Is Depression management getting you down?

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Faculty/Presenter Disclosures

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- **Relationships with financial sponsors:**
  - **Grants/Research Support:** Alberta College of Family Physicians; Toward Optimized Practice, CIHR, PRIHS, etc
  - **Speakers Bureau/Honoraria:** Alberta College of Family Physicians;
  - **Consulting Fees:** N/A
  - **Patents**: N/A
  - **Other:**

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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 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?

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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%

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TFP 203. January 15 2018. https://gomainpro.ca/wp-content/uploads/tools-for-practice/1515521430_tfp2032-questionscreenfv.pdf. BMJ. 2005 Oct 15;331(7521):884.

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.

TFP 203. January 15 2018. https://gomainpro.ca/wp-content/uploads/tools-for-practice/1515521430_tfp2032-questionscreenfv.pdf. BMJ. 2005 Oct 15;331(7521):884.

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".

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

1) Ann Intern Med. 2005;143 :415-26. 2) Arch Gen Psychiatry 2006; 63: 1217-23. 3) Lancet 2004;363:1341-5. 4) Lancet. 2018 Apr 7;391(10128):1357-1366. 5) BMC Psychiatry (2017) 17:58.

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.

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1) Lancet 2004;363:1341-5. 2) J Affect Disorders 2009; 118: 1–8. 3) BMC Psychiatry 2017;17:58. 4) Ann Intern Med 2008;149(10): 734-50 5) BMJ 2004;328:879-83.

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

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NEJM 2008; 358: 252-60

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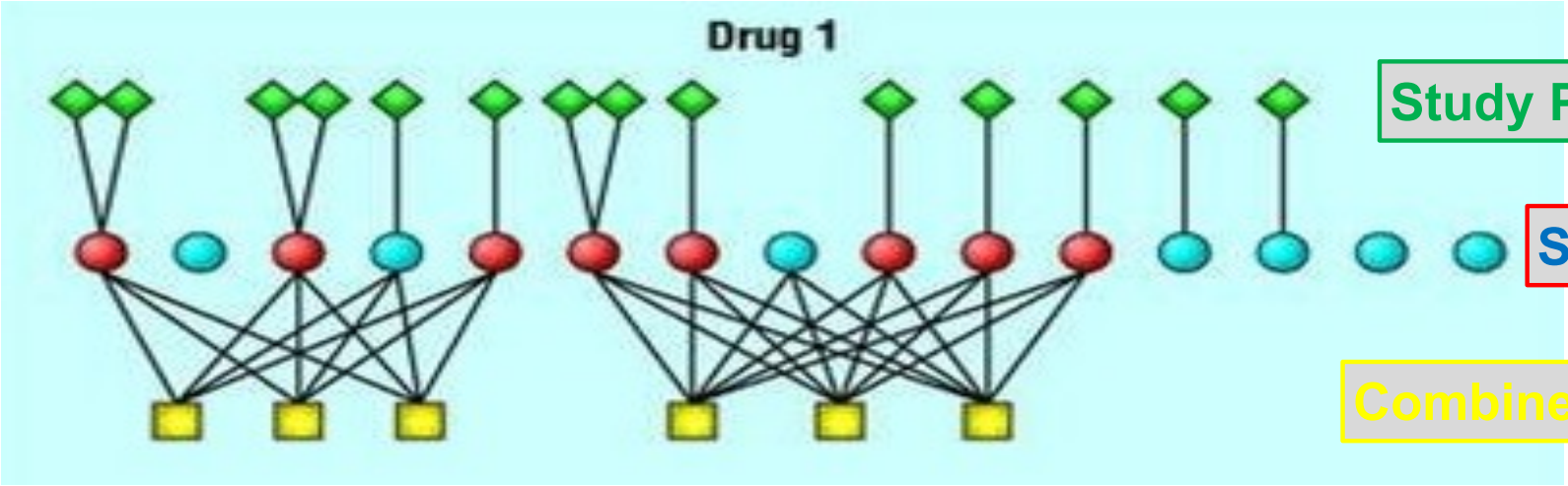
SSRI: Super Selective Reporting Information

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



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

Melander. et al, BMJ, 2003; 326: 1171-73

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 find[2,3]
  - Placebo drives 68% of the effect seen in patients
  - Mean difference over placebo is in Ham D: ~2

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

1) PLOS Med 2008; 5(2): 0260. 2) J Affect Disorders 2009; 118:1–8. 3) BMC Psychiatry 2017;17:58. Katakam. Acta Neuropsychiatrica 2018.

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%

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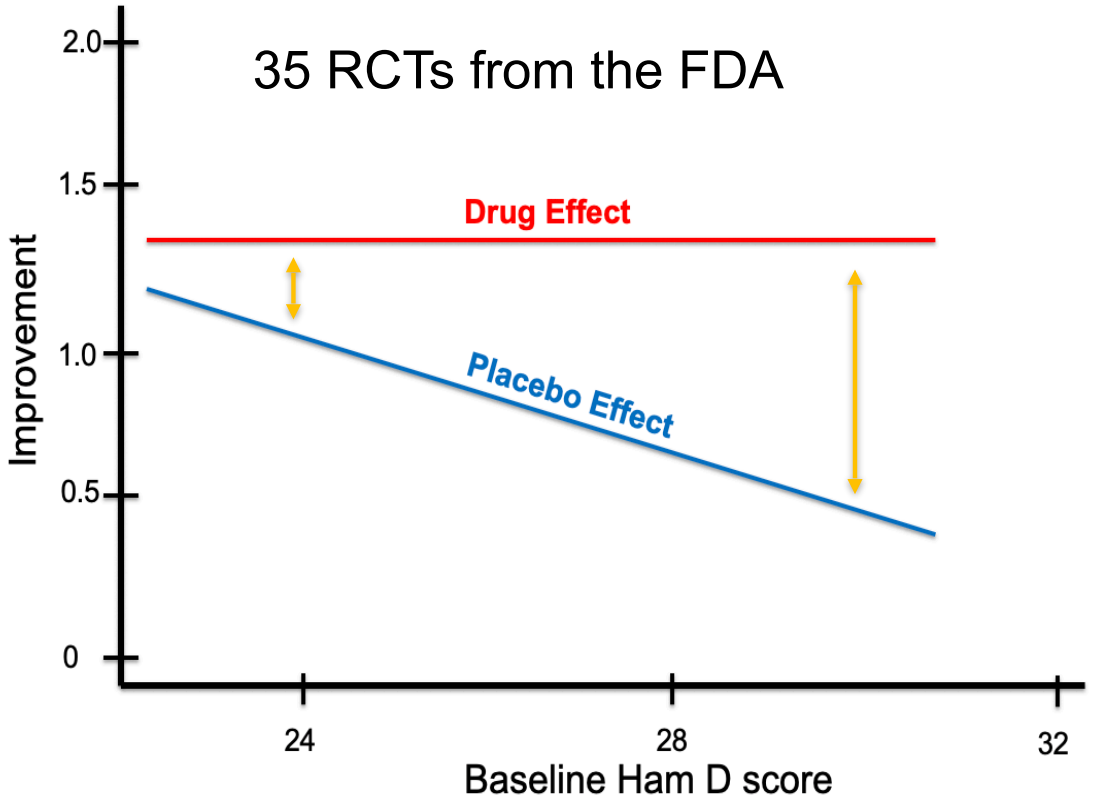
1) CMAJ 2008;178(3):296-305. 2) Lancet. 2018 Apr 7;391(10128): 1357-1366.

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.

PLoS Med. 2008 Feb;5(2):e45

JAMA. 2010;303(1):47-53

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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Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007954.

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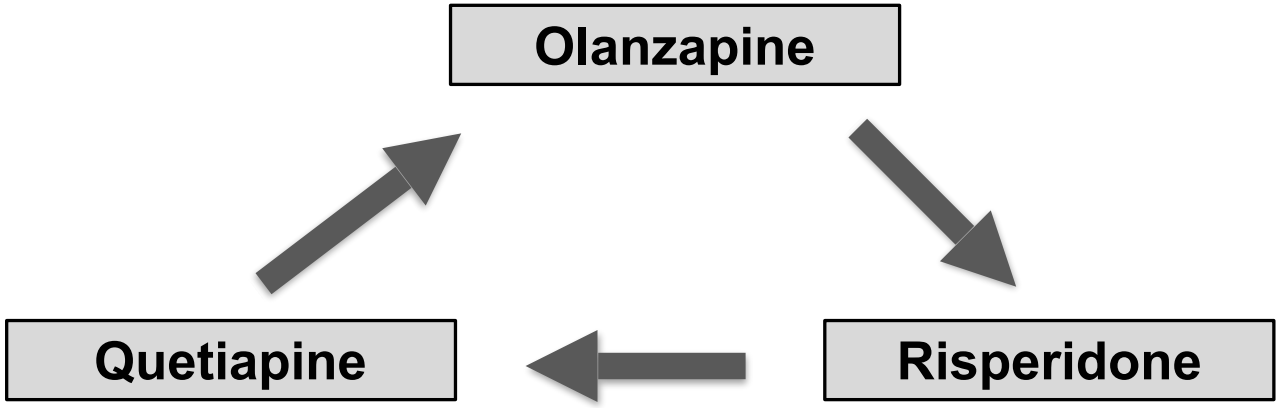
Reviews and Overviews

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



Am J Psychiatry. 2006 Feb;163(2):185-94.

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: esocitalopram 1.13 > citalopram (MCID=2)
  - Sponsorship may play a role in these subtle differences

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Ann Intern Med. 2005;143 :415-26. Ann Intern Med. 2008;149:734-750.

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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Lancet 2009; 373: 746–58. Lancet. 2018 Apr 7;391(10128):1357-1366.

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.

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Dosing: Is bigger better?

- Low doses as effective as high doses.
  - Flouxetine (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.

1) Psychopharm Bull 1988; 24: 183-8. 2) BMJ. 2002;325:991-5. 3) Br J Psychiatry 2006;189:309–16. 4) J Clin Psychiatry. 2018 May/Jun;79(3). 5) BMC Psychiatry (2017) 17:58. & Acta Neuropsychiatrica 2018.

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).

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Acta Psychiatr Scand 2010;121:174–9. J Clin Psychiatry. 2018 Jan/Feb;79(1).

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How Fast do they Work?

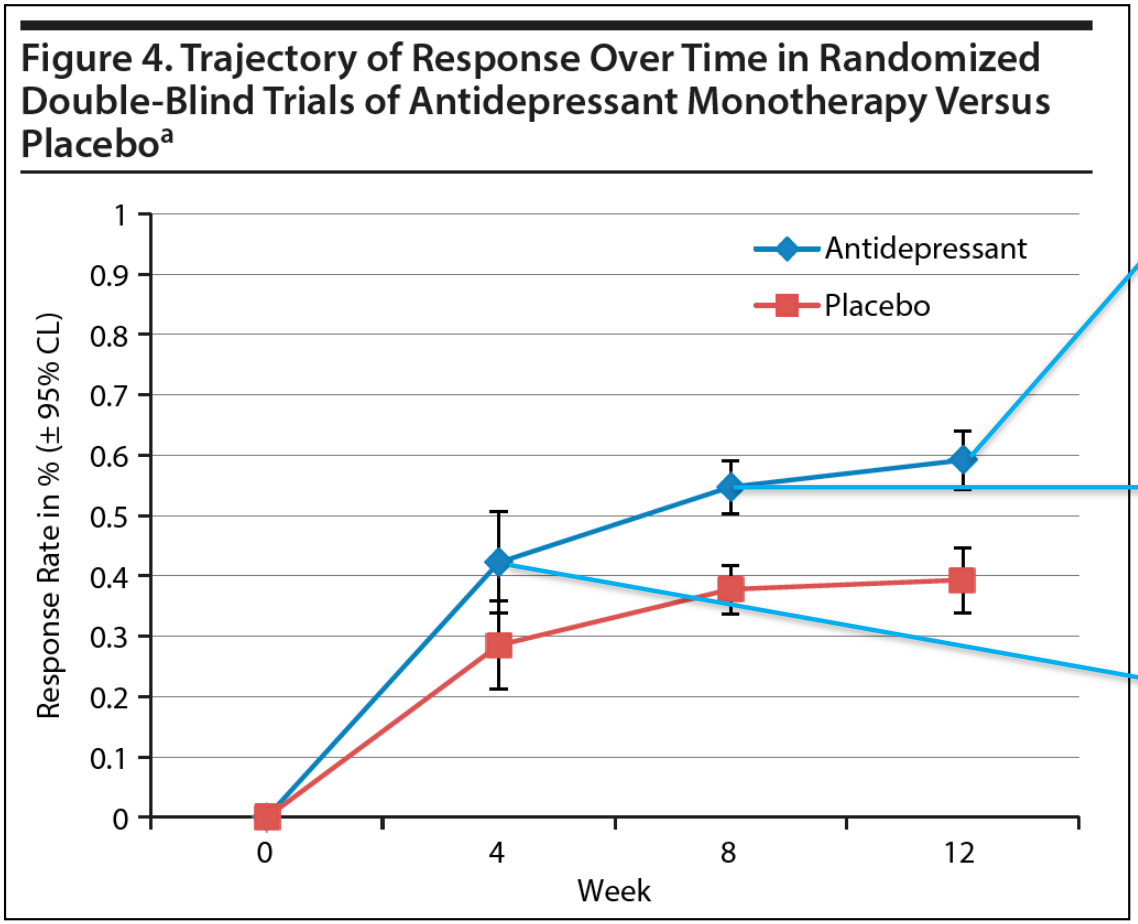
- Meta-analysis[1] of 50 trials (10,121 patients) looking at response to SSRI medications over time.
  - 1/3 of the total benefit in first 7 days (based on 6 weeks)
  - NNT of 25 for 50% improved over placebo at 7 days.
- Results confirmed those of another meta-analysis[2]
  - Improvement in clinically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

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

1) Arch Gen Psychiatry 2006;63:1217-23. 2) J Clin Psychopharmacol 2006;26:56–60. 3) Euro Psych 2013;28: 362–71

Response rate over time?

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



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.

J Clin Psychiatry. 2018 May/Jun;79(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

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Am J Psychiatry 2006; 163:28–40

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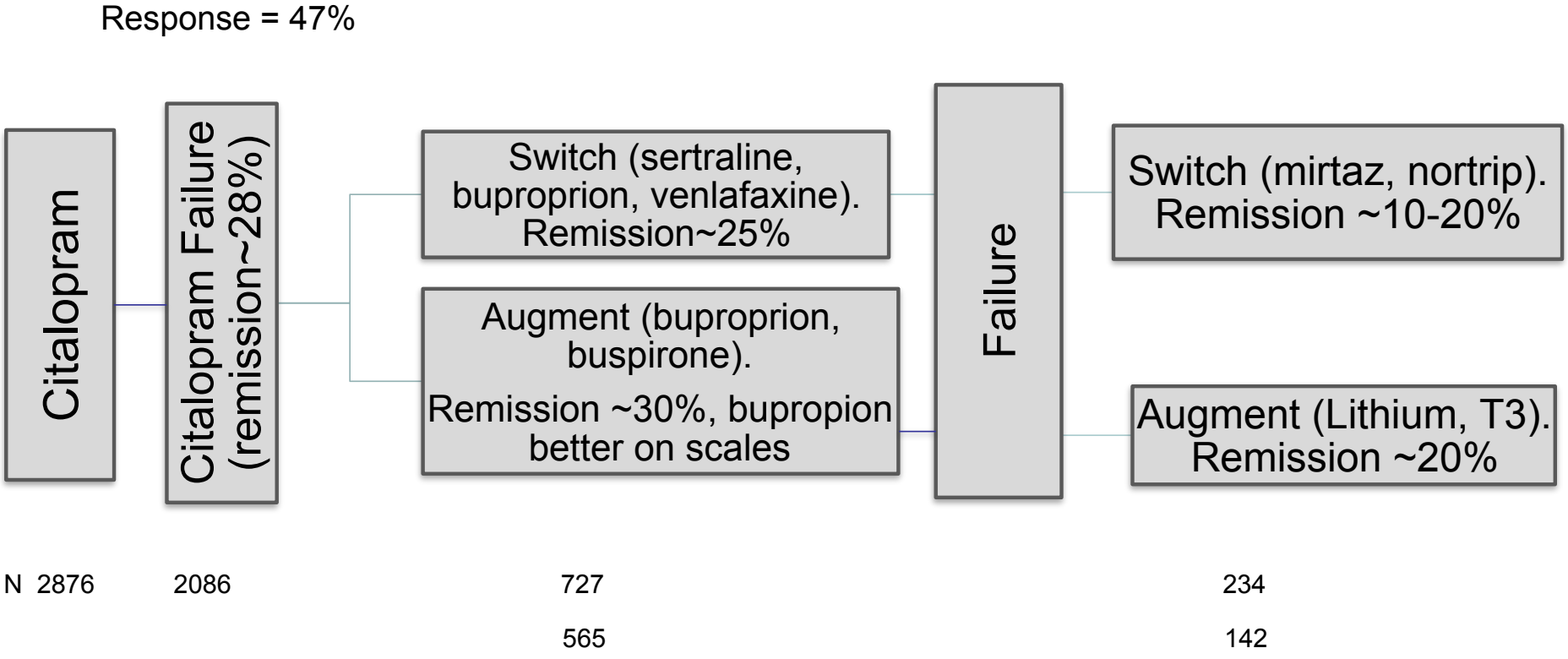
Shooting STAR*D



N Engl J Med 2006;354:1231-42. Am J Psychiatry 2006; 163:28–40. EBMH November 2008; 11(4): 97-9.

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).

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Am J Psychiatry 2009; 166:599–607. 2. J Psychopharmacol 2008;22:343–96.

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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 Fuoxetine (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

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

Am J Psychiatry 2010; 167:281–288. Am J Psychiatry. 2011 Jul;168(7):689-701.

Anti-Psychotics & Depression

- 2010 Cochrane reveiw[1] (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.

Anti-Psychotics & Depression

- Canadian[2] and American[3] 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.**

TFP #60 1) Cochrane Database Syst Rev. 2010 Dec 8; (12):CD008121. 2) CANMAT MDD Guideline:J Affect Disord. 2009; 117 Suppl 1:S26-43. 3) APA MDD Guideline: http://psychiatryonline.org/content.aspx?bookid=28&sectionid=1667485#654001

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%

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

1) Lancet 2003; 361: 653–51. 2) Psychother Psychosom. 2007;76(5): 266-70 3) Am J Psychiatry 2000; 157:229–233. 4) Australian and New Zealand Journal of Psychiatry 2010; 44:697–705

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.

1) Lancet 2003; 361: 653–51. 2) Psychother Psychosom. 2007;76(5): 266-70 3) Am J Psychiatry 2000; 157:229–233. 4) Australian and New Zealand Journal of Psychiatry 2010; 44:697–705

CBT Therapy

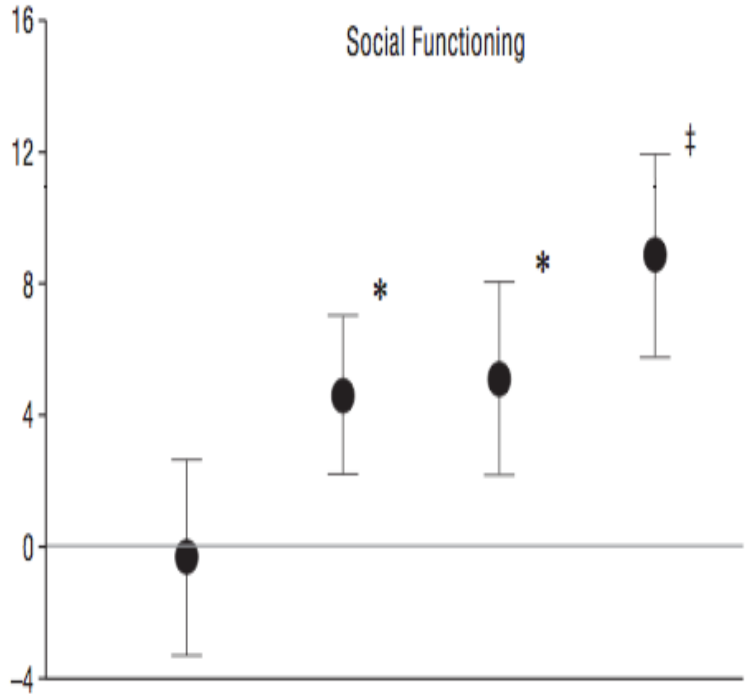
- Mean effects: around 0.77 SMD versus wait-list
  - Lots of heterogeneity[1]
  - Not as good if some form of attention OR depression is severe
- Meta-analysis[2] with comparator: less effect (0.28) & hetero less[3]
- Psychotherapy[3,4]: high risk of publication bias
  - Effect goes from 0.67 to 0.42.
  - In another study 0.52 to 0.39
- **Bottom-Line**: CBT works, and is similar anti-depressants likely.

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

1) Aust N Zeal J Psych 2006;40:9-19. 2) Psych Med 2010; 40: 9-24. 3) B J Psych 2010;196: 173-178. 4) PLoS ONE 10(9): e0137864. doi:10.1371/journal.pone.0137864

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%)



PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

Cochrane 2009:(3): CD004366. & TFP #130, Jan 19, 2015. Arch Intern Med. 2009;169:269-278

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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 reliable 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.