Medical Considerations with Psychiatric Treatment

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Advances in Internal Medicine, 2015

Disclosure

I have nothing to disclose
Where to Start

• You inherit a 71 y-o overweight man with type II diabetes, hypertension, hyperlipidemia and coronary artery disease.

• He also has a history of depression and subtle paranoia for which he takes citalopram 40mg every morning and risperidone 1mg every night.

• What concerns should you have?

Goals

• How do psychiatric treatments impact the systems in the human body?

• What medical illnesses need special consideration when also treating a psychiatric illness?

• What are some recommendations to minimize medical risks?
Which of the following has the largest impact on the QTc interval?

1. Citalopram (Celexa) 60mg
2. Methadone 50mg
3. Aripiprazole (Abilify) 20mg
4. Bupropion (Wellbutrin) 300mg
5. Amitriptyline (Elavil) 100mg
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) **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

*Psychosomatics 2013:54:1–13*
Antidepressants and QT

Antipsychotics and QT

<table>
<thead>
<tr>
<th></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>Aripiprazole</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Clozapine</td>
<td>−</td>
<td>(but ↑↑ risk SD)</td>
</tr>
</tbody>
</table>

* BMJ 2013;346:f288

* Psychosomatics 2013:54:1–13
Antipsychotics and QT

- Change in QTc (ms)
- Medications: Clozapine, Haloperidol 15mg, Olanzapine 20mg, Risperidone 16mg, Quetiapine 750mg, Ziprasidone 160mg, Thioridazine 300mg
- Source: Pharmacology & Therapeutics 135 (2012) 113-122

Antipsychotics & Cardiac Death

- Retrospective Cohort
- Tennessee Medicaid:
  - 1990-2005
  - Ages 30-74
- Non-Users (n = 186,600)
- Conventional (n = 44,218)
  - RR = 1.99
- 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 (≥ 90mmgh)
  - Duloxetine (60mg) → Average ↑4mmhg SBP

- Stimulants
  - Meta-analysis 2013 (10 clinical trials between 1979 & 2012)
  - Variable dosing
  - Average of ↑2mmhg SBP


Orthostatic Hypotension

- Antipsychotics
  - Most frequent vascular effect of antipsychotics
  - Reported in up to 40% of patients
  - Blockade of peripheral α1-adrenoceptors
  - Much more common in the elderly

- Trazodone
  - 2nd most commonly prescribed for insomnia
  - Orthostasis seen at doses as low as 50mg

### Orthostatic Hypotension

<table>
<thead>
<tr>
<th>Medication</th>
<th>Alpha-1A Adrenoceptor Affinity</th>
<th>Orthostasis</th>
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<tbody>
<tr>
<td>Clozapine</td>
<td>160</td>
<td>+++</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>15</td>
<td>+++</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>2</td>
<td>+++</td>
</tr>
<tr>
<td>Quetipine</td>
<td>12</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1</td>
<td>++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0.55</td>
<td>+</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.35</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.30</td>
<td>+</td>
</tr>
<tr>
<td>Aripirazole</td>
<td>0.02</td>
<td>+/-</td>
</tr>
</tbody>
</table>

*Pharmacology & Therapeutics 135 (2012) 113–122*

### Hematology
SSRIs & Bleeding

• First case report 1990 (44 F, ↑BT 2nd fluoxetine)
• First epidemiological study published in 1999
• By 2010, 34 observational epidemiological studies. Moderately increased risk of bleeding.
• UGIB odds ratio pooled from 14 studies = 1.7
  o SSRI: OR=1.8
  o NSAID: OR=3.3
  o Combined (SSRI + NSAID): OR=9.1
  o Offset by use of antacids
• Study of 520 surgery patients → double blood loss


SSRIs & Bleeding

• Post Partum Bleeding and SSRI
  o Karolinska University Hospital (2007 – 2011)
  o Deliveries: 500 on SSRI vs. 40,000 non-users
  o PPH(18% vs. 8.7%); Anemia (12.8% vs. 8.7%); Blood Loss(484ml vs. 397ml)
• Warfarin and SSRI (atrial fibrillation)
  o N = 9186 at Kaiser, followed for a median of 6 years
  o Warfarin - Hemorrhage risk: 1.30 per hundred person years
  o W + TCA - Hemorrhage risk: 1.35 per hundred person years
  o W + SSRI - Hemorrhage risk: 2.32 per hundred person years *(p<0.001)
• SSRI and Brain Hemorrhage (meta-analysis)
  o 2493 citations → 16 reviewed (506,411 patients)
  o SSRI: Intracranial Hemorrhage RR = 1.48

3) Neurology 79 October 30, 2012
Anticonvulsant Mood Stabilizers

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

- **Clobazam**
  - 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%)

*J Clin Psychiatry 74:6, June 2013*

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Endocrinology

- Hypothalamus
  - Exipoline: m9-115, m9-161a
  - Gonadotropin-releasing hormone: mR-151, mR-222
- Pituitary
  - Growth hormone: mR-101b, mR-109
- Liver
  - Insulin-like growth factor 1 (mR-44)
    - mR-126, mR-375a, mB-223
- Thyroid
  - Thyroxin: mR-21, mR-146a
    - mR-211, mR-204
- Pancreas
  - Insulin: mR-37, mR-181a
    - mR-214
- Adrenal Cortex
  - Aldosterone: mR-214
  - mR-214
- Ovary
  - Estrogen: mR-7, mR-21, mR-186a, mR-198
  - Progesterone: mR-151, mR-89, mR-181a, mR-124
Antipsychotics & Metabolic Syndrome

- Metabolic Syndrome – Predictive of CAD and DM
  - Central Obesity
  - ↑ Blood Pressure
  - ↑ Fasting Plasma Glucose
  - ↑ Triglycerides
  - ↓ HDL
- The prevalence of antipsychotic-related metabolic syndrome generally falls between 10% and 35%.
- “First do no harm.” A systematic review of the prevalence and management of antipsychotic adverse effects.

Metabolic Syndrome

<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>
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<td>Paliperidone</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>
<td>+/-</td>
</tr>
</tbody>
</table>

- East Asian Arch Psychiatry 2013, Vol 23., No. 1
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>
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<tbody>
<tr>
<td>Clozapine</td>
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<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>
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• Curr Atheroscler Rep (2013) 15:292

Monitoring Protocol with SGAs

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<thead>
<tr>
<th></th>
<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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<tr>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Waist Circ.</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>Blood Pressure</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Glucose</td>
<td>X</td>
<td></td>
<td>X</td>
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<td>Lipids</td>
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<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Diabetes Care 2004; 27(2): 599
SIADH

- ↑ release of ADH from posterior pituitary
- ↑ water retention in collecting ducts
- SSRIs and SNRIs 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%

Pschomastics 48:1, Jan-Feb 2007

Neurology
Question #2

• A 74 y-o man with dementia has had delusions for 2-months that ghosts have been stealing his food. He does not see them but is certain they visit while he is asleep or away from home. He believes this happens a couple times a week and thinks it is the ghosts of dead relatives.
• In general he is alert and calm but annoyed about the ghosts. He denies SI/HI/AH/VH.
• He is started on haloperidol 2mg po daily, but after 2-weeks of treatment, the delusions are unchanged. His MSE remains the same.

In addition to patient-education which of the following would you do next?

1. Continue haloperidol 2mg daily
2. ↑ haloperidol to 5mg and add benztropine (Cogentin) 0.5mg twice a day
3. D/C haloperidol and start risperidone (Risperdal) 1mg twice a day
4. D/C haloperidol and start quetiapine (Seroquel)50mg nightly and titrate up slowly
5. D/C haloperidol and monitor
Dementia and Antipsychotics

- Per the 2000 Medicare report, dementia affects 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.
Antipsychotics and Stroke

- 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
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 -


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**Sexual Dysfunction & Psych Meds**

- **Antidepressants**
  - Rates vary from 0-80% depending on the medication
  - Montejo (2001) observational study of 1022 subjects (SSRI’s)
    - Spontaneous Reports → Incidence of SD = 14.2%
    - 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, a-adrenergic, histamine
- **Anticonvulsants & Lithium**
  - Paucity of studies. Mild SD
- **Anxiolytics**
  - Paucity of studies. Mild SD

Clinical Pharmacology and Therapeutics., 89(1), Jan 2011
Antidepressants & SD

% of pts with SD

Bupropion  Placebo  Mirtazapine  Escitalopram  Duloxetine  Imipramine  Fluoxetine  Paroxetine  Citalopram  Venlafaxine  Sertraline


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)

"I'll call it - DIALYSIS!"
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 37.5%


Have you prescribed an antidepressant to a woman between the ages of 15 and 45?

1. Yes
2. No
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