Mixing and Matching: Layering Psychopharmacology

Dr. Jon Davine

VANCOUVER CONVENTION CENTRE

THE COLLEGE OF FAMILY PHYSICIANS OF CANADA

LE COLLÈGE DES MÉDECINS DE FAMILLE DU CANADA

Presenter Disclosure

Presenter: Dr. Jon Davine MD, FCFP, FRCP©

Relationships with financial sponsors:

- **Any direct financial relationships, including receipt of honoraria:** Trillium Health Partners, William Osler Health System, Peterborough FHT, Pri-Med Canada/Humber R. Hosp., McMaster U. CE, KW Family Medicine, Ont. Coll. Of Family Phys., Touchstone Institute, CME Away by Sea Courses

- **Membership on advisory boards or speakers' bureaus:** No

- **Patents for drugs or devices:** No

- **Other:** CAMH, Co-Editor of book, "Psychiatry in Primary Care"

Disclosure of Financial Support

This program has not received financial support

This program has not received in-kind support

Potential for conflict(s) of interest:

Dr. Jon Davine has not received payment/funding for this program

Objectives

- Discuss different examples of combining psychiatric drugs that may be pertinent to the primary care situation

DEPRESSION AUGMENTATION

Depression Augmentation

- Partial Response of Depression, ONLY.

- Augment after “optimizing” original antidepressant
- This may involve going over the usual maximum
- Involves the highest dose without side effects

Depression Augmentation/Optimizing Initial

- First optimize the Initial antidepressant
- E.g. –Start sertraline 50 mg. po od.
- Increase by 50 mg. increments q2-3 weekly depending on response

OPTIMIZE

- As long as someone is improving, don’t change the dose. Once they have reached a plateau, increase by same increment
- If no improvement is occurring, after initial dose and one bump, do not increase further. This is a flat dose response curve
- Proceed to X-Crossover

OPTIMIZING

- Except Venlafaxine which has linear dose response curve
- Must go 75-150-225 q3weekly, even if nothing happening .
- Possible Noradrenaline response

X-CROSSOVER

- Lower initial drug by usual increment q7days
- e.g. Sertraline 100 to 50 to d/c
- Start second antidepressant at half usual starting dose along with initial dose level of first drug, e.g. venlafaxine 37.5 mg. po od
- When you stop the first drug, increase the second drug to its usual starting level (e.g. Venlafaxine 75 mg. po od) and then proceed as usual

Optimizing

- If you do get a partial response, increase up to the usual max, or the maximum tolerated dose
- Defined as 25% improvement
- In fact can go one or two increments above the usual range as long as no side effects (except citalopram and escitalopram)
- If still not back to near normal, this is when we augment with a second drug
- We do not augment meds that do not produce at least a partial response

Augmentation – CANMAT 2023

- **First-Line Options:**
  - Aripiprazole – Level 1 2-10 mg.
  - Brexiprazole—Level 1 0.5-2.0 mg.

- **Second-line:**
  - Buproprion 150-450 mg.
  - Intranasal esketamine 56-84 mg. intranasally
  - IV racemic ketamine 0.5-1.0 mg./kg. IV
  - Olanzapine 2.5-10 mg.
  - Quetiapine XR 150-300 mg.
  - Risperidone 1-3 mg.
  - Lithium 600-1200 mg. (0.5-0.8mmol/L)
  - .

Augmentation – CANMAT 2023. Less Evidence

Cariprazine	1.5-3 mg.
Mirtazapine	30-60 mg.
Modafinil	100-400 mg
Triiodothyronine	25-50 mcg.

Augmentation Strategies – Atypicals

- Options
  - FIRST LINE:
  - Aripiprazole (Abilify) 2-4-6- up to 15 mg. po hs
  - Brexiprazole (Rexulti) 0.5--1--1.5—2mg. po qhs
  - SECOND LINE:
  - Quetiapine (Seroquel) 50-100-150 mg po daily (150-300 mg.)
  - Wait 2-3 weeks between raises

Combination Strategies

- Second-line
- Wellbutrin XL (bupropron)
  - 150-300 mg po QAM
- Mirtazapine (less evidence)
  - 30-60 mg po QHS

Which Antidepressants?

- CANMAT studies

- Cipriani studies (2009, 2018)

CANMAT 2023---- First Line

Escitalopram, Sertraline, Paroxetine, Citalopram, Fluoxetine, Fluvoxamine (SSRI'S)

Venlafaxine and Desvenlafaxine

Duloxetine. (NSRI'S)

Buproprion (DNRI)

Mirtazapine. (NaSSa)

Vortioxetine (like an SSRI)

Levomilnacipran (SPARI), SSRI plus partial S. agonist)

Vilazodone (SARI), SNRI plus partial S. antagonist)

CANMAT 2023---Superior Efficacy (5-15% better)

Escitalopram

Sertraline

Venlafaxine XR

Mirtazapine

Paroxetine

Buproprion

Vortioxetine

Cipriani *et al.*, *Lancet*. 373:764-758, 2009

- Escitalopram and sertraline showed important differences with respect to efficacy and acceptability
- Sertraline also has better cost factor

Cipriani et al, February 21, 2018.

- 21 antidepressants

- 522 double blind trial
- 116,477 participants
- Efficacy at 8 week
- Acceptability—dropouts at 8 weeks
- 18 and over
- Both genders

Cipriani, 2018

- All antidepressants more effective than placebo (OR 1.37 (Reboxitene)---2.13 (Amitryptyline)

- Head to Head:
- 7 showed greater efficacy:

- Agomelatine, Amitryptyline,Escitalopram,Mirtazapine,Paroxitene, Venlafaxine,Vortioxetine

Cipriani, 2018

- Head to Head:
- More tolerable:

- Agomelatine, Citalopram, Escitalopram,Fluoxetine,Sertraline,Vortioxetine

Overall Studies

- Higher response, lower dropout:

- Escitalopram, Mirtazapine, Paroxitene, Agomelatine,Sertraline

SLEEP MEDS

Sleep meds

- Use after sleep hygiene
- NO CAFFEINE
- CBT—Insomnia very effective

Sleep meds

- Can be used in addition to antidepressants or antipsychotics.
- I prefer Trazodone 25-50 mg. po hs.
- Can increase by 25 mg. increments as necessary
- Can go up to 75, 100, or 150 mg./day
- Priapism, 1 in 800

Sleep Meds

- Melatonin 3-6 mg. hs or 5-10 mg. hs
- Recent 2 year study showed no ill effects with regular use

Sleep Meds

- Mirtazapine, 15-30 mg. HS

- Low dose Doxepin 3-6 mg. HS
- Studies show efficacy, reasonable side effects
- Low dose means low side effects

Sleep Meds

- I would then use Zopiclone
- 3.75-7.5 mg. po hs
- Can increase by 3.75 mg. increments. Range is up to 15 or even 22.5 mg. hs
- This pill is addictive, though apparently not as much as the benzodiazepines

Sleep Meds

- Benzos
- I prefer using mid half life (8-14 hours). Not short, not long

- I prefer:

- Lorazepam 1-2 mg. po hs. Mid half life.

- Clonazepam, Diazepam-- long half life. I don’t use
- Triazolam is short half life (not really used)

- These are addictive

OK, WHAT ABOUT SEROQUEL ??

- I recommend against this, unless… ?augmenting

I am very concerned about metabolic risk—diabetes type 2

If using, please make it brief. Be aware of risks

APA recommended against using this for sleep

Choosing Wisely also recommended against

Tricyclics

- Sometimes tricyclics are used for sleeping. Typically Amitryptyline or Nortriptyline.

- I would always use Nortriptyline due to more favourable side effect profile.

- Start at 10 mg. po hs and increase by 10 mg. increments qweekly. Usual range is 20-60 mg. hs

Tricyclics

- Also useful for pain management, both organically based and psychologically amplified

- I would also do an EKG as dosing rises as they are type 1 antiarrhythmics (quinidine effect)

Lancet, open access, July/22. Crescenzo et al.

- Also Includes Andrea Cipriani
- Adults > 18
- 154 RCT's, 44,000 people.
- Eszopiclone and Lemborexant (DORA, dual orexin receptor antagonist)) performed better for acute and long term insomnia
- Eszopiclone-dizziness, nausea
- Lemborexant– safety data inconclusive, headaches

When NOT to Mix

- Be aware of certain P450 Cytochrome problems:
- P450 2D6
- If using Codeine for pain relief. This goes to desmethylcodeine, the active ingredient, through 2D6
- Fluoxetine and Paroxitene block 2D6. Don’t use with codeine

When NOT to Mix

- Amitriptyline and Nortriptyline are metabolized through P450 2D6.
- These can be used for sleep or pain control
- Thus do not use with Fluoxetine or Paroxitene
- Level may rise up to 2-3 times

When NOT to Mix

- Coumadin is metabolized through P450 1A4
- Fluvoxamine blocks 1A4
- Thus don’t use with Coumadin

When NOT to Mix

- Never use a reuptake inhibitor (SSRI, SNRI, DNRI, NaSSA) along with a degradation blocker (MAOI, RIMA)
- Need 2 weeks washout. Six weeks if starting with Fluoxetine.
- Hypertensive Crisis, Serotonergic Syndrome

BIPOLAR DEPRESSION

Bipolar Depression

- So someone is on lithium for bipolar disorder, and they get depressed.

- What do you do??

Bipolar Depression

- If on Lithium, can first increase lithium to a somewhat higher level
- Lithium has Level 1A evidence as an acute antidepressant for bipolar depression
- Can run up to 0.8-0.9 as an acute antidepressant

Lamotrigine

- Can add Lamotrigine to the mood stabilizer. This also has Level 1A evidence as an acute antidepressant for bipolar depression.
- Watch for rash—Stevens-Johnson Syndrome. D/C if happens
- Start at 25 mg. po qhs, and increase by 25 mg. increments q2weekly. Usually run between 100 to 200 mg./day
- Increasing too quickly increases the risk of a rash

Bipolar Depression--Antidepressants

- Interestingly, antidepressants only have Level 1B evidence for bipolar depression
- Important never to use a “naked” antidepressant if someone is bipolar
- NB: In primary care, if someone presents with a unipolar depression, ALWAYS screen for past hypomanic episodes

Atypical Neuroleptics in Bipolar Depression

- Atypical Neuroleptics can be used as **acute** antidepressants in bipolar depression
  - Quetiapine now approved for bipolar depression, 1st line, level 1A (CANMMAT 2018)

Atypicals for Bipolar Depression

- Lurasidone is approved for bipolar depression
- Start at 20 mg. po od. Range is 20-60 mg. po od.
- Efficacy not increased 80-120 mg./day
- Must be taken with food (>350 cal.)
- At this time, appears less metabolic risk
- Level 1A according to CANMAT 2018.

1st Line for Depression (2018 CANMAT)

• Quetiapine	Level 1
• Lurasidone + Li/DVP	Level 1
• Lithium	Level 2
• Lamotrigine	Level 2
• Lamotrigine (adj)	Level 2

2nd line Depression (CANMAT 2018)

- Divalproex Level 2
- SSRI's/Buproprion (adj) Level 1
- ECT Level 3
- Cariprazine Level 1
- Olanzapine-Fluoxetine Level 2

MANIA

Atypical Neuroleptics

- Risperidone, Olanzapine, Quetiapine, Ziprasidone and Aripiprazole are all approved for use as anti manic agents

- Risperidone--1-4 mg/day
- Olanzapine 5-20 mg/day
- Quetiapine 200-800 mg/day
- Aripiprazole 10 -15 mg/day
- Ziprasidone 20-80 mg BID

CANMAT 2018: 1st Line Mania

- Lithium
- Quetiapine
- Divalproex
- Asenapine
- Aripiprazole
- Paliperidone (>6 mg.)
- Risperidone
- Cariprazine

All Level 1

CANMAT (2018)
First line combination, Acute Mania

Quetiapine + Li/DVP	Level 1
Aripiprazole + Li/DVP	Level 2
Risperidone + Li/DVP	Level 1
Asenapine + Li/DVP	Level 2

Bipolar- Mania

- If someone is manic, there are two or three drugs we would use together
- First, start with a mood stabilizer
- Lithium and Epival both have anti manic effects. Lamictal does not
- Usual starting dose is Lithium 300 mg. po bid.
- For Epival, it is 250 mg. po bid

Bipolar--Mania

- Can increase Lithium by 300 mg. increments qweekly until in range
- Do 12 hour trough levels qweekly to see if adjustment needed
- Can do the same for Epival, except start at 250 mg.po bid, and increase by 250 mg. increments

Anti Psychotics In Bipolar Mania

- These are used along with mood stabilizer as both anti-manic and anti-psychotics

- CANMAT recommends: Risperidone, Quetiapine, Olanzapine, Ziprasidone, Aripiprazole

Anti-Psychotics

- We keep using the antipsychotics until approximately two months of stability—psychosis free and mania free
- Then we would wean off the neuroleptics over the next month.
- The goal is just to be on a mood stabilizer once the acute episode has passed

Mania—Benzodiazepines

- Benzos are often used in acute manic episodes
- I would recommend clonazepam as it has a long half life
- Usual dose is 0.5-1.0 mg. po bid to tid
- We wean people off this fairly quickly, usually days to weeks

ANXIETY DISORDERS --GAD

- GAD
- Duloxetine, Escitalopram, paroxetine, sertraline, venlafaxine XR, pregabalin (Katzman 2014 Anxiety Guidelines)

Use benzodiazepines as adjuncts

- For GAD, I favour clonazepam due to longer half life
- Buspar not seen as effective

- 0.25-0.5 mg. are the typical aliquots of clonazepam (0.25 = 5 mg. Diazepam)

Anxiety Disorders--GAD

- Pregabalin is first line for both GAD and Social Anxiety Disorder

- Can augment with this, or use alone if SSRI’s or SNRI a problem

ANXIETY—Panic Disorder

- 1st line:
- Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Venlafaxine XR
- (Katzman 2019 Anxiety Guidelines)

- For panic disorder, I favour lorazepam 0.5-1.0 mg. aliquots prn. Shorter half life.

- This can be effective until the SSRI/SNRI kicks in

- Also very effective in someone's pocket when doing systematic desensitization

ANXIETY--PTSD

- SSRI's and SNRI's are the mainstay
- Fluoxetine, Paroxitene, Sertraline, Venlafaxine XR
- (Katzman 2014 Anxiety Guidelines)

- Benzos used but with caution. High rates of substance abuse
- Neuroleptics can be used as adjunctive. I would leave for psychiatry
- Prazosin has been used for PTSD nightmares. 1 mg., 2 mg., 5 mg. Has Level 1 evidence

ANXIETY --OCD

- SSRI's are the mainstay. SNRI's not level 1 for this disorder
- Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
- Can use clomipramine as adjunctive or primary therapy
- Can add or substitute neuroleptics for resistant cases, though I would leave for psychiary

Depression with Psychotic Features

- Start antidepressant and neuroleptic together.
- Keep them on neuroleptic until 2 months psychosis free
- Keep them on antidepressants for 1 year, 2 years, or forever, depending on which episode this is

Thank you!

Please fill out your session evaluation now!

#myfmf

FamilyMedicineForum

FamilyMedForum

FamilyMedForum