Mixing and Matching: Layering Psychopharmacological Medications as Family Physicians

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Jon Davine, CCFP, FRCP(C)
McMaster University

1

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2

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3

4

5

Objectives

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

6

DEPRESSION AUGMENTATION

7

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

8

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

9

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

10

OPTIMIZING

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

11

X-CROSSOVER

- Lower initial drug by usual increment q5days
- 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

12

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
- 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

13

Augmentation – Adding a different agent CANMAT Guidelines (2016)

- **First-Line Options:**
  - Aripiprazole – Level 1, 2-15 mg.
  - Quetiapine– Level 1 150-300 mg.
  - Risperidone – Level 1, 1-3 mg.

14

Augmentation, 2nd Line Options

- Buproprion-- Level 2 150-300 mg.
- Lithium—Level 2 600-1200 mg.
- Mirtazapine—Level 2 30-60 mg.
- Modafinil—Level 2 100-400 mg.
- Olanzapine—Level 1 2.5-10 mg.
- Triiodothyronine—Level 2 25-50 mcg.

15

Depression Augmentation--Atypicals

- Aripiprazole 2.0—4.0— 6.0 mg./day (can be up to 15)
- Risperidone 1-3 mg. I start at 0.5 mg. and go up by 0.5 mg. increments q2-3 weekly.

16

Augmentation--Quetiapine

- Level 1
- I sometimes use it because it has approval for monotherapy in bipolar 1 and 2 depression, and monotherapy in unipolar depression when no other antidepressants have worked
- Dose is 150-300mg./day. I will often start at 50, and increase by 50 mg. increments q2-3 weekly
- Have to do fasting metabolic q4monthly while on this

17

Depression Augmentation

Buproprion XL 150 mg. po qam x 2-3 weeks, then 300 mg. po qam (Range 150-300 mg./day)'

- I use when more of a psychomotor retarded state, increased sleep, low energy, etc.
- Mirtazapine 15 mg. po qhs x 2-3 weeks, increase by 15 mg. increments (Range 30-60 mg./day)
- I use when more of an agitated state (decreased sleep, anxious, etc.)
- This are referred to as combination/augmentation

18

Augmentation--Cytomel

- Considered second line according to CANMAT guidelines
- Start Cytomel(T3), 25 micrograms po once daily x 2-3 weeks
- Depending on response, can increase to 50 micrograms po once daily
- Literature reports 50% efficacy

19

How Long Augmenting Agents

- 1st episode depression—6-8 months of feeling good. Total of about a year. Leave augmenting
- 2nd episode—18-24 months. Leave augmenting
- 3rd episode—indefinite for antidepressant. I would stop the augmenting agent after 1 year, and just leave on antidepressant

20

Which Antidepressants?

- Would not be faulted for any of the 6 SSRI's, 3 NSRI's,
- DNRI, NaSSa, Vortioxetine

- I favour Sertraline, Escitalopram, Venlafaxine, Mirtazapine

- CANMAT studies

- Cipriani studie (2009, 2018)

21

CANMAT-2016: Drugs with superior efficacy against comparators:

- **Escitalopram** – level 1 evidence
- **Sertraline** – level 1 evidence
- **Venlafaxine** – level 1 evidence
- Mirtazapine– level 1 evidence

- **Agomelatine– level 2 evidence**
- **Citalopram—level 2 evidence**

  - Suggested to use one of these as 2nd antidepressant if 1st drug not effective

22

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

23

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

24

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

25

Cipriani, 2018

- Head to Head studies:
- Four showed less efficacy:
- Fluoxetine, Fluvoxamine,Reboxitene, Trazodone

26

Cipriani, 2018

- Head to Head:
- More tolerable:
- Agomelatine, Citalopram, Escitalopram,Fluoxetine,Sertraline,Vortioxetine

27

Cipriani, 2018

- Head to Head:
- Less tolerable:
- Amitryptyline, Clomipramine,Duloxetine, Fluvoxamine,Reboxitene,Trazodone, Venlafaxine

28

Overall Studies

- Higher response, lower dropout:
- Escitalopram, Mirtazapine, Paroxitene, Agomelatine,Sertraline

29

Overall Studies

- Poorer Efficacy and Higher Dropout:
- Reboxitene, Trazodone, Fluvoxamine

30

SLEEP MEDS

31

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

32

Sleep Meds

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

33

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

34

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

35

Sleep Meds

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

- I prefer:

- Lorazepam 1-2 mg. po hs

- Oxazepam 15-30 mg. po hs

- Clonazepam, Diazepam-- long half life
- Triazolam is short half life (not really used)

- These are addictive

36

OK, WHAT ABOUT SEROQUEL ??

- I recommend against this

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

37

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

38

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)

39

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

40

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

41

When NOT to Mix

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

42

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

43

BIPOLAR DEPRESSION

44

Bipolar Depression

- So someone is on lithium for bipolar disorder, and they get depressed.
- What do you do??

45

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

46

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

47

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

48

Atypical Neuroleptics in Bipolar Depression

- Atypical Neuroleptics can be used as **acute** antidepressants in bipolar depression
  - Quetiapine now approved for bipolar depression (CANMMAT)
  - I use less because of metabolic issues.

49

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

50

1st Line for Depression (2018 CANMAT)

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

51

2nd line Depression (CANMAT 2018)

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

52

MANIA

53

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

54

CANMAT 2018: 1st Line Mania

- Lithium — All Level 1
- Quetiapine
- Divalproex
- Asenapine
- Aripiprazole
- Paliperidone (>6 mg.)
- Risperidone
- Cariprazine

55

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

56

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

57

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

58

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

59

Anti-Psychotics

- We keep using the antipsychotics until approximately two months of stabillity—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

60

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

61

ANXIETY DISORDERS --GAD

- GAD, Panic Disorder, PTSD
- Treatment of choice is SSRI, NSRI (Martin Katzman,August 2014 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)

62

Anxiety Disorders

- 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

63

ANXIETY—Panic Disorder

- 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

64

ANXIETY--PTSD

- SSRI's and SNRI's are the mainstay
- 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

65

ANXIETY --OCD

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

66

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

67

jdavine1@gmail.com

68