APPROACH TO DEPRESSION IN PRIMARY CARE

Family Medicine Forum
October 31, 2019.
Vancouver, BC.

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Faculty/Presenter Disclosure

- **Faculty:** Jon Davine
- **Relationships with financial sponsors:**
  - **Speakers Bureau/Honoraria:**
    - Toronto East Hospital Network
    - Ontario Medical Association
    - Touchstone Institute
    - Ontario College of Family Physicians
    - McMaster University Department of Psychiatry
    - University of Alberta, Department of Psychiatry
    - Canadian Psychiatric Association
    - Pri-med, University of Toronto Family Medicine
  - **Consulting Fees:** None
  - **Patents**: None
  - **Other:** None

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Disclosure of Financial Support

- **This program has not received financial support.**
- **Potential for conflict(s) of interest:**
  - Jon Davine has received honoraria only from not for profit organizations. He prepared the slides on his own.

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Objectives

- Exposure to a brief differential diagnosis of the sad state
- Learn how to choose, start, and increase antidepressant medication
- Learn recent recommendations re augmentation techniques
- Learn about ECT, TMS as treatment techniques

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Sad State – Differential Diagnosis

- Rule out organic
- Adjustment disorder with depressed mood
- Unipolar depression
- Bipolar disorder, depressed phase

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R/O Organic

- TSH, CBC
- Anything else where history and physical take you
- Check re alcohol use– Choosing Wisely Canada says hold off on treatment and see if Etoh can be d/c'd

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Adjustment Disorder with Depressed Mood

- Usually within 3 months of a stressor
- Usually goes away within 3 months of stressor getting dealt with
- Can go on for years if stressor continues
- Tx:
- Counselling ONLY!!

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Bipolar Disorder Type 2, Depressed Phase

- Always screen for past hypomanic episodes
- What looks like depression is actually bipolar type 2, depressed phase
- Treatment:
- Mood stabilizers NOT naked antidepressant

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Hypomanic Screen

"Have you ever had a period or feeling better than good, not for an hour or an evening, but for days and days where you were unusually full of energy and had a decreased need for sleep? Has this ever happened to you?"

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Important to Remember

- r/o past depressive episodes
  - This has treatment implications: **length of time**

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Unipolar Depression

- 15% lifetime prevalence
  - 10% men
  - 20% women

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Diagnosis – SIGECAPS

- Low mood/irritable mood for at least 2 weeks, **but** I would say 3-4 weeks minimum
  - **S**leep
  - **I**nterests (and pleasure)
  - **G**uilt
  - **E**nergy
  - **C**oncentration
  - **A**ppetite
  - **P**sychomotor agitation/retardation
  - **S**ex, **S**uicide

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Depression Screen

"Have you ever had a period of sadness not for a day or two, not for a week or two, but for many weeks and months? You had no energy, no interest in things, and you weren't eating or sleeping well. Has this ever happened to you?"

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Counselling

- Stress diathesis model of depression
- Counselling can decrease stress, and increase supports
- Supportive therapy
- Cognitive Behaviour Therapy (CBT)
- Mind over Mood by Christine Padesky

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Psychopharmacology

- So you've ruled out organic, it's not bipolar, it's not an adjustment disorder
- You're going to start meds
- How do you do this?

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Medications

- 60-80% recover vs. 20-40% placebo
- Efficacy fairly equal in studies
- Therefore, side-effect profile important

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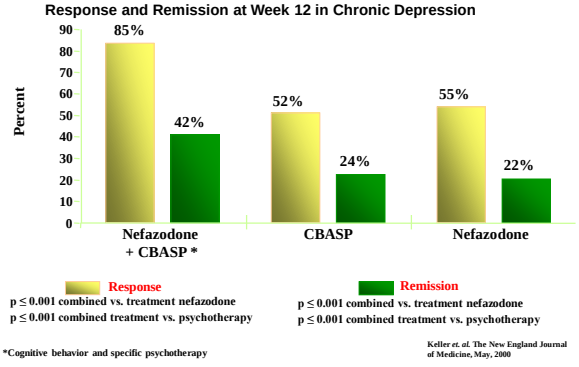
Combination Pharmacotherapy and Psychotherapy is More Effective than Either Alone



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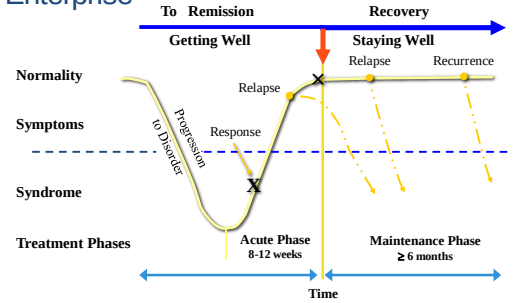
Treating Depression is a Long-Term Enterprise



Depression is associated with high rates of relapse and recurrence

Adapted from Kupfer. 1991. Adapted from CANMAT Guidelines, June 2001.

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SSRIs

Drug (Brand name)	Initial Dose (per day)	Range (per day)
Citalopram (Celexa)	20 mg	20-40 mg
Escitatalopram (Cipralex)	10 mg	10-20 mg
Fluoxetine (Prozac)	20 mg	20-60 mg
Fluvoxamine (Luvox)	50 mg	100-300 mg
Paroxitene (Paxil)	20 mg	20-60 mg
Sertraline (Zoloft)	50 mg	50-200mg

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Other Antidepressants

- **SNRI**
  - Venlafaxine (Effexor)
    - Range: 75-225 mg per day
  - Desvenlafaxine (Pristiq)
    - Range: 50 mg per day
  - Duloxetine (Cymbalta)
    - Range 30-60 mg per day
- **NaSSA** (Noradrenergic and Serotonergic Specific Antidepressant)
  - Mirtazapine (Remeron)
    - Range: 15-45 mg per day

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Other Antidepressants (2)

- **DNRI**
  - bupropion (Wellbutrin)
    - Range: 150-300 mg per day

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New Antidepressant

- Vortioxetine (Trintellix) 10-20 mg./day

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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

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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

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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

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Excluded

- Treatment Resistant Depression

- Psychotic Depression

- Bipolar Disorder

- Serious Concomitant Medical Illness

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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

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Cipriani, 2018

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

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Cipriani, 2018

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

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Cipriani, 2018

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

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Overall Studies

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

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Overall Studies

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

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Optimizing Dose

- Increase dose q2-3 weeks depending on response
- Increment of increase = starting dose
- If doing better, don't adjust
- Once they plateau, increase, unless back to normal

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The issue of non-adherence

- Early non-adherence is high among patients treated for depression
  - **28% stop** taking antidepressants during the first month, mostly during the first two weeks
  - **44% stop** taking antidepressants by the third month

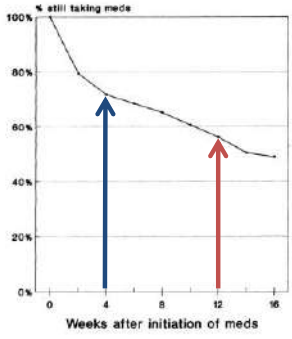

Figure adapted from Keller et al. *Medical Care,* 1995, 33(1):66-74.

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Compliance with Antidepressants in General Practice

Reasons for Drop Out & Time of Event			
Proportion of respondents	**Reason**	**Time of drop out**	**Potential MD strategies**
35%	Feel better	6.1 weeks	Reminder to stay on
30%	Side effects	4.5 weeks	Ask/address side effects
17%	Other (e.g., fear of dependence)	8 weeks	Explain antidepressants are non-addictive
15%	Told by doctor	3.2 weeks	Stay on medication, if well
15%	Lack of Efficacy	1-4 weeks	Remind efficacy begins later

"52% stopped taking their medication during a 12 week period. Two-thirds did not inform their GP"
Psychoeducation makes a difference in improving response rates

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Recurrence and Treatment Length

- **1 episode: 50% recurrence rate**
  - Treat for 6-9 months of feeling good, overall ~1 year
- **2 episodes: 70% recurrence rate**
  - Treat for 12-18 months of feeling good
  - If 2 difficult episodes, treat indefinitely
- **3 episodes: 90% recurrence rate**
  - Treat indefinitely

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Management Approaches to Insomnia

- Wait for tolerance to occur
- Change the timing of antidepressant administration
- Reduce dose (main issue: efficacy could be lost)
- Switch antidepressant
- Pharmacological management:
  - Trazodone (25-50 mg.)
  - Melatonin (5-10 mg.)
  - Remeron (15-30 mg.)
  - TCAs—low dose doxepin (3-6 mg.)
  - Zopiclone (?less addictive)
  - Benzodiazepines

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Choosing Wisely Canada/APA

- NO QUETIAPINE FOR SLEEP!!

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Management Approaches to Hypersomnia / Fatigue / Apathy

- Wait for tolerance to occur
- Bedtime dosing
- Reduce dose (main issue: efficacy could be lost)
- Switch antidepressant

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Management Approaches to Nausea

- Lower dose
- Wait for tolerance
- Symptomatic treatment
  - Gravol
- Switch antidepressant

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Sexual Side Effects

- Affect different phases of sexual response
  - Interest / desire / libido
  - Arousal
  - Orgasm
- Drugs with low sexual side-effects:
  - Bupropion
  - Mirtazapine

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Management Approaches to AD-Induced Sexual Dysfunction

- Possible pharmacological antidote
  - Sildenafil
  - Dose reduction (main issue: potential for relapse)
- Switch antidepressants
  - Bupropion
  - Mirtazapine

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Augmentation – Increasing Dose

- For partial response
  - Defined as 25% of the usual range or greater
- Go above the usual range
  - Often take meds one to two increments higher, as long as side effects are not a problem

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Augmentation – Adding a different agent

- **First-Line Options:**
  - Aripiprazole – Level 1 2-15 mg.
  - Quetiapine—Level 1 150-300 mg.
  - Risperidone – Level 1 1-3 mg.
- **Second-line:**
  - Lithium 600-1200 mg. (therapeutic)
  - Olanzapine (level 1) 2.5-10 mg.
  - Triiodothyronine 25-50 mcg.
  - Combination with bupropion 150-300 mg.
  - Combination with mirtazapine 30-60 mg.
  - Modafinil 100-400 mg.
  - Brexiprazole (level 1) 1-3 mg.

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Combination Strategies

- Second-line (CANMAT 2016)
- Wellbutrin XL (bupropron)
  - 150-300 mg po QAM
  - 150 for 2-3 weeks, then 300 if necessary
- Mirtazapine
  - 30-60 mg po QHS
  - 15 mg. hs, then increase by 15 mg. increments q2-3 weekly

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Augmentation Strategies – Atypicals

- First Line
  - Aripiprazole (Abilify) (2.0-15 mg.)
  - 2-4-6-8 q2-3 weekly
  - Risperidone (risperdal) (1-3 mg.)
  - 0.5 – 1.0 – 1.5 – 2.0 q2-3 weekly
  - Quetiapine (Seroquel) (150-300 mg.)
  - 50-100-150 q2-3 weekly

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Augmentation Strategies – T3 (Cytomel)

- Second line
- Recommendation:
  - 25 micrograms per day for 2 weeks
  - If no response increase to 50 micrograms per day
- Approximately 60% response rate

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X-Crossover

- For use when switching to a different antidepressant
- Lower first drug by typical increment q5days
- Start 2nd drug at half dose along with starting dose of first drug for 5 days
- Increase second drug to full starting dose while discontinuing the 1st drug

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ECT – Electroconvulsive Therapy

- Highest rate of therapeutic success
- No absolute contraindications
- Chief side effects are cognitive
  - Memory impairment typically resolves in a few weeks after cessation of treatment
  - Rarely, more pervasive and persistent cognitive disruption
- Method
  - Unilateral, non-dominant
  - Fewer side effects (e.g., cognition disruption)

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ECT – Indications

- Non-response to antidepressant medication
- Food refusal leading to nutritional compromise
- Unable to tolerate antidepressant medications
- Past response to ECT
- Medical condition precludes use of antidepressant medications

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ECT (in Hollywood)

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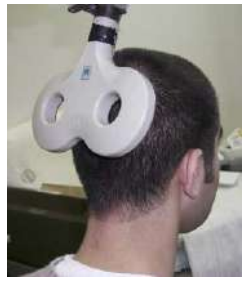
TMS

- Transcranial Magnetic Stimulation
- Has helped some people



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TMS

- Health Quality Ontario
- Recommends TMS when ECT has failed or contraindicated

- 23 RCT's TMS vs. sham, mean difference on Hamilton Depression Scale: 2.31
- <3 (pre-specified clinically important treatment effect)
- "marginally effective"

- rTMS vs. ECT favoured ECT (Weighted mean difference 5.97) Risk ratio for remission and response were 2.20 and 1.72 favouring ECT

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Final Recommendation from OHTAC

- "The Ontario Health Technology Advisory Committee recognizes that ECT is the most effective treatment for non-psychotic, treatment-rssistant depression. The Committee therefore recommends that repetitive TMS be publicly funded for patients with non-psychotic, treatment-resistant depression only when ECT is not an option."

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Pediatric Depression

- Depression can present a little differently
- Watch for decreased school performance
- Use Fluoxetine (RCT evidence)
- Increased suicidal ideation and behaviours (not completed suicides)
  - True in kids, not in adults
- NNH-143

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Patient Health Questionnaire (PHQ)

- Self report
- Does not replace clinical interview
- Supports diagnosis and can follow treatment effects

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End

- Questions?

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