 5 articles related to the request that were categorised as follows:

Table 2. Study designs of articles retrieved by search

| Study Design | Number included |
|---|-----------------|
| Systematic reviews or meta-analyses | 4 |
| Evidence-based clinical practice guidelines | 0 |
| Randomised controlled trials | 0 |
| Controlled trials, cohort or case-control analytic studies | 1 |
| Case series, consensus reports, Narrative reviews | Excluded |

Articles were excluded from further appraisal as follows:

Table 1: Reasons for exclusion of articles retrieved by search

| Reason for exclusion | Number |
|--|--------|
| Systematic review (protocol only - review is in progress) | 1 |
| Review addressing bipolar depression in general and not specific to pregnant women | 2 |
| Retrospective study-examined the protective effect of pregnancy | 1 |

This left only one systematic review for appraisal. We have critically appraised the systematic review. We are reasonably confident this article represents the most important findings published to date based on our refinements, searching and reporting constraints.

EVIDENCE SUMMARIES

Format

Evidence summaries are in the form of spreadsheets reproduced at the end of this report. Each spreadsheet contains the article citation, the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

REFERENCES

ARTICLES CRITICALLY APPRAISED FOR THIS REPORT

1. Austin M P, Mitchell P B (1998). Psychotropic medications in pregnant women: treatment dilemmas. Medical Journal of Australia, **169**(8), 428-431.

ARTICLES NOT CRITICALLY APPRAISED

Protocol only - review in progress

1. Hoffbrand S, Howard L, Crawley H. Antidepressant drug treatment for postnatal depression (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 1, 2001. Oxford: Update Software. Date of most recent substantive amendment: 22 February 2000 Review expected to be published in: Issue 2, 2000

Review not specific to pregnant women

1. Sachs, G. S., C. L. Koslow, et al. (2000). "The treatment of bipolar depression." Bipolar Disorders **2**(3): 256-260.

2. Schou, M. (1999). "Perspectives on lithium treatment of bipolar disorder: action, efficacy, effect on suicidal behavior." Bipolar Disorders **1**(1): 5-9.

Retrospective study-examined the protective effect of pregnancy

1. Grof, P., W. Robbins, et al. (2000). "Protective effect of pregnancy in women with lithium-responsive bipolar disorder." Journal of Affective Disorders **61**(1-2): 31-9.

APPENDIX

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Levels of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

| | |
|-------------|--|
| Level I | Evidence obtained from a systematic review of all relevant randomised controlled trials. |
| Level II | Evidence obtained from at least one properly designed randomised controlled trial. |
| Level III-1 | Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method). |
| Level III-2 | Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case control studies, or interrupted time series with a control group. |
| Level III-3 | Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group. |
| Level IV | Evidence obtained from case series, either post-test or pre-test/post-test. |

| | |
|---|--|
| <h2>Evidence Summary</h2> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>Mood stabilisers in the management of bipolar mood disorder in pregnancy</p> </div> | <p>Study 1</p> <p>Marie-Paule V Austin and Philip B Mitchell (1998). Psychotropic medications in pregnant women: treatment dilemmas. Med J Australia 169: 428-431</p> |
| <p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p> | <p>Systematic Review (Level I)</p> |
| <p>DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p> | <p>Patients: Infants and their mothers who had been exposed to psychotropic medications during pregnancy. These mothers were treated for medical conditions including depression during pregnancy. Intervention: Treatment (psychotropic medications including lithium and sodium valproate). Comparison: Varied across studies (see full article). Outcomes: Congenital anomalies, perinatal complications and neurobehavioural sequelae. Inclusion criteria: All studies focusing on adverse effects associated with psychotropic drug use during pregnancy. Prospective controlled studies, retrospective studies and case studies were included.</p> |
| <p>VALIDITY: Methodology, rigour, selection, opportunity for bias</p> | <p>Search strategy: MEDLINE and EMBASE (1976-1998) using medical subject headings, and bibliographies of retrieved articles. Search was confined to English articles only. Assessed validity: No. Consistent results: No. Potential for bias: Literature search was limited to two databases. Did not search for unpublished materials</p> |
| <p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p> | <p>23 studies were identified (9 were prospective non randomised): five of these involved antidepressants (tricyclic antidepressants [TCAs] and selective serotonin reuptake inhibitors [SSRIs]), one each involving lithium and carbamazepine, and two involving benzodiazepines.</p> <ul style="list-style-type: none"> • Lithium: Conflicting results. The two studies with pooled data and one prospective study reported significantly increased rates of cardiovascular malformations. One cohort study (60 children) found no significant difference in congenital anomalies compared with non-exposed siblings and the other cohort found no difference in developmental milestones compared to a matched control group. • Sodium valproate: The observational study found an incidence of spina bifida in 1% to 5% of exposed infants. The case series mentioned withdrawal seizures in exposed infants. • Fluoxetine: One prospective study that controlled for maternal age and past obstetric history reported no increase in rates of major anomalies and obstetric complications in women taking fluoxetine compared to two control groups (women with depression on TCA and non-exposed, not depressed women). Groups with depression had increased rates of miscarriage and neonatal complications and a number of minor physical anomalies. The other prospective study found no increase in miscarriage or major anomalies but found a significant increase among those exposed in infants with three or more anomalies. The two non-controlled studies reported conflicting results. One study reported no increase in neurodevelopmental deficits or developmental delays compared with non-exposed children at aged four years. • Tricyclics: The review that pooled results from 338 women reported no increased risk of major structural anomalies with first-trimester exposure. "Findings from the 2 prospective studies were identical to those reported for fluoxetine". Case reports mentioned neonatal TCA withdrawals syndromes and anticholinergic effects. One study reported no increase in neurodevelopmental deficits or developmental delays compared with non-exposed children. • Other antidepressants: MAOIs (one study): higher rate of congenital anomalies in exposed infants. Mianserin (one cohort of 48 infants): one case of congenital anomaly. No studies on moclobemide, venlafaxine, or nefazodone were identified. • Benzodiazepines: Results were conflicting. One review based on birth registry data of several hundred women found the relative risk for cleft palate and lip to be approximately 2 to 3 fold with diazepam and 7-fold with alprazolam. One prospective study (137 women) found no increase in congenital anomalies after first trimester exposure to benzodiazepines (drug not specified) but an |

| | |
|---|---|
| | <p>approximately two-fold increase in miscarriage. One prospective study (17 infants) reported developmental delays at 18 months. One review (550 infants followed up for a maximum of four years): found no increase in neurobehavioural sequelae.</p> <ul style="list-style-type: none"> • Carbamazepine: Conflicting results. The observational study found an incidence of spina bifida in 0.5% to 1% of infants exposed in the first trimester. The prospective study found no developmental delays or cognitive impairment in exposed infants. • Chlorpromazine: Inconsistent results. The review found that low dose in first trimester may increase congenital anomalies by 0.4%. The follow-up study found no increase in abnormalities in exposed infants. Case reports of chlorpromazine and other typical antipsychotics in the third trimester mentioned neonatal restlessness, tremor, poor suckling, abnormal movements, jaundice and functional bowel obstruction. • Trifluoperazine (one review): no increase in congenital anomalies. • Haloperidol (two small retrospective studies): no increase in congenital anomalies. |
| <p>AUTHORS COMMENTS: Risk/benefit, limitations</p> | <p>"While some psychotropes are associated with congenital anomalies and perinatal complications, mental illness <i>per se</i> may also be associated with an adverse outcome in the infant. Clearly, the risks to both mother and infant need to be carefully weighed and discussed with the parents."</p> |
| <p>REVIEWER'S COMMENTS: Risk/benefit, methodology, conclusions</p> | <p>Strengths</p> <ul style="list-style-type: none"> • The research aims were stated and outcomes were clear. • Clear and broad inclusion criteria. • Reported search strategy • A systematic review of the available evidence <p>Weaknesses</p> <ul style="list-style-type: none"> • Search was limited to English language • Only Medline and EMBASE databases were searched. Unpublished materials were not identified (possible publication bias). • How the papers were selected for review was not clarified • Validity of the included studies was not assessed • Not clear how data were extracted for review • Not clear how the differences between the studies were investigated |