

Mood stabilisers

Medicines used to control manic, mixed and depressive episodes of bipolar disorder and to delay their return, grouped here by the clinical job they do rather than by a shared molecular target, because lithium, the anticonvulsant agents and the atypical antipsychotics arrive at that job by entirely separate routes.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/mood-stabilisers>

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Quick revision

One Liner: Mood stabiliser names a job, not a mechanism: lithium, several anticonvulsants and several atypical antipsychotics all hold this role while sharing almost nothing pharmacologically.

1. Lithium's boxed warning states that its toxicity is closely related to serum lithium concentrations and can occur at doses close to therapeutic concentrations. [1]
2. The same warning directs that facilities for prompt and accurate serum lithium determinations should be available before treatment is started. [1]
3. Lithium's label states that the mechanism of action of lithium as a mood stabilising agent is unknown, so the class cannot be taught from a receptor diagram. [1]
4. Lithium is filtered by the glomerulus and roughly 80% is reabsorbed passively in the proximal tubule, which is why it behaves so much like sodium. [1]
5. NSAIDs reduce renal blood flow and therefore reduce renal clearance of lithium; ACE inhibitors and angiotensin receptor blockers raise steady-state concentrations; and diuretic-induced sodium loss does the same. [1]
6. Lithium concentrates within the thyroid and can inhibit thyroid synthesis and release, and long-term use is associated with nephrogenic diabetes insipidus and a chronic tubulointerstitial nephropathy. [1]
7. Valproate given for mood carries the same boxed warnings as in epilepsy: hepatotoxicity, fetal risk and life-threatening pancreatitis. [2]
8. UK regulators state that valproate medicines must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met. [9]
9. For the bipolar indication the MHRA describes an absolute contraindication to valproate in pregnancy, a stricter position than the one that applies in epilepsy. [9]
10. Lamotrigine carries a boxed warning for life-threatening rashes, and coadministration with valproate is among the listed factors that may increase that risk. [3]
11. Lamotrigine's bipolar licence is for maintenance, to delay the time to occurrence of mood episodes; the label says effectiveness in acute treatment of mood episodes has not been established. [3]
12. Carbamazepine is a potent inducer of hepatic CYP3A4 and its boxed warning directs HLA-B*1502 screening in patients with ancestry in genetically at-risk populations. [4]

Overview

1. A mood stabiliser is defined by what it does to the course of bipolar illness, not by how it does it. Lithium is licensed as monotherapy for bipolar I disorder, covering acute manic and mixed episodes and maintenance in patients seven years and older. Extended-release carbamazepine holds an indication for acute manic or mixed episodes; divalproex sodium is indicated for the manic episodes associated with bipolar disorder; and lamotrigine is licensed for maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes. Four agents, four unrelated pharmacological stories, one clinical category. [1][5][2][3]
2. Regulatory text is unusually frank about how little of the underlying pharmacology is settled. Lithium's label says its

mechanism as a mood stabilising agent is unknown. The extended-release carbamazepine label says the mechanism of action of carbamazepine in the treatment of acute manic or mixed episodes associated with bipolar disorder is unclear. The European regulator says olanzapine's exact mechanism of action is unknown, describing only that it attaches to several different receptors on the surface of nerve cells in the brain. A student who tries to memorise one unifying mechanism is memorising something no label claims. [1][5][10]

3. What genuinely separates these medicines is the monitoring each one demands and the harm each one brings. Lithium is dominated by its narrow margin between effect and toxicity, and by its renal and thyroid consequences. Valproate is dominated by reproductive toxicity. Lamotrigine is dominated by skin. Carbamazepine is dominated by enzyme induction and by boxed haematological and dermatological risks. The atypical antipsychotics are dominated by metabolic change and by the class warning on increased mortality in elderly patients with dementia-related psychosis. [1][9][3][4][6]

4. Combinations are anticipated by the labels rather than improvised at the bedside. Olanzapine is indicated for acute manic or mixed episodes both as monotherapy and in combination with lithium or valproate; aripiprazole carries the same pairing; and quetiapine holds a maintenance indication as an adjunct to lithium or divalproex. Adding an antipsychotic to a mood stabiliser therefore adds a second monitoring burden rather than replacing the first. [6][8][7]

Classification and drug examples

Intro: Grouped by the route each agent takes into the same clinical role. The grouping is deliberately not mechanistic, because no mechanism is shared: what the three groups have in common is an evidence base in bipolar disorder, and what separates them is everything else.

1. Name: Lithium salts

1. Note: A single element, with the narrowest therapeutic margin in routine psychiatry and a monitoring requirement written into its boxed warning.

Name: Lithium carbonate

Lithium

Route: Oral

Note: Indicated as monotherapy for bipolar I disorder, for acute manic and mixed episodes and for maintenance, in patients seven years and older. Its elimination half-life is approximately 18 to 36 hours and it is excreted in urine in proportion to its serum concentration. [1] [1]

2. Name: Anticonvulsant mood stabilisers

2. Note: Agents that entered psychiatry from epilepsy. They keep their antiepileptic safety profiles unchanged, which is why the boxed warnings a student learned for seizure control apply here without softening.

1. Name: Sodium valproate

Valproate

1. Route: Oral and intravenous

1. Note: The valproate moiety carries boxed warnings for hepatic failure with fatalities, for major congenital malformations including neural tube defects, and for life-threatening pancreatitis in children and adults. [2]

2. Name: Valproic acid

2. Route: Oral

2. Note: The free acid. Its family shares dose-related thrombocytopenia and a hyperammonaemia that may be present despite normal liver function tests. [2]

3. Name: Divalproex sodium

Valproate semisodium

3. Route: Oral

3. Note: The formulation that carries the US indication for treatment of the manic episodes associated with bipolar disorder. It is contraindicated in known mitochondrial disorders caused by mutations in mitochondrial DNA polymerase gamma. [2]

4. Name: Carbamazepine

4. Route: Oral

4. Note: Formulation matters. The plain tablet label lists epilepsy and trigeminal neuralgia only, while the extended-release capsule is described as a mood stabiliser indicated for acute manic or mixed episodes of bipolar I disorder. [4][5]

5. Name: Lamotrigine

5. Route: Oral

5. Note: The maintenance agent of the group, licensed to delay the time to occurrence of mood episodes in adults already treated for an acute episode with standard therapy. [3] [2][5]

3. Name: Atypical antipsychotics used in bipolar disorder

3. Note: A pharmacologically distinct class that overlaps this one only in indication. They bring a shared boxed warning about deaths in elderly patients with dementia-related psychosis and a shared metabolic liability.

1. Name: Olanzapine

Zyprexa

1. Route: Oral and intramuscular

1. Note: Indicated for acute manic or mixed episodes as monotherapy and in combination with lithium or valproate, and for maintenance treatment of bipolar I disorder as monotherapy in adults. [6]

2. Name: Quetiapine

2. Route: Oral

2. Note: The member with a monotherapy indication for the acute treatment of depressive episodes associated with bipolar disorder, and a maintenance indication as an adjunct to lithium or divalproex. [7]

3. Name: Aripiprazole

Abilify

3. Route: Oral

3. Note: Indicated for acute manic and mixed episodes of bipolar I disorder as monotherapy and as an adjunct to lithium or valproate. Akathisia is its characteristic burden. [8] [6][7]

Mechanism of action

Summary: There is no class mechanism, and the labels say so. Lithium's action as a mood stabilising agent is stated to be unknown; carbamazepine's action in acute manic or mixed episodes is stated to be unclear; and olanzapine's exact mechanism is stated to be unknown, with only receptor attachment described. What can be taught with confidence is how each agent is handled by the body, because that is what predicts the interactions and the monitoring.

Target: Undefined at class level; lithium acts by an unknown mechanism, the anticonvulsant members act on neuronal membranes, and the atypical antipsychotics attach to serotonin and dopamine receptors

Cidal Static: Episode-suppressing and relapse-delaying rather than curative

Kill Kinetics: Effect depends on continued exposure, and for lithium on a serum concentration held within a narrow band

1. Step: 1

1. Title: Lithium acts by a mechanism its label does not claim to know

1. Detail: The lithium carbonate label states that the mechanism of action of lithium as a mood stabilising agent is unknown. Patient-facing NHS material goes no further, saying only that it is thought lithium may protect and help create more neurons. This is not a gap in the teaching; it is the state of the evidence, and a page that invents a receptor for lithium is inventing one. [1][11]

2. Step: 2

2. Title: Lithium is handled by the kidney as though it were sodium

2. Detail: Lithium is filtered by the glomerulus and about 80% is reabsorbed by passive diffusion in the proximal tubule, and it is excreted in urine in proportion to its serum concentration. Every important lithium interaction follows from this

one fact rather than from any central action. [1]

3. Step: 3

3. Title: The anticonvulsant members act on the neuronal membrane, with an antimanic effect that remains unexplained

3. Detail: Carbamazepine and lamotrigine both come to bipolar disorder from epilepsy. The extended-release carbamazepine label states that the mechanism of action of carbamazepine in the treatment of acute manic or mixed episodes associated with bipolar disorder is unclear, and lamotrigine's label identifies it simply as an antiepileptic drug. Their membrane-stabilising pedigree is the reason they sit in this mechanism family, not proof of how they lift mania. [5][3]

4. Step: 4

4. Title: The atypical antipsychotics work through monoamine receptor blockade

4. Detail: The European regulator describes olanzapine's beneficial effect as due to its blocking receptors for the neurotransmitters 5-hydroxytryptamine, also called serotonin, and dopamine, while stating that its exact mechanism of action is unknown. This is a genuinely different route into the same clinical role, and it brings a different set of harms with it. [10]

5. Step: 5

5. Title: Enzyme induction is a mechanism in its own right

5. Detail: Carbamazepine is a potent inducer of hepatic CYP3A4 and also induces CYP1A2, 2B6 and 2C8/9/19, and it induces its own metabolism so that its half-life is variable. Induction is not an adverse effect bolted on to the drug; it is a pharmacological action that changes the concentration of everything else a patient takes. [4][5]

6. Step: 6

6. Title: Renal clearance is the lever that moves lithium concentrations

6. Detail: Because reabsorption of lithium tracks sodium handling, anything that depletes sodium or cuts renal perfusion pushes the serum concentration up. The label names NSAIDs, ACE inhibitors, angiotensin receptor blockers and diuretics, and adds that protracted sweating or diarrhoea reduces tolerance. NHS material warns against a low-sodium diet for the same reason. [1][11]

Major clinical uses

1. Drug: Lithium carbonate

1. Organism: Not applicable

1. Indication: Bipolar I disorder: acute manic and mixed episodes, and maintenance

1. Line: first-line, long established

1. Note: Licensed as monotherapy in patients seven years and older for both the acute and the maintenance phase, which is why it remains the reference agent against which others are judged. [1]

2. Drug: Divalproex sodium

2. Organism: Not applicable

2. Indication: Manic episodes associated with bipolar disorder

2. Line: established, heavily restricted

2. Note: Efficacy is not the constraint. Reproductive toxicity is, and in the UK the regulator's position on the bipolar indication is stricter than its position in epilepsy. [2][9]

3. Drug: Carbamazepine

3. Organism: Not applicable

3. Indication: Acute manic or mixed episodes associated with bipolar I disorder

3. Line: alternative agent

3. Note: Carried by the extended-release capsule, which is described in its label as a mood stabiliser. The plain tablet label does not list a psychiatric indication at all. [5][4]

4. Drug: Lamotrigine

4. Organism: Not applicable

- 4. Indication: Maintenance treatment of bipolar I disorder, delaying the time to occurrence of mood episodes
- 4. Line: maintenance only
- 4. Note: Licensed in adults already treated for acute mood episodes with standard therapy, and explicitly not established for the acute treatment itself. [3]
- 5. Drug: Quetiapine
- 5. Organism: Not applicable
- 5. Indication: Acute depressive episodes of bipolar disorder as monotherapy, and maintenance as an adjunct
- 5. Line: widely used
- 5. Note: The bipolar depression indication is unusual in this group, and the maintenance indication is specifically as an adjunct to lithium or divalproex rather than alone. [7]
- 6. Drug: Olanzapine
- 6. Organism: Not applicable
- 6. Indication: Acute manic or mixed episodes, and maintenance treatment of bipolar I disorder
- 6. Line: widely used
- 6. Note: Holds both a monotherapy indication and a short-term combination indication with lithium or valproate for acute manic or mixed episodes in adults. [6]
- 7. Drug: Aripiprazole
- 7. Organism: Not applicable
- 7. Indication: Acute manic and mixed episodes associated with bipolar I disorder
- 7. Line: widely used
- 7. Note: Available as monotherapy or as an adjunct to lithium or valproate, with akathisia reported far more often in the adjunctive setting than with monotherapy. [8]

Pharmacokinetics

- 1. Drug: Lithium carbonate
- 1. Route: Oral
- 1. Absorption: Oral
- 1. Csf Penetration: Not applicable
- 1. Metabolism: Not metabolised in the hepatic sense; the label describes urinary excretion proportional to serum concentration
- 1. Elimination: Renal, with glomerular filtration and about 80% passive reabsorption in the proximal tubule
- 1. Half Life: Approximately 18 to 36 hours
- 1. Dose Adjust: Geriatric patients often respond to reduced dosage and may show toxicity at serum concentrations ordinarily tolerated by other patients [1]
- 2. Drug: Carbamazepine
- 2. Route: Oral
- 2. Absorption: Oral
- 2. Csf Penetration: Not applicable
- 2. Metabolism: Hepatic; the drug is a potent inducer of CYP3A4 and induces CYP1A2, 2B6 and 2C8/9/19
- 2. Elimination: Hepatic
- 2. Half Life: Variable, because carbamazepine induces its own metabolism
- 2. Dose Adjust: Autoinduction is completed after 3 to 5 weeks of a fixed dosing regimen, so an early concentration does not predict the later one [4][5]
- 3. Drug: Lamotrigine
- 3. Route: Oral
- 3. Absorption: Oral
- 3. Csf Penetration: Not applicable

- 3. Metabolism: Subject to very large interaction effects in both directions, as the label's own concentration data show
- 3. Elimination: Not characterised on this page
- 3. Half Life: Altered by co-medication rather than fixed
- 3. Dose Adjust: Valproate increases lamotrigine concentrations more than two-fold, while carbamazepine, phenytoin, phenobarbital and primidone decrease them by approximately 40% [3]
- 1. This page gives no dose regimens and no target concentrations to aim for. Choosing an agent, adjusting it and deciding how often to measure anything are matters for the treating clinician working from a current prescribing reference and the individual patient's circumstances.
- 2. Lithium is the only member whose serum concentration must be measured as a condition of using it safely, and its label makes availability of that assay a prerequisite for starting treatment. [1]
- 3. Two of the anticonvulsant members are pharmacokinetic opposites in a shared regimen: carbamazepine drives lamotrigine concentrations down, while valproate drives them up. [3]

Adverse effects

- 1. Effect: Early lithium effects
 - 1. Detail: Fine tremor, lightheadedness, lack of coordination and weakness are described as mild signs, and early symptoms include fine hand tremor, polyuria, mild thirst and nausea. The difficulty is that these overlap with the first signs of toxicity. [1]
- 2. Effect: Somnolence with quetiapine
 - 2. Detail: Somnolence was reported in 18% of patients treated with quetiapine in the trials summarised in its label, and patients are cautioned about tasks needing mental alertness until they know how they are affected. [7]
- 3. Effect: Akathisia with aripiprazole
 - 3. Detail: Reported in 13% of adults given aripiprazole as monotherapy for bipolar mania against 4% on placebo, and in 19% when it was added to lithium or valproate against 5% on adjunctive placebo. [8]
- 4. Effect: Weight gain with olanzapine
 - 4. Detail: Its label directs that the potential consequences of weight gain are considered before treatment starts and that patients receive regular monitoring of weight. [6]
- 1. Effect: Lithium toxicity
 - 1. Detail: The boxed warning states that lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to therapeutic concentrations. The label places toxic concentrations at or above 1.5 mEq/L, immediately adjacent to the range quoted for acute treatment of 0.8 to 1.2 mEq/L.
 - 1. Action: Its label makes the availability of prompt and accurate serum determinations a precondition of starting treatment, and any change to therapy is a decision for the treating clinician. [1]
 - 2. Effect: Encephalopathic syndrome with lithium and an antipsychotic
 - 2. Detail: An encephalopathic syndrome has occurred in patients treated with lithium together with an antipsychotic, in some cases followed by irreversible brain damage. The carbamazepine label separately warns that giving carbamazepine with lithium may increase the risk of neurotoxic side effects.
 - 2. Action: Directly relevant because combining a mood stabiliser with an antipsychotic is a licensed strategy in mania, so the combination is common rather than unusual. [1][4]
 - 3. Effect: Renal injury with long-term lithium
 - 3. Detail: Chronic treatment is associated with nephrogenic diabetes insipidus producing polyuria and polydipsia, usually reversible on stopping but only partially so after long exposure, and with a chronic tubulointerstitial nephropathy showing tubular atrophy, interstitial fibrosis and nephron atrophy with cyst formation.
 - 3. Action: Renal function is checked before treatment and followed during it; the interval and the response belong to the treating clinician. [1]
 - 4. Effect: Thyroid and parathyroid disturbance with lithium
 - 4. Detail: Lithium is concentrated within the thyroid and can inhibit thyroid synthesis and release, which can lead to

hypothyroidism. Cases of hyperthyroidism including Graves' disease and toxic multinodular goitre have also been reported, and long-term treatment is associated with persistent hyperparathyroidism and hypercalcaemia.

4. Action: The label directs thyroid function testing before starting, at three months, and every six to twelve months thereafter. [1]

5. Effect: Hepatotoxicity and pancreatitis with valproate

5. Detail: Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives, and cases of life-threatening pancreatitis have been reported in both children and adults. These boxed warnings are unchanged by the fact that the indication being treated is psychiatric.

5. Action: New abdominal symptoms or evidence of hepatic dysfunction require prompt medical assessment rather than watchful waiting. [2]

6. Effect: Fetal harm with valproate

6. Detail: Valproate can cause major congenital malformations, particularly neural tube defects such as spina bifida, and children exposed in utero have lower cognitive test scores than children exposed to another antiepileptic drug. UK figures put physical birth defects at around 10 in every 100 exposed babies against a background of 2 to 3 in 100, and neurodevelopmental disorders at approximately 30 to 40 in every 100 exposed children.

6. Action: This is the single most consequential fact on the page, and it governs whether the drug can be offered at all rather than how it is monitored. [2][9]

7. Effect: Life-threatening rash with lamotrigine

7. Detail: Cases of life-threatening serious rashes including Stevens-Johnson syndrome, toxic epidermal necrolysis and rash-related death have been caused by lamotrigine, and the rate is greater in paediatric patients than in adults. In adults treated for mood disorders the label reports serious rash in 0.08% on initial monotherapy and 0.13% on adjunctive therapy.

7. Action: Both the initial dose and the rate of escalation are listed as factors that may raise the risk, so any acceleration of either is a clinician's decision made against that warning. [3]

8. Effect: Dermatological and haematological toxicity with carbamazepine

8. Detail: Its boxed warning reports serious and sometimes fatal dermatologic reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome, and separately that aplastic anaemia and agranulocytosis carry a risk 5 to 8 times greater than in the general population.

8. Action: Ancestry-directed HLA-B*1502 testing precedes treatment in at-risk populations, and haematological change is a reason to reconsider the drug. [4][5]

9. Effect: Increased mortality in elderly patients with dementia-related psychosis

9. Detail: A boxed warning shared by olanzapine, quetiapine and aripiprazole. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death, and none of these agents is approved for that use.

9. Action: It restricts where an antipsychotic may be used for behavioural disturbance, which matters whenever bipolar illness and dementia coexist. [6][7][8]

10. Effect: Metabolic harm with the atypical antipsychotics

10. Detail: Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported with atypical antipsychotics including olanzapine, and clinically significant elevations in triglycerides above 500 mg/dL have been observed. Hyperglycaemia, dyslipidaemia and weight gain are identified as the metabolic changes of this class.

10. Action: Metabolic monitoring is part of using these agents at all, and it applies to bipolar use exactly as it does to use in psychosis. [6][7][8]

11. Effect: Neuroleptic malignant syndrome and tardive dyskinesia

11. Detail: A potentially fatal symptom complex referred to as neuroleptic malignant syndrome has been reported with antipsychotic drugs including olanzapine. A syndrome of potentially irreversible involuntary dyskinetic movements may also develop, and the risk is believed to rise with duration of treatment and cumulative dose.

11. Action: These are reasons the antipsychotic members are not interchangeable with lithium in a maintenance role, even where the indications overlap. [6]

1. Drug: Lithium

1. Effect: Hyponatraemia through decreased sodium reabsorption by the renal tubules, leading to sodium depletion; also postmarketing reports of a possible association with unmasking of Brugada syndrome, and cases of pseudotumor cerebri with increased intracranial pressure and papilloedema. [1]

2. Drug: Valproate

2. Effect: Thrombocytopenia that varies with plasma concentration, alongside a raised ammonia which the label notes can occur while liver function tests remain normal. [2]

3. Drug: Carbamazepine

3. Effect: Hyponatraemia, in many cases caused by the syndrome of inappropriate antidiuretic hormone secretion, with a risk that appears dose-related. [4]

4. Drug: Lamotrigine

4. Effect: Beyond the boxed rash warning, its label carries separate warnings for drug reaction with eosinophilia and systemic symptoms and for aseptic meningitis. [3]

5. Drug: Quetiapine

5. Effect: Lens changes have been observed in adults, children and adolescents during long-term treatment, and syncope was reported in 1% of treated patients. [7]

6. Drug: Aripiprazole

6. Effect: Akathisia is markedly more frequent than with the other members listed here, reaching 25% in the adjunctive depression trials against 4% on placebo. [8]

Contraindications, precautions and interactions

1. Valproate must not be used in women and girls of childbearing potential in the UK unless the conditions of the Pregnancy Prevention Programme are met, and then only where other treatments are ineffective or not tolerated. [9]

2. For the bipolar disorder indication the MHRA sets an absolute contraindication to use in pregnancy, without the exception for absent alternatives that applies in epilepsy. [9]

3. Divalproex is contraindicated in patients with known mitochondrial disorders caused by mutations in mitochondrial DNA polymerase gamma. [2]

4. For migraine prophylaxis, the same label contraindicates valproate in pregnant women and in women of childbearing potential who are not using effective contraception, which shows how the restriction shifts with the indication. [2]

1. Patients with ancestry in genetically at-risk populations should be screened for HLA-B*1502 before carbamazepine is started, and the screening direction sits inside the boxed warning rather than in a footnote. [4]

2. Older patients frequently respond to a reduced lithium dosage and may show signs of toxicity at serum concentrations that other patients tolerate without difficulty. [1]

3. Sodium and fluid balance are part of lithium safety: a normal diet including salt and adequate fluid intake is essential, tolerance falls with protracted sweating or diarrhoea, and NHS material warns that a low-salt diet can raise blood lithium levels. [1][11]

4. Early voluntary reports to international birth registries suggested an increase in cardiovascular malformations, especially Ebstein's anomaly, with first-trimester lithium use. [1]

5. None of the atypical antipsychotics used in bipolar disorder is approved for treating patients with dementia-related psychosis. [6]

6. Lamotrigine is withdrawn gradually rather than abruptly; its label describes discontinuation over a period of at least two weeks by roughly halving the amount each week. [3]

1. With: NSAIDs

1. Effect: They decrease renal blood flow, which decreases renal clearance of lithium and increases serum lithium concentrations. [1]

2. With: ACE inhibitors and angiotensin receptor blockers
2. Effect: Concomitant use increases steady-state serum lithium concentrations, so more frequent measurement is called for when one is started or stopped. [1]
3. With: Diuretics, including thiazides
3. Effect: Diuretic-induced sodium loss may reduce lithium clearance and increase serum lithium concentrations, which is the opposite of what the word diuretic suggests to a student. [1]
4. With: Antipsychotics given with lithium
4. Effect: An encephalopathic syndrome has been reported with this pairing, in some cases followed by irreversible brain damage. [1]
5. With: Carbamazepine given with lithium
5. Effect: Concomitant administration may increase the risk of neurotoxic side effects. [4]
6. With: Valproate given with lamotrigine
6. Effect: Valproate increases lamotrigine concentrations more than two-fold, and is separately listed among the factors that may increase the risk of serious rash. [3]
7. With: Enzyme inducers given with lamotrigine
7. Effect: Carbamazepine, phenytoin, phenobarbital and primidone decrease lamotrigine concentrations by approximately 40%. [3]
8. With: Hormonal contraceptives given with carbamazepine
8. Effect: Induction of CYP3A4 lowers plasma hormone concentrations, and breakthrough bleeding and unintended pregnancies have been reported. [4][5]

Comparison tables

Title: What actually governs each agent

Caption: Each member is limited by a different thing. Selection and monitoring belong to the treating clinician working from a current prescribing reference.

1. Key: drug
1. Label: Drug
1. Is Row Header: true
2. Key: route_in
2. Label: Route into the class
3. Key: monitoring
3. Label: Principal monitoring demand
4. Key: signature
4. Label: Signature problem
1. Drug: Lithium carbonate
1. Route In: Its own, by a mechanism the label calls unknown
1. Monitoring: Serum lithium concentration, plus renal and thyroid function
1. Signature: Toxicity at concentrations close to the therapeutic range [1]
2. Drug: Valproate
2. Route In: From epilepsy
2. Monitoring: Hepatic status, and formal pregnancy-prevention requirements in the UK
2. Signature: Reproductive toxicity that determines whether it can be used at all [2][9]
3. Drug: Carbamazepine
3. Route In: From epilepsy, through the extended-release formulation
3. Monitoring: Haematological indices, and awareness of induced co-medications
3. Signature: Broad enzyme induction, and HLA-B*1502-linked severe skin reactions [4][5]
4. Drug: Lamotrigine

- 4. Route In: From epilepsy, as a maintenance agent
- 4. Monitoring: Vigilance for rash, and awareness of concentration-shifting co-medication
- 4. Signature: Life-threatening rash, worsened by concurrent valproate [3]
- 5. Drug: Olanzapine
- 5. Route In: From antipsychotic pharmacology
- 5. Monitoring: Weight, glucose and lipids
- 5. Signature: Metabolic change, with the dementia mortality warning limiting its use in the old [6]
- 6. Drug: Quetiapine
- 6. Route In: From antipsychotic pharmacology
- 6. Monitoring: Metabolic indices, with lens changes noted on long-term use
- 6. Signature: Sedation, reported as somnolence in 18% of treated patients [7]
- 7. Drug: Aripiprazole
- 7. Route In: From antipsychotic pharmacology
- 7. Monitoring: Movement disorder, particularly in the adjunctive setting
- 7. Signature: Akathisia, far more frequent when added to lithium or valproate [8]

High-yield exam pearls

- 1. Pearl: Lithium's boxed warning ties toxicity to serum concentration and requires that assay facilities exist before treatment begins.
- 1. Why: It is the clearest example in the syllabus of a monitoring requirement written into a boxed warning rather than into a monitoring section. [1]
- 2. Pearl: Lithium is filtered and then about 80% reabsorbed in the proximal tubule, so anything that depletes sodium or reduces renal perfusion raises the level.
- 2. Why: One fact explains NSAIDs, ACE inhibitors, angiotensin receptor blockers, thiazides, dehydration and a low-salt diet all at once. [1][11]
- 3. Pearl: Valproate's UK restriction is not uniform across its indications: bipolar disorder attracts an absolute contraindication in pregnancy, epilepsy does not.
- 3. Why: Examiners test whether a student knows that the same molecule can carry different restrictions depending on why it is being given. [9]
- 4. Pearl: Valproate does two things to lamotrigine at once: it more than doubles the concentration and it is listed as a factor that may raise rash risk.
- 4. Why: A single co-prescription therefore appears in both the pharmacokinetics answer and the safety answer. [3]
- 5. Pearl: HLA-B*1502 screening before carbamazepine applies to patients with ancestry in genetically at-risk populations.
- 5. Why: It is the standard worked example of pharmacogenomic testing appearing as a pre-treatment condition inside a label. [4]
- 6. Pearl: Three separate regulatory documents in this class decline to state a mechanism: lithium's is unknown, carbamazepine's in mania is unclear, and olanzapine's exact mechanism is unknown.
- 6. Why: It is the evidence for the central teaching point, that a mood stabiliser is defined by role rather than by target. [1][5][10]
- 7. Pearl: Lithium given with an antipsychotic has produced an encephalopathic syndrome, sometimes followed by irreversible brain damage.
- 7. Why: The combination is licensed and common in mania, so the warning is about a routine regimen rather than an exotic one. [1]

Common exam traps

- 1. Trap: Treating mood stabiliser as though it named a pharmacological class.

1. Correction: It names a clinical role. The agents that fill it are an element whose action is unknown, several antiepileptics, and several antipsychotics, and they share indication rather than target. [1][5][10]
2. Trap: Reaching for lamotrigine to treat an acute manic episode.
2. Correction: Its bipolar licence is for maintenance, delaying the time to occurrence of mood episodes, and the label states that effectiveness in the acute treatment of mood episodes has not been established. [3]
3. Trap: Expecting a thiazide to lower the serum lithium level because it increases urine output.
3. Correction: Sodium loss caused by a diuretic reduces lithium clearance and raises the concentration, so the interaction runs in the direction opposite to intuition. [1]
4. Trap: Assuming lithium's thyroid effect is always underactivity.
4. Correction: Hypothyroidism is the usual direction, because lithium concentrates in the thyroid and can inhibit hormone synthesis and release, but hyperthyroidism including Graves' disease and toxic multinodular goitre has also been reported. [1]
5. Trap: Assuming any carbamazepine product may be used for mania.
5. Correction: The plain tablet label lists epilepsy and trigeminal neuralgia only, while the extended-release capsule holds the indication for acute manic or mixed episodes of bipolar I disorder. [4][5]
6. Trap: Believing that valproate's warnings are relaxed when it is given for mood rather than for seizures.
6. Correction: The boxed warnings for hepatic failure, major congenital malformations and life-threatening pancreatitis travel with the molecule and do not soften with the indication. [2]

Self-test questions

1. Question: Which statement matches the boxed warning on the lithium carbonate label?
 1. Lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to therapeutic concentrations
 2. Lithium toxicity occurs only after prolonged treatment at high concentrations
 3. Lithium requires screening for a specific HLA allele before treatment begins
 4. Lithium is contraindicated in all patients with any thyroid abnormality

1. Explanation: The boxed warning ties toxicity directly to serum concentration and notes that it can occur near therapeutic levels, which is why the label also requires that assay facilities be available before treatment starts. [1]
2. Question: A patient stable on lithium is started on a thiazide diuretic for hypertension. What is the expected effect on the serum lithium concentration?
 1. It rises, because diuretic-induced sodium loss reduces lithium clearance
 2. It falls, because increased urine flow washes lithium out
 3. It is unchanged, because lithium is cleared hepatically
 4. It falls, because thiazides block proximal tubular reabsorption of lithium

2. Explanation: The label states that diuretic-induced sodium loss may reduce lithium clearance and increase serum lithium concentrations, so a diuretic pushes the level up rather than down. [1]
3. Question: How does the MHRA position on valproate in pregnancy differ between bipolar disorder and epilepsy?
 1. For bipolar disorder there is an absolute contraindication in pregnancy, with no exception for absent alternatives
 2. For bipolar disorder the restriction is looser, because manic relapse is less dangerous than a seizure
 3. The two indications carry identical wording with no practical difference
 4. The restriction applies only to epilepsy and not to psychiatric use at all

3. Explanation: The MHRA sets an absolute contraindication to valproate in pregnancy for the bipolar indication, whereas in epilepsy use may still be considered where no suitable alternative exists. [9]
4. Question: Which co-prescription is listed in the lamotrigine label as a factor that may increase the risk of serious rash?
 1. Valproate
 2. Lithium carbonate

3. Quetiapine

4. Aripiprazole

4. Explanation: Coadministration with valproate appears alongside exceeding the recommended initial dose and exceeding the recommended dose escalation among the factors that may raise rash risk, and valproate also more than doubles lamotrigine concentrations. [3]

5. Question: Which pre-treatment step does the carbamazepine boxed warning direct for patients with ancestry in genetically at-risk populations?

1. Screening for the HLA-B*1502 allele

2. Baseline visual field perimetry

3. Measuring serum lithium concentration

4. Testing for mitochondrial DNA polymerase gamma mutations

5. Explanation: The boxed warning directs HLA-B*1502 screening before carbamazepine is started in those populations, because of serious and sometimes fatal reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome. [4]

6. Question: Lamotrigine's licence in bipolar I disorder is best described as which of the following?

1. Maintenance treatment to delay the time to occurrence of mood episodes

2. First-line treatment of acute mania

3. Monotherapy for acute depressive episodes of bipolar disorder

4. Short-term adjunct to lithium for acute mixed episodes

6. Explanation: The label gives maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in adults already treated for acute episodes, and states that effectiveness in acute treatment has not been established. [3]

7. Question: Which of these labels explicitly declines to state a definite mechanism for its mood effect?

1. Lithium carbonate, extended-release carbamazepine and olanzapine all do

2. Only lithium carbonate does

3. None of them do; each names a specific receptor

4. Only the antipsychotic labels do

7. Explanation: Lithium's mechanism as a mood stabilising agent is stated to be unknown, carbamazepine's mechanism in acute manic or mixed episodes is stated to be unclear, and the European regulator states that olanzapine's exact mechanism of action is unknown. [1][5][10]

8. Question: Which adverse outcome has been reported when lithium is given together with an antipsychotic?

1. An encephalopathic syndrome, in some cases followed by irreversible brain damage

2. Aplastic anaemia and agranulocytosis

3. Hyperchloraemic metabolic acidosis

4. Permanent bilateral visual field constriction

8. Explanation: The lithium label describes an encephalopathic syndrome occurring in patients treated with lithium and an antipsychotic, sometimes followed by irreversible brain damage, which matters because the combination is a licensed strategy in mania. [1]

Frequently asked questions

1. Question: Is mood stabiliser a pharmacological class?

1. Answer: No. It is a description of clinical function. The agents that hold the role reach it by unrelated routes: lithium by an action its label says is unknown, carbamazepine and lamotrigine from antiepileptic pharmacology, and olanzapine, quetiapine and aripiprazole from antipsychotic pharmacology. Grouping them together is useful for revising indications and dangerous for reasoning about mechanism. [1][5][10][7]

2. Question: Why does lithium need blood-level measurement when most medicines do not?

2. Answer: Because the gap between an effective concentration and a toxic one is very small. Its label places toxic

concentrations at or above 1.5 mEq/L while quoting 0.8 to 1.2 mEq/L for acute treatment, and it makes the availability of prompt and accurate serum determinations a condition of starting the drug at all. [1]

3. Question: Why do so many ordinary medicines matter for someone taking lithium?

3. Answer: Because lithium leaves the body through the kidney and its reabsorption tracks sodium handling. NSAIDs reduce renal blood flow and so reduce its clearance, ACE inhibitors and angiotensin receptor blockers raise steady-state concentrations, and sodium loss from a diuretic has the same effect. Dehydration and salt restriction pull in the same direction. [1][11]

4. Question: Does valproate become safer in pregnancy when it is prescribed for bipolar disorder rather than epilepsy?

4. Answer: The opposite. The molecule's boxed warnings are unchanged, and UK regulators are stricter for the psychiatric indication, setting an absolute contraindication in pregnancy for bipolar disorder while allowing epilepsy use to be considered where no suitable alternative exists. Physical birth defects occur in around 10 in every 100 exposed babies and neurodevelopmental disorders in approximately 30 to 40 in every 100 exposed children. [9][2]

5. Question: What organ system does each member threaten over the long term?

5. Answer: Lithium threatens the kidney and the thyroid, with nephrogenic diabetes insipidus, tubulointerstitial nephropathy, hypothyroidism and hypercalcaemia all described. Valproate threatens the liver and the pancreas, and the fetus above all. Carbamazepine threatens the bone marrow and the skin. The antipsychotic members threaten metabolic health, with hyperglycaemia, dyslipidaemia and weight gain named together in their labels. [1][2][4][6]

6. Question: Why is combining these medicines so common?

6. Answer: Because several of the licences are written for combination use. Olanzapine and aripiprazole are both indicated for acute manic or mixed episodes as an adjunct to lithium or valproate, and quetiapine's maintenance indication is specifically as an adjunct to lithium or divalproex. Each addition brings its own monitoring, and the lithium label's warning about an encephalopathic syndrome with an antipsychotic applies within exactly these regimens. [6][8][7][1]

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