



Psychopharmacology in the Medically Ill

Fundamentals of Consultation-Liaison Psychiatry
Pre-Conference Course, ACLP Virtual Annual Meeting 2021

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ACADEMY OF CONSULTATION-LIAISON PSYCHIATRY
Advancing Integrated Psychiatric Care for the Medically Ill



CLP 2021

Disclosure: J.J. Rasimas

With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between the party listed above (and/or spouse/partner) and any for-profit company which could be considered a conflict of interest.



Learning Objectives

- Appreciate pharmacokinetic changes relevant to psychotropic prescribing in patients with significant medical comorbidities
- Answer clinical dilemmas in the psychiatric management of categories of patients with non-standard whose risk / benefit profiles around psychotropic medications
- Learn options for creative use and delivery of psychotropic medications in patients with somatic disease that complicates standard prescribing



Limitations Of Evidence-Based Medicine In The C-L Context

- Studies, if any, are typically small and / or open-label
 - Case series reporting dominates the literature of interest
- Patients with significant medical problems are typically excluded from medication trials in psychiatric research

Challenge for this activity:

Discussion of general principles is not directly relevant and painfully boring. A string of useful clinical pearls lacks solid evidentiary foundation and logical organization.



Curio rowleyanus



General Principles

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Pharmacokinetics

Phase	Location	Factors that may impact this phase in medically ill
Absorption (and F)	Gastric and intestinal	Gastro-intestinal disorders and surgeries Presence / absence of food (and what type)
	First pass metabolism	Cytochrome Enzymes (P450) P-Glycoprotein system
Distribution	Various fluid / tissue compartments	Volume (overload, edema) Protein binding alterations Body habitus differences
Metabolism	Mostly hepatic (GI, lung, CNS) Phase 1: CYP enzymes Phase 2: Sulfatases, acetylases, . UGT (Uridine 5'-diphospho- . glucuronosyltransferase)	All major organ diseases (not just hepatic) Inflammation Other medications / CYP influencers
Excretion	Renal (mostly)	Low perfusion states, renal impairment



Pharmacokinetics: Metabolism

- Most metabolism occurs in liver & gut wall, some in lung, some in brain
- Most psychotropics: hepatic metabolism & clearance
- Hepatic metabolism/biotransformation

Phase I: oxidation (Cytochrome P450), reduction, hydrolysis

Phase II: conjugative metabolism- glucuronidation, acetylation, sulfation

- Most prominent Phase II enzyme family: Uridine 5'-diphospho-glucuronosyltransferases (UGTs)

Limited by rate of drug delivery (Hepatic Blood Flow) and capacity of enzymes



Pharmacokinetics: Elimination

- Excretion by kidneys
- Excretion into bile or feces
- Elimination through sweat, saliva, tears
- Elimination via respiration (volatile compounds like EtOH)

- Elimination half-life = amount of time needed to excrete half of the drug from the body

Changes in V_d , metabolic capacity, and the function of relevant excretory organs will affect elimination half-life



Kidneys Are The Way Out

Psychotropics that are almost entirely dependent on renal excretion:

Lithium
Gabapentin
Pregabalin
Topiramate

– Most psychotropics will have clearance reduced in renal disease –

Some data exist for paroxetine, venlafaxine, others...

Here we should exercise **more** care, not merely following pharmacy guidelines indicating no need to reduce doses with renal impairment.





Helpful Facts Regarding Pharmacokinetics In The Medically Ill

- IV, IM, TD and (to a lesser degree) rectal administration bypass first-pass metabolism
 - Correlates to greater potency on a mg – mg basis (but TD kinetics are slow)
 - F for IV administration is 1, and for IM it is nearly 1 (but rectal absorption may be erratic)
- Most drug - drug interactions occur through inhibition/competition in the CYP450 system. For a comprehensive discussion with a table see *Levenson & Ferrando's Clinical Manual of Psychopharmacology in the Medically Ill, second edition, p 35-44.*
 - *Emerging data indicate drug-drug interactions can also occur at the P-gp transporter (paroxetine-itraconazole) and via other enzymes like UGT (valproate-lamotrigine)*
- Protein binding can impact drug monitoring in medically ill. In these cases, free-drug levels (as opposed to total) can be useful if available on actionable timetables



Monitoring / Interpretation Of Serum Concentrations

- Troughs are used to simplify interpretation
 - Removes issue of having to account for impact of ongoing absorption from last dose
 - 12 hours usually sufficient, and fits outpatient care routines (AM draws)
 - Technically, lowest trough in a regular dosing regimen would be best
 - Elimination half-life, which depends heavily on V_d , determines how long it takes to reach a given trough depth
- Last dose timing is central to interpreting a result
- Steady state is achieved with consistent dosing over about 5 elimination half-lives for the compound in question
 - Only steady state concentrations define psychiatric therapeutics

Outside steady state, efficacy and toxicity can occur with “low” “therapeutic” or “high” levels, depending on the scenario...



Loading

- Assuming no compound in the body to start
- Absorption & distribution are much faster than elimination
- Let's start with a single dose:

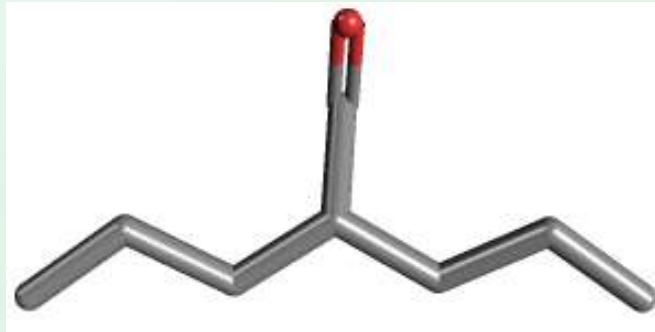
$$\text{Dose} = \text{Concentration} * \text{Vd} * \text{Weight} / \text{F}$$

Concentration is the target level

F = 1 for IV dosing, almost always 1 for IM

- If starting concentration is non-zero, subtract current level from desired level, and use the same formula

Case Example



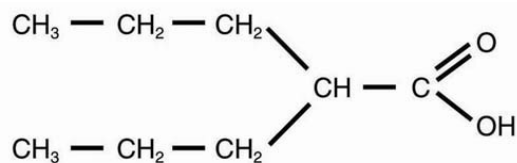
- A 60 year-old, 80 kg cirrhotic man is agitated and delirious from sepsis with a QTc of 529 msec and a HR of 65 bpm on 1.3 $\mu\text{g}/\text{kg}/\text{hr}$ of dexmedetomidine
- A vicious cycle of confused unrest and re-sedation has occurred using both benzodiazepines and propofol
- To achieve therapeutic sedation, a loading dose of $80 \text{ (mg/L)} * V_d 0.5 \text{ (L/kg)} * 80 \text{ (kg)} = 3200 \text{ mg}$ of IV Valproic Acid is given over one hour



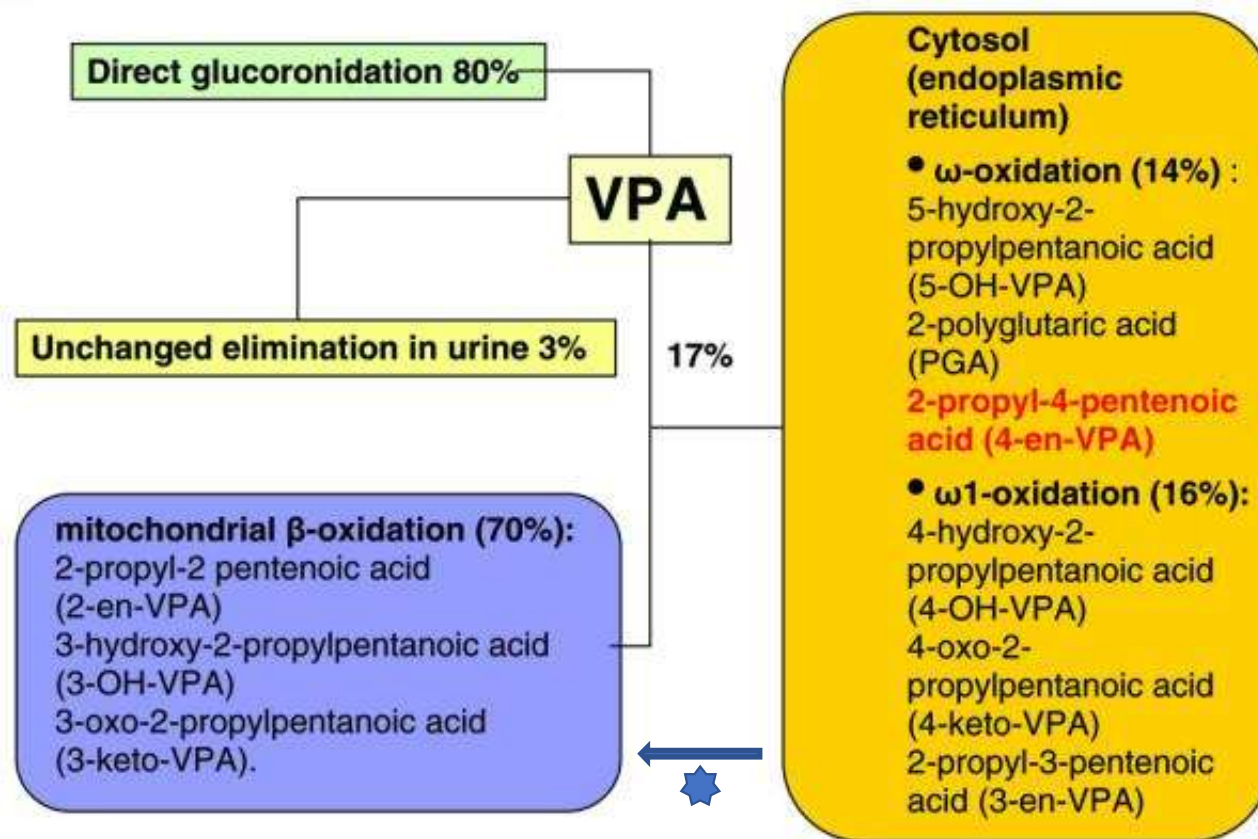
Course

- VPA 500 mg IV q8h given to follow the load
- Agitation decreased 36 hours after the initiation of VPA
- [VPA] checked at the 48-hour point after initiation of therapy = 51 mg/L
- In light of clinical improvement, VPA was continued as dosed
- Manifestations of sepsis began to diminish
- Dexmedetomidine was weaned at the 96-hour point, when [VPA] = 89 mg/L
- VPA dose was decreased to 250 mg IV q8h
- Extubation accomplished 132 hours after initiation of VPA, which was halted next day

– How do we make sense of this ? –



VPA Metabolism



CARNITINE



Lheureux PE, et al. Crit Care. 2005 Oct 5;9(5):431-40.
 Anil M, et al. J Child Neurol. 2009 Jan;24(1):80-6.



Valproate Drug Interactions

- Aspirin
 - \uparrow Free VPA, Platelet dysfunction
- Carbamazepine
 - \downarrow [VPA]
- Lamotrigine
 - \uparrow [LTG]
- Topiramate
 - Increased risk of \uparrow NH₃
- Increases levels of other AEDs, as well
- Lorazepam and Diazepam
 - VPA may decrease clearance
- Warfarin
 - VPA may increase unbound fx of warfarin
- Carbapenems may \downarrow [VPA]
- Antivirals may \downarrow [VPA]
- Inducers of hepatic metabolism \downarrow [VPA]
 - Glucuronyl-transferases not CYPs

– The upshot is need for frequent monitoring, especially in outpatient settings –



System-Specific Considerations

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Psychotropics In Liver Disease - 1

- Liver damage and liver dysfunction are NOT equivalent
 - “LFTs” are actually liver damage tests
 - Bilirubin, prothrombin time, and measures of protein, ketone, and acid/base status = function
 - All ADs & All APs require Phase 1 metabolism which is compromised in failing liver
- Acute hepatitis: no dose adjustment needed
- Chronic hepatitis: depends on severity of liver dysfunction
- Cirrhosis: decrease initial doses and titrate more slowly
- Hepatic encephalopathy:
 - Benzodiazepines worsen the condition; flumazenil may actually provide transient benefit *
 - TCAs worsen the condition via central AND peripheral anticholinergia (intestinal stasis)



Psychotropics In Liver Disease - 2

- Most Benzodiazepines require intact Phase 1 systems (those below do not):
 - Oxazepam
 - Temazepam *“Outside The Liver (OTL)”*
 - Lorazepam
- Most Mood Stabilizers require intact Phase 1 systems
 - **All AEDs except gabapentin and pregabalin**
 - Carbamazepine and valproic acid have potential to CAUSE hepatotoxicity, so chronic use in those with established liver disease must be done with caution and monitoring
- Even renally excreted agents (e.g. lithium) can be difficult to safely manage in severe liver disease
 - Ascites, diuretics, hyponatremia, and diarrhea



Psychotropics And The Gastrointestinal System

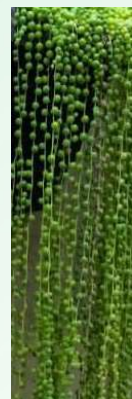
- Conditions involving delayed gastric emptying
 - Diabetic gastroparesis, iatrogenic surgical causes
 - Avoid anticholinergic drugs
- Constipation
 - IBS-C, et al.
 - Avoid anticholinergic drugs
- Diarrhea
 - IBS-D, et al.
 - Serotonergics and lithium may exacerbate
- Malabsorption states
 - Chronic pancreatitis, Inflammatory bowel disease, s/p gastric bypass



Irritable Bowel Syndrome And Antidepressants

- Depression and anxiety are highly comorbid with IBS
- Multiple meta-analyses indicate that ADs are beneficial for IBS symptoms *
 - SSRIs and TCAs have the supporting data, not newer SNRIs
 - Beneficial effects on comorbid psychiatric symptoms are not as clearly demonstrated
 - Insufficient study of IBS subtypes (IBS-D, IBS-C, and mixed)
- Current best practice: IBS-D = Rx TCA. IBS-C = Rx SSRI.

* Ruepert et al 2011 Cochrane Database Syst Rev. 2011 Aug 10;(8):CD003460.
Rahimi R et al. World J Gastroenterol. 2009 ;15:1548-53.
Trinkley & Nahata. J Clin Pharm Ther. 2011;36:275-82.
Enck et al Eur J Gastroenterol Hepatol. 2010;22:1402-11.
Remes-Troche et al. Rev Gastroenterol Mex. 2010;75:42-66.
Chao & Zhang. Intern Med. 2013;52:419
Kulak-Bedja et al Pharmacol Rep. 2017;69:1366-1379
Ford et al. Am J Gastroenterol. 2019;114:21-39





Psychotropics And Malabsorption / Gastric Bypass

- Malabsorption and procedures that cause it (e.g. gastric bypass, bowel resection) decrease the surface area where most drug absorption occurs
- Gastric bypass reduces exposure to gastric acid
- Most (not all) bypass patients on SSRIs / SNRIs have decreased absorption *
- **Use IR forms, crushed tablets and liquids, avoiding enteric-coated or ER forms**
- Lithium toxicity is common after bypass when patients stay on presurgical doses #
 - Changes in fluid status and tissue distribution (effective Vd) due to weight loss
- Significant weight loss usually necessitates decrease in previously therapeutic drug doses (and psychiatric status itself often changes after surgery)
 - **Watch for emergent substance abuse that could impact safe prescribing (EtOH, cannabis)**

* Ther Drug Monit.2015;37:408-12; Am J Psychiatry 2012;169:256-63;
Surg Obes Relat Dis.2012;8:62-6; J Clin Psychopharmacol. 2013;33:479.

J Clin Psychopharmacol. 2011;31:261-2; BMJ Case
Rep.2016 Mar 18;2016; Psychosomatics.2018;59:206.





Renal Disease

- Most psychotropics carry an indication for some dose adjustment according to creatinine clearance for renal patients
- As previously mentioned, even when most may be hepatically altered before elimination, the small fraction of active drug excreted unchanged can be relevant in the setting of severe renal dysfunction
- Renal insufficiency also affects liver function over time, adding another factor to the need for frequent monitoring and adjustments

Hepatic, GI, and Renal Disease all constitute reasons for frequent therapeutic drug monitoring – perhaps even for agents not typically followed using blood tests

Dose Adjustments Recommended In Renal Impairment

Antidepressants

- Venlafaxine
 - Levomilnacipran
 - Mirtazapine
- Desvenlafaxine
Bupropion
- Duloxetine
Paroxetine

Antipsychotics

- Risperidone
 - Paliperidone
- Ziprasidone (IM)
Brexpiprazole
- Lurasidone

Mood Stabilizers and AEDs

- Lamotrigine
 - Oxcarbazepine
- Topiramate
Gabapentin
- Pregabalin
Lithium

Other

- Buspirone
 - Lorazepam
- Galantamine
Memantine



Psychotropics In Renal Impairment

In patients with CKD 2 or greater but not on HD, the two-thirds rule generally holds

Lithium comes with a risk to kidney function over time, but its efficacy for bipolar disorder is unmatched

- Rec to use lowest effective dose, perhaps consolidating once-daily -- but studies are not consistent
- Amiloride (5 - 10 mg daily) could be reno-protective
- Lithium can be given in HD patients, typically a single dose of 300 – 600 mg once after each HD run

Other Psychotropics and Hemodialysis:

- Mirtazapine and amitriptyline levels decrease significantly after HD runs (clinical relevance?)
- The steady states for fluoxetine and its metabolite norfluoxetine after 8 weeks of treatment were comparable in HD patients and controls
- Increased concentrations of conjugated form of tricyclic antidepressants were found in HD patients, while the elimination half life was longer in HD patients than in controls



Psychotropics And The Lung

- **Evidence of Safety and Some Efficacy for Comorbid Psychiatric Conditions:**
- Antidepressants: Citalopram, Sertraline, Paroxetine, Nortriptyline, and Desipramine
- Anxiolytics: Buspirone
- Stimulants: Modafinil, Atomoxetine
- Non-benzodiazepine sedatives: Zolpidem, Zopiclone
- Melatonin and Ramelteon

- Benzodiazepines
 - Avoid in CO₂ retainers when possible
 - Avoid in those with Obstructive Sleep Apnea (along with TCAs and Mirtazapine)
 - May be safe and beneficial in those with Asthma and COPD *
 - Comorbid anxiety is common





Cardiovascular Disease And Psychotropics – Safety First

■ TCAs (and Carbamazepine) – safer than we generally think

- Orthostasis, Type 1A antiarrhythmic effects
- Generally safe in selected patients with stable heart disease, lacking major rhythm problems
- Contraindicated after MI (associated with increased mortality)

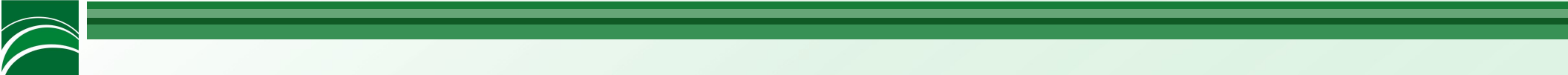
■ Stimulants – generally safe

- Still there is a Black Boxed Warning; PDR says contraindicated in structural heart disease (?)
- No ↑ CV risk in minors. (N Engl J Med 2011; 365:1896)
- No ↑ CV risk in adults. (Am J Psychiatry 2012; 169:178) -- small ↑ in VT, but inverse dose relationship.

■ Antipsychotics – chronic metabolic risk is likely the most important

- Hypotension: avoid low-potency agents and clozapine (due to α 1-adrenergic blockade)
- All antipsychotics may ↑ QTc (Read Beach SR, et al. Psychosomatics. 2018 Mar-Apr;59(2):105-122.)
- Screen for already ↑ QTc, other QTc prolonging drugs, personal or family Hx of unexplained syncope, sudden death. Control the controllable variables. Remember the hospital is the best place for TdP!





Cardiovascular Disease And Common Antidepressants

- **Sertraline** - good safety record for patients with CAD (SADHART, ENRICHD trials)
 - Glassman AH et al : Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288(6):701-709.
- **Mirtazapine** (MIND-IT trial) - no cardiac side effects; sedating
 - Van den Brink RH et al: Treatment of depression after myocardial infarction and the effects on prognosis and quality of life –rationale of the Myocardial Infarction and Depression Intervention Trial (MIND-IT) *Am Heart J*. 2002 Aug;144(2):219-25.
- **Citalopram** (CREATE trial) - was initially reported as safe and efficient for patients with CAD up to 40mg; subsequently was found to potentially increase QTc in doses > 60mg
 - Lespérance F, et al: Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease; *JAMA*. 2007 Jan 24;297(4):367-79.
- **Escitalopram** (DECARD trial) - considered safe
 - Hanash et al: Cardiovascular safety of one-year escitalopram therapy in clinically nondepressed patients with acute coronary syndrome: results from the Depression in patients with Coronary Artery Disease (DECARD) trial. *J. Cardiovasc Pharmacol*. 2012 Oct;60(4):397-405.
- **Venlafaxine, Duloxetine, and Bupropion** – monitor for emergent hypertension
- **Trazodone** – orthostasis can be problematic in those without good pump function
- **Buspirone** – safe record



Specific Populations

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Neurology: Traumatic Brain Injury

- Many TBI patients will have had pre-existing mental illness including but not limited to ADHD, mood disorders, psychotic illnesses, and addictions
- The “neurochemical rules” may be altered by their injuries
- Sensitivity to movement side effects from dopamine antagonists and serotonergics

- Cognitive rehabilitation/enhancement
 - Psychostimulants, dopamine enhancers
 - Other agents: SSRIs, milnacipran, propranolol, mood stabilizers (especially VPA), antipsychotics (atypicals when possible), memantine, cholinesterase inhibitors



Neurology: Stroke

- A form of TBI...
- Depression is a common sequel of CVA, and SSRIs are commonly given *
 - Data are somewhat mixed, leading to differences in practice with some advocating prophylactic Rx after ischemic stroke in the cortex
 - Some data for improved neurologic recovery in those given SSRIs, as well
- Abulia / Apathy accompany some strokes
 - Psychostimulants have a role, as may bupropion
- In the immediate wake of a stroke, drugs that cause (orthostatic) hypotension should be avoided
 - trazodone, mirtazapine, quetiapine and other APs, alpha-2 agonists
 - **Prudent to avoid starting an SSRI in the wake of hemorrhagic stroke**





Neurology: Other Pearls

- Pseudobulbar affect may be managed with SSRIs (sertraline, citalopram)
 - DXM/Quinidine is FDA approved but an expense (DXM alone could be given QID)
- Migraine patients can safely take SSRIs and triptans
- Depression in Parkinson Disease may respond to pramipexole
 - Watch out for emergent impulsivity / pathological gambling
- Psychosis in Parkinson Disease is difficult to manage
 - Balancing regional effects of both D2 blockade and agonism
 - Clozapine has data, but a heavy side effect burden
 - Quetiapine may be first choice, other atypicals can be used carefully
 - Pimavanserin is approved, but currently a fortune
 - Don't forget that ECT is the only intervention that might improve both issues



Patients Taking SSRIs – Bleeding ?

- Cerebral
- Gastrointestinal
- Postpartum
- Perioperative



SSRIs And GI Bleeding: The Data Are Mixed

- Studies show risk from no ↑ risk to large ↑ relative risk (~ 2x)
- Meta-analyses: risk increased about 36% (from 12% to 64%)
- Risk is even higher, ~4X if also taking NSAIDs or anti-platelet drugs
- Much higher if patient taking multiple anti-platelet drugs
 - SSRI + NSAID + clopidogrel



SSRIs And GI Bleeding

- The absolute risk is small.
 - Number needed to harm for upper GI bleeding with SSRIs in low-risk patients was 3,177, and 881 in a high-risk patients.
- Usually not clinically significant
- No increased mortality from SSRI-associated GI bleeds.
- **Caution is warranted in high-risk patients: Thrombocytopenia, platelet disorders, coagulopathy, multiple antiplatelet drugs**
 - Older age and comorbid NSAID use bring in morbidity / mortality risk



Bleeding Risk With SSRIs + Anticoagulants ?

- SSRIs plus warfarin
 - Reports are mixed
 - U.S. FDA does not warn of this interaction
- No increased risk with enoxaparin
- No reports of additional bleeding when SSRIs are co-administered with dabigatran, rivaroxaban, or apixaban



SSRIs And Other Bleeding Risks

- Stroke: Studies are mixed whether ↑risk
 - **Depression & anxiety are associated with increased risk for hypertension and stroke**
 - SSRIs are not contraindicated in thrombotic stroke including those receiving thrombolysis
 - As above, prudent not to start an SSRI soon after a hemorrhagic stroke
- Postpartum: least studied
 - **Do not stop SSRIs just before delivery (postpartum depression risk is significant)**
 - Caution warranted only in those at high bleeding risk
- Perioperative: half of studies show no ↑risk, half show some ↑risk.
 - Small ↑relative risk, small absolute risk, unlikely clinically significant except in high-risk patients – though when elective, many variables can be controlled
 - **Recommendation – Do not routinely stop SSRIs before surgery**



Continue Or Halt Psychiatric Medications Prior To Elective Surgery

- Risks of continuing psychiatric drugs in the perioperative period:
 - Adverse interactions with anesthetics, analgesics
 - Interference with hemodynamic management (e.g. causing hypotension or hypertension)
 - Postoperative complications (e.g. excessive sedation, ileus, contribution to delirium)
- Risks of stopping drugs prior to surgery:
 - Loss of therapeutic effect
 - Rebound exacerbation of the mental disorder
 - Withdrawal syndromes (e.g. benzodiazepines, serotonergics, etc.)
- Which risks are greater? – Evidence is scant, and RCTs unlikely

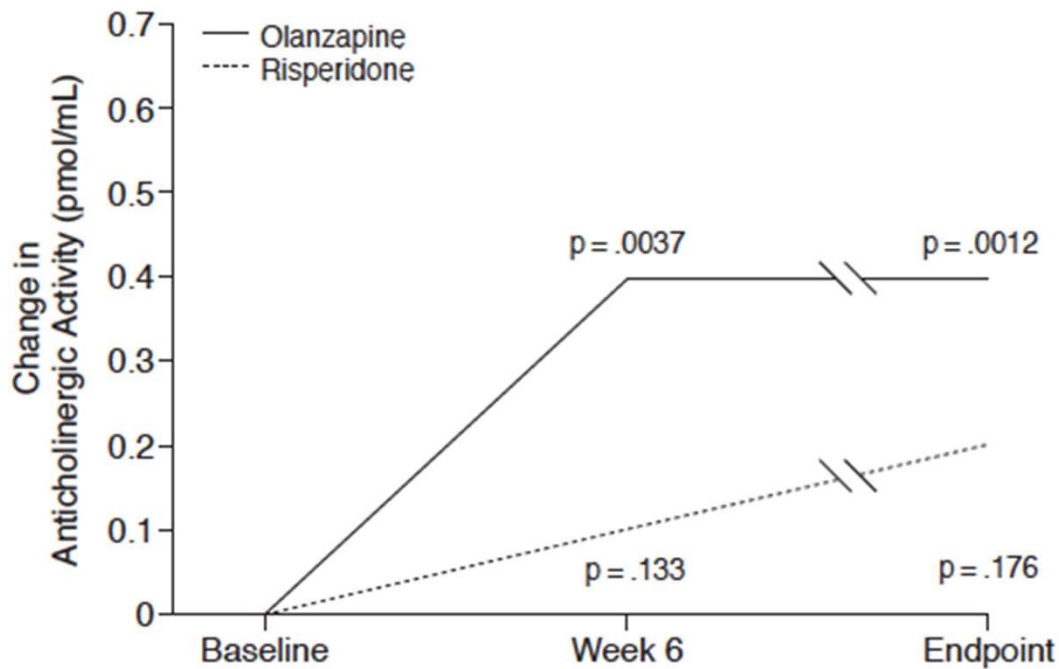


Perioperative Psychiatric Drugs: Guiding Principles

- Risks of discontinuation may exceed the risks of continuing most psychotropic drugs
 - SSRIs may be an exception in patients at very high risk for perioperative bleeding
 - Planning ahead regarding the use of other serotonergics in and after the OR is advised
 - Significant doses of anticholinergics (TCAs, Atypical APs) could be decreased to try to avoid delirium as well as ileus and urinary retention
- 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, nonspecific cholinesterase inhibitors should be stopped prior to surgery
 - Remember that there are more drugs than the ones we prescribe, and they will necessarily be halted around the operative period. Frank discussions with patients about substance use can head off serious discomfort. –

Vulnerable Brains Should Be Spared This Burden

Figure 1. Change in Anticholinergic Activity From Baseline for Dementia Patients Treated With Risperidone Versus Olanzapine^a

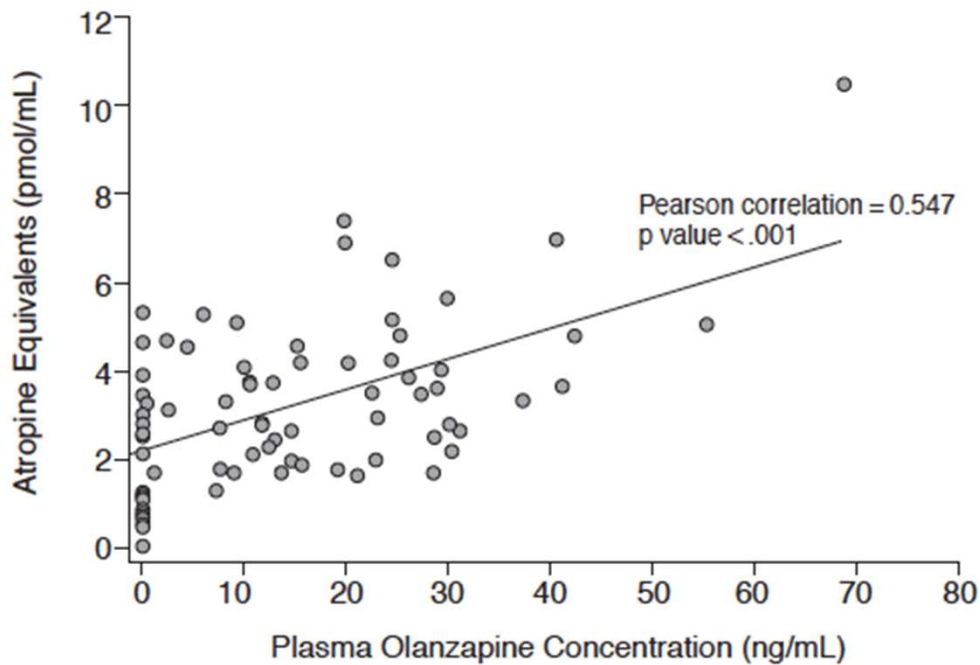


- Dementia patients w/ psychosis
- Treated w/ efficacious doses of AP
 - RSP vs. OLZ
- Serum tested for anticholinergia
 - OLZ > RSP
 - Greater activity associated with more delusions, anxiety, motor unrest
- Cognition tested with Trails A
 - Anticholinergia → impairment

Dose (Concentration) Effect

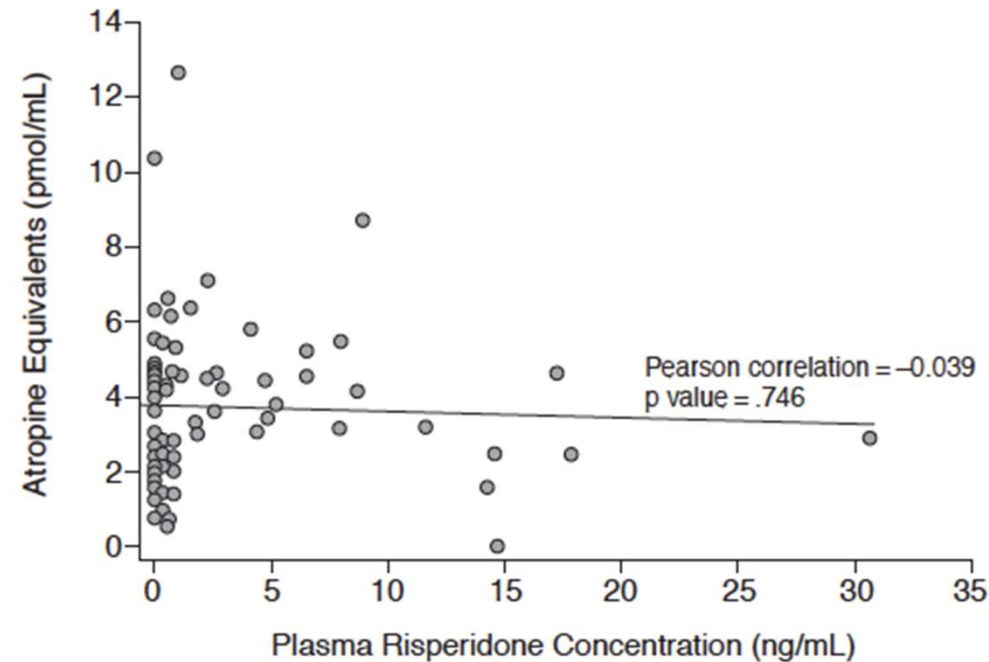
Figure 2. Correlations of Anticholinergic Activity and Medication Dose

A. Olanzapine-Treated Patients



Mulsant, et al. J Clin Psychiatry 2004; 65:1708-14

B. Risperidone-Treated Patients





Food For Thought

- Anticholinergic burden in patients at risk for delirium correlates with CNS impairments
- Anticholinergia is major player in the pathophysiology of delirium
- Might we take the opportunity of the acute medical situation (with its risks and its corresponding advantage of closer monitoring) to at least temporarily relieve burden of such medications ?
 - We can always reintroduce them quickly if psychiatric symptoms flare

More pointedly:

Why would we routinely choose agents with anticholinergic activity (QTP, OLZ) in the management of delirious patients when alternatives (RSP, HLD) are available ?



Psychotropic Medications In Organ Transplantation

- Psychiatric symptoms are common in transplant patients
- Immunosuppressants and other requirements of the transplantation process directly cause a host of neuropsychiatric problems
- Psychotropic medications, in turn, have side effects that are potentially relevant to organ recipients:
 - Direct organ toxicity (valproic acid, disulfiram, lithium)
 - Leukopenia (AEDs, APs, mirtazapine)
 - Metabolic acidosis (topiramate)
 - Hyperprolactinemia (APs) – may increase the post-transplant immune response
 - Drug-drug interactions (that impact immunosuppressant levels and vice versa)



Immunosuppressant → Psychotropic Interactions

- Cyclosporine
 - P-glycoprotein inhibition
 - Carbamazepine, lamotrigine, phenytoin
 - Paroxetine, venlafaxine
 - Olanzapine, quetiapine, risperidone
 - CYP 3A4 inhibition
 - Quetiapine, ziprasidone, iloperidone
 - Fentanyl, meperidine, tramadol
 - Some benzodiazepines (e.g. alprazolam, clonazepam)
- Tacrolimus – inhibits 3A4 (see above)
- Corticosteroids – induce 3A4
 - Decreased levels of substances listed above





Psychotropic → Immunosuppressant Interactions

- 3A4 inhibitors (fluvoxamine, nefazodone)
 - Increase levels of cyclosporine, tacrolimus, sirolimus, corticosteroids → toxicity
- 3A4 inducers (carbamazepine, modafinil, St. John's Wort)
 - Decrease levels of cyclosporine, tacrolimus, sirolimus, corticosteroids → graft rejection
- RECOMMENDATIONS
 - Work in conjunction with transplant teams around prescribing
 - Assay drug levels frequently
 - Monitor closely for effects and side effects



Creative Medication Use and Delivery

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Non-Psychiatric Use Of Psychotropic Medications

- Doxepin for pruritus *
- SSRIs for pruritus – Sertraline #
- Appetite stimulation (in oncology patients)
 - Mirtazapine ^
 - Olanzapine ^^
- Hot flashes
 - In breast cancer: Mirtazapine, Venlafaxine (1)
 - In menopause: Escitalopram, Venlafaxine (2)

* Groene D, et al. Exp Dermatol 2001;10:110–7

Mayo MJ, et al. Hepatology 2007; 45(3):666-74

^ Riechelmann RP, et al. American Journal of Hospice & Palliative Medicine 2010; 27(2):106-10

^^ Naing A, et al. Supp Care Cancer. 2015; 23:2649-2654. Hocking & Kichenadasse. Supp Care Cancer. 2014;22(4):1143-51

(1) Biglia N. et al. Breast Journal 2007;13(5):490-5. Ramaswami R et al. Breast Cancer Res Treat 2015;152(2):231-7

(2) Dobkin R, et al. Annals of Clinical Psychiatry 2009;21(2), 70-6






Psychotropic Medications For Pain

- TCAs, Duloxetine, Milnacipran, Venlafaxine (?)
 - diabetic neuropathy, fibromyalgia, chronic musculoskeletal pain... thinking ahead after trauma
- Expecting a neuropathic component
 - **Carbamazepine**: Na⁺ channel antagonism, 5-HT and NE effects *
 - IL-6 & IL-10 modulation may benefit addicted patients
 - Promising animal model work
 - **Gabapentin**: Ca⁺⁺ modulation, GABA trafficking #
 - Post spinal, craniotomy, knee arthroplasty, prevent phantom limb, fractures (? If dose higher)
 - Added benefit in those with EtOH, THC problems
- Valproic Acid in cephalgia (not in trauma / surgical pain)
- A role for **Atypical Antipsychotics** ? ^

* Salimi A, et al. Eur J Pharmacol 2017;812:184-188. Wiffen PJ, et al. Cochrane Database Syst Rev. 2011; 19;(1):CD005451.
Wiffen P, et al. Cochrane Database Syst Rev 2005;(3):CD001133. Peng C, et al. Medicine (Baltimore) 2017;96(15):e6463.
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^ Fishbain DA, et al. Pain Med 2004;5(4):359-65





Pain, Palliative Care, And Ketamine

- Ketamine is already used by other specialists for pain
- Ketamine has a role in resistant depression
 - Some depression is “resistant” due to the nature of the stressors (e.g. somatic disease) and the timetable available for our standard treatments to work
- Ketamine has abuse / addictive potential
 - C-L Psychiatrists can be key advocates in opening conversations about the balance of risks and benefits in patients with severe, life-shortening conditions
- IV ketamine regimens for pain management may be modified for mood
 - “Two birds with one stone” treatment
 - **Oral F is low and somewhat variable, but data exist for efficacy in depression ***
 - Intranasal delivery is now an option (esketamine)



Psychotropic Delivery When PO Is Not An Option

- First remember that lack of oral intake does not always mean the gut cannot be used
 - Dysphagia for pills may make dissolving tabs or liquids viable
 - Liquid ADs: Doxepin, Escitalopram, Fluoxetine, Imipramine, Nortriptyline, Paroxetine, Sertraline
 - Dissolving ADs: Mirtazapine, Selegiline
 - Liquid APs: Aripiprazole, Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Mesoridazine, Molindone, Risperidone, Thioridazine, Trifluoperazine
 - Dissolving APs: Olanzapine, Risperidone (Clozapine no longer manufactured as of 2019)
 - Liquid BZDs: Alprazolam, Diazepam, Lorazepam, Midazolam
 - Dissolving BZDs: Alprazolam, Clonazepam
 - Liquid AEDs: Carbamazepine, Gabapentin, Levetiracetam, Oxcarbazepine, Valproic Acid
 - Other Liquids: Amphetamine, Galantamine, Lithium, Memantine, Methylphenidate (IR and ER), Naltrexone, Rivastigmine
 - Coordinate with Speech Pathology regarding safe options
 - Utilize Feeding Tubes, G Tubes, and J Tubes creatively – **N.B. some solids will obstruct them**



Sometimes It Is truly NPO

- Post-operative ileus
- Stomatitis, e.g. due to chemotherapy
- Severe nausea and vomiting (hyperemesis gravidarum, chemotherapy)
- Severe Dysphagia
- Malabsorption syndromes
- Short-bowel syndrome
- Prolonged imposed bowel rest



Alternate Routes of Administration

- Intravenous (IV) / Intramuscular (IM):
 - 100% bioavailability with IV, and nearly that with IM
 - **many agents can be given subcutaneously (SQ) – consult with a pharmacist regarding safety**
- Sublingual (SL) / Buccal:
 - fewer GI side effects; rapid absorption and good bioavailability for small lipid-soluble drugs
 - **essentially any compound that does not cause direct tissue damage can be attempted (taste ?)**
- Rectal (PR):
 - incomplete and erratic absorption but 50% less first-pass metabolism
- Transdermal (TD):
 - involve less patient involvement / compliance behavior
 - steady, continuous levels (but take time to reach therapeutic onset)
- Inhalable / Intranasal (IN):
 - limited number of preparations, but perhaps the best alternatives for rapid delivery



Alternate Formulations – Antidepressants

- Parenteral: none for use in U.S.
 - Citalopram and others in Europe
- Rectal suppositories
 - TCAs, trazodone
- Transdermal
 - Selegiline
- Buccal (using oral disintegrating tablets):
 - Selegiline (not studied in depression and degree of absorption unclear)
 - Mirtazapine (degree of absorption not known)
- Sublingual
 - Fluoxetine solution has been used
 - Theoretically, other high-concentration liquids and ODTs can be employed in this manner





Alternate Formulations – Sedatives

- IV: Lorazepam, Midazolam, Diazepam, Phenobarbital
 - flunitrazepam, clonazepam in Europe / Japan
- IM: Lorazepam, Midazolam, Phenobarbital
 - Avoid IM Diazepam (absorption kinetics are unreliable)
- Sublingual
 - Lorazepam in Canada (IV liquid can be used the same way in the U.S.)
 - Many BZDs, including Lorazepam, may be given SL as tablets
 - Zolpidem
- Intranasal: Lorazepam, Midazolam
- Rectal: Phenobarbital, Diazepam gel, other BZDs in liquid solution can be used
- Intrathecal: Lorazepam, Midazolam

Alternate Routes of Administration: Sedatives

Sedative	IV	IM	SL	R	TD	IN
Alprazolam			(orally disintegrating only)			
Clonazepam			(orally disintegrating only)			
Diazepam	Y	Y		Y		
Flunitrazepam	O					
Lorazepam	Y	Y				Y
Midazolam	Y	Y				Y
Temazepam			O			
Triazolam			(↑ F compared to PO using tablet)			
Phenobarbital	Y	Y		Y		
Zolpidem			Y			

IV=intravenous IM=intramuscular SL=sublingual / buccal R=rectal TD=transdermal IN=intranasal
 Y=available N=not available O=outside the US only



Alternate Formulations – Antipsychotics

- IV: Haloperidol, Chlorpromazine
 - Droperidol withdrawn in UK; black-boxed warning in North America
 - Olanzapine not FDA approved, but being used more widely (the IM preparation)
- IM:
 - Haloperidol, Chlorpromazine, Fluphenazine, Prochlorperazine
 - Ziprasidone, Olanzapine, Aripiprazole
- Sublingual: Asenapine
 - Olanzapine and risperidone oral disintegrating tablets can deliver a fraction of drug this way
- Subcutaneous: Haloperidol, fluphenazine
 - Methotrimeprazine in Canada / Europe
- Inhaled: Loxapine
- Transdermal: Asenapine

Alternate Routes of Administration: Antipsychotics

Antipsychotic	IV	IM	SL	R	TD	IN
Droperidol	Y	Y				
Haloperidol	Y	Y (and SQ)				
Chlorpromazine	Y	Y				
Fluphenazine		Y (and SQ)				
Loxapine						Y
Prochlorperazine	Y	Y				
Olanzapine		Y	(Orally disintegrating only)			
Risperidone			(Orally disintegrating only)			
Ziprasidone		Y				
Asenapine			Y		Y	
Aripiprazole		Y				

IV=intravenous IM=intramuscular SL=sublingual / buccal R=rectal TD=transdermal IN=inhaled
 Y=available N=not available O=outside the US only



Additional Alternate Formulations

- Mood stabilizers
 - IV: Valproic acid, carbamazepine
 - Rectal: Carbamazepine, lamotrigine, topiramate
- Stimulants
 - Transdermal: Methylphenidate
- Cholinesterase inhibitors
 - Transdermal: Rivastigmine



Alternate Routes of Administration

Mood stabilizer	IV	IM	SL	R	TD	IN
Carbamazepine	Y			Y		
Lamotrigine			(orally disintegrating only)	Y		
Topiramate				Y		
Valproic acid	Y					
Lithium						
Stimulant	IV	IM	SL	R	TD	IN
Methylphenidate					Y	
Methamphetamine						
Mixed Amphetamine Salts						
Cholinesterase Inhibitor	IV	IM	SL	R	TD	IN
Donepezil						
Rivastigmine					Y	
Galantamine						



Suggested readings and references

- Clinical Manual of Psychopharmacology in the Medically Ill edited by James L. Levenson and Stephen J. Ferrando, 2nd edition, APA publishing, 2016
 - **Recommendation comes with a major acknowledgement to Dr. Levenson for help with this talk**
- The APA Publishing Textbook of Psychosomatic Medicine and Consultation Liaison Psychiatry, edited by James L. Levenson, 3rd edition, APA publishing, 2018
- MGH Handbook of General Hospital Psychiatry, edited by Theodore A. Stern, Oliver Freudenreich, Felicia A Smith, Gregory L. Fricchione, and Jerrold F. Rosenbaum. 7th edition, Elsevier, 2018.
- Micromedex, etc. – starting point from which to apply parameters to specific patients