Affective Disorders

Psychopharmacology for MRCPsych

(With BAP reading/references)

Why do antidepressants take long to act than, say benzodiazepines?

Mechanisms

Case 1

32 year old man presents to the ED BIBP having been found wandering naked on the M56. He has had one previous admission for depression aged 24 during a period of stressful examinations. He has no regular medication except Fluoxetine 40mg od po. During his last admission he was treated with Fluoxetine and Olanzapine. He has not taken Olanzapine for 2 years, having titrated downwards. He is pressured in speech, frankly disinhibited, speaks about the special powers he has to “heal the world ecosystem of plant fibres and chlorophyll – it’s colourful”,

Case 1 - Questions

What is the short, medium and long term medication plan?

What are this man’s short, medium and long term risks?

What is the available evidence about efficacy and side effects?

Lithium reduces suicide

- 48 randomised controlled trials
- N = 6674 participants, 15 comparisons
- Lithium was more effective than placebo in reducing the number of suicides (odds ratio 0.13, 95% CI 0.03 - 0.66)
- Deaths from any cause (0.38, 0.15 to 0.95)
- No clear benefits were observed for lithium compared with placebo in preventing deliberate self harm (0.60, 0.27 to 1.32).
- In unipolar depression, lithium was associated with a reduced risk of suicide (0.36, 0.13 to 0.98) and also the number of total deaths (0.13, 0.02 to 0.76)
- When lithium was compared with each active individual treatment a statistically significant difference was found only with carbamazepine for deliberate self harm. Lithium tended to be generally better than the other active comparators, with small statistical variation between the results.

Lithium prevents mood episodes

Severus et al. International Journal of Bipolar Disorders 2014, 2:15
http://www.journalbipolardisorders.com/content/2/1/15

International Journal of Bipolar Disorders
a SpringerOpen Journal

RESEARCH Open Access

Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis

Emanuel Severus[1*†], Matthew J Taylor[2†], Cathrin Sauer[1], Andrea Pfennig[1], Philipp Ritter[1], Michael Bauer[1] and John R Geddes[3]

- Lithium v Anticonvulsants: seven trials (n =1,580 participants)
- Lithium was more effective than placebo in preventing
  - overall mood episodes (random effects RR 0.66, 95% CI 0.53 to 0.82)
  - manic episodes (random effects RR 0.52, 95% CI 0.38 to 0.71)
  - depressive episodes (random effects RR 0.78, 95% CI 0.59 to 1.03; fixed effect RR 0.73, 95% CI 0.60 to 0.88).
- Lithium was inferior to placebo in leading to drop-outs for reasons other than a mood episode (random effects RR 1.33, 95% CI 1.07 to 1.65)
- Superior to placebo on study completion (random effects RR 1.69, 95% CI 1.12 to 2.55).
- Lithium v Placebo : seven trials were included (n = 1,305).
- In prevention of manic episodes, lithium showed superiority compared to anticonvulsants (random effects RR 0.66, 95% CI 0.44 to 1.00).
- However, there was no significant difference regarding prevention of overall mood episodes, depressive episodes, dropping-out to reasons other than a mood episode, or study completion.

Case 2

- 64 year old woman attends OPD referred by GP with 3 month history of declining mood, worsening anhedonia, declining self care, disturbed sleep and weight loss. She has a history of recurrent mild to moderate depressive episodes previously treated by her GP with Diazepam 5mg qds and Amitryptiline 25mg nocte which she has been on for 20 years.
- She has a medical history including treated hypertension, previous mastectomy for node –ve Breast Cancer 10 years ago.

thebmj Visual Abstract

Systematic review and network meta-analysis

Non-surgical brain stimulation

Comparative efficacy and acceptability for the acute treatment of major depressive episodes in adults

Summary

The findings provide evidence to consider non-surgical brain stimulation techniques as alternative or add-on treatments

Data sources

113 RCTs

Overall risk of bias: High 17%, Low 34%, Unclear 50%

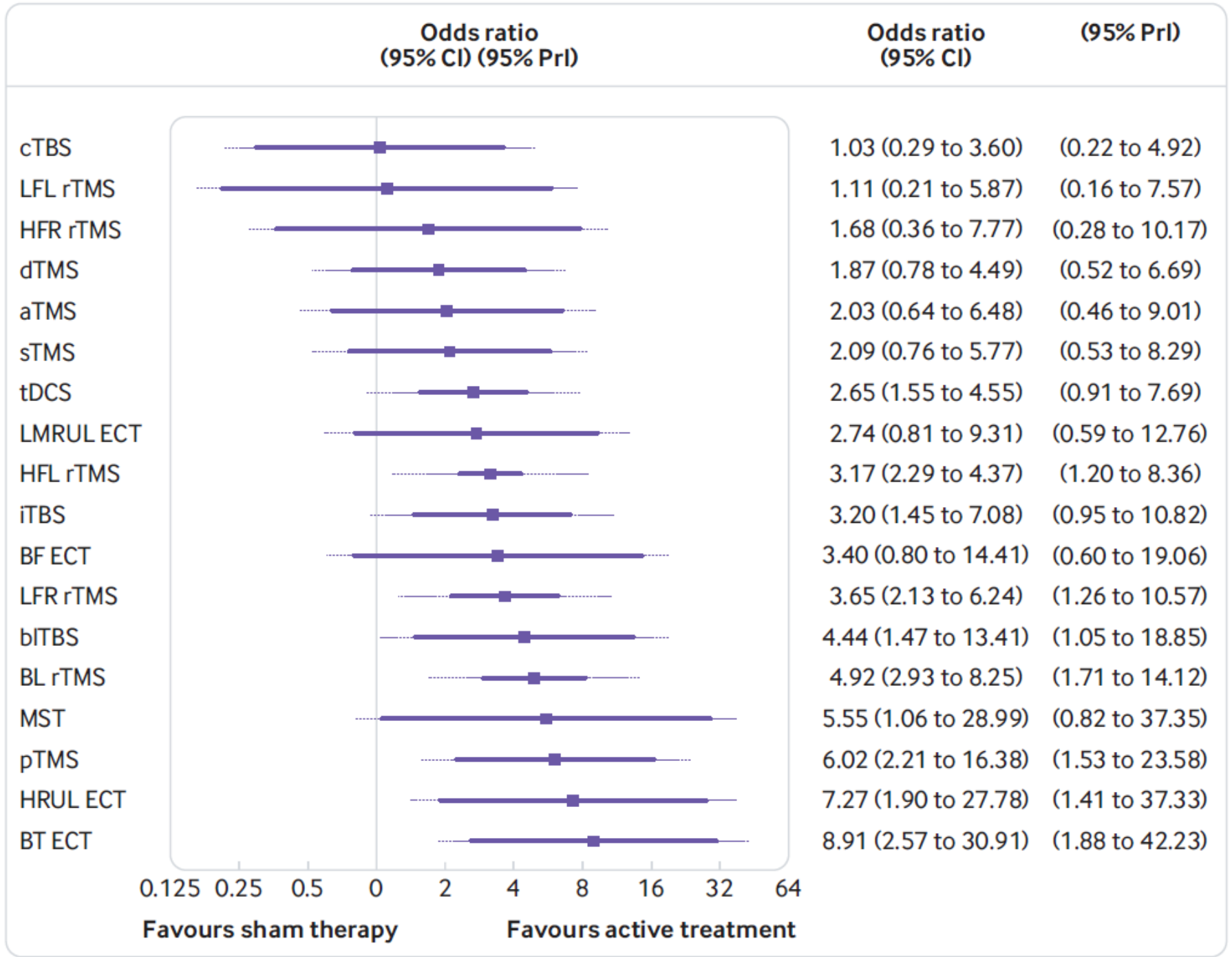
6750

Adults with major depressive disorder or bipolar depression

Results

Active vs sham treatment comparisons

Read the full article online: http://bit.ly/BMJstim


Odds ratio (95% CI) (95% PrI)
Odds ratio (95% CI)
(95% PrI)
cTBS 1.03 (0.29 to 3.60) (0.22 to 4.92)
LFL rTMS 1.11 (0.21 to 5.87) (0.16 to 7.57)
HFR rTMS 1.68 (0.36 to 7.77) (0.28 to 10.17)
dTMS 1.87 (0.78 to 4.49) (0.52 to 6.69)
aTMS 2.03 (0.64 to 6.48) (0.46 to 9.01)
sTMS 2.09 (0.76 to 5.77) (0.53 to 8.29)
tDCS 2.65 (1.55 to 4.55) (0.91 to 7.69)
LMRUL ECT 2.74 (0.81 to 9.31) (0.59 to 12.76)
HFL rTMS 3.17 (2.29 to 4.37) (1.20 to 8.36)
iTBS 3.20 (1.45 to 7.08) (0.95 to 10.82)
BF ECT 3.40 (0.80 to 14.41) (0.60 to 19.06)
LFR rTMS 3.65 (2.13 to 6.24) (1.26 to 10.57)
blTBS 4.44 (1.47 to 13.41) (1.05 to 18.85)
BL rTMS 4.92 (2.93 to 8.25) (1.71 to 14.12)
MST 5.55 (1.06 to 28.99) (0.82 to 37.35)
pTMS 6.02 (2.21 to 16.38) (1.53 to 23.58)
HRUL ECT 7.27 (1.90 to 27.78) (1.41 to 37.33)
BT ECT 8.91 (2.57 to 30.91) (1.88 to 42.23)
0.125 0.25 0.5 0 2 4 8 16 32 64
Favours sham therapy
Favours active treatment

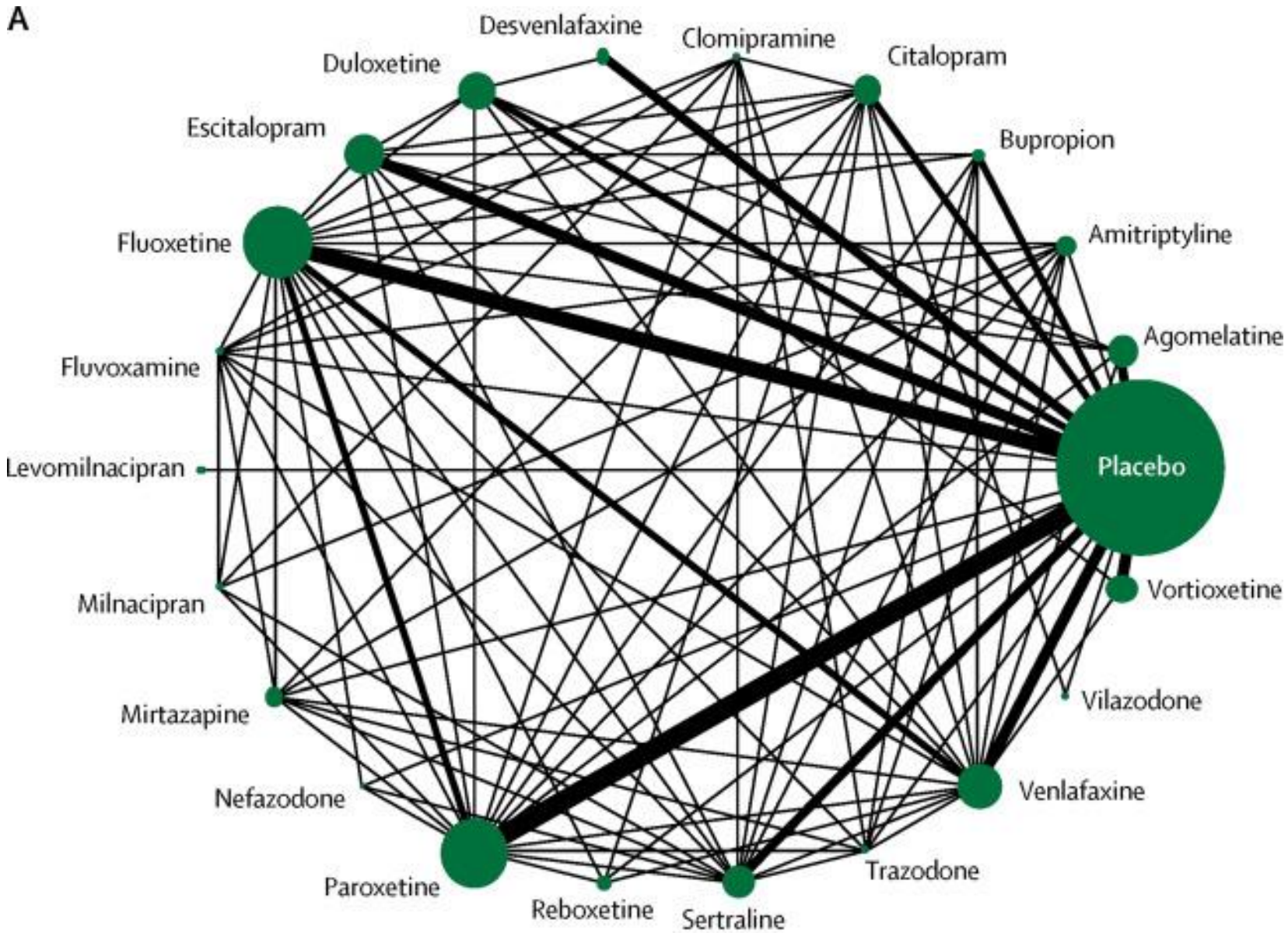
Case 3

32 year old woman presents to your clinic with a 12 month history of depression. Her HAMD24 is 21. She has not been able to work (secretary) for the last 8 months. She has one son aged 10 and lives with him in a council flat. She has been on Sertraline 100mg for 16 weeks since last seen in clinic. Before that she was on Citalopram from her GP, initially 10mg (3 months) then 20mg (3 months) with no evidence of response. She has had no significant side effects of medication, except mild GI upset on initiation or up-titration of dose.

STAR*D

- 55 million dollar waste of money
- Fiddled inclusion exclusion criteria
- Low power by 4th tier
- Non-standard treatments
- People weren’t very depressed

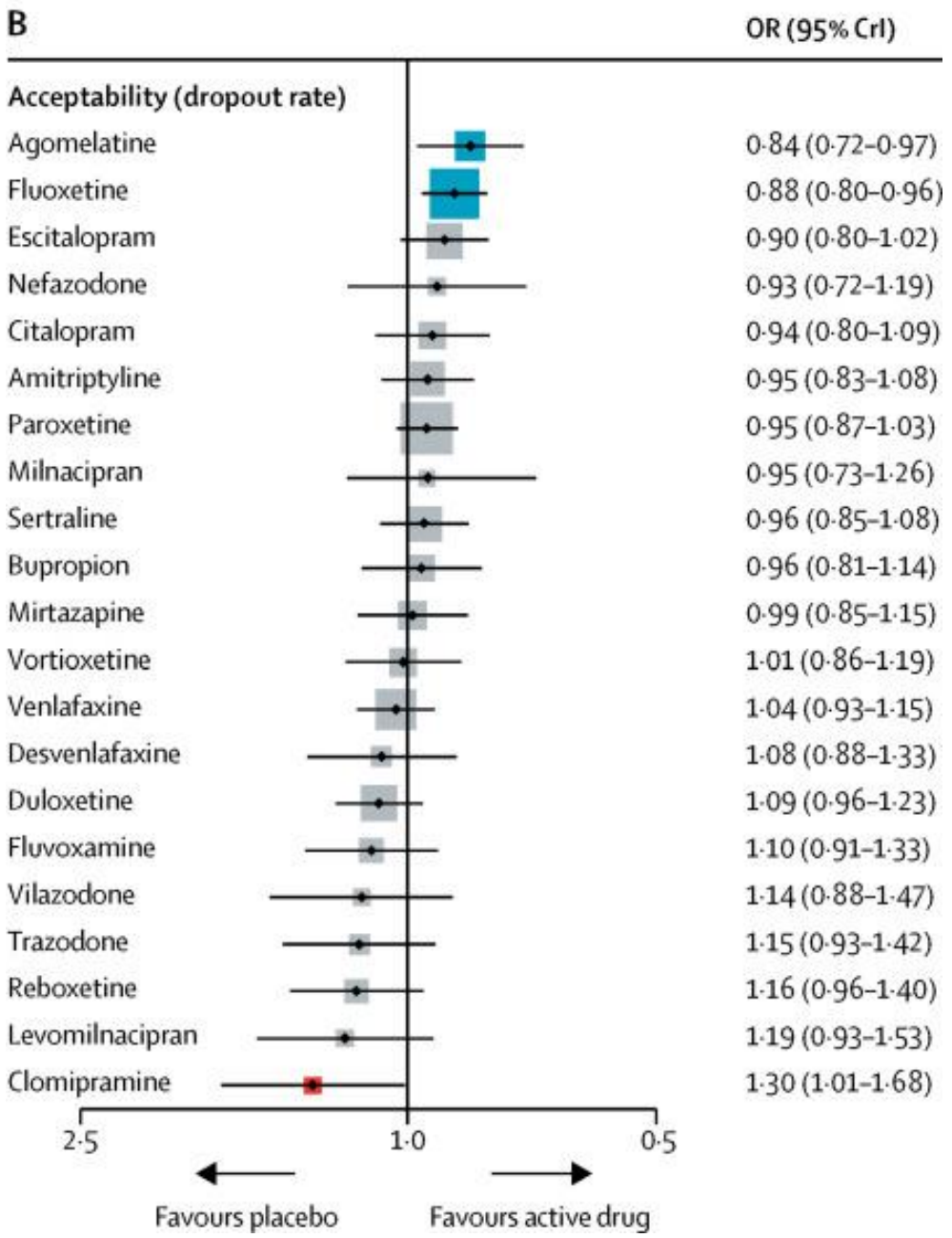
- Depression can be hard to treat



https://mtm.uoi.gr/

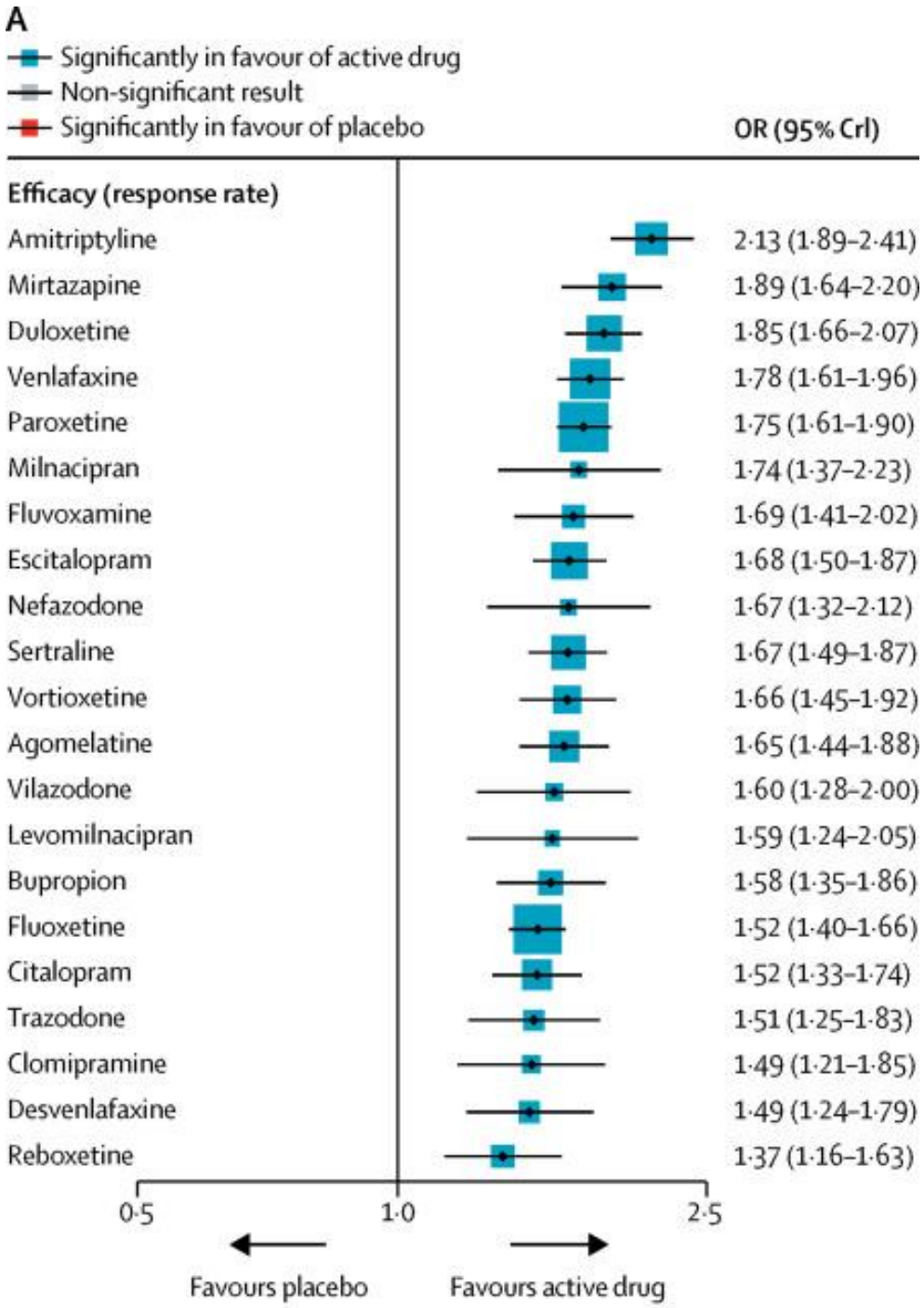
Cipriani, Geddes 2018

- N = 116,000
- 10,000 > 65
- Network Meta analysis
- Tolerability

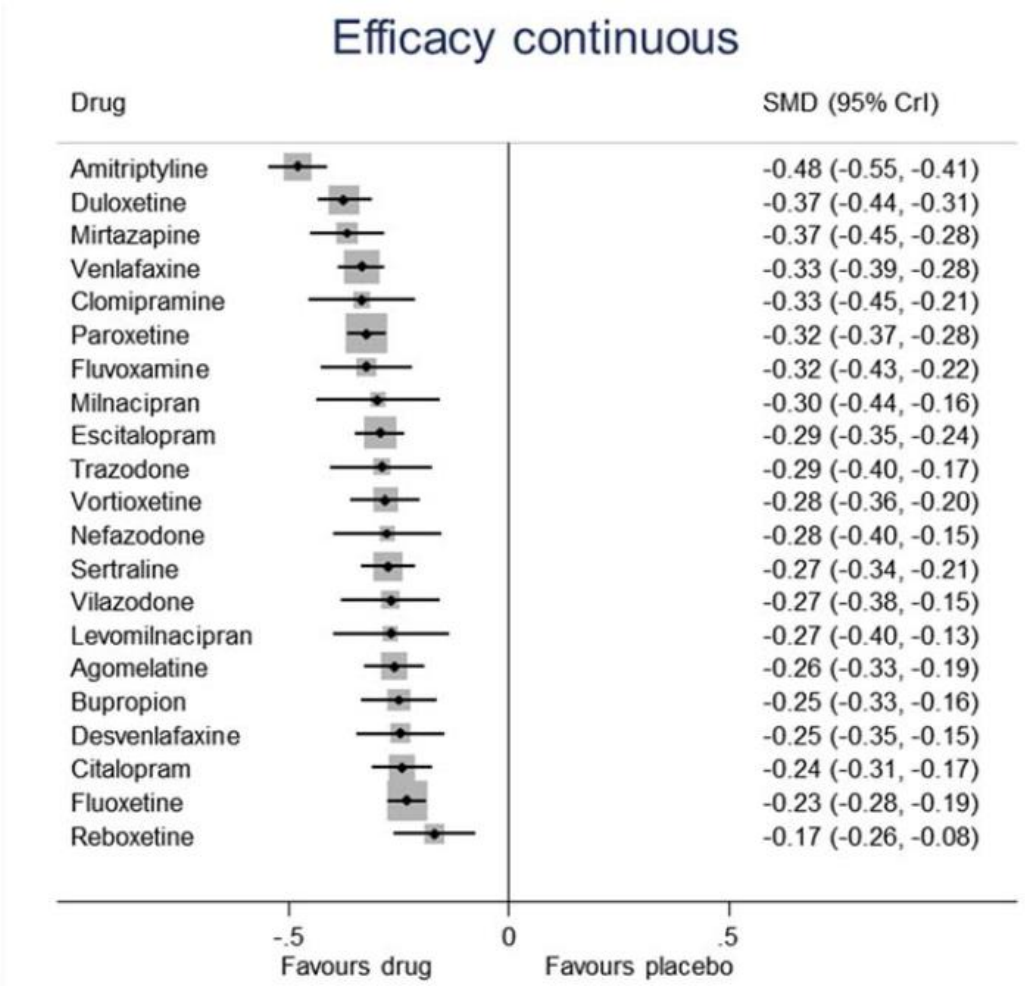


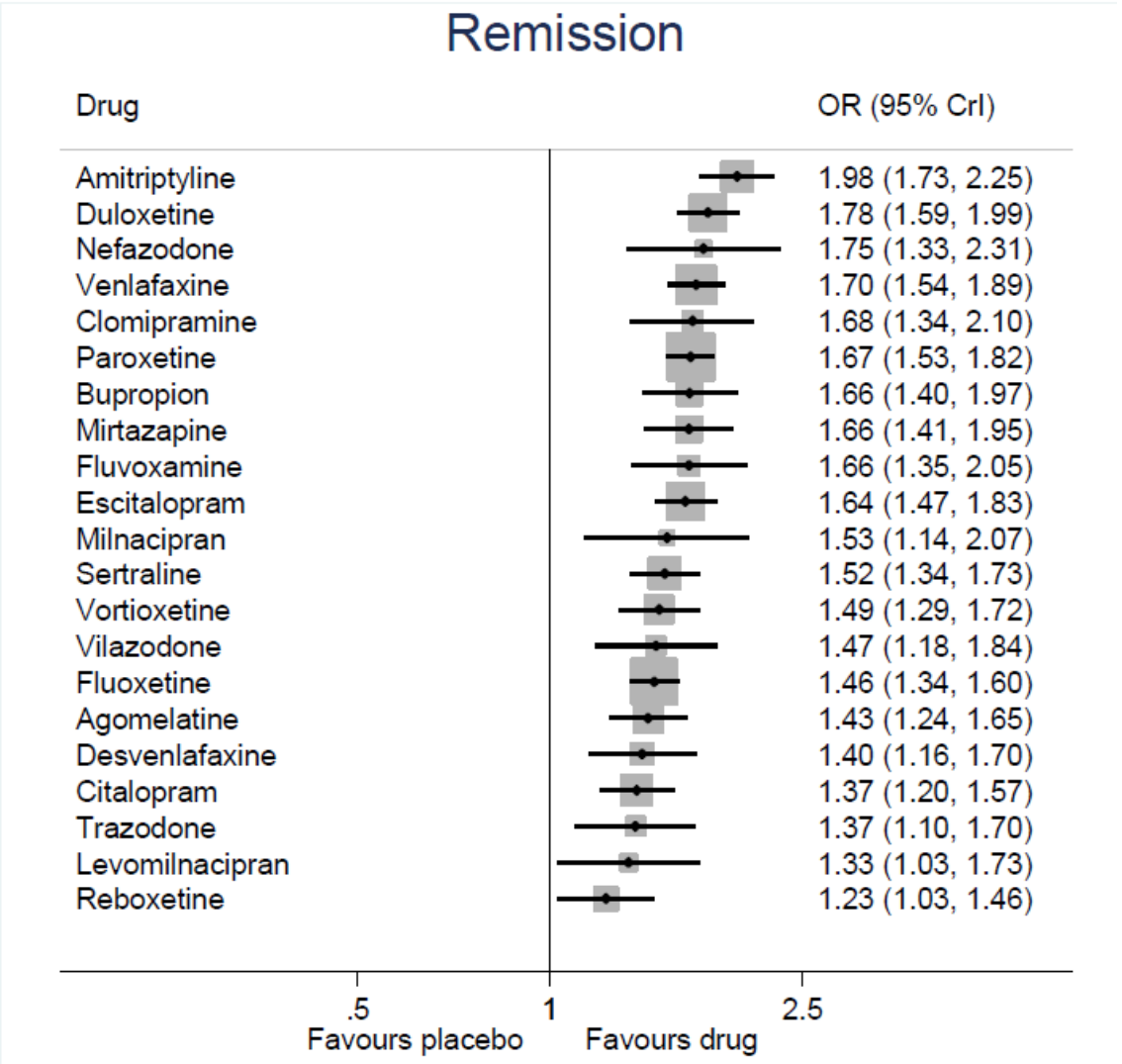
Cipriani, Geddes 2018

- N = 116,000
- 10,000 > 65
- Network Meta analysis
- Efficacy



245 pages of supplementary material





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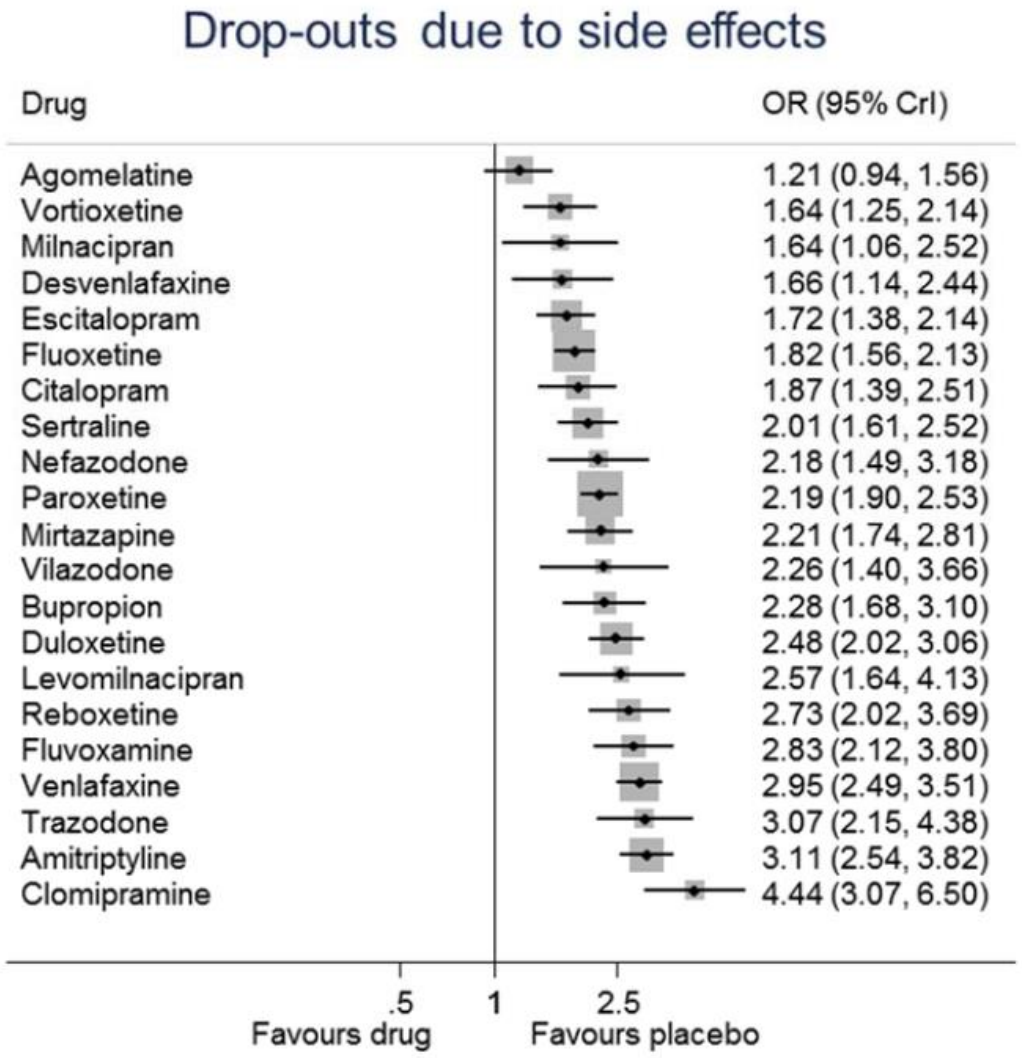

Case 4

54 year old man with history of bipolar affective disorder diagnosed 10 years after onset of depression. 3 manic episodes in history, 18 depressive episodes with increasing, now twice yearly depressions. Worked as an accountant up to last year, but now has significant difficulty attending to his own house and self-care. This episode has lasted 3 months. Some suidicality, usually fleeting. Currently on Amlodipine 5mg od po, Aspirin, Fluoxetine 60mg od po (12/12), Mirtazapine 30mg nocte (2/12), Olanzapine 10mg nocte (4y), Valproate 500mg bd (10y).

BAP Guidance (*** strength, I-IV evidence)

- *For patients* not *already taking long-term treatment for bipolar disorder.* Consider quetiapine, lurasidone or olanzapine (***). Dopamine antagonists have the inherent advantage of being anti-manic treatments (I).
- Antidepressants (meaning drugs for a major depressive episodein a unipolar illness course) have not been adequately studied in bipolar disorder. Only the combination of fluoxetine with olanzapine has support as a specific treatment (***).
- The common use of other antidepressants in patients with bipolar disorder is an extrapolation from effects established in a unipolar illness course. When considered, they should be co-prescribed with a drug for mania (e.g. dopamine antagonists, lithium, valproate) in patients with a history of mania (S). Consider initial treatment with lamotrigine, with the necessary incremental dosing schedule, usually as an addition to agents preventing recurrence of mania (****). Consider ECT for patients with high suicidal risk, treatment resistance, psychosis, severe depression during pregnancy or life-threatening inanition (***).
- Consider simplifying pre-existing polypharmacy, which may have raised the seizure threshold. It is very unusual for ECT to be used under mental health legislation without a patient's consent; fears that this may occur should be allayed. When depressive symptoms are less severe, and despite limited evidence, lithium may be considered, especially as a prelude to long-term treatment (**). Consider family-focused, cognitive behaviour therapy or interpersonal rhythm therapy as an additional treatment, when available, since these may shorten the acute episode (**).

BAP Guidance (*** strength, I-IV evidence)

For patients already taking long-term treatment for bipolar disorder. (c) Choice of drug for a depressive episode. Treatment preference cannot be securely based on the current database of RCTs (IV).

The available network meta-analyses may not be stable because rankings are strongly influenced by inclusion criteria and indirect comparisons sometimes contradict the findings from direct comparisons.

There is a risk of a switch to mania or mood instability during treatment for depression (I). While this will often reflect the natural history of the disorder, it may be increased by monotherapy with antidepressants. The dual-action monoamine re-uptake inhibitors (venlafaxine, duloxetine, amitriptyline and imipramine) (II)) carry a greater risk of precipitating a switch to mania than single action drugs (especially selective serotonin re-uptake inhibitors) (II).

Antidepressant drugs appear unlikely to induce mania when used in combination with a drug for mania (I). In bipolar II disorder, if an antidepressant is prescribed as monotherapy, any increase in dose should be gradual and there should be vigilance for and early management of any adverse reactions such as hypomania, mixed states or agitation (IV).

In contrast to the common use of antidepressants, audit data suggest that lamotrigine is too little used outside specialist centres, given its efficacy in bipolar I, and suitability for bipolar II disorder. If successful treatment has been initiated for depression de novo in a bipolar illness course, long-term treatment should be considered (see below) (S).

Important studies

Summations:

- Olanzapine + fluoxetine is the optimal treatment for bipolar depression
- Olanzapine, quetiapine, lurasidone, valproate, SSRIs, lithium and TCAs also appear to be effective in bipolar depression, but with varied acceptability
- The use of lamotrigine, MAOIs, ziprasidone, aripiprazole and risperidone is not supported by this analysis

Considerations:

- Our multiple-treatments model could not for the most part distinguish statistically between treatments because of the sparse network of trials and the limited number of trial subjects
- Outcomes of individual trials are likely to have been affected by the co-administration or otherwise of other mood-stabilising drugs

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Meta-analysis

Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis

Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis.

Objective: Treatment of bipolar depression is complicated by variable response and risk of switch to mania. Guidance is informed by the strength of evidence rather than by comparative data.
Method: We performed a multiple-treatments meta-analysis of randomised, double-blind, controlled comparisons of 4–16 weeks in adults in bipolar depression. The primary efficacy outcome was effect size. The primary acceptability outcome was 'switch to mania'. Secondary outcomes were likelihood of response and withdrawals from trials.
Results: Twenty-nine studies were included (8331 participants). Olanzapine + fluoxetine and olanzapine performed best on primary outcome measure being ranked highest for effect size. Switch to mania was least likely with ziprasidone and then quetiapine. Olanzapine + fluoxetine was also ranked the highest for response with lurasidone second, but olanzapine + fluoxetine and olanzapine had the optimal effect on response and withdrawal from treatment when the two parameters were considered together. Several treatments [monoamine oxidase inhibitors (MAOIs), ziprasidone, aripiprazole and risperidone] have limited or no therapeutic activity in bipolar depression.
Conclusion: Olanzapine + fluoxetine should be first-line treatment. Olanzapine, quetiapine, lurasidone, valproate and selective serotonin re-uptake inhibitors are also recommended. Tricyclic antidepressants and lithium are worthy of consideration but lamotrigine (high risk of switching, less robust efficacy) and MAOIs, ziprasidone, aripiprazole and risperidone (no evidence of efficacy) should not be used.

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Key words: bipolar disorder; depression; antidepressives; antipsychotics

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Summations

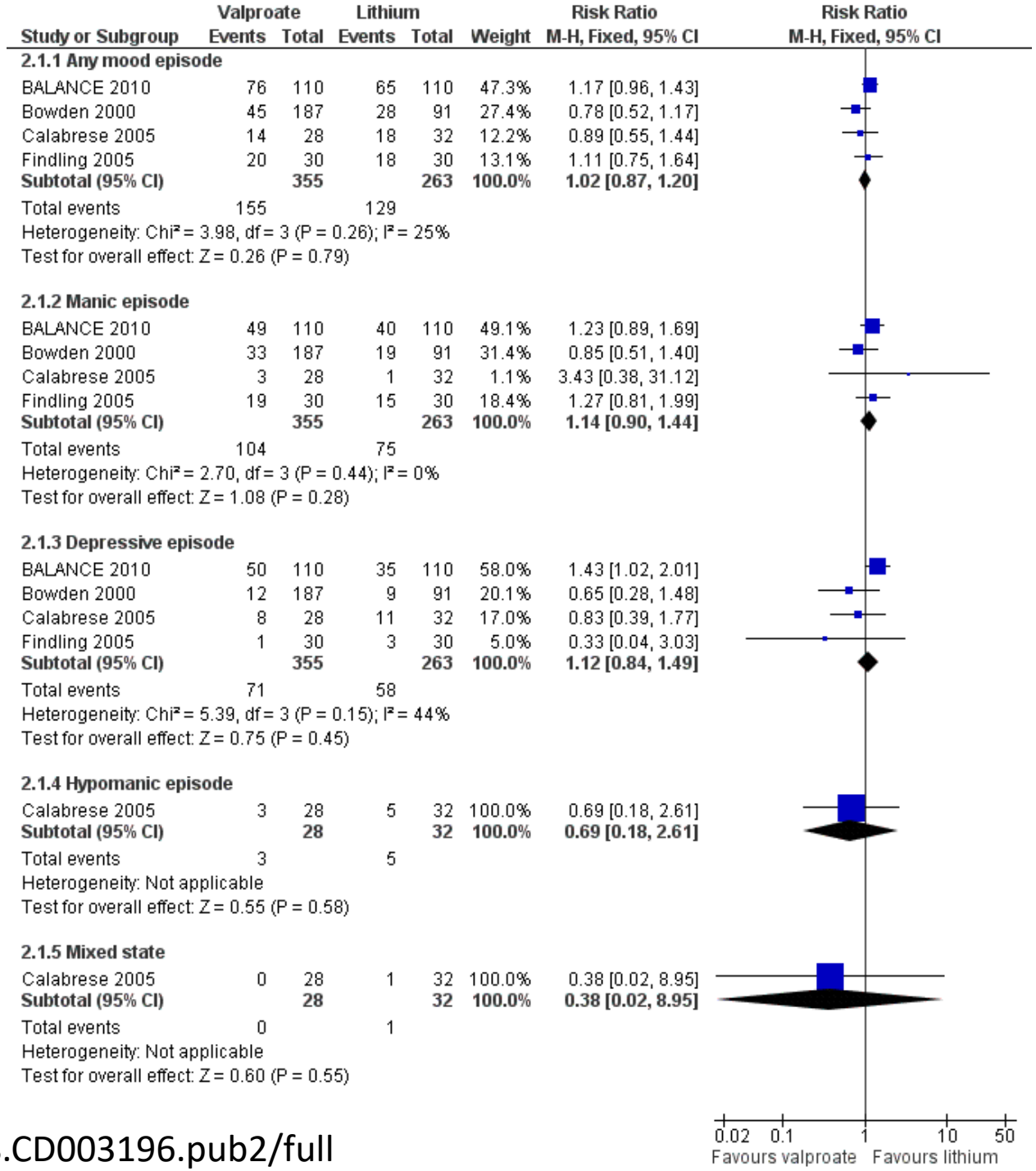
- Olanzapine + fluoxetine is the optimal treatment for bipolar depression
- Olanzapine, quetiapine, lurasidone, valproate, SSRIs, lithium and TCAs also appear to be effective in bipolar depression, but with varied acceptability
- The use of lamotrigine, MAOIs, ziprasidone, aripiprazole and risperidone is not supported by this analysis

Considerations

- Our multiple-treatments model could not for the most part distinguish statistically between treatments because of the sparse network of trials and the limited number of trial subjects
- Outcomes of individual trials are likely to have been affected by the co-administration or otherwise of other mood-stabilising drugs

Important studies

- Six RCTs (876 participants) (2013 Review)
  - Two studies (overall 312 participants) compared valproate with placebo,
  - four studies (overall 618 participants) valproate with lithium,
  - one study (overall 23 participants) valproate with olanzapine
  - one study (overall 220 participants) valproate with the combination of valproate plus lithium.
- Valproate was more effective than placebo in preventing study withdrawal due to any mood episode (RR 0.68, 95% CI 0.49 to 0.93; NNTB 8),
- No difference in efficacy was found between valproate and lithium (RR 1.02, 95% CI 0.87 to 1.20).
- Valproate was associated with fewer participants dropping out of treatment for any cause when compared with placebo or lithium (RR 0.82, 95% CI 0.71 to 0.95 and RR 0.87, 95% CI 0.77 to 0.98, respectively).
- However, combination therapy with lithium plus valproate was more likely to prevent relapse than was monotherapy with valproate (RR 0.78, 95% CI 0.63 to 0.96). Significant differences in adverse event frequencies were found, and lithium was associated with more frequent diarrhoea, polyuria, increased thirst and enuresis, whereas valproate was associated with increased sedation and infection.



https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003196.pub2/full

Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis

Andrea Cipriani, Corrado Barbui, Georgia Salanti, Jennifer Rendell, Rachel Brown, Sarah Stockton, Marianna Purgato, Loukia M Spineli, Guy M Goodwin, John R Geddes

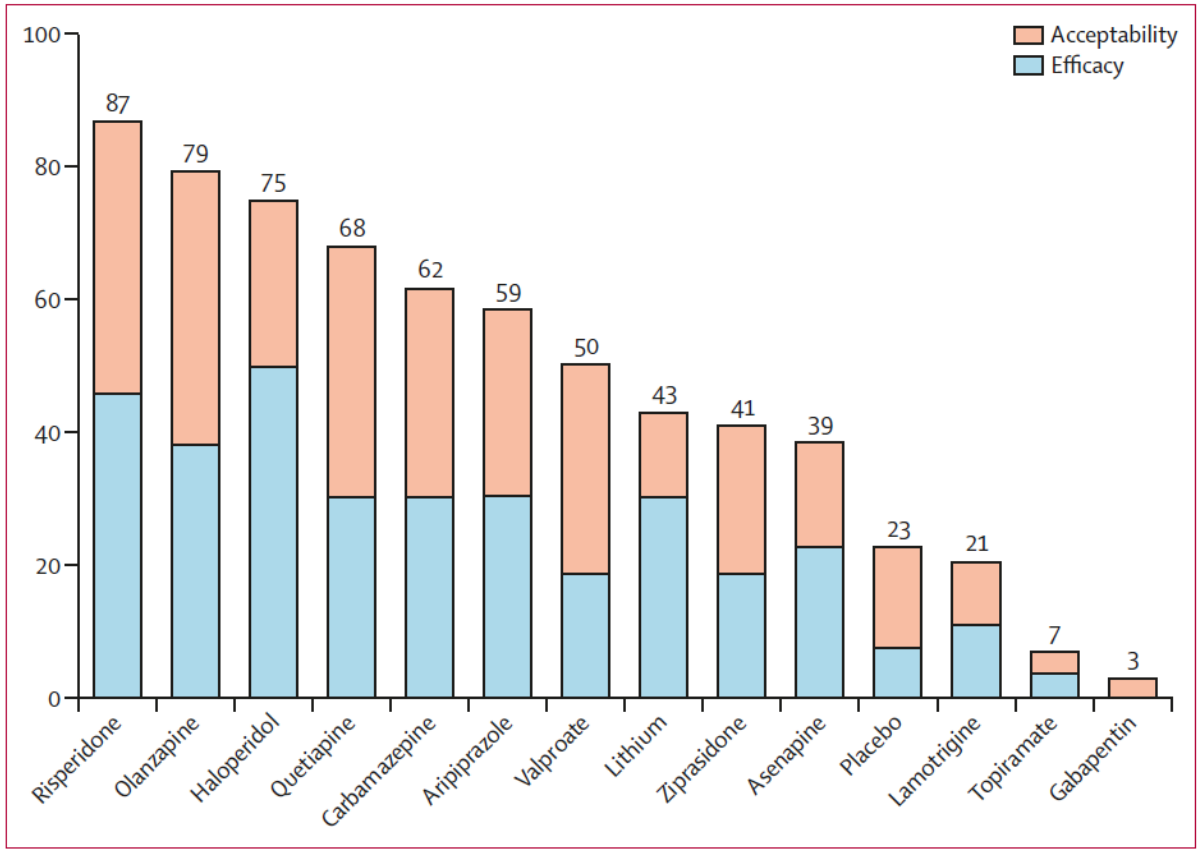


Figure 5: **Drugs ordered by their overall probability to be the best treatment in terms of both efficacy and dropout rate, showing the separate contributions to the overall scores of efficacy and dropout**
The cumulative percentages after normalisation (0–100) are shown in the key. Every drug was scored with points up to a maximum of 50 for efficacy and 50 for acceptability (overall maximum score 100), with data from rankograms and SUCRAs.

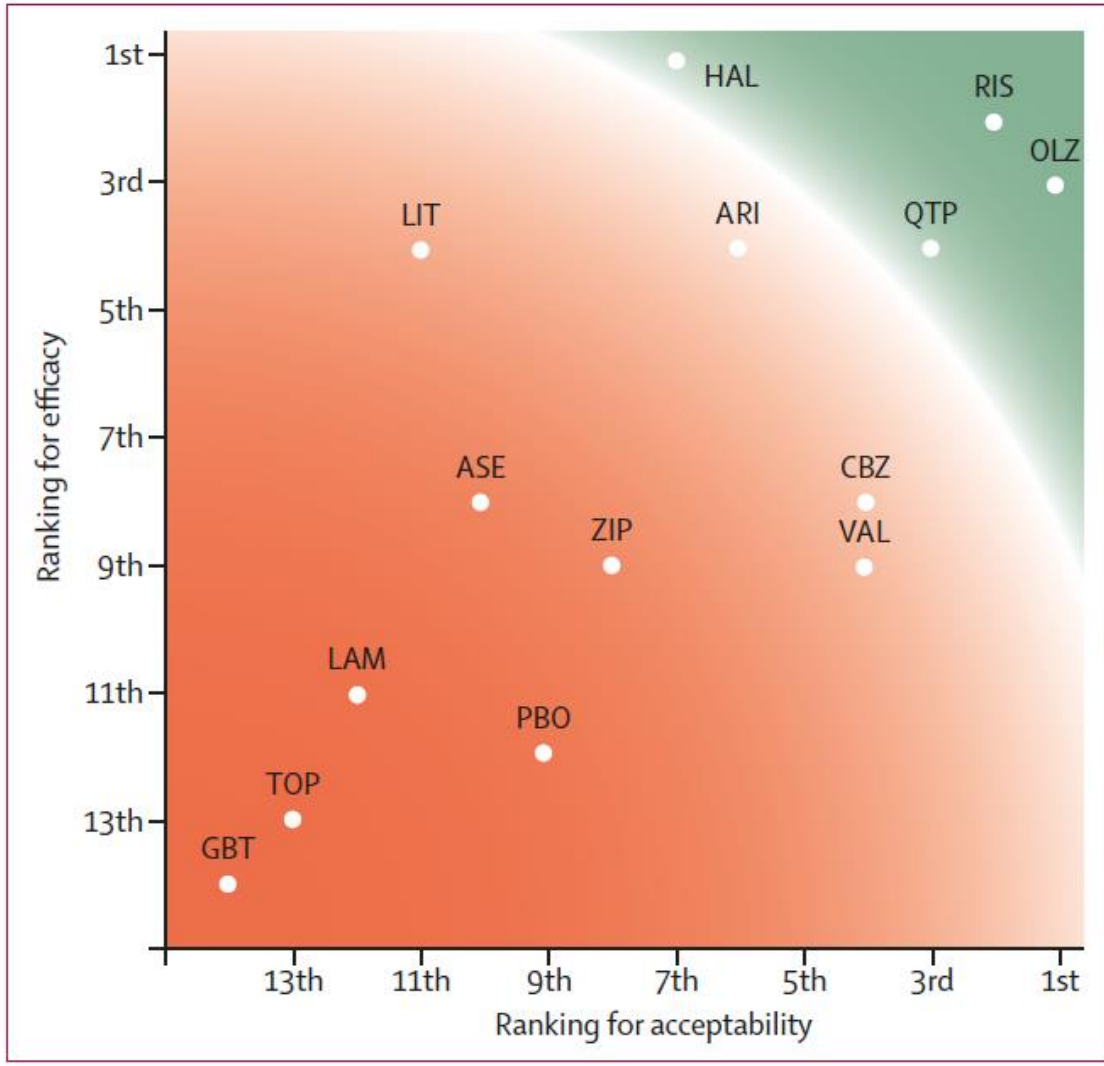


Figure 6: **Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcome) and dropout rate**
Red colour represents worst treatment and green represents best treatment in a qualitative approach. ARI=aripiprazole. ASE=asenapine. CBZ=carbamazepine. VAL=valproate. GBT=gabapentin. HAL=haloperidol. LAM=lamotrigine. LIT=lithium. OLZ=olanzapine, PBO=placebo. QTP=quetiapine. RIS=risperidone, TOP=topiramate. ZIP=ziprasidone.