Bipolar disorder

The *EBMH* Notebook summarises key messages about bipolar disorder, sourced from: *Clin Evid Concise* 2003;**10**:208–9. For this review, *Clinical Evidence Concise* searched and appraised material published until April 2002.

Definition

Bipolar disorder (bipolar affective disorder, manic depressive disorder) is characterised by marked mood swings between mania (mood elevation) and bipolar depression that cause significant personal distress or social dysfunction, and are not caused by drugs or known physical disorder. **Bipolar type I disorder** is diagnosed when episodes of depression are interspersed with mania or mixed episodes. **Bipolar type II disorder** is diagnosed when depression is interspersed with less severe episodes of elevated mood that do not lead to dysfunction or disability (hypomania). Bipolar disorder has been subdivided in several further ways.[1]

Incidence/prevalence

One 1996 cross-national community based study (38 000 people) found lifetime prevalence rates of bipolar disorder ranging from 0.3% in Taiwan to 1.5% in New Zealand.[2] It found that men and women were at similar risk, and that the age at first onset ranged from 19–29 years (average of 6 years earlier than first onset of major depression).

Aetiology/risk factors

The cause of bipolar disorder is uncertain, although family and twin studies suggest a genetic basis.[3] The lifetime risk of bipolar disorder is increased in first degree relatives of a person with bipolar disorder (40–70% for a monozygotic twin; 5–10% for other first degree relatives). If the first episode of mania occurs in an older adult, it may be secondary mania due to underlying medical or substance induced factors.[4]

Prognosis

Bipolar disorder is a recurring illness and is one of the leading causes of worldwide disability, especially in the 15–44 year age group.[5] One 4 year inception cohort study (173 people treated for a first episode of mania or mixed affective disorder) found that 93% of people no longer met criteria for mania at 2 years (median time to recover from a syndrome 4.6 weeks), but that only 36% had recovered to premorbid function.[6] It found that 40% of people had a recurrent manic (20%) or depressive (20%) episode within 2 years of recovering from the first episode. A meta-analysis, comparing observed suicide versus expected rates of suicide in an age and sex matched sample of the general population, found that the lifetime prevalence of suicide was about 2%, or 15 times greater than expected, in people with bipolar disorder.[7]

What are the effects of treatments in mania?

BENEFICIAL

Lithium

One RCT in people with bipolar type I disorder experiencing a manic episode found that lithium increased the proportion of people who responded after 3–4 weeks compared with placebo. One systematic review found that lithium increased the proportion of people who had remission of manic symptoms at 3 weeks compared with chlorpromazine, and found no significant difference in symptoms at 3–6 weeks between lithium and haloperidol, olanzapine, valproate, lamotrigine, or clonazepam. One RCT found that lithium was less effective than risperidone in reducing manic symptoms at 4 weeks. Lithium can cause a range of adverse effects. The RCTs provided insufficient evidence about how the adverse effects of lithium compared with those of other antipsychotic drugs.

Olanzapine

One systematic review in people with bipolar type I disorder found that olanzapine increased the proportion of people who responded at 3–6 weeks compared with placebo, both as monotherapy and as add on therapy to lithium or valproate, and found no significant difference in symptoms at 28 days between olanzapine and lithium. RCTs found that olanzapine was more effective in reducing symptoms than valproate, but was also more likely to cause adverse effects such as sedation and weight gain. The acceptability of olanzapine may be limited by weight gain.

Valproate

One systematic review in people with bipolar type I disorder experiencing a manic episode found that valproate increased the proportion of people who responded over 3 weeks compared with placebo. It found no significant difference in response at 1–6 weeks between valproate and lithium, haloperidol, or carbamazepine. It found that valproate was less effective in reducing manic symptoms than olanzapine, but was also less likely to cause adverse effects such as sedation and weight gain.

LIKELY TO BE BENEFICIAL

Carbamazepine

RCTs in people with bipolar type I disorder experiencing a manic episode found no significant difference in manic symptoms at 4–6 weeks between carbamazepine and lithium or valproate.

Clonazepam

We found no RCTs comparing clonazepam versus placebo in people with bipolar mania. RCTs in people with bipolar type I disorder experiencing a manic episode suggest that clonazepam may be as effective as lithium in improving manic symptoms at 1–4 weeks.

Haloperidol

We found no RCTs comparing haloperidol versus placebo in people with bipolar mania. RCTs in people with bipolar type I disorder experiencing a manic episode found no significant difference in manic symptoms at 1–3 weeks between haloperidol and lithium or valproate, although haloperidol was associated with more extrapyramidal adverse effects and sedation than valproate.

Risperidone

We found no RCTs comparing risperidone versus placebo in people with bipolar mania. One RCT in people with bipolar type I disorder experiencing a manic episode found that risperidone reduced manic symptoms at 4 weeks compared with lithium. It gave no information on adverse effects.

UNKNOWN EFFECTIVENESS

Chlorpromazine

One very small RCT in people with mania found limited evidence that chlorpromazine may improve manic symptoms over 7 weeks more than placebo or imipramine. One systematic

review found that fewer people had remission of symptoms at 3 weeks with chlorpromazine than with lithium.

Lamotrigine
We found no RCTs comparing lamotrigine versus placebo in people with bipolar mania. One RCT in people with bipolar type I disorder experiencing a manic episode found no significant difference in manic symptoms at 4 weeks between lamotrigine and lithium.

What are the effects of treatments in bipolar depression?

LIKELY TO BE BENEFICIAL

Lamotrigine
One RCT in people with bipolar type I disorder experiencing a major depressive episode found that lamotrigine increased the proportion of people who responded over 7 weeks compared with placebo.

TRADE OFF BETWEEN BENEFITS AND HARMS

Antidepressants
Systematic reviews found that antidepressants improved depressive symptoms at the end of the trial (unspecified) compared with placebo. They found limited evidence that selective serotonin reuptake inhibitors were more effective than tricyclic antidepressants, and found no significant difference in symptoms between monoamine oxidase inhibitors and tricyclic antidepressants or between selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors. The reviews provided insufficient evidence to assess whether antidepressants induce bipolar mania.

UNKNOWN EFFECTIVENESS

Carbamazepine; lithium
One systematic review identified no RCTs of sufficient quality to assess these treatments in people with bipolar depression.

Psychological treatments; valproate
We found no RCTs of these treatments in people with bipolar depression.

What are the effects of interventions to prevent relapse of mania or bipolar depression?

BENEFICIAL

Lithium
RCTs have found that lithium reduces relapse over 2 years compared with placebo, and have found no significant difference in relapse between lithium and valproate, carbamazepine or lamotrigine.

LIKELY TO BE BENEFICIAL

Carbamazepine
We found no RCTs comparing carbamazepine versus placebo in preventing relapse. One systematic review found no significant difference between carbamazepine and lithium in the proportion of people who relapsed over 1–3 years.

Education to recognise symptoms of relapse
One RCT found limited evidence that an educational programme to recognise symptoms of relapse reduced manic relapse over 18 months, but that it may increase depressive episodes.

Lamotrigine (bipolar depressive episodes)
Three RCTs have found that lamotrigine reduces relapse compared with placebo. However, secondary analyses in two of the RCT suggested that lamotrigine protected against depressive relapse, but not manic relapse. RCTs have found no significant difference between lamotrigine and lithium in the proportion of people who relapse.

Valproate
One RCT found that valproate reduced relapse over 12 months compared with placebo. One systematic review found no significant difference between lithium and valproate in relapse over 12 months.

UNKNOWN EFFECTIVENESS

Antidepressant drugs
One systematic review provided insufficient evidence to assess antidepressants in preventing relapse of bipolar disorder.

Family focused psychoeducation
One RCT found that 21 sessions of family focused psychoeducation reduced relapse over 12 months compared with two family sessions plus crisis management.

JOHN GEDDES, MD
Department of Psychiatry
University of Oxford, UK

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4 Tohen M, Shulman KI, Satlin A. First-episode mania in late life. *Am J Psychiatry* 1994;**151**:130–2.
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