NHS
Sussex Partnership
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Adverse effects and risks associated with medication used in acute disturbance (HDAT risks)

Jules Haste

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College of Mental Health Pharmacy

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Adverse effects

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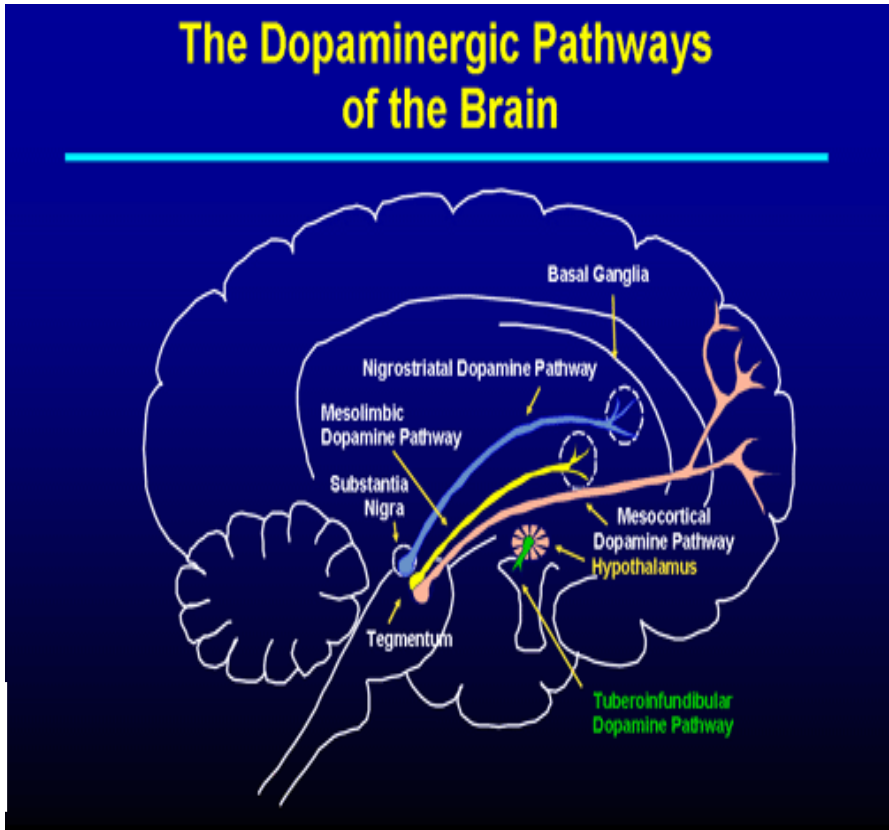
  - Over sedation (H_1)



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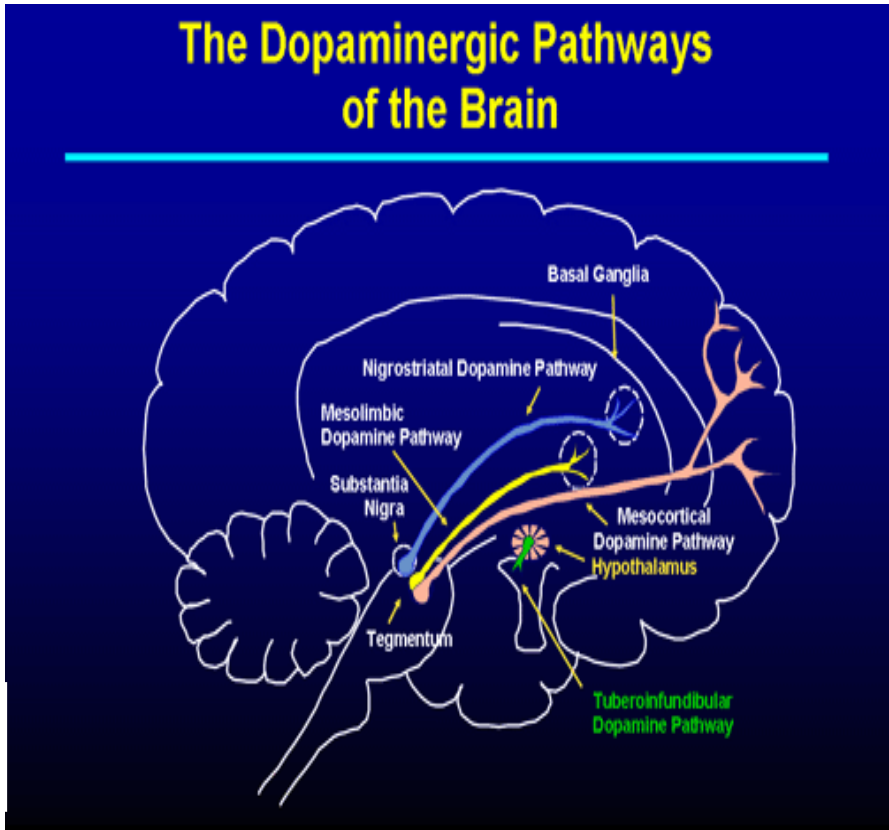

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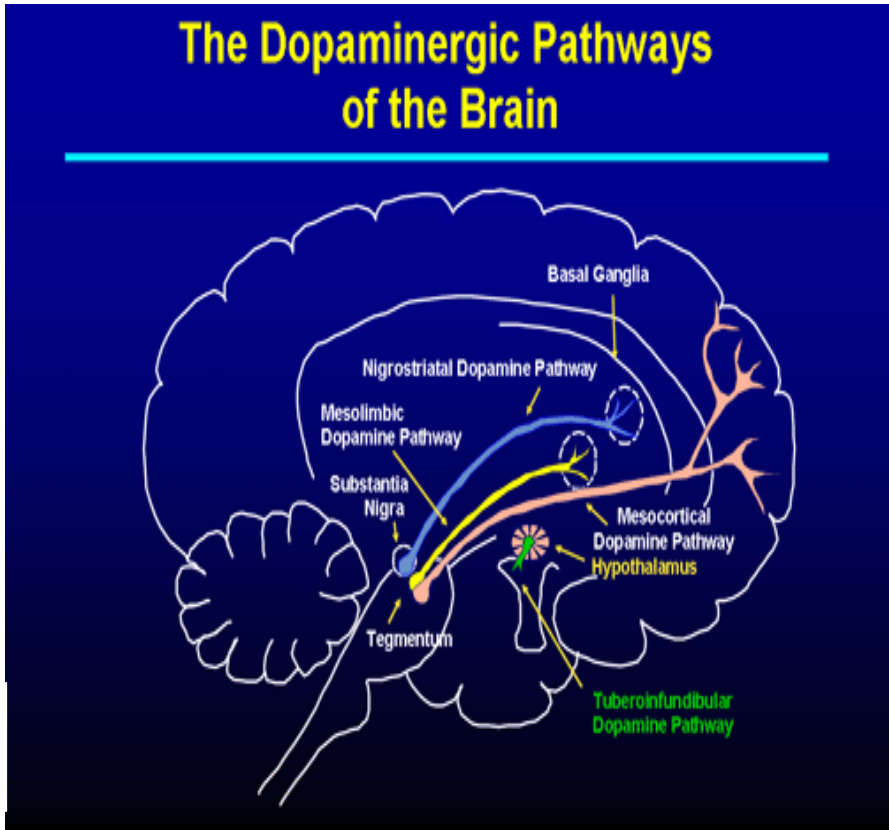

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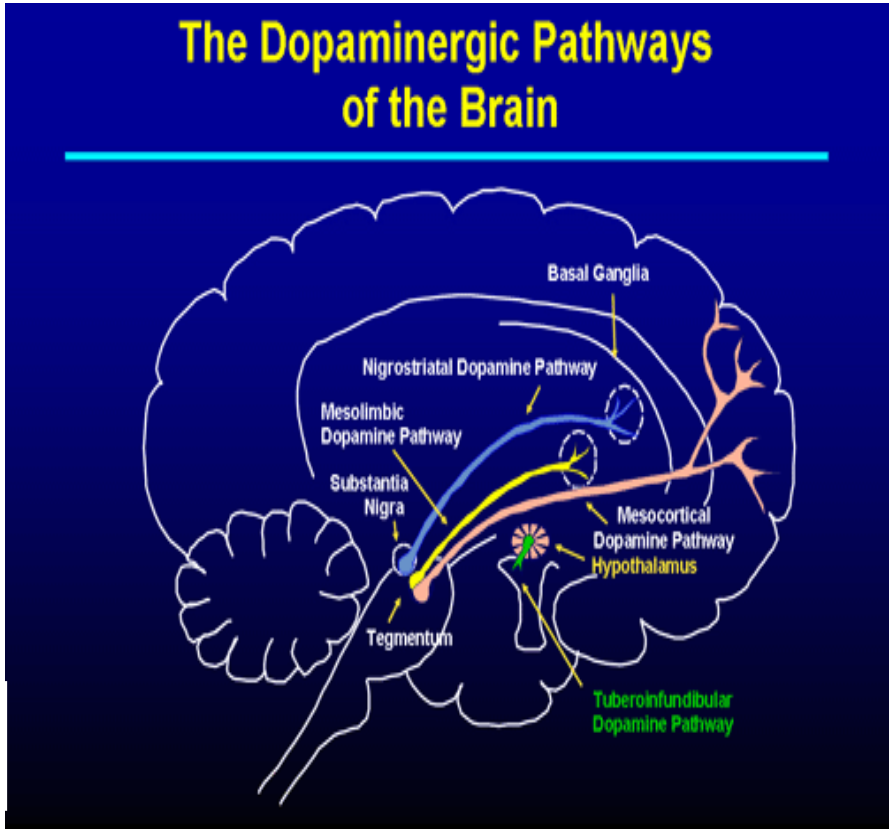

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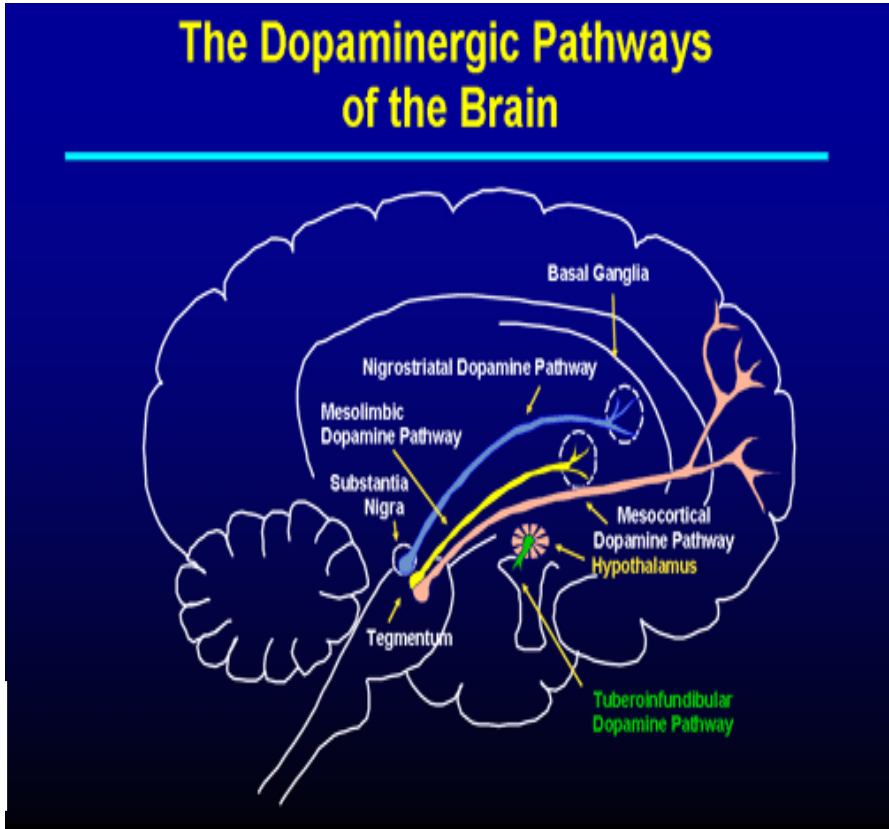

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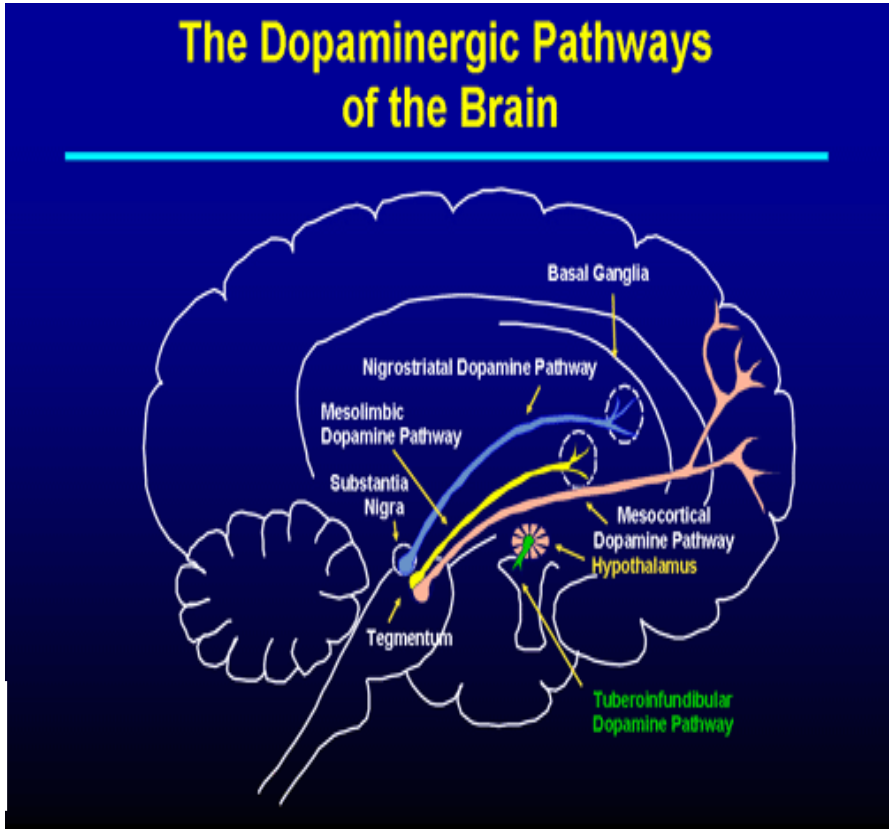

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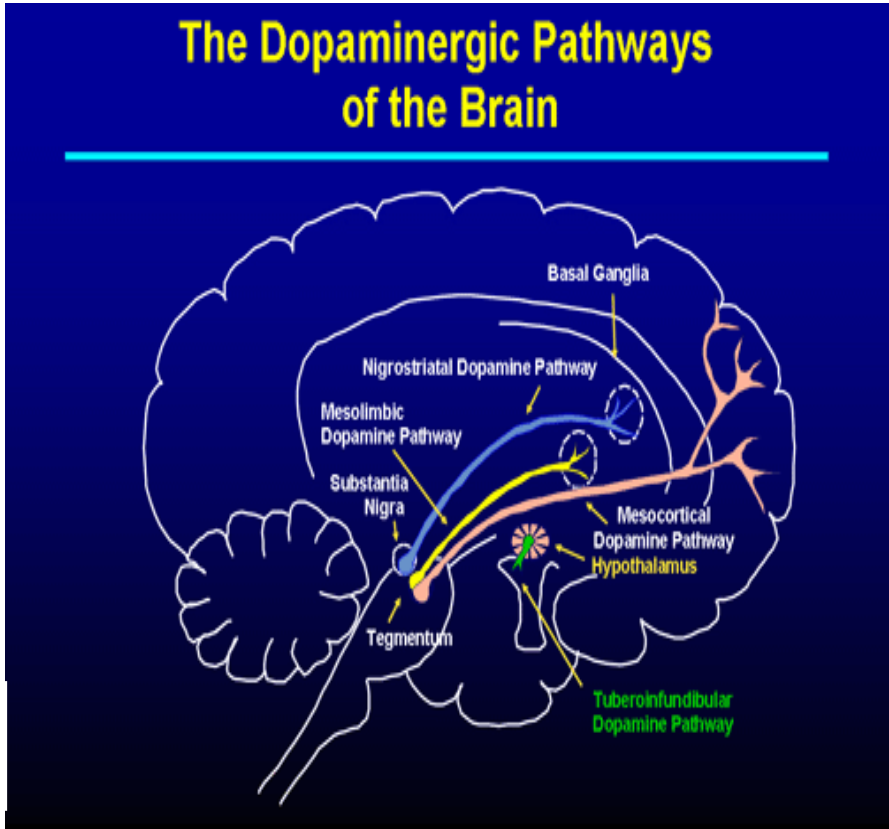

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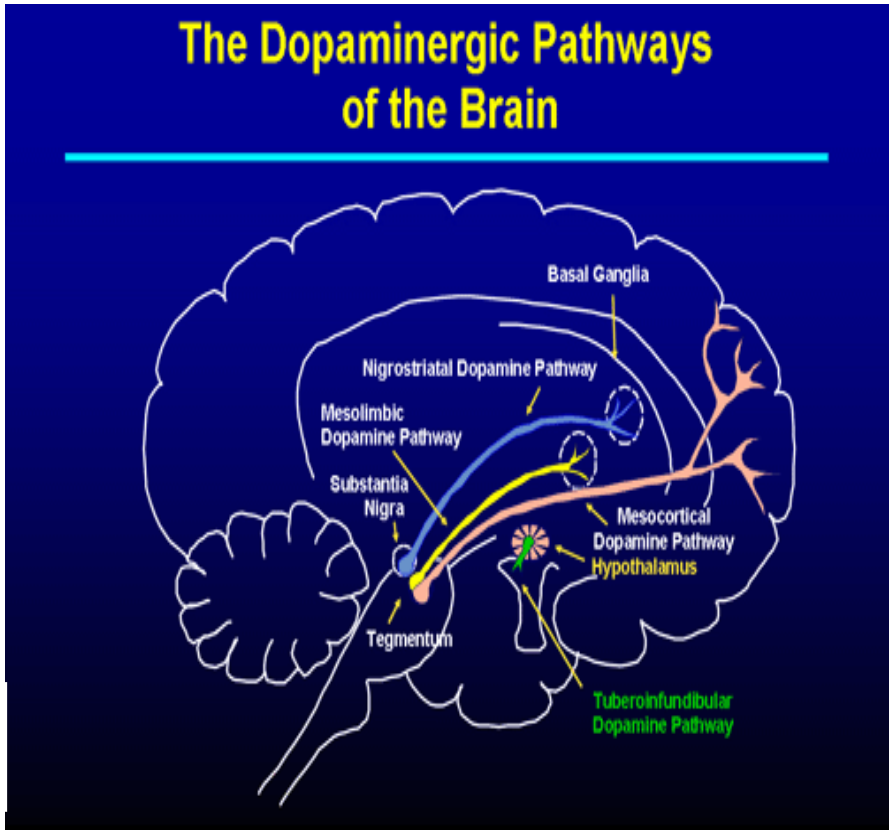
- **Caution with accumulation (long T1/2)**



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CNS depression

- **Over sedation**
  - IM midazolam has been found to be
    - More sedating than IM lorazepam, with an increased risk of respiratory depression
    - More sedating than IM antipsychotics alone or in combination with IM promethazine

- **Respiratory depression**
  - Parenteral benzodiazepines have safety concerns due the risk of respiratory depression.
  - **Flumazenil** (benzodiazepine antagonist) must be immediately available.
  - If respiratory rate drops <10/min or below 90% sat after administration of benzodiazepines
  - Intravenous (IV) administration only (Drs to give)
  - Dose: 200µg IV over 15 seconds. If required level of consciousness is not regained, then 100µg IV every 1 minute as required. Usual dose 300–600µg; maximum 1 mg per course or in 24 hours.
  - Contraindicated in patients with epilepsy who are receiving long-term benzodiazepines.
  - Has a short half-life therefore subsequent doses may be necessary e.g. with diazepam
  - If respiratory rate does not normalise with doses of flumazenil, urgently consider other causes of sedation

Orthostatic hypotension

- Commonest cardiac side effect seen with antipsychotics and can occur with benzodiazepines
- IM administration route, rapid dose increases and polypharmacy increase risks of clinically relevant orthostatic hypotension
- Increased fall risk and in older patients increase risk of hip fractures (lorazepam has greatest risk)

Can confirm with repeating lying/standing BP

- Treatment:
  - Ensure standing up slowly
  - Hydrate (if not fluid restricted)
  - Titrate slower and according to patient tolerance

- IM olanzapine and IM benzodiazepines not within 1 hour (SmPC)
  - Case series IM olanzapine and benzodiazepines were safe in patients who had not ingested alcohol.
- IM olanzapine and IM promethazine also not within 1 hour (extrapolated as both have hypotension listed)

Disinhibition/agitation reactions with benzodiazepines

- The overall incidence of disinhibitory reactions is small.
- Increased risk with those with impulse control problems, neurological disorders, learning disabilities, the under 18s and the over 65s are at significant risk.
- Be aware of the ability of benzodiazepines to cause behavioural disinhibition and to maintain a high degree of vigilance when these drugs are administered to patients known to be at risk.
- In patients who have experienced behavioural disinhibition with benzodiazepines, antipsychotic drugs should be used to modify behaviour in any future emergencies.

Extrapyramidal side effects (EPSE/EPS)

- Acute dystonia, oculogyric crisis or acute dyskinesias reactions
  - Can be very painful and frightening
  - **Give 5-10mg IM procyclidine**

- IM haloperidol, when administered alone, has a greater propensity to cause acute EPS and therefore its use as a single agent is not recommended

- Starts days – weeks after starting/dose increase

Treatments:

- Reduce dose
- Switch to lower propensity agent
- Anticholinergic (procyclidine, trihexyphenidyl) – rebalancing between Ach and dopamine action. Avoid in evenings as can be alerting and worsen sleep pattern

Akathisia

- Severity varies from feelings of general unrest to a compulsion to move and feelings of being unable to control actions, worsening or unpredictable agitation/aggression (can also be mistaken for agitation).

- Potential link with increased suicidality.

Starts hours-weeks of starting/increasing AP. Can become chronic in nature.

Treatment:

Reduce dose
Switch to lower propensity agent (olanzapine, quetiapine, clozapine)
Low dose propranolol
Low dose mirtazapine (15mg) or mianserin (30mg)
Benzodiazepine
Anticholinergics are usually NOT helpful (unless other EPSE's present)

Neuroleptic malignant syndrome (NMS)

- Rare but potentially fatal idiosyncratic reaction to neuroleptic drugs.

- The underlying pathological abnormality is thought to be central D_2 receptor blockade or dopamine depletion in the hypothalamus and nigrostriatal/spinal pathways.

- Risk factors
  - High potency FGAs, (haloperidol), rapid increase/decrease of dose, abrupt withdrawal of anticholinergics, polypharmacy, physical illness, male, younger age, agitation and dehydration.

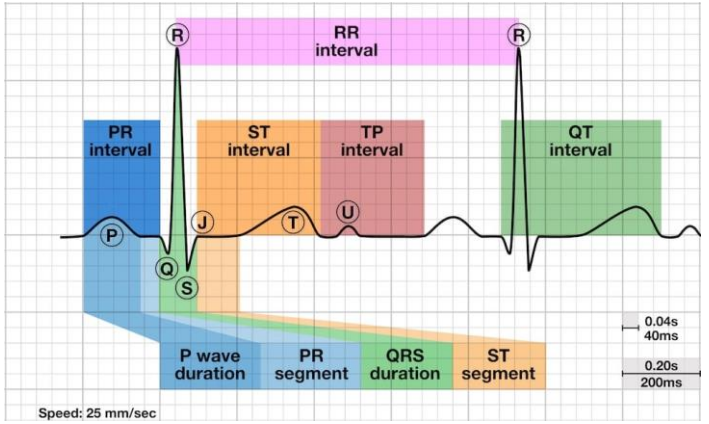
Neuroleptic malignant syndrome (NMS)

- Sign and symptoms
  - Fever, muscular rigidity, altered mental status and autonomic dysfunction (BP, tachycardia), elevated CK, leucocytosis, altered LFTs.

- Treatment
  - Withdrawal medication, monitor temperature, pulse, BP. Consider benzodiazepine. Send to medical/A&E. Hydrate, dopamine agonists, sedation, artificial ventilation.

- Future
  - Can restart antipsychotics but allow symptoms to resolve, consider SGAs, monitor CK and symptoms. Avoid depots/LAI.

ECG changes (QTc prolongation)



- All antipsychotics have a degree of cardiac risk including sudden cardiac death, arrythmias and Torsades de Pointes (TdP)

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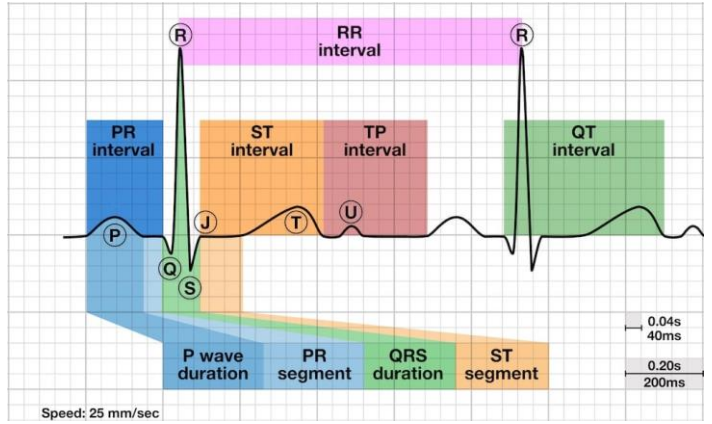

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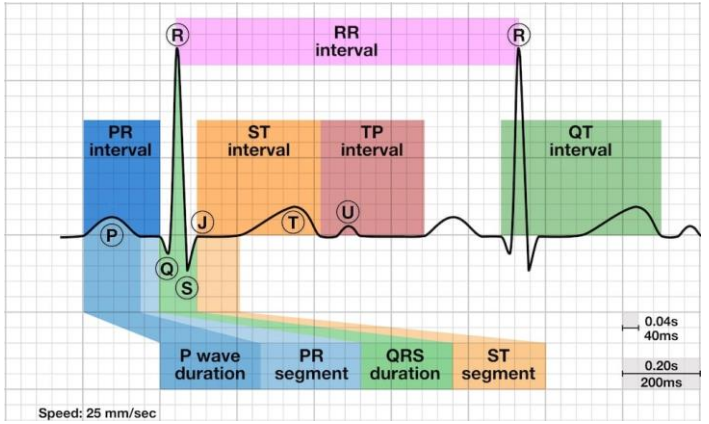

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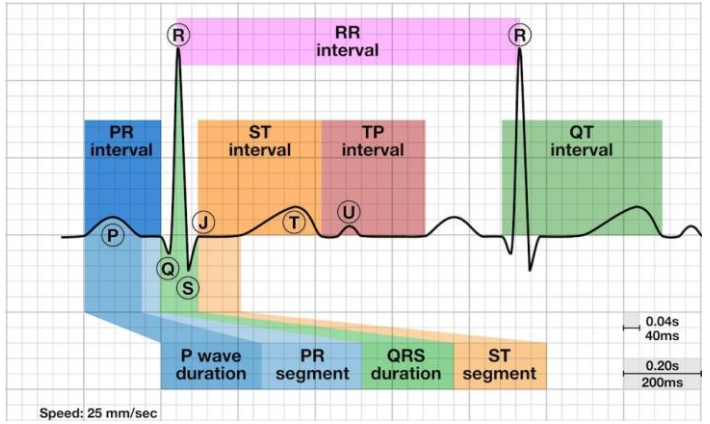

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- Normal QTcs: Men <440ms, Women <470ms

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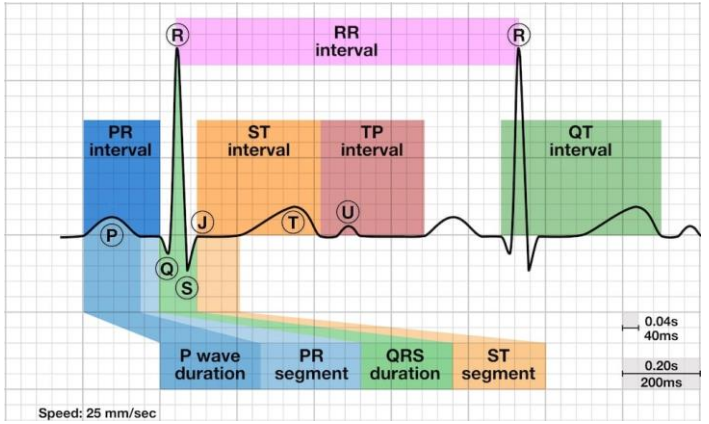

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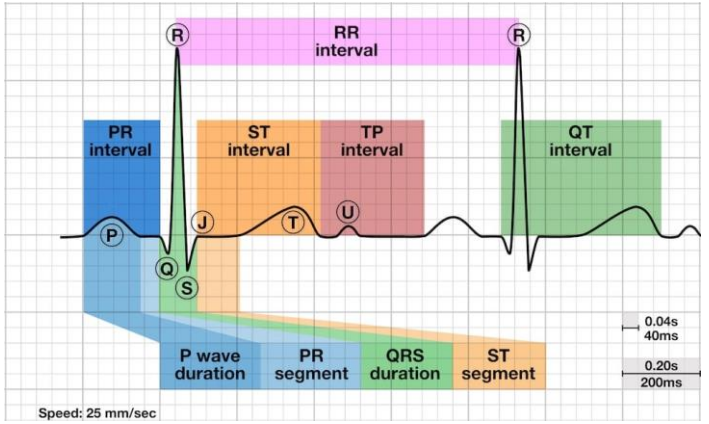

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- Broadly speaking the more prolonged the QTc, the greater the potential for TdP to develop
- Normal QTcs: Men <440ms, Women <470ms
- QTc >500ms have evidential basis of increased arrythmia risk and TdP
- QTc >650ms much more likely to invoke TdP

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ECG changes (QTc prolongation)

- Blockade of the HERG potassium channel involved in myocardial repolarization
- Antipsychotics have been broadly categorised as having "no effect" to "high effect" on QTc and a table can be found in the current Maudsley prescribing guidelines
- Antipsychotic polypharmacy, HDAT and co-prescribed medications with a QTc prolongating potential have an additive effect on overall cardiac risk and QTc
- Be alert for newly prescribed medications that could increase risk e.g. clarithromycin, methadone etc.
- Electrolyte imbalances (particularly hypomagnesaemia and hypokalaemia) along with pre-existing cardiac risks should be considered when starting an antipsychotic

ECG changes (QTc prolongation)

Comparison of myocardium to plasma ratio, brain to plasma ratio, lipophilicity, HERG channel inhibition and clinical cases of arrhythmia, or sudden deaths for various antipsychotic drugs

Drug	Myocardium/ plasma ratio	Brain/plasma ratio	Lipophilicity log *P*	HERG IC50 nM	Published cases of QT prolongation, arrhythmia, or sudden deaths
Clozapine	2.2	24	3.62	–	3
Olanzapine	2.7	5.4	2.97	6013	0
Hydroxyrisperidone	2.9	0.04	2.32	–	–
Sertindole	3.1	6.7	–	2.7	0
Risperidone	4.4	0.22	3.04	167	7
Dehydrosertindole	4.7	–	–	–	–
Haloperidol	6.4	22	3.36	1	16

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Actions to be taken post ECG

- DO NOT assume normal ECG won't produce QTc prolongation

- Risk factors for QTc prolongation
  - Systemic disease
  - Electrolyte imbalance
  - Cardiac disease
  - Female gender
  - Taking concurrent medications that also prolong the QTc.

- Correct electrolyte disturbances (potassium and magnesium) if QTc prolonged

QTc	Action
<440ms(men) or <470ms (women)	No action required unless abnormal T wave morphology in which case refer to a cardiologist
>440ms (men) or >470ms (women) but <500ms (men and women)	Consider a lower dose or switching to a medicine of lower effect. Repeat ECG after change and consider referral to cardiologist.
>500ms (men and women)	Stop suspected causative medicine(s) and switch to a medicine of lower effect (if required). Repeat ECG after change. Refer to a cardiologist immediately.
Abnormal T – wave morphology	Review treatment. Consider switching to a medicine of lower effect. Refer to a cardiologist immediately.

Venous thromboembolism

- Overall there is small but defined increase risk of DVT/PE
- New users of antipsychotics and younger patients more at risk
- Slightly higher risk with high dose therapies
- First 3 months or so of treatment may be highest risk period
- Mechanism not understood, but proposed mechanisms include:
  - Sedation
  - Obesity
  - Hyperprolactinaemia
  - Elevated platelet aggregation, homocysteine or anti-phospholipid antibodies
- Monitor for signs of VTE and ensure VTE risk assessments are performed
- Encourage good hydration and mobility
- Review treatments regularly to achieve lowest effective dosing strategy

Medication related risks - summary

Benzodiazepines - **over-sedation,** drowsiness, ataxia and potentially cardiovascular collapse, **hypotension** with the associated risk of falls, loss of consciousness, disinhibition and **respiratory depression**.

Antipsychotics – EPS (acute oculogyric crises and acute dystonic reactions) and akathisia, **sedation, QTc prolongation**, decreased seizure threshold and **NMS**.

Promethazine - **drowsiness,** agitation, confusion, dizziness, hypotension, CNS depression, lowering of seizure threshold, anticholinergic effects, EPS (including tardive dyskinesia), and rarely also NMS, blood dyscrasias and allergic reactions.

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Medication considerations (BAP)

- Oral and IM haloperidol a **baseline ECG** is advised before use due to the risk of QTc prolongation (within 3 months or significant changes).
- Parenteral benzodiazepines have safety concerns due the risk of respiratory depression. Thus, wherever they are used, **flumazenil** must be immediately available.
- IM haloperidol is **not recommended as monotherapy** even though it has evidence of effectiveness, and a **baseline ECG** is advised, as measures need to be in place to offset its adverse effects and especially for the risk of acute dystonia.
- **RT IM monotherapy** should be considered before RT IM combinations (except haloperidol)
- Oral PRN or pre-RT can lead to high dose (greater than BNF doses – HDAT or pHDAT) and an enhanced burden of side effects. Consider current medicine regimen

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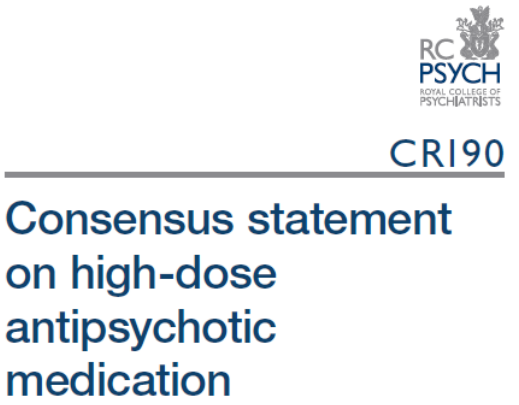
HDAT (High Dose antipsychotic treatment)

- Consensus statement on high-dose antipsychotic medication. Royal college of Psychiatrists. November 2014
- Above BNF dose or combined therapy/polypharmacy above BNF doses (%)
- Higher risk when using regular and then RT or oral PRN – also consider depots/LAIs
- No evidence for increased effectiveness
- Higher risk of dose related adverse effects
    - EPSE
    - NMS
    - Arrhythmias and sudden cardiac death – QTc prolongation
    - Cognition
    - Hepatic and haematological impairment/disorders (longer term)
- **REVIEW if not effective reduce**



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HDAT (High Dose antipsychotic treatment)

ANTIPSYCHOTIC DOSAGE READY RECKONER - VERSION 9.1

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Depot/long-acting injection and IM antipsychotics

Depot/LAI: dose calculated as mg/week

IM/Inhaled: dose in mg/day

Percentage of BNF maximum adult dosage

		5	10	15	20	25	30	33	40	45	50%	55	60	67	70	75	80	85	90	95	100%
Aripiprazole	Long-acting										50										100
Flupentixol	Depot	20	40	60		100					200					300					400
Haloperidol	Depot							25			37.5			50							75
Olanzapine	Long-acting										75										150
Paliperidone *	Long-acting													25							37.5
Paliperidone Trevicta**	Long-acting																				43.75
Risperidone	Long-acting										12.5					18.75					25
Zuclopenthixol	Depot			100				200			300			400			500				600
Aripiprazole	IM							10			15			20							30
Chlorpromazine	IM		25			50					100					150					200
Haloperidol	IM					5					10					15					20
Levomepromazine	IM		25			50					100					150					200
Olanzapine	IM					5					10					15					20
Zuclopenthixol acetate***	IM													50							75
Loxapine	Inhaled										9.1										18.2

* Maintenance dose licensed to be given monthly. ** Formulation licensed to be given every 3 months. ***A maximum of 150 mg in any 48-hour period and a maximum cumulative dose of 400 mg in any two week period.

To calculate a total daily prescribed antipsychotic dose as a percentage of the BNF maximum: determine the percentage of BNF maximum dosage for each antipsychotic that is prescribed, and then sum the percentages. For example, for a person prescribed clozapine 400mg a day and oral haloperidol 5mg PRN up to 3 times a day, the respective percentages would be 44% and 75%, giving a total antipsychotic prescribed dosage of 119% of the BNF maximum.

Contact pomh-uk@rcpsych.ac.uk to order copies of this Ready Reckoner www.rcpsych.ac.uk/pomh

ANTIPSYCHOTIC DOSAGE READY RECKONER - VERSION 9.1

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POMH-UK CCQI — PRESCRIBING OBSERVATORY FOR MENTAL HEALTH-UK

Oral antipsychotics

Dose in mg/day

Percentage of BNF maximum adult daily dosage

		5	10	15	20	25	30	33	40	45	50%	55	60	67	70	75	80	85	90	95	100%
Amisulpride	Oral							400			600			800				1000			1200
Aripiprazole	Oral							10			15			20							30
Asenapine	Oral					5					10					15					20
Benperidol	Oral							0.5			0.75			1							1.5
Cariprazine	Oral					1.5					3					4.5					6
Chlorpromazine	Oral		100	150			300				500		600			750					1000
Clozapine	Oral			150				300		400	450			600							900
Flupentixol	Oral			3				6			9			12				15			18
Haloperidol	Oral		2			5					10		12			15					20
Levomepromazine	Oral		100			250					500					750					1000
Lurasidone	Oral					37					74					111					148
Olanzapine	Oral					5		7.5			10					15					20
Paliperidone	Oral					3					6					9					12
Pericyazine	Oral					75		100			150			200							300
Pimozide	Oral		2		4		6		8		10		12								20
Promazine	Oral			150				300			400					600					800
Quetiapine*	Oral		75	100	150				300		375		450				600				750
Risperidone	Oral		2			4		6			8					12					16
Sulpiride	Oral			400				800			1200			1600				2000			2400
Trifluoperazine**	Oral		5		10		15		20		25		30		35		40		45		50
Zuclopenthixol	Oral		20		30			50						100							150

* 750mg/day max for schizophrenia; 800mg/day max for mania or if XL preparation used; % given for schizophrenia.
** No max dose stated in BNF or SPC; 50mg used by convention.

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