# I cant fight that feeling: Stopping (and Starting) SSRIs

McMaster University | HEALTH SCIENCES Family Medicine

THE MEDS CONFERENCE
Medications, Evidence & Decision Support

**Dee Mangin**

# Disclosure

- **Faculty:** Dee Mangin

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Public funding only (CIHR, NIHR, NHS, Labarge Optimal Aging Fund, Ontario Health Services research Fund)
  - **Speakers Bureau/Honoraria:** Nil
  - **Consulting Fees:** Nil
  - **Other**: I have provided expert witness reports for the plaintiff in class action legal cases taken against pharmaceutical companies. Any fees are donated to an independent patient drug side effect information and reporting website RxISK.org


  - **Contact details:** mangind@mcmaster.ca

**@DeeMangin**

# Mitigating Potential Bias

- Not applicable

# A typical Monday?

You check your labs and find the MSU culture is actually negative on a woman who came in with dysuria and frequency.

9:00 65 year old woman with chest infection and signs of pneumonia needing admission to hospital

9:15 69 year old woman repeat prescription of Fluoxetine 40mg which she has been taking for 5 years without problems

9:45 Mother at the end of her tether trying to deal with tantrums in her 2 year old, has heard iron deficiency can cause behaviour problems

10:00 A 85 year old woman who is confused, bought in by her daughter with a bag with 9 medicines in it

10:15 A 90 year old woman recently discharged after carpal tunnel release, started on a statin in hospital and anxious about her 'heart condition'

- Examine evidence for effectiveness in primary care patients
- The context of prescribing SSRIs in multimorbidity
- Evidence for prescribing in multimorbidity
- Common adverse reactions and interactions to watch for
- Evidence for maintenance therapy in primary care
- How to stop

# Generalisability considerations

- Primary care setting
- Publication bias
- Trial quality
- Multimorbidity

# Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis

Andrea Cipriani, Toshiaki A Furukawa, Georgia Salanti, John R Geddes, Julian P T Higgins, Rachel Churchill, Norio Watanabe, Atsuo Nakagawa, Ichiro M Omori, Hugh McGuire, Michele Tansella, Corrado Barbui

Lancet 2009; 373: 746–58

Published Online January 29, 2009 DOI:10.1016/S0140-6736(09)60046-5

See Comment page 700

Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Italy (A Cipriani PhD, C Barbui MD, Prof M Tansella MD); Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan (Prof T A Furukawa MD, N Watanabe PhD, I M Omori PhD); Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Greece (G Salanti PhD); Department of Psychiatry, University of Oxford, UK (A Cipriani, Prof J R Geddes MD); MRC Biostatistics Unit Institute of Public Health, University of Cambridge, UK (J P T Higgins PhD); Cochrane

## Summary

**Background** Conventional meta-analyses have shown inconsistent results for efficacy of second-generation antidepressants. We therefore did a multiple-treatments meta-analysis, which accounts for both direct and indirect comparisons, to assess the effects of 12 new-generation antidepressants on major depression.

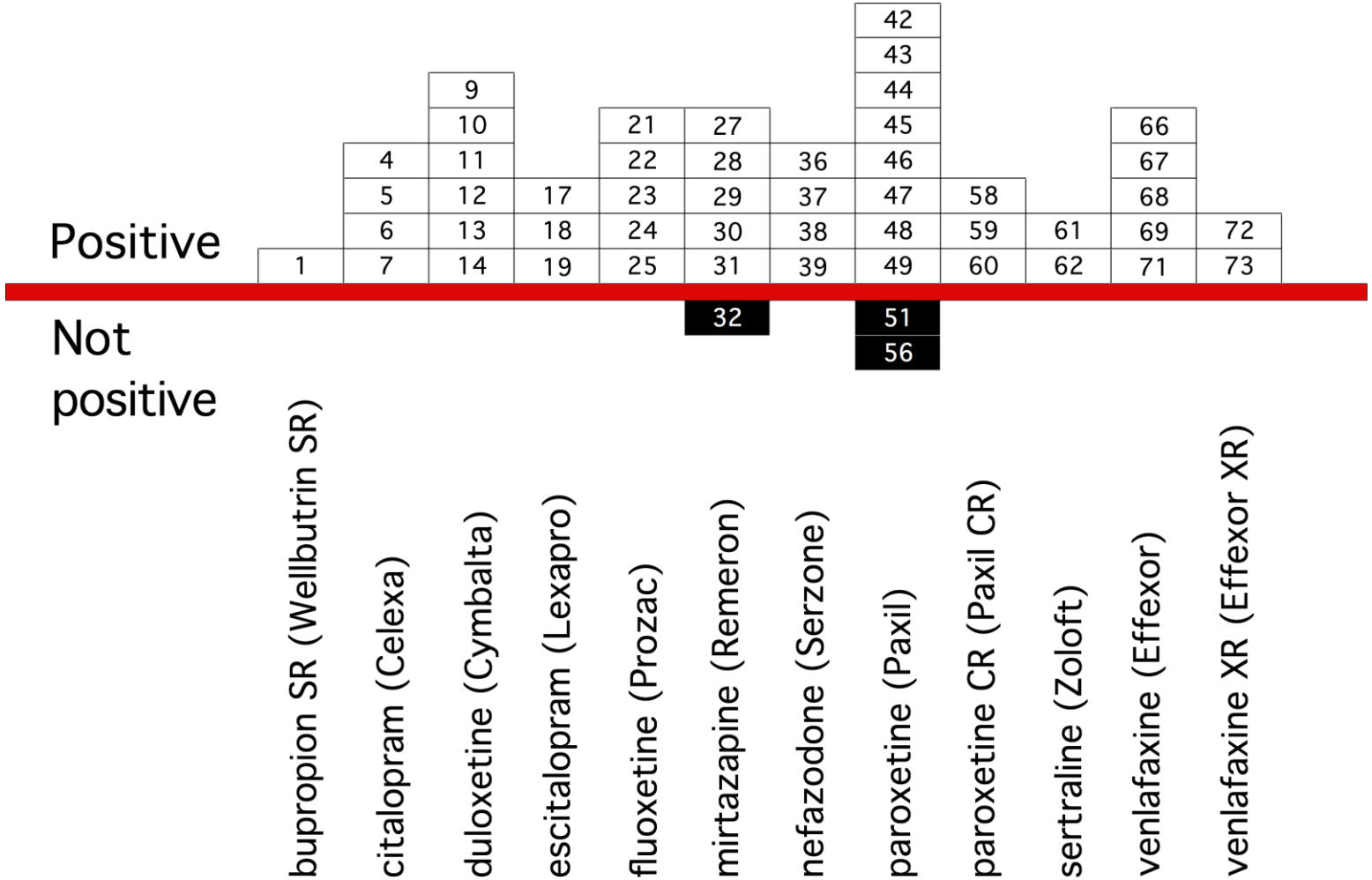
**Methods** We systematically reviewed 117 randomised controlled trials (25 928 participants) from 1991 up to Nov 30, 2007, which compared any of the following antidepressants at therapeutic dose range for the acute treatment of unipolar major depression in adults: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine. The main outcomes were the proportion of patients who responded to or dropped out of the allocated treatment. Analysis was done on an intention-to-treat basis.

**Findings** Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine (odds ratios [OR] 1·39, 1·33, 1·30 and 1·27, respectively), fluoxetine (1·37, 1·32, 1·28, and 1·25, respectively), fluvoxamine (1·41, 1·35, 1·30, and 1·27, respectively), paroxetine (1·35, 1·30, 1·27, and 1·22, respectively), and reboxetine (2·03, 1·95, 1·89, and 1·85, respectively). Reboxetine was significantly less efficacious than all the other antidepressants tested. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine.

**Interpretation** Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost.

**Funding** None.

# What we know about publication bias in studies of acute treatment

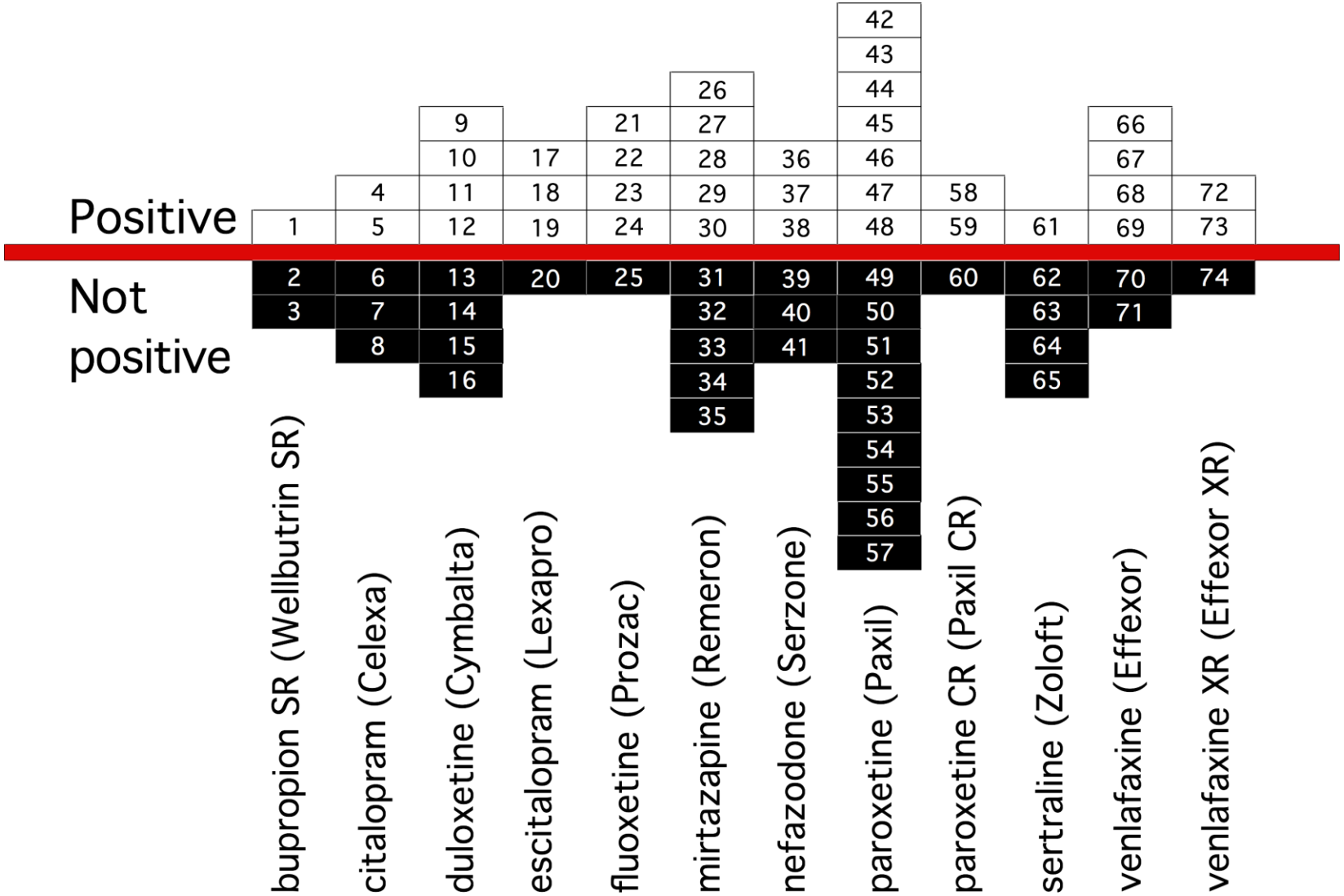



McMaster University | HEALTH SCIENCES Family Medicine

Reproduced with permission of Dr Erick Turner

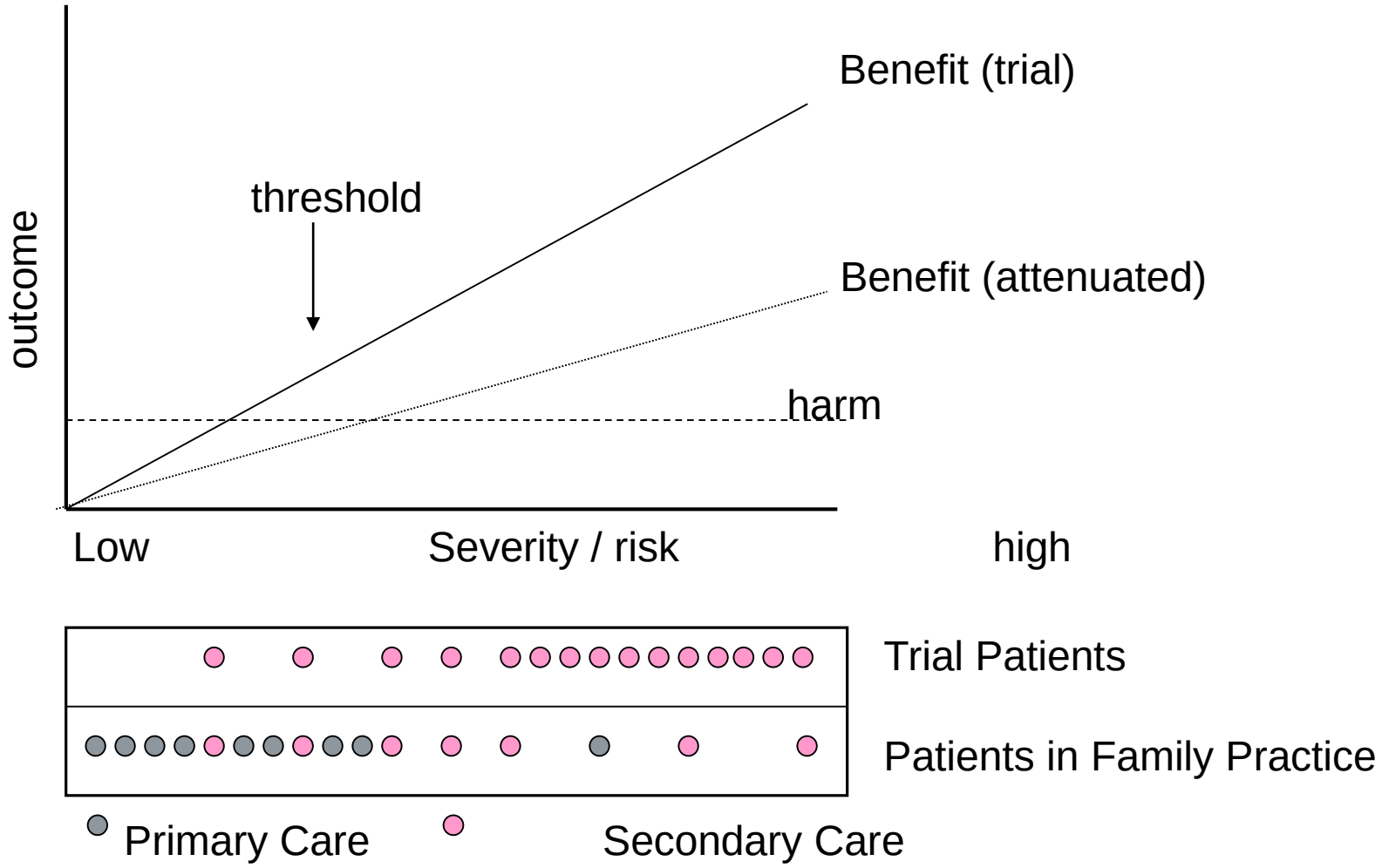
Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. NEJM . 2008

Michael G. DeGroote SCHOOL OF MEDICINE




Reproduced with permission of Dr Erick Turner

Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. NEJM . 2008

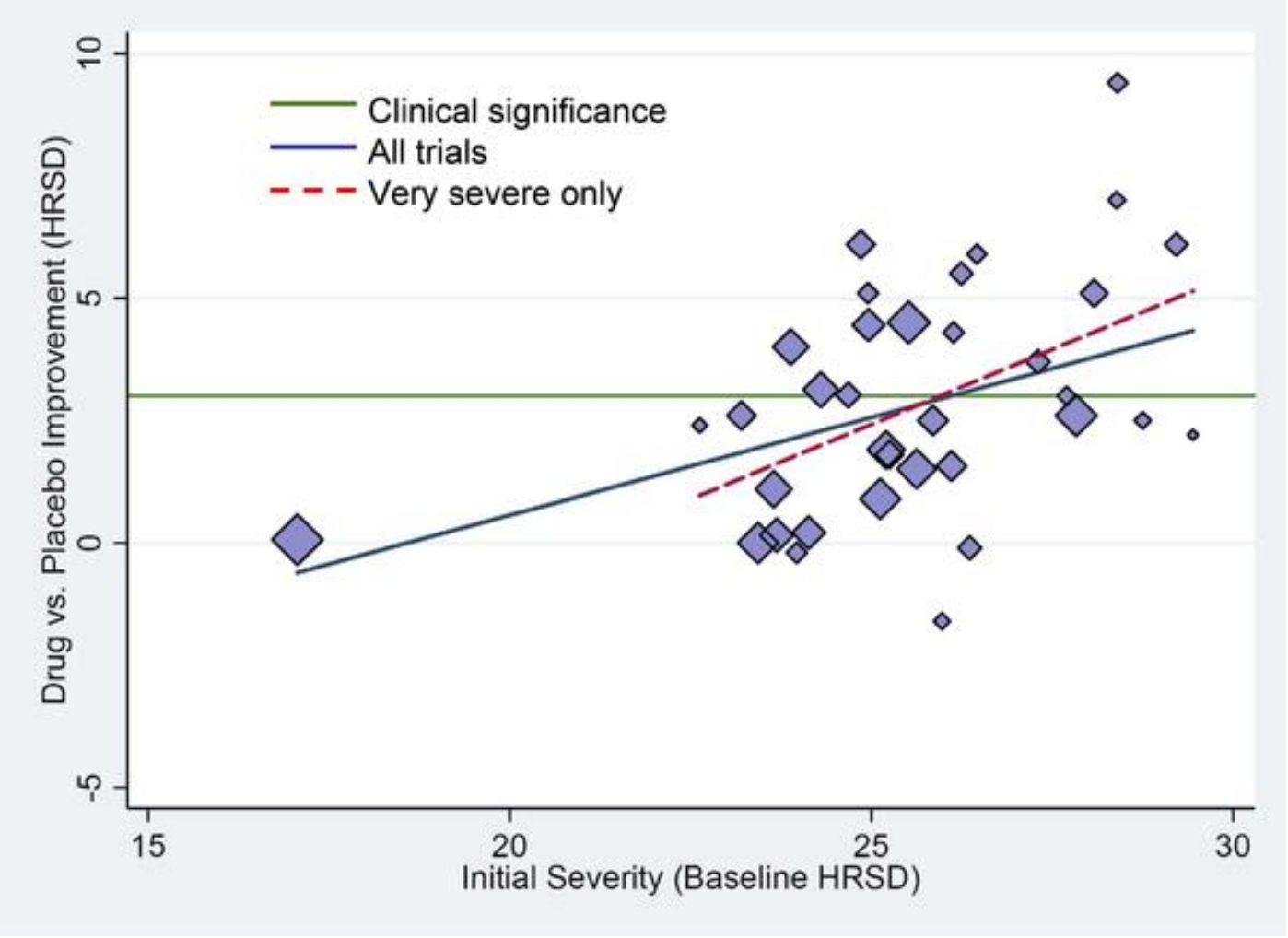



Kendrick Hegarty Glasziou BMJ 2008 Oct 24;337

- Efficacy in adults in primary care
- Effect size around 15% (NNT 7-8)
- Effect is likely overestimated due to publication bias
- Studies mostly included more severe category depression

Arroll B, Chin W-y, Martis W, Goodyear-Smith F, Mount V, Kingsford D, et al.. -Antidepressants for treatment of depression in primary care: a systematic review and meta-analysis. Journal of Primary Health 2016;8(4)

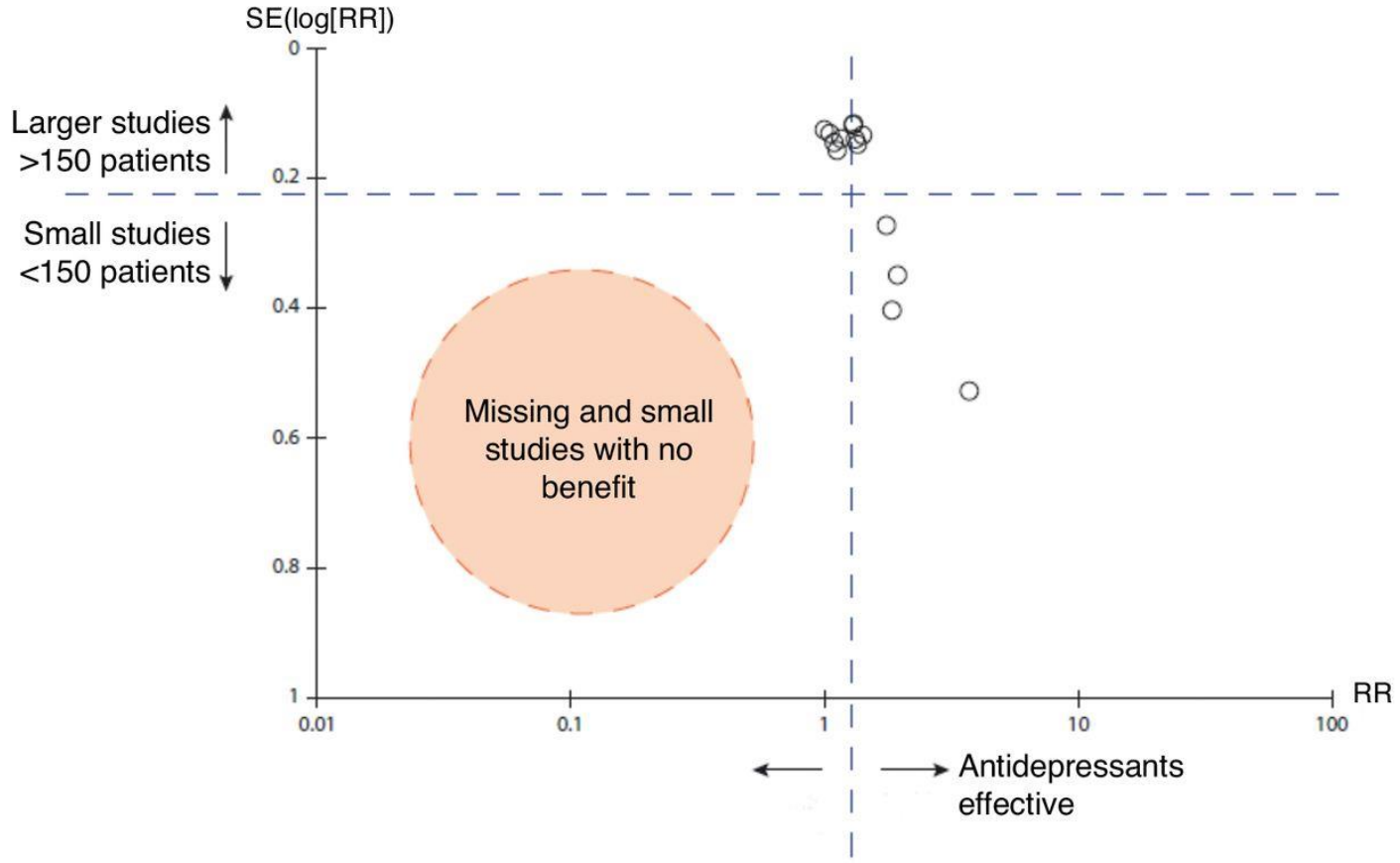
# Figure 4. Mean Drug–Placebo Difference Scores as a Function of Initial Severity




Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, et al. (2008) Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration. PLOS Medicine 5(2): e45. http://doi.org/10.1371/journal.pmed.0050045

http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050045

# Publication bias:
# Funnel plot of SSRI and TCA versus placebo from primary care trials




**From: Arroll et al. Br J Gen Pract Open 2017**

- Antidepressants offer modest clinical benefit in relieving symptoms of depression
- There is no strong evidence that there is any difference in efficacy
- Dropout rates are reasonably high
- Adverse effect rates are similarly high (63%)

Arroll B, Chin W-y, Martis W, Goodyear-Smith F, Mount V, Kingsford D, et al. AnCare. 2016;8(4):325-tidepressants for treatment of depression in primary care: a systematic review and meta-analysis. Journal of Primary Health Care.

Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation ntidepressants for treating major depressive disorder: An updated meta-analysis. Ann Int Medicine. 2011

- There is no evidence supporting difference in efficacy in different symptom ‘clusters’
  - ‘activated’ / anxiety Sx
  - Melancholic
  - Somatising

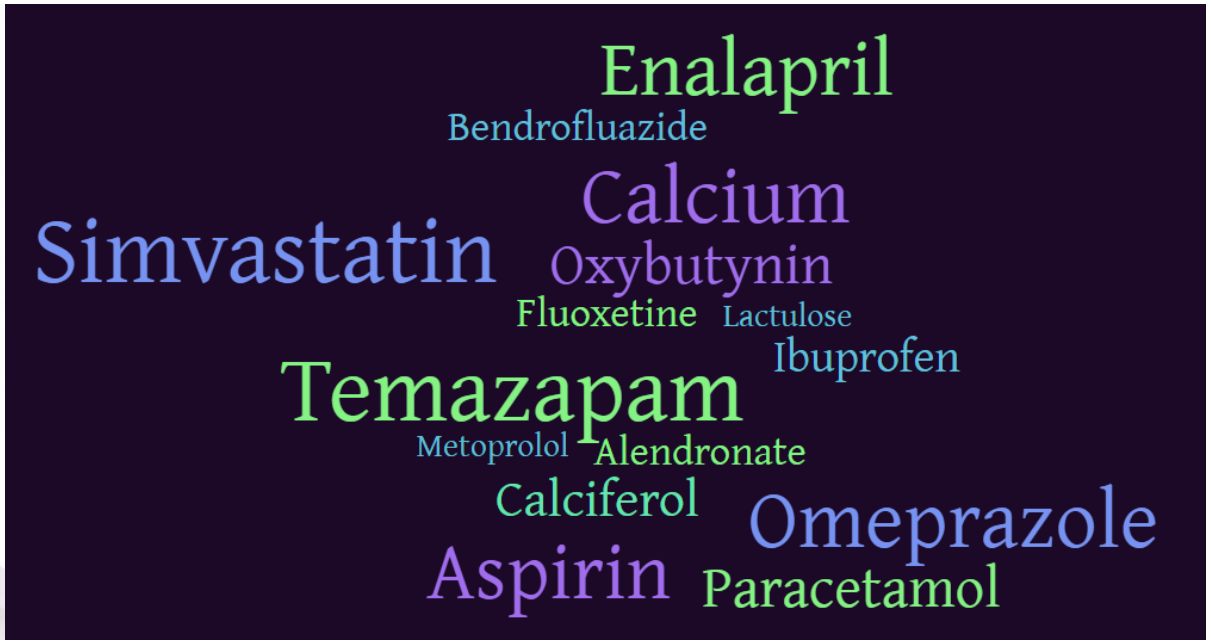
- Except where insomnia was a prominent Sx in the cluster, where trazodone was more effective

Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: An updated meta-analysis. Annals of Internal Medicine. 2011;155(11):772-85.

- There is evidence of different adverse effect profiles
- Some people may not be able to stop
- Some antidepressants are harder to stop
- Shared decision making is the best approach

# Matching treatment thresholds to evidence

| PHQ-9 score | Depression severity | |
|---|---|---|
| 0–4 | None–minimal | |
| 5–9 | Mild | |
| 10–14 | Moderate | |
| 15–19 | Moderate–severe | |
| 20–27 | Severe | |


Enalapril
Bendrofluazide
Calcium
Simvastatin
Oxybutynin
Fluoxetine
Lactulose
Ibuprofen
Temazapam
Metoprolol
Alendronate
Calciferol
Omeprazole
Aspirin
Paracetamol



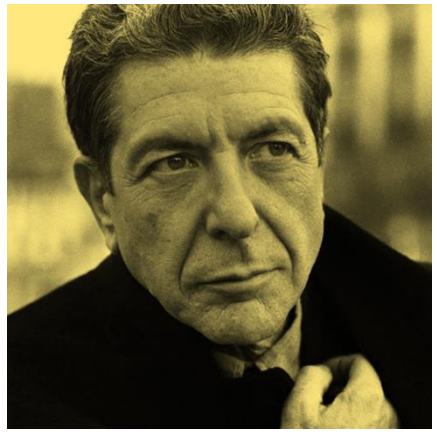










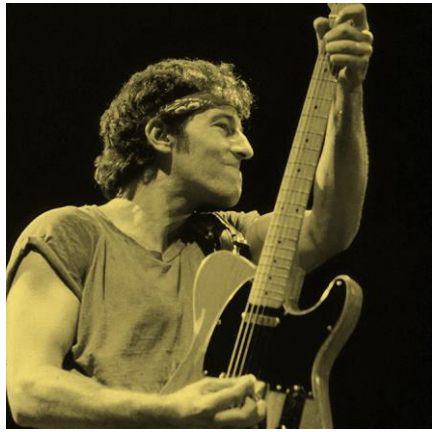






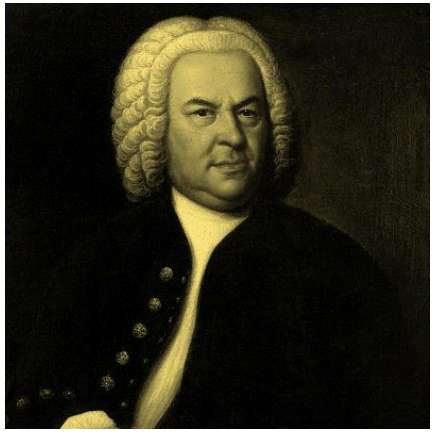


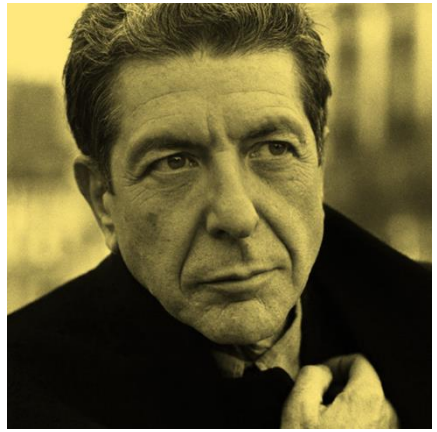


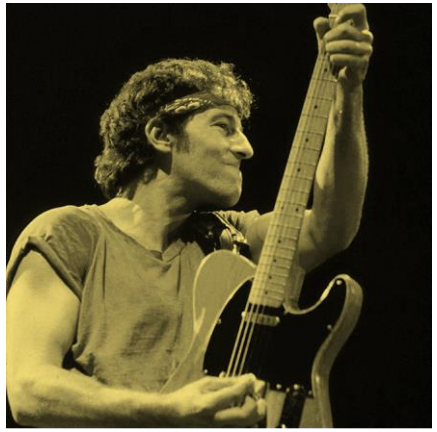












# The Invisible Pandemic

# Canada: Adverse drug effects requiring medical care 13% of those on ≥ 5 medications (>1/3 of our senior patients)

Research

Original Investigation

National Trends in US Hospital Admissions for Hyperglycemia and Hypoglycemia Among Medicare Beneficiaries, 1999 to 2011

Kasia J. Lipska, MD, MHS; Joseph S. Ross, MD; Yun Wang, PhD; Silvio E. Inzucchi, MD; Karl Minges, MPH; Andrew J. Karter, PhD; Elbert S. Huang, MD; Mayur M. Desai, PhD, MPH; Thomas M. Gill, MD; Harlan M. Krumholz, MD, SM

IMPORTANCE The increasing intensity of diabetes mellitus management over the past decade may have resulted in lower rates of hyperglycemic emergencies but higher rates of hospital admissions for hypoglycemia among older adults. Trends in these hospitalizations and subsequent outcomes are not known.

Editor's Note

Supplemental content at jamainternalmedicine.com

Research

Original Investigation

Antihypertensive Medications and Serious Fall Injuries in a Nationally Representative Sample of Older Adults

Mary E. Tinetti, MD; Ling Han, MD, PhD; David S. H. Lee, PharmD, PhD; Gail J. McAvay, PhD; Peter Peduzzi, PhD; Cary P. Gross, MD; Bingqing Zhou, PhD; Haiqun Lin, PhD

# Specific Problems

**Morbidity**

falls, balance and strength, cognition and memory problems, sleep, nutrition, fatigue……

# Older Adults (>60)

- Much less evidence
- Suggests that antidepressants could be modestly effective though effect size less:
  - Absolute difference around 9% NNT 11 for response (less for remission)
- Those with long (>10years) history of illness and more severe illness most likely to respond
- No primary care evidence
- Lack of evidence in those with multimorbidity or frailty

Nelson JC, Delucchi KL, Schneider LS. Moderators of outcome in late-life depression: a patient-level meta-analysis. Am J Psychiatry. 2013

Nelson JC, Delucchi K, Schneider LS. Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. Am J Geriatr Psychiatry. 2008.

- HOWEVER Comorbidities, polypharmacy and ageing all contribute to an increased susceptibility to the adverse effects of antidepressants, as well as increased potential for interactions
- Frail older adults and those with multimorbidity are excluded

- Antidepressants, given with normal care, are **not** clinically effective (compared with placebo) for depression in patients with dementia

Banerjee S, Hellier J, Romeo R, Dewey M, Knapp M, Ballard C, et al. Study of the use of antidepressants for depression in dementia: the HTA-SADD trial--a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine. Health technology assessment (Winchester, England). 2013;17(7):1-166.

# Side effects (initial)

- 63% of patients experience side effects in short term trials
- Diarrhea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction, sweating, tremor, and weight gain were most commonly reported
- Duloxetine and venlafaxine were discontinued more often for AEs in RCTs

Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: An updated meta-analysis. Ann Int Medicine. 2011

# Specific differences

- Venlafaxine: nausea and vomiting
- Sertraline: diarrhoea
- Mirtazepine: weight gain
- Trazodone: somnolence
- Venlafaxine and paroxetine: antidepressant withdrawal syndrome most common (fluoxetine least common)
- Bupropion causes significantly less sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline
- Venlafaxine may carry higher CV risk

Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: An updated meta-analysis. Ann Int Med 2011

# Less clear longer term adverse effects?

- Increased bleeding risk
- Increased risk of falls and fractures in seniors
- Drug interactions (Serotonin syndrome)
- Sleep disturbance
- Reduced bone density
- Reduced emotional reactivity
- Antidepressant withdrawal syndrome

- Increased bleeding risk OR1.67; 95%CI 1.13-2.5
  - GI bleeding; transfusion after hip surgery
  - Risk increased with coprescribed NSAIDs OR 4.25 95% CI 2.82-6.42

References in additional slide in presentation file

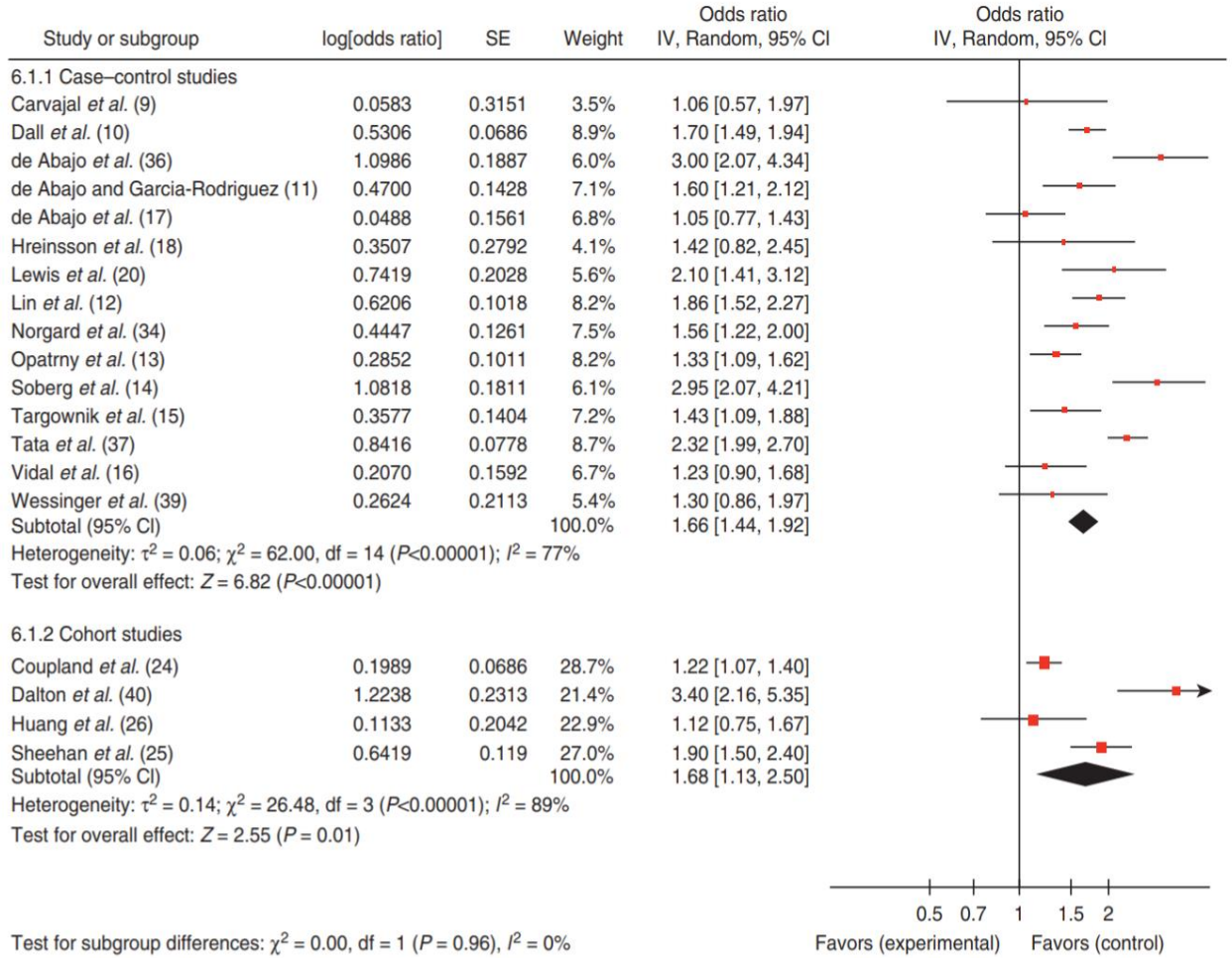



**Figure 2.** Combined Forest plot for the risk of upper gastrointestinal (GI) bleeding with selective serotonin reuptake inhibitor (SSRI) medications.

Anglin R, Yuan Y, Moayyedi P, Tse F, Armstrong D, Leontiadis GI. Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. Am J Gastroenterol. 2014

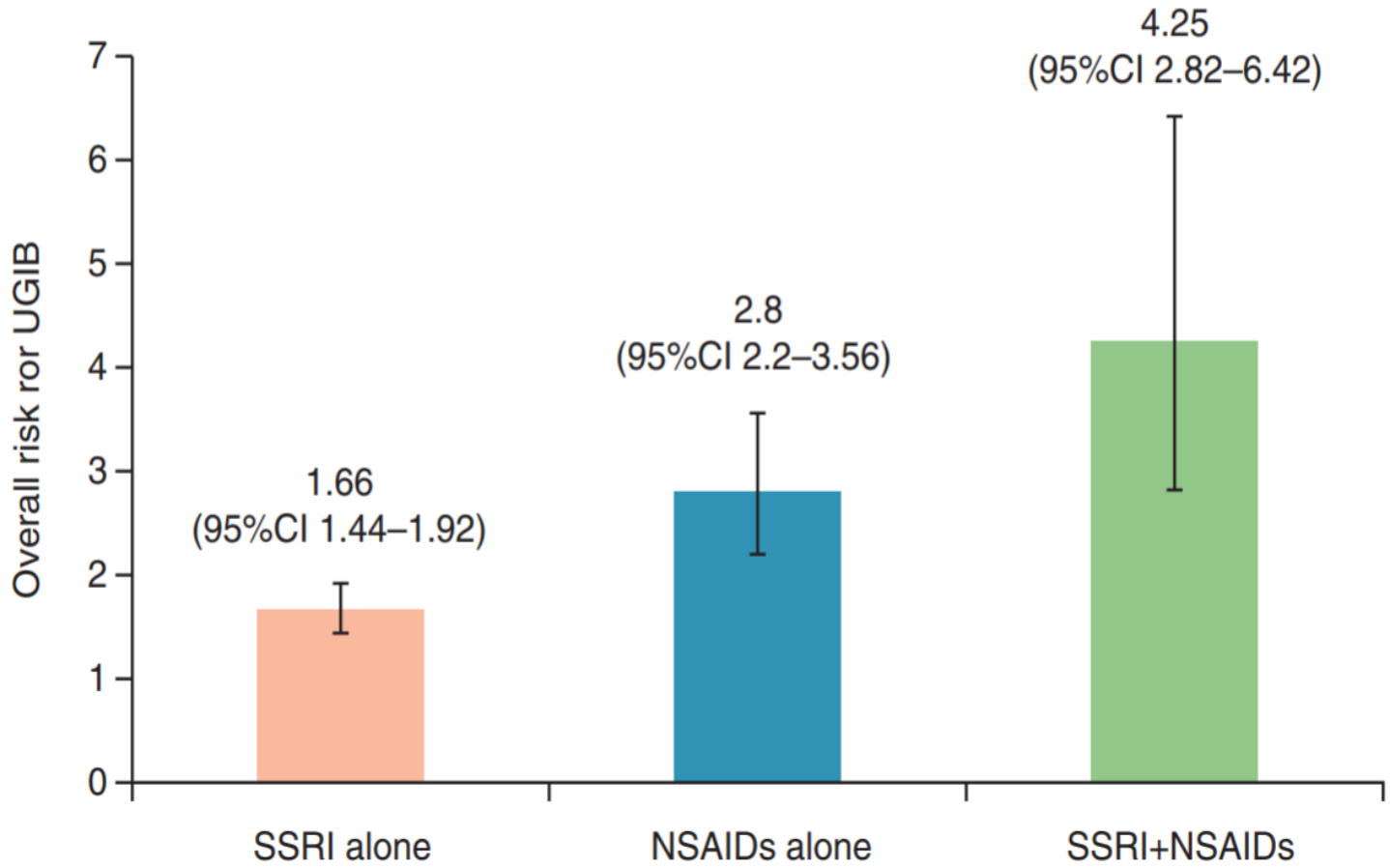



**Figure 3.** Relative contributions of selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatorys (NSAIDs) to the risk of upper gastrointestinal (GI) bleeding.

- Sleep disturbance  e.g.
  - community dwelling older women sleep duration of 5 hours or less multivariate odds ratio (MOR)=2.15, 95% confidence interval (CI)=1.04-4.47),
  - sleep efficiency less than 70% (OR=2.37, 95% CI=1.32-4.25),
  - sleep latency of 1 hour or more (MOR=3.99, 95% CI=2.29-6.96) and eight or more long wake episodes (MOR=1.75, 95% CI=0.99-3.10)

- Increased risk of falls in seniors  e.g. OR: 1.66, 95%CI: 1.36-2.02) Comparative risk consistently higher in SSRIs than TCAs
  - Consistent association and dose response
- Increased fractures  e.g.
  - OR 1.76 (95% CI 1.33-2.32) compared with H2A PPI users;
  - HR, 1.68; 95% CI, 1.32-2.14 for 10 year fracture risk -Canadian study

- Hyponatremia in seniors
- Reduced emotional reactivity  (unclear what proportion and whether differs between drugs)
- Serotonin syndrome in combination with other drugs
- Drug interactions

# Common interactions

# Serotonin Toxicity - Is dose related and may include:

| Neuromuscular effects | Autonomic effects | Mental status changes |
|---|---|---|
| Hyperreflexia | Tachycardia | Agitation |
| Clonus | Hyperthermia | Hypomania |
| Myoclonus | Sweating | Anxiety |
| Shivering | Flushing | Confusion |
| Tremor | Mydriasis | |
| Hypertonia/rigidity | | |

[Medsafe 2010]

# Serotonin Toxicity - dose related & includes:

| Neuromuscular effects | Autonomic effects | Mental status changes |
|---|---|---|
| Hyperreflexia | Tachycardia | Agitation |
| Clonus | | Hypomania |
| Myoclonus | | Anxiety |
| Shivering | | Confusion |
| Tremor | Mydriasis | |
| Hypertonia/rigidity | | |

OLDER ADULTS

[Medsafe 2010]

# Drugs with potential for serotonin toxicity when used in combination

- SSRIs, SNRIs
- Some TCAs
- Opioids – especially tramadol
- Illicit substances
- Rizatriptan, sumatriptan
- OTC: St John's Wort, cough mixtures
- Lithium
- MAOIs
- Buspirone
- Isoniazid

# Bleeding

- NSAIDS
- Antiplatelet agents
- Warfarin and other anticoagulants
- Atorvastatin?

# QT prolongation

- Unpredictable and invisible
- Risk increases with age, electrolye abnormalities (watch for PPIs diuretics)

QT prolongation resource : crediblemeds.org

# Depression in multimorbid/frail older adults

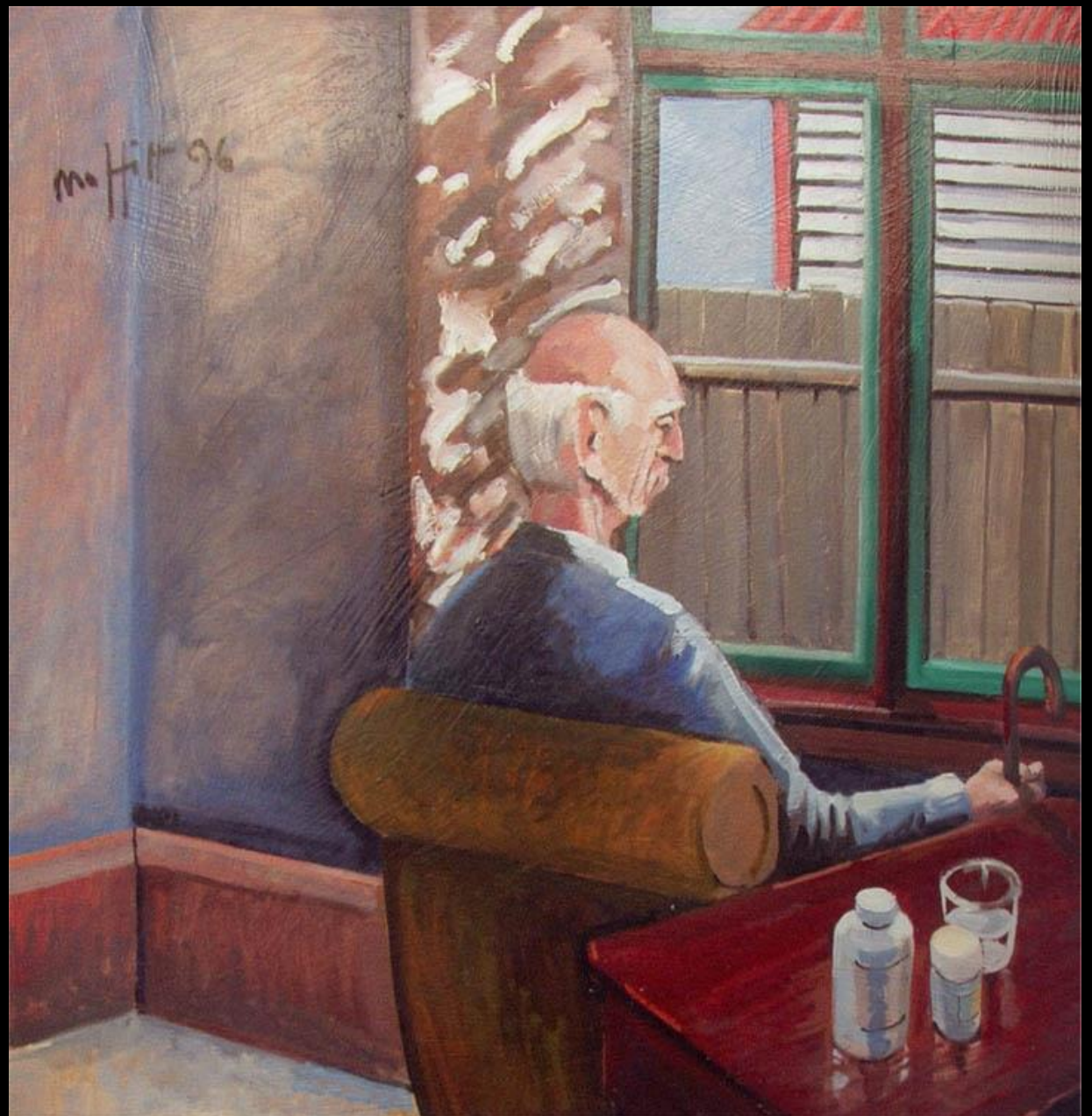
- Consider other causes (DSM)
- Consider drug causes
- Consider other treatments
- Consider context

# The Empty Mailbox

**T Moffitt**

With kind permission of Moffitt family

# OK Grandad, You Look Out the Window and I'll be Back in 3 Hours



**T. Moffitt**

With kind permission of
Moffitt family

- Risks of AEs are higher
- For mild to moderate depression psychotherapy is the treatment of choice
- Use antidepressants with restraint

# SSRIs: Duration and monitoring

# SSRIs Duration and Monitoring

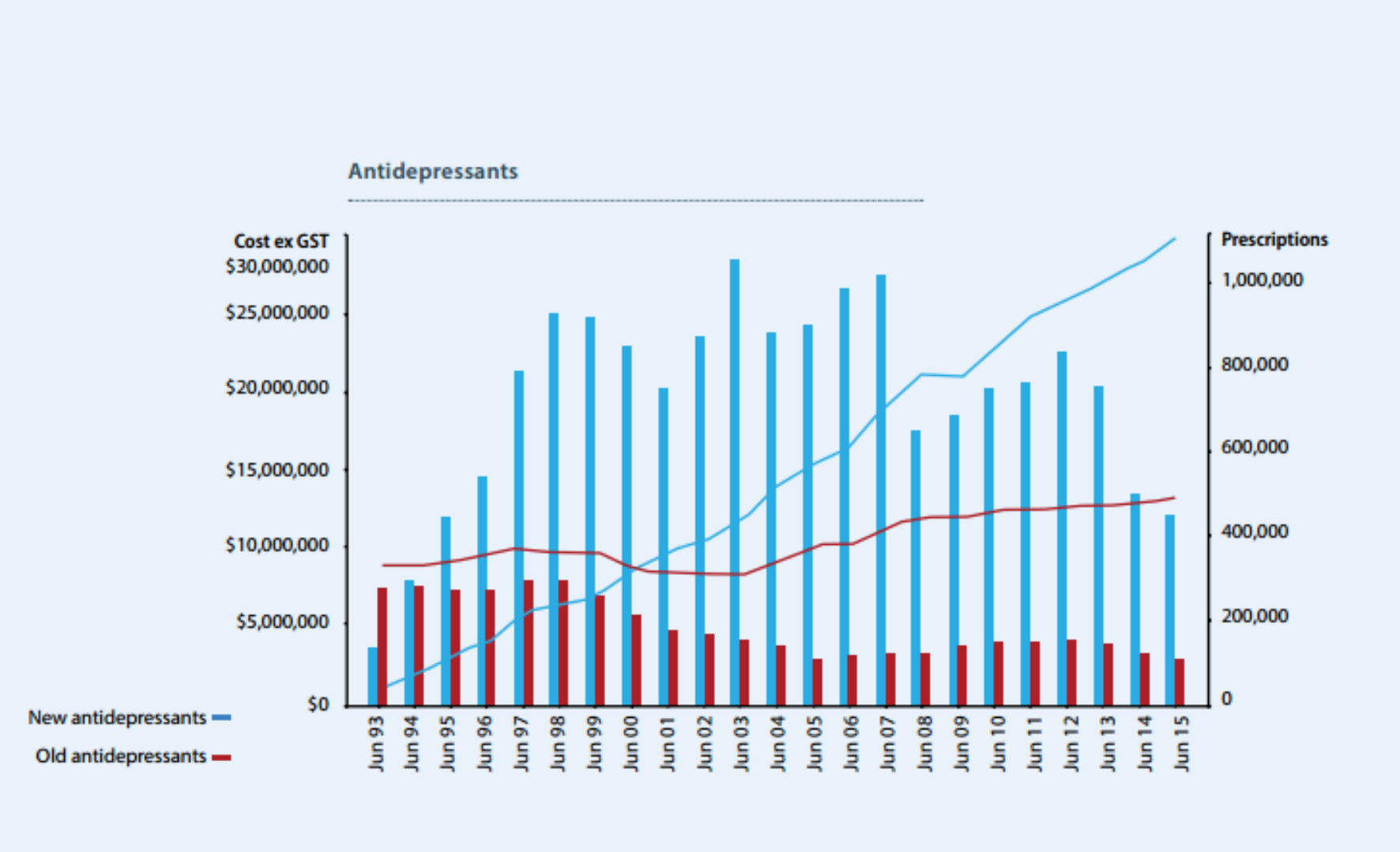
- Trials largely only extend to 8 weeks.
- Evidence suggests continuation to 6 months likely to be of benefit, more lmited evidence for 12 months
- General recommendations are for 6-9 months after remission (the duration of an episode)
- Set up patients expectations for the duration of the treatment ‘course’ AT THE OUTSET and note in the chart with stopping reminder

Glue P, Donovan MR, Kolluri S, Emir B. Meta-analysis of relapse prevention antidepressant trials in depressive disorders. Australian and New Zealand Journal of Psychiatry. 2010;44(8):697-705.

# Monitoring

- Frequently early and until response
- Na+ in selected patients (Hx, hyponatremia, on diuretics, older)
- Discuss discontinuation syndrome, adverse effects including rare red flag events
- Discuss time to response

# STOPPING




Source: PHARMAC Year in Review 2015

TREATING X for TWO

McMaster University | HEALTH SCIENCES Family Medicine

Michael G. DeGroote SCHOOL OF MEDICINE

# Legacy Drugs

# Legacy Drugs

| | |
|---|---|
| **Antidepressants** | **46%** |
| **Bisphosphonates** | **14%** |
| **PPIs** | **45%** |

Current prescription >60%

Mangin D, Lawson J, Cuppage J et al 2017

# Maintenance treatment recommendations

*‘3 or more episodes’*

*‘additional risk factors for recurrence (e.g. ongoing psychosocial stressors)’*

*‘patient preference’*

*‘comorbid conditions’*

***‘In many patients……. treatment will be required indefinitely’***

American Psychiatric Association

# Summary of The Problem

- Many guidelines for primary care recommend maintenance treatment with SSRIs in certain patients:
- There is little evidence to support this but it is driving widespread SSRI use
- There are increasing reports of adverse effects of long term use

# Examining the evidence base for benefit

- Meta-analysis of maintenance treatment  after initial response to SSRIs show relapse rate 41% on placebo vs 18% on active treatment
- Absolute difference 23% NNT 4-5

Geddes et al Lancet 2005

# Trial design flaws

- Almost all trials before need for tapering known
- Many short duration or still during the acute treatment phase
- Outcome measures  inadequate  (‘return of symptoms’)
- No trials in primary care population where 90% of prescription occurs

# Primary care trial

- In primary care, maintenance antidepressants prevent an episode of depression in the subsequent 18 months in 12.8% of patients.  NNT (18 months) is 8
- **7/8 patients taking long term SSRI experienced no benefit**
- For every 16 taking medication one is unable to discontinue because of intolerable withdrawal symptoms. (NNH 16)
- It seems reasonable to trial withdrawal NNTrial = 2

# Are patients worse off for trying to stop?

On measures of interviewer and patients reported mood, quality of life and functioning, overall psychological distress / symptoms, social and occupation functioning….

**No suggestion of poorer outcomes at 18 months for those who trial discontinuation**

# Domains of withdrawal symptoms

**Somatic**

- disequilibrium (e.g. dizziness, ataxia, vertigo),
- gastrointestinal symptoms (e.g. nausea, vomiting)
- flu-like symptoms (e.g. fatigue, lethargy, myalgia, chills)
- sensory disturbances (e.g. parasthesiae, electric shock sensations)
- sleep disturbances (e.g. insomnia, vivid dreams)

**Psychological**

- anxiety/agitation, irritability and bouts of crying

**Do** sometimes result in a change in depression scale scores (i.e. they can like the original indication)

From: Discontinuation Emergent Signs and Symptoms Scale

# How to stop

- Little evidence to guide best way to stop SSRIs
- Evidence that some have more significant discontinuation symptoms than others (paroxetine, venlafaxine): an important consideration when you are choosing a treatment to start
- Various approaches advocated
  - Switch to longer half life (as with benzos: NO EVIDENCE THIS IS HELPFUL)
  - Taper off (seems rational but no evidence for rate of taper)
  - Alternating days: unhelpful especially with shorter half life drugs

# Leaping into the void….

(evidence free) practical suggestions

**P-E-T**

# 1 Preparation

- Explain to the patient that stopping can be easy or more difficult
- Patients on antidepressants for longer may need a longer taper:
    - On them for months – take weeks to stop
    - On them for years – take months to stop
- Prepare the patient for discontinuation effects, and reassure them they (especially unusual sensations) are not harmful or life threatening
- Rare but important: Warn specifically about emergent suicidal ideation and akathisia and what to do

# 2 Engagement

- Let patients know they will be no worse off for trying to discontinue
- Suggest they engage family and friends as supports
- Optimise non pharmacological  management options

# 3 Taper

- All SSRIs need tapering (yes fluoxetine too)
- A test drop in dose of say 10% may signal the required rate of taper
- Put control of the taper rate in the patients hands
- Suggest:
  - If 10% is OK try dropping by 25% steps
  - If not stay at 10% or less increments
- Some patients have trouble with the final drop – if this appears to be happening suggest an exponential decay rather than linear drop (e.g. halve or quarter the previous dose each time)

# Taper - monitoring

Have a clear plan about

- **What** to monitor
- **Who** will monitor
- **How often**
- What the agreed **criteria for considering restarting** are

Patients will feel more reassured about trialling a taper if it is framed as ‘pause and monitor’ knowing they can restart. This is one of patient’s expressed fears about deprescribing of any medication.

- For those needing smaller increment drops you can tablet split or get  a liquid preparation (find a local compounding pharmacy)
- If the patient cannot afford compounding, most tablet form, non extended release SSRIs can be dissolved and a proportion of the resultant (well shaken) liquid can be calculated (Consult a pharmacist near you to confirm solubility and support pt) *
- Some people may not be able to discontinue completely and the lowest dose required to control discontinuation symptoms will minimise harms  (***"Dose size does matter"*** McCormack, J)

*dissolved tabs liquid cant be stored

# P4 Quaternary prevention

Mangin D, Heath I. Multimorbidity and Quaternary Prevention RBMFC 2015

McMaster University

# HEALTH SCIENCES

## Family Medicine

Department of Family Medicine
Michael G. DeGroote School of Medicine
Faculty of Health Sciences

fhs.mcmaster.ca/fammed
@McMasterFamMed