Pharmacology of antidepressants and mood stabilisers

Dr Peter S Talbot  MD, FRCPsych
University of Manchester &
Specialist Service for Affective Disorders (SSAD)
peter.talbot@manchester.ac.uk
Summary

- Antidepressants and ‘mood stabilisers’
- Focussing on mechanism of action, evidence base and indications
  - Antidepressants
  - Lithium
  - Valproate
  - Lamotrigine
  - Carbamazepine
  - Oxcarbazepine and eslicarbazepine

  - Best referred to as antiepileptic drugs (AEDs) or anticonvulsants, rather than ‘mood stabilisers’
  - None is as effective as lithium in all 3 phases of bipolar disorder
Antidepressants: 5-HT and NA release, reuptake and degradation

- 5-HT and NA released into synaptic cleft
- Act at a range of pre- and postsynaptic receptors
- Signal is terminated by 2 methods: reuptake and enzymatic degradation:

  **Serotonin (5-HT):**
  - 5-HT reuptake transporter (5HTT, SERT)
  - Monoamine oxidase (MAO-A)

  **Noradrenaline:**
  - Noradrenaline reuptake transporter (NET, NAT)
  - MAO-A
  - Catechol-O-methyl transferase (COMT)
MAOI antidepressants

MAO-A inhibitors:
- Inhibit the breakdown of 5-HT and NA, so increase synaptic levels of both
- MAO-A inhibitors:
  - Irreversible: phenelzine, tranylcypromine
  - Reversible: moclobemide
  - NB: can’t metabolise other monoamines e.g. dietary tyramine (cheese, marmite etc) → hypertensive crisis!
Tricyclic antidepressants

- Block the SERT and NET, so synaptic levels of 5-HT and NA increase
  - They also act at a range of other receptors which give rise to (usually) unwanted side effects

- SNRIs block the SERT and NET, and have less actions at other receptors

- SSRIs are selective for the SERT, so increase synaptic levels of 5-HT
Tricyclic antidepressants

- Prototypical drug is imipramine (introduced late 1950s)
- 3-ring structures, analogues of imipramine
- Classified according to the substitution of the terminal amino group (derived from ammonia, NH₃) of the side chain into tertiary and secondary amines:

<table>
<thead>
<tr>
<th>Tertiary</th>
<th>Secondary</th>
<th>Chemical class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine</td>
<td>Desipramine</td>
<td>Dibenzazepine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lofepramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Nortriptyline</td>
<td>Dibenzocycloheptadiene</td>
</tr>
<tr>
<td>Dosulepin</td>
<td></td>
<td>Dibenzothiepin</td>
</tr>
<tr>
<td>Doxepin</td>
<td></td>
<td>Dibenzoxapine</td>
</tr>
<tr>
<td>Amoxapine</td>
<td></td>
<td>Dibenzoxazepine</td>
</tr>
</tbody>
</table>
### Receptor-mediated adverse effects

<table>
<thead>
<tr>
<th>M₁ antagonism (‘anticholinergic’)</th>
<th>α-adrenergic antagonism</th>
<th>Cardiotoxicity</th>
<th>Sedation</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• dry mouth</td>
<td>• orthostatic hypotension and reflex tachycardia</td>
<td>• delayed conduction</td>
<td>• H₁ antagonism</td>
<td>• Most evidence for H₁, 5-HT₂ₐ, 5-HT₂¢, ACh M₃, adrenergic α₁, α₂ antagonism</td>
</tr>
<tr>
<td>• sore throat</td>
<td>• small pupils</td>
<td>• M₁ antagonism</td>
<td>• α adrenergic antagonism</td>
<td>• effects on leptins</td>
</tr>
<tr>
<td>• blurred near vision</td>
<td></td>
<td>• α-adrenergic antagonism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• tachycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• urinary retention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• abuse potential</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• acute confusion in overdose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Tricyclic antidepressants

<table>
<thead>
<tr>
<th>Name</th>
<th>Action</th>
<th>Notes on TCAs</th>
<th>$H_1$ (Ki, nM)</th>
<th>$M_1$ (Ki, nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomipramine</td>
<td>SRI&gt;&gt;NRI</td>
<td>Highest SERT affinity of TCAs</td>
<td>31</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most sexual dysfunction of TCAs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>SRI&gt;NRI</td>
<td>Second highest SERT affinity after clomipramine</td>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolised to desipramine (a noradrenergic TCA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Weak SRI</td>
<td>Strong antihistamine; sedative</td>
<td>0.27</td>
<td>58</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>SRI&gt;NRI</td>
<td>‘Not recommended’ in BNF</td>
<td>1.03</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most antimuscarinic ($M_1$) of TCAs; sedative ($H_1$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolised to nortriptyline (adrenergic TCA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosulepin (dothiepin)</td>
<td>SRI&gt;NRI</td>
<td>Dosulepin and doxepin the most fatal in overdose Sedative; ‘initiate by specialist’ in BNF</td>
<td>3.6</td>
<td>25</td>
</tr>
<tr>
<td>Doxepin</td>
<td>SRI≈NRI</td>
<td>Dosulepin and doxepin the most fatal in overdose</td>
<td>0.21</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Highest $H_1$ affinity of TCAs; sedative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>NRI&gt;SRI</td>
<td>Manufacturer advises monitor plasma levels above 100mg, but usefulness uncertain</td>
<td>8.2</td>
<td>94</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>NRI&gt;SRI</td>
<td>Least antihistamine (sedative) of TCAs</td>
<td>360</td>
<td>67</td>
</tr>
</tbody>
</table>
Tricyclic and SSRI antidepressants

- Antidepressants have a range of differential affinities for SERT, NET and DAT

![Diagram showing the differential affinities of various antidepressants for SERT, NET, and DAT](chart)

- Fluoxetine: Lower affinity for SERT, NET, and DAT
- Citalopram: Selective affinity for SERT
- Paroxetine: Potent affinity for SERT, NET, and DAT
- Sertraline: Selective affinity for SERT
- Clomipramine: Lower affinity for SERT, NET, and DAT
- Desipramine: Lower affinity for SERT, NET, and DAT
- Duloxetine: Lower affinity for SERT, NET, and DAT
- Venlafaxine: Lower affinity for SERT, NET, and DAT
- Bupropion: Lower affinity for SERT, NET, and DAT

5-HT transporter

NA transporter

DA transporter

**K_i or IC_{50} (nM)**

**Higher affinity**

**Lower affinity**

Courtesy of Dr Sasha Gartside, British Association for Psychopharmacology
5-HT and NA interactions

NA stimulation at $\alpha_1$ adreno-receptor on 5-HT cell body tends to ↑ 5-HT cell firing

NA stimulation at $\alpha_2$ auto- and heteroreceptors on NA and 5-HT neurons tends to ↓ cell firing
Newer antidepressants: mirtazapine

Mirtazapine is principally an adrenergic $\alpha_2$ receptor antagonist.

Adrenergic $\alpha_2$R antagonism blocks the negative feedback which is tending to reduce NA release.

Net effect is ↑ NA release.

Adrenergic $\alpha_2$R antagonism also blocks the negative feedback tending to reduce 5-HT release. Net effect is ↑ 5-HT release.
Antidepressants: clinical indications

Licensed for:

- Depressive disorder
  - Not usually indicated for mild depression (unless chronic)

Many are also licensed for:

- Obsessive-compulsive disorder (OCD)
  - Escitalopram, fluoxetine, paroxetine, fluvoxamine, sertraline, clomipramine

- Panic disorder
  - Escitalopram, citalopram, paroxetine, sertraline,

- Generalised anxiety disorder
  - Escitalopram, paroxetine, venlafaxine, duloxetine,

- Social anxiety
  - Escitalopram, paroxetine, sertraline, venlafaxine, moclobemide

- PTSD
  - Paroxetine, sertraline,

- Bulimia nervosa
  - Fluoxetine

- Menopausal symptoms in women with breast cancer
  - Fluoxetine, paroxetine, venlafaxine,

- Diabetic neuropathy; urinary incontinence; abdominal pain; neuropathic pain; migraine prophylaxis; chronic tension headache; nocturnal enuresis
  - e.g. duloxetine; amitriptyline; imipramine

Best to refer to these drugs by their class e.g. SSRI, SNRI, TCA, RIMA, MAOI, NaSSA than ‘antidepressant’

- 522 double-blind RCTs
- n=116,477
- published, unpublished, ongoing
- 21 antidepressants
  - vs placebo
  - head-to-head
- mod-severe MDD
- first-line treatment
- acute effects (med=8w)
- excludes TRD and psychosis

All second-generation ADs approved in USA, Europe, Japan
Also: amitriptyline, clomipramine, trazodone, nefazodone
All antidepressants **more effective than placebo** (OR: 2.13-1.37) in MDD

Differences between ADs are modest

More effective than other ADs:
- agomelatine
- paroxetine
- amitriptyline
- venlafaxine
- escitalopram
- vortioxetine
- mirtazapine

Least efficacious:
- fluoxetine
- reboxetine
- fluvoxamine
- trazodone
Lithium

- Lithium is an alkali metal usually administered as a salt (carbonate, citrate)
- First used in psychiatric disorder by Australian psychiatrist John Cade
  - Guinea pigs injected i.p. became lethargic and unresponsive
  - Then orally on himself
  - Open trial on psychotic patients; manic patients responded (Cade 1949)
- Absorbed rapidly from upper GIT:
  - Cmax ~2-3 hr
  - Distribution phase 5-7 hr
  - No significant fluctuations in blood levels by 12 hr: after single dose at night, take blood sample at 12±0.5 hr
  - Elimination half-life: 10-24 hr, depending on renal function
  - Steady state by 5 half-lives
- Not bound to plasma proteins, is not metabolised, and is excreted unchanged almost solely by the kidney
- M/R tablets (Priadel, Camcolit 400, Liskonum) delay dissolving:
  - Lower peak serum levels → ↓ incidence of nausea and tremor
  - If too slowed, less will be absorbed and more delivered lower GIT → colonic irritation and osmotic effect on drawing water into GIT → diarrhoea
Lithium: clinical indications

- Indications:
  - Moderate to severe mania (NNT=6)
  - Maintenance/prophylaxis in bipolar disorder; Li is first line mood stabiliser (NICE, BAP)
  - Protection against mania (NNT=10) > against depression (NNT=14)
  - Antidepressant augmentation in major depressive disorder

- Lithium is a **first-line treatment for all phases of bipolar disorder** (acute mania, acute depression, maintenance). i.e. it is a true ‘mood stabiliser’

- Reduces risk of **attempted and completed suicide** in bipolar disorder (by 80%) and in MDD (slightly smaller effect size)

- Narrow therapeutic index:
  - Minimum therapeutic concentration: 0.4 mmol/L

- Recommended in bipolar disorder:
  - Initially 0.6-0.8 mmol/L
  - If still unstable, trial of 0.8-1.0 mmol/L

- Reliable risk of toxicity at $\geq 1.5$ mmol/L
Lithium: mechanisms of action

- Wide range of immediate and long-term effects.
- However, their relative contributions, if any, to the therapeutic benefits of lithium remains unclear.
- Effects include:
  - ↑ 5-HT and GABA (inhibitory) neurotransmission
  - ↓ glutamate and DA neurotransmission
    ➢ Possibly via effects on adenylate cyclase, inositol metabolism and protein kinase C activity
  - ↓ oxidative stress
  - ↑ trophic and protective factors e.g. BDNF and the anti-apoptotic factor B-cell lymphoma-2 (Bcl-2)
    ➢ preserves or increases the volume of brain structures involved in emotional regulation such as the prefrontal cortex, hippocampus and amygdala
Clinical use of lithium: antimanic

Ranking of antimanic drugs according to primary outcomes: efficacy and dropout rate (Cipriani et al. 2011)
Efficacy of antimanic drugs vs placebo (Yildiz et al. 2015).

MTM=multiple treatment meta-analysis (i.e. ‘network’ meta-analysis)

SPM=standard pair-wise meta-analysis
CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder (Yatham et al, 2018)

<table>
<thead>
<tr>
<th>TABLE 12</th>
<th>Hierarchical rankings of first and second-line treatments recommended for management of acute mania</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of evidence by phase of treatment</strong></td>
<td><strong>Maintenance</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>First-line treatments: Monotherapies</strong></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Divalproex</td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td></td>
</tr>
<tr>
<td>Paliperdone (&gt;6 mg)</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
<td></td>
</tr>
<tr>
<td><strong>First-line treatments: Combination therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Quetiapine + Li/DVP</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole + Li/DVP</td>
<td></td>
</tr>
<tr>
<td>Risperidone + Li/DVP</td>
<td></td>
</tr>
<tr>
<td>Asenapine + Li/DVP</td>
<td></td>
</tr>
<tr>
<td><strong>Second-line treatments: Combination therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Olanzapine + Li/DVP</td>
<td></td>
</tr>
<tr>
<td>Lithium + DVP</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
</tr>
<tr>
<td>ECT</td>
<td></td>
</tr>
</tbody>
</table>

DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium.

- level 1 evidence; • level 2 evidence; ● level 3 evidence; ◆ level 4 evidence; ■ level 1 negative evidence; □ level 2 negative evidence; ◼ level 3 negative evidence; ◻ level 4 negative evidence; n.d., no data; – Limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; ++++, significant impact on treatment selection.
CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder (Yatham et al, 2018)

<table>
<thead>
<tr>
<th>First-line treatments</th>
<th>Level of evidence by phase of treatment</th>
<th>Considerations for treatment selection</th>
<th>Maintenance</th>
<th>Tolerability concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maintenance</td>
<td>Acute</td>
<td>Safety concerns</td>
<td>Tolerability concerns</td>
</tr>
<tr>
<td></td>
<td>Prevention of any mood episode</td>
<td>Prevention of depression</td>
<td>Prevention of mania</td>
<td>Depression</td>
</tr>
<tr>
<td>Lithium</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>⬤</td>
<td>⬤</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Divalproex</td>
<td>⬤</td>
<td>⬤</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>⬤</td>
<td>⬤</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Asenapine</td>
<td>⬤</td>
<td>n.d.</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Quetiapine + Li/DVP</td>
<td>⬤</td>
<td>⬤</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Aripiprazole + Li/DVP</td>
<td>⬤</td>
<td>n.d.</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>⬤</td>
<td>n.d.</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Aripiprazole OM</td>
<td>⬤</td>
<td>n.d.</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second-line treatments</th>
<th>Level of evidence by phase of treatment</th>
<th>Considerations for treatment selection</th>
<th>Maintenance</th>
<th>Tolerability concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maintenance</td>
<td>Acute</td>
<td>Safety concerns</td>
<td>Tolerability concerns</td>
</tr>
<tr>
<td></td>
<td>Prevention of any mood episode</td>
<td>Prevention of depression</td>
<td>Prevention of mania</td>
<td>Depression</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone LAI</td>
<td>⬤</td>
<td>n.d.</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone LAI (adj)</td>
<td>⬤</td>
<td>n.d.</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>⬤</td>
<td>⬤</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Paliperidone (+6 mg)</td>
<td>⬤</td>
<td>n.d.</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Lurasidone + Li/DVP</td>
<td>⬤</td>
<td>n.d.</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Ziprasidone + Li/DVP</td>
<td>⬤</td>
<td>n.d.</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

DVP, divalproex; LAI, long-acting injectable; Li, lithium; OM, once monthly.
- ⬤, level 1 evidence; ⬤, level 2 evidence; ⬤, level 3 evidence; ⬤, level 4 evidence; ⬤, level 1 negative evidence; ⬤, level 2 negative evidence; ⬤, level 3 negative evidence; ⬤, level 4 negative evidence; n.d., no data; – limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; ++++, significant impact on treatment selection.
CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder (Yatham et al, 2018)

**Table 14** Hierarchical rankings of first and second-line treatments recommended for management of acute bipolar I depression

<table>
<thead>
<tr>
<th>Level of evidence by phase of treatment</th>
<th>Considerations for treatment selection</th>
<th>Maintenance</th>
<th>Tolerability concerns</th>
<th>Safety concerns</th>
<th>Tolerability concerns</th>
<th>Safety concerns</th>
<th>Tolerability concerns</th>
<th>Risk of manic/hypomanic switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>++</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Lurasidone + Li/DVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>++</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>++</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Lurasidone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Lamotrigine (adj)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>++</td>
<td>+</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Second-line treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalprox</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>SSRIs/bupropion (adj)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.d.</td>
<td>-</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>ECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.d.</td>
<td>+</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Cariprazine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.d.</td>
<td>-</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine-fluoxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.d.</td>
<td>+</td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>

adj, adjunctive; DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium; SSRIs, selective serotonin reuptake inhibitors.

- level 1 evidence; ≠ level 2 evidence; ≠ level 3 evidence; ≠ level 4 evidence; ≠ level 1 negative evidence; ≠ level 2 negative evidence; ≠ level 3 negative evidence; ≠ level 4 negative evidence; n.d., no data; — limited impact on treatment selection; — minor impact on treatment selection; ++, moderate impact on treatment selection; +++., significant impact on treatment selection.
Lithium augmentation in TRD: 1st vs 2nd generation ADs

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lithium</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>1.1.1 TCAs or 1st Generation Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kantor et al 1986</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Zusky et al 1988</td>
<td>3</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Schöpf et al 1989</td>
<td>7</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Brown et al 1990</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Joffe et al 1993</td>
<td>9</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Katona lofepramine 1995</td>
<td>9</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Nierenberg et al 2003</td>
<td>2</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>34</td>
<td>21</td>
<td>79</td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 6.52, df = 6 (P = 0.37); I² = 8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.92 (P = 0.003)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.1.2 SSRIs or 2nd Generation Agents</th>
<th>Lithium</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Katona fluoxetine 1995</td>
<td>10</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Baumann et al 1996</td>
<td>6</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Joffe et al 2006</td>
<td>3</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>36</td>
<td>38</td>
<td>34.8%</td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.59, df = 2 (P = 0.45); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.31 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total (95% CI) | 115 | 122 | 100.0% | 2.89 [1.65, 5.05] |
| Total events   | 53  | 31  |         |                     |
| Heterogeneity: Chi² = 8.13, df = 9 (P = 0.52); I² = 0% |
| Test for overall effect: Z = 3.72 (P = 0.0002) |
| Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88); I² = 0% |
Valproate

- Valproate - a generic term used to describe:
  - valproic acid
  - sodium valproate (the sodium salt of the acid)
  - valproate semisodium (a coordination complex of valproic acid and sodium valproate in a 1:1 molar relationship). AKA divalproex sodium (divalproate) in the USA.

- Both semisodium and sodium valproate are metabolised to valproic acid, which is the pharmacologically active component.
Valproate: history

- valproic acid (2-propylpentanoic acid)
  - a branched-chain fatty acid derived from valeric acid which is naturally produced by the perennial flowering plant valerian (Valeriana officinalis)
  - first synthesised by Burton in 1882, but there was no known clinical use until its anticonvulsant properties were fortuitously discovered by Eymard in France in 1962 while using it as a solvent for preclinical drug testing (Löscher 1999).
  - introduced into clinical practice for epilepsy in 1967 and is used worldwide as a major anticonvulsant drug for all forms of epilepsy.
  - subsequently shown to be effective in bipolar disorder and in the prevention of migraine headaches.
In the UK, **Depakote** (valproate semisodium) and **Episenta** (sodium valproate) are the only available valproate preparations licensed for use in bipolar disorder, for the following therapeutic indications (BNF 2018):

- Treatment of **manic episode** in bipolar disorder when lithium is contraindicated or not tolerated
- The **continuation of treatment** after manic episode could be considered in patients who have responded [to Depakote or sodium valproate] for acute mania
Valproate: mechanism of action

- Wide range of immediate and long-term biochemical and genomic effects (Rosenberg 2007).
- However, their relative contributions, if any, to the therapeutic benefits of valproate, and whether these differ between epilepsy, bipolar disorder, and migraine prophylaxis, remains unclear.

<table>
<thead>
<tr>
<th>Acute effects</th>
<th>Longer-term effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ GABA</td>
<td>Changes in:</td>
</tr>
<tr>
<td>↓ neuronal excitability via the blockade of voltage-</td>
<td>o glucocorticoid, 5-HT and DA neurotransmitter systems</td>
</tr>
<tr>
<td>gated Na+ channels</td>
<td>o inositol metabolism and protein kinase C activity</td>
</tr>
<tr>
<td></td>
<td>o Wnt/β-catenin cell signalling pathway</td>
</tr>
<tr>
<td></td>
<td>o brain lipids and their metabolism</td>
</tr>
<tr>
<td></td>
<td>↑ trophic and protective factors e.g. BDNF and the anti-apoptotic factor B-cell lymphoma-2 (Bcl-2)</td>
</tr>
<tr>
<td></td>
<td>Class I histone deacetylases (HDAC) inhibition → altered gene expression</td>
</tr>
</tbody>
</table>
Clinical use of valproate: bipolar disorder

- The great majority of clinical trials of valproate in mental disorders have used valproate semisodium (Depakote; divalproex).

- In bipolar disorder, valproate is effective for all illness phases:
  - acute mania (moderate-to-good)
  - acute depression (weaker)
  - maintenance (moderate)

- It is included among first-line treatments for acute mania and maintenance treatment of bipolar I disorder in national and international guidelines (e.g. Yatham et al. 2018; Goodwin et al. 2016).
Clinical use of valproate: antimanic

1. Acute antimanic efficacy

- Network meta-analyses rank valproate lower than:
  - $D_2$ receptor antagonists/partial agonists (antipsychotics)
  - lithium
- the differences are not great and valproate has modest tolerability advantages over lithium and some antipsychotics (Cipriani et al. 2011; Yildiz et al. 2015).
Clinical use of valproate: antimanic

Ranking of antimanic drugs according to primary outcomes: efficacy and dropout rate (Cipriani et al. 2011)
Clinical use of valproate: antimanic

Efficacy of antimanic drugs vs placebo (Yildiz et al. 2015).

MTM=multiple treatment meta-analysis (i.e. ‘network’ meta-analysis)
SPM=standard pair-wise meta-analysis
## CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder (Yatham et al, 2018)

### TABLE 12 Hierarchical rankings of first and second-line treatments recommended for management of acute mania

<table>
<thead>
<tr>
<th>Level of evidence by phase of treatment</th>
<th>Considerations for treatment selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</td>
<td>Safety concerns</td>
</tr>
<tr>
<td>Acute mania</td>
<td>Prevention of any mood episode</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>First-line treatments: Monotherapies</td>
<td>-</td>
</tr>
<tr>
<td>Lithium</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>-</td>
</tr>
<tr>
<td>Divalproex</td>
<td>+</td>
</tr>
<tr>
<td>First-line treatments: Combination therapies</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine + Li/DVP</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole + Li/DVP</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone + Li/DVP</td>
<td>+</td>
</tr>
<tr>
<td>Asenapine + Li/DVP</td>
<td>+</td>
</tr>
<tr>
<td>Second-line treatments: Combination therapies</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine + Li/DVP</td>
<td>+</td>
</tr>
<tr>
<td>Lithium + DVP</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+</td>
</tr>
<tr>
<td>ECT</td>
<td>+</td>
</tr>
</tbody>
</table>

DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium.

- Level 1 evidence; ●, level 2 evidence; ●, level 3 evidence; ●, level 4 evidence; □, level 1 negative evidence; □, level 2 negative evidence; □, level 3 negative evidence; □, level 4 negative evidence; n.d., no data; - Limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; ++++, significant impact on treatment selection.
2. Maintenance treatment

• RCT evidence for valproate is weak
• Efficacy in reducing manic and depressive relapses in bipolar I disorder is strongly supported by good long-term naturalistic data
• Nevertheless, current guidelines advocate using lithium as initial monotherapy above other maintenance treatments due to its
  o superior evidence for prevention of new episodes (both mania and depression)
  o greater evidence base documenting the risks of prolonged exposure
  o efficacy in reducing the risk of suicide.
CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder (Yatham et al, 2018)

**TABLE 17** Hierarchical rankings of first- and second-line treatments recommended for maintenance treatment in bipolar disorder

<table>
<thead>
<tr>
<th>Level of evidence by phase of treatment</th>
<th>Considerations for treatment selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</td>
<td>Acute</td>
</tr>
<tr>
<td>Prevention of any mood episode</td>
<td>Safety concerns</td>
</tr>
<tr>
<td>Prevention of depression</td>
<td>Safety concerns</td>
</tr>
<tr>
<td>Prevention of mania</td>
<td>Safety concerns</td>
</tr>
<tr>
<td>Acute</td>
<td>Safety concerns</td>
</tr>
<tr>
<td>Depression</td>
<td>Safety concerns</td>
</tr>
<tr>
<td>Mania</td>
<td>Safety concerns</td>
</tr>
</tbody>
</table>

**First-line treatments**

- **Lithium**
  - Prevention of any mood episode: ●
  - Prevention of depression: ●
  - Prevention of mania: ●
  - Depression: ●
  - Mania: ●
  - Safety concerns: +
  - Tolerability concerns: +

- **Quetiapine**
  - Prevention of any mood episode: ●
  - Prevention of depression: ●
  - Prevention of mania: ●
  - Depression: ●
  - Mania: ●
  - Safety concerns: +
  - Tolerability concerns: ++

- **Divalproex**
  - Prevention of any mood episode: ●
  - Prevention of depression: ●
  - Prevention of mania: ●
  - Depression: ●
  - Mania: ●
  - Safety concerns: -
  - Tolerability concerns: +

- **Lamotrigine**
  - Prevention of any mood episode: ●
  - Prevention of depression: ●
  - Prevention of mania: ●
  - Depression: ●
  - Mania: ■
  - Safety concerns: +
  - Tolerability concerns: -

- **Asenapine**
  - Prevention of any mood episode: ●
  - Prevention of depression: ●
  - Prevention of mania: ●
  - Depression: ●
  - Mania: ■
  - Safety concerns: +
  - Tolerability concerns: -

- **Quetiapine + Li/DVP**
  - Prevention of any mood episode: ●
  - Prevention of depression: ●
  - Prevention of mania: ●
  - Depression: ●
  - Mania: ●
  - Safety concerns: +
  - Tolerability concerns: ++
  - Safety concerns: ++
  - Tolerability concerns: +

- **Aripiprazole + Li/DVP**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: +
  - Tolerability concerns: +%c
  - Safety concerns: +
  - Tolerability concerns: +

- **Aripiprazole**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: -
  - Tolerability concerns: +

- **Aripiprazole OM**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: -
  - Tolerability concerns: -

**Second-line treatments**

- **Olanzapine**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: +
  - Tolerability concerns: ++
  - Safety concerns: +++
  - Tolerability concerns: +

- **Risperidone LAI**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: -
  - Tolerability concerns: +

- **Risperidone LAI (adj)**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: +
  - Tolerability concerns: ++
  - Safety concerns: +++
  - Tolerability concerns: +

- **Carbamazepine**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: +
  - Tolerability concerns: ++
  - Safety concerns: +
  - Tolerability concerns: +

- **Paliperidone (+6 mg)**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: -
  - Tolerability concerns: +

- **Lurasidone + Li/DVP**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: +
  - Tolerability concerns: ++
  - Safety concerns: ++
  - Tolerability concerns: +

- **Ziprasidone + Li/DVP**
  - Prevention of any mood episode: ○
  - Prevention of depression: ○
  - Prevention of mania: ○
  - Depression: ●
  - Mania: ●
  - Safety concerns: ++
  - Tolerability concerns: ++
  - Safety concerns: +

---

DVP, divalproex; LAI, long-acting injectable; Li, lithium, OM, once monthly.

●, level 1 evidence; ○, level 2 evidence; ◇, level 3 evidence; ◇, level 4 evidence; ■, level 1 negative evidence; □, level 2 negative evidence; £, level 3 negative evidence; £, level 4 negative evidence; n.d., no data; - limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; ++++, significant impact on treatment selection.
3. Acute bipolar depressive episodes

- Valproate has evidence for effectiveness in reducing depressive symptoms and improving the chances of both response and remission (Bond et al. 2010; Smith et al. 2010).

- However, the average effect size and the evidence base are small, and a larger more convincing RCT is needed to establish efficacy (Goodwin et al. 2016).

- In recent guidelines valproate is included among second line treatments for bipolar I depression and third line treatments for bipolar II depression and maintenance (Yatham et al. 2018).
CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder (Yatham et al, 2018)

### Table 14: Hierarchical rankings of first and second-line treatments recommended for management of acute bipolar I depression

<table>
<thead>
<tr>
<th>Level of evidence by phase of treatment</th>
<th>Considerations for treatment selection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute depression</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>First-line treatments</strong></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>○</td>
</tr>
<tr>
<td>Lurasidone + Li/DVP</td>
<td>●</td>
</tr>
<tr>
<td>Lithium</td>
<td>○</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>○</td>
</tr>
<tr>
<td>Lurasidone (adj)</td>
<td>○</td>
</tr>
<tr>
<td>Lamotrigine (adj)</td>
<td>○</td>
</tr>
<tr>
<td><strong>Second-line treatments</strong></td>
<td></td>
</tr>
<tr>
<td>Divalproex</td>
<td>○</td>
</tr>
<tr>
<td>SSRIs/bupropion (adj)</td>
<td>○</td>
</tr>
<tr>
<td>ECT</td>
<td>○</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>○</td>
</tr>
<tr>
<td>Olanzapine-fluoxetine</td>
<td>○</td>
</tr>
</tbody>
</table>

adj: adj: adjuvant; DVP: divalproex; ECT, electroconvulsive therapy; Li, lithium; SSRIs, selective serotonin reuptake inhibitors.

○, level 1 evidence; ●, level 2 evidence; ○, level 3 evidence; ●, level 4 evidence; □, level 1 negative evidence; □, level 2 negative evidence; □, level 3 negative evidence; □, level 4 negative evidence; n.d., no data; −, limited impact on treatment selection; , minor impact on treatment selection; ++, moderate impact on treatment selection; ++++, significant impact on treatment selection.
Clinical use of valproate: other disorders

Major depressive disorder (MDD; ‘unipolar’ depression)

• several small open studies and case reports have found benefits of antidepressant augmentation with valproate in resistant depression (Davis et al. 2000; Ghabrash et al. 2016).

• However, recent treatment guidelines have found no RCT evidence in the literature (Cleare et al. 2015).
Clinical use of valproate: other disorders

Schizophrenia

- Clear benefits of use for prophylaxis of clozapine-induced myoclonic jerks and seizures.
- Little if any benefit as an adjunct to antipsychotics for reduction of core symptoms in treatment-resistant schizophrenia.
  - Open trials report small improvement in total psychopathology with the addition of valproate, but no significant improvement in RCTs or studies beyond four weeks duration (Tseng et al. 2016; Wang et al. 2008).
  - Aggression scores were lower in patients receiving valproate, but the evidence quality was very low.
  - Further randomised, blinded studies are necessary before any clear recommendation can be made, and on current evidence no single co-treatment strategy, let alone valproate, can be recommended for patients with schizophrenia (Correll et al. 2017).
Symptom reduction in personality disorders

- Modest evidence that valproate is superior to placebo (Huband et al. 2010; Citrome and Volavka 2011):
  - outpatient men with recurrent impulsive aggression
  - impulsively aggressive adults with cluster B personality disorders (antisocial, borderline, histrionic and narcissistic)
  - youths with conduct disorder
- In borderline personality disorder (BPD), valproate was superior to placebo for interpersonal problems and depression, but not for impulsivity or suicidal thoughts (Stoffers et al. 2010).
- However, the evidence base is very small, and the current NICE guidelines do not recommend drug treatment for BPD (National Institute for Health and Clinical Excellence 2009).
Clinical use: starting, monitoring and stopping

- Check **FBC** and **LFTs** before starting, after six months treatment, and when symptoms of liver or blood disorders occur (Sie 2014).
- The SmPC recommends checking **FBC**, **bleeding time** and **coagulation tests** before starting valproate or before surgery, and in case of spontaneous bruising or bleeding.
- Measure **weight** or **BMI** before initiation and monitor regularly.
- Some preliminary naturalistic evidence to suggest that abrupt withdrawal of valproate and some other maintenance medications in bipolar disorder (carbamazepine, antipsychotics and antidepressants) is also associated with increased risk of relapse into a mood episode, particularly mania or hypomania (Franks et al. 2008).
- In the absence of better evidence, **if valproate is to be withdrawn it should be done slowly over at least four weeks.**
Clinical use: serum levels

- Reference range for trough total serum valproate quoted by UK laboratories is 50-100 mg/L
  - ‘Trough’ = 12-hour post-dose for OD dosing; pre-dose for BD dosing
  - Based on the epilepsy literature
- Therapeutic range for bipolar disorder is unclear
  - Clinical trials have used **50-125 mg/L**, and this has become generally accepted
- For acute mania:
  - correlation between levels and therapeutic effects is generally weak
  - one study found response only >70 and best at >94 mg/L (Allen et al. 2006).
  - some patients may benefit from levels in the 100-125 mg/L range
- For maintenance:
  - level below 50 mg/L is unlikely to be effective
  - between 50-100 mg/L is probably optimal
  - 100-125 mg/L may confer benefit in some cases
Lamotrigine: history

- A phenyltriazine compound synthesised as one of a sequence of folic acid antagonists based on evidence dating from the mid-1960s that folate was proconvulsant (Brodie 1992).

- Human phase I studies started in the early 1980s, and it was first approved for the treatment of epilepsy in 1990 in Ireland and in the UK in 1991 (Yasam et al. 2016).

- For epilepsy: used worldwide to treat partial seizures, primary and secondary tonic-clonic seizures, seizures associated with Lennox-Gastaut syndrome, and typical absence seizures in children and adolescents.

- Based on early reports of improved mood and communicativeness in patients taking it for epilepsy, lamotrigine started to be used off-license in the early 1990s for individual patients with bipolar disorder.

- It showed promising results in a number of open-label trials, before being commercially developed in a large programme of randomised controlled trials (RCTs) (Weisler et al. 2008).
Lamotrigine is currently licensed in the UK at doses up to 200 mg/day for prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes.
Lamotrigine: mechanism of action

- Inhibits voltage-gated Na\(^+\) channels which reduces neuronal excitability
- Reduces the presynaptic release of excitatory amino acid neurotransmitters such as glutamate and aspartate
- These effects are likely to contribute to its anticonvulsant properties.
- Mechanism of action in bipolar disorder has not been established:
  - Inhibition of voltage-gated Na\(^+\) channels is likely to be important
  - Potential contributions from blockade of L-, N-, and P-type voltage-gated Ca\(^{2+}\) channels and weak 5-HT\(_3\) receptor antagonism.
1. Bipolar depression

- Lamotrigine has established acute efficacy for bipolar depression both as a monotherapy and in combination with lithium and quetiapine (Geddes, Calabrese, and Goodwin 2009; van der Loos et al. 2009; Geddes et al. 2016)

- Very low risk of inducing a switch to mania (Taylor et al. 2014).
2. Maintenance treatment

- Protective against relapse of depression but less effective against mania (Goodwin et al. 2004; Geddes et al. 2016)
- Usually needs to be combined with a more effective agent preventing recurrence of mania.

3. Acute antimanic efficacy

- Lamotrigine is not effective as an acute antimanic agent (Cipriani et al. 2011; Yildiz et al. 2015).
Lamotrigine is among first- or second-line treatments for:

- acute episodes of depression in bipolar I and bipolar II
- maintenance in bipolar I and II, particularly when depression is the major burden (for example, Yatham et al. 2018; Goodwin et al. 2016).

### CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder (Yatham et al, 2018)

**TABLE 14** Hierarchical rankings of first and second-line treatments recommended for management of acute bipolar I depression

<table>
<thead>
<tr>
<th></th>
<th>Level of evidence by phase of treatment</th>
<th>Considerations for treatment selection</th>
<th>Maintenance</th>
<th>Risk of manic/hypomanic switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Lurasidone + Li/DVP</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Lithium</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Lamotrigine (adj)</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Second-line treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalproex</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>SSRIs/bupropion (adj)</td>
<td>⬤</td>
<td>n.d.</td>
<td>⬤</td>
<td>n.d.</td>
</tr>
<tr>
<td>ECT</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>⬤</td>
<td>n.d.</td>
<td>⬤</td>
<td>n.d.</td>
</tr>
<tr>
<td>Olanzapine-fluoxetine</td>
<td>⬤</td>
<td>n.d.</td>
<td>⬤</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

adj: adjunctive; DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium; SSRIs, selective serotonin reuptake inhibitors. ⬤, level 1 evidence; ⬤, level 2 evidence; ⬤, level 3 evidence; ⬤, level 4 evidence; ⬤, level 1 negative evidence; ⬤, level 2 negative evidence; ⬤, level 3 negative evidence; ⬤, level 4 negative evidence; n.d., no data; --, limited impact on treatment selection; ++, moderate impact on treatment selection; ++++, significant impact on treatment selection.
CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder (Yatham et al, 2018)

**TABLE 17** Hierarchical rankings of first- and second-line treatments recommended for maintenance treatment in bipolar disorder

<table>
<thead>
<tr>
<th>Level of evidence by phase of treatment</th>
<th>Considerations for treatment selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</td>
<td>Acute</td>
</tr>
<tr>
<td></td>
<td>Safety concerns</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
</tr>
<tr>
<td>First-line treatments</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>●</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>●</td>
</tr>
<tr>
<td>Divalproex</td>
<td>●</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>●</td>
</tr>
<tr>
<td>Asenapine</td>
<td>●</td>
</tr>
<tr>
<td>Quetiapine + Li/DVP</td>
<td>●</td>
</tr>
<tr>
<td>Aripiprazole + Li/DVP</td>
<td>●</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>●</td>
</tr>
<tr>
<td>Aripiprazole OM</td>
<td>●</td>
</tr>
<tr>
<td>Second-line treatments</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>●</td>
</tr>
<tr>
<td>Risperidone LAI</td>
<td>●</td>
</tr>
<tr>
<td>Risperidone LAI (adj)</td>
<td>●</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>●</td>
</tr>
<tr>
<td>Paliperidone (+6 mg)</td>
<td>●</td>
</tr>
<tr>
<td>Lurasidone + Li/DVP</td>
<td>●</td>
</tr>
<tr>
<td>Ziprasidone + Li/DVP</td>
<td>●</td>
</tr>
</tbody>
</table>

DVP, divalproex; LAI, long-acting injectable; Li, lithium, OM, once monthly.
●, level 1 evidence; ●, level 2 evidence; ●, level 3 evidence; ●, level 4 evidence; ■, level 1 negative evidence; ■, level 2 negative evidence; ■, level 3 negative evidence; ■, level 4 negative evidence; n.d., no data; - limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++ significant impact on treatment selection.
Major depressive disorder (MDD; ‘unipolar’ depression)

- Meta-analysis: augmentation of an antidepressant with lamotrigine 50-200 mg/day is not significantly better than placebo (Zhou et al. 2015).

- However, because of the need for slow titration, short-term treatment trials may not be the optimum design to assess the effectiveness of lamotrigine.

- Larger and longer RCTs are needed at optimum doses for an adequate duration.
# RCTs of lamotrigine augmentation of ADs

Table courtesy of Prof Hamish McAllister-Williams, Newcastle University

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnoses</th>
<th>N</th>
<th>Interventions</th>
<th>Duration</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normann et al. J Clin Psychiatry. 2002</td>
<td>Acute depressive episode, 7 with bipolar disorder; variable treatment resistance</td>
<td>40</td>
<td>Parox 40 mg/d + lamot 200 mg/d or placebo</td>
<td>9 weeks</td>
<td>NS on HAM-D</td>
<td>Sign. on CGI-S and other secondary outcomes</td>
</tr>
<tr>
<td>Barbosa et al. J Clin Psychiatry. 2003</td>
<td>MDD (n=15) or bipolar II disorder (n = 8); failed at least 1 previous trial of an antidepressant</td>
<td>23</td>
<td>Fluox 20 mg/d + lamot 100 mg/d or placebo</td>
<td>6 weeks</td>
<td>NS on HAM-D</td>
<td>Sign. on CGI-S and CGI-I (responders: lamotrigine 85%, placebo 30%)</td>
</tr>
<tr>
<td>Santos et al. Prim Care Companion J Clin Psychiatry. 2008</td>
<td>MDD with nonresponse to 2 antidepressants</td>
<td>34</td>
<td>AD + lamot or plac</td>
<td>8 weeks</td>
<td>NS on MADRS</td>
<td>NS of CGI</td>
</tr>
<tr>
<td>Barbee et al. J Clin Psych 2011</td>
<td>MDD with failure of ≥ 1 antidepressant and HAM-D ≥ 15 after 8 weeks of prospective treatment with paroxetine</td>
<td>96</td>
<td>Parox (up to 62.5 mg/d) + lamot (up to 400 mg/d) or placebo</td>
<td>10 weeks</td>
<td>NS on MADRS</td>
<td>NS on HAM-D, CGI-Severity and CGI-I</td>
</tr>
</tbody>
</table>

AD – Antidepressant; NS - not statistically significant; HAM-D - Hamilton Depression Rating Scale; CGI - Clinical Global Impression Scale; CGI-S - CGI Severity; CGI-I - CGI Improvement; MADRS - Montgomery Asberg Depression Rating Scale.
Schizophrenia

1. Augmentation of non-clozapine antipsychotics:
   - Several small trials: improvements in total, positive, and negative symptoms of medium-to-large effect size
   - However, the studies had methodological limitations and their quality was not considered high enough to warrant recommending augmentation with lamotrigine over antipsychotic monotherapy for clinical care guidelines (Correll et al., 2017).

2. Augmentation of clozapine
   - Lamotrigine does not outperform placebo and cannot be recommended on current meta-analytic evidence (Correll et al., 2017).
Clinical use of lamotrigine: other disorders

Borderline personality disorder

• Earlier small, short-term trials suggested benefits for anger and impulsivity (Lieb et al. 2010; Stoffers et al. 2010).

• However, a recent much larger (n=276), 52-week, placebo-controlled RCT found no benefits for overall borderline psychopathology or a range of secondary outcomes including depressive symptoms, deliberate self-harm, social functioning, health-related quality of life, or resource use and costs (Crawford et al. 2018).

• On current evidence, therefore, the use of lamotrigine in people with borderline personality disorder cannot be considered clinically- or cost-effective.
Lamotrigine: starting, monitoring and stopping

- Must be introduced slowly to minimise risk of serious skin rashes
- Dose adjustments are necessary for patients also taking valproate or enzyme inducing drugs.
- Serum concentration monitoring is not usually warranted, and a therapeutic range has not been established:
  - Trough concentration of 2.5-15 mg/L has been suggested (Maudsley Prescribing Guidelines 2015).
  - Monitoring is advised to guide dose adjustments if used during pregnancy and the puerperium.
- Stopping lamotrigine:
  - SmPC indicates that clinical trials found no increase in adverse events following abrupt termination of lamotrigine compared to placebo.
  - It is therefore suggested that patients may terminate lamotrigine without a step-wise dose reduction.
Carbamazepine

- Carbamazepine is a dibenzazepine derivative and chemically related to the tricyclic antidepressants, particularly imipramine.
- Synthesised by Walter Schindler at Swiss company J. R. Geigy in 1953 as a possible competitor for the recently introduced antipsychotic chlorpromazine (Brodie 2010).
- The first study in epilepsy was carried out in 1963, and it was licensed for use in epilepsy in the UK in 1965 and in the US in 1968.
- It is used worldwide as an anticonvulsant for generalised tonic-clonic and partial seizures. It is not usually effective in absences (petit mal) and myoclonic seizures.
- Also used for pain in trigeminal neuralgia and diabetic neuropathy, and as adjunctive treatment in acute alcohol withdrawal.
Carbamazepine: bipolar disorder

- Investigated in bipolar mania in the early 1970s in Japan, where lithium was not yet available. Early open trials found significant acute antimanic and prophylactic efficacy (Okuma et al. 1973; Takezaki and Hanaoka 1971).

- First report outside Japan was of antimanic and antidepressant benefits in bipolar patients who had not responded favourably to lithium (Ballenger and Post 1978, 1980).

- Not approved for bipolar disorder in the USA until 2005.

- Not commonly used in the UK any more, particularly due to its pharmacokinetic interactions with a wide range of other medications and its adverse effect profile in longer-term use.

- However, it still has a place in the antimanic and maintenance treatment of patients with bipolar disorder who have not adequately responded to lithium and other first-line treatments.
In the UK, carbamazepine is licensed for prophylaxis of bipolar disorder unresponsive to lithium.
Carbamazepine: mechanism of action
(Rapoport et al. 2009; Drugbank: carbamazepine).

- Carbamazepine inhibits sustained repetitive neuronal firing by blocking voltage-gated Na$^+$ channels in their inactivated state.
  - VGNC block in trigeminal nucleus believed to underlie its effects on pain.
  - Seizure control may be due to reduction of post-tetanic potentiation of synaptic transmission in the spinal cord.

- Mechanisms in bipolar disorder are not well understood:
  - blockade of voltage-gated Na$^+$ channels is likely to contribute
  - reduced release of glutamate
  - actions via dopamine D$_2$ and glutamate NMDA receptors to downregulate the arachidonic acid cascade, with neuroprotective effects including increased BDNF and Bcl-2
  - effects on adenosine receptors, adenylate cyclase, and protein kinase C activity
  - effects on monoamine neurotransmitter systems including noradrenaline reuptake inhibition
Carbamazepine: evidence for effectiveness

Acute antimanic efficacy

- Carbamazepine has good evidence as an antimanic agent, with efficacy broadly comparable to antipsychotics and lithium, and slightly better than valproate (Cipriani et al. 2011; Yildiz et al. 2015).

- However, due to safety and tolerability concerns, guidelines recommend it among second-line antimanic treatments when first-line options have failed, or in combination with lithium or valproate among third-line treatments in more resistant mania (Yatham et al. 2018; Goodwin et al. 2016).
Clinical use of carbamazepine: antimanic

Ranking of antimanic drugs according to primary outcomes: efficacy and dropout rate (Cipriani et al. 2011)
Clinical use of carbamazepine: antimanic

Efficacy of antimanic drugs vs placebo (Yildiz et al. 2015).

MTM=multiple treatment meta-analysis (i.e. ‘network’ meta-analysis)
SPM=standard pair-wise meta-analysis
## Table 12: Hierarchical rankings of first and second-line treatments recommended for management of acute mania

<table>
<thead>
<tr>
<th>Level of evidence by phase of treatment</th>
<th>Considerations for treatment selection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute mania</strong></td>
<td><strong>Maintenance</strong></td>
</tr>
<tr>
<td><strong>Prevention of any mood episode</strong></td>
<td><strong>Prevention of mania</strong></td>
</tr>
<tr>
<td><strong>Safety concerns</strong></td>
<td><strong>Tolerability concerns</strong></td>
</tr>
<tr>
<td><strong>Risk of depressive switch</strong></td>
<td></td>
</tr>
</tbody>
</table>

### First-line treatments: Monotherapies

- **Lithium**
- **Quetiapine**
- **Divalproex**
- **Asenapine**
- **Aripiprazole**
- **Paliperidone (>6 mg)**
- **Risperidone**
- **Cariprazine**

### First-line treatments: Combination therapies

- **Quetiapine + Li/DVP**
- **Aripiprazole + Li/DVP**
- **Risperidone + Li/DVP**
- **Asenapine + Li/DVP**

### Second-line treatments: Combination therapies

- **Olanzapine**
- **Carbamazepine**
- **Olanzapine + Li/DVP**
- **Lithium + DVP**
- **Ziprasidone**
- **Haloperidol**
- **ECT**

---

DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium.

- Level 1 evidence; •, level 2 evidence; ●, level 3 evidence; ○, level 4 evidence; ■, level 1 negative evidence; □, level 2 negative evidence; △, level 3 negative evidence; △△, level 4 negative evidence; n.d., no data; ▴, Limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; ++++, significant impact on treatment selection.
Carbamazepine: evidence for effectiveness

Maintenance treatment in bipolar disorder

• Bipolar I: protective against manic relapse but less effective than lithium and poorly protective against depressive relapse.
  o Recommended as an option when a range of first-line options have been ineffective

• Some evidence that it may be more effective than lithium in patients with bipolar II disorder, schizoaffective disorder, and those who do not have the classical pattern of episodic euphoric mania (Kleindienst and Greil 2000).
CANMAT and ISBD 2018 guidelines for the management of patients with bipolar disorder (Yatham et al, 2018)

**Table 17** Hierarchical rankings of first- and second-line treatments recommended for maintenance treatment in bipolar disorder

<table>
<thead>
<tr>
<th>First-line treatments</th>
<th>Maintenance</th>
<th>Acute</th>
<th>Considerations for treatment selection</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevention of any mood episode</td>
<td>Prevention of depression</td>
<td>Prevention of mania</td>
<td>Depression</td>
</tr>
<tr>
<td>Lithium</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Divalproex</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Asenapine</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Quetiapine + Li/DVP</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Aripiprazole + Li/DVP</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Aripiprazole OM</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Second-line treatments</td>
<td>Prevention of any mood episode</td>
<td>Prevention of depression</td>
<td>Prevention of mania</td>
<td>Depression</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Risperidone LAI</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Risperidone LAI (adj)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Paliperidone (&gt;6 mg)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Lurasidone + Li/DVP</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Ziprasidone + Li/DVP</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

DVP, divalproex; LAI, long-acting injectable; Li, lithium, OM, once monthly.

●, level 1 evidence; ●, level 2 evidence; ●, level 3 evidence; ●, level 4 evidence; ■, level 1 negative evidence; ■, level 2 negative evidence; ■, level 3 negative evidence; ■, level 4 negative evidence; n.d., no data; −, limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; ++++ significant impact on treatment selection.
Carbamazepine: evidence for effectiveness

Acute bipolar depression

- the evidence is poor and recommendations either omit carbamazepine (Goodwin et al. 2016) or relegate it to patients with bipolar I depression who fail to respond to multiple first-and second-line agents (Yatham et al. 2018).
- Carbamazepine does not appear to be effective for depression in bipolar II disorder.
Clinical use of carbamazepine: other disorders

Major depressive disorder (MDD; ‘unipolar’ depression)

- There is a small amount of evidence for possible benefit as monotherapy (Zhang et al. 2008) or when combined with lithium (Kramlinger and Post 1989)
- Small open-label study: did not augment the antidepressant efficacy of mirtazapine (Schule et al. 2009)
- PK effects of carbamazepine to reduce the serum concentrations of a wide range of other drugs are a particular problem, and large well-conducted RCTs which control for drug serum levels are required.
- Carbamazepine is not recommended for unipolar depression in current guidelines.
Clinical use of carbamazepine: other disorders

Schizophrenia
- On current RCT evidence, carbamazepine is not effective in reducing core symptoms of schizophrenia, either in monotherapy or when combined with an antipsychotic (Leucht et al. 2014; Correll et al. 2017).

Alcohol withdrawal syndrome
- Effective as adjunctive treatment (Hammond et al. 2015).

Borderline personality disorder
- no significant benefits in well-controlled trials (Stoffers et al. 2010)

Aggression and impulsivity
- Good evidence for an effect is lacking (Huband et al. 2010)
Carbamazepine: starting, monitoring and stopping

- Baseline: U&Es, FBC, and LFTs; repeat after 6 months.
- Baseline: weight or BMI; monitor during treatment
- Check Na levels at least annually due to the risk of hyponatraemia.
- Before starting, patients from high-risk Asian populations should be genotyped for the HLA-B*1502 allele, which confers a high risk for SJS and toxic epidermal necrolysis (TEN) with carbamazepine.
- Serum trough levels of 7-12 mg/L are suggested for bipolar disorder (Maudsley Prescribing Guidelines 2015), although there is no established relationship between efficacy and serum levels.
- Serum level monitoring:
  - 2-4 weeks after a dose increase
  - routinely every 6-12 months
  - when clinically indicated to check for treatment adherence or to make sure levels are not in the toxic range
Carbamazepine: starting, monitoring and stopping

• Carbamazepine induces the metabolism of many other drugs
  o patients on carbamazepine and other medications should have serum levels of all psychotropic medications monitored, particularly when clinical response is poor, in case dose adjustments are necessary.
  o Similarly, carbamazepine may impair the effectiveness of hormonal contraception and women of child bearing potential should be advised to use alternative contraceptive methods.

• Given preliminary evidence that abrupt withdrawal of carbamazepine may increase the risk of relapse in bipolar disorder, particularly of mania or hypomania (Franks et al. 2008), in the absence of better evidence carbamazepine should be withdrawn slowly over at least four weeks.
Oxcarbazepine and eslicarbazepine

Oxcarbazepine

- A structural derivative of carbamazepine, by adding an extra oxygen atom to the benzylcarboxamide group.
- **Not** a metabolite of carbamazepine.
- The structural change helps reduce the risk of bone marrow toxicity and the strength of induction of hepatic metabolism associated with carbamazepine.
- Oxcarbazepine is a prodrug with little intrinsic activity itself
  - It is metabolised to the active 10-monohydroxy metabolite
  - This metabolite has been named licarbazepine
  - Its active S enantiomer has been developed and marketed as **eslicarbazepine acetate**
- Oxcarbazepine and eslicarbazepine are licensed and effective for partial seizures +/- secondarily generalised tonic-clonic seizures.
Oxcarbazepine and eslicarbazepine:

Mechanism of action

- The mechanism of action of oxcarbazepine and eslicarbazepine is considered to be the same as carbamazepine.
- In comparison with CBZ, oxcarbazepine and eslicarbazepine induce hepatic metabolic enzymes (mainly CYP3A4, CYP3A5, and UDP-glucuronyl transferases) only weakly, so have less effects on the levels of other drugs.
- Nevertheless, the induction is not negligible and oxcarbazepine/eslicarbazepine can reduce the serum levels and effectiveness of other drugs including hormonal contraceptives and the many psychotropic drugs metabolised via CYP3A4.
Oxcarbazepine and eslicarbazepine

Clinical use: evidence for effectiveness

- Clear evidence for antimanic or prophylactic effectiveness in bipolar disorder is lacking

- Oxcarbazepine has been thought of as a safer version of CBZ:
  - Indications for CBZ have tended to be applied to oxcarbazepine by extrapolation (Goodwin et al. 2016).
  - Recommended as an alternative to CBZ among third-line combination treatments for acute mania in adults, but requires further evaluation (Yatham et al. 2018).

- Not an effective treatment in children and adolescents with bipolar disorder (Wagner et al. 2006).

- Eslicarbazepine is not an effective antimanic agent
  - Possibly some efficacy in prevention (Grunze et al. 2015).
  - More data are needed before it can be considered a useful alternative to established medications.
References 1

References 2


• Davis LL et al, 2000. 'Comprehensive review of the psychiatric uses of valproate', Journal of Clinical Psychopharmacology, 20: 1S-17S.


References 3


- Kramlinger KG & Post RM, 1989. 'The addition of lithium to carbamazepine. Antidepressant efficacy in treatment-resistant depression', Archives of General Psychiatry, 46: 794-800.
References 4

- Rosenberg G, 2007. 'The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees?', Cellular & Molecular Life Sciences, 64: 2090-103.
References 5


• Yatham LN et al, 2018. 'Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder', Bipolar Disorders, 20: 97-170.
