Prescribing Antipsychotics: Does gender matter?

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Overview

- Background
- Physiological Factors (absorption, bioavailability, distribution, metabolism, renal clearance)
- Treatment response
- Adverse effects (EPSE, metabolic, endocrine)
- Reproductive phases and antipsychotics
- Antipsychotic prescribing across the age range
- Sociocultural factors influencing antipsychotic prescribing

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Physiological Factors (Pharmacokinetics)

- Absorption and bioavailability
  - Gastric emptying slower

- Distribution
  - Smaller total blood volume
  - Higher fat:lean ratio

- Metabolism
  - Differences in Cytochrome P450
  - Men have >CYP1A2, women >CYP3A4
  - Men have >drug transporter, P-glycoprotein

- Renal clearance, slower in women than men
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Inhibitor</th>
<th>Inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Clozapine, haloperidol olanzapine</td>
<td>Fluvoxamine, grapefruit juice, antibiotics</td>
<td>Carbamazepine, smoking, brassica vegetables</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Aripiprazole, chlorpromazine, clozapine, haloperidol, olanzapine, perphenazine, risperidone, thioridazine, zuclopenthixol</td>
<td>Bupropion, fluoxetine, paroxetine, citalopram, duloxetine, fluvoxamine, fluphenazine, moclobemide, chlorpromazine, haloperidol, perphenazine, propranolol, antibiotics</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Aripiprazole, clozapine, haloperidol, quetiapine, risperidone, sertindole, ziprasidone</td>
<td>Fluoxetine, fluvoxamine, olanzapine, nefazodone, grapefruit juice, erythromycin, ketoconazole, St John’s Wort</td>
<td>Carbamazepine, St John’s Wort</td>
</tr>
</tbody>
</table>
How do physiological factors (pharmacokinetics) affect antipsychotic effects in Women compared with Men?

1. For the same weight a man will clear a drug quicker and have lower plasma levels than a woman.

2. Men cleared olanzapine 38% faster than women (Bigos et al CATIE 2008, JCP).

3. Women are therefore at greater risk of adverse antipsychotic effects because the drug stays in the body for longer.

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Schizophrenia is commoner in men than women (McGrath et al 2004)


Neuroleptic-naive women respond quicker than neuroleptic-naive men (Robinson et al 1999)

Gender predicted response at 1 year, with women being more likely to respond to antipsychotic treatment than men (Robinson et al 1999)
In those who are likely to respond to antipsychotics, women respond quicker than men. In Tx resistant – no gender difference in response (Meltzer et al 1997).

SOHO study 2007 – 10,000 people across 10 European countries, gender predicted response, with women responding more quickly.
Women need less antipsychotic than men – Why?

- Men need more antipsychotic (up to 2x) to achieve remission than women (Melkersson et al 2001, Tang et al 2007)
- **Oestrogen hypothesis** (Mary Seeman, 1982)
  - She suggested that oestrogen may protect women against psychosis because of its effects on neurodevelopment and neurotransmission and thereby its antidopaminergic properties (premenopausal vs postmenopausal women, Salokangas 2004)
- **Pharmacokinetic reasons**
  - More antipsychotic accumulates therefore women achieve a larger antipsychotic dose than men, but more risk of adverse effects.
  - Muller et al 2006, same response and side effects but women had higher plasma levels of amisulpride.
Epigenetic Factors and Antipsychotic response

- Non-genetic factors may be responsible for difference in antipsychotic response
- Evidence of epigenetic mediation of environmental influences in schizophrenia (these may be mediated by gender)
- e.g. Oestrogen may modulate gene expression so women present schizophrenia differently to men.
- Environmental factors affect DNA-methylation and these may be gender-specific.
- ?Do epigenetic factors also influence response to antipsychotics

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AP Adverse Effects

Comparative Receptor Binding Profiles

Haloperidol

Clozapine

Seroquel

Olanzapine

Sertindole

Ziprasidone

Risperidone
Reasons for variation in AP side effects

- Different receptor binding profiles
- Extent and site of D2 blockade
- Atypical APs – don’t cause EPS at clinically effective doses
- Pharmacodynamic and pharmacokinetic effects in individuals
- Idiosyncratic reactions in individuals
- Prescribing factors in doctors
- Dose-related side effects
Adverse Reactions

- Neurological (EPSE)
- Cardiovascular/Metabolic
- Endocrine
Extrapyramidal Side Effects (EPSE)

- Dystonic reactions – young men most at risk
- Tardive dyskinesia – women less likely than men (van Os et al 1999, Zhang et al 2009)
- Parkinsonism – Halliday et al 2002 inc in males, Thanvi and Treadwell 2009, no gender difference
- Akathisia – more likely in young men than women (Keepers et al 1983)
CVS/Metabolic Risk

- QTc interval and arrhythmias
- Weight gain
- Diabetes
- Dyslipidaemia
- Hypertension
Drug-Induced Cardiac Arrhythmia

- Some ECG changes are predictors of ventricular arrhythmia. (Czekalla 2001).
- Ventricular arrhythmia may cause dizziness and fainting or precipitate more serious events such as torsade de pointes and ventricular fibrillation which may lead to sudden death (Appleby 2000).
- QTc interval is a predictor of risk of torsade de pointes.
Risk Factors and QTc Prolongation – Pharmacological factors

- Concomitant medications
  - those that raise plasma levels of antipsychotics that prolong QTc (Haverkamp 2000)
  - those that prolong QTc themselves (Health Canada, therapeutic products programme 2000)

- Overdose of medication

No clear consensus on what is a safe QTc

- QTc prolongation >450 msec in males and >470 msec in females (potential concern) (Moss 1993).
- QTc prolongation >500 msec (high risk of sudden death) (Morganroth 1993).
Obesity and SMI

- Female, waist circumference >88cm, 34”
- Male, waist circumference > 102cm, 40”
- Usually men lay down visceral fat, women subcutaneous fat.
- Women with SMI on antipsychotics appear to be laying down visceral fat preferentially to subcutaneous fat
- Associated with
  - Sudden death
  - Coronary Heart Disease
  - Congestive Heart Failure
  - Stroke

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Antipsychotics and weight gain - mechanisms

- **Hyperprolactinaemia** (Baptista et al 2001)
- **Leptin secretion**
- **Serotonin (5HT2)**
- **Histamine blockade** (Zhang et al 2004)
Role of Antipsychotics - obesity

One-year weight gain: mean change from baseline weight

- Olanzapine (15 mg)
- Olanzapine (All doses)
- Quetiapine
- Risperidone
- Ziprasidone
- Aripiprazole

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The role of insulin

- Control of cellular uptake in certain tissues -
  - Mainly glucose (muscle and adipose)
  - Important in carbohydrate and lipid metabolism
- Increase of DNA replication and protein synthesis via control of amino acid uptake.
- Modification of the activity of numerous enzymes.
Relationship between visceral adipose tissue and insulin action


<table>
<thead>
<tr>
<th>Visceral Adipose Tissue Volume Per Unit Surface Area (mL/m²)</th>
<th>Glucose Disposal (mg/kg LBM/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>18</td>
</tr>
<tr>
<td>2000</td>
<td>16</td>
</tr>
<tr>
<td>3000</td>
<td>14</td>
</tr>
<tr>
<td>4000</td>
<td>12</td>
</tr>
<tr>
<td>5000</td>
<td>10</td>
</tr>
</tbody>
</table>

Women

Men

Shubulade Smith, Maudsley Masterclass
2010
Insulin Resistance (IR) and diabetes

- Insulin resistance is underlying mechanism for type II diabetes
- Precursor to IGT and diabetes
- IR associated with ↑ glc, ↑ BP, cig smoking, dyslipidaema i.e. several CVS risk factors
- IR – an accomplice in the pathogenesis of CVD in DM
- HOMA-IR (fasting glc/fasting insulin ÷ 22.5)
- Low HOMA-IR = high insulin sensitivity (low insulin resistance),
- High HOMA-IR = high insulin resistance = prediabetic state
Insulin Resistance and diabetes

- Women more resistant to insulin than men (Mittendorfer, Curr Op Clin Natl Metab 2005)
- Androgens may ↑ DM risk in women, ↓ risk in men (Ding et al, JAMA 2006)
- Inc risk of AP-induced DM in women than in men
- Women with DM at higher risk of complications than men
  - 4-6 x ↑ risk of CAD in cf 2-3x ↑ risk in men with DM
  - DM assoed more death post-MI in females than males
  - DM hazard ratio risk for females is much greater than for males (Juntilainen et al, Diabetes Care 2004)

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Abnormalities in Insulin Resistance During Antipsychotic Therapy

Newcomer et al., Arch Gen Psychiatry 2002;59:337

Homeostatic model assessment (HOMA) insulin resistance ([fasting insulin (µU/mL) x fasting glucose (mmol/L)]/22.5)

* p = .06; † p = .05
Antipsychotics and diabetes

- Some SGA antipsychotics (e.g., clozapine and olanzapine, quetiapine) may increase diabetes risk
- Increased risk may be independent of weight gain
- New/ongoing diabetes cases
  - Impaired glucose tolerance/new cases of diabetes occur over extended time frame
  - Often, but not always, associated with weight gain

Diabetes, hyperglycaemia and diabetic ketoacidosis: case reports

<table>
<thead>
<tr>
<th>Year of introduction</th>
<th>New cases</th>
<th>Exacerbations</th>
<th>DKA</th>
<th>Deaths</th>
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<tbody>
<tr>
<td><strong>Clozapine</strong>¹</td>
<td>1990*</td>
<td>242</td>
<td>54</td>
<td>80</td>
</tr>
<tr>
<td><strong>Risperidone</strong>²</td>
<td>1993</td>
<td>78</td>
<td>46</td>
<td>26</td>
</tr>
<tr>
<td><strong>Olanzapine</strong>³</td>
<td>1996</td>
<td>188</td>
<td>44</td>
<td>80</td>
</tr>
<tr>
<td><strong>Quetiapine</strong>⁴</td>
<td>1998</td>
<td>34</td>
<td>8</td>
<td>21</td>
</tr>
</tbody>
</table>

*Into widespread use
DKA = diabetic ketoacidosis
Obesity and dyslipidaemia

- Weight gain is usually associated with increase in lipids
- Insulin resistance is a key factor in dyslipidaemia
- Good fat = High Density Lipoprotein (HDL)
- Bad fat = triglyceride and Low Density Lipoprotein (LDL)
- Inc TG – independent risk factor for MetSyn
- Low HDL – independent risk factor for MetSyn
- 10% reduction/increase in cholesterol ~ 20-30% reduction/increase in CVS risk
Dyslipidaemia in women

- Fat transport occurs 2x as fast in women as in men
- Oestrogen – protects arterial wall against LDL cholesterol deposition i.e. Reduces risk of atherosclerosis (fat plaques that cause clogging of arteries and subsequent CHD)
- HDL is more meaningful indicator in women, low HDL levels – inc risk of CVS disease
- NB. Obesity increases oestrogen levels in women

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Antipsychotics and Dyslipidaemia

Hyperlipidaemia following treatment with second-generation antipsychotic medications

Referent = conventional antipsychotic use
Adjusted for age, gender, race, primary diagnosis, duration of exposure, number of prior antipsychotic medications; Study Period 2002-2004. Odds ratio of 1.0 means that there is no relationship between variables. An odds ratio >1.0 indicates a positive relation.
Obesity and hypertension

- Blood pressure determined by a complex series of circulating hormones found in adipose tissue and kidneys
  - Control diameter of arteries and thereby control BP

High rates of hypertension in SMI

- Hypertension occurs despite blood pressure lowering effect of many antipsychotics?
  - Effect of insulin resistance
  - Obesity

- 1kg weight loss ~ 1-2mmHg decrease in BP
- 1kg weight gain ~ 1-2 mmHg increase in BP
Metabolic Syndrome

(Enger et al., 2004; McEvoy et al., 2005, CATIE).

- Men with schizophrenia – 36% had metabolic syndrome.
- Women with schizophrenia – 51% had metabolic syndrome (p < 0.0002).
- Men 138% more likely to have metabolic syndrome than N controls.
- Women 251% more likely to have metabolic syndrome than N controls.
- Controlling for BMI – men 85% more likely, women 137% more likely than N controls to have metabolic syndrome (all regardless of age and ethnicity).
- Metabolic syndrome is a source of CVS risk in schizophrenia, especially in women.
Reproductive Phases

- Premenopausal women
  - OCP/no OCP
- Pregnant women
- Breast-feeding women
- Postmenopausal women
Women – physiological variants

- Menstrual cycle – plasma levels fall in late luteal phase, may require variable doses of meds during different stages of cycle to control symptoms
- Oral contraceptive pill – may interact with APs
- Pregnancy – massive changes in drug kinetics and dynamics. Increased risk of foetal abnormalities
- Menopause – women become more like men, but some drugs metabolised more quickly, some more slowly than men of same age.

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Effect of hyperprolactinaemia on sexual and reproductive function

- Reduced libido
- Hypogonadism (↓ testosterone, oestrogen, progesterone)
- Infertility
- Prolactin elevation
- Ejaculatory dysfunction
- Vaginal response abnormalities
- Anorgasmia

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Antipsychotics and Sexual Dysfunction

- Related to progesterone and oestradiol levels (Smith 2009, unpublished thesis)
- Low gonadal hormones related to prolactin
- Progesterone negatively affects sexual function (Meston & Frohlich 2000)
- Testosterone drives libido in women
- Prolactin lowers gonadal hormones (probably also testosterone in women).
- Sexual dysfunction in women is related to antipsychotic-induced hyperprolactinaemia (unlike men whose sexual dysfunction is mainly related to non-hormonal effects of antipsychotics).
75% of the women and 34% of the men had raised prolactin levels.

Highly significant relationship between dose of medication and prolactin levels in all patients, p<0.001.

85% of the women were not ovulating.

Only 3 of the 8 women who reported normal menstrual cycles were ovulating.

10% of the women had oestrogen levels indicating severe hypo-oestrogenism.

45% had sexual dysfunction
Women, Antipsychotics and Prolactin

- Women show increased sensitivity of the lactotrophs to antipsychotic-induced prolactin stimulation compared with men.
- For the same dose of antipsychotic, women produce more prolactin than men (and it’s a dose-dependent response).
- Not all women become hyperprolactinaemic with antipsychotics – but most do (75% cf 34% males, Smith et al 2003).
- Antipsychotic-induced hyperprolactinaemia is associated with hypogonadism and sexual dysfunction.
Antipsychotics, prolactin and BMD (Meaney et al 2004)

- 57% males and 32% females osteopenic or osteoporotic in one or more vertebrae
- High prolactin associated with high doses of prolactin-raising medication
- Low BMD associated with high prolactin and low gonadal hormone levels.
Risk factors for Osteoporosis

- Smoking*
- Excess alcohol*
- Hypogonadism*
- Sedentary life style*
- Steroids
- Malabsorption
- Missing periods >6 months (excluding pregnancy) or hypogonadism in males should be investigated (Royal College of Physicians 1999)

- 25% patients with schizophrenia have had 1 or more atraumatic osteoporotic fracture (Abraham et al, 1996)

- Antipsychotics are associated with osteoporosis (Howard et al 2007)
Figure 3.6  SEM of normal trabecular bone showing thick trabecular plates, which are all interconnected. Courtesy of Professor Alan Boyd

Figure 3.7  SEM of osteoporotic trabecular bone showing marked thinning and disconnection of trabeculae. Courtesy of Professor Alan Boyd.
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Prescribing antipsychotics across the age range

- **Children**
  - Male children much more likely to receive antipsychotics
  - Female children more likely to suffer adverse effects, especially endocrine

- **Elderly**
  - Commonly used for controlling disturbed behaviour in dementia
  - 14% of people die within 6 months of starting an antipsychotic
  - Majority of elderly patients in psychiatric care are female
Sociocultural factors affecting antipsychotic prescribing

- Women more likely to seek help for mental health problem
- Women more likely to adhere to treatment
- Women less likely to suffer from the factors that negatively influence compliance, but more likely to suffer adverse effects
- Women more likely to be carers – impact of adverse effects on parenting/caring ability e.g. Sedation, weight gain, EPS
- Doctor attitudes towards women with psychosis

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Antipsychotic use in Women

- Some EPSE, but mainly...
- **Weight gain**
- **Dyslipidaemia**
- **Impaired glucose control**
- **Hypo-oestrogenism**
  - Reduced energy
  - Skin changes (androgenising – acne/coarsening, hirsuitism, hair thinning)
  - Sexual dysfunction
  - Menstrual dysfunction – oligomenorrhoea/amenorrhoea
  - Osteoporosis
  - *Increased risk of cardiovascular disease – loss of cardioprotective effects of oestrogen*

**Antipsychotics → premature ageing in women**

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Conclusions

- Antipsychotics affect men and women differently
- Men are more likely to suffer from the visible side effects of APs, women are more at risk of the long-term less obviously visible side effects
- Women are likely to have problems with the hormonal side effects of antipsychotic drugs
- Women taking antipsychotics are more likely to have metabolic problems than men taking these drugs
Clinical Implications

- Regard women as at higher risk for developing the negative long-term sequelae of antipsychotics.

- Mental health practitioners (MHPs) should be aware of the particular issues for women taking antipsychotic medication.
  - Women should be made aware of the increased risk to their gonadal function (more of a risk than EPSE).
  - MHPs should pay more attention to the increased CVS risks in women taking antipsychotic medication and target women as a high risk group for CVS disease and direct them towards healthy living groups etc.

- Consider your prescribing and its long-term effects on the person sitting in front of you “TAILOR THE TREATMENT ACCORDING TO THE INDIVIDUAL”.

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