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Meta-analysis in bipolar depression

Bipolar disorder CHAPTER 2 Bipolar depression Bipolar depression shares the diagnostic criteria for an episode of major depressive disorder, but episodes may differ in severity, time course, liability to recurrence and response to drug treatment. Episodes of bipolar depression are, compared with unipolar depression, more rapid in onset, more frequent, more severe, shorter and more likely to involve delusions and reverse neuro-vegetative symptoms such as hyperphagia and hypersomnia.1–3 Around 15% of people with bipolar disorder commit suicide,4 a statistic that reflects the severity and frequency of depressive episodes. Bipolar depression affords greater socioeconomic burden than either mania or unipolar major depression5 and comprises the majority of symptomatic illness in bipolar affective disorder with respect to time.6,7 In the UK, NICE recommends the combination of fluoxetine with olanzapine or quetiapine on its own (assuming an antipsychotic is not already prescribed).8 Lamotrigine is considered to be second-line treatment. BAP guidelines9 have lamotrigine as a first- line option, albeit with the caveat that a mood stabiliser or antipsychotic will be needed to protect against mania in the longer term. Lurasidone is also a first-line option in the BAP guidelines. The 2020 RANZCP guidelines10 recommend the use of lithium, lamotrigine, valproate, quetiapine, lurasidone and cariprazine either as individual agents or in combinations of two or three different drugs (including the addition of an antidepressant). Olanzapine and carbamazepine are considered second-line drugs. Similar recommendations are made in the more recent (2023) Canadian guidelines.11 Differences include the relegation of valproate to a second-line treatment and the inclusion of lumateperone (also as a second- line drug). Lurasidone is suggested as a first-line agent but only as an adjunct. Olanzapine plus fluoxetine is second line but olanzapine itself is demoted to third-line use. Tables 2.9, 2.10 and 2.11 give some broad guidance on treatment options in bipolar depression. Meta-analysis in bipolar depression Meta-analytical studies in bipolar depression are constrained by the variety of methods used to assess efficacy. This means that many scientifically robust studies cannot be included in some meta-analyses because their parameters (outcomes, duration, etc.) are not shared with other studies and so cannot be compared with them. Early lithium studies are an important example – their short duration and cross-over design preclude their inclusion in meta-analysis. BAP guidelines are somewhat dismissive (perhaps correctly) of network meta-analyses because outcome is heavily

influenced by inclusion criteria and because findings often contradict direct comparisons.9 A 2021 network meta-analysis of 18 RCTs found that, looking only at antipsychotic drugs, lurasidone, quetiapine, olanzapine and cariprazine were all effective, with cariprazine having the smallest effect size.12 A more recent (2024) review13 of 16 RCTs of FDA-licensed antipsychotics added lumateperone to the list of robustly effective agents. Olanzapine showed the lowest rate of withdrawals from trials and quetiapine was the least well tolerated. The largest network meta--analysis (101 RCTs) was published in 2023.14 In this, olanzapine plus fluoxetine was the most effective, followed in order by quetiapine, olanzapine alone, lurasidone, lumateperone, cariprazine and lamotrigine (the least effective). Recent meta-analyses of ketamine and esketamine15,16 have concluded that ketamine formulations are probably effective in bipolar depression but with a low certainty of evidence.

320 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Table 2.9 Established treatments (listed in alphabetical order). Drug/regimen Comments Lamotrigine1,17–21 Lamotrigine appears to be effective both as a treatment for bipolar depression and as prophylaxis against further episodes. It does not induce switching or rapid cycling. It is as effective as citalopram and causes less weight gain than lithium. Overall, the effect of lamotrigine is difficult to be clear about, with numerous equivocal trials22 that perhaps failed to allow for the time taken for full titration of the drug. It may be useful as an adjunct to lithium23 or as an alternative to it in pregnancy.24 A later trial25 suggested robust efficacy when combined with quetiapine. There is a small anti-manic effect of lamotrigine.26 Treatment is somewhat complicated by the small risk of rash, which is associated with speed of dose titration. The necessity for titration may limit clinical utility. A further complication is the question of dose: 50mg/day has efficacy, but 200mg/day is probably better. In the USA, doses of up to 1200mg/day have been used (mean around 250mg/day). Plasma concentrations (only the range for anti-convulsant effects is known) may guide the need for higher doses. Lithium1,17,27–29 Lithium is probably effective in treating bipolar depression but supporting data are methodologically questionable.30 There is some evidence that lithium prevents depressive relapse but its effects on manic relapse are considered more robust. There is fairly strong support for lithium in reducing suicidality in bipolar disorder.31,32 Lurasidone Three RCTs show a good effect for lurasidone either alone33 or as an adjunct to mood stabilisers.34,35 A further RCT reported good outcome in bipolar depression with sub- syndromal hypomanic symptoms.36 Pooled analysis suggests response is dose-related.37 A network meta-analysis suggested lurasidone is more effective than aripiprazole and ziprasidone but not quetiapine or olanzapine.38 Mood stabiliser + antidepressant39–45 Antidepressants are still widely used in bipolar depression, particularly for breakthrough episodes occurring in those on mood stabilisers. They have been assumed to be effective, although there is a risk of cycle acceleration and/or switching. Studies suggest mood stabilisers alone are just as effective as mood stabilisers/antidepressant combination although subanalysis suggested higher doses of antidepressants may be effective.46–48 Tricyclics and MAOIs are usually best avoided. SSRIs are generally recommended if an antidepressant is to be prescribed. Venlafaxine and bupropion (amfebutamone) have also been used. Venlafaxine may be more likely to induce a switch to mania.49,50 Continuing antidepressant treatment after resolution of symptoms may protect against depressive relapse51,52 although only in the absence of a mood stabiliser.53 At the time of writing, there is no consensus on whether or not to continue antidepressants long term.54 The most recent findings suggest that switch rates are no higher with sertraline alone than with lithium + sertraline,55 but also that there may be no protective effect against depressive episodes.56

Some guidelines recommend the use of antidepressants in bipolar II depression57 and there is evidence that sertraline does not increase switch rates in these patients.55 Olanzapine ± fluoxetine17,30,58–61 This combination (Symbyax®) is more effective than both placebo and olanzapine alone in treating bipolar depression. The dose is 6 and 25mg or 12 and 50mg/day (so presumably 5/20mg and 10/40mg are effective). It may be more effective than lamotrigine. There is reasonable evidence of prophylactic effect. It is recommended as first-line treatment by NICE8 but not in other guidelines. Olanzapine alone is effective when compared with placebo62 but the combination with fluoxetine is more effective. (This is possibly the strongest evidence for a beneficial effect for an antidepressant in bipolar depression.)

Bipolar disorder CHAPTER 2 Table 2.10 Alternative treatments (refer to primary literature before using). Drug/regimen Comments Antidepressants76–84 ‘Unopposed’ antidepressants (i.e. without mood-stabiliser protection) are generally to be avoided in bipolar depression because of the risk of switching and inducing rapid cycling. There is also evidence that they are relatively less effective (perhaps not effective at all) in bipolar depression than in unipolar depression although dose may be critical.48 Short-term use of fluoxetine, venlafaxine and moclobemide seems reasonably effective and safe even as monotherapy. A meta-analysis suggested a large effect size for tranylcypromine in the absence of any risk of switching.85 Overall, however, unopposed antidepressant treatment should be avoided, especially in bipolar I disorder.54 Cariprazine86 One RCT suggests that cariprazine at 1.5mg/day is effective in bipolar I depression. A second, larger study showed 1.5 and 3mg/day to be effective.87 The most recent study87 found benefit for 1.5mg/day but not 3mg/day. Usually has lowest efficacy among effective drugs in meta-analyses. Ketamine88–91 An IV dose of 0.5mg/kg is effective in refractory bipolar depression with a very high response rate. Dissociative symptoms are common but brief. Now accepted as standard treatment for refractory bipolar depression.92,93 IV racemate is possibly more effective than intranasal esketamine.94 Switching to mania is a potential problem95 although probably a remote risk. Pramipexole96,97 Two small placebo-controlled trials suggested useful efficacy in bipolar depression. Effective dose averages around 1.7mg/day. Both studies used pramipexole as an adjunct to existing mood-stabiliser treatment. Neither study detected an increased risk of switching to mania/hypomania (a theoretical consideration) but data are insufficient to exclude this possibility. A meta-analysis of studies showed a robust effect on response but not remission.98 RCT, randomised controlled trial. Drug/regimen Comments Quetiapine63–67 Five large RCTs have demonstrated clear efficacy for doses of 300 and 600mg daily (as monotherapy) in bipolar I and bipolar II depression. A later study in Chinese patients demonstrated the efficacy of 300mg/day68 in bipolar I depression. It may be superior to both lithium and paroxetine. Quetiapine also prevents relapse into depression and mania69,70 and so is one of the treatments of choice in bipolar depression. It appears not to be associated with switching to mania. Valproate1,17,71–75 Limited evidence of efficacy as monotherapy but recommended in some guidelines. Several very small RCTs but many are negative; however meta-analyses do support antidepressant efficacy.74 Probably protects against depressive relapse but database is small. Not recommended because of its teratogenic effects in both men and women. MAOIs, monoamine oxidase inhibitors; RCT, randomised controlled trial. Table 2.9 (Continued)

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