Treating depression in primary care: antidepressant medication versus alternatives

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- No conflicts of interest to declare

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Learning Objectives

- To have a balanced understanding of the benefits and limitations of antidepressant medication
- To be aware of evidence-based alternatives to antidepressant medications that are suitable for primary care

Overview

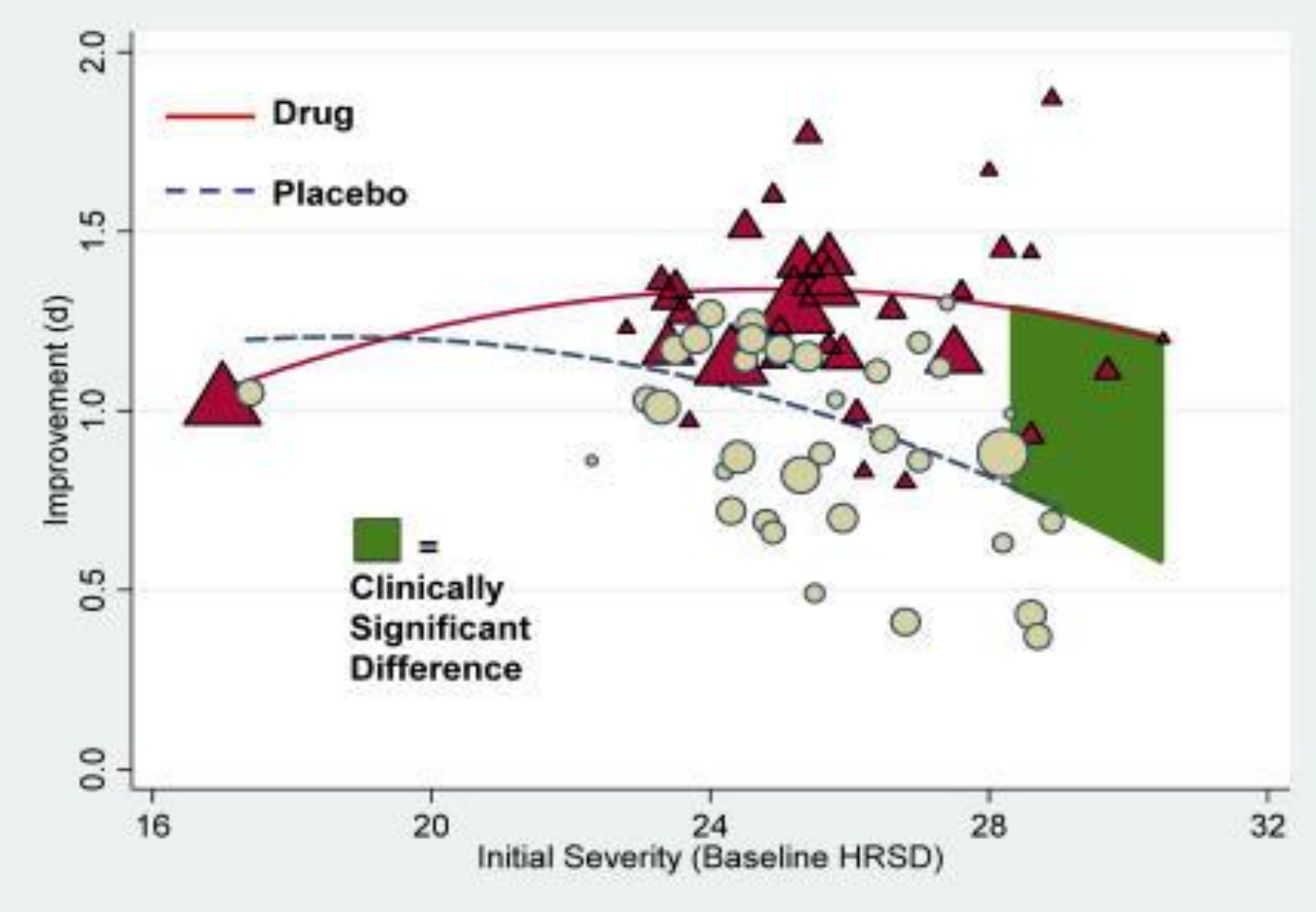
- The “controversy” about antidepressants
  - Critical reports and meta-analyses
  - The alternative perspectives
  - A balanced perspective
- If not antidepressant medication, then what?

American College of Physicians Guideline on MDD: Non-pharmacologic versus pharmacologic treatment

- "Select between either CBT or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient"
- Grade: strong recommendation, moderate-quality evidence

Qaseem et al, Ann Intern Med, 2016

Severity of depression and response to drug vs placebo



Kirsch et al, PLoS Med, 2008

SSRI versus placebo in patients with MDD

Meta analysis of 131 RCTs, including 27,422 participants…***authors'*** *conclusions:*

"SSRIs might have statistically significant effects on depressive symptoms, but all trials were at ***high risk of bias*** and the ***clinical significance seems questionable***. SSRIs significantly increase the risk of both ***serious and non-serious adverse events***. The potential small beneficial effects seem to be outweighed by harmful effects."

Jakobsen et al, BMC Psychiatry, 2017

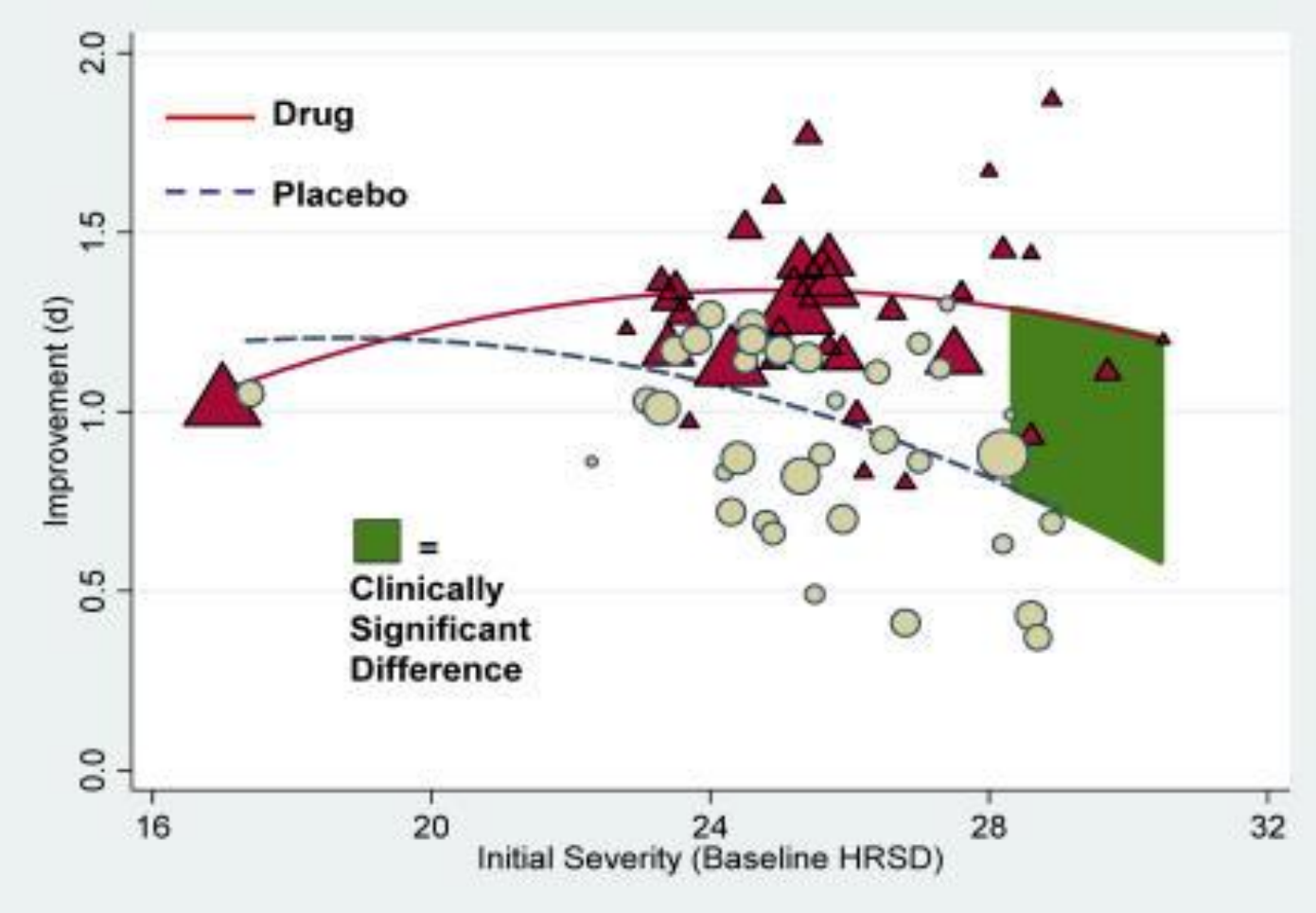
Possible (but unbalanced) conclusions from Kirsh et al 2008, and Jakobsen et al 2017:

1. Antidepressants have a trivial therapeutic benefit except for the very most severely depressed patients
2. Antidepressants should usually be avoided because benefits are of minimal clinical significance and high adverse effect potential

Important perspectives in a balanced appraisal of the merits of antidepressant Rx - I:

- Placebo response in a clinical trial is ***not*** just the response to inert ingredients:
  - Repeated, intensive, frequent study visits means a high level of non-specific support
  - Regression to the mean is expected in an illness with a variable course
  - Both of these factors contribute to “placebo response” in clinical trials
  - “Placebo response” is a relatively high standard

Important perspectives in a balanced appraisal of the merits of antidepressant Rx - II:



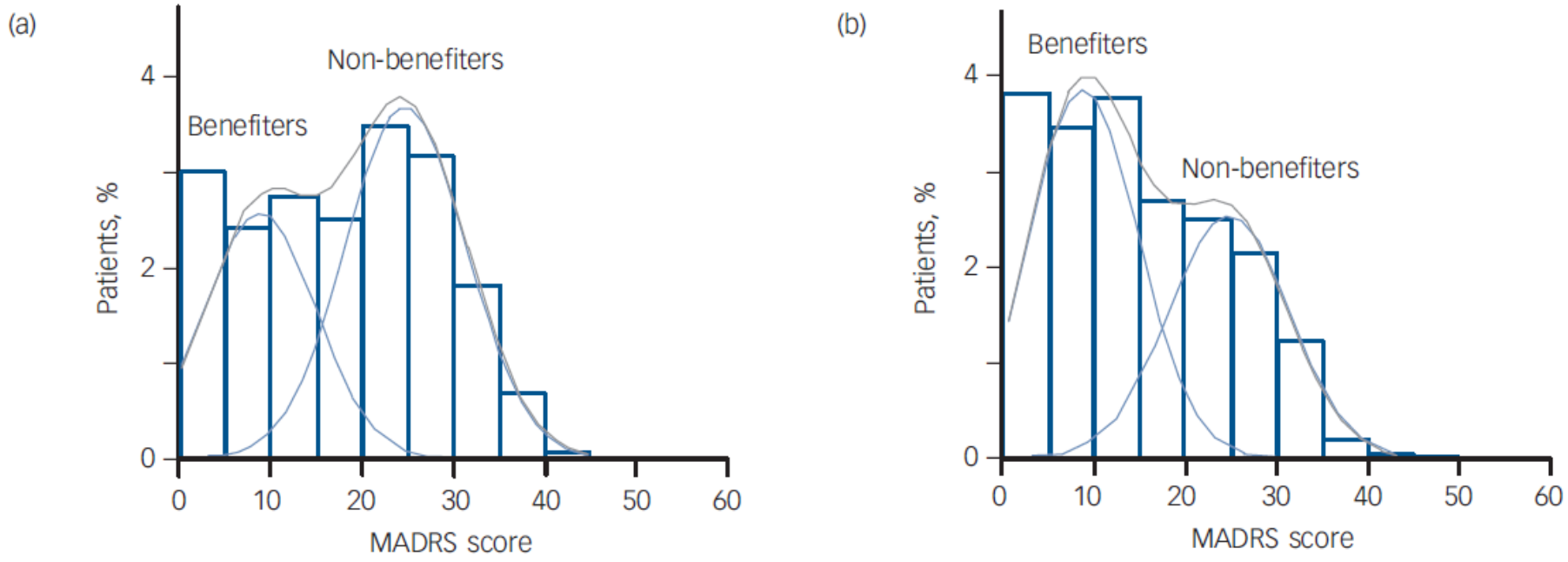
Kirsch et al 2008

Important perspectives in a balanced appraisal of the merits of antidepressant Rx - III:

- A small mean change in ratings in RCTs does not reflect a small response in all patients:
- Outcome data in clinical trials “fit” much better with a model that includes a “good responder” group – AND this group shows very large responses: -15.9 MADRS points and NNT = 5*

*Thase et al, Br. J. Psychiatry, 2011

Figure from Thase et al, 2011
Distribution of week 8 scores on MADRS



(a) = placebo group (b) = escitalopram group

Important perspectives in a balanced appraisal of the merits of antidepressant Rx - IV

- Antidepressant Rx and CBT work approximately equally well in MDD*
- If antidepressant Rx “doesn’t work very much if at all” then CBT doesn’t work very well either…

*Cuijpers et al, Can. J. Psychiatry 2013

*Weitz et al, JAMA Psychiatry 2015

Important perspectives in a balanced appraisal of the merits of antidepressant Rx - V:

- Response to antidepressant medication appears to be symptom specific:
- Depressed mood, guilt, suicide ideation, psychic anxiety and general somatic sx (e.g. fatigue, headache, backache) show larger improvement with Rx versus CBT*

Boschloo et al, World Psychiatry, 2019

Important perspectives in a balanced appraisal of the merits of antidepressant Rx - VI:

- Reminder: The discoveries of early ADMs:
- Isoniazid (MAOI) – tx of tuberculosis
  - Clinical trials found improved mood, energy, appetite, and sleep
- Imipramine (TCA) – tx of schizophrenia
  - Clinical trials found improved mood, energy, activity, and enjoyment

Hillhouse & Porter, Exp Clin Psychopharm, 2015

Alternative Summary

- As severity increases, the advantage of antidepressant Rx over placebo increases
- Antidepressants may also cause significant side effects, especially in the elderly population
- Alternatives to antidepressant medication warrant routine consideration:
  - If **standard** in-person CBT is accessible OR
  - If depression symptoms are mild to moderate AND
  - The patient preference is non-medication AND
  - There is adequate patient motivation to adhere to the requirements of non-medication treatments

Psychological Treatments for Major Depression

Therapy modality	Acute Treatment	Maintenance
Cognitive Behavioral Therapy (CBT)	**1st line; level 1**	**1st line; level 1**
Interpersonal Therapy (IPT)	**1st line; level 1**	2nd line; level 2
Behavioral Activation (BA)	**1st line; level 1**	2nd line; level 2
Mindfulness Based Cognitive Therapy	2nd line; level 2	**1st line; level 1**
Short Term Psychodynamic Therapy	2nd line level 2	Limited evidence
Internet and Computer Assisted Therapy	2nd line; level 2	Limited evidence
Telephone delivered CBT or IPT	2nd line; level 2	Limited evidence

Access to and Coverage for CBT

- Many Employee Assistance Plans provide “CBT”
- Many health insurers cover some (limited) psychology care
- HSC Mental Health Program has 4 session “CBT classes”
- CBT books
  - **“Mind Over Mood”** (Greenberger & Padesky)
  - **“Feeling Good”** (David Burns)
- Low-cost internet-based CBT: **“MoodGym”**
- Free App-based CBT:
  - **“Depression CBT”** (Android)
  - **“Mood Tools”** (iOS and Android)
- Low-cost App-based Mindfulness Meditation:
  - **“Headspace”**
  - **“Calm”**

Limitations of inexpensive alternatives to "standard" CBT

- Lower grade evidence
- Not clear that they are "equally effective"
- Missing non-specific interpersonal elements of in-person psychological treatment
- Patient motivation may be low
- Patient adherence may be low
- *The "prescriber" of self-help psychological approaches needs to be knowledgeable about the content*
- The "prescriber" should still follow up and assess adherence and outcome

Physical and Meditative Treatments for MDD

Intervention	Indication	Priority	Evidence	Alone?
Exercise	**Mild/Mod MDD**	**1st line**	**Level 1**	**Monotherapy**
Exercise	Mod to severe MDD	2nd line	Level 1	Adjunct
Light therapy	**Seasonal MDD**	**1st line**	**Level 1**	**Monotherapy**
Light therapy	Mild/moderate MDD	2nd line	Level 2	Mono/Adjunct
Yoga	Mild/moderate MDD	2nd line	Level 2	Adjunct
Acupuncture	Mild/moderate MDD	3rd line	Level 2	Adjunct
Sleep deprivat	Mod/severe MDD	3rd line	Level 2	Adjunct

CANMAT 2016 Guidelines

Limitations of exercise therapy as an alternative to ADM

- "Willing study participants" in exercise studies may not be representative of typical practice
- Not clear that it is "equally effective"
- Large motivational and adherence issues
- "Probably" best to be aerobic, *at least* 3 times per week, *at least* 30-45 minutes duration
- The "prescriber" should still follow up to evaluate adherence and outcome

Limitations of light therapy as an alternative to ADM

- Lower grade evidence in non-seasonal MDD
- Not clear that it is equally effective in non-seasonal MDD
- Adherence issues esp. in patients who don't rise early
- Needs to be done "right"
  - Morning light exposure
  - Bright full spectrum light = 10,000 lux
  - Typically 30 minutes exposure
- Needs the right equipment
  - (e.g. **Northern Light Technologies**)

Natural Health Products or "Nutraceuticals"

Intervention	Indication	Priority	Evidence	Alone?
St. John's Wort	**Mild/Mod MDD**	**1st line**	**Level 1**	**Monotherapy**
St. John's Wort	Mod/Severe MDD	2nd line	Level 2	Adjunct
Omega-3	Mild/Mod MDD	2nd line	Level 1	Mono/Adjunct
Omega-3	Mod/Severe MDD	2nd line	Level 2	Adjunct
SAM-e	Mild/Mod MDD	2nd line	Level 1	Adjunct
SAM-e	Mod/Severe MDD	2nd line	Level 2	Adjunct
Tryptophan	Mild/Mod MDD	Don't Use	Level 2	

Limitations of St. John's Wort as an alternative to ADM

- Variability in the available products
- Not inexpensive, if used as in most studies (ie. 300 mg of standardized extract TID)
- Not side-effect-free (e.g. G.I. upset, allergy, fatigue, restlessness, photosensitivity)
- Should not be combined with SSRI type medications
- The "prescriber" should still follow up to assess adherence and outcome

What about watchful waiting?

- WW has only been tested in milder illness
- WW is not “doing nothing” and per protocol requires scheduled follow-up visits (e.g. 6 – 8 visits over 10 – 12 weeks)
- ADM is not consistently superior to WW in primary care, though overall outcomes do favor ADM*
- You may still end up using an ADM

*Iglesias-Gonzalez et al, Eur Psychiatry, 2018

N.I.C.E "Stepped Care" Approach (updated April 2018)

Focus of the intervention	Nature of the intervention
STEP 4: Severe and complex depression; risk to life; severe self-neglect	Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multiprofessional and inpatient care
STEP 3: Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression	Medication, high-intensity psychological interventions, combined treatments, collaborative care[b] and referral for further assessment and interventions
STEP 2: Persistent subthreshold depressive symptoms; mild to moderate depression	Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions
STEP 1: All known and suspected presentations of depression	Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions

National Institute for Health and Care Excellence, 2018

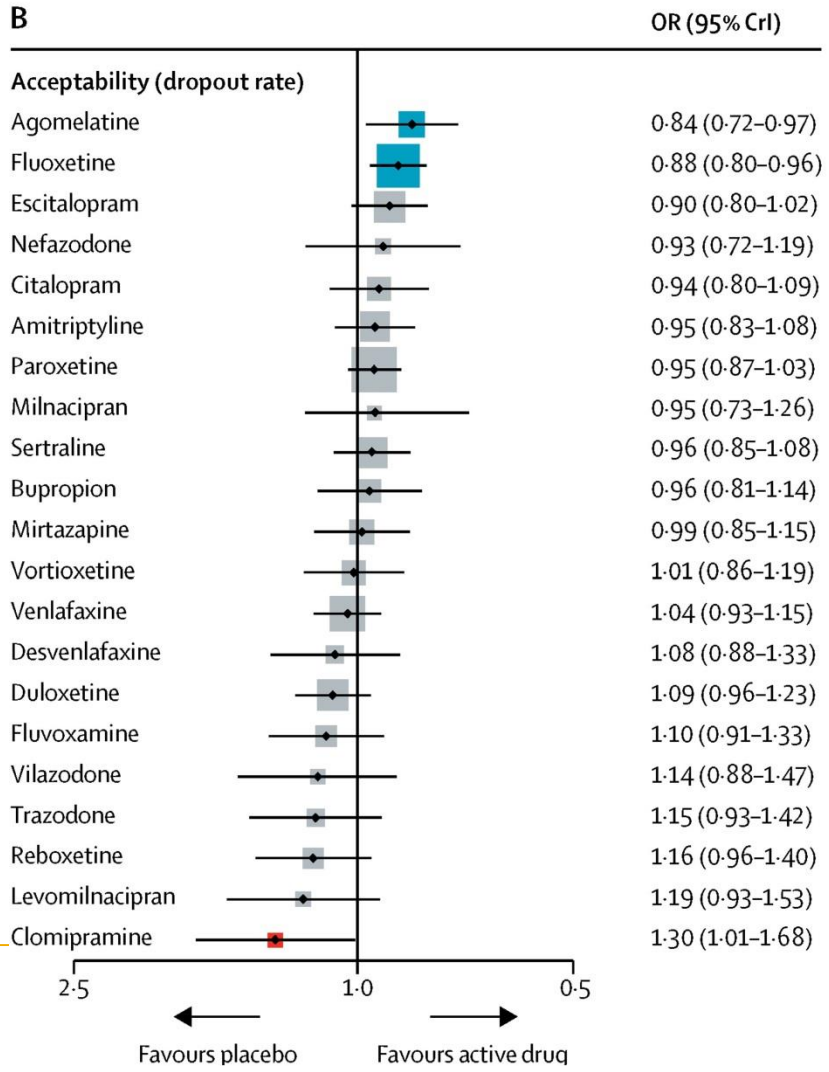
Minimizing harms from ADM

- Choose an agent with high acceptability
- Initiate therapy with a low dose “lead in”
- Monitor outcome with a rating of depression severity (e.g. PHQ9)
- Be prepared to de-prescribe and/or change therapy in response to non-response
- Combine with other non-medication approaches

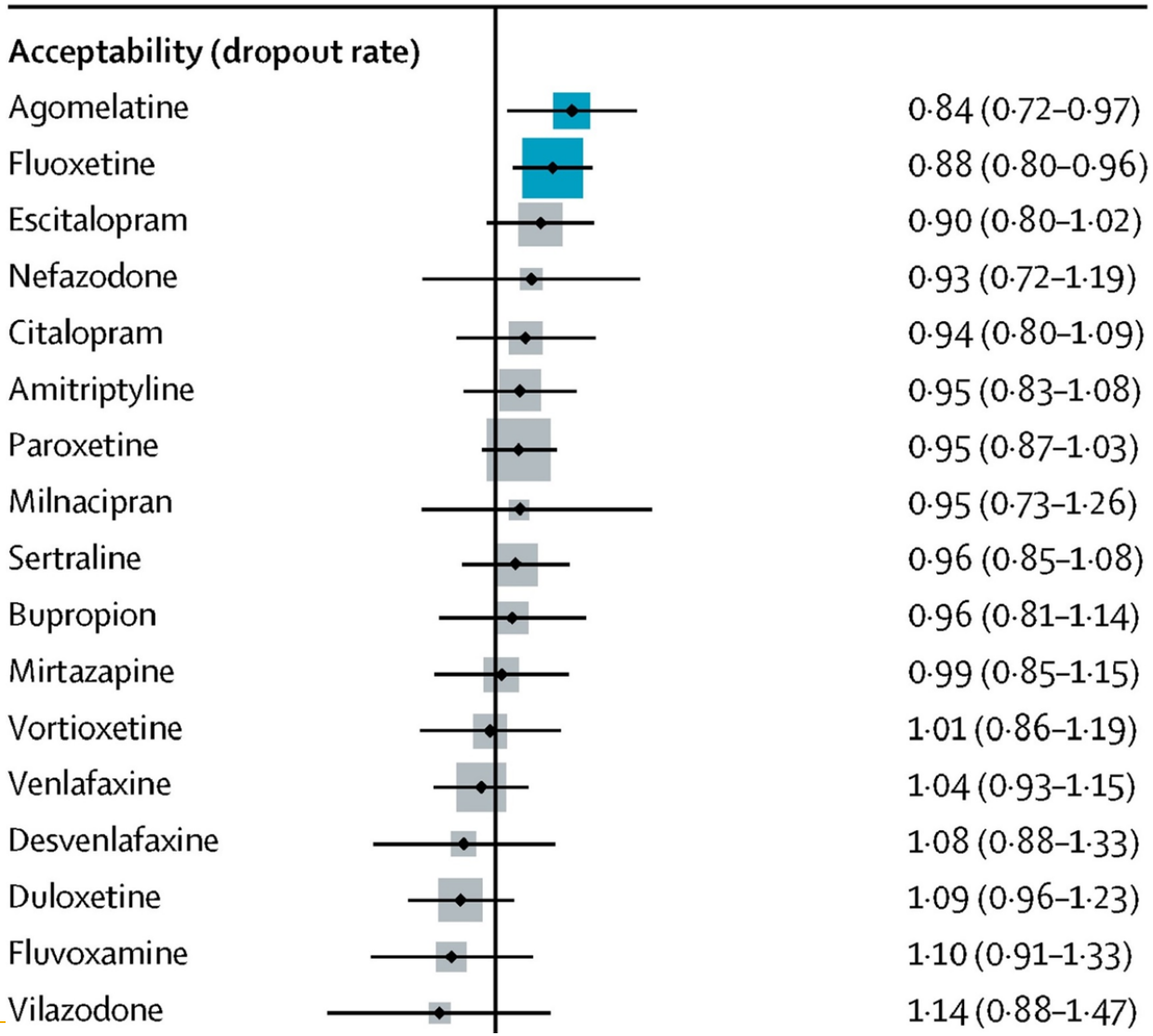
Cipriani et al, Lancet, April 2018: "Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for Major Depressive Disorder"

- Very large network meta-analysis
- 522 double-blinded clinical trials included
- 116,477 adult participants
- Mean age 44 years; 62% women
- Median duration of treatment = 8 weeks

Acceptability Comparison of Antidepressants



Cipriani et al, 2018


Acceptability (dropout rate)
Agomelatine
0·84 (0·72–0·97)
Fluoxetine
0·88 (0·80–0·96)
Escitalopram
0·90 (0·80–1·02)
Nefazodone
0·93 (0·72–1·19)
Citalopram
0·94 (0·80–1·09)
Amitriptyline
0·95 (0·83–1·08)
Paroxetine
0·95 (0·87–1·03)
Milnacipran
0·95 (0·73–1·26)
Sertraline
0·96 (0·85–1·08)
Bupropion
0·96 (0·81–1·14)
Mirtazapine
0·99 (0·85–1·15)
Vortioxetine
1·01 (0·86–1·19)
Venlafaxine
1·04 (0·93–1·15)
Desvenlafaxine
1·08 (0·88–1·33)
Duloxetine
1·09 (0·96–1·23)
Fluvoxamine
1·10 (0·91–1·33)
Vilazodone
1·14 (0·88–1·47)

Network meta analytic data from "Head to Head" comparisons

- Superior acceptability combined with favorable efficacy data –
  - *escitalopram,*
  - *sertraline,*
  - *vortioxetine*
  - Odds ratios ranging 0.51 to 0.84 vs other ADs

Cipriani et al, 2018; Cipriani et al, 2009 Lancet

Cipriani & Geddes, BMC Medicine, 2014

- “As clinicians, we make decisions every day, integrating individual clinical expertise and patients' preferences and values with the best, up-to-date research data. The quality of scientific information must be improved, but we still think that valid conclusions to help clinical practice can be drawn from a critical and cautious use of the best available, if flawed, evidence.”

- **QUESTIONS?**