Mixing and Matching:
Layering Medications as Family Physicians

Family Medicine Forum

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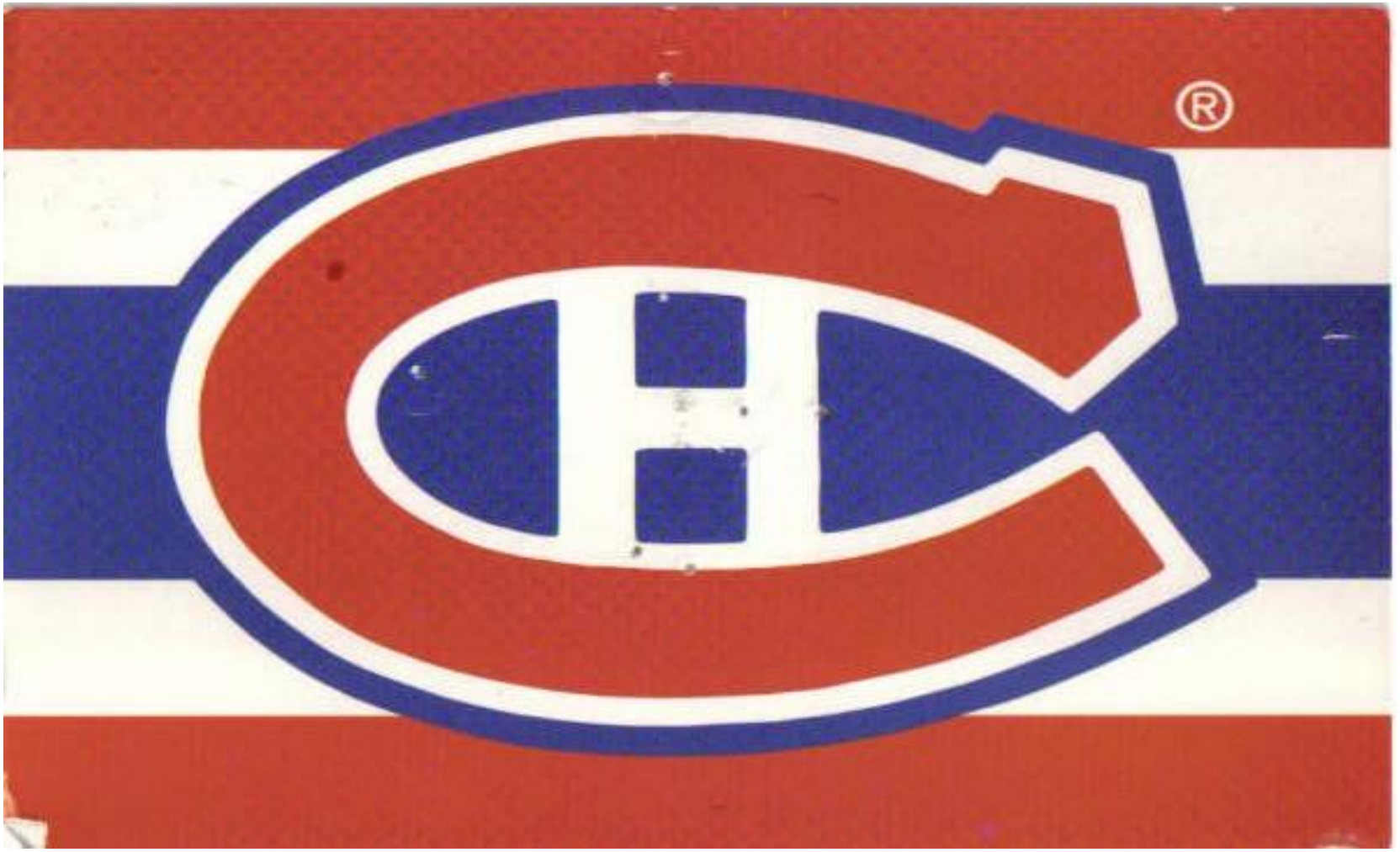
Objectives

- 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 q3-4 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 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

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

Augmentation – Adding a different agent CANMAT Guidelines

- **First-Line Options:**
  - Lithium – Level 1
  - Aripiprazole – Level 1
  - Risperidone – Level 1
  - Olanzapine (added to fluoxetine) – Level 1
- **Second-line:**
  - Quetiapine
  - T3
  - Combination with bupropion or mirtazapine

Depression Augmentation

- Wellbutrin 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.
- Remeron 15 mg. po qhs x 2-3 weeks, increase by 15 mg. increments (Range 15-45 mg./day)
- I use when more of an agitated state (decreased sleep, anxious, etc.)
- This are referred to as combination/augmentation

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

Augmentation--Quetiapine

- This only has second line approval according to CANMAT
- I still use it because it has approval for monotherapy in bipolarn1 and 2 depression, and monotherapy in unipolar depression when no other antidepressants have worked
- Dose is 50—100—150mg./day. Increase q2-3 weekly
- Have to do fasting metabolic q4monthly while on this

Augmentation

- Lithium
- 600-900 mg./day
- Start at 300 mg. po bid x 2-3 weeks, then increase to 300 and 600 mg./day

Depression Augmentation--Atypicals

- Risperidone 0.5—1.0—1.5—2.0 mg./day.
- Increase at 2-3 week intervals
- Aripiprazole 2.5—5.0—7.5 mg./day
- Olanzapine 2.5—5.0—7.5 mg./day

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

Which Antidepressants?

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

- I favour Sertraline, Escitalopram, Venlafaxine

- CANMAT studies

- Cipriani study

CANMAT: Drugs with superior efficacy against comparators:

- **Escitalopram** – level 1 evidence
- **Sertraline** – level 1 evidence
- **Venlafaxine** – level 1 evidence
- **Duloxetine** – level 2 evidence
- **Mirtazapine** – level 2 evidence

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

Treatment Resistant Depression

- Modafinil (Alertec)--stimulant
- Methylphenidate(Ritalin)—stimulant
- No RCT’s supporting use. Some “small n” studies. Needs further study. I don’t use at this time

SLEEP MEDS

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

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

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)

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
- This 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

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

- These are addictive

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 recently recommended against using this for sleep

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 (CANMMAT)
  - I use less because of metabolic issues.

CANMMAT (09):1st Line Treatments for Bipolar Depression

- **Monotherapy:**
  - Lithium, lamotrigine, quetiapine
  - Combination Therapy:
  - Lithium and divalproate
  - Lithium or divalproate plus SSRI or buproprion
  - Olanzapine and SSRI

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

CANMMAT (09):1st Line Treatments for Mania

- **Monotherapy**: Lithium, divalproex, Risperidone, Olanzapine, Quetiapine, Ziprasidone, Aripiprazole
- **Combination:** Lithium or divalproex ***plus*** Atypicals, except Ziprasidone (increases response by 20%)
- **Rapid Cycling/Mixed**: Divalproex
- **Discontinue antidepressant, stimulant meds

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 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

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, Panic Disorder, Social Phobia, PTSD

- Treatment of choice is SSRI, NSRI (August 2006 CPA 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—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

ANXIETY--PTSD

- SSRI’s and NSRI’s are the mainstay
- Benzos used but with caution. High rates of substance abuse
- Neuroleptics can be used as adjunctive

- Prasocin has been used for PTSD nightmares

- Clonidine has ben used for nightmares, hypervigilance

ANXIETY --OCD

- SSRI’s and NSRI’s are the mainstay
- Can use clomipramine as adjunctive or primary therapy
- Can add or substitute neuroleptics for resistant cases

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

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