Central and North West London NHS
NHS Foundation Trust

Prescribing Pearls for Women

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Wellbeing for life

Objectives

- **Women** and mental health
- Patients and their medication **concerns**
- Specific **prescribing considerations** for women
- Gender specific **pharmacokinetic** parameters

Women and Mental Health

- Women are **underrepresented** in clinical trials
- Important **physiological differences** exist between men and women
- Differences affect drug **pharmacokinetics** and **pharmacodynamics**
- Consequently the **therapeutic response** and **adverse effects** of drugs can differ

Do we always consider theses differences when prescribing?

Women in PICU

Mental health disorders in female PICUs:

- Bipolar disorder – mood stabilisers
- Schizoaffective disorder – antipsychotics including depot
- Delusional disorder
- Drug-induced psychosis
- Psychotic depression

- Short-term management – Rapid tranquillisation and benzodiazepines

Patient Concerns

Compliance
Side effects
Injections
Restraint
Stigma
Family

Prescribing considerations - Side Effects

Studies have indicated that **women** are at **greater risk** of developing some medication related **side effects**

Metabolic	Weight gain, diabetes, dyslipidaemia
EPSEs	Tardive dyskinesia, acute dystonia
Cardiac	Prolonged QT interval, abnormal cardiac rhythm
Endocrine	Hyperprolactinaemia - loss of libido, irregular menstrual cycle, reduced fertility

Prescribing Considerations – Pregnancy & Breastfeeding

- Vulnerabilities – **sexual exploitation**, unplanned pregnancies, **postpartum psychosis**
- Significant **change** in drug **pharmacokinetics** during pregnancy
- Drugs can be **teratogens** – agents that disturb the development of an embryo or foetus causing birth defects
- **Prioritise mother** and her mental health
- Assessment of **risks** and **benefits**

CNTD

Prescribing Considerations – Teratogens CNTD

- **Sodium valproate** is associated with **neural tube effects** with increased risk of **neurodevelopmental abnormalities**

- MHRA have also strengthened warnings

Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).

- NICE (2014) advices against use of sodium valproate in women of child bearing potential

- **Lithium** use increases the risk of the foetus developing **Ebstein's anomaly**. As reported by UKTIS expected absolute risk is 1 in 1500

Prescribing Considerations – Teratogens CNTD

Prescribing implications

Decisions to initiate or continue treatments in women who are of **child bearing potential** or **pregnant** should consider:

- Contraception
- Risks and benefits to the patient
- Severity of illness
- Risk of relapse
- Discussion with patient
- Current national and local guidelines
- Referral to the obstetrician
- Breastfeeding

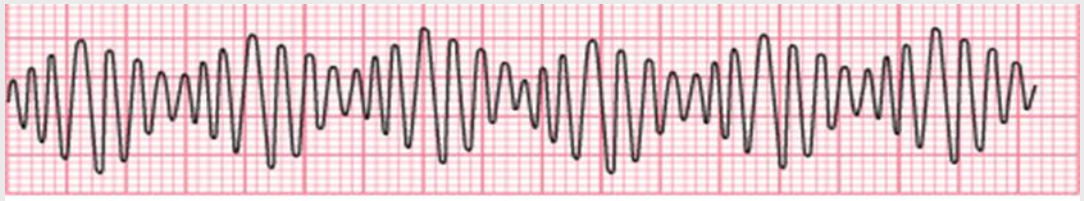
Gender Specific Parameters

Table 1 – Gender specific differences

Parameter	Women
% body fat	Higher
% body water	Lower
Hormones	Menopausal imbalances
Gut motility	Slower
Renal blood flow and GFR	Lower
Enzyme activity	Generally lower
QTc prolongation	Risk of Torsade de Pointes

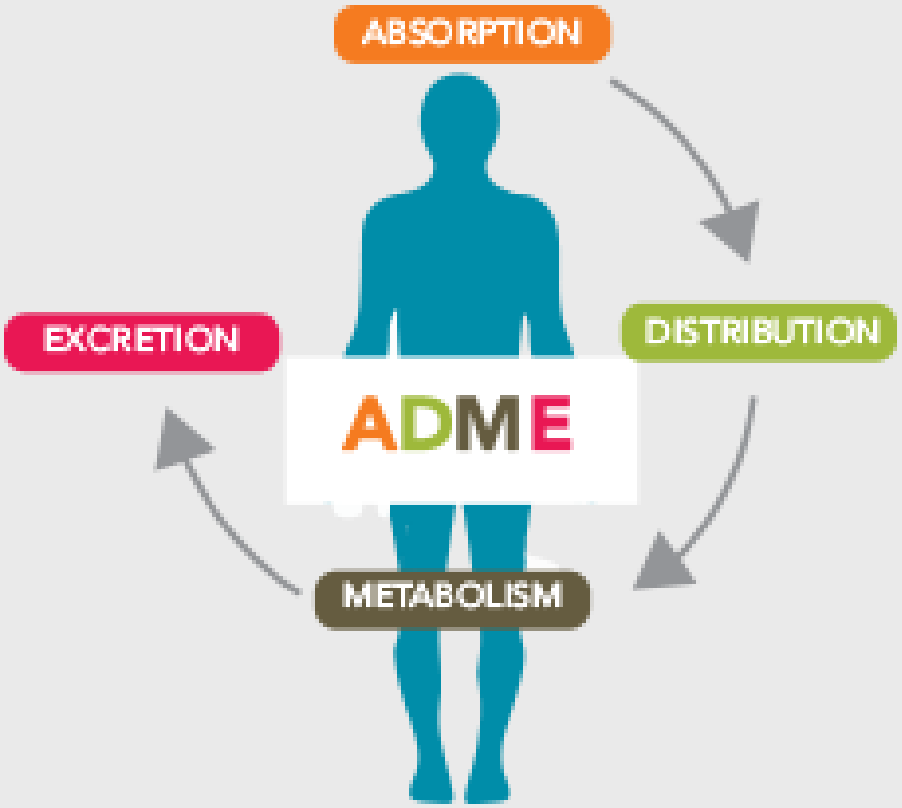
Cardiac effects – Torsade de Pointes

LONGER QT interval RISK of developing **Torsade de Pointes** (TdP)



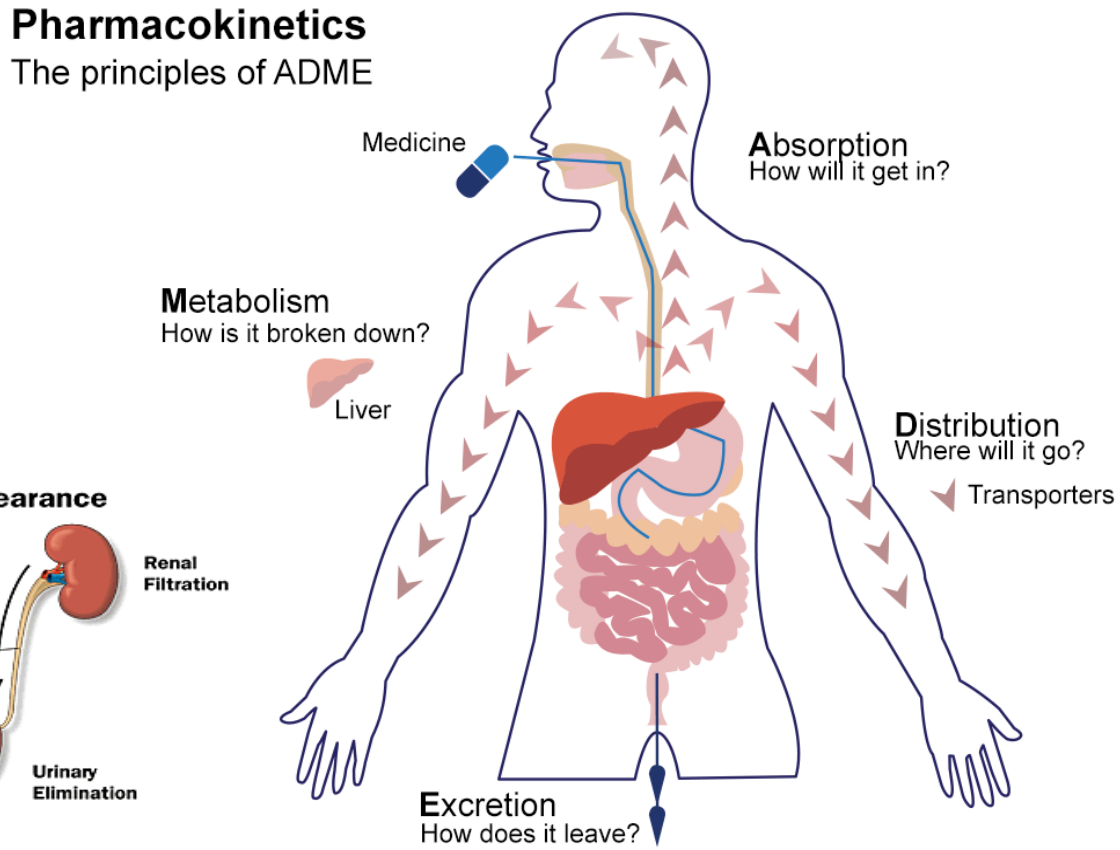
- Abnormal cardiac rhythm seen on ECG
- Prolongation of QT interval increases risk of developing TdP - this includes drug induced QT prolongation e.g. haloperidol
- Women have a longer QTc by 2-6% therefore are at higher risk of developing TdP

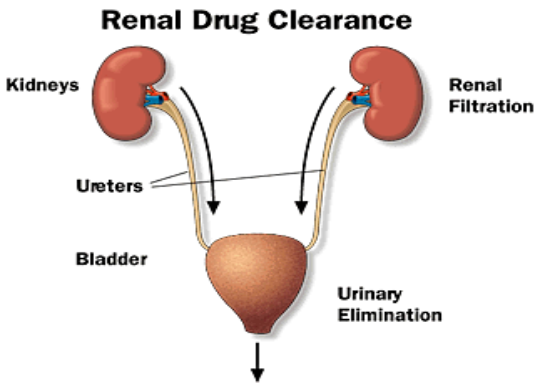
Pharmacokinetics - ADME



- **All stages** of pharmacokinetics can **differ** between men and women
- Differences in **METABOLISM** have the most impact on prescribing
- ADME will effect **therapeutic response** and **adverse effects** experienced

Pharmacokinetics –ADME





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Absorption

SLOWER GI **TRANSIT** rate **LOWER** basal **GASTRIC ACID** secretion

- Delayed transit of drug to small intestine - greatest absorptive capacity
- Extent of gastric acid secretion can affect absorption of drugs

Prescribing Implications

- **longer interval** between **food consumption** and **drug ingestion** when advised to take on an empty stomach
- **Slower absorption** & **delayed peak plasma** levels
- **Increased absorption** of **basic** drugs e.g. Benzodiazepines
- **Decreased absorption** of **acidic** drugs e.g. Phenytoin

Distribution

HIGHER % body **FAT** and **LOWER** % body **WATER**

- These factors effect **Volume of Distribution (Vd)** of drugs
- Body fat can increase with age in women
- Studies suggest women have higher cerebral blood flow

Prescribing Implications

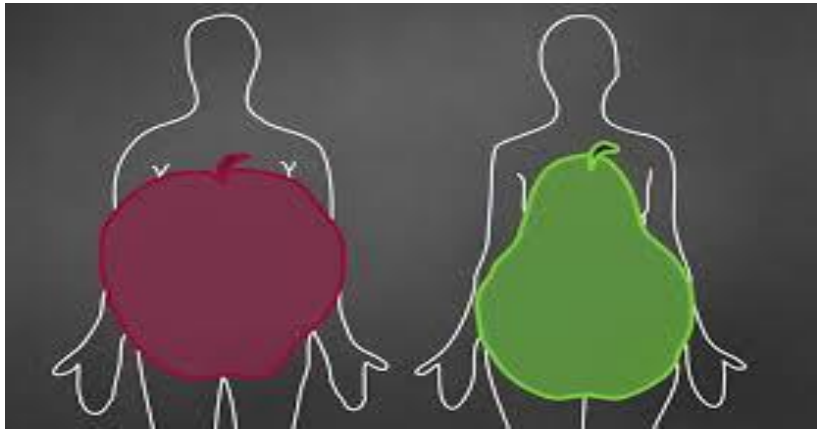
- **Lipophilic** (fat soluble) drugs e.g. benzodiazepines have a **higher Vd** and can **accumulate** in body fat
- **Half-life** is **extended**, **higher serum levels** and possibly **toxic effects** are observed
- Lipophilic drugs can be considered at **lower doses in women**

Distribution - Depot administration

CNTD

Upper

Chest & abdomen



Lower

Hips & legs

- **Accumulation** of **lipophilic antipsychotics** seen after **IM administration**

Prescribing implications

- After a steady state is achieved, **dosing intervals** for women can be **longer** than for men
- E.g. Haloperidol decanoate, flupenthixol decanoate

Distribution - Depot administration

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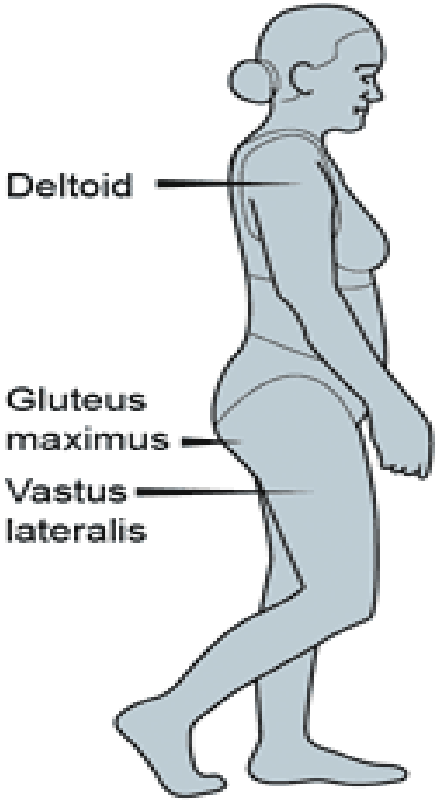
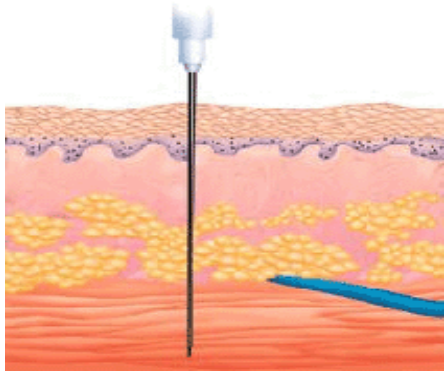


Administration implications

- Gender differences in fat depth show women tend to have more fat in gluteal regions
- Needles that are too short will not reach IM regions
- Choice of needle can be based on **gender, BMI** and **visual assessment**



Available needles

25mm

38mm

50mm

Rapid tranquillisation (RT)

CNTD

Safety | Privacy | Dignity

- Similar pharmacokinetics as depots but **RT is SHORT acting**
- **Dosage adjustments** for women are **not necessary**
- Review treatment- **optimise regular medication** and **minimise** use of **RT**

Pregnancy considerations

- Pregnant woman should be treated by the same principles
- Choice of RT – antipsychotic or benzodiazepine with a short half life
- Adapted restraint

Metabolism

LOWER enzyme **ACTIVITY**

- Drug metabolism consists of **phase I** and **phase II** reactions
- Phase I reactions are mainly mediated by **hepatic CYP450 enzymes**
- Some enzymes have known **gender specific activity** which cause differences in **therapeutic effect** and **ADRs**

Example Prescribing Implications

↓**CYP1A2 activity** - clozapine and olanzapine

↑**CYP2D6 activity** - haloperidol and antidepressants

Metabolism

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- **Smoking** induces CYP1A2 enzyme activity
- **Cessation** can cause an **increase** in **clozapine plasma levels** between 50 and 72%
- **TDM** - monitor plasma levels of clozapine before stopping smoking, reduce the dose gradually by approximately 25% and recheck 4 weeks later

Table 2 showing effects of various agents on CYP1A2 and CYP2D6

Enzyme	Substrate	Inhibitor	Inducer
CYP1A2	Clozapine, olanzapine	Fluvoxamine, grapefruit juice, some antibiotics	Carbamazepine, smoking
CYP2D6	Aripiprazole, zuclopenthixol	Fluoxetine, Paroxetine, chlorpromazine	

Elimination

LOWER renal **BLOOD FLOW SLOWER GFR**

- Phase II of metabolism prepares the Phase I metabolite for renal excretion
- **Slower elimination** of drugs via renal route

Prescribing implications

- E.g. Amisulpride undergoes renal clearance - may observe higher levels in women
- **Active metabolites** may **remain** in the body for longer
- Consideration in **overdose**, switching drugs etc.

Summary

Do we always consider theses differences when prescribing?

- Despite the differences in drug pharmacokinetics, for most drugs sex-specific dosage recommendations do not exist
- Differences in metabolism are believed to be the major cause of differential pharmacokinetics
- Treatment should be tailored to the individual

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Questions