Adverse Reactions

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What you need to know about Adverse Drug Reactions (ADRs)

a) Understanding of dose-related as distinct from ‘idiosyncratic’ ADRs.

b) The major categories of ADRs associated with the main groups of drugs used in psychiatry and those associated with appropriate corrective action.

c) The importance of assessing risks and benefits for every individual patient in relation to his medication. Risks and benefits of psychotropic drugs in acute, short- and long-term use including effects of withdrawal. Where appropriate, knowledge of official guidance on the use of particular drugs (e.g. the Royal College Guidelines on the use of Benzodiazepines, NICE guidance).

d) The information database for adverse drug reactions and how to report them

What is an adverse drug reaction?

- An **adverse drug reaction** (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an **adverse** event is at least a reasonable possibility. (ref: MHRA)
- Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.
- The reaction may be a known side effect of the drug or it may be new and previously unrecognised.

Scenario

- A young lady with Bipolar 1 says that she is allergic to olanzapine. She had it during her first episode. This is documented in her GP notes as ‘Allergy: OLANZAPINE’. Other PMHx include asthma, eczema and appendicitis. She is currently manic with grandiose delusions.
- What will you do?

Allergy and adverse reactions

- A dose dependent predictable side effect is not an allergy.
- Anaphylactic reactions are IgE mediated reactions. Can be fatal. Can be caused by drug, carrier or contaminant. May start with abnormal behaviour.
- Anaphylactoid (non IgE mediated) responses caused by a substance causing non-immunological degradation of mast cells (eg CT contrast, pabrinex, parvolex).
- Type IV hypersensitivity reactions, slower histamine related e.g. dermatitis

Reporting adverse drug reactions

- Yellow card system in BNF (now part of NICE) – now on-line
- MHRA safety reporting for drugs and devices
- Adverse Incident reporting systems for experimental drugs
- Local reporting – DATIX, pharmacy etc.
- Police if suspicion of crime (Stepping Hill)

Dose dependent effects

- Understanding pharmacodynamics and pharmacokinetics, as well as specific drug interactions is key.
- eg benzodiazepines. As drug concentration increases, respiratory depression/sedation more likely.
- Purely dose dependent, however other factors will shift curve to left.

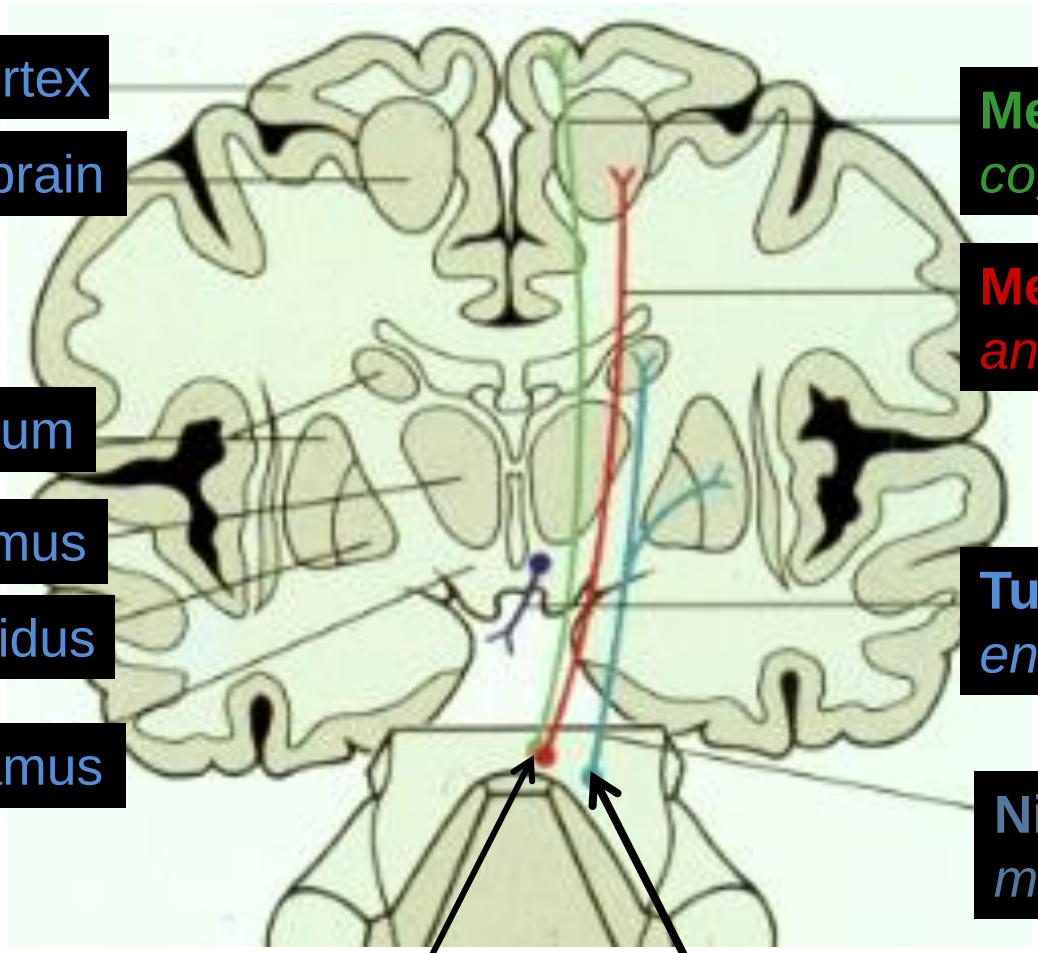
Time related side effects

- Tardive dyskinesia with antipsychotics
- Diabetes Insipidus with Lithium (rare <5 yrs, up 40% at 10 years)
- Tolerance effects with benzodiapines
- (autoinducing effects of carbamazepine)

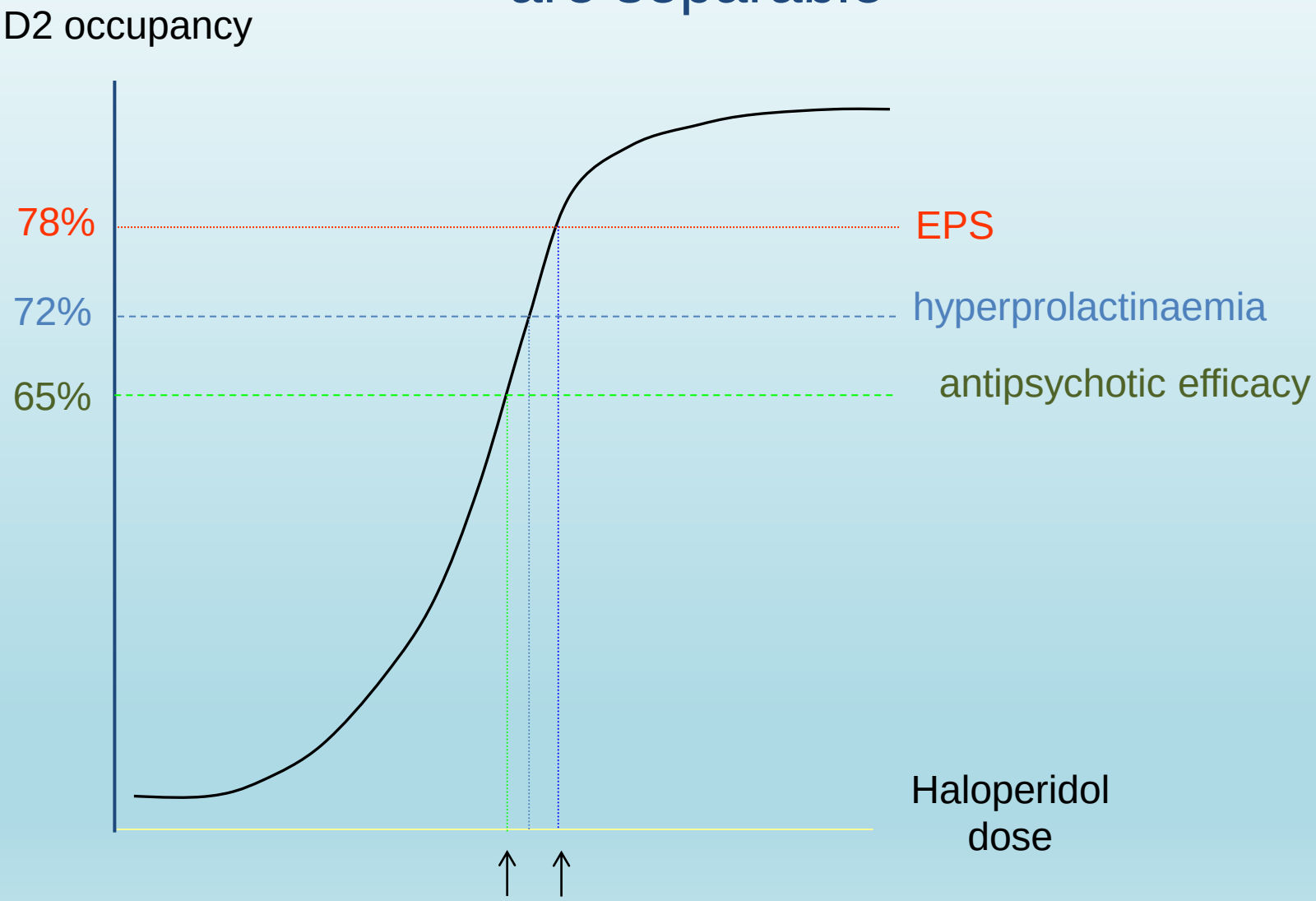
Antipsychotics

- Weight gain, metabolic syndrome with atypicals
- EPSEs with typicals
- Constipation and sedation with both
- Hyperprolactinaemia leading to osteoporosis
- Stroke in dementia patients (especially olanzapine)

Dopamine pathways in human brain



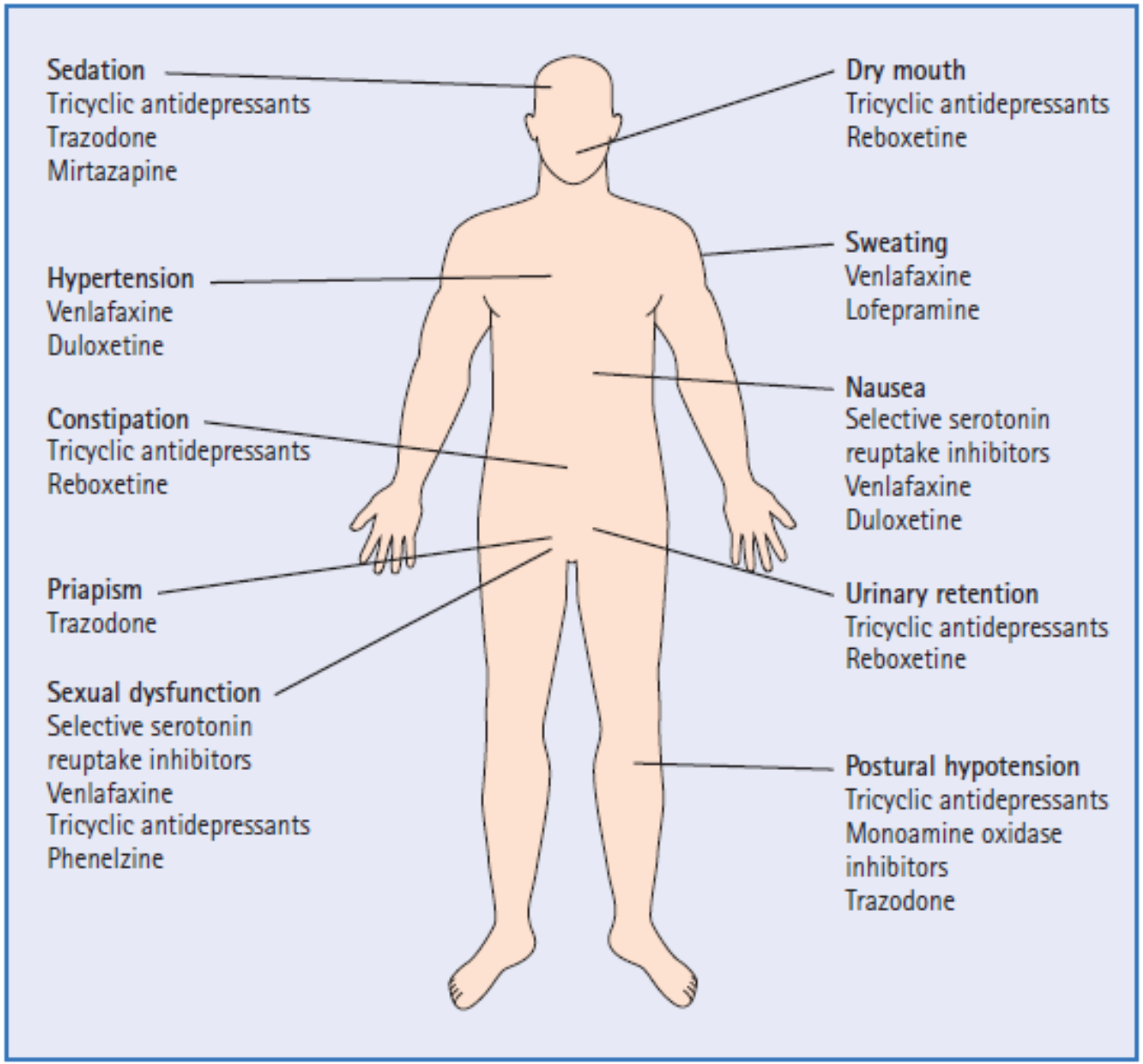
Therapeutic and motor side effects of haloperidol are separable



Kapur et al - Am J Psych 2000

Common adverse effects – antidepressants

- SIADH in SSRIs, tricyclics, carbamazepine, phenothiazines and others.
- ‘Cheese sandwich reaction’ (tyramine) and MAOI-B blockade
- Sexual side effects. Mirtazepine, moclobemide and agomelatine least. 5-HT active drugs most likely to cause anorgasmia and reduced ejaculation
- SSRIs and GI bleeds. Parallel action with other antiplatelets/ anticoagulants/ gastric irritants


Sedation
Tricyclic antidepressants
Trazodone
Mirtazapine
Hypertension
Venlafaxine
Duloxetine
Constipation
Tricyclic antidepressants
Reboxetine
Priapism
Trazodone
Sexual dysfunction
Selective serotonin reuptake inhibitors
Venlafaxine
Tricyclic antidepressants
Phenelzine
Dry mouth
Tricyclic antidepressants
Reboxetine
Sweating
Venlafaxine
Lofepramine
Nausea
Selective serotonin reuptake inhibitors
Venlafaxine
Duloxetine
Urinary retention
Tricyclic antidepressants
Reboxetine
Postural hypotension
Tricyclic antidepressants
Monoamine oxidase inhibitors
Trazodone

Mood stabilisers

- Lithium – narrow therapeutic index. Dose related, time related adverse effects.
- Valproate – sudden termination causes seizures. (now not recommended for women of potential child bearing age)
- Lamotrigine – steven-johnson syndrome
- Teratogenicity.

NMS vs Serotonin syndrome

	NMS	Serotonin Syndrome
Hyperthermia/Fever	+	+
Encephalopathy/AMS	+	+
Tachycardia	+	+
MSK	Muscle Rigidity	Hyperreflexia
Autonomic Symptoms	None	Diaphoresis, Diarrhea
Onset	Days	Hours
Cause	Antipsychotics	MAOs, SSRIs, SNRIs, TCAs, MDMA
Treatment	Dantrolene	Cyproheptadine

Prescribing in pregnancy

- Pregnancy (first trimester)
- Risk of spontaneous malformations: 2-3%
- Carbamazepine, Valproate = Neural tube defects possibly dose related
- Lamotrigine, Benzodiazepine – risk of oral cleft
- Lithium = Ebsteins anomaly (risk 1:1000, highest in first 6 weeks after conception)

Prescribing in pregnancy

- Antidepressants – Fluoxetine and Setraline.
  Tricyclics were used before this, most safety date relates to older drugs.
- Second line: discuss with a specialist
- Avoid Paroxetine due to risk of CVS (septal) defects
- Bipolar depression: SSRI
- Mood stabilisation / Puerperal Psychosis – Aripiprazole, Quetiapine
- Primary psychosis: discuss with a specialist

Prescribing in pregnancy

Pregnancy (third trimester)

- Blood volume expands by 30%
- Renal clearance and GFR increased
- Hepatic metabolism changes - CYP2D6 activity is increased by almost 50% by the end of pregnancy while the activity of CYP1A2 is reduced by up to 70%

- Neonatal withdrawal and breastfeeding

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Renal impairment

- Get the GFR
- Scrutinise ALL drugs on chart - what could worsen renal function?
- Half life? Active or inactive metabolites?

- Avoid
  - Drugs that are mostly cleared renally
  - Drugs that may prolong QTc
  - Drugs with significant anticholinergic effect

Renal Impairment- Prescribing tips

- Consult BNF
- Psychosis: Haloperidol 2-6mg daily, Olanzapine 5mg daily
- Clozapine: can commence but be aware of risk of anticholinergic, sedative and hypotensive side effects. Rare reports of interstitial nephritis and acute renal failure. If GFR<10 consult with renal team re: titration
- Depression: Citalopram and Sertraline

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Hepatic failure

- Reduced drug metabolism
- Toxicity from drugs usually protein bound
- Elevated levels of drugs usually subject to first pass metabolism in cirrhosis
- Patience required for drugs to reach steady state
- Increase dosing intervals
- Avoid sedative, constipating drugs

Hepatic Failure- Prescribing tips

- Psychosis: Haloperidol, amisulpiride, sulpiride
- Try to avoid: Clozapine
- Definitely avoid: chlorpromazine

- Depression: citalopram/escitalopram/paroxetine
- Half dosing: venlafaxine and Mirtazepine
- Avoid: Tricyclics, MAOIs and Duloxetine

- Mood stabilisation: Lithium (care re: ascites)

Prescribing in epilepsy

- Depression
  - SSRI's, Moclobemide
  - Venlafaxine and Lithium proconvulsive in overdose
  - Avoid TCA's altogether if possible

- Psychosis
  - Haloperidol and sulpiride good choices
  - Risperidone reasonably safe
  - Care required with Olanzapine and Quetiapine
  - Aripiprazole: data pending
  - Clozapine – try not to
  - Chlorpromazine and depots - AVOID

MCQs

- A man complains of delayed ejaculation and reduced libido after starting citalopram. He requests another antidepressant. Which of the following is least likely to cause sexual side effects:
- A. Paroxetine
- B. Imipramine
- C. Mirtazepine
- D. Trazadone
- E. Phenelzine

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- Adverse reactions are different from allergies
- Know the main, common adverse reactions from each group
- Think holistically when prescribing to avoid adverse reactions
- Know how to report adverse reactions
- This is neuroscience and psychopharmacology in action!

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- Any questions?