How Research Informs Clinical Practice

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5 Feb 2024

What kind of psychiatric research can you do?

- Epidemiology
- Randomised controlled trials
- Genetics
- Imaging
- Cognitive neuroscience
- Social science
- Immunology
- Endocrinology

Prevention

- study aetiology of illness
- advice on prevention

Treatments

- develop new treatments
- evaluate treatments - RCTs

Understanding

- mechanisms of illness
- patients want to understand their illness

ANTIDEPRESSANT EFFECTIVENESS

Increased prescription of antidepressants

- 30m prescriptions in 2005
- 61m prescriptions in 2015
- 76m prescriptions in 2020

- The increase has been in long term or maintenance treatment
- In 2017, 17% of people in England received a prescription
- There are about 1.5m people in England who have been on antidepressants for 2 or more years

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*

Summary

Background Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.

Methods We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016. We included placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalised criteria. We excluded quasi-randomised trials and trials that were incomplete or included 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness. We extracted data following a predefined hierarchy. In network meta-analysis, we used group-level data. We assessed the studies' risk of bias in accordance to the Cochrane Handbook for Systematic Reviews of Interventions, and certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework. Primary outcomes were efficacy (response rate) and acceptability (treatment discontinuations due to any cause). We estimated summary odds ratios (ORs) using pairwise and network meta-analysis with random effects. This study is registered with PROSPERO, number CRD42012002291.

Lancet 2018; 391: 1357–66

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See Comment page 1333

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522 trials

116,477 participants

Antidepressant trials: existing evidence

- Usually conducted decades ago for regulatory purposes by pharmaceutical industry
- Poor quality: 82% at moderate/high risk of bias
- Larger more recent placebo-controlled trials -> smaller effect sizes, perhaps reflecting more rigorous methods
- Most trials done in secondary care; eligibility criteria based on diagnosis and severity - not used in clinical practice and never validated

The clinical effectiveness of sertraline in primary care and the role of depression severity and duration (PANDA): a pragmatic, double-blind, placebo-controlled randomised trial

Gemma Lewis, Larisa Duffy, Anthony Ades, Rebekah Amos, Ricardo Araya, Sally Brabyn, Katherine S Button, Rachel Churchill, Catherine Derrick, Christopher Dowrick, Simon Gilbody, Christopher Fawsitt, William Hollingworth, Vivien Jones, Tony Kendrick, David Kessler, Daphne Kounali, Naila Khan, Paul Lanham, Jodi Pervin, Tim J Peters, Derek Riozzie, George Salaminios, Laura Thomas, Nicky J Welton, Nicola Wiles, Rebecca Woodhouse, Glyn Lewis

Summary

Background Depression is usually managed in primary care, but most antidepressant trials are of patients from secondary care mental health services, with eligibility criteria based on diagnosis and severity of depressive symptoms. Antidepressants are now used in a much wider group of people than in previous regulatory trials. We investigated the clinical effectiveness of sertraline in patients in primary care with depressive symptoms ranging from mild to severe and tested the role of severity and duration in treatment response.

Lancet Psychiatry 2019

Published Online September 19, 2019 https://doi.org/10.1016/S2215-0366(19)30366-9

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what are the indications for Prescribing ANtiDepressAnts that will lead to a clinical benefit?

Clinical implications

- Main benefits of sertraline in early weeks of treatment are on reducing anxiety symptoms such as worry and restlessness
- Any effect of depression is more modest and takes longer to emerge
- An improvement in anxiety symptoms in someone with depressive symptoms is likely to be of clinical benefit
- Sertraline leads to anxiety reductions in a wider range of patients than previously studied, including those with milder depressive symptoms who do not meet diagnostic criteria for depression or GAD

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Headlines


Daily Mail

FRIDAY, DECEMBER 29, 2017 www.dailymail.co.uk NEWSPAPER OF THE YEAR 65p

GPs treble doses of anti-depressants as Britain heads towards top of world table

A NATION HOOKED ON HAPPY PILLS

BRITAIN is becoming hooked on anti-depressants, a global study suggests today.

Prescription rates have nearly trebled in 15 years, putting the UK fourth among 29 Western nations.

Britons take nearly twice as many of the 'happy pills' as counterparts in France, Italy and the Netherlands. Experts last night said patients were demanding a quick fix to avoid feeling down.

Others blamed GPs for fobbing off depressed patients with pills because waiting lists for in-depth treatment were too long.

The UK rate of consumption for anti-depressants is 94.2 doses a day for every 1,000 inhabitants, according to the Organisation for Economic Co-operation and Development. This is up from 37.6 doses in 2000.

The research body's study said patients were increasingly willing to ask for help, meaning every rich nation had seen a rise in use of drugs such as Prozac.

But it added: 'There is significant variation in consumption of anti-depressants between

By Ben Spencer
Medical Correspondent

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Stop dishing out pills for depression, doctors told

Kat Lay Health Editor

Doctors should prescribe fewer anti-depressants and for a shorter time, experts said, after a review found no strong evidence that the drugs were effective.

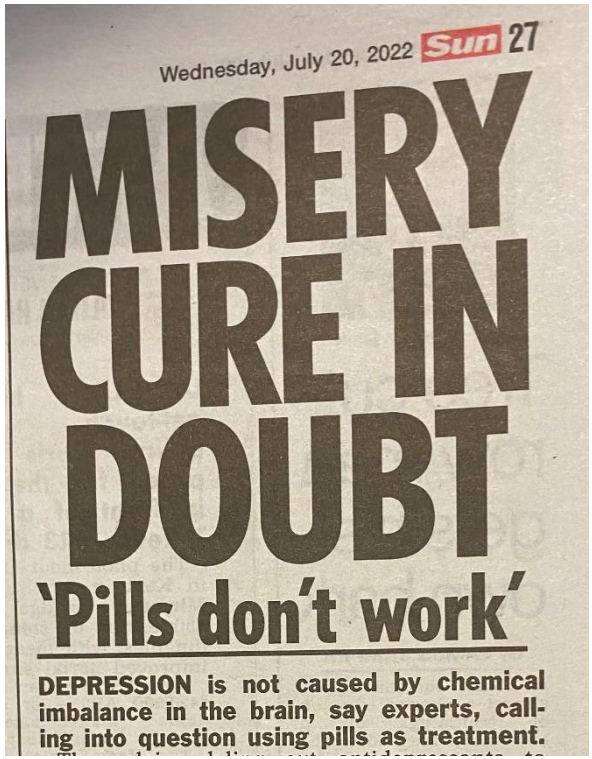
The benefits of the medication were uncertain but many patients had side effects and withdrawal symptoms, which could be severe, researchers said.

Trial data had failed to show a "clinically relevant" difference between the drugs and a placebo, according to the findings, published online in the Drug and Therapeutics Bulletin.

An estimated 7.8 million people in England — roughly one adult in six — were given at least one prescription for antidepressants in 2019-20. Rates were 50 per cent higher in women and the number of youngsters aged between 12 and 17 who were prescribed the drugs more than doubled between 2005 and 2017.

The researchers, from University College London and Royal Cornwall Hospitals NHS Trust, said the balance between benefit and harm from the drugs was uncertain and that "we should revisit the widespread — and growing — prescription of antidepressants".

Although the drugs might have a role for some people with severe depression, their widespread long-term use is


Wednesday, July 20, 2022 Sun 27

MISERY CURE IN DOUBT

'Pills don't work'

DEPRESSION is not caused by chemical imbalance in the brain, say experts, calling into question using pills as treatment.

“Antipsychiatry” Critiques of the current evidence base

1. Treatment size is not clinically important
2. RCTs are unblinded because of side effects
3. Relapses are confused with withdrawal symptoms

BINARY OUTCOMES

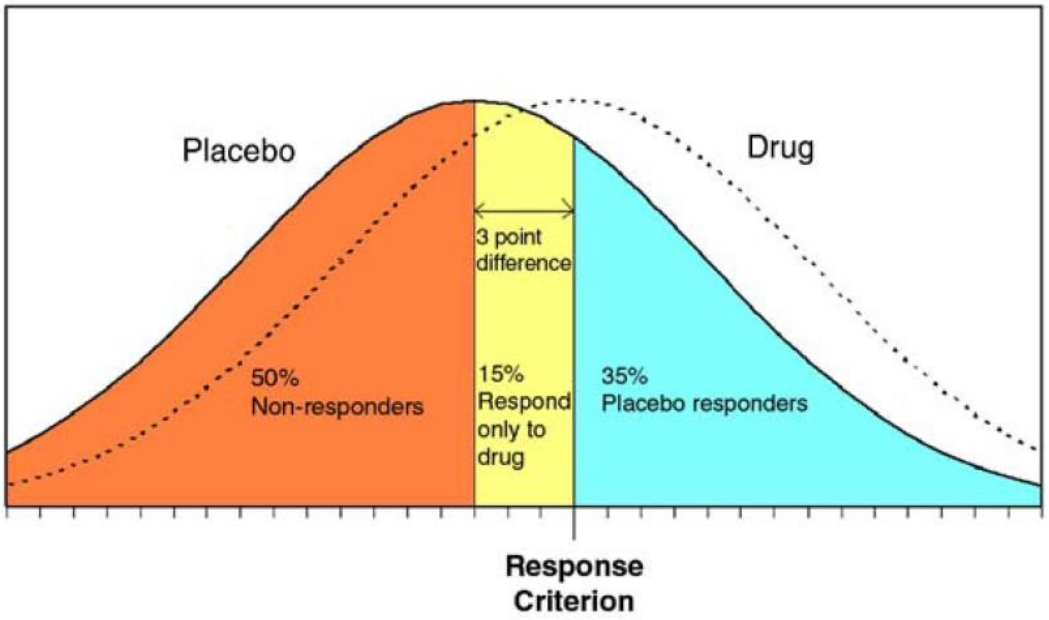
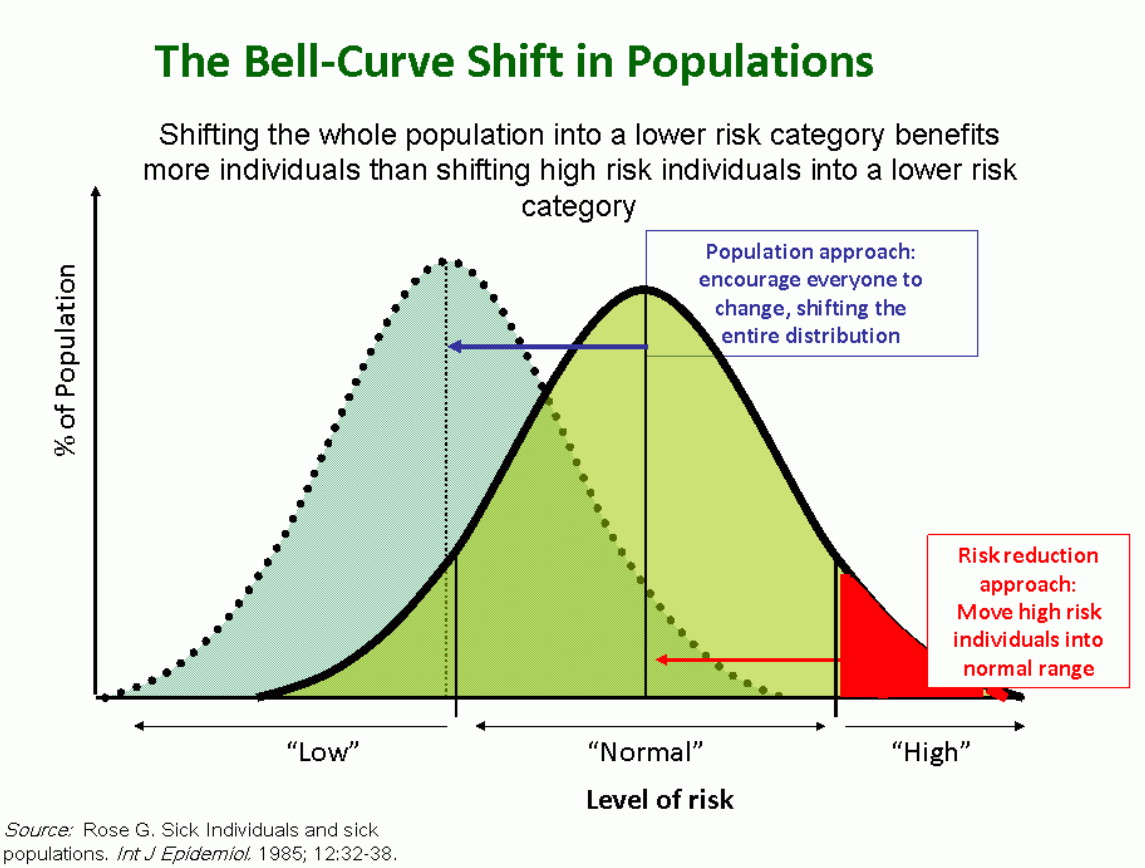


Fig. 1. A 3-point drug-placebo difference on the Hamilton Rating Scale for Depression is relatively small in terms of clinical significance, but it corresponds to an impressive 15% difference in expected response rates.

"Response rates from continuous data do not add information and they can create an unwarranted illusion of clinical effectiveness"

Kirsch Moncrieff 2007; 28: 348-51

Categories vs continua



Rose G Sick Individuals and Sick populations *Int J Epidemiol* 1985 12:32-28

Self-rated global improvement

- “Compared to when we last saw you [2 weeks ago] how have your moods and feelings changed?”
  - Better
  - Slightly Better
  - Same
  - Slightly Worse
  - Worse

- Made binary: feeling the same or worse (0) and feeling slightly better or better (1)

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Self reported improvement

Feeling better on global rating scale (n=586)						
	2 weeks		6 weeks		12 weeks	
	n	n (%)	n	n (%)	n	n (%)
Placebo	292	89 (30)	285	132 (46)	265	112 (42)
Sertraline	279	110 (39)	267	157 (59)	264	156 (59)
Odds ratio (95% CI) p						
Average	1.96 (1.45 to 2.63) <0.0001					
At each Follow Up	1.64 (1.06 to 2.53)		1.90 (1.24 to 2.91)		2.42 (1.56 to 3.75)	
Group by time interaction P value: 0.16						

59% feel better on sertraline vs 42% on placebo

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Categorising using latent class methods

- Used individual data from FDA database
- 232 studies, N=73,388
- Classified outcomes using latent class methods

- “Large response” 24.5% drug vs 9.6% placebo

- “Minimal response” 12.2% drug vs 21.5% placebo

Stone et al *BMJ* 2022; 378: e067606

CONTINUOUS OUTCOMES

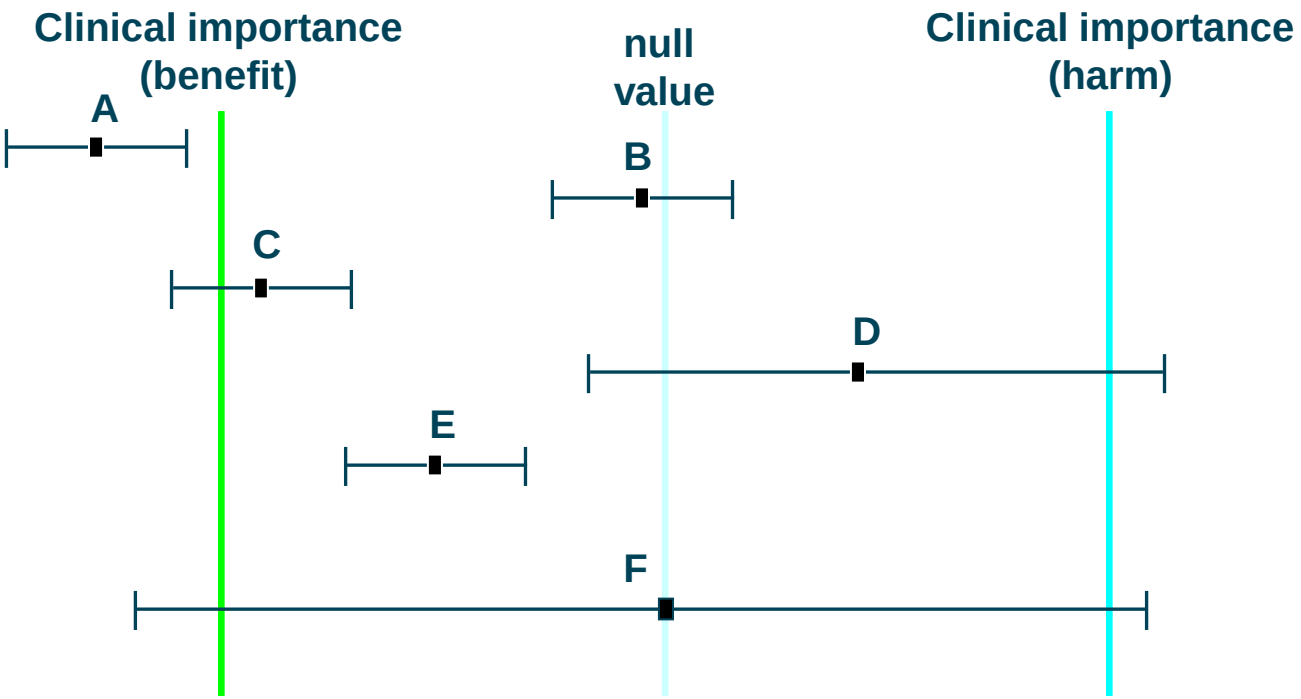
“Effect sizes”

- These rely upon dividing the mean difference by the standard deviation
- Which standard deviation is used varies between studies
- A standard deviation is not a constant – it is a measure of a population and may not be generalisable
- From Cipriani review was about 0.27 standard deviations

Minimal Clinically Important Difference (MCID)

- “The smallest change in a treatment outcome that a patient would identify as important”
- Important for determining the statistical power of a study
- Important for interpreting the results of trials
- “Statistically significant but not clinically significant”

Interpretation of confidence intervals



Methods of determining MCID

- NICE depression guidelines – “consensus”
- “Reliable change index” Jacobson Truax 1991
  - Relies upon distinguishing healthy and ill groups, and the standard deviations of measurement
- None involve the patient perspective
- We used the “anchor” method

Global rating of change

- "Compared to when we last saw you [2 weeks ago] how have your moods and feelings changed?"
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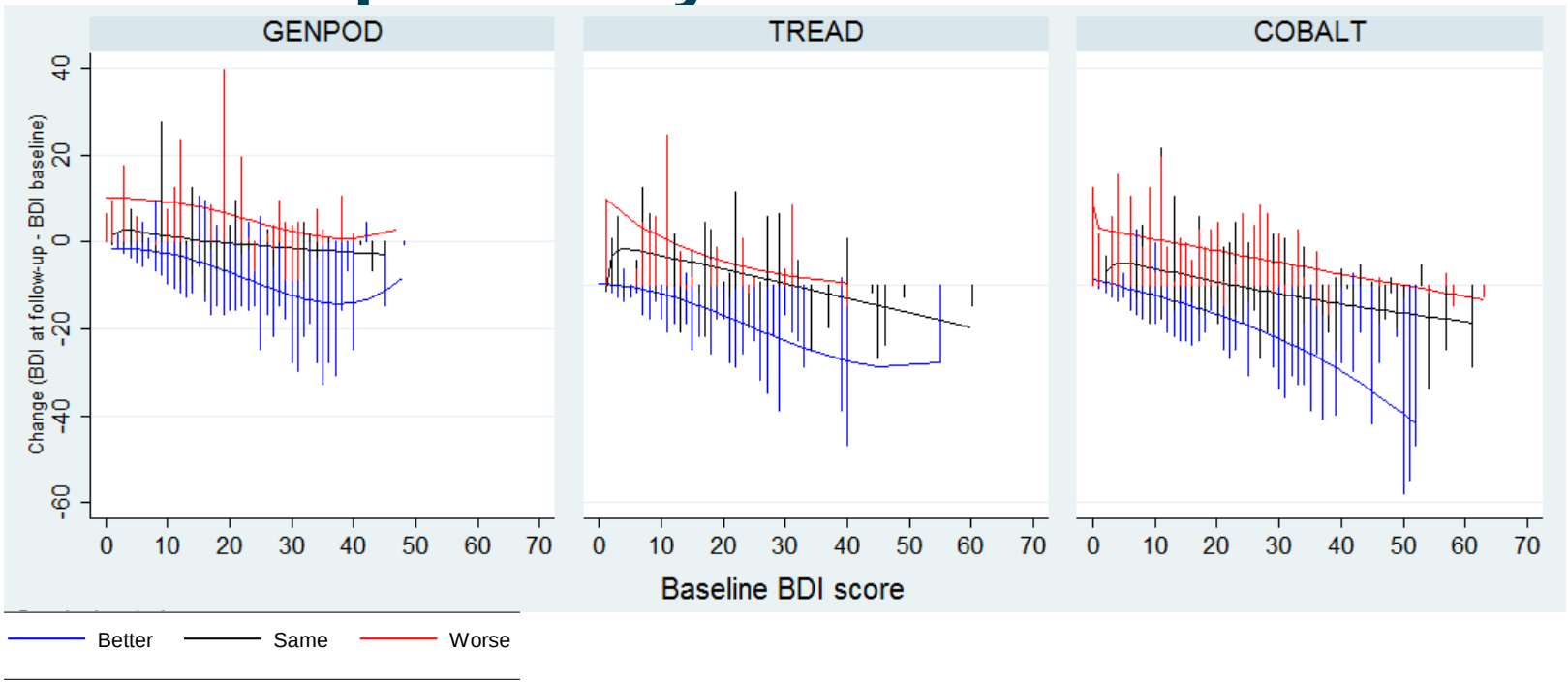
Mean differences in BDI according to Global rating

			Mean (SD)	% change (IQR)
GENPOD	93	Much better	−9.2 (8.2)	−0.54 (−0.77 to −0.27)
	147	Better	−5.0 (7.6)	−0.27 (−0.53 to 0.00)
	49	Same	−0.08 (6.7)	−0.04 (−0.22 to 0.12)
	37	Worse	4.7 (7.7)	0.16 (0.00 to 0.53)
	2	Much worse	19.5 (29.0)	0.99 (−0.12 to 2.10)

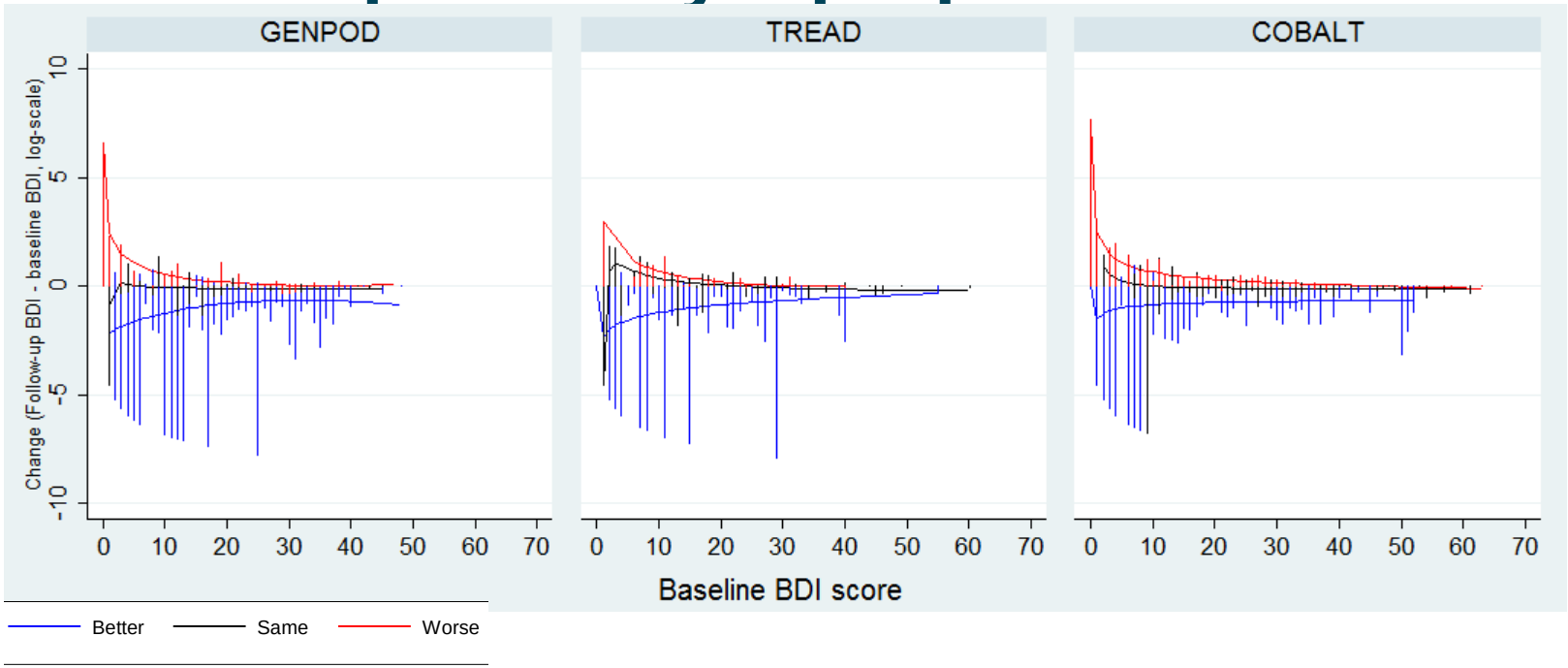
Button et al 2015 *Psychol Med* 45: 3269-3279

Baseline dependency



Button et al *Psychol Med* 2015; 45: 3269-79

Baseline dependency – proportions



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MCID by severity

Instrument Scale	Severity	Threshold score	Threshold as % of baseline	95% change as % of baseline
PHQ9	≤11	−2.0	48.2	(65.1 37.1)
	12–19	−1.7	21.3	(27.9 16.7)
	20+	−2.4	19.7	(24.2 16.4)
BDI	≤11	−5.0	51.7	(66.6 41.6)
	12–19	−3.5	23.8	(30.9 18.6)
	20+	−4.4	19.7	(23.4 16.9)
GAD-7	≤11	−2.2	72.1	(97.3 54.8)
	12–19	−1.5	26.7	(36.2 20.7)
	20+	−0.8	8.9	(10.9 7.3)

Kounali et al *Psychol Med* 2022; 52: 1875-1882

MCID

- MCID varies according to baseline severity
- Percentage reduction (~20%) may be more constant - at least at higher ranges of severity
- At lower severity MCID increases as a %
- At lower severity, it becomes more difficult for patients to detect improvement

Results

Symptoms	Percentage difference: 6 weeks	Percentage difference: 12 weeks
Depressive symptoms	5%	13%
Anxiety symptoms	21%	23%

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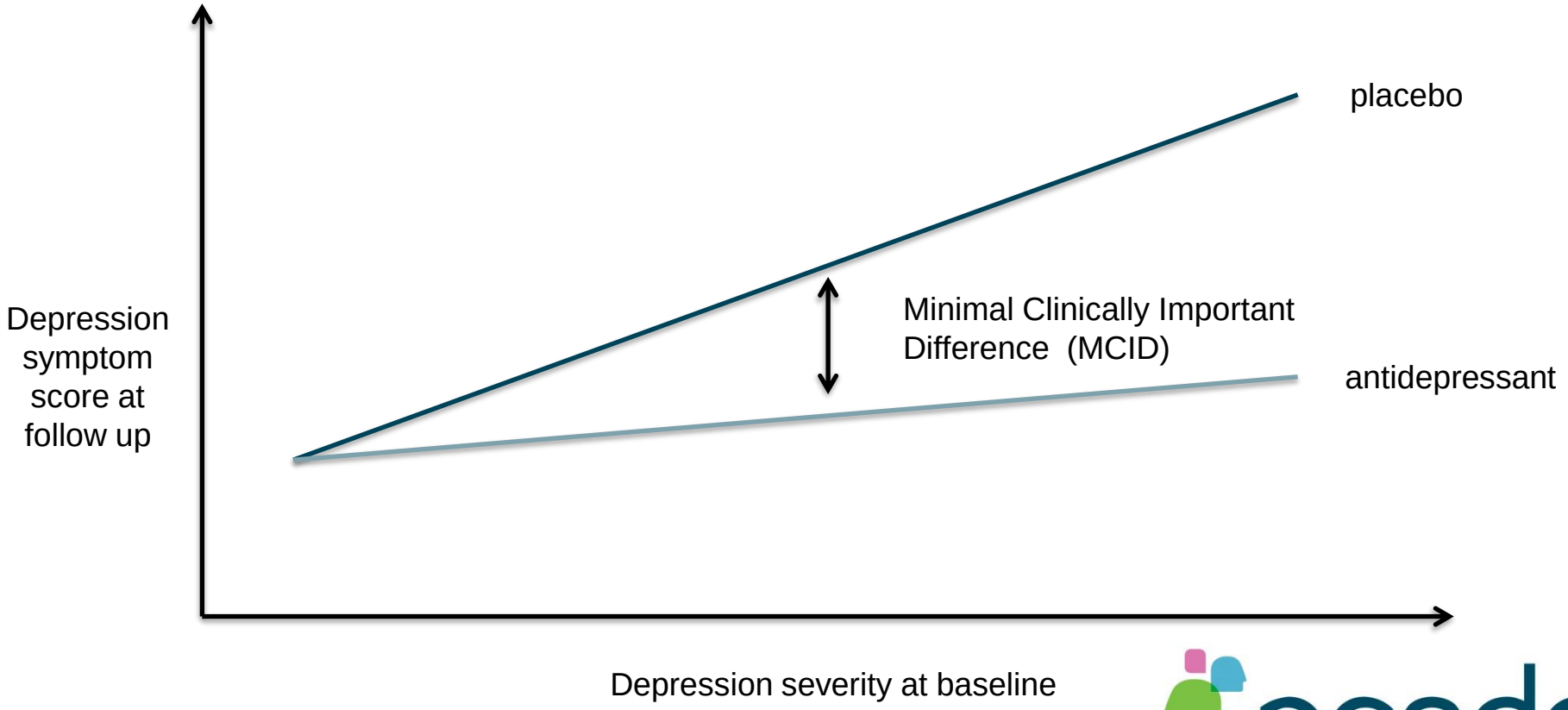
Schematic demonstration of hypothesis



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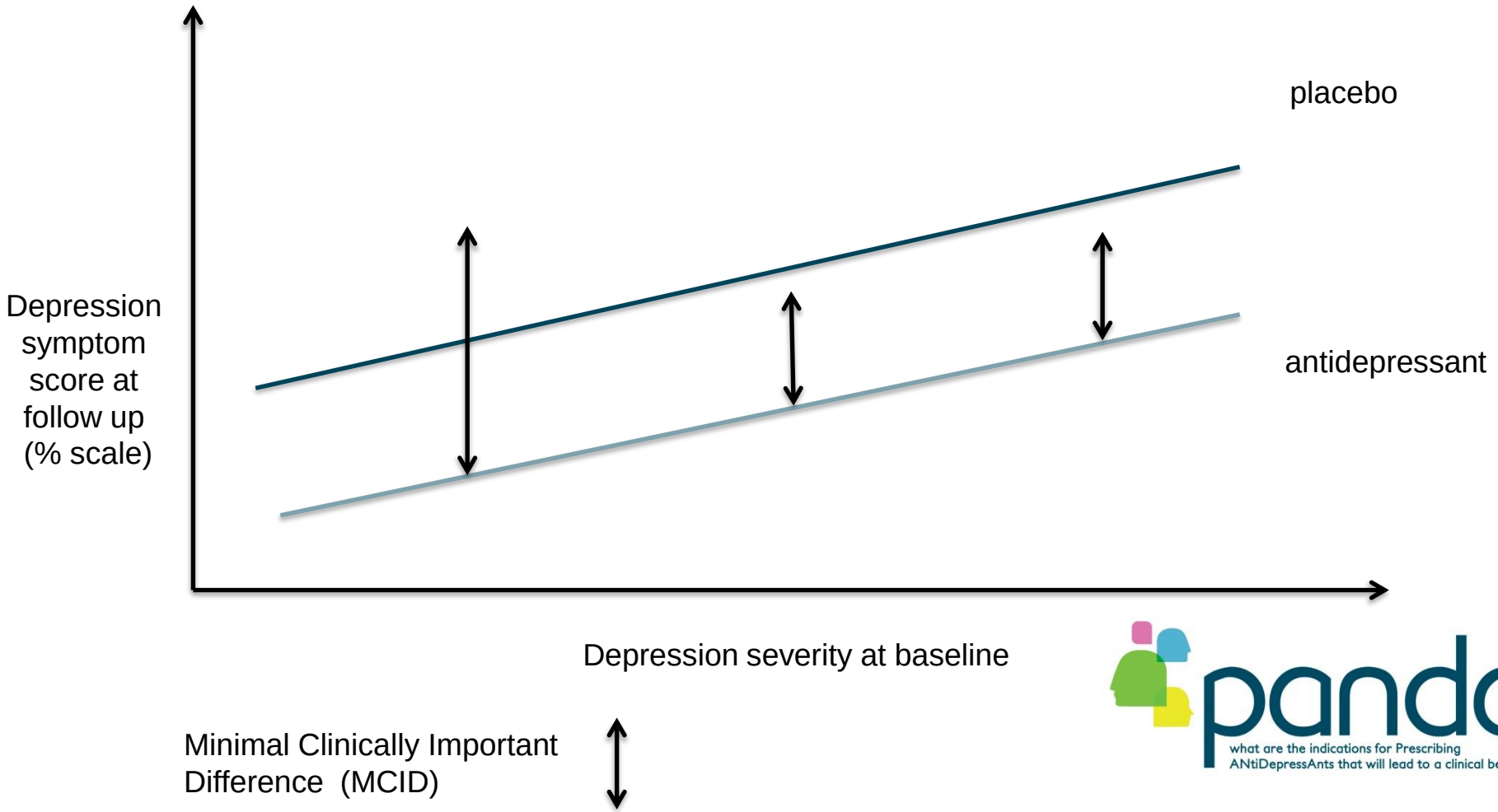

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How much change is enough

- Antidepressants produce a clinically important change on average, at least for generalised anxiety symptoms
- A substantial improvement is more likely on antidepressants
- BUT a lot of people are not helped

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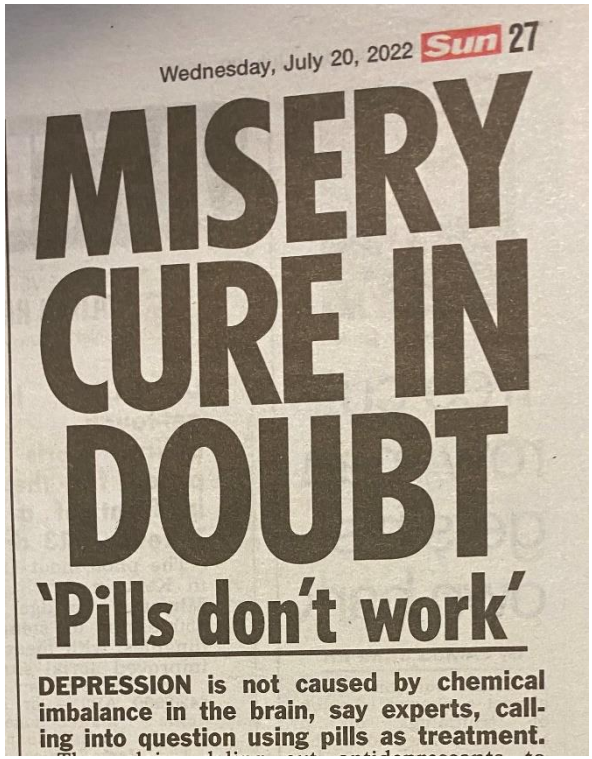
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headlines

- ‘I lost a decade of my life to prescription drugs’
- ‘I spent years living like a medicated zombie’
- ‘All hell broke loose’: the truth about coming off of antidepressants
- The inconvenient truth about antidepressants
- Doctors should stop dishing out antidepressants as there is no ‘decent proof they work better than placebo’
- DRUGS DON’T WORK Common antidepressant sertraline ‘barely treats depression’, shock study finds

Twitter conspiracy

In the last 2 months we learned antidepressants never worked and Alzheimer's research was all fake.

But sure, keep trusting peer-reviewed studies.

We need to restore sanity in health care.

80% of **antidepressants** are being prescribed by a primary care physician. Why? Pharma marketing directly to them. Unless ethical primary care doctors change... nothing changes.

Where are the leaders?

Ever since the most recent study disproving biochemical theory of mental illness was published all I've seen are articles stating it's a false theory but hey those drugs still work. Big pharma is hard at work.

All this is simple manipulation, patients are the pawns in this process of manipulation, harming patients is the intended outcome.

Here are almost 8000 "stats" (i.e. victims of antidepressant-induced self-inflicted death), by no means comprehensive, but reported in enough detail in various newspapers in England & Wales between 2003 & 2020.
antidepaware.co.uk/inquest-report

Conclusions

- We need a lot more research in psychiatry and all types of research can be or will be clinically relevant
- Applying and explaining research findings to patients will allow them to make their own decisions
- We need to be open with patients about what we know and what we don’t know

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