Medical Considerations with Psychiatric Treatment

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The QT interval

- Normal
  - Men < 430ms
  - Women < 450ms
- Borderline
  - Men 431 – 450ms
  - Women 451 – 470ms
- Prolonged
  - Men > 450ms
  - Women > 470ms
- ↑QTc → ↑Mortality

Antidepressants and QT

- All TCA’s ↑QTc via sodium channel blockade
  - Generally avoid in patients with IVCD or CAD
  - 2004 review found 13 case reports of TdP
    - amitriptyline & maprotiline
  - ECG on all patients prior to starting a TCA
- SSRI’s and QTc
  - Citalopram (20mg→8.5ms; 60mg→18.5ms) \textbf{Black Box}
  - Escitalopram (10mg→4.5ms; 30mg→10.7ms)
  - 13 negative studies on fluoxetine & paroxetine
  - Sertraline, most studied in cardiac patients, seems safe
- SNRI’s, bupropion, mirtazapine also seem safe

Antidepressants and QT

- BMJ 2013;346:f288
- Psychosomatics 2013:54:1–13
Antipsychotics and QT

<table>
<thead>
<tr>
<th>Medication</th>
<th>Association with QTc</th>
<th>Association with TdP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Haloperidol (IV)</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Haloperidol (PO/IM)</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Clozapine</td>
<td>−</td>
<td>? (but ↑ risk SD)</td>
</tr>
</tbody>
</table>

Antipsychotics & Cardiac Death

- Retrospective Cohort
- Tennessee Medicaid
  - 1990-2005
  - Ages 30-74
- Non-Users (n = 186,600)
- Conventional (n = 44,218)
  - RR = 1.99
  - 9.1% developed SDBP (≥ 90mmHg)
- Atypical (n = 46,089)
  - RR = 2.26
- Clozapine > Thioridazine > Risperidone > Olanzapine > Quetiapine > Haloperidol

Hypertension

- SNRI’s and TCA’s
  - Noradrenergic properties
  - Highly dose dependent
    - Imipramine (200mg) → Average ↑4mmHg DBP
    - Venlafaxine (300mg) → Average ↑6mmHg DBP
    - After five weeks, 9.1% developed SDBP (≥ 90mmHg)
    - Duloxetine (60mg) → Average ↑4mmHg SBP
- Stimulants
  - Meta-analysis 2013 (10 clinical trials between 1979 & 2012)
  - Variable dosing
  - Average of 12mmHg SBP
Lipids

- Multiple studies
- 2011 Taiwan study: hazard ratio = 1.4
- ↑ triglycerides, ↑ total cholesterol, ↓ LDL, ↓ HDL
- Check fasting lipids at baseline, 12 weeks and every 5 years.
- Little consensus on antidepressants.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
</tr>
<tr>
<td>FGAs (low)</td>
<td>++</td>
</tr>
<tr>
<td>FGAs (high)</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
</tr>
<tr>
<td>Aripirazole</td>
<td>–</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>–</td>
</tr>
</tbody>
</table>

SSRIs & Bleeding

- First case report 1990 (44 F, 18 T 2nd fluoxetine)
- First epidemiological study published in 1999
- By 2010, 34 observational epidemiological studies. Moderately increased risk of bleeding.
- SNRIs are also implicated

- UGIB odds ratio pooled from 14 studies = 1.7
  - SSRI (OR=1.8) + NSAID (OR=3.3) = Combined OR=9.1
  - Offset by use of antacids
  - Study of 520 surgery patients → double blood loss
  - Antithrombotic effects are inconclusive

Anticonvulsant Mood Stabilizers

- Valproic Acid
  - thrombocytopenia (5-60%)
  - hypofibrinogenemia (frequency 5-30%)

- Carbamazepine
  - aplastic anemia, agranulocytosis, pancytopenia (1:40,000 – 1:10,000)
  - mild anemia (~5%),
  - mild leukopenia (transient~7%: persistent~2%)

- Lamotrigine
  - rare bone marrow suppression (case reports)

Clozapine

- Atypical antipsychotic
- Treatment resistant SCPT
- Anti-suicide
- Anti-aggression
- Neutropenia 3%
- Agranulocytosis 0.7%
- Mandatory monitoring
  - Fatalities now rare (<0.03%)
Antipsychotics & Diabetes

- Metabolic Syndrome – Predictive of type 2 DM
  - Obesity, dyslipidemia, glucose intolerance, insulin resistance and HTN
  - Dysfunctional adipose tissue → inflammatory cytokines → insulin resistance.
- Weight Gain
  - Histamine & serotonin receptor blockade, aberrant folate metabolism, genetic markers, neurotrophic factors
- Diabetes Mellitus
  - Weight gain, hypothalamic regulation of serum glucose, anticholinergic activity, prolactin, serotonin receptor antagonism, leptin resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Type 2 DM</th>
<th>Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++ (44lbs x 2yrs)</td>
<td>+++ (OR = 5.8)</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>++ (OR = 2.2)</td>
<td>+</td>
</tr>
<tr>
<td>FGAs (low)</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>FGAs (high)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>+/-</td>
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</table>

Monitoring Protocol with SGAs

<table>
<thead>
<tr>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>5 years</th>
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</thead>
<tbody>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Waist Circ.</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Blood Pressure</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Glucose</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipids</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
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</tr>
</tbody>
</table>

SIADH

- ↑ release of ADH from posterior pituitary
- ↑ water retention in collecting ducts
- SSRI and SNRI worst culprits
- Unclear pathogenesis
- Typically occurs within first few weeks of treatment
- Many case reports but general incidence unclear (~0.1% – 1.0%)
- Elderly at much greater risk with estimates as high as 12%
Dementia and Antipsychotics

- Per the 2000 Medicare report, dementia effects 5 to 8 million Americans.
- More than half have behavioral and psychological symptoms of dementia (BPSD)
- Psychiatric symptoms and disruptive or unsafe behaviors (Psychosis, Aggression, Agitation)
- 2006 Cochrane Review
  - Risperidone and olanzapine may be better than placebo
- 2008 (CATIE-AD)
  - Risperidone and olanzapine more effective than placebo but efficacy is offset by high rates of adverse effects

Antipsychotics and Stroke

- 2002 – Canadian Health Regulatory Agency
  - Raised concerns about risperidone and CVAE’s
- 2003 – Food and Drug Administration
  - Published warnings and required changes in prescribing
- 2004 – European Agency for the Evaluation of Medicinal Products
  - Public advisory about ↑ risk CVAE’s and ↑ overall mortality
- 2005 – FDA issues black box: Atypicals not for BPSD
  - 17 placebo-controlled trials. 1.6 to 1.7 fold ↑ mortality
- 2008 – FDA extends black box warning to FGAs
  - Wang NEJM 2005. 22,890 patients. 7 more deaths per 100 pts. using FGAs

- 2011 review by Mittal et al on the risk of CVAE’s
- Extensive data base search from 1990 to 2010
- 2 Placebo-controlled trials and 20 other studies (majority were population-based or retrospective)
- Summary:
  - Risk of CVAE’s is 1.3 to 2 times higher in the drug-treated group
  - Risk of CVAE’s is similar in typical versus atypical antipsychotics
  - Risk remains elevated for 20 months
  - ↑Dose, ↑age, CVD, atrial fibrillation → increase risk
- Theoretical Mechanisms:
  - orthostasis, hyperprolactinemia, dehydration, tachycardia

Extrapyramidal Symptoms

- High-Potency FGA > Low-Potency FGA ≥ SGA
- Pseudoparkinsonism
  - Tremulousness, rigidity, bradykinesia, shuffling gait
  - Rx: dose-reduction, oral anticholinergics
- Akathisia
  - Inner restlessness, pacing, unable to sit still
  - Rx: dose-reduction, propranolol(20-80mg), mirtazapine(15mg)
- Acute Dystonia
  - spastic contractions of the muscles
  - Rx: IV or IM anticholinergics
- Tardive Dyskinesia
  - Involuntary movements following long-term treatment
  - Rx: Clonazepam and ginkgo biloba

Mittal, American Journal of Alzheimer’s Disease & Other Dementias 26(1), 2011

Mittal, American Journal of Alzheimer’s Disease & Other Dementias 26(1), 2011

Mittal, American Journal of Alzheimer’s Disease & Other Dementias 26(1), 2011

Muench and Hammer, American Family Physician 81(5), March 2010
Psychopharmacology of Sex

DESIRE
DA + Melanocortin + Testosterone + Estrogen + Prolactin – 5HT –

AROUSAL
NO + NE + Melanocortin + Testosterone + Estrogen + Ach + DA + 5HT –

ORGASM
DA +/- NE + NO +/- 5HT –

Sexual Dysfunction & Psych Meds

• Antidepressants
  - Rates vary from 0-80% depending on the medication
  - Montejo (2001) observational study of 1022 subjects [SSRI’s]
    1. Spontaneous Reports → Incidence of SD = 14.2%
    2. SD Specific Questionnaire → Incidence of SD = 58.1%

• Antipsychotics
  - Risperidone, Olanzapine and Haldol: ~50-70% SD rates
  - Aripiprazole and Quetiapine: Little to no SD
  - DA-blockade, prolactin, anticholinergic, α-adrenergic, histamine

• Anticonvulsants & Lithium
  - Paucity of studies. Mild SD

• Anxiolytics
  - Paucity of studies. Mild SD

Antidepressants & SD

Nephrology

• Vast majority of psychotropic medications do not need to be adjusted based on renal function.

• Notable exceptions:
  - Risperidone
  - Paliperidone
  - Duloxetine
  - Venlafaxine
  - Paroxetine
  - Lithium (NDI, CRF, ARF)

*Sql call it – EALYSESI*
Gastroenterology

- Cytochrome p450
  - 2D6, 3A4, 1A2
  - Smoking induces CYP
- 90% of all serotonin receptors are in the GI tract
  - N/V/D/C (~20-30%)
- Direct Liver Toxicity
  - Depakote (-1-5%)
- Anticholinergics
  - GI Hypomotility
  - Clozapine
- Review of 102 cases
  - Mortality 37.3%

Pregnancy

- Antenatal Depression
  - Trimester point prevalence: 6.5% to 12.9%
  - Combined point prevalence: 19.2%
- Psychological Distress
  - Affect child over lifespan
  - Abnormal cortisol response

Antidepressants during Pregnancy

- ↑ Risk of spontaneous abortion (odds ratio = 1.68)
  - SSRI (OR = 1.61); SNRI (OR = 2.11); Combination (OR = 3.51)
- ↑ Risk of preterm birth
  - OR = 1.96 to 2.2
- Birth weight: No robust evidence
- Cardiac Septal Defects
  - SSRI (OR = 1.99). (prevalence 0.5% placebo vs. 0.9% drug)
- Persistent Pulmonary Hypertension
  - Late pregnancy only (OR = 2.50). Very low rates overall.
- Infant and child development
  - No demonstrable effect out to 71 month

Antidepressants & Analgesia

- Tricyclics:
  - Diabetic neuropathy, postherpetic neuralgia, post-stroke pain, tension and migraine headaches
- SSRI:
  - Variable and inconsistent results
  - Fluoxetine: fibromyalgia
- SNRI:
  - Venlafaxine: neuropathic pain
  - Duloxetine: neuropathic pain, fibromyalgia, musculoskeletal