Is Depression management getting you down?

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Faculty/Presenter Disclosures

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Outline

1. Can we quickly rule out depression?
2. What are the challenges for anti-depression evidence?
3. How well do anti-depressants work?
   a) Does severity matter,
   b) Do they work in primary care?
4. Is there clear evidence that one anti-depressant is better?
5. Does dosing matter?
6. What about switching?
7. How long does it take for antidepressants to take to work?
8. What are reasonable second line options.
9. How long do you stay on the medication?
10. How well does non-drug therapy work?

2 Question Screen

- 3 cohorts with 1893 patients, most in primary care:
  - During the past month have you often been bothered by,
    1) Feeling down, depressed, or hopeless?
    2) Little interest or pleasure in doing things?
  - No to both (negative) response:
    - Sensitivity 96-97% & Negative Likelihood Ratio 0.05
    - If pretest probability = 15%, Post-test Probability = ~1%
2 Question Screen

- Yes to 1 or 2 (positive) responses:
  - Specificity 57-78% & Positive Likelihood Ratio 4.4
  - Note: 23-37% will screen +ve so not diagnostic – need PHQ-9 of similar.

- **Bottom-Line:** Excellent screen for excluding depression, but not good for diagnosis.

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Research Quality Issues

- 10-20 yrs ago: Most research low quality.
  - From 46 RCTs - Only 9% good quality excluded\(^1\)
    - 85% industry funded (11% affiliated, 4% not reported)
  - Others similar\(^2,3\)

- Reviews from last few years.
  - 522 RCTs (all types): 9% high risk of bias, 73% moderate, 18% low risk.\(^4\)
  - 131/131 Placebo controlled RCTs at high risk of bias based on incomplete/selective reporting & poor blinding.\(^5\)

- **Bottom-Line:** Quality maybe improving over time but also likely driven in part by “reducing the bar”.

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Important Nuance

- Subjective:
  - Clinicians report/score benefit > pts, Examples\(^1,2\)
    - Clinicians\(^1\) found patients' benefited in 33% of scales but patients self rated benefit in 0%
    - Clinicians (experts) rated benefit 2.76 greater than patient self-rated.\(^2\)

- Scales:
  - ↑ numbers = easier to find stat (not clinical) significance, Examples\(^3-5\)
    - Ham D scale change over placebo ~2 (scale = 0-52, MCID 3)
    - MADRS scale, escitalopram vs citalopram = 1.1 (scale 0-60, MCID 2)
    - Children's depression rating scale- revised: Improve 2.7 on a 113 scale.

What role does industry play

- Hiding trials and selectively reporting data within trials.
- Focus on first: FDA records of 12 SSRI/SNRI’s vs Published
- 74 Trials:
  - 38 Positive: 37 published, 1 not published.
  - 36 Negative: 3 published as negative, 11 published as positive, 22 not published.
- 94% appear positive if looking at published RCTs vs 51% FDA

NEJM 2008; 358: 252-60
SSRI: Super Selective Reporting Information

- What happens to SSRI RCTs: +ve trials published 4.4x each (vs 1.3)

  ![Study Diagram]

- **Bottom-Line**: We need to keep in mind that what we see is the best Anti-depressants could be.


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**How well do they work?**

- 35 RCTs of 4 SSRI/SNRI
- Statistical significance common, Clinical over placebo?
  - Starting Ham D scores: 17-30.5
  - Mean Change was 9.6 for med & 7.8 for placebo (1.8 difference)
  - 81.5% of anti-depressants effect is from “placebo”
- Other studies find²,³
  - Placebo drives 68% of the effect seen in patients
  - Mean difference over placebo is in Ham D: ~2

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How well do they work: Part 2

- **Paroxetine** example: Actual numbers for ≥50% improvement;
  - 53% taking paroxetine vs 42% with placebo
  - Difference is 11% (or NNT 9)

- “Antidepressants improve response 50%”
  - 552 RCTs with 116,477 patients – no real numbers
  - Example: Citalopram Odds Ratio 1.52 (1.33 – 1.74)
  - Convert to Risk Ratio it is 1.26 (1.18-1.34)
  - Convert to Absolute risks 50% vs 40%

Severity Matters,… Kind-off

- Combine patient data 6 RCTs:
  - 3 imipramine, 3 Paroxetine, baseline Ham D= 14-23.
- Results: ↑ severe, ↑ benefit
  - Clin Sign Diff = 3 on Ham-D
- NNT: 16, 11 and 4 (mild/mod, severe, very severe).
- **Bottom-Line**: Severity impacts drug effect over placebo.

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35 RCTs from the FDA

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What about in Primary care?

• Clinical response (any response) Primary Care
  • TCA’s (8 RCTs, 1058 patients)
    • Risk ratio: 1.24 (1.11, 1.38), 62% vs 49%, NNT ~8
  • SSRI (5 trials, 1269 patients)
    • Risk ratio: 1.28 (1.15, 1.43), 58% vs 45%, NNT ~8

• Bottom-Line: ~50-60% of patients will have some response to medications (and 40-50% on placebo).

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Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

Olanzapine

Quetiapine

Risperidone

Is any antidepressant better?

- 46 RCTs\(^1\) (11.5 K pts), ≥3 months: No Diff Quality of Life
  - Examples where Ham D better for one
    - Venlafaxine > Fluoxetine: RR 1.12 (1.02-1.23) & NNT16
    - Sertraline > Fluoxetine: RR 1.1 (1.01-1.2) & NNT 17
  - Benefit = always 5% in favour of sponsored drug (NNT 20)

- 171 RCTs\(^2\) ≥6 weeks (indirect comparisons), Effectiveness similar.
  - Few stat sign relative benefit, but none clinically significant
    - Example: MADRS 60 pt scale: escitalopram 1.13 > citalopram (MCID=2)
  - Sponsorship may play a role in these subtle differences

Lancet Studies

- Both studies examined Treatment Response (≥50% scale improvement) & Withdrawal, used indirect comparisons & Odds Ratios

- 117 RCTs\(^1\) treatment response & withdrawal, used indirect methods
  - Efficacy Top 4: mirtazapine, escitalopram, venlafaxine, sertraline
  - Tolerability Top 4: escitalopram, sertraline, bupropion, citalopram

- 522 RCTs\(^2\) (116,477 pts), Mean duration 8 weeks.
  - Efficacy: Odds Ratio=1.49-1.89 for 19 of 21 anti-depressants. Elavil (2.13) & Reboxetine (1.37)
    - Note: Now escitalopram #8, sertraline #10.
  - Tolerability: Same as placebo except Fluoxetine (OR=0.88) and clomipramine (OR=1.30)
  - Newer drugs seemed better

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Summing Up

- Bias is common & therefore estimates are uncertain
- Using indirect comparisons & odds ratios makes things worse
  - Venlafaxine: OR 1.78, convert RR=1.36, actual response=54.4%
  - Fluoxetine: OR 1.52, convert RR=1.26, actual response=50.4%
  - Any difference in the range of sponsorship bias alone.

- **Bottom-Line:** No real difference in efficacy. Use the one that you are comfortable with. Weigh costs, patient history, adverse events, etc.

Dosing: Is bigger better?

- Low doses as effective as high doses.
  - Fluoxetine (5 vs 20 vs 40mg)\(^1\) & Tricyclics (50-100 vs >100mg)\(^2\)
  - 8 Studies: Increasing doses in poor response not much help.\(^3\)
    - At least not until 8 weeks have past.
  - 9 RCTs, after waiting 3-6 weeks, generally double dose vs stay same dose.
    - Change in scale: SMD 0.053 (-0.143 to 0.248)
    - Response: OR 1.124 (0.778 – 1.625)
  - Pooling 135 placebo trials\(^5\) – dosing did not impact outcomes
  - **Bottom-Line:** don’t rush to increase dose as little evidence it helps.

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Switching to a New SSRI

- 3 RCTs found no difference in switching after 6-7 weeks.
  - Odds ratio 0.85 (0.55-1.30) - favoring not switching
- 8 RCTs, 1627 patients, On ≥2 weeks, switch 4-12 weeks
  - Change in depression scale: SMD 0.031 (-0.258 to 0.319)
  - Response: Odds Ratio 0.97 (0.69-1.36).
- Note STAR*D waited a mean of 12 weeks
- **Bottom-Line**: Don’t rush to switching as this does not seem to work (over continuing).

How Fast do they Work?

- Meta-analysis\(^1\) of 50 trials (10,121 patients) looking at response to SSRI medications over time.
  - 1/3 of the total benefit in first 7 days (based on 6 weeks)
  - NNT of 25 for 50% improved over placebo at 7 days.
- Results confirmed those of another meta-analysis\(^2\)
  - Improvement in clinically important outcomes in the first week.
- New research verifies early response.\(^3\)
- **Bottom-Line**: Response to anti-depressants can be quick.

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Response rate over time?

Figure 4. Trajectory of Response Over Time in Randomized Double-Blind Trials of Antidepressant Monotherapy Versus Placebo.

- **12 weeks**: ~60% better
- **8 weeks**: ~55% better
- **4 weeks**: ~42% better

Bottom-Line:
Response rates highly depend on time. Almost 1 in 5 patients will benefit just from staying the course from month 1 to 3.


Shooting STAR*D: Findings

- 2876 people were put on Citalopram
- More like real patients
  - (mix of general and specialty)
- 80% had chronic or recurrent depression
- Many complicating Psychiatric conditions.
  - 18% had attempted suicide.
- Mean Ham D = 21.8
- Mean exit dose of citalopram = 42 mg/day

Am J Psychiatry 2006; 163:28–40
Shooting STAR*D

Response = 47%

Citalopram

Citalopram Failure (remission~28%)

Switch (sertraline, buproprion, venlafaxine). Remission~25%

Augment (buproprion, buspirone). Remission ~30%, buproprion better on scales

Failure

Switch (mirtaz, nortrip). Remission ~10-20%

Augment (Lithium, T3). Remission ~20%


Shooting STAR*D: Summary

• Efficacy population = 52% response versus 39% in effectiveness or pragmatic STAR*D population.
• Take home messages
  1. Maybe choosing the type of alternative antidep doesn’ t matter.
  2. Maybe specialist care is not a lot different from GP
  3. Choice of augmentation uncertain (guidelines\(^2\) put lithium & antipsychotics ahead of choices here).
Combining anti-depressants

- Some studies find combined regular anti-depressants at the start may be helpful,
  - E.g. RCT of 105 pts x 6 weeks, Fluoxetine (20) vs Mirtazapine (30) plus Fluoxetine (20) or Venlafaxine (225) or Bupropion (150)
  - Remission rates with combo average NNT 4
- Others find it is not helpful
  - E.g. RCT of 665 pts x12 weeks, Escitalopram (20) vs Buproprion (400) + escitalopram (20) vs Venlafaxine (300) + mirtazapine (45).
  - All groups: Remission 38-39% & Response 52%
- Bottom-Line: No clear indication to start 2


Anti-Psychotics & Depression

- 2010 Cochrane review¹ (28 trials, 8487 patients)
  - Antipsychotic versus antidepressant: Equivalence is uncertain
    - Olanzapine (5 trials): 2 studies antidepressants superior (3 no diff)
    - Quetiapine: equivalent but only one trial.
  - Quetiapine (4 trials, 2069 patients) versus placebo:
    - Response NNT 8 and remission NNT 17.
  - Antipsychotic augmenting antidepressants: 12 trials using aripiprazole, olanzapine, quetiapine, or risperidone
    - Response NNT 7-12 and remission NNT 7-12.
  - Adverse events common,
    - Typical of antipsychotic studied (e.g. 4kg weight gain with olanzapine).
    - More patients stopped due to adverse events: NNH 6-13 used alone and NNH 12-50 as augmentation.

¹2010 Cochrane review: Antipsychotic versus antidepressant: Equivalence is uncertain. Olanzapine (5 trials): 2 studies antidepressants superior (3 no diff). Quetiapine: equivalent but only one trial. Quetiapine (4 trials, 2069 patients) versus placebo: Response NNT 8 and remission NNT 17. Antipsychotic augmenting antidepressants: 12 trials using aripiprazole, olanzapine, quetiapine, or risperidone: Response NNT 7-12 and remission NNT 7-12. Adverse events common, typical of antipsychotic studied (e.g. 4kg weight gain with olanzapine). More patients stopped due to adverse events: NNH 6-13 used alone and NNH 12-50 as augmentation.
Anti-Psychotics & Depression

• Canadian and American depression guidelines include the option of second-generation antipsychotics alone or as augmentation therapy in patients who have failed first-line antidepressants.

• Bottom-line: Second-generation antipsychotics appear effective in treating depression when given to augment antidepressants. One antipsychotic (quetiapine) appears effective in treating depression alone but equivalence to antidepressants is uncertain. The evidence has a high risk of bias and adverse events are common.

A Trial of Separation?

• In Meta-analysis of 31 RCT (of all types)\(^1\)
  • Meds stopped after 4-28 weeks (most 6-16)
  • Relapse at 12 months: 41% Placebo vs 18%
  • NNH 5 for stopping.

• Dose reduction similar (5 RCT)\(^2\)
  • 25% low dose vs 15% in previous dose (NNH of 10)

• Newer data suggestions similar (54 RCTs, 9268 patients)\(^4\)
  • Relapse in staying on treatment vs quitting early Odds Ratio 0.38 (0.34-0.41)
  • Convert to relative risks: 52%
  • Relapse rates: 22.5% vs 43.6%

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A Trial of Separation?

- Recurrence (hard to separate out one)³
  - From a cohort of 318 depressed pts, 60% had previous depression
  - After 1 yr, 25% of the cohort had a recurrence
  - If second, 41% in 1 year.
  - Add 16% for each subsequent episode
  - 36% did not have a recurrence in 5 years.

- **Bottom-Line**: Recurrence is relatively common if treatment stopped early. How long to treat not entirely clear but likely ~12 months. Patients with recurrent episodes could consider longer term, perhaps even indefinite therapy.

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CBT Therapy

- Mean effects: around 0.77 SMD versus wait-list
  - Lots of heterogeneity¹
  - Not as good if some form of attention OR depression is severe
- Meta-analysis² with comparator: less effect (0.28) & hetero less³
- Psychotherapy³,⁴: high risk of publication bias
  - Effect goes from 0.67 to 0.42.
  - In another study 0.52 to 0.39
- **Bottom-Line**: CBT works, and is similar anti-depressants likely.
Exercise on Quality of Life

• Exercise for Depression
  • 23 trials: 0.82 SMD
  • 3 best studies, 0.42 SMD
  • NNT 8-12

• RCT: 464 females, none or 3 levels of exercise
  • 8 QOL measures (mental & physical): dose dependent relationship (change 2-10%)


Summing up

1. Two questions can help exclude depression.
2. 50-60% of primary care patients taking antidepressants will get a good response.
   a) As severity increases so does effect over placebo
3. There is no clear evidence that one antidepressant is reliably more effective.
4. Anti-depressant can work within 7 days but response continues for 3 months
5. Dose and Switching should not occur too quickly.
6. It is reasonable to switch or augment (anti-psychotics, bupropion, others)
7. Patients should likely stay on the meds 12 months, longer if recurrent.
8. CBT is similarly effective (to antidepressants)
9. Don’t forget activity.