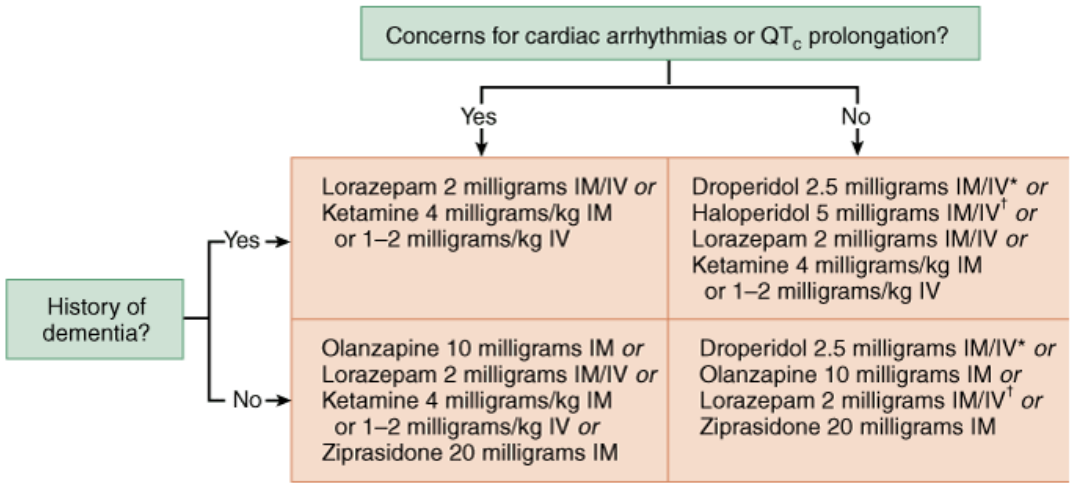
PSYCHOTROPIC MEDICATIONS AND RAPID TRANQUILISATION

RAPID TRANQUILISATION:

- The ideal sedative for rapid tranquilisation would be:
  - Easily administered
  - Rapid onset of action
  - Well tolerated with good side effect profile
  - No addictive properties
- Current options are antipsychotics and anxiolytics (most often benzodiazepines)
- IM route is preferred
- Beware preceding coingestion of alcohol or other respiratory suppressants
- Suggested algorithm shown below:

Figure 285-1.



Suggested algorithm for the ED management of patients with acute undifferentiated agitation. *Droperidol dosing may be repeated if clinically indicated. †Consider reduced dosing in the elderly; lorazepam, 1 milligram IM, haloperidol, 2 milligrams IM, and ketamine, 2 milligrams/kg IM.

- FDA black warning for droperidol and haloperidol in those with QTc prolongation, but not definitively linked to torsades
- All agents carry potential risks:
  - Excessive sedation
  - Aspiration
  - Adverse haemodynamics
  - Allergic reactions
- THE USE OF A SEDATIVE FOR CHEMICAL RESTRAINT CANNOT BE BASED ON STANDING ORDERS

ANTIPSYCHOTICS (NEUROLEPTICS):

INDICATIONS:

- Used in the management of schizophrenia, acute mania, anxiety and agitation
- There are two main classes
    - TYPICAL:
        - Have low, medium or high potency that relates to the dosing of the drug for effective response
        - Low-potency drugs have more sedating qualities
        - High potency medications are more frequently assocaitedw tih EPSE (tremors, rigidity, muscle spasms, akathisia)

Table 285-1 Commonly Prescribed Typical Antipsychotics

Generic Name	Brand Name	Relative Potency	U.S. Food and Drug Administration Warnings
Phenothiazines			
Chlorpromazine	Thorazine	Low	
Mesoridazine	Serentil	Intermediate	QT_c prolongation
Thioridazine	Mellaril	Intermediate	QT_c prolongation
Perphenazine	Trilafon	Intermediate	
Trifluoperazine	Stelazine	High	
Fluphenazine	Prolixin	High	
Thioxanthenes			
Loxapine	Loxitane	Intermediate	
Thiothixene	Navane	High	
Dihydroindolone			
Molindone	Moban	Intermediate	
Butyrophenones			
Haloperidol	Haldol	High	QT_c prolongation and torsades de pointes
Droperidol	Inapsine	High	QT_c prolongation and torsades de pointes

        - Medication induced QTc prolongation is not considered significant unless it is >500ms
            - However, QTc prolongation does not directly correlate with clinical risk of dysrhythmias or the development of torsades
    - ATYPICAL ANTIPSYCHOTICS:
        - Generally newer medications that more specifically target the dopamine receptors or inhibit the reuptake of serotonin
        - Adverse effects (sedation, EPSE, QTc prolongation and tardive dyskinesia) are generally reduced but not completely eliminated
        - Increased risk of CVA, cardiovascular events and mortality has been associated in older populations particularly particularly
        - Commonly prescribed agents shown below:

Table 285-2 Commonly Prescribed Atypical Antipsychotics		
Drug	**U.S. Food and Drug Administration–Approved Indications**	**Warnings and Common Side Effects (BLACK BOX WARNINGS IN CAPS)**
Clozapine (Clozaril)	Treatment-resistant schizophrenia	Sedation, dizziness, hypotension, tachycardia, salivation, weight gain, hyperthermia.
	Reduction in the risk of recurrent suicidal behavior in schizophrenic or schizoaffective disorders	AGRANULOCYTOSIS, SEIZURES, MYOCARDITIS, OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS
Olanzapine (Zyprexa)	Schizophrenia	CVAE, sedation, postural hypotension, hyperglycemia, weight gain, dizziness
	Bipolar disorder	
	Agitation associated with schizophrenia and bipolar I mania	
Quetiapine (Seroquel)	Bipolar mania	NMS, hyperglycemia, sedation, hypotension, headache, weight gain
	Schizophrenia	
		CATARACT FORMATION
Risperidone (Risperedal)	Schizophrenia	Extrapyramidal effects, hyperglycemia, hypotension, hyperprolactinemia, weight gain
	Bipolar mania	
Ziprasidone (Geodon)	Schizophrenia	Sedation, rash, dizziness, hypotension, hyperglycemia, extrapyramidal effects
	Bipolar mania	
	Acute agitation in schizophrenic patients	QT PROLONGATION AND RISK OF SUDDEN DEATH
Aripiprazole (Abilify)	Schizophrenia	NMS, CVAE, hyperglycemia, seizure, hypotension, headache, akathisia
	Bipolar disorder	

- SIDE EFFECTS OF ANTIPSYCHOTICS:
  - Antipsychotics block dopamine receptors:
    - In the mesolimbic area accounts for their antipsychotic properties
    - Blockade in the nigrostriatal tract is responsible for the majority of motor side effects, including acute dystonias, akathisia and Parkinson syndrome
  - ACUTE DYSTONIA:
    - Most common side effect seen in ED
    - Muscle spasm of the neck, face and back most commonly
      - Can also get laryngospasm
      - Often misdiagnosed as a primary neurologic disorder or patient restlessness
    - TREAT WITH BENZTROPINE 1-2MG IV or DIPHENHYDRAMINE 25-50MG IV
    - Often recur despite dosage reduction or discontinuation of the offending agent ➔ continue coadministration of benztropine or diphenhydramine
  - AKATHISIA:
    - Sensation of motor restlessness with a subjective desire to move
    - Often misdiagnosed as anxiety or exacerbation of psychiatric illness, akathisia is aggravated by subsequent increases in antipsychotic medications
    - Coexistent EPSE ➔ cogwheel rigidity, shuffling gait
    - If possible, decrease the dose of antipsychotic, otherwise, trial of β-blocker (propranol most often)
  - PARKINSONISM:

        - Particularly common in elderly patients
        - Usually begins in the first month of treatment
        - Complete Parkinson syndrome can occur ➔ bradykinesia, resting tremor, cogwheel rigidity, shuffling gait, masked facies, drooling
        - Dose reduction plus anticholinergic medication is usually sufficient
        - High potency antipsychotics have EPSE, whereas low-potency have more prominent anticholinergic and antiadrenergic effect
    - ANTICHOLINERGIC EFFECTS:
        - Range from mild sedation to delirium
            - Peripheral manifestations ➔ dry mouth/skin, blurred vision, urinary retention, constipation, paralytic ileus, cardiac dysrhythmia, angle-closure glaucoma
            - Central manifestations ➔ dilated pupils, dysarthria and agitated delirium
    - CARDIOVASCULAR EFFECTS:
        - Orthostatic hypotension, tachycardia
            - Likely related to anticholinergic and adrenergic blockade
            - Normally easily managed with IV fluids ➔ vasopressors if severe
        - Effects on specific potassium channels in the myocardium which is believed to be responsible for QTc prolongation and induction of Torsades de Pointes
    - NEUROLEPTIC MALIGNANT SYNDROME:
        - Uncommon IDIOSYNCRATIC REACTION to neuroleptic drugs
        - Manifested by:
            - Rigidity
            - Fever
            - Autonomic instability (tachycardia, diaphoresis, BP anomalies)
            - Confusional state
        - High mortality rate (20%)
        - All antipsychotics implicated (typical and atypical)
        - Management:
            - Cessation of antipsychotics
            - Hydration
            - Meticulous supportive care in ICU setting
            - Anticholinergics NOT HELPFUL
            - Dantrolene or bromocriptine often utilised

Respiratory and circulatory support

Treatment of NMS must focus on supportive care, prevention of complications and cessation of dopamine antagonists (see Antidotal therapy). Aggressive fluid replacement is usually required and patients with hypotension should be given fluid replacement (see Circulation). In severe cases with muscle rigidity involving the chest wall, the patient may require respiratory support with intubation, sedation and paralysis.

Cooling for hyperthermia

If the patient's temperature is greater than 39 °C, the patient should be cooled with tepid sponging and ice packs. Antipyretic drugs are ineffective (see Key management issues).

Sedation

Many patients require sedation for confusion and agitation or, in severe cases, for intubation and paralysis. For drug and dosing recommendations, see Sedation.

Antidotal therapy

Although the effectiveness of antidotal therapy has not been demonstrated in controlled trials, clinical experience and case reports support the use of bromocriptine (a dopamine agonist). Use:

bromocriptine 2.5 mg orally or via nasogastric tube, 8-hourly; the dose can be gradually increased based on clinical response up to 5 mg, 4-hourly.

Bromocriptine should be titrated to clinical effect, looking for a lowering of the temperature and reduction of muscle rigidity. Severe NMS should be discussed with a clinical toxicologist or a unit experienced in treatment of this rare condition.

- OTHER SIDE EFFECTS:
  - Atypical antipsychotics have been associated with the additional side effects of seizures, weight gain and hyperglycaemia (independent of weight gain)
  - All atypical antipsychotics carry a black box warning citing their association with increased mortality in elder patients with dementia-related psychosis

ANXIOLYTICS:

INDICATIONS:

- Severe emotional distress, acute grief, or illicit substance use may warrant treatment with anxiolytics
- Sleep induction, sedation, treatment of seizures
- The main features distinguishing these agents are half-life and route of administration (see below)

SIDE EFFECTS:

- **Relatively wide therapeutic window**
- COMMON SIDE EFFECTS ➔ Somnolence, sedation, amnesia, ataxia
- Severe respiratory depression if coingested with alcohol or if given in overdose
- The abrupt cessation after long-term use is associated with a WITHDRAWAL SYDNROME ➔ similar to alcohol withdrawal ➔ restlessness, tremors, tachycardia, hypertension and seizures

Table 285-3 Benzodiazepines Available in the U.S.				
Generic Name	**Brand Name**	**U.S. Food and Drug Administration–Approved Indications**	**Route of Administration**	**Approximate Half-Life (hours)**
Short Acting				
Estazolam	ProSom	Insomnia	Oral	10–24
Flurazepam	Dalmane	Insomnia	Oral	2.3
Midazolam	Versed	Sedation, anxiolysis, and amnesia:	Oral	1.8–6.4
		Preoperative	Parenteral	
		Preprocedural		
		Preinduction		
		During mechanical ventilation		
Temazepam	Restoril	Insomnia	Oral	3.5–18.0
Triazolam	Halcion	Insomnia	Oral	1.5–5.0
Long Acting				
Alprazolam	Xanax	Anxiety disorder	Oral	9–20
		Panic disorder		
Chlordiazepoxide	Librium	Anxiety disorder	Oral	24–48
			Parenteral	
Clonazepam	Klonopin	Panic disorder	Oral	30–40
		Seizure		
Clorazepate	Tranxene	Anxiety disorder	Oral	48
		Partial seizure		
Diazepam	Valium	Anxiety disorder	Oral	35
		Acute alcohol withdrawal	Parenteral	
		Skeletal muscle spasm	Rectal	
		Convulsive disorder		
Halazepam	Paxipam	Anxiety disorder	Oral	30
Lorazepam	Ativan	Status epilepticus	Oral	10–20
		Preanesthesia	Parenteral	
Oxazepam	Serax	Anxiety disorder	Oral	4–15
		Acute alcohol withdrawal		
Quazepam	Doral	Insomnia	Oral	25

ANTIDEPRESSANTS:

- Prescribed for varying conditions ➔ depression, neurogenic pain or smoking cessation

SSRI:

- Because of their ease of dosing, safety profile and tolerability, SSRI are a first-line medication for depression
- COMMON SIDE EFFECTS:
  - Headaches, dizziness, sexual dysfunction, nausea, diarrheoa, insomnia and agitation
  - Less commonly ➔ akathisia and apathy
  - These agents lack anticholinergic and cardiac effects typical of TCA
- WITHDRAWAL:
  - SSRI discontinuation syndrome has been described, more common with shorter half-life agents (sertraline, paroxetine) ➔ flulike symptoms and delirium ➔ slow taper advised
- SEROTONIN SYNDROME:
  - POTENTIALLY LIFE-THREATENING

- Occurs when pharmacologic agents cause excessive serotonin neurotransmission (MAOI, tramadol, St John wort)
- Syndrome is manifest by:
  - Neuromuscular hyperactivity (tremor, myoclonus, clonus, hyperreflexia, seizure)
  - Altered mental status (restlessness, agitation, excitement, confusion)
  - Autonomic hyperactivity (tachycardia, tachypnoea, fever, diaphoresis)
  - GI irritability (nausea, vomiting, diarrhoea)
- TREATMENT IS SUPPORTIVE
- Prolonged washout of several days to weeks is required before other medications that increase serotonin levels can be started

- OVERDOSE:
  - Low lethality, even in overdose
  - In many cases, no symptoms develop

TRICYCLIC ANTIDEPRESSANTS (AKA HETEROCYCLICS)

Table 285-5 Commonly Used Heterocyclic Antidepressants

Generic Name	Brand Name	U.S. Food and Drug Administration–Approved Indications	Comments
Amitriptyline	Elavil	Depression	Especially effective in endogenous depression
		Enuresis	Off-label uses include treatment of insomnia, migraine, chronic pain, neurogenic pain, IBS
Amoxapine	Asendin	Depression, panic disorders, bipolar disorder	Especially effective in depression with agitation, neurotic or psychotic features
			Can cause neuroleptic malignant syndrome
Clomipramine	Anafranil	Depression, OCD, panic attack, narcolepsy, premature ejaculation, chronic pain, enuresis	Also used in pediatrics for OCD
			Under investigation for usefulness in preventing relapses in cocaine addicts and for anxiety disorders
Desipramine	Norpramin	Depression	Useful in chronic pain syndromes and attention-deficit disorders
Doxepin	Sinequan	Depression	Especially useful in depression associated with alcoholism or other organic disease and depression with psychotic features
			Off-label uses include anxiety disorder, extreme itching, insomnia, alcohol withdrawal, GI ulcerations (has histamine-2 receptor antagonism), chronic pain, headaches
Imipramine	Tofranil	Depression, childhood enuresis	Prototypical heterocyclic antidepressant; currently second line after selective serotonin reuptake inhibitors
			Also used for panic attacks, ADHD, postconcussive syndrome, chronic pain
Nortriptyline	Pamelor	Depression	Off-label uses include treatment of panic disorder, IBS, chronic pain, neuralgia, and ADHD, and migraine prophylaxis; an effective smoking cessation aid and also useful for chronic pain
Maprotiline	Ludiomil	Depression	Also used for the symptomatic treatment of anxiety or insomnia
			Strongly sedative in the first few weeks of treatment before antidepressant effects are present; especially useful in agitated depression

- Therapeutic effect related to secondary down-regulation of noradrenaline and serotonine postsynaptic receptors after initial blockade of presynaptic reuptake of noradrenaline and serotonin
- SIDE EFFECTS:

    - Have LOW THERAPEUTIC INDEX, with therapeutic doses close to toxic doses
    - Side effects are common and similar among the various drugs
    - Toxicity increases with age and is higher with comorbid cardiac disease
    - Majority of toxic effects ➔ ANTICHOLINERGIC OR CARDIOTOXIC
    - ANTICHOLINERGIC:
        - Particularly likely to occur with use of other anticholinergic drugs
        - Peripheral ➔ dry mouth, metallic taste, blurred vision, constipation, paralytic ileus, urinary retention, angle-closure glaucoma
        - Central ➔ sedation, mydriasis, agitation, delirium
    - CARDIOVASCULAR EFFECTS:
        - Nonspecific T-wave changes
        - Prolonged QTc
        - Varying degrees of atrioventricular block
        - Atrial or ventricular arrhythmia
- OVERDOSE:
    - First presents with anticholinergic symptoms that develop within 120 minutees of ingestion
    - Condition then rapidly deteriorates in those with severe poisoing ➔ coma, seizures and CV collapse may develop
    - The initial clinical presentation does not predict the seriousness of the overdose and mortality is high

MONOAMINE OXIDASE INHIBITORS:

- Monoamine oxidase catalyses the oxidation of biogenic amines (tyramine, serotonin, dopamine and noradrenaline) throughout the body
- The therapeutic effect is probably related to their ability to increase noradrenaline and serotonin in the CNS
- Two agents ➔ PHENELZINE, TRANYLCYPROMINE
- SIDE EFFECTS:
    - Orthostatic hypotension
    - CNS irritability:
        - Agitation
        - Motor restlessness
        - Insomnia
        - Autonomic side effects ➔ dry mouth, constipation, urinary retention, delayed ejaculation
    - HYPERTENSIVE CRISIS:
        - Block oxidative deamination of tyramine and may precipitate a sometimes fatal hypertensive crisis when certain drugs or tyramine-containing foods are ingested
        - Drugs of concern ➔ sympathomimetic amines, L-dopa, narcotics (especially pethidine), TCA
        - Tyramine-containing food ➔ aged cheese, beer, wine, pickled herring, yeast, chopped liver, yoghurt, sour cream and fava beans

- ADMINISTRATION OF BETA-BLOCKERS IS **CONTRAINDICATED as this may intensify vasoconstriction and worsen hypertension ➔ nitroprusside and phentolamine are the preferred options**

MISCELLANEOUS ANTIDEPRESSANTS:

Table 285-6 Mechanisms of Action of Miscellaneous Antidepressants

Generic Name	Brand Name	Drug Class
Bupropion	Wellbutrin	Dopamine reuptake inhibitor
Mirtazapine	Remeron	Serotonin and norepinephrine reuptake inhibitor
Trazodone	Desyrel	Serotonin (5-HT_2) antagonist/reuptake inhibitor
Venlafaxine	Effexor	Serotonin and norepinephrine reuptake inhibitor

BUPROPION:

- An effective and well-tolerated antidepressant that inhibits reuptake of dopamine and noradrenaline
- Less weight gain than TCA, and lower sexual side effect than SSRI
- Dose-related increase in seizures
    - Caution if taking anticonvulsants, has epilepsy or other condition that lowers the seizure threshold

MIRTAZAPINE:

- Antagonises inhibitory noradrenaline autoreceptors and thus causes increased release of noradrenaline
- Rapidly effective in treatment of anxiety and sleep disturbances related to depression

VENLAFAXINE:

- Approved for the treatment of adults with depression, generalised anxiety disorder
- It is structurally distinct form other antidepressants and conceptually is a combination of a TCA and SSRI in that in enhances both noradrenaline and serotonine (SNRI) through reuptake blockade
- No affinity for muscarinic, histaminic and β-adrenergic receptors
- Has caused serotonin syndrome
- False positive for PCP in drug screen

MOOD STABILISERS:

- Used in treatment of mood instability, most commonly bipolar disorder

Table 285-7 Mood Stabilizers			
Generic Name	**Brand Name**	**FDA Approval Status for Use as Mood Stabilizer**	**Comments/Side Effects (BLACK BOX WARNING IN CAPS)**
Lithium carbonate	Eskalith, Lithonate, Lithotabs	Approved for treatment of BD	Effective for both phases of BD.
			Narrow therapeutic window; toxicity common.
Valproic acid	Depakene, Depakote, Depacon	Approved for treatment of BD	Dose-related side effects that clear with lower dosages.
			Predominant side effects are GI.
			Wide therapeutic window.
			Monitor liver and renal functions.
Carbamazepine	Tegretol	Only recently approved for BD, but used for many years	Dose-related side effects; AGRANULOCYTOSIS.
			Regular complete blood count and drug level monitoring required.
Oxcarbazepine	Trileptal	Not FDA approved for BD but commonly used	Does not cause blood dyscrasias.
Lamotrigine	Lamictal	Approved; especially effective for bipolar depression	Stevens-Johnson syndrome is rare complication but potentially fatal.
Topiramate	Topamax	Not FDA approved for BD but occasionally used	Clinical trials show mixed results regarding usefulness in BD.

LITHIUM:

- Used for both acute mania and maintenance in bipolar disorder
- Mechanism of action unknown, but may relate to reduction of doaminergic function, enhancement of serotonergic function or reduction in excessive signalling by phosphtidyinositol system
- SIDE EFFECTS:
    - NARROW THERAPEUTIC WINDOW
    - GI distress, dry mouth, excessive thirst, fine tremors, polyuria, peripheral oedema are COMMON
    - Long-term problems ➔ nephrogenic DI, benign diffuse goitre, hypothyroidism, skin rashes/ulceration, psoriasis
- TOXICITY AND OVERDOSE:
    - Severity is related to level and duration of elevated level but symptoms in acute overdose may not manifest for 48 hours
    - May result in neurologic sequelae and should be considered a medical emergency

ANTICONVULSANTS AS MOOD STABILISER ➔ SEE TABLE ABOVE