Prescribing Pearls for Women

Denusha Kuganathan
Specialist Pharmacist
Central and North West London NHS Foundation Trust
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?
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
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**
Prescribing Considerations – Teratogens

- 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) advises 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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>% body fat</td>
<td>Higher</td>
</tr>
<tr>
<td>% body water</td>
<td>Lower</td>
</tr>
<tr>
<td>Hormones</td>
<td>Menopausal imbalances</td>
</tr>
<tr>
<td>Gut motility</td>
<td>Slower</td>
</tr>
<tr>
<td>Renal blood flow and GFR</td>
<td>Lower</td>
</tr>
<tr>
<td>Enzyme activity</td>
<td>Generally lower</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>Risk of Torsade de Pointes</td>
</tr>
</tbody>
</table>
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

Pharmacokinetics
The principles of ADME

Absorption
How will it get in?

Metabolism
How is it broken down?

Distribution
Where will it go?

Renal Drug Clearance

Excretion
How does it leave?

Renal Filtration

Liver

Transporters

Central and North West London NHS Foundation Trust

Wellbeing for life
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**
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
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)

- 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
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

- **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

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Inhibitor</th>
<th>Inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Clozapine, olanzapine</td>
<td>Fluvoxamine, grapefruit juice, some antibiotics</td>
<td>Carbamazepine, smoking</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Aripiprazole, zuclopenthixol</td>
<td>Fluoxetine, Paroxetine, chlorpromazine</td>
<td></td>
</tr>
</tbody>
</table>
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.
Do we always consider these 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.
References

Questions