

Substance Abuse

1> ALCOHOL

For chronic alcohol use, do not stop alcohol suddenly but suggest structured reduction because acute alcohol withdrawal can be fatal.

Risk factors: family history, starting at early age, regular drinking, MH, social anxiety, depression, PTSD, preference for sweet tastes, ignorance

Risk of chronic alcohol consumptions:

1. Cognitive impairment
e.g., alcohol dementia, long term neuropathy, cerebral atrophy – brain shrinking
2. Wernicke-Kosakoff syndrome (WKS)
- Thiamine deficiency
- Wernicke's encephalopathy is a neurodegenerative brain disorder caused by lack of thiamine: confusion, apathy, disorientation, vomiting, disturbed memory
- 1) Acute treatment with Pabrinex 5mL IM or IV for 3-5 days (multi vitamin + thiamine)
- 2) Maintenance oral thiamine of 100mg TDS (spread out bc poor oral absorption)

Pharmacology treatment

Detoxification	Chlordiazepoxide (benzodiazepine)	Hospital use Long-acting benzo, anticonvulsant, cross tolerant with alcohol Start at high dose of 20-40mg four times/day then reduced over around 9 days Not for elderly or those with hepatic impairment (reduce dose or use short acting benzo e.g., lorazepam, oxazepam) Combine this with vitamin supplement
	Disulfiram (Antabuse)	Not used as much these days Pro-drug that activates in the liver, prevents conversion of acetaldehyde to acetic acid and dopamine to noradrenaline Cause vasodilation, palpitations and headaches (like Asian flush) Combination with alcohol can be fatal
Maintenance therapy	Acamprostate (campral)	Glutamate antagonist, better safety profile Work as reducing reward, but effectiveness marginal
	Naltrexone	Opiate antagonist Well tolerated and has significant effect on drinking behaviour as it blocks the rewarding effects from heroin and alcohol
	Nalmefene	Opioid antagonist Effective in reducing heavy drinking days by reducing reward Can be used on when required basis: <ul style="list-style-type: none"> - For people who failed abstinence and reduction strategy more suitable - People that cannot achieve abstinence but require some form of intervention with psychosocial support

FAST alcohol screening

Audit C score (0-12): 5-7 hazardous drinking 8-10 harmful drinking 11-12 alcohol dependence

2> Opioids

Assessment – detoxification – maintenance – gradual discontinuation

COWS (clinical opioid withdrawal scale) – used to titrate detoxification over several days to curb withdrawal symptoms

Patients do not die from opioid withdrawal, but die from toxicity, therefore management of withdrawal should be done with ibuprofen, loperamide, paracetamol etc.

Maintenance pharmacotherapy for opioid dependence		
Dosage	Methadone 20-30mg/day increase 5-10mg every few days Takes 5 days for blood level to reach steady state Maintenance optimal dose 40-120mg/day	Buprenorphine Sublingual tablets with naloxone → Prevent drug injection Buvinal (weekly, monthly) Sixmo (implanted rods 6-12 months)
Notes	Full agonist → replace heroine, no peak buzz Longer half-life than diamorphine GREEN so can tell if diluted	Partial agonist Longer half-life than methadone Not orally absorbed
S/E	CNS: euphoria, RR <8, histaminergic effect (airway constriction), reduce menstrual cycle, constipation (opioid slow passage of food), dental problems, QT prolongation: if over 100mg/d offer ECG every 6-12months	
Advantages	Cheap Sedating Orally absorbed Good evidence based	More difficult to use on top Safer in overdose Less stigmatised Less sedating
Disadvantages	Easy to overdose, can use on top Stigmatised drug Syrup rots teeth Long detoxification Toxic for drug naïve adults 40mg or child 10mg	Unpleasant taste (SL) Difficult to supervise Can be injected Less sedating Expensive

Support drug to remain opioid free: **Naltrexone** – long acting opioid antagonist

- Test dose of 25mg for at least 7 days after last dose of opioid
- 50mg/day continue for at least 3 months
- Fatal if relapse while taking naltrexone

Opioid overdose: pinpoint/constricted pupils, nausea/vomiting, pale skin colour, bluish tinge lips, tip of nose, under eyes, fingertips or nails, low BP (hypotension, slow pulse (bradycardia), sedation getting worse, breathing problems

→ **Naloxone**: Opioid receptor antagonist

When to contact prescriber immediately if:

- Three or more consecutive doses missed or any titration doses missed (likely taken something)
- Concerns about dose/prescription
- Dispensing error or near miss
- Present intoxicated, unacceptable behaviour
- Whole dose not consumed

*Record everything

*Needle syringe provision

- 3> Benzodiazepines and hypnotic
- Diazepam, lorazepam, temazepam, zolpidem, zopiclone etc.
 - Sudden cessation of long term high dose use can cause seizures e.g., >50mg/day

Prescriptions must have clear treatment plan, discussed, agreed (at least 2 positive drug screen, no negative benzodiazepine screen in last 4 months, review regularly)

Benzo detox – takes months to years

- Give divided dose, load at night
- Change benzos to diazepam (slow and long acting)
- May be necessary to increase dose to alleviate symptoms before reducing again
- Don't reduce dose more than 4 weeks

4> Gabapentinoids

- Pregabalin and gabapentin: anticonvulsants, neuropathic pain, anxiety indication

Pregabalin: reduce daily dose at max of 50-100mg/week

Gabapentin: reduce daily dose at max 300mg every four days

Depression

Main risk factors: genetics, anxiety, gender, lack of parental care or childhood sexual abuse, social adversity, stress, physical illness (CKD/diabetes x5 risk), chronic insomnia, vit D deficiency, quitting smoking, mother having postnatal depression, drugs

Recurrent unipolar depression risk factors: history of frequent episodes, onset after age of 60, long duration of individual episodes, FH, poor symptom control during episode, co-morbid anxiety disorder or substance abuse

Drug induced depression: alcohol, steroids (dexamethasone), benzodiazepines, antipsychotics, anticonvulsants (carbamazepine, lamotrigine etc), NSAIDs (ibuprofen), CVD (beta-blocker or CCB), caffeine

Severity is determined by number, time and degree of functional impairment			
Key symptoms	Associated symptoms	Differential diagnosis	Co-morbidity
*Persistent sadness/low mood *Marked loss of interest/pleasure *Lack of energy (ICD10)		*Bipolar depression *GAD *Drug induced *Schizophrenia *ADHD (poor sleep?) *Substance misuse *Personality disorder *Bereavement *Physical illness *Dementia *Panic disorder *SAD	*GAD *Psychosis *Insomnia (caused by depression) *OCD *PTSD *Panic disorder *Dementia
ICD 10 of at least 2 of key symptoms most days for at least 2 weeks, minimum 4 symptoms	*Disturbed sleep *Change in appetite/weight *Fatigue or loss of energy *Agitation or slowing of movements *Poor concentration or indecisiveness *Feeling of worthlessness or excessive inappropriate guilt *Suicidal thoughts or acts		
DSM IV at least 1 key symptoms, most days for at least 2 weeks, minimum 5 symptoms			

Stepped care of depression		
→ Social support is crucial in all treatment		
Step 1 Suspected presentation of depression	Assessment, support, psychoeducation, active monitoring, onward referral for further assessment and intervention	
Medication not recommended for mild depression – poor risk-benefit ratio (unless history of moderate-severe depression, depressive symptoms longer than 2 years)		
Step 2 Mild to moderate depression	Medication Low intensity psychological or psychosocial interventions, onward referral	Guided self-help, being active, computer-based CBT
Step 3 Moderate to severe depression	Medication High intensity psychological interventions, combine treatments and collaborative care, onward referral	
Step 4 Severe and complex depression	Medication High-intensity psychological interventions, ECT (electroconvulsive therapy), crisis service, combined treatments, multi-professional and inpatient care, TMS (transcranial magnetic stimulation)	Psychological therapy, CBT, interpersonal therapies, mindfulness, counselling, general support and advice

Use of antidepressants		
Should consider		
- Duration of episode - Previous antidepressant response - Likelihood of adherence, potential adverse effects, and patient preference		

- Almost all antidepressants are more tolerable at lower initial dose (half the standard) and increased to target dose over few days or weeks (except mirtazapine)
- Tricyclics are difficult to get the therapeutic dose due to the wide range of side effects giving poor tolerability
- Combination/augmentation (for resistant depression): consider lithium, antipsychotic or another antidepressant
- Antipsychotic choice: aripiprazole, olanzapine, quetiapine, risperidone

First line antidepressants			
Drug group	Drugs	Dose	Comments
SSRIs	Nausea, sexual dysfunction, antiplatelet activity, diarrhoea	Citalopram Escitalopram Fluoxetine Sertraline	20-40mg/d 10-20mg/d 10-20mg/d 50-100mg/d
		Duloxetine Mirtazapine	40-80mg/d 30mg/d
		Venlafaxine	75-375mg/d
		Vortioxetine	10-20mg/d
SNRIs	Slight sedation, slight lower BP, nausea, sexual dysfunction	Clomipramine Lofepramine	125-150mg/d 140-210mg/d
		Quetiapine XL	150-300mg/d
Second line antidepressants			
SSRIs	Fluvoxamine, paroxetine (short half life)		
Related	Agomelatine, reboxetine, trazodone		
TCAs	Amitriptyline, doxepin, imipramine, nortriptyline, trimipramine Dose – 125-150mg/d -> much lower for Caucasian with CYP2D6 deficient - Has anticholinergic S/E and toxic when overdose		
	MAOIs	Isocarboxazid, phenelzine – requires tyramine free diet (drugs not used much) Moclobemide	
Adjunctive		Lithium – usually used for bipolar	
Unlicensed		St John's wort	OTC drug for mild to moderate depression. Mode of action unclear but may include SNRI and MAOI activity

Antidepressant counselling points		
General advice	*Start at lower dose (to minimise side effects) *S/E can be managed *Not addictive treatment but treat them with respect *Duration will depend on individual but reassure them of long-term use	
Dose times	*SSRI should be taken in morning – can affect REM sleep * Mirtazapine (SNRI) should be taken at night – bc serotonin reuptake is counteracted by 5HT2 and 5HT3 blockade, significant histamine blocker making us sleepy *Agomelatine (melatonin receptor agonist) improves sleep	
Onset of Action	*Response not immediate, can see benefit after 1-2 weeks, but need at least 4-6 weeks *If no improvement after 4 weeks of therapeutic dose, switch (but check adherence) *If minimal improvement, continue until week 6 *For elderly time may need to be increased *Patient should be seen every 2-4 weeks for first 3 months	
Duration of treatment	*Continue for as long as needed to reduce relapse 1 st episode: 6months after recovery at same dose minimises the risk of relapse	

	2 nd episode: 1-2 years may reduce relapse 3 rd or subsequent episode: 3-5 years or longer significantly reduces relapse	
Switching antidepressants	<p>1> Try another SSRI or newer generation antidepressants</p> <ul style="list-style-type: none"> * If tolerance is the issue try different mode of action, chemical group or from same group * If lack of efficacy is the problem try different class or mode of action * Cross-taper SSRI/SNRIs carefully to avoid serotonin syndrome * Tricyclics can interact with some SSRIs * Mirtazapine improves sleep, can be used in combination and is an easy-to-use antidepressant to switch to and from or can be combined with citalopram * Paroxetine and venlafaxine discontinuation symptoms due to short half-life * Fluoxetine has long half-life, tf when switching be cautious <ul style="list-style-type: none"> ➔ To reversible MAOI e.g., moclobemide: taper and stop fluoxetine and wait 5-6 weeks ➔ From non-reversible MAOI: need 2 week washout period <p>2> Any more than 2 failed antidepressants (adequate dose+duration) need to review diagnosis</p>	
Serotonin syndrome	<p>Symptoms: restlessness, myoclonus (sudden involuntary muscle spasm), tremor, rigidity, hyperreflexia, shivering, elevated temperature, arrhythmias, anxiety, confusion, sweating, diarrhoea, and vomiting</p> <p>Can be fatal due to cardiac collapse but rarely life threatening</p> <p>Can occur with combination of serotonergic drugs: SSRI, SNRI, Tramadol, Triptans</p>	
Suicide risk	<p>Potential increased risk of suicide and self-harm within the first month of therapy</p> <p>Get worse before it gets better</p>	
Discontinuation	<p>Withdrawal phenomena</p> <ul style="list-style-type: none"> - SSRI symptoms: dizziness, sleep disturbance, agitation, electric shock in head, nausea, fatigue, headache, flu-like symptoms - SNRI symptoms: SSRI symptoms + restlessness, abdominal distension, congested sinuses - Symptoms commence w/i 1-3 days of stopping or reducing dose - Usually short-lived for 1-2 weeks and rapidly suppressed by re-introducing drug - Relapse may occur within 2 weeks after discontinuation - Can occur even with missed dose with shorter half-life drugs e.g., paroxetine • Avoid stopping while still in high relapse risk • For less than 8 weeks treatment, withdraw stepwise over 1-2 weeks • After 6-8 months treatment, taper over 6-8 weeks • After long-term maintenance treatment, reduce dose by 25% every 4-6 weeks 	
Interactions	<p>Alcohol – mainly due to increased sedation</p> <p>SSRIs, venlafaxine, vortioxetine, nortriptyline and clomipramine – less effect w/ alcohol</p> <p>Mirtazapine, amitriptyline, mianserin, trazodone, doxepin – additive effects</p> <p>NSAIDs – with SSRI threefold increased risk of upper GI bleed (prescribe PPI)</p> <p>Warfarin – SSRI raise INR significantly – fluoxetine more than sertraline and citalopram</p> <p>Tamoxifen – paroxetine may increase risk of recurrence of breast cancer</p> <p>Smoking lowers duloxetine levels (SNRI)</p> <p>St John's Wort effect decreased</p> <p>Antiretrovirals, cyclosporin, oral contraceptives, digoxin</p> <p>Clozapine levels increased with fluvoxamine and SSRIs</p> <p>Carbamazepine decreases tricyclic effect</p> <p>Valproate increases tricyclic effect</p>	
Side effect management		
Anticholinergic	Blurred vision	Do not drive, wears off but if not adjust dose
	Constipation	Fibre, cereal, fruit, drink fluid, keep active, exercise, prescribe laxative e.g., lactulose
	Dry mouth	Suck boiled sweets, wine gum, use mouth spray

	Urinary retention	Immediate medical intervention may be needed
Central	Anxiety	Start at low dose increase stepwise over long period, split doses
	Seizures	Rare but if happens, needs change or much slower titration
	Confusion	Rare except for tricyclics, need change or much slower titration
	Dizziness	Take evening dose before going to bed
	Headache	Paracetamol
	Insomnia and sleep disturbance	Take dose in morning not at night, split doses
	Nausea	Takw with food, split dose try XL if available
	Sleepiness or sedation	Antihistaminic effect, so don't drive or use machine
	Suicidal ideation	Mirtazapine – start at 30mg/d (less sleepiness than 15mg/d)
Others	Hyponatraemia	Symptoms of tiredness, confusion, headaches, unable to concentrate, muscle cramps, and fits -> refer to doctor immediately Higher incidence if started in last month or change in dose or elderly female
	Postural hypotension	Do not stand up too quickly, no driving, check BP
	Palpitations	Beta blocker if needed
	Sexual dysfunction	Libido – more related to depression and antidepressant Erectile dysfunction due to NOS inhibition – prescribe PDE5 inhibitors Anorgasmia due to 5HT2A stimulation – time dose to less sex, delay a dose **Mirtazapine and agomelatine have lower risk of this
	Sweating	Dose adjustments
	Weight gain	A diet full of vegetables, cereal and fibre may prevent
Prescribing for special patient groups		
Children and adolescence	<p>1 Fluoxetine 10mg – licensed for depression in age 8-17 after 4-6 sessions of psychological therapy</p> <p>2 Sertraline – licensed for OCD in age 6-17 (not depression)</p> <p>Citalopram should not be used under 18</p>	
	<p>Antidepressant use under 20:</p> <ul style="list-style-type: none"> • Positively exclude any possibility of bipolar • Start slowly titrating up watching tolerability • Counsel family possibility of suicidal ideation • Use of antidepressant under 15 can increase suicidal ideation and behaviour 	
Pregnancy	<ul style="list-style-type: none"> • Avoid paroxetine • Most other antidepressants may have risks but can be managed • Little or no evidence of any detrimental effect on postnatal development 	
Elderly	<ul style="list-style-type: none"> • No ideal antidepressant but SSRI better tolerated than TCAs (but increased risk of bleed) • SSRI increase risk of hyponatraemia, postural hypotension, falls and haemorrhagic stroke • Start low go slow 	
Cardiac Disease	<ul style="list-style-type: none"> • SSRI recommended – antiplatelet activity risk of bleeding, can increase QT interval, protect against MI (Sertraline for post MI) • Mirtazapine suitable alternative for bleed disorders • CBT ineffective post MI unless depression present pre-MI • Citalopram C/I with QT prolongation (only be used w/ caution with electrolyte disturbances and bradycardia) • Escitalopram C/I with QT prolongation (only used w/ caution with patient at risk of torsade de pointes, recent MI, bradyarrhythmia, hypokalaemia, or hypomagnesaemia) 	

	<ul style="list-style-type: none"> • Monitoring crucial • Haloperidol antipsychotic also prolong QT interval
Renal Impairment	<ul style="list-style-type: none"> • Greater renal impairment, greater potential for drug accumulation • ADR: confusion, postural hypotension, sedation • Start dose low go slow – care needed • Serum creatinine levels may be normal in elderly even with renal impairment • More care needed for anticholinergic drugs e.g., TCAs or MAOIs – may cause urinary retention
Hepatic Impairment	<ul style="list-style-type: none"> • SSRI and TCAs are hepatically metabolised • Start low and go slow, regularly monitor LFTs • Care needed for high first pass clearance • In severe liver disease antidepressant may cause sedation or constipation • Paroxetine use by some specialised liver units with fewer apparent problems

1st agent ▼	SSRI	TCA *	Venlafaxine	Duloxetine	Mirtazapine	Reboxetine**	Agomelatine
2nd agent ▶							
SSRI except for fluoxetine	Discontinue first SSRI gradually and stop - start second SSRI at low dose the following day <i>or</i> Immediate switch	Discontinue SSRI gradually and stop - start TCA the following day. If the SSRI being stopped is paroxetine or fluvoxamine, ideally leave a gap of a few days <i>or</i> Cross-taper cautiously with very low dose of TCA*	Cross-taper cautiously, starting with venlafaxine 37.5mg daily and increase very slowly <i>or</i> Immediate switch (caution if fluoxetine or paroxetine used)	Immediate switch starting with duloxetine 60mg daily has been well tolerated	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously
Fluoxetine 20mg OD	Stop fluoxetine abruptly – start second SSRI at half the normal starting dose 4 to 7 days later	Stop fluoxetine abruptly – start TCA at low dose 4 to 7 days later and increase dose very slowly	Stop fluoxetine abruptly – start venlafaxine 37.5mg daily and increase dose very slowly	Immediate switch starting with duloxetine 60mg daily has been well tolerated	Cross-taper cautiously starting with mirtazapine 15mg daily	Cross-taper cautiously	Cross-taper cautiously
TCA*	Gradually reduce the dose of TCA to 25-50mg daily - start SSRI then slowly withdraw TCA* over next 5 to 7 days	Cross-taper cautiously	Cross-taper* cautiously, starting with venlafaxine 37.5mg daily	Cross-taper cautiously starting with duloxetine* 30mg daily and increase dose very slowly	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously
Venlafaxine	Cross-taper cautiously starting with half the normal starting dose of SSRI e.g. paroxetine 10mg daily <i>or</i> Immediate switch (caution if fluoxetine or paroxetine used)	Cross-taper* using a very low starting dose of TCA e.g. amitriptyline 25mg daily		Discontinue venlafaxine gradually and stop – start duloxetine 30mg daily the following day and increase dose slowly [2]	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously
Duloxetine	Paroxetine or fluoxetine: Discontinue duloxetine gradually and stop – start SSRI the following day Citalopram/escitalopram or sertraline: Cross-taper cautiously using half the normal starting dose of SSRI e.g. citalopram 10mg	Cross-taper cautiously using a very low starting dose of TCA e.g. amitriptyline 25mg daily	Discontinue duloxetine gradually and stop – start venlafaxine the following day		Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously
Mirtazapine	Cross-taper cautiously	Cross-taper cautiously using a very low starting dose of TCA e.g. amitriptyline 25mg daily	Cross-taper cautiously	Cross-taper cautiously starting with duloxetine 30mg daily and increase dose slowly		Cross-taper cautiously	Cross-taper cautiously
Reboxetine	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously		Cross-taper cautiously
Agomelatine	Stop agomelatine abruptly – start SSRI the next day (except fluvoxamine – see notes)	Stop agomelatine abruptly – start TCA the next day	Stop agomelatine abruptly – start venlafaxine the next day	Stop agomelatine abruptly – start duloxetine the next day	Stop agomelatine abruptly – start mirtazapine the next day	Stop agomelatine abruptly – start reboxetine the next day	

Anxiety

Types of anxiety: Generalised anxiety disorder (GAD), OCD, PTSD, Panic disorder, Phobia e.g., social phobia, specific phobia

Activation of amygdala by induction of fear.

Key clinical features: fearful anticipation, irritability, worrying thoughts

Physical symptoms: dry mouth, constriction of chest, palpitations, tremor, headache, hyperventilation, breathlessness, insomnia, night terrors

Main treatments for anxiety				
	Drugs	Dosage	Notes	Counselling Points
SSRIs	Escitalopram	5mg/d	First line treatment for anxiety	<p>Response not immediate can take 12 weeks</p> <p>Symptoms tend to get worse before getting better</p> <p>Start low dose and increase every two weeks or as tolerated</p>
	Fluoxetine	5-10mg/d		
	Paroxetine	5-10mg/d		
	Sertraline	25mg/d		
	Citalopram	5-10mg/d		
Benzodiazepines	Lorazepam		Shorter acting – greater withdrawal	<p>Short term benzo can help initial anxiety</p>
	Diazepam		Has long half-life so effects of dose reduction take about 4 weeks, leave plenty of time to reduce dose	
	Oxazepam			
	Clobazam			
Antipsychotics	Risperidone			<p>Many side effects, but used as sedative when harm to themselves or others</p>
	Olanzapine			
	Quetiapine			
	Pericyazine			
Venlafaxine			Low dose (SSRI), High dose (SNRI)	
Duloxetine			Used for GAD	
Tricyclic antidepressants	Clomipramine		Often used for OCD	<p>For panic disorders when SSRI not suitable</p>
	Imipramine			
Pregabalin			Used for GAD, neuropathic pain or epilepsy (check indication), now controlled drug due to misuse	Usually adjunct with SSRI or SNRI
Mirtazapine			Unlicensed in anxiety Used in depression or sleep issues, it has antihistaminic sedative effect	
Buspirone		10mg TDS	Not used often, as it takes 4 weeks to respond But benefits of no abuse or withdrawal symptoms	
Beta-blockers	Propranolol	40-100mg	Relieve physical symptoms	
Antihistamines	Promethazine			
	Hydroxyzine			

Nonpharmacological interventions: counselling, CBT, anxiety management, self-help methods of lifestyle changes, caffeine avoidance or reduction, relaxation techniques

Diagnosis of GAD		
➔ Severe social occupational impairment for at least 6 months		
Major symptoms x2	PLUS	Additional symptoms x3
Excessive anxiety and worry about several events and activities		Restlessness or feeling keyed up or on edge
		Being easily fatigued
		Difficulty concentrating or mind going blank
Difficulty controlling the worry	Irritability	
	Muscle tension	
	Sleep disturbance	
Need differential diagnosis with depression, schizophrenia, dementia, substance misuse, physical illness such as thyrotoxicosis (assess thyroid function, AF) and hypoglycaemia (test blood glucose HbA1c)		

OCD

- Repeated intrusive, obsessional thoughts, impulses, images or compulsive acts. Resisting the thoughts lead to anxiety and performing the ritual relieves tension

First line treatment of SSRI or clomipramine

- Maximum tolerated dose for 3 months and for relapse prevention minimum of 1-2 years
- Discontinuation over several months

Clomipramine	250-300mg/d	
Fluoxetine	60-80mg/d	
OCD	100-200mg/d	

Social Phobia

- Excessive anxiety evoked by social situations – anticipation anxiety included
- First line management by SSRI escitalopram or venlafaxine (both licensed)
- Treatment for at least 12 weeks
- Use of benzodiazepine far less damaging than alcohol misuse and dependence

Panic Disorder

- SSRI first line – escitalopram, sertraline, citalopram, paroxetine licensed
- Venlafaxine licensed
- Second line – imipramine or clomipramine (unlicensed) if SSRI not suitable or no improvement after 12 weeks
- NICE do not recommend benzodiazepines for panic disorders except for emergency management

Bipolar Disorder

→ Stages of mania, hypomania, depression and mixed episodes, mood can be stable (euthymia) but functioning impaired

Risk factors: FH, genetics, male

Physical risks from bipolar: obesity, heart disease, high blood pressure x5, poor memory, respiratory problems x3, infections x2, life expectancy 10 years less

Mental risk from bipolar: suicide x14, substance misuse, ½ alcohol dependent, 2/5 drug abuse

Life risk from bipolar: relationships damaging, work school performance poor, violence, promiscuous

Cause: hallucinogens (LSD), CNS stimulants (amphetamines, caffeine), antidepressants switching from depression to mania, antipsychotics (olanzapine, risperidone, quetiapine, haloperidol)

Clinical features of bipolar		
	Symptoms	Diagnosis
Hypomania	Euphoric, impulsive decision, decreased need for sleep, flight of ideas, abnormal elation of mood, risk taking (gambling, promiscuity), intrusive, inability to concentrate, pressure of speech	Duration of symptoms 4 days or more Decreased or increased function
Mania		Duration of symptoms 7 days or more Severe functional impairment May have psychotic features
Bipolar depression	Lethargy, poor sleep, doing less, loss of interest, self-harm urges	Antidepressants ineffective (may turn into manic episode)

Bipolar categories

Bipolar I	Classic manic depression – mania, severe depression or mania alone
Bipolar II	Depression with at least one hypomanic episode
Bipolar III	Pseudo unipolar bipolar disorder – recurrent depression and mixed states (presence of high+low at same time), hypomania switching and mix states may be caused with antidepressant
Rapid cycling	4 or more mood episodes in a year

	Option 1	Option 2
Acute mania		
Mania relapse prevention		
Acute bipolar depression		
Bipolar depression relapse prevention		

Treatment options of Bipolar

Drug	Monitoring	Dosing	S/E	Notes
Quetiapine (acute bipolar)	Baseline: Risk of DM - weight, BMI, HbA1c Risk of HT - pulse, BP Risk of hyperlipidaemia – lipid Risk of arrhythmia - ECG (if risk QT interval)	300mg day 1, 600mg day 2, 800mg after	Headache, akathisia (inner restlessness), anticholinergic S/E, sleepy	Postural hypotension in 10% of people, highly sedative at low dose

Olanzapine				
Aripiprazole				
Lamotrigine				
Valporate				
Carbamazepine				
Haloperidol				
Risperidone				
Benzodiazepines				

FROM WS

Over activity, intrusive bizarre behaviour: metaxipine (all-rounder useful drug, not the most effective), lorazepam (short term use to settle someone down)

Lack of sleep/up all night: zopiclone (2 days ideal, longer use lead to dependence, short term), treat underlying depression or mania

Aggression: lorazepam (oral use, extreme case IV injection 15m first hour monitoring)

Mood stabilisation and relapse prevention: lithium (long term prophylaxis, strict blood test regulations, adherence not good), carbamazepine if lithium not tolerated (anti-epileptic mood stabiliser, has many interactions, own metabolism inducer)

Mood stabilising antipsychotics – olanzapine

Low mood: quetiapine (good for high, good for low, good for preventions), TCA, SSRI, SNRI

Acute mania/hypomania:

Bipolar depression and relapse prevention: continue what worked for acute treatment, but

Schizophrenia

- Incidence of 0/3 in 1000, occurs late adolescence/early adulthood
- Same in male and women, but later onset for women
- Mortality rate doubled

Positive symptoms

Hallucinations	<ul style="list-style-type: none"> - Sensory experience or perception w/o external stimuli - Visual, auditory, olfactory, gustatory and tactile (insects on body) - Auditory most common (God or devil, relatives or neighbours) - Running commentary as third person - Negative talk in nature
Delusions	<ul style="list-style-type: none"> - Fixed false belief cannot be corrected, idiosyncratic (not part of patient's culture) - Somatic false belief of ones physical illness, grandiose (special powers), paranoid
Thought insertion Echo Withdrawal Broadcasting	<ul style="list-style-type: none"> - Thought insertion - Thought withdrawal - Thought broadcasting - Thought echo <p>→ All known as thought interference</p>
Disorganized speech	<ul style="list-style-type: none"> - Word salad – jumbled use of words - New word invented – neologism - Overall incoherent speech - Thought dissociation (conversation end pointlessly or constant change in topic)
Disorganized or catatonic behaviour	<p>Catatonia – unresponsive to normal stimuli awake, state of rigidity</p> <p>Difficulty carrying out activities of daily living, abnormal behaviours, unpredictable interactions:</p> <p>Suite 136 instead of the police office for mental health patients</p> <p>Section 3 is a treatment order – up to 6months can be changed or can be revoked early</p> <ul style="list-style-type: none"> - First 3 months can give medication without consent then after need consent - T3 form (consent) 2 doctors need to agree on medication -

Negative symptoms: flattened mood (unable to express emotion, lack of facial expression, eye contact, gestures), avolition (lack of goal, difficulty following schedule, fail to initiate activity, require direction), apathy (lack sense of caring), alogia (poverty of speech), Anhedonia (failure to enjoy positive emotion, joy neglected, little interest in relationship, sexual interest decline), isolation, withdrawal, slow movements, poor self-care, self-neglect

Cognitive symptoms: memory, attention, executive functions such as decision making, problem solving, not affected by antipsychotic treatment

Diagnosis	
ICD10	DSM5
- For at least 1 month	<ul style="list-style-type: none"> - Disturbance for at least 6 months plus 1 month of symptoms
AT LEAST ONE OF:	<ul style="list-style-type: none"> - Need to have social/occupational dysfunction <p>NEED to have two or more of the following (at least one of 1,2,3):</p> <ul style="list-style-type: none"> 1> delusions 2> hallucinations 3> disorganized speech 4> grossly disorganized or catatonic behaviour 5> negative symptoms
OR, AT LEAST TWO OF:	<ul style="list-style-type: none"> 1> Persistent hallucination 2> Break in train of thought, incoherent speech

3>	Catatonic behaviour e.g., excitement, posturing	
4>	Negative symptoms e.g., apathy, paucity speech	
5>	Significant and consistent change in overall quality of personal behaviour	

Differential diagnosis:
Substance induced psychotic disorder, Depression (mood disorders with psychotic symptoms), Bipolar, General medical condition e.g., sepsis, cerebral tumour, OCD, dementia

First generation antipsychotic (FGA) – D2 antagonist (histamine, muscarinic, alpha 1R) → High Extrapyramidal S/E (EPSE) due to nigrostriatal pathway D2 receptor blockage

Chemical	Drugs	Formulation	Note
Phenothiazine	Chlorpromazine	Oral, IM, suppository	
	Levomepromazine	Oral, IM	
	Promazine	Oral	
	Pericyazine	Oral	
	Trifluoperazine	Oral	
	Fluphenazine X	Oral	
	Perphenazine	Depot	
Butyrophenones	Prochlorperazine	Oral	
	Haloperidol	Oral, IM	25mg test dose 50-300mg /4weeks **increased risk of EPSE
Thioxanthenes	Benperidol	Oral, IM, Depot	
	Flupentixol	Oral, Depot	20mg test dose 50mg /4weeks up to 400mg/week **increased risk of EPSE
Diphenylbutylpiperidines	Zuclopentixol	Oral, Depot	100mg test dose 200-600/week or 4 weeks **increased risk of EPSE
	Pimozide	Oral	
Substituted benzamides	Sulpiride	Oral	
	Amisulpride	Oral	

Second generation antipsychotic (SGA) – like TCA → Superior efficacy against negative symptoms → Metabolic syndrome (weight gain, insulin resistance, hyperlipidaemia), blood disorders

Drugs	Formulation	Note
Clozapine	Oral, IM	Licensed to treat resistant schizophrenia Weak antagonist at D2R, act strongly at 5-HT2AR and strong anticholinergic, antihistaminergic and alpha 1 adrenergic blocking
Olanzapine	Oral, IM, LAI	150mg /4weeks to 300mg/2weeks (risk of post injection syndrome 3H)
Risperidone	Oral, LAI	25-50mg every 2 weeks
Paliperidone	Oral (rare), LAI	50-150mg monthly after stabilised for 4 months can move on to 3 monthly 175-525mg /3 months
Quetiapine	Oral	
Aripiprazole	Oral, IM, LAI	300mg-400mg monthly (loading dose required) **Akathisia common SE
Lurasidone	Oral	
Depot and long-acting injections		

- For FGA is use injection, test given for oil base and EPSE sensitivity	
- For SGA oral treatment first, no dose test for injection bc use aqueous base	
Advantages	Disadvantages
- Continuous antipsychotic release and delivery - Patient adherence better (no need to take daily) - Clinicians can be notified for non-adherence - Drug remains in the system for one to two weeks after missed dose - Reduced relapse and hospitalisation - Avoid first-pass metabolism tf, easy to dose and better blood level of drugs - Smooth release profile tf less S/E	- IM injection painful and uncomfortable - Oral to LAI not easy - Difficult preparation harder dose titration - Adverse effect persist until drug cleared from system - Poor injection techniques e.g., injecting into blood vessels can cause issues

GENERAL PRINCIPLES of antipsychotic prescription

- 1) Minimum effective dose to minimise SE
- 2) Use single antipsychotic (avoid polypharmacy – increased risk of AT prolongation and sudden cardiac death)
- 3) Only use combination antipsychotic where response to single antipsychotic (clozapine as well) is inadequate
- 4) Antipsychotic should not be used as when required (PRN)
- 5) Recognise rating scale and document patient outcome
- 6) Monitor physical health – blood pressure, pulse, ECG, plasma glucose, plasma lipids
- 7) Withdrawal management

High dose antipsychotic (HDAT)

- Single antipsychotic prescribed above BNF limit
 - 2 or more antipsychotic prescribed concurrently that maximum daily dose total more than 100% (inc. PRN)
- Document target symptoms, therapeutic response, SE, close physical monitoring required

Need for rapid tranquillisation

- Use intra-muscular medication if urgent sedation required
 - To reduce risk of harm to themselves or others (remain safe environment)
 - Do not induce sleep or unconsciousness to further assess and treat
- IM lorazepam on its own or IM haloperidol with IM promethazine

Resistant psychosis

- Treatment with at least 2 different antipsychotics, including an SGA for at least 4-6 weeks
- CLOZAPINE – only supplied with valid blood results
- Patient must be approved with clozapine blood monitoring service to minimise risk of agranulocytosis or neutropenia (low neutrophil levels, blood disorders)
- Blood monitoring must be done before starting treatment, then weekly for first 18 weeks, then every two weeks until 1 year then monthly

Results		Action
Green	WBC more than or equal to 3500/mm ³ ANC more than or equal to 2000/mm ³	Routine test can supply
Amber	WBC between 3500 – 3000 ANC between 2000 – 1500	Repeat test twice weekly until either red or green (no supply yet)
Red	WBC below 3000 ANC below 1500	Must be stopped Sample blood daily until recovery

Withdrawal management:

- Do not cause psychological dependence, but has discontinuation symptoms on abrupt discontinuation
- Occurs with 4 days and last 1-2 weeks
- Symptoms (cholinergic rebound SE): nausea, vomiting, sweating, diarrhoea, muscle pain, insomnia, restlessness, anxiety, seizures, EPSEs
- Risk of psychotic symptoms reoccurring

- Slow and gradual discontinuation essential, hyperbolic regimen, educate patient
- Short term use of benzodiazepine for anxiety or sleep disturbance or use anticholinergic drugs e.g., procyclidine (more in treating EPSE)
- ALWAYS cross taper when switching antipsychotics

Adverse Effects

FGA: EPSE, Neurological S/E (acute (akathisia, dystonia, parkinsonism), tardive dyskinesia), anticholinergic, cardiac, hyperprolactinaemia, sexual dysfunction
SGA: metabolic S/E (weight gain, hyperglycaemia, hyperlipidaemia), anticholinergic, cardiac, hyperprolactinaemia, sexual dysfunction

		Symptoms	Treatment options
Extrapyramidal Side Effect (EPSE) *associated with high dose of high potency FGA e.g., haloperidol	Dystonia	Muscle spasm e.g., eye rolling upward (oliguric crisis), head and neck twisted to the side (torticollis) – can be painful 10% of patients (more in young male)	Anticholinergics - Procyclidine (oral, IM, IV) - Switch to SGA
	Parkinsonism	Tremor and or rigidity Bradykinesia: deceased facial expression, monotone voice, slow body movements, inability to move 20% of patients (more in female)	Reduce dose Switch meds Anticholinergic: procyclidine
	Akathisia	Inner restlessness Constant pacing across the room, unable to sit, constant twitching or tapping of legs 15% - common when starting aripiprazole	Dose reduction Switch meds Short course of benzo when starting aripiprazole
	Tardive Dyskinesia	Wide variety of movements: Lip smacking, tongue protrusion, choreiform hand movement (piano playing) 5% - older age, takes years to develop	Stop anticholinergic meds Reduce antipsychotic Switch to either clozapine or quetiapine
Metabolic side effects *associated with SGA	Weight gain	- Monitor baseline waist circumference, fasting blood glucose, HbA1c and blood lipid level every 12 weeks then annually	
	Hyperglycaemia	*Every 3 months for clozapine and olanzapine in first year - Weekly weighing for first 6 weeks, 3 months then annually Diet and lifestyle interventions	
	Symptoms and examples	Treatment options	
Cardiac SE	Orthostatic/postural hypotension Myocardial infarction Ventricular arrhythmia Increased QT interval Cardiomyopathy Myocarditis – stop medication immediately Risk: venlafaxine, flupentixol, HDAT	Monitoring: baseline BP, pulse, ECG repeat 12 weeks then annually + monitor plasma electrolytes e.g., potassium levels to detect abnormalities - Review medication - Avoid polypharmacy	
	e.g., FGA and clozapine, olanzapine, quetiapine at high doses Central: Cognitive impairment, delirium, hyperthermia, confusion Peripheral: dry mouth, constipation, blurred vision, glaucoma, urinary retention	Olanzapine is contraindicated to patients with narrow angle glaucoma Review concurrent meds Start low increase gradually Switch antipsychotic	
Hyperprolactinaemia	>Dopamine inhibits prolactin release (tuberohypophyseal)	Reduce dose	

	<ul style="list-style-type: none"> ->Dopamine antagonists increase prolactin plasma levels e.g., Amisulpride, paliperidone, risperidone, sulpiride, FGAs - Often asymptomatic - Sexual dysfunction, menstrual disturbances, breast growth, pregnancy delusion - Long term: bone mineral density reduction, risk of breast cancer 	<ul style="list-style-type: none"> - Switch to a prolactin sparing antipsychotic - Maybe add a low dose aripiprazole - E.g., clozapine, quetiapine
Sexual dysfunction	<p>Most common with risperidone (SGA) and haloperidol (FGA)</p> <p>Less likely with aripiprazole and quetiapine (SGA)</p>	<ul style="list-style-type: none"> - Monitor prolactin levels - Adjust dose - Switch or stop - Add 3-6mg aripiprazole (off license use) - Phosphodiesterase 5 inhibitor e.g., sildenafil, tadalafil or vardenafil -> help erectile dysfunction
Sedation	e.g., clozapine, olanzapine, quetiapine can cause	<ul style="list-style-type: none"> - Impact on driving/operating machinery - Avoid psychostimulants like modafinil - Give bigger dose at night
SE of Clozapine	CVD	<p>Thromboembolism, myocarditis (6-8 weeks of treatment)</p> <p>Monitor for hypotension, tachycardia, fever, flu like symptoms, fatigue, dyspnoea with increased respiratory rate, chest pain</p> <p>Cardiomyopathy (9months later)</p> <p>Baseline monitoring: CRP, FBC, troponin, ECG</p> <p>Daily pulse, BP, temp, respiratory rate</p> <p>If CRP more than 100mg/L stop clozapine</p>
	Blood disorders	<p>Agranulocytosis – 0.4% patients</p> <ul style="list-style-type: none"> - Lowe neutrophil levels <p>WCC platelets checked weekly for 18weeks, then every fortnight for a year then monthly check</p>
	Constipation	<p>Usually dose related</p> <p>Mechanism anticholinergic and antihistaminergic and antagonism at 5HT3R -> anticholinergic effects</p> <p>NO OPIOIDS OR TCA</p> <p>Dietary change, exercise, laxatives</p>
	Hypersalivation	<p>Usually dose related may improve</p> <p>Particularly at night during early stage of treatment</p> <ul style="list-style-type: none"> - Aspiration pneumonia <p>No licensed treatments</p> <p>Hyoscine hydrobromide (antimuscarinic)</p> <p>Chew gum during day</p> <p>Elevating pillow, place towel</p>
	Neuroleptic malignant syndrome (NMS)	<p>Rare but fatal 0.1%</p> <p>Symptoms: fever, rigidity, confusion, fluctuating consciousness, fluctuating BP, tachycardia, elevated creatinine kinase, leukocytosis, altered LFTs</p> <p>Risk factors: high potency FGA, recent or rapid dose increase, abrupt withdrawal, polypharmacy, psychosis, alcoholism, young male, agitation, dehydration</p> <p>Stop antipsychotics, monitor temp, pulse, BP, consider benzos, call ambulance</p> <ul style="list-style-type: none"> - Rehydration, bromocriptine, dantrolene, sedation, artificial ventilation <p>Restarting antipsychotics:</p> <ul style="list-style-type: none"> - Allow at least 5 days before attempts - Start low dose slow - Quetiapine, clozapine, aripiprazole good option choice (due to lower dopamine affinity bind) - Avoid depot or LAI

LB



Bipolar Disorder

JOANNE HEADSPETH
SPECIALIST MENTAL HEALTH CLINICAL PHARMACIST
NORFOLK AND SUFFOLK MENTAL HEALTH TRUST

Overview

mood disorder
Bipolar Disorder, has stages of **mania/hypomania**, depression and **mixed episodes**. **manic-depressive**

Between episodes the mood can be stable (euthymia) but functioning is frequently impaired

It is a life-long with a high **suicide rate (15-20%)** ↑
and co-morbidity → anxiety, substance misuse, personality disorders, ADHD, alcohol dependency, poor impulse control, eating disorders

It is significantly **under-diagnosed or misdiagnosed** with a delay in treatment

Use of medication is frequently **sub-optimal**

Mood stabilisers have a poor uptake and compliance
→ lithium, anti-convulsants, anti-psychotics
→ poor uptake + compliance

Epidemiology

1% of the Population diagnosed with Bipolar

Up to 5% on the Bipolar spectrum → bipolar 1,2,3

The incidence is similar in both **genders and all ages, races, ethnic groups and social classes**

Can occur at any age, although the first diagnosed episode is often between the ages of **18-24 years of age**.

There is increased general mortality regardless of age

At least 70% people with bipolar disorder have at least one close relative with the illness or with unipolar depression

Bipolar disorder is the sixth leading cause of disability in the world

Risk Factors For Developing Bipolar Disorder

Risk factors:

Family history and genetics identical twins if one has - 50% chance the other
Being male (only a very slight increase over women)

Triggers for an episode:

Life events such as e.g. **trauma, physical, sexual, or emotional abuse**

Stopping a mood stabiliser suddenly, especially **lithium**

Potentially being on an antidepressant without a mood stabiliser (bipolar)

Having **ECT** for depression → later

Spring and summer - **mania or hypomania** → **fall/winter depression**

↳ Goal attainment events?

Disrupted Circadian rhythms e.g. shift-working

Risks to the individual of having bipolar mood disorder

PHYSICAL	MENTAL	LIFE
Physical health: Obesity is more common Heart disease and high blood pressure X 5 Poor Memory more likely	Mental Health: Suicide x 14 greater risk Substance misuse is common 1 in 2 dependent on alcohol and 2 in 5 may be dependent on other drugs	Social, relationships and work: Symptoms can be highly damaging to the person (social life, family relationships and work) unpredictable, firing - poor job prospect Poor work or school performance Financial problems from reckless spending and being impulsive when high Violence to others when disturbed, especially when high or low, or on drugs/ alcohol Being promiscuous
Dying from a respiratory problem X 3 Dying from an infection is twice as likely Life expectancy is about 10 years less		Joint, embarrasment, family conflict
↳ delay in diagnosis/treatment - substance misuse		

Causes Of Drug Induced Mania

The most common symptoms of drug-induced mania are **increased activity, rapid speech, elevated mood and insomnia**

Causes can include:

Hallucinogens e.g. LSD

CNS stimulants e.g. amphetamines, caffeine

• **Antidepressants** - switching from depression to mania

• **Antipsychotics** olanzapine, risperidone, quetiapine ... old antipsychotic: haloperidole

Clinical Features, Categories and Diagnosis Of Bipolar Disorder

Joanne Headspeath
Specialist Mental Health Pharmacist
Norfolk and Suffolk Mental Health Trust

Clinical Features Of Mania/Hypomania

main diagnostic symptoms

- Abnormal elation of mood.
- Inability to concentrate, easily distracted
- Flight of ideas → rapidly change subject
- Obsessive preoccupation with some idea, activity or desire → lots of great ideas, important plans
- May be overactive and intrusive
- Risk taking and disinhibition e.g. spending money, sexual promiscuity

main presenting symptoms

- Euphoric and labile mood
- Bright or untidy appearance : bright colour makeup
- Low sleep requirement not sleepy
- Increased drive and energy
- Reduced insight not because they are on an episode
- Pressure of speech, flight of ideas, expansive thought, overactive and intrusive manner.

↑ life threatening due to physical exhaustion

Diagnostic Difference Between Mania and Hypomania (DSM V)

Mania

7 days

- Duration of elevated and irritable mood needs to be for 7 days or more
- severe functional impairment
- May have psychotic features

Hypomania

4 days

- Duration of elevated and irritable mood needs to be for 4 days or more
- decreased or increased function
- Psychotic features absent

Clinical Features Of Bipolar depression

*longer lasting than uni-polar depression - much more difficult to treat
→ antidepressants ineffective

Decreased energy and fatigue (lethargy)

Sleeping badly

Doing less

Poor sleep (too much or too little)

Loss of interest in things that used to be enjoyable

Feelings of wanting to self-harm

What's The Difference Between Depression and Bipolar Depression?

- Depression is a condition in its own right, and is the predominant symptom of unipolar depression, of which there are other symptoms e.g. loss of interest, poor sleep etc
→ could be a symptom for other diseases

- Bipolar depression is a symptom of a phase or part of bipolar mood disorder, of which includes several other phases e.g. manic or mixed episodes, as well as remission or euthymia. Each of those have separate symptoms

Categories Of Bipolar Disorder

The main categories of bipolar disorder are generally accepted as (DSM V and ICD 10)

Bipolar I (classic manic-depression)

- Mania and severe depression, or mania alone

Bipolar II

- depression with at least one hypomanic episode

• May be genetically distinct from Bipolar I

Bipolar III (Pseudounipolar Bipolar Disorder)

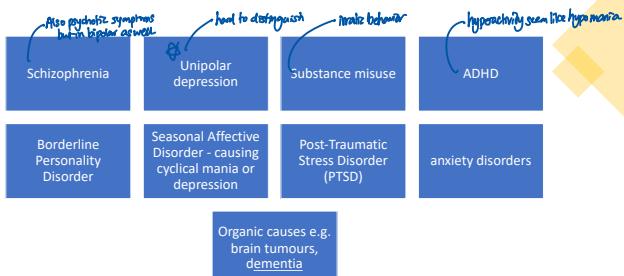
- Recurrent depression and mixed states → presence of high + low at the same time

• Antidepressants may induce hypomania switching to anti-mania states

Rapid-cycling

- 4 or more mood episodes in a year.

Differential Diagnosis





Treatment of Bipolar Disorder

Joanne Headspeath
Specialist Mental Health Pharmacist.
Norfolk and Suffolk Mental Health Trust

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Non-Pharmacotherapy

Psychological Therapies

- Psychological treatments i.e. talking therapies such as psychotherapy, CBT and family therapy can be useful for some people, especially early on in treatment, when used with medicines and perhaps in people with difficult-to-treat symptoms
- Overall CBT doesn't seem to help to stop highs or lows in Bipolar Disorder
- Psychosocial interventions may have an important part to play. Reduces stress and helps manage symptoms
- Psychotherapy and CBT are recommended by NICE, which takes the view that because these may help Unipolar Depression they must help Bipolar Depression too

Self-help:

- Mania is susceptible to stresses e.g. changes in time zone, irregular sleep, substance misuse



2

Pharmacotherapy

Goals are different

Mood stabilisation and relapse prevention	Acute hypomania/mania	Bipolar depression
• Reduction in the frequency and/or severity of manic, depressive and/or mixed episodes.	• Management and harm-reduction in manic or hypomanic episodes	• Management of acute bipolar depression.

3

General Prescribing Principles For Mania

General principles for managing mania:

1. Discontinue any manicogenic agents, including antidepressants and stimulants.
2. Stabilise any medical conditions.
3. Start non-specific calming medications, e.g. benzodiazepines, antipsychotics.
4. Start specific mood-stabilisers or relapse prevention agents, preferably when the person is able to consent to longer-term therapy.
5. Hypnotic/sedative use should be considered appropriate as a night of sleep deprivation is likely to escalate any manic patient to a higher degree of mania.
6. Any co-morbid substance misuse must also be tackled, as recovery is poorer in people with a history of substance abuse.

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LITHIUM- SEE SEPARATE PODCAST

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A summary of the available drugs and licensing:

Medicine(s):	Pole:	Mania/hypomania Acute	Relapse prevention	Bipolar depression Acute	Relapse prevention
First-line:					
1. Lithium	L	L	L	L	L
2. Valproate	L	L	-	-	-
3. Carbamazepine	L	L	U	U	U
4. Quetiapine	L	L	L	L	L
5. Aripiprazole	L	L	X	X	X
Second-line:					
Carbamazepine	L	L	L	L	L
Risperidone	L	L	X	X	X
Asenapine	L	U(L)	X	X	X
Benzodiazepines	U	U	X	X	X
Haloperidol	U	U	X	X	X
Lurasidone	-	-	U(L)	U(L)	U(L)
Antidepressants	X	X	U	X	X
Olanzapine + fluoxetine	-	-	U(L)	U(L)	U(L)

Key:

- L = Licensed
- U = Unlicensed but some evidence (benzodiazepines and haloperidol are not licensed specifically for acute mania).
- U(L) = Not licensed in UK for this indication, but is in some other major countries
- = No evidence
- X = Shown not to work

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→ only drug licensed for acute bipolar in UK



Quetiapine ~ Seroquel

Status

- Licensed as monotherapy for acute mania and relapse prevention, acute bipolar depression and relapse prevention
- Also acute mania and relapse prevention in people who respond in acute state over 2 years
- Doses and titration varies for different indications.

Base-line monitoring

- Weight/BMI: ↑ weight risk of stroke
- Pulse & BP after each dose change
- Weight/BMI weekly for first 6 weeks, then at 12 weeks
- Blood glucose or HbA_{1c}
- Blood lipid profile at 12 weeks
- Response to treatment
- Side effects
- Emergence of movement disorders
- Adherence

Ongoing monitoring

- Weight/BMI: ↑ weight risk of stroke
- Pulse & BP after each dose change
- Weight/BMI weekly for first 6 weeks, then at 12 weeks
- Blood glucose or HbA_{1c}
- Blood lipid profile at 12 weeks
- Response to treatment
- Side effects
- Emergence of movement disorders
- Adherence

*↑ can increase QT interval.
Risk of diabetes: weight/BMI, HbA_{1c}, Risk of hypertension, Lipids
Risk of HT: pulse, BP
Risk of arrhythmia: ECG, QTc, No plasma test*

Quetiapine is the only drug currently licensed for the treatment of acute bipolar depression in UK

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Quetiapine Prescribing and Counselling Points

Example Of Dosing

- Mania:**
 - Quetiapine XL in bipolar depression:
 - Day 1: 50mg at bedtime
 - Day 2: 100mg at bedtime
 - Day 3: 200mg at bedtime
 - Day 4 onwards 300mg at bedtime
 - Onset of action is within one week
- Depression:**
 - Quetiapine XL in bipolar depression:
 - Day 1: 50mg at bedtime
 - Day 2: 100mg at bedtime
 - Day 3: 200mg at bedtime
 - Day 4 onwards 300mg at bedtime
 - Onset of action is within one week

Selected list of adverse effects

- Very common:**
 - Sleepiness - late at night/take day time
 - Dizziness
 - Dry mouth - anticholinergic side effect/pause
 - Weight gain
 - Postural hypotension
- Common:**
 - Headache
 - Akathisia (involuntary)
 - Anticholinergic side effects

Prescribing Advice

- Initial dose titration must be slow due to the risk of postural hypotension in about 10% people
- Although highly sedating at low doses (e.g. 25mg) the sedation is not proportional to dose
- Quetiapine XL vs Plain tablets - Dependent on Trust and Patient

Interactions- See BNF

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Olanzapine

Status

- Licensed for mania and relapse prevention in people who have responded to it acutely and are lithium or valproate non-responders
- Widely used as an antimanic and as a mood stabiliser

Monitoring

- Same as Quetiapine

Formulations

- Available as tablets, short-acting IM injection and orodispersible tablet and (Depot) (restricted use). → see BNF
- In USA olanzapine is available as a combination product with fluoxetine (Symbax) for bipolar depression but not for UK

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Olanzapine Prescribing and Counselling Advice

Selected adverse effects

- Very common:**
 - Sedation (antihistaminic effect)
 - Weight gain
- Common:**
 - Postural hypotension
 - Dry mouth
 - Peripheritis
 - Peripheral oedema
 - Diabetes
 - Long-term effects may include weight gain, metabolic syndrome (e.g. diabetes, plus raised lipids and cholesterol)

Interactions

- Smoking:** → a central cause induces CYP2D6 that metabolizes olanzapine. → smoking cessation can lead to higher blood levels
- See BNF:** Olanzapine interacts with many other drugs

Prescribing Advice

- Starting dose in acute mania is 15 mg/d as monotherapy or 10 mg/d as an adjunct
- Do not give benzodiazepines within an hour of short-acting IM olanzapine use (reports of deaths)

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3



Aripiprazole

Status

- Licensed for acute mania and manic relapse prevention in people who have responded acutely including in adolescents aged 13 years or older

Monitoring

- See Quetiapine

Formulations

- Available as tablets, orodispersible, liquid and injection (plus long-acting depot injection)

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Aripiprazole Prescribing and Counselling Advice

Selected list of adverse effects:

- Very common:**
 - Sedation which can be counter-productive in mania/hypomania)
 - Insomnia (not always can be taken morning)
 - Stomach upset
 - Constipation
 - Blurred vision
- Common:**
 - Movement disorders (extra-pyramidal side effects)
 - Postural hypotension
 - Palpitations

Prescribing Advice

- For mania can start at 15mg, and increase to 30mg/d
- Relapse prevention dose can be 15-30mg/d
- Due to aripiprazole's partial agonist, start aripiprazole at 5mg/d if the person has had another antipsychotic in the system. D₂ blockade by antipsychotic will reduce dopamine activity, patching out 5% of the normal activity helps us acting up to 30% less affinity → disrupt other receptors → cause dramatic changes brain function.

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4

Lamotrigine

Status

- Licensed for prevention of relapse of bipolar depression.
- No efficacy in mania, mixed, rapid-cycling or unipolar depression nor acute bipolar depression (long titration due to this)
- Efficacy shown in severely depressed bipolar patients

Selected List of Adverse Effects

- Most common:
 - Drowsiness and dizziness
 - Headache
 - Nausea
 - Blurred vision
- Rare but serious side effects:
 - Geddes
 - Bone marrow suppression
 - Symptoms of unexpected bruising, infections, and pemphigus
 - Stevens-Johnson syndrome
 - Cards: Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN).
 - Red rashes across the face and body blisters and inflammation in the nose, mouth and eyes - looks a bit like serious burning or sunburn

Prescribing Points

- Lamotrigine titration must be "by the book".
- Starting dose must be low and slowly titrated as per BNF
- 25mg/d to 2/52, 200mg/d for 1/52, then increase by 50-100mg/d every 1-2 weeks to be over liver and start of being Valproate
- This almost abolishes the risk of the potentially rapidly fatal Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis



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Valproate (sodium valproate, valproate semisodium, valproic acid)

No clinical differences between these - does it matter what you use but dosage/dose different

Epilim® Chrono® 500mg Prolonged Release Tablets
Sodium Valproate & Valproic Acid
100 Tablets
For Oral Use
SANOFI

Depakote® 250 mg Tablets
Valproate semisodium (also known as disperox sodium USAN)
30 gastro-resistant tablets
For Oral Use
SANOFI

WARNING FOR WOMEN AND CHILDREN
This medicine can seriously harm a unborn baby. It may cause birth defects if taken during pregnancy or if you become pregnant. Tell your doctor straight away if you are pregnant or think you may be.

Monitoring

- Baseline: height, weight, FBC, LFTs + hepatic enzymes
- Blood cell count, including platelet count, urinalysis and blood glucose before treatment starts then during first 6 months
- LFTs before starting, then over next 6/12 months
- Ongoing Monitoring: LFTs once a year at 6 months

Formulation and Dosing

- Oral loading doses are of valproate are more rapidly effective in mania, e.g. 20 mg/kg/d may give a rapid response, often within three days
- Maintenance dose not established
- Epilim is available in tablets, prolonged release tablets and liquid

Plasma monitoring if toxicity suspected

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Valproate Patient Counselling Advice

Selected List of Adverse Effects

- Very common:
 - Increase in appetite and weight gain
- Common:
 - Gastric irritation, diarrhoea
 - Hair loss –
 - Nausea
- Uncommon:
 - Sleepiness
 - Impaired liver function
- Rare but serious:
 - Chromosomal damage and impaired foetal function
 - Hepatitis – in first 6/12 months
 - Gastritis – abdominal pain, nausea, vomiting
 - PCOS
 - Link to weight gain

Interactions

- Carbamazepine (reduced valproate levels)
- Anticonvulsants (increased valproate levels)
- 24% have > 25% increase in valproate levels
- 24% have an increase of > 50% in valproate levels
- 23% have a > 25% decrease in valproate levels

Patient and carer advice

- Valproate use by women and girls
- Pregnancy Protection Programme (next slide)
- Complications in females and women not to use during pregnancy
- Animal studies show teratogenicity with valproate
- Not stop taking valproate without first discussing it with their doctor
- Notify if female under 18
- Recognise signs and symptoms of blood or liver disorders and advised to seek immediate medical attention
- Pancreatitis
- Recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention
- Abnormal PMS, menstruation, ovulation

SEE BNF

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Valproate risk in those of fathering potential

Risk

- New data from August 2023
- Valproate can cause infertility, this may be reversible upon withdrawal or reduction
- Animal studies show teratogenicity with valproate
- Estimated rate of foetal malformations – highest in males under 55
- MHRA determine risk to be highest in males under 55

Action

- From February 2024:
 - All males under the age of 55 must have a risk acknowledgement form complete when starting valproate
 - Two specialists must confirm that alternative treatment is not appropriate and sign the form
 - Patients must be informed of the risk and provided with a patient guide
 - No mandatory requirement in existing valproate users or those over 55 – but risk may still be present

Address w/ patients

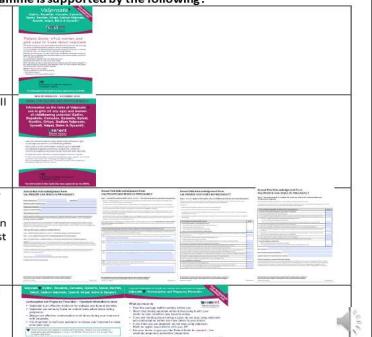
The Valproate Pregnancy Prevention Programme is supported by the following:

Patient Booklet – to be provided to girls (of any age) and women of childbearing potential or their parent/caregiver/ responsible person) taking any medicine containing valproate

Booklet for healthcare professionals – for all prescribers, pharmacists, and other healthcare providers involved in the care of women and girls of childbearing potential using valproate medicines

Annual Risk Acknowledgement Form* – for the specialist and patient (or their parent/caregiver/ responsible person) to sign at initiation and at treatment reviews at least every year. Copies of the form should be filed in the specialist notes and given to patient and patient's GP

Patient Card – to be given by pharmacists to all female patients who are dispensed valproate medicines to inform them of the risks



Options For Women Of Childbearing Potential and Prescribed Valproate *Don't Judge by age*

Management

- Stop valproate, gradually
- Switch to another medicine
- Continue valproate and become part of the "Valproate Pregnancy Prevention Programme", but only if valproate is for epilepsy, and there is no alternative

The female must

- Discuss with a doctor or family planning clinic to get professional information and advice on effective contraception
- Rapidly consult Dr if a pregnancy is planned or is confirmed
- Have a Valproate Annual Risk Acknowledgement Form, where everything should be explained, with a signed document.
- Get a Patient Guide from the prescriber
- Carry a Patient warning card

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OTHER TREATMENTS

ANTIDEPRESSANTS

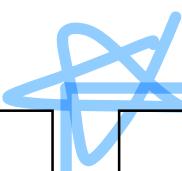
- The use of antidepressants in **bipolar depression** is common and logical (based on the symptoms) but lacks an evidence base:
- There is a potential for switching to mania
- If used, antidepressants can be safe if combined with a mood stabiliser**
- Accelerated episode frequency is considered possible

If someone is manic/hypomanic and on an antidepressant, the antidepressant should be stopped stepwise (not suddenly)

Antidepressants can help in the short-term if combined with a mood stabiliser

The antidepressant should then be stopped once the acute episode has resolved

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COMBINATIONS	
Bipolar mania	Quicker onset and more effective in the short-term
Antipsychotic and/or mood stabiliser + benzodiazepines	
Bipolar depression	To reduce the risk of mood switching from depression to mania in bipolar depression and to stabilise mood
Lithium, lamotrigine or valproate, quetiapine, risperidone or olanzapine	
Any combination	Relapse prevention
Relapse prevention	
Mood stabilisers	May be more effective as a combination
Mood stabilisers + antidepressants	May be more effective as a combination in short-term
Lamotrigine + antidepressants	Antidepressants to resolve depression and lamotrigine for relapse prevention

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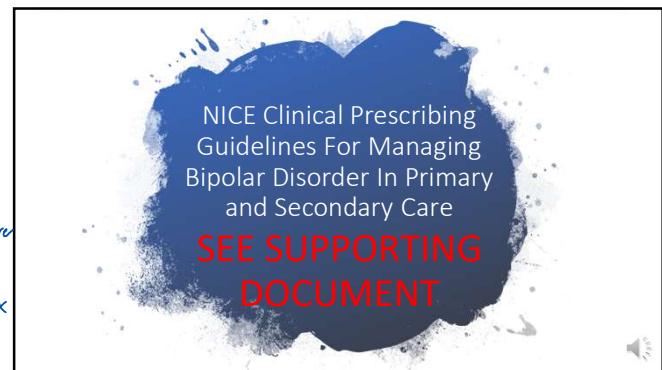
Prescribing In Special Patient Groups

Consult the most up-to-date resources

Hepatic impairment: most antidepressants metabolised by liver
exception - amisulpride and sulpiride

Renal impairment: lithium should be avoided
*Spc break, but amisulpride & sulpiride X

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Bipolar Support Groups

Some useful charities, support groups and associations include:

- [Bipolar UK](#)
- [Carers UK](#)
- [Mind](#)
- [Rethink](#)
- [Samaritans](#)
- [SANE](#)

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Lithium Therapy

A guide on the treatment and management of Lithium

By Joanne Headspeath
Clinical Pharmacist

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Therapeutic Indication for Lithium Treatment

- Prophylaxis against bipolar disorders
- In the management of acute manic or hypomanic episodes (must have previously responded to Lithium and symptoms not severe)
- Recurrent depression
- Control of aggressive behaviour or intentional self harm

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#Blood levels monitoring issues
#mania - rarely used bc delayed onset of 5-7 days
#best taken long term

Mechanism of Action

- Lithium is an alkali metal (similar to salt) available for medical use as lithium carbonate or lithium citrate.
- The mode of action of lithium is still not fully understood. However, lithium modifies the production and turnover of certain neurotransmitters, particularly serotonin, and it may also block dopamine receptors.

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AVAILABLE FORMULATIONS

- Preparations vary widely in bioavailability.
- Ensure patient is maintained on the same brand.

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AVAILABLE FORMULATIONS

- At NSFT we stock Priadel M/R Tablets 200mg and 400mg (Lithium Carbonate) and Priadel Liquid 520mg/5ml (Lithium Citrate).
- Dose conversion between Priadel M/R tablets and Priadel Liquid NOT comparable.
- 5ML of Lithium Citrate liquid 520mg/5ml is approximately equal to ONE Lithium Carbonate 200mg M/R tablets.
- Other brands include Camcolit, Liskonum and Li-Liquid.

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Contraindications For Lithium Therapy

- Hypersensitivity to lithium or to any of the excipients.
- Cardiac disease.) lithium affect QT interval
- Cardiac insufficiency.
- Severe renal impairment. - kidney excretion
- Untreated hypothyroidism. - affect thyroid
- Breast-feeding → excreted in breastmilk
- Patients with low body sodium levels, e.g. dehydrated patients or those on low sodium diets.
- Addison's disease.
- Brugada syndrome- hereditary disease of the cardiac sodium channel

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Cautions for Lithium Therapy

- Pregnancy - AVOID unless exceptional circumstances, esp first trimester → risk of cardiac abnormalities
- Renal Impairment
- ECT and other medication that can decrease epileptic Threshold
- QT interval prolongation and medication that increases QT



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Physical Monitoring before Initiating Treatment

- E.C.G – can increase QT interval.
- Renal Function (Egfr)- Lithium is excreted via Kidneys.
- Thyroid function- Hypothyroidism can be mistake for depression.
- Weight/BMI, Ca, U&E's and FBC



lithium can cause hypercalcemia

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Lithium Monitoring During Treatment

- Lithium has a narrow therapeutic window
- Regular blood tests required to ensure therapeutic dose maintained and to monitor for toxicity.
- Plasma levels must be taken weekly until stable concentrations maintained for 4 weeks.
- Plasma levels should 4-7 days after each dose change until stable.
- NICE- take plasma levels every 3 months for 1st year at NSFT we continue this then 6 monthly unless at risk



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3months

Older population,
people taking drugs that
interact w/ lithium,
risk of renal /thyroid function
poor adherence, poor symptom control
people who lost plasma lithium levels : 0.8mmol or higher

8pm take → 8am test

- Blood test should be taken 12 hours post dose.
- Range should be 0.4 to 1 mmol/L (higher end in Mania).
- Lower range in elderly.
- Renal Function (Egfr) and Thyroid function (TSH and T4) monitored every 6 months.
- Weight/BMI, Ca, U&E's



* Lithium levels 3months
* Renal / thyroid 6months

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one lithium level higher than 1mmol/L
can cause impaired renal function

Dosage of Lithium

- Dosage must be individualised depending on serum lithium levels and clinical response.
- Usual starting dose 200mg in elderly and 400mg in Adults. *taken at night*
- Usual dose range 400mg-1.2g Daily
- Reduced dose in renal impairment (avoid if possible) and patients <50KG.



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Side Effects of Lithium

- Upset stomach-particularly at start of treatment.
- FINE tremor of the hands.
- Metallic taste in the mouth.
- Swelling of ankles- dose reduction.
- Increase thirst and urine output- renal impairment.
- Weight gain- up to 27KG.



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Lithium Toxicity

- Blood concentrations over 1.5mmol/L (over dosage) may be fatal and have a toxic effect.
- Blood concentrations over 2mmol/L (severe over dosage) requires urgent medical attention.

check compliance



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Signs and Symptoms Of Lithium Toxicity

- SEVERE hand tremor
- Stomach ache with nausea and diarrhoea
- Muscle Weakness
- Unsteady on feet
- Slurring of words
- Blurred Vision
- Confusion
- Unusually Sleepy
- Muscle Twitches

metabolic task in mind?



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Signs and Symptoms of Lithium Toxicity

Severe Toxicity may lead to

- Convulsions
- Coma
- Renal and circulatory failure
- Hyperreflexia- overactive reflexes
- Toxic Psychoses



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Drug interactions that can INCREASE Lithium Levels (Including OTC medicine)

- ACE inhibitors-e.g Ramipril → can reduce thirst → mild dehydration → ↓ sodium levels in renal tubule → ↑ sodium reabsorption in kidney → ↓ lithium levels
- Angiotensin II receptor antagonist- e.g Candesartan
- NSAIDS AVOID concomitant use → paracetamol or panadol
- cyclo-oxygenase (COX) 2 inhibitors- e.g Ketorolac, AVOID
- Metronidazole)
- SSRI's *
- Diuretics and Aldosterone antagonists –e.g Bumetanide/Furosemide(least risk),Bendroflumethiazide and Spironolactone

thiazide must be reduce lithium renal clearance w/few days



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Drug Interactions that can DECREASE Lithium Levels

- Sodium bicarbonate containing products
- Caffeine

Other Interactions

- Ventricular Arrhythmia can be caused by concomitant use with Amiodarone-AVOID
- Increased risk of neurotoxicity with Methyldopa and some antipsychotics e.g Clozapine



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Other Risks for Increase Lithium Levels

Sodium depletion increases Lithium concentration due to competitive re absorption at the renal level

Patient should be monitored for

- Dehydration**- Ensure adequate fluid intake *2L a day*
- Changes in Salt levels in diet
- Infection
- Vomiting and Diarrhoea



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Counselling Advice

- Once daily at NIGHT to minimise renal damage
- Effectiveness takes 6/12 to fully establish
- Duration of treatment 2-3 years minimum
- Take it regularly – erratic compliance is dangerous
- Lithium must not be stopped rapidly ↑ risk of suicide, relapse
- Should be stopped stepwise over at least 4 weeks, preferably longer e.g. 6 months
- Make sure plasma level monitoring is regular (3 months) to reduce renal damage potential
- Keep up fluid intake – “don't ignore feelings of thirst”, particularly after sweating, hot climates
- Seek medical attention if develop diarrhoea or vomiting
- Lithium may lose a little efficacy if stopped and restarted so don't risk it
- Warn patients not to take OTC NSAIDs

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NPSA Lithium Therapy Purple Booklets

- NPSA advises that all patients initiated and maintained on lithium must be issued a Lithium Therapy Booklet.
- Contains Information booklet, record book and Lithium Alert card



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NPSA Lithium Therapy Purple Booklets

- Alert Card-contains brand and dose of Lithium, NHS number and emergency details.
- Record book- includes lithium blood levels, Thyroid and renal function and weight chart- must be presented when obtaining Lithium from community Pharmacy.
- Information Pack-Advice for patients.



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