DISCLOSURES

• I have no relevant financial conflict of interest.

• I may discuss some indications and routes of administration that are not FDA-approved.
TOPICS COVERED

- SSRIs and bleeding risk
- GI: irritable bowel syndrome, gastric bypass
- Neuro: Parkinson’s, seizure risk
- Cardiac: QTc prolongation risk
- Pulmonary: safety of sedatives
- Renal: Lithium
- Perioperative risks
- Hyperprolactinemia and osteoporosis risk
- Drugs with suicide risk
Meta-analysis: Overall bleeding risk is increased at least 36% (from 12% to 64%)

SSRIS AND BLEEDING RISK

- Gastrointestinal
- Perioperative
- Postpartum
- Cerebral
STUDIES OF SSRIS AND GI BLEEDING: THE DATA ARE VERY MIXED

• Studies showing large ↑ relative risk, e.g. 2x
  Loke et al, Aliment Pharmacol Ther 2008;27:31-40
  Ahsberg et al, Scand J Gastroenterol. 2010;45:1404-15

• Studies showing small ↑ risk, e.g. 1.3x
  Targownik et al, Am J Gastroenterol. 2009;104:1475-82

• Studies showing no ↑ risk.
  Vidal X, Drug Saf. 2008;31:159-68
SSRIS AND GI BLEEDING

• No increased mortality from SSRI-associated GI bleeds.
  Ahsberg et al, Scand J Gastroenterol. 2010;45:1404

• The risk increases considerably if patient taking multiple anti-
  platelet drugs, e.g. SSRI+NSAID+clopidogrel
  Dall et al, Clin Gastroenterol Hepatol. 2009;7:1314
  Loke et al, Aliment Pharmacol Ther 2008;27:31

• \textit{H. pylori} \uparrow risk of SSRI-GI bleed by 2.7X
SSRIS AND GI BLEEDING: META-ANALYSES

• The risk of bleeding is 1.3-2X higher.
• Risk is even higher 4X if also taking NSAIDs or anti-platelet drugs.
• Risk not increased if taking acid-suppressants.
• Number needed to harm for upper GI bleeding with SSRIs in low-risk patients was 3,177, and 881 in a high-risk patients.

Pharmacol Res. 2017;118:19-32
Clin Gastroenterol Hepatol. 2015;13:42
Am J Gastroenterol. 2014;109:811
Biol Pharm Bull. 2014;37:947
SSRIS AND GI BLEEDING

• SNRIs may not increase risk.
  Medicine (Baltimore). 2015;94:e2022

• SSRIs plus warfarin increase bleeding?
  • Reports are mixed Am J Cardiol. 2014;114(4):583
  Pharmacoepidemiol Drug Saf. 2009;18:412-6
  • U.S. FDA does not warn of this interaction

• No increased risk with exoxaparin
  Ann Pharmacother. 2017;51:226-231

• No reports of SSRI-bleeding with dabigatran etexilate, rivaroxaban, or apixaban
SSRIS AND GI BLEEDING: BOTTOM LINE

• The data vary, but there does seem to be a 1.5-2x increase in relative risk; the absolute risk is small.
• Risk is increased with concomitant NSAIDs.
• Caution advised with other antiplatelet drugs, thrombocytopenia, platelet dysfunction.
DO SSRIS INCREASE PERIOPERATIVE BLEEDING?

Retrospective studies (in some only a fraction got SSRIs)

- Major surgery (n=530,416), bleeding ↑1.09  
- Breast cancer (n=14,464), bleeding → reop ↑2.3X  
  BMC Surg 2010;10:3
- Cosmetic breast (n=2285), bleeding ↑4X  
  Aesthetic Plast Surg. 2013;37:561
- Hip replacement (n=1318), 93 cc more blood lost  
  Basic Clin Pharmacol Toxicol. 2014;115:77
- Orthopedic (n=285), ↑risk of bleeding, clinically insignificant  
  Anesthesiology. 2010;112:631
- Hip fracture (n=175), no ↑risk  
  Eur J Anaesth. 2006;23:9090
- CABG (n=1380), no ↑risk  
  Am J Cardiol. 2009;103:1391
- CABG (n=246), no ↑risk  
- Face-lift (n=250), no ↑risk  
  Arch Facial Plast Surg. 2012;14:248
- Invasive dental (n=92), no ↑risk  

Caveats: serious bleeding rare, not RCTs, many potential confounds.
DO SSRIS INCREASE PERIOPERATIVE BLEEDING?

• A systematic review of 13 studies concluded that serotinergic antidepressants increased risk, with odds ratios 1.21-4.14


• **Bottom line:** small ↑relative risk, small absolute risk, unlikely clinically significant except in high risk patients.
DO SSRIS CAUSE CNS BLEEDING?

- Mixed evidence that SSRIs increase stroke risk.
  - Meta-analysis found same ↑risk 1.4X with ischemic and hemorrhagic stroke  
    J Neurol. 2014;261:686
  - 2.6X risk with SSRI in stroke  
  - SSRI after ischemic stroke ↓CV events and ↑GI bleeding  
    (not IC) Stroke. 2013;44:420
- But depression & anxiety are associated with increased risk for hypertension and stroke.
- Small ↑ risk (1.17X) with SSRIs vs TCAs  
  JAMA Neurol. 2017;74:173-180
SUMMARY: SSRIS AND BLEEDING

• There probably is increased risk.
• The absolute risk is small in most patients.
• It is rarely serious.
• Caution is warranted in high risk patients
  • Thrombocytopenia, platelet disorders
  • Coagulopathy
  • Acute intracerebral hemorrhage
  • Multiple antiplatelet drugs
PSYCHOTROPICS IN GI DISEASES

• Malabsorption syndromes
  • Chronic pancreatitis, IBD, gastric bypass, etc.

• Delayed gastric emptying
  • Diabetic gastroparesis, iatrogenic, etc.
  • Avoid anticholinergic drugs

• Constipation
  • Avoid anticholinergic drugs
ANTIDEPRESSANTS FOR IRRITABLE BOWEL SYNDROME

• Depression and anxiety are very common in IBS.
• Multiple meta-analyses have concluded that antidepressants (TCAs and SSRIs) are beneficial for IBS Sx.

IBS AND ANTIDEPRESSANTS

• Insufficient study of subtypes (diarrhea-predominant vs. constipation-predominant vs. mixed).

• Insufficient study of relative effects on comorbid anxiety and depression.
IBS AND ANTIDEPRESSANTS: BOTTOM LINE

Practically speaking, patients with constipation-predominant IBS may benefit from SSRIs, while patients with diarrhea-predominant IBS may benefit from TCAs.
HOW IS DRUG ABSORPTION AFFECTED AFTER GASTRIC BYPASS SURGERY?

ANTIDEPRESSANTS ARE THE MOST COMMONLY USED MEDICATION CLASS AMONG PREOPERATIVE BARIATRIC SURGERY PATIENTS.
EFFECTS OF GASTRIC BYPASS ON ABSORPTION

• Reduces exposure to gastric acid.
  • Increased pH reduces solubility of some drugs
  • Increased pH will ↑absorption of weak bases (most Ψ drugs).
• Reduces intestinal exposure where most drug absorption occurs.
  • This will ↓absorption of many drugs
  • Change in exposure to CYP3A4 and P-gp in gut wall
  • Change in first pass metabolism
DRUGS AFTER BARIATRIC SURGERY

- Avoid XR preparations, instead preferring IR forms, crushed tablets and liquid forms.
- Significant weight loss will usually mean need to reduce lipophilic drugs (almost all psych drugs) because the volume of distribution is ↓.
- Post-op vomiting (2-3 months).
EFFECTS OF GASTRIC BYPASS ON ABSORPTION

• Multiple reviews conclude we have little data.
• Most but not all patients on SSRIs and SNRIs had a significant decrease in absorption.
  • Escitalopram concentrations were 33% (4%-71%) lower in four patients 2 weeks postop
    - Marzinke Ther Drug Monit. 2015;37:408-12
• Two cases of lithium toxicity after bypass surgery.
  - J Clin Psychopharmacol. 2011;31:261-2
EFFECTS OF GASTRIC BYPASS ON ABSORPTION

No published information on:

- Other antidepressants (TCAs, mirtazapine, trazodone, bupropion)
- Benzodiazepines
  - Single dose midazolam more rapidly absorbed but total amount unchanged *Pharmacotherapy*. 2015;35:361-9
- Antipsychotics
- Valproate, lamotrigine
- Stimulants
How should patients with Parkinson’s Disease who require antipsychotics be managed?
PSYCHOSIS IN PARKINSON’S

• Psychotic Sx occur in up to 60% at some point.


• Visual hallucinations and paranoid delusions are the most common, usually in PD patients with dementia.

• Side effect of dopaminergic drugs.
  • Step 1: Reduce dose of DA agonists.
  • **Beware: Abrupt discontinuation can cause NMS!**

• Antipsychotics make PD worse.
TREATMENT OF PSYCHOSIS IN PD

**Clozapine**: Effective in several RCTs at low-dose (6.25–50mg/day) without worsening PD.

**Pimavanserin (New)**: FDA approved, one +RCT, no PD worsening

Costly: $24K/year wholesale  
Lancet.2014;383:533-40

**Quetiapine**: Safe but not proven effective (2 small RCTs negative, one tiny RCT positive).

**Olanzapine**: 2 RCTs, ineffective, worse PD.

**Risperidone**: Worse PD.

**Aripiprazole**: 2 open trials, ineffective, worse PD.

**Ziprasidone**: 1 tiny RCT vs. clozapine, =

**Cholinesterase inhibitors**: 2 neg RCTs, 1 + RCT.

**Deep brain stimulation**: 1 tiny + open trial
TREATMENT OF PSYCHOSIS IN PD

- A U.S. VA study of 2,597 patients with PD+psychosis found that quetiapine was most frequently prescribed (66%), but 30% received high-potency APs. Clozapine was rarely prescribed (<2%).


- Canadian study of 479 nursing home patients with PD+psychosis: 40% quetiapine, 39% risperidone, 17% olanzapine, 4% other.

  Herrmann et al, Drugs Aging.2013;30:19-22
ANTIPSYCHOTICS RX FOR PARKINSON DISEASE PATIENTS
DATA FROM ANTHEM 2013-2016 (VA, MO, NV, ME)

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Percent of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>43.7</td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.5</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>1.0</td>
</tr>
<tr>
<td>Risperidone,paliperidone, iloperidone and FG antipsychotics</td>
<td>18.3</td>
</tr>
<tr>
<td>Other SG antipsychotics</td>
<td>36.5</td>
</tr>
</tbody>
</table>
PSYCHOSIS IN PD: BOTTOM LINE

While clozapine and pimavanserin are the only drugs with RCT evidence of efficacy and without worsening PD, it is reasonable to try quetiapine first because of fewer other adverse effects.
But NOT high potency D2 blockers!
Which psychiatric drug carries the greatest seizure risk?
PSYCHOTROPICS IN NEURO DISEASES

• Epilepsy
  • Risk of seizure is about 0.1-0.5% for most antidepressants and antipsychotics
  • Most can be given safely if pt receiving anticonvulsants
  • ?Slight increased risk with bupropion
    Gen Hosp Psychiatry.2010;32:216
  • Increased risk with clozapine (1-2%) and low-potency typical antipsychotics
PSYCHOTROPICS IN CARDIAC DISEASE

• TCAs
  • Orthostasis, Type 1A antiarrhythmic effects
  • Generally safe in selected pts with stable heart disease
  • Contraindicated after MI

• SSRIs
  • Safety shown for sertraline in SADHRT and citalopram in CREATE
  • Uncommonly cause bradycardia

• Mirtazapine— Safety shown in MIND-IT

• Stimulants—generally safe
  • But there is a Black Box warning; PDR says contraindicated in structural heart disease.
  • No ↑ CV risk in adults? Am J Psychiatry 2012; 169:178 (small absolute ↑ in VT, RR 1.8 but inverse dose relationship)
How much risk do antipsychotics pose for prolonged QTc and torsade de pointes?

For an excellent review, see Beach et al, Psychosomatics 2013;54;1-15
Interpretation of the QTc interval

- Automated ECG estimates not accurate.
- At high HR, actual QT is shorter than calculated.
- At very slow HR, actual QT is longer.
- QT is misleading in patients with bundle branch blocks.
ANTIPSYCHOTICS AND QT INTERVAL

• All AP’s prolong QTc to some degree.

• Risk of sudden death 2-4 per 10,000 person years of exposure in healthy people. Glassman et al Am J Psychiatry 2001; 158:1774

• Users of antipsychotics compared to non-users had 2X sudden death risk Ray et al NEJM 2009;360:225
  • Nonetheless, absolute risk was small
  • 0.0015 deaths per person year of exposure
  • NNH over one year of treatment is 666 persons
ANTIPSYCHOTICS AND QT INTERVAL

• The risk of torsades increases when QTc is above 500 msec.
• Patients getting IV haloperidol should be on cardiac monitor.
• Contrary to what my residents may say, patients getting oral antipsychotics do not need repeated EKGS.
• The real risk is when patient has a high dose antipsychotic plus other risks for prolonged QTc.
RISK FACTORS FOR TORSADE DE POINTES

• Familial long QT syndrome
• Baseline QTc prolongation
• Female gender, older age
• Chronic heavy alcohol use
• Anorexia nervosa
• Low ejection fraction
• $\downarrow K^+, Ca^{++}, Mg^{++}$
• Structural heart disease
• Concurrent treatment with multiple drugs that prolong QT interval or inhibit metabolism of a QT-prolonging drug
QTC PROLONGATION AND ANTIPSYCHOTICS

**Drugs with greatest risk**
- Thioridazine
- Chlorpromazine
- Haloperidol (esp. IV)
- Ziprasidone

**Drugs with lowest risk**
- Aripiprazole
- Olanzapine
WHAT ABOUT CITALOPRAM AND QT PROLONGATION?

• FDA overreacted in advising no dose >40mg, 20 mg in over age 65.
• Risk of significant ↑QTc is very small, and torsades extremely rare.
• If the patient is doing well on a higher dose, with a QTc<500 msec, leave it alone.
HOW SAFE ARE SEDATIVE HYPNOTICS IN PULMONARY DISEASE?
SEDATIVE-HYPNOTICS IN PULMONARY DISEASE FOR ANXIETY

• Benzodiazepines are very often Rx’d in COPD
  • In a population-based study (n=111,445), 1/3 of older adults with COPD got a new benzodiazepine Rx, even more often in those with more severe COPD. *Drugs Aging.* 2013;30:183

• Over 100 RCTs for Rx of anxiety in asthma or COPD; none of them with psychotropics.

• Mixed reports on safety of benzos in COPD.
  • For review see *Sleep Medicine* 2009;10:19
  • 20% ↑mortality in severe COPD *BMJ.* 2014 Jan 30;348:g445

• Buspirone
  • One small RCT: safe in mild COPD, ↑exercise tolerance *Respiration* 1993;60:216
HYPNOTICS IN PULMONARY DISEASE

Paucity of RCTs of hypnotics in COPD.

• Benzodiazepenes
  • A few small RCTs show benzos and Z-hypnotics with no effect on resp function and safe in mild COPD. Respir Med. 2010;104:518-24; Int J Chron Obstruct Pulmon Dis 11:675-85, 2016; Sleep 1993;16:318

• Trazodone, mirtazapine—no data

• Melatonin, ramelteon, suvorexant: no effect on resp function
SEDATIVE-HYPNOTICS IN PULMONARY DISEASE: MY ADVICE

• Benzodiazepines contraindicated in CO₂ retainers, and in OSA with steep desaturation.
• For GAD+COPD: Buspirone or SSRIs instead of benzos.
• For acute treatment of panic in severe COPD, antipsychotic is first choice.
PSYCHOTROPICS IN RENAL DISEASE

• Rule of 2/3 for most drugs?
  • Venlafaxine clearance reduced 50%
• Lithium, gabapentin, and pregabalin are renally excreted
  • They are dialyzable, as are valproate and topiramate
• In hemodialysis, lithium can be given as a single dose (300-600mg) after dialysis
How much risk does Lithium pose to the kidney?
LITHIUM’S RENAL RISK: NO CONSENSUS

• Progression of Li⁺ nephrotoxicity to ESRD is rare (0.2-0.7%) and requires Li⁺ use for several decades Presne et al. Kidney Int 2003;64:585

• Meta-analysis: any Li⁺-induced effect on renal function is quantitatively small and probably clinically insignificant. Paul et al. Psychopharmacol. 2010;24:1425

• About 1/3 of patients taking lithium for 10-29 years had evidence of chronic renal insufficiency but only 5% were in the severe or very severe category. Aiff et al. J Psychopharmacol. 2015;29:608

• However, other factors contribute to ↓renal function:
  • Age, episodes of Li⁺ toxicity, other meds (analgesics, substance abuse), and comorbid disorders (hypertension, diabetes).
LITHIUM’S RENAL RISK: BOTTOM LINE

• After all these years, it is still controversial.
• Lithium is so efficacious in bipolar disorder that the risk of renal dysfunction during chronic use is considered acceptable with yearly monitoring of renal function.
  • Monitor levels of lithium and creatinine, aim for lowest effective Li level, treat diabetes and hypertension, avoid chronic NSAIDs
How should psychotropics be managed in the peri-operative period?
RISKS OF CONTINUING PSYCHIATRIC DRUGS IN THE PERIOPERATIVE PERIOD

- Adverse interactions with anesthetics.
- Interference with hemodynamic management (e.g. causing hypotension or hypertension).
- Postoperative complications (e.g. excessive sedation, ileus).
RISKS OF DISCONTINUING PSYCHIATRIC DRUGS IN THE PERIOPERATIVE PERIOD

- Loss of therapeutic effect.
- Rebound exacerbation of the mental disorder.
- Withdrawal syndrome

Which risks are greater?
Evidence is scanty, and RCTs unlikely
PERIOPERATIVE PSYCHIATRIC DRUGS: BOTTOM LINE #1

- Risks of discontinuation usually exceed the risks of continuing most psychotropic drugs.
  - SSRIs may be an exception especially in patients at high risk for perioperative bleeding.
- The exception is the cholinesterase inhibitors
  - Synergistically ↑ effects of depolarizing neuromuscular blockers (e.g. succinylcholine) and ↓ effects of nondepolarizing agents (e.g. atracurium). Given low risk of temporary cessation of Rx, cholinesterase inhibitors should be stopped prior to surgery.

What is the risk of osteoporosis with psychototropic-induced hyperprolactinemia?
HYPERPROLACTINEMIA

• Risk for hyperprolactinemia increases with degree of D2 blockade.
  • High Risk: butyrophenones, phenothiazines, risperidone
  • Intermediate Risk: olanzapine, quetiapine
  • Low Risk: aripiprazole, ziprasidone
• Other agents: SSRIs, opioids, phenothiazine antiemetics
• Hyperprolactinemia induces hypogonadism, lowering E in women and T in men.
• Decreased E and T are associated with decreased bone mineral density and osteoporosis.
AP-INDUCED HYPERPROLACTINEMIA AND OSTEOPOROSIS

- Decreased bone mineral density (BMD) in 32-60% of young to middle aged women and men treated 10+ years with antipsychotics (Meaney et al. Br J Psychiatry. 2004;184:503-8). Proportional to:
  - Medication dose
  - Reduction in serum T in men
- Patients receiving PRL-raising (risperidone, amisulpride, depot) compared to olanzapine developed decline in BMD over 1 year. (Meaney and O’Keane Schizophr Res. 2007;93:136-43)
- Effect mitigated by treatments to augment BMD.
MONITORING FOR HYPERPROLACTINEMIA

- PRL monitoring currently recommended only for symptomatic patients
- No specific recommendations for BMD measurement
- Appears prudent to monitor:
  - For evidence of sexual dysfunction, menstrual disturbance, galactorrhoea and gynaecomastia
  - PRL yearly in patients receiving high potency and/or high dose D2 antagonists
  - BMD in patients with sustained elevations in PRL
MANAGEMENT FOR HYPERPROLACTINEMIA

• Prevention: Calcium and Vitamin D supplements, exercise
• Decrease dose of AP
• Change to lower-risk AP (e.g., aripiprazole – Mir et al., 2008)
• Treat with dopamine agonist (e.g., bromocriptine – Smith 1992 - warning re: exacerbation of psychosis)
• Medications to increase BMD
  • Bisphosphonates, raloxiphene (women only)
  • HRT (estrogens in women, testosterone in men)
DRUGS CAUSING SUICIDALITY?

*FDA warns about all of these:*

Interferon-α? Yes, clear risk

Isotretinoin? Rare (↑risk with acne)

Anticonvulsants? No (↑risk with epilepsy)

Leukotriene-modifying agents? No
What can we do for patients who cannot take psychotropic drugs PO?
ALTERNATE ROUTES OF ADMINISTRATION
Antidepressants

• Parenteral: none for use in U.S.
  • Citalopram in Europe
• Rectal suppositories
  • TCAs, trazodone
• Transdermal
  • Selegiline
• Buccal (oral disintegrating tablets):
  • Selegiline for PD (not studied in depression)
  • Mirtazapine (absorption not known)
• Sublingual: fluoxetine solution
**ALTERNATE ROUTES OF ADMINISTRATION**

**Benzodiazepines**

- IV: lorazepam, midazolam, and diazepam
- IM: lorazepam, midazolam
  - Avoid IM diazepam
- Sublingual
  - SL lorazepam in Canada; many BZs given as tablets
- Nasal: lorazepam, midazolam
- Intrathecal: lorazepam, midazolam
- Rectal: diazepam gel, other Bzs in solution
ALTERNATE ROUTES OF ADMINISTRATION

Antipsychotics

• IV: Haloperidol
• IM: Haloperidol and other FGAs, ziprasidone, olanzapine, aripiprazole
• Sublingual: Asenapine
• Subcutaneous: Haloperidol, fluphenazine
ALTERNATE ROUTES OF ADMINISTRATION

Mood stabilizers

• IV: Valproic acid
• Rectal: Carbamazepine, lamotrigine, topiramate

Stimulants

• Transdermal: Methylphenidate

Cholinesterase inhibitors

• Transdermal: Rivastigmine