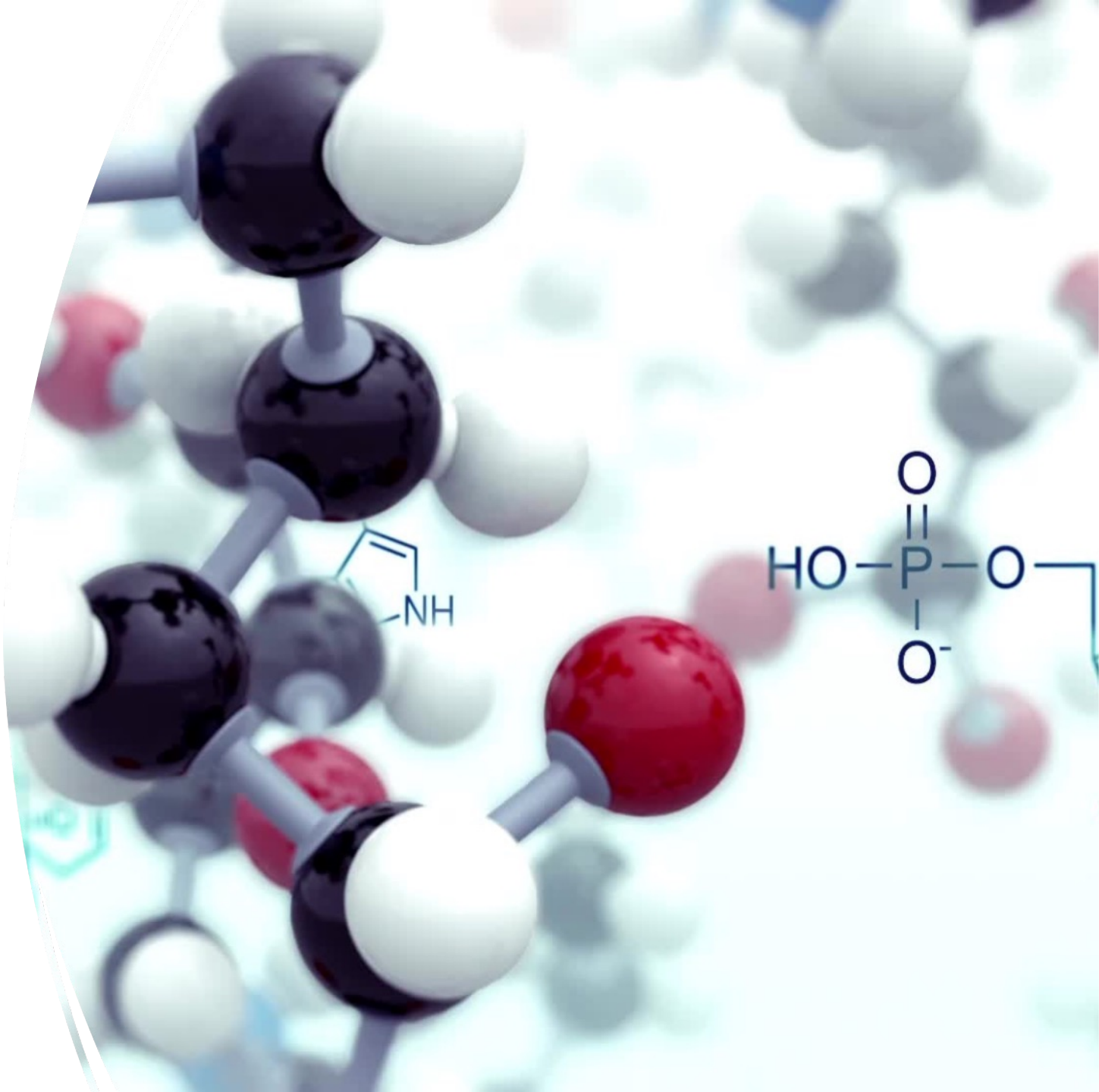
Myths about chemical imbalances and chemical cures: how drug treatment in psychiatry has been misrepresented, including on suicide

Professor Joanna Moncrieff, UCL, London,

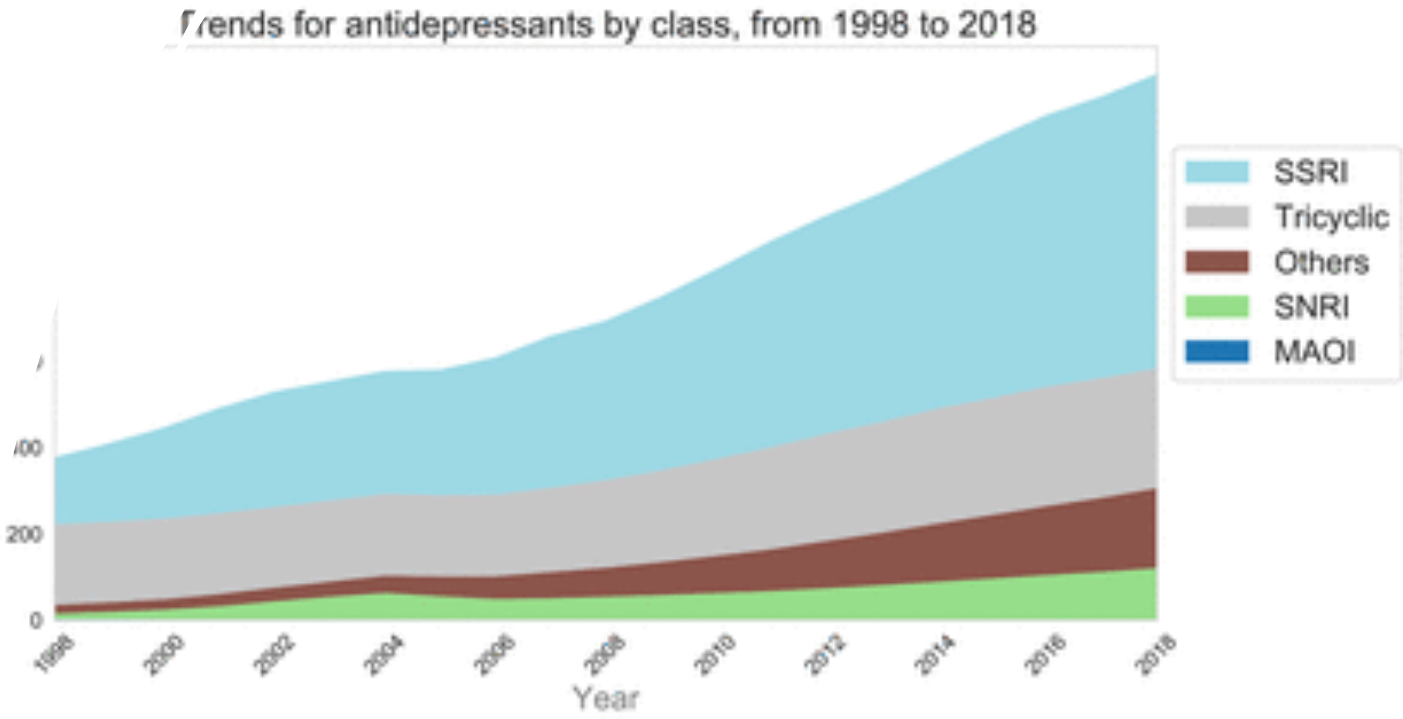
Talk for

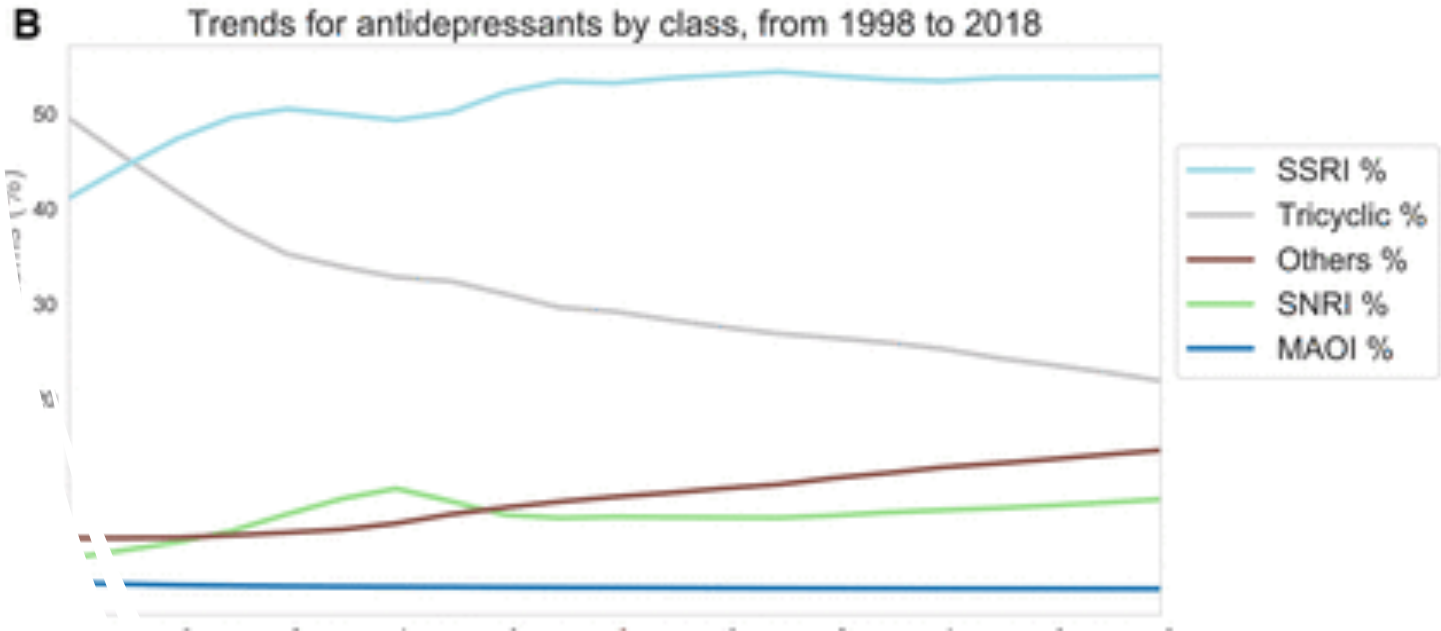
8th VILNIUS CONFERENCE ON SUICIDE INTERVENTION METHODS

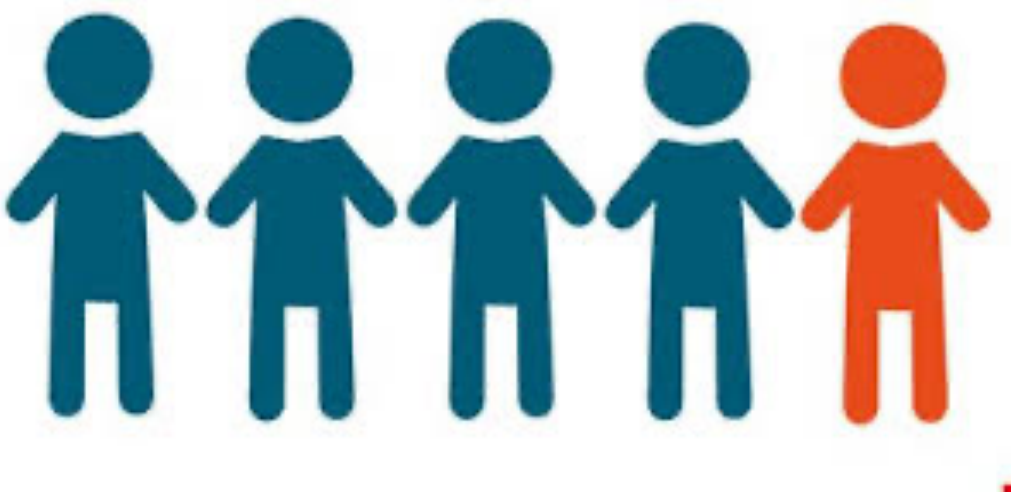
8th December, 2023



Increasing prescription of antidepressants: 1998-2018 (18.4 million to 70.9 million- a 3.85x increase)





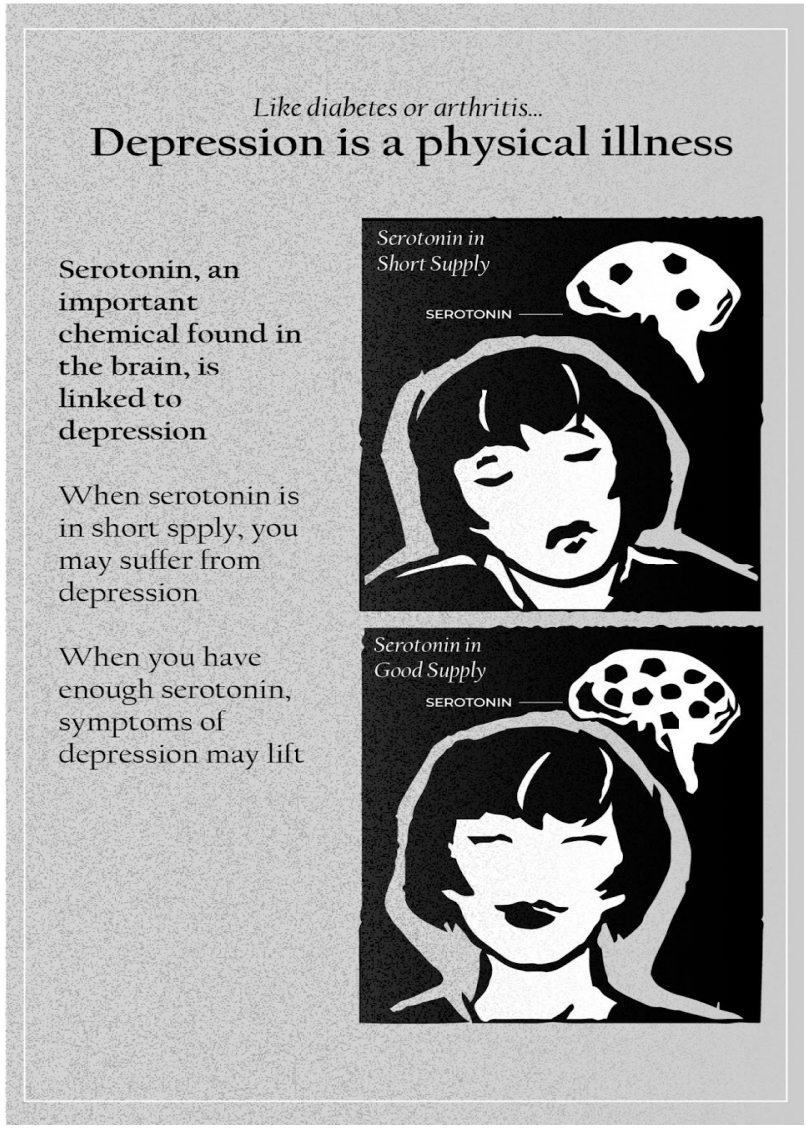


17% of population of England were prescribed an antidepressant in 2017

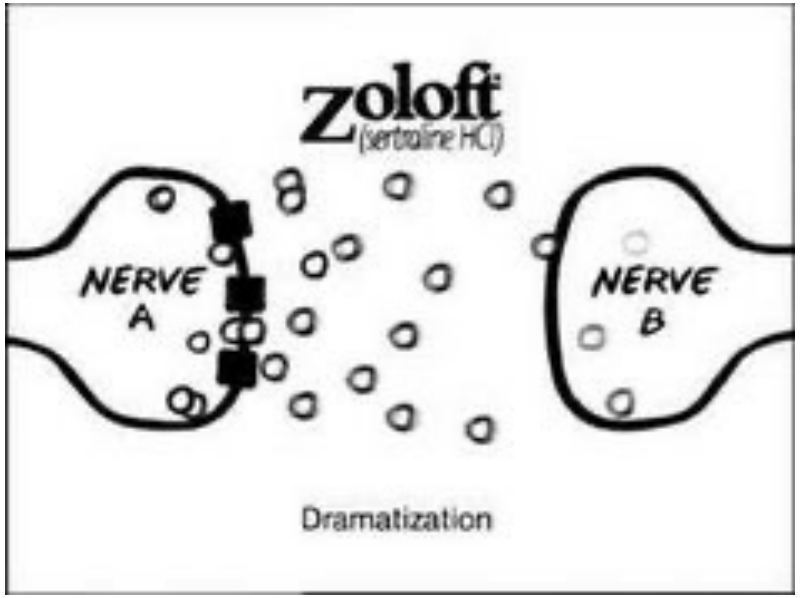
23% in US taking a medication for a mental health problem in 2022 in last month

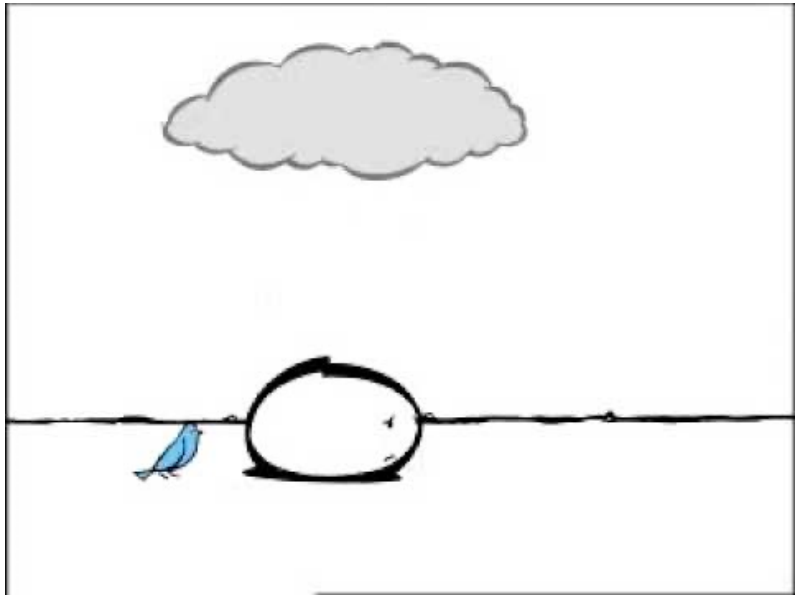
SSRI marketing

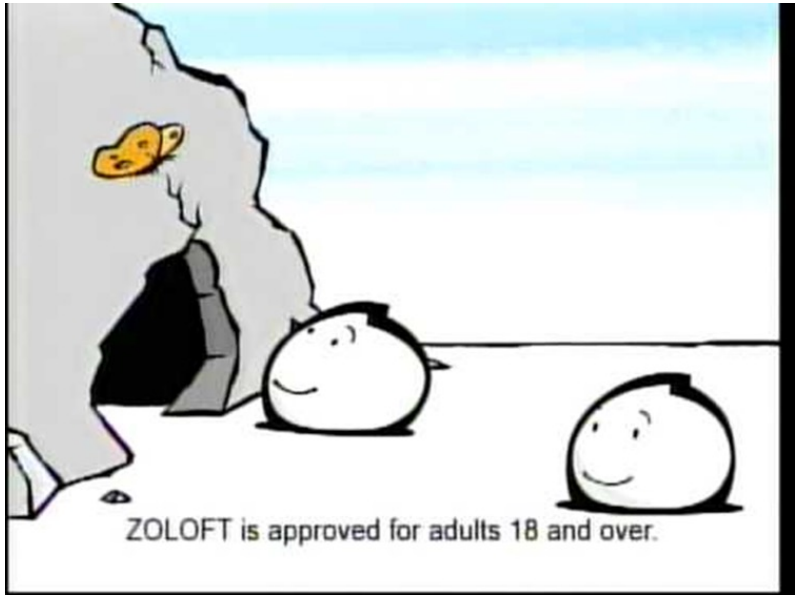
- Chemical imbalance theory was an integral part of the marketing of SSRIs
- ‘serotonin, an important chemical found in the brain is linked to depression’ (Eli Lilly pamphlet, mid 1990s, cited in Valenstein)
- It was also disseminated y professional organisations e.g. the APA: “Differences in certain chemicals in the brain may contribute to symptoms of depression” APA, 2023



‘Although the cause is unknown, depression may be related to an imbalance of natural chemicals in the brain.. Zoloft works to correct this imbalance’ 2003







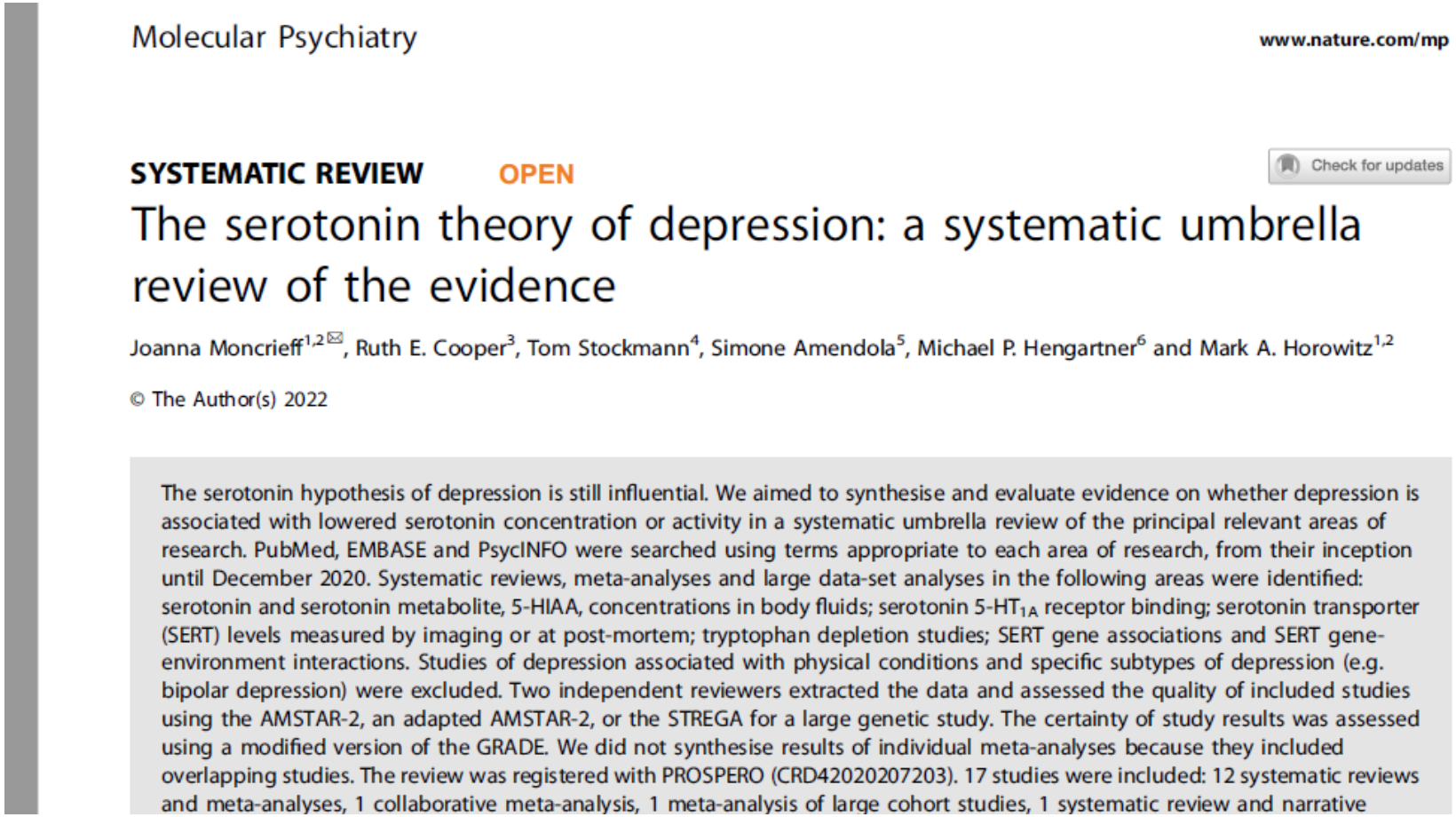
Public surveys

- US 2006: 80% believed depression is caused by a chemical imbalance (Pescolidao et al, 2015

- US 2006: 87%
- (France et al, 2007)

- Australia 2003/4: 88%
- (Pilkington et al, 2013)

It had been suggested before, but in 2022, we showed clearly that the serotonin theory of depression is not proven.



Molecular Psychiatry www.nature.com/mp

SYSTEMATIC REVIEW OPEN

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The serotonin theory of depression: a systematic umbrella review of the evidence

Joanna Moncrieff[1,2]✉, Ruth E. Cooper[3], Tom Stockmann[4], Simone Amendola[5], Michael P. Hengartner[6] and Mark A. Horowitz[1,2]

The serotonin hypothesis of depression is still influential. We aimed to synthesise and evaluate evidence on whether depression is associated with lowered serotonin concentration or activity in a systematic umbrella review of the principal relevant areas of research. PubMed, EMBASE and PsycINFO were searched using terms appropriate to each area of research, from their inception until December 2020. Systematic reviews, meta-analyses and large data-set analyses in the following areas were identified: serotonin and serotonin metabolite, 5-HIAA, concentrations in body fluids; serotonin 5-HT_{1A} receptor binding; serotonin transporter (SERT) levels measured by imaging or at post-mortem; tryptophan depletion studies; SERT gene associations and SERT gene-environment interactions. Studies of depression associated with physical conditions and specific subtypes of depression (e.g. bipolar depression) were excluded. Two independent reviewers extracted the data and assessed the quality of included studies using the AMSTAR-2, an adapted AMSTAR-2, or the STREGA for a large genetic study. The certainty of study results was assessed using a modified version of the GRADE. We did not synthesise results of individual meta-analyses because they included overlapping studies. The review was registered with PROSPERO (CRD42020207203). 17 studies were included: 12 systematic reviews and meta-analyses, 1 collaborative meta-analysis, 1 meta-analysis of large cohort studies, 1 systematic review and narrative

Conclusions

No evidence that depression is associated with lower serotonin concentrations or activity

A little evidence from some studies (receptors and SERT) that it may be associated with higher serotonin levels, but evidence was inconsistent (different areas in different studies), and results likely to be false positives or due to consequences of antidepressant use

Some evidence that taking antidepressants is associated with lowered serotonin (not higher)- plasma serotonin study and metabolite study (and may explain receptor and SERT findings)

Genetic studies were convincingly negative (very large and well conducted)- also showed strong association with adverse life events/stressors

Implications for antidepressants

- We cannot say that antidepressants are reversing an underlying brain abnormality or targeting an underlying biological mechanism that produces depression or symptoms of depression
- There may be other biological mechanisms (apart from serotonin, and there are numerous theories) but these have not been established either

- Therefore we have to consider other possible ways that antidepressants might be having their effects (e.g. amplified placebo effects, emotional blunting)
- These have different implications for deciding whether antidepressants are useful and for thinking about how they might be harmful

Models of drug action

Disease centred model	Drug centred model
Drugs correct an abnormal brain state	Drugs change the normal state of the brain and body
Therapeutic effects arise from drugs effects on the biological mechanisms that produce symptoms	Resulting changes in mental activity temporarily superimposed on underling thoughts, feelings and behaviour
Example (general medicine): asthma treatments, aspirin, paracetamol	Examples: alcohol, opiate anaesthetics

The drug-centred model: Psychoactive drugs

- Psychoactive drugs changes in sensations, mental activity, behaviour as well as physical functioning
- The changes can be pleasant or unpleasant

- These changes can temporarily over-ride mental distress or other abnormal or unwanted mental states or behaviours

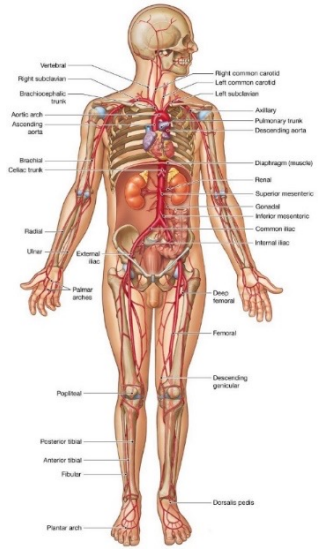
- Cause dependence and withdrawal
- And predictable and unpredictable harmful effects

What caused the drug-centred model to be replaced by the disease-centred model?

- Not scientific evidence!
- Placebo controlled trials do **not** distinguish disease-centred from drug-centred model
- Little other evidence (Moncrieff & Cohen, 2005; Moncrieff 2008)
- Unless there is good evidence for the disease centred model, we should assume the drug-centred model

A drug-centred understanding of antidepressants

- What physical and mental alterations do antidepressants produce?
- Are these helpful in people with depression?



Antidepressants-induced alterations

- Antidepressants come from many different chemical classes
- Some have quite subtle effects, some more obvious effects

- Many produce lethargy, tiredness, weight gain, some insomnia and some produce irritability, tension and emotional lability- especially have these effects in young people- may be related to increased risk of suicidal behaviour (from volunteer and patient studies e.g. Hermann & McDonald, 1978; Dumont et al, 2005; Goldsmith & Moncrieff, 2011)
- Not pleasant (no or low abuse potential)
- Emotional blunting: ‘distanced from life’ (46%-70% report it: Goodwin et al, 2017; Read & Williams, 2018; quote from Goldsmith & Moncrieff, 2011)
- Sexual dysfunction – common

Emotional blunting with antidepressants occurs in volunteers (Langley et al, 2023)

Scientists explain emotional ‘blunting’ caused by common antidepressants

Scientists have worked out why common anti-depressants cause around a half of users to feel emotionally ‘blunted’. In a study published today, they show that the drugs affect reinforcement learning, an important behavioural process that allows us to learn from our environment.

Media enquiries

Craig Brierley

External Affairs and Communications team

Published

23 Jan 2023

Image

Man looking out of window

Credit: Ethan Sykes

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- These alterations (emotional blunting, lethargy) may reduce depression scores directly
- Antidepressants may also produce ‘amplified’ placebo effects

- So are they actually helpful?

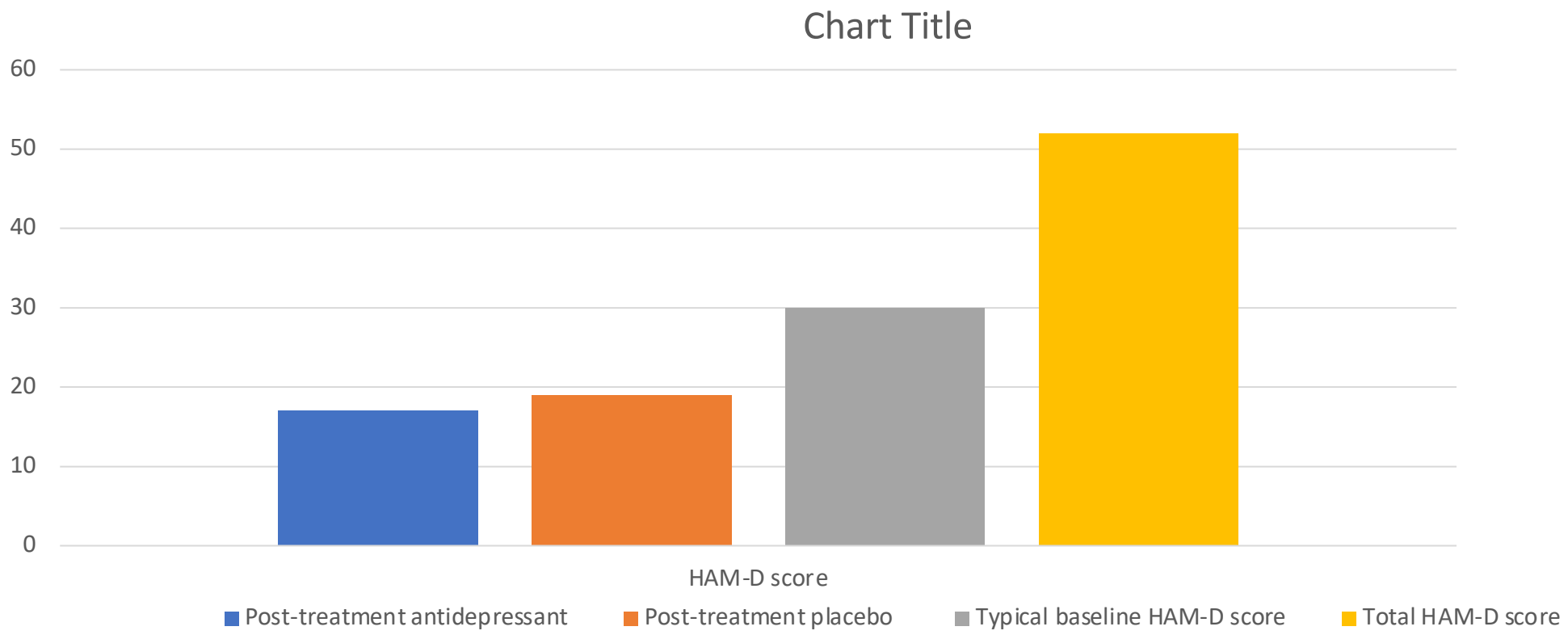
"Antidepressants work!"

The drugs do work: antidepressants are effective, study shows

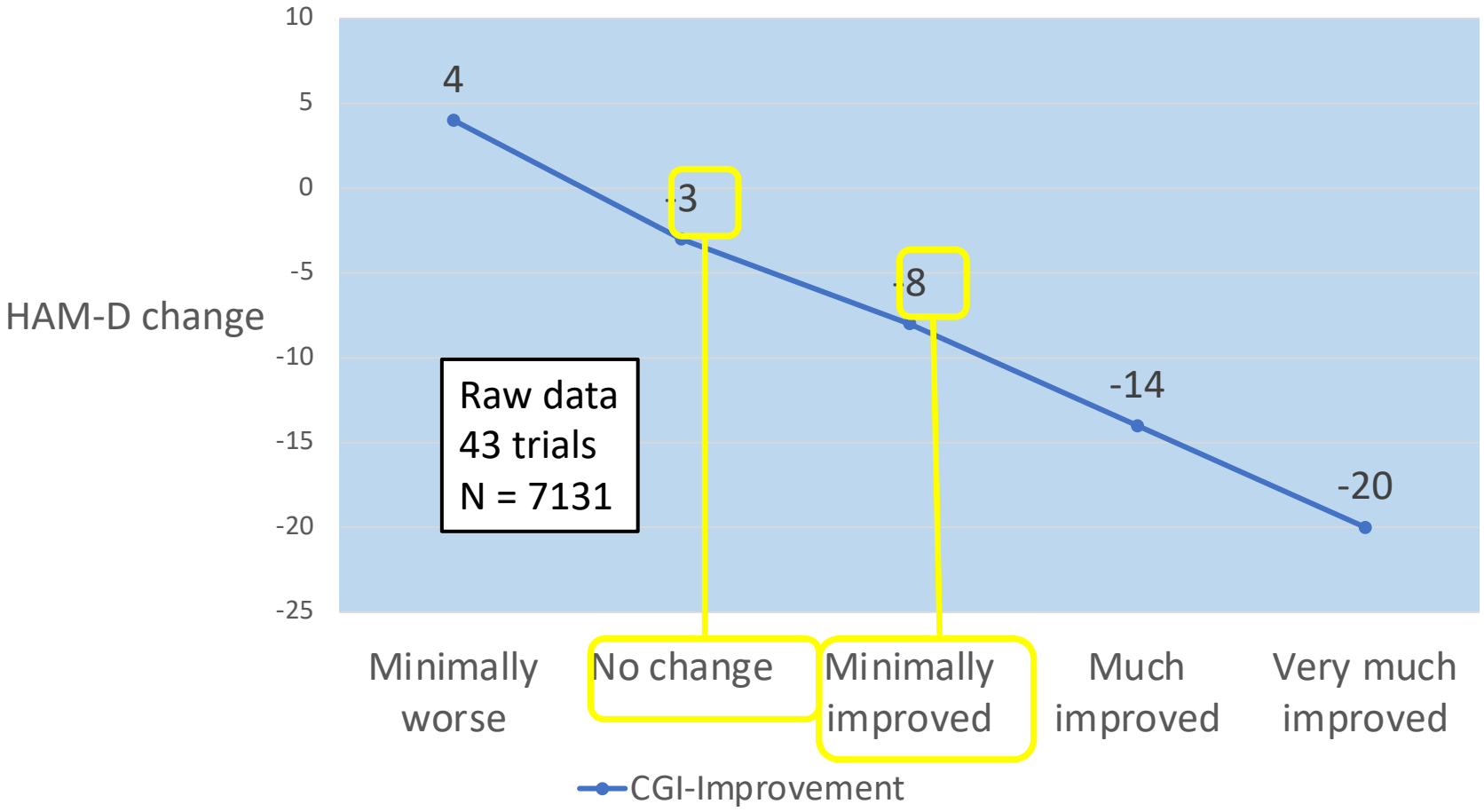
Doctors hope study will put to rest doubts about the medicine, and help to address global under-treatment of depression

It's official: antidepressants are not snake oil or a conspiracy

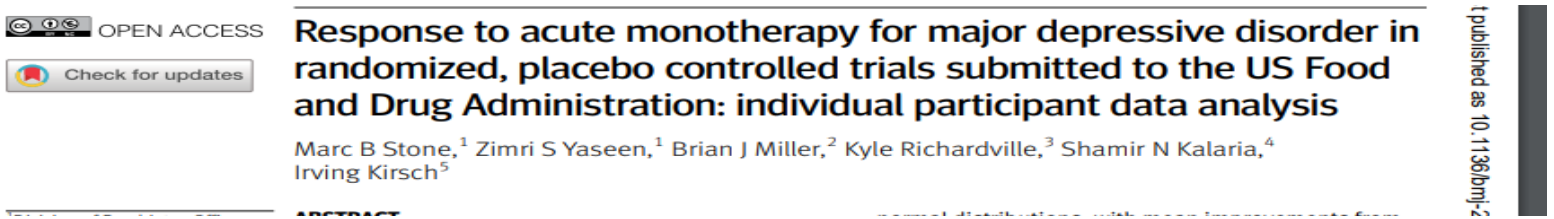
Average difference in placebo controlled antidepressant trials is 2 points or less on the Hamilton depression scale (Cipriani et al, 2018; Kirsch et al, 2002; Stone et al, 2023)



This is far below what is thought to be a clinically meaningful effect e.g. HAM-D and CGI-Improvement (Leucht et al., 2013)



Do antidepressants work for some people? Stone et al, 2022 FDA data analysis



OPEN ACCESS

Check for updates

Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: individual participant data analysis

Marc B Stone,[1] Zimri S Yaseen,[1] Brian J Miller,[2] Kyle Richardville,[3] Shamir N Kalaria,[4] Irving Kirsch[5]

t published as 10.1136/bmj-2

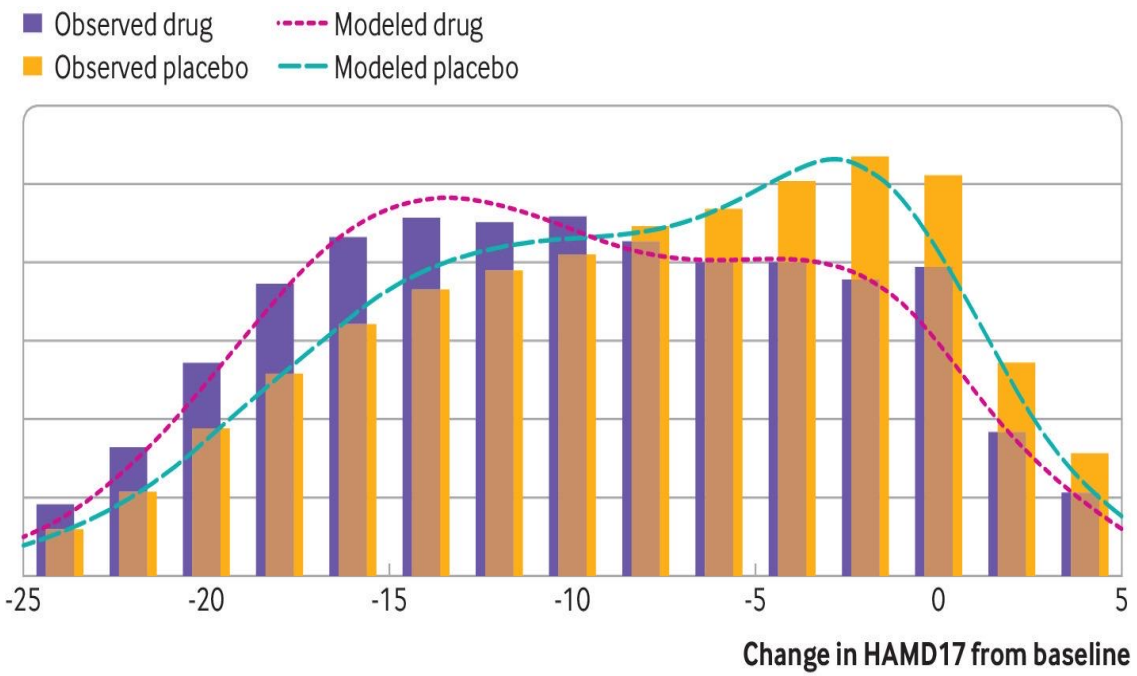
- Average difference between antidepressants and placebo is 1.75 points

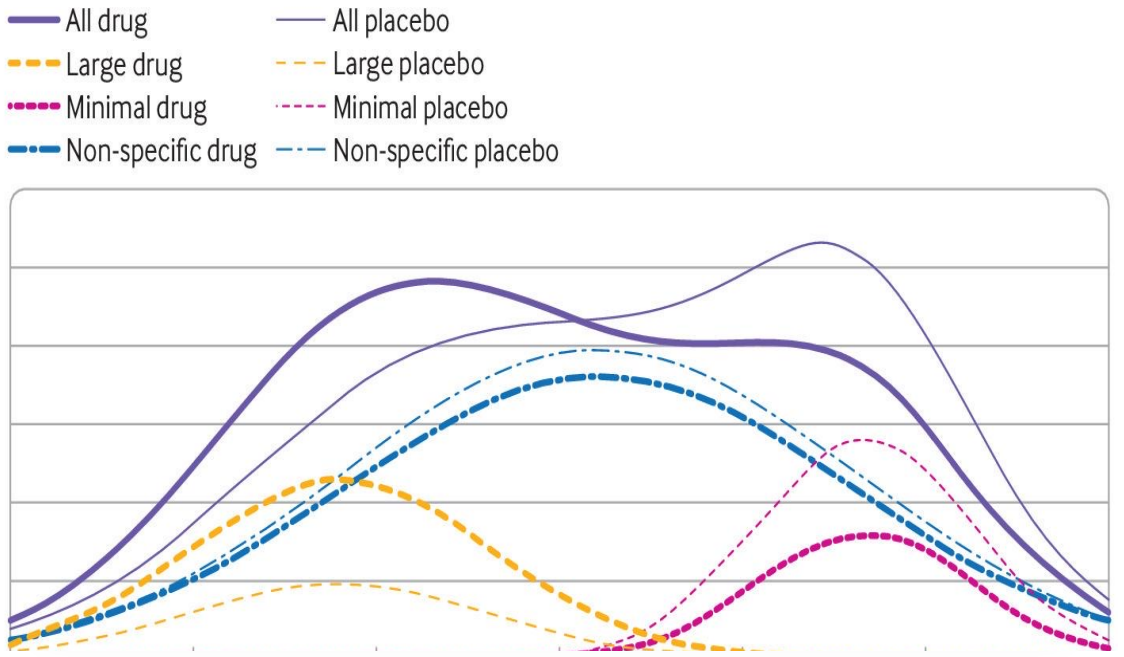
Stone et al, BMJ, 2022

-an exploratory analysis proposed 3 types of outcome: good, middle and poor and that people on antidepressants were more likely to be in the good outcome group and people on placebo in the poor outcome group but that most people on both drugs were in the middle

- **it did not identify subgroups of people who responded better or worse to antidepressants**

-a similar previous analysis found a two group pattern (Thase et al, 2011)





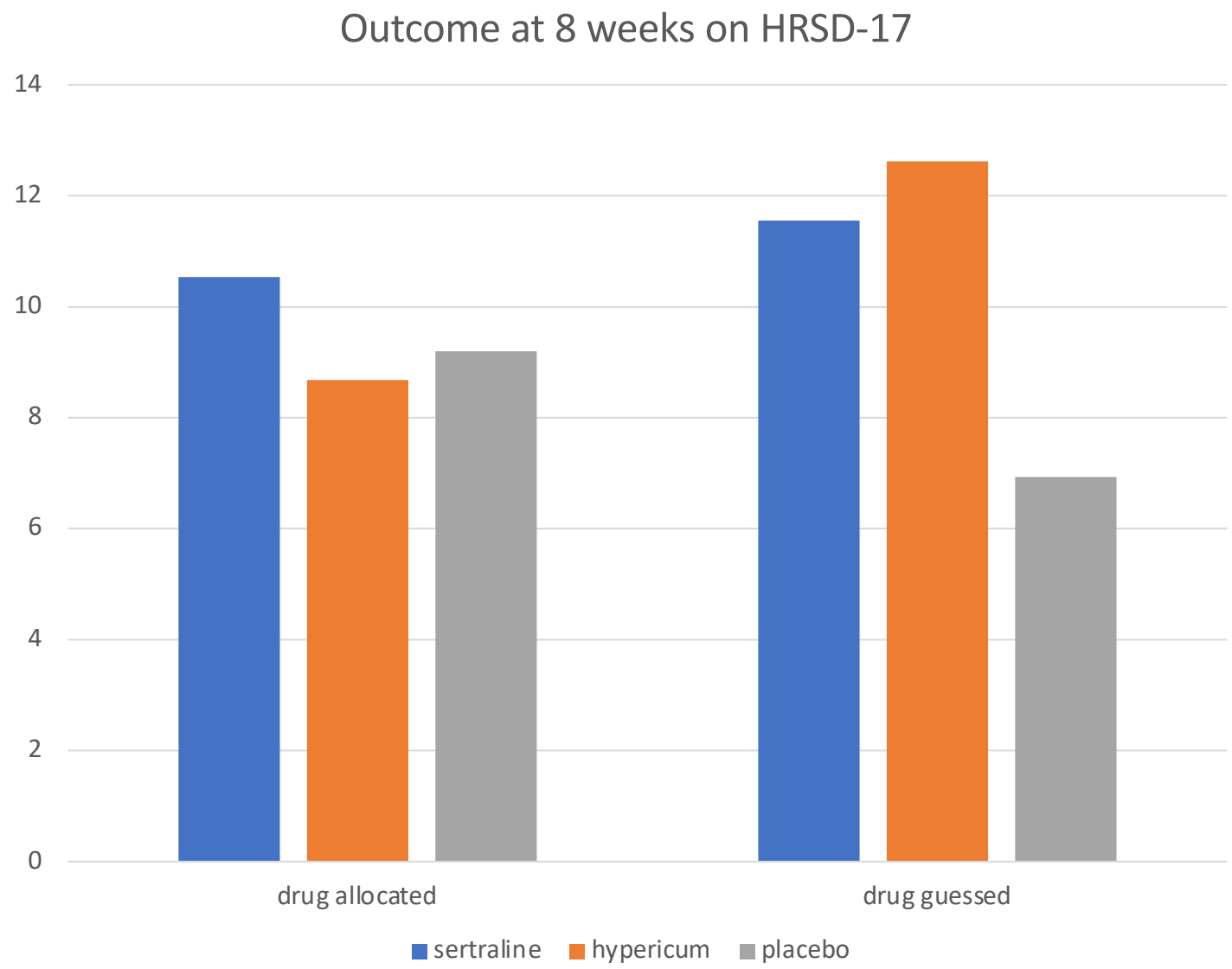
Even this small difference may not be a real difference due to ‘Unblinding’ in antidepressant trials

- Mostly not tested (7% of antidepressant trials from 2010-2020 (Lin et al, 2022)
- Some studies find evidence of unblinding, but not all (Scott et al, 2022; Lin et al, 2022)

- E.g. Kranzler et al 1996 (a trial in people with alcohol problems- negative for effects on drinking and mood)

80% of people allocated to fluoxetine correctly identified their allocation p=0.01 (vs 56% allocated to placebo)

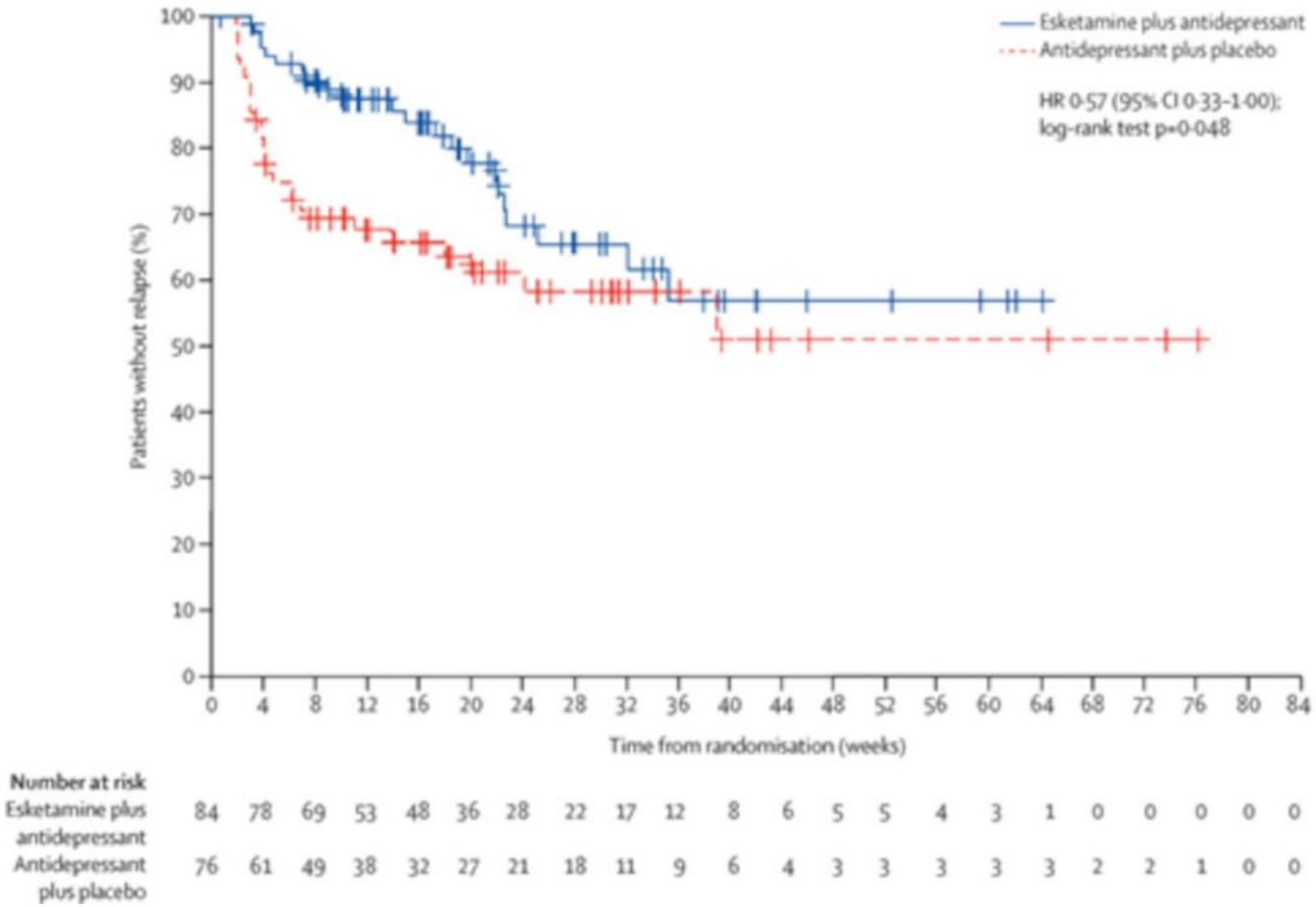
Effects of guesses in an RCT of sertraline vs hypericum vs placebo (Davidson et al, 2002; Chen et al, 2011)



Even less evidence for long-term treatment

- Most antidepressant trials last less than 8 weeks.
- Long-term treatment or relapse prevention trials are confounded by withdrawal effects occurring in people transferred to placebo

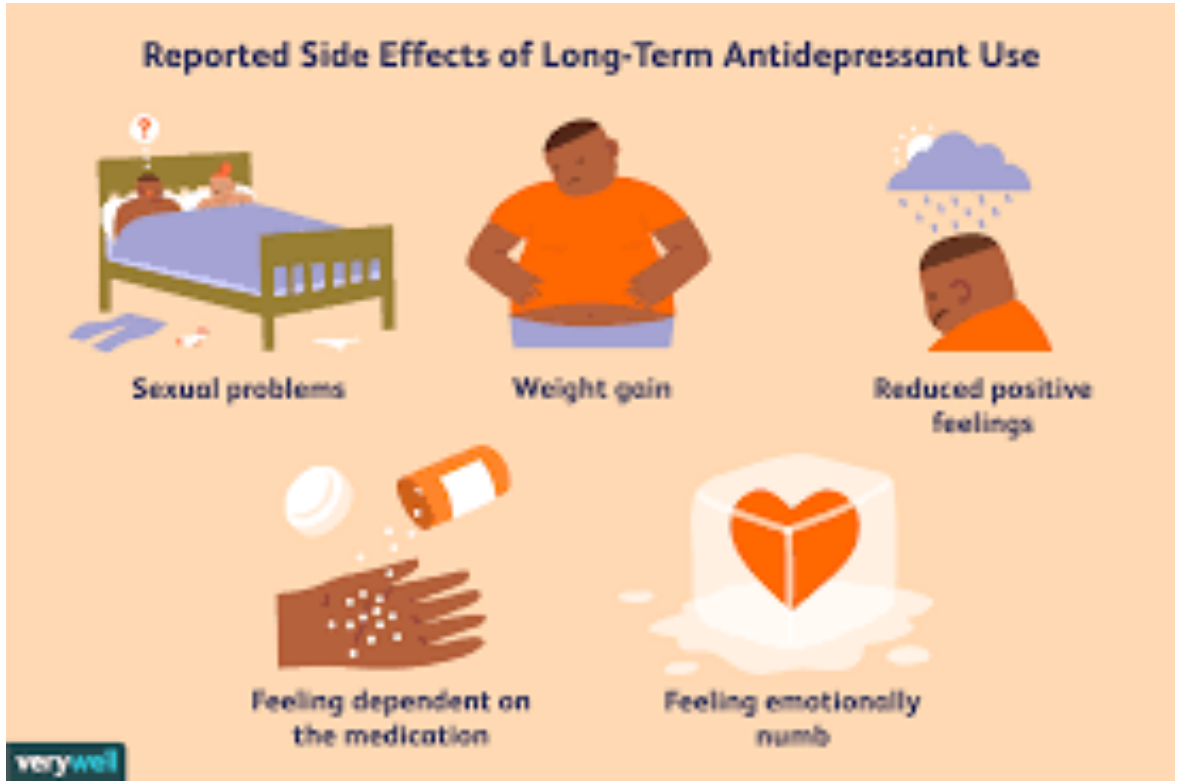
Time to relapse among people with treatment-resistant depression randomised to esketamine plus antidepressant or placebo plus antidepressant.



Joanna Moncrieff et al. BMJ EBM doi:10.1136/bmjebm-2021-111743

BMJ Evidence-Based Medicine

Adverse effects of antidepressants



- Physical dependence – around 25% have severe withdrawal symptoms- **they can last months and years** (Davies & Read, 2018)

- Sexual dysfunction - **can be persistent**

Rare but serious

- Fetal abnormalities
- Bleeding
- Fractures
- Suicidal behaviour in young people

Conclusions on antidepressants

- There is no evidence antidepressants correct an underlying biological abnormality
- They alter normal brain chemistry and functioning in ways we do not fully understand
- Evidence for beneficial effects is minimal
- They have under-researched and under-appreciated serious and common adverse effects with long-term use including protracted withdrawal and persistent sexual dysfunction

Antidepressants and suicide: do they save lives?

Antidepressants helped our columnist after her diagnosis (Image: Getty Images)

Mirror

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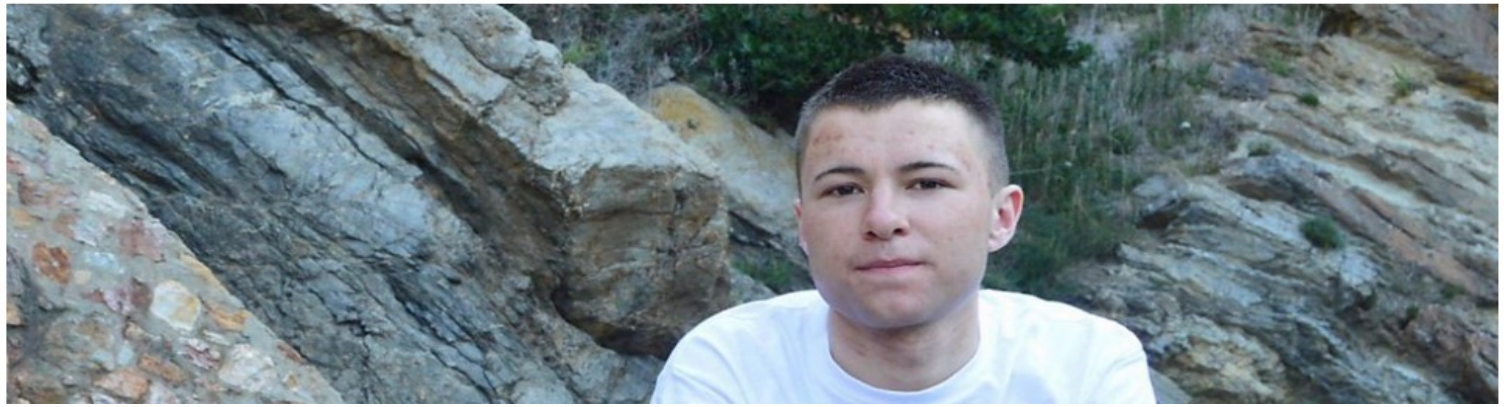
'Antidepressants saved my life after my diagnosis and talking therapy helped me'

Rachael Bletchly says it was a 'huge relief' when a doctor diagnosed her with clinical depression in 2004 – and antidepressants helped her neurotransmitters replenish naturally

Or increase the risk of suicide?

Antidepressants: I wasn't told about the side effects

9 August



Antidepressants and suicide

The argument that antidepressants reduce suicide is based on the idea that they effectively treat depression

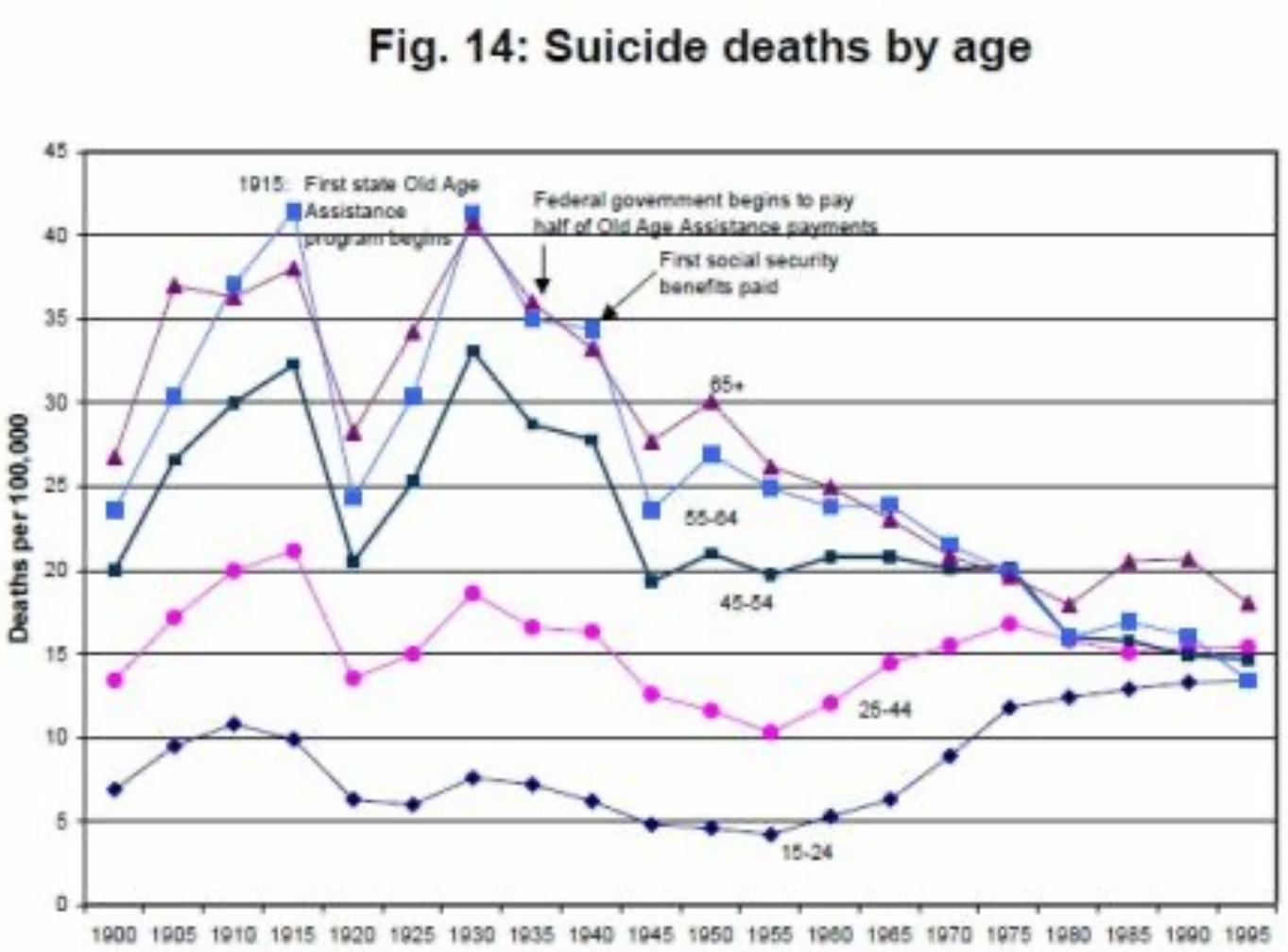
Ecological data is inconsistent

RCT data shows slight increase in suicidal behaviour (attempts and suicidal ideas)

No RCTs have been designed to test the anti-suicidal effects of antidepressants

Suicide is affected by major social events, not prescriptions

US suicide trends over 20th century.
Cutler & Meara, 2003
(In Perspectives on the Economics of Ageing, Ed D. Wise)



An example of the mis-interpretation of ecological data

e.g. ***Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study***
BMJ 2014; 348 doi: http://dx.doi.org/10.1136/bmj.g3596 (Published 18 June 2014) Cite this as: BMJ 2014;348:g3596

- Claimed that reduced antidepressant prescribing increased suicide attempts among young people
- Found no association with completed suicide which continued on downward trend
- But, counted all drug poisonings as suicide attempts, when data show an increase in accidental (non suicidal) poisonings in young and older people (Mosholder, FDA, rapid response, 2014)
- Other more valid measures of suicide attempts showed no increase (Azrael, rapid response, 2014)

Evidence that antidepressants increase the risk of suicide and suicidal behaviour

Association between SSRIs and suicidal behaviour:

- Case studies in 1990s (Teicher et al, 1990; Rothschild & Locke, 1991)
- Meta-analyses in adults (Fergusson et al, 2005)
- Meta-analyses in children (Dubicka et al 2006; Olfson et al, 2006; Whittington et al, 2004; Wohlfarth et al, 2006)
- Some meta-analysis negative (Beasley et al, 1991; Khan et al, 2003)

Sharma et al, BMJ, 2016 https://www.bmj.com/content/352/bmj.i65

- Meta-analysis of data in clinical study reports of trials of SSRIs vs placebo
- Increased suicidal ideation and behaviour in young people on antidepressants
- Increased aggression in young people on antidepressants
- No differences in adults
- Under-reporting and mis-reporting common

Lithium and suicide

- Frequently claimed that lithium has specific anti-suicidal properties

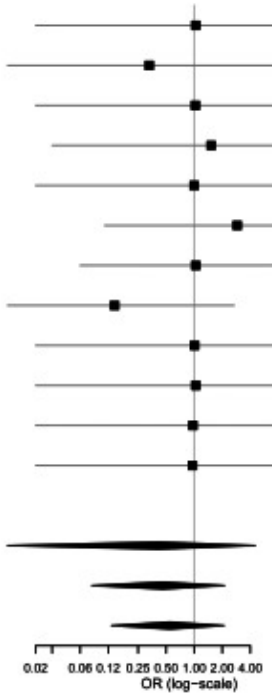
- Lithium's antisuicidal properties are 'proven', 'umambiguous evidence' (Lewitazka et al, 2015)
- 'intrinsic anti-suicidal property' (Del Matto *et al*., 2020)
- Recommended as a preventive treatment by the US VA guidelines (2019)
- Some people suggest adding it to drinking water (Daly 2020)

- An influential meta-analysis in 2013 claimed there was evidence from RCTs that lithium reduced suicide (Cipriani et al, 2013)

Meta-analysis of Lithium and suicide, Nabi et al, 2022

Suicides – Main Analysis

Study	Lithium n/N	Control n/N	OR	95%–CI	w
Amsterdam 2010	0 / 26	0 / 27	1.04	0.02–54.22	0.00%
Bauer 2000	0 / 14	1 / 15	0.33	0.01– 8.88	16.09%
Bowden 2000	0 / 91	0 / 94	1.03	0.02–52.60	0.00%
Bowden 2003	0 / 46	0 / 70	1.52	0.03–77.75	0.00%
Calabrese 2003	0 / 121	0 / 121	1.00	0.02–50.80	0.00%
Girlanda 2014	1 / 29	0 / 27	2.89	0.11–74.15	16.09%
Katz 2022	1 / 255	1 / 264	1.04	0.06–16.64	28.85%
Lauterbach 2008	0 / 84	3 / 83	0.14	0.01– 2.68	38.96%
Nierenberg 2013	0 / 141	0 / 142	1.01	0.02–51.10	0.00%
Sackeim 2001	0 / 28	0 / 29	1.04	0.02–53.95	0.00%
Weisler 2011	0 / 418	0 / 404	0.97	0.02–48.83	0.00%
Wilkinson 2002	0 / 25	0 / 24	0.96	0.02–50.35	0.00%
Sum	**2 / 1278**	**5 / 1300**			
Exact			**0.42**	**0.01–4.5**	
Bayesian – uninf. prior			**0.46**	**0.08–2.11**	
Bayesian – inf. prior			**0.55**	**0.13–2.09**	



Lauterbach et al, 2008

- The suicide rate was lower than they predicted, recruitment was hard and they struggled to get people to be compliant (NB a similar trial in Italy had to stop prematurely- Girlanda et al, 2014)

- Although it was supposed to be double blind, the blind was broken if people's lithium levels were not high enough or if they were thought to be at high risk of suicide **and they were given additional monitoring**

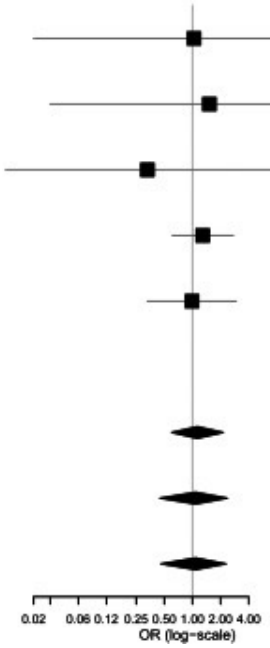
- The proportion of people who were non-compliant is likely to have been high because the average lithium level was below the intended target for most of the trial

- There is evidence that increased monitoring can reduce suicide (Tondo et al., 2006; Sakinofsky, 2014)

Meta-analysis lithium and suicide attempts, Nabi et al, 2022

Suicide attempts – Main Analysis

Study	Lithium n/N	Control n/N	OR	95%−CI	w
Amsterdam 2010	0 / 26	0 / 27	1.04	0.02−54.22	0.00%
Bowden 2003	0 / 46	0 / 70	1.52	0.03−77.75	0.00%
Calabrese 2003	0 / 121	1 / 121	0.33	0.01− 8.20	2.42%
Katz 2022	16 / 255	13 / 264	1.29	0.61− 2.74	66.36%
Lauterbach 2008	7 / 84	7 / 83	0.99	0.33− 2.95	31.22%
Sum	**23 / 532**	**21 / 565**			
Exact			**1.13**	**0.6−2.14**	
Bayesian − uninf. prior			**1.08**	**0.45−2.36**	
Bayesian − inf. prior			**1.08**	**0.46−2.29**	



Drug treatment and suicide conclusions

- There is no evidence that any sort of drug treatment for any disorder reduces suicide or suicidal behaviour
- The only trials specifically aimed at testing anti-suicidal effects of drugs have involved lithium and are negative overall

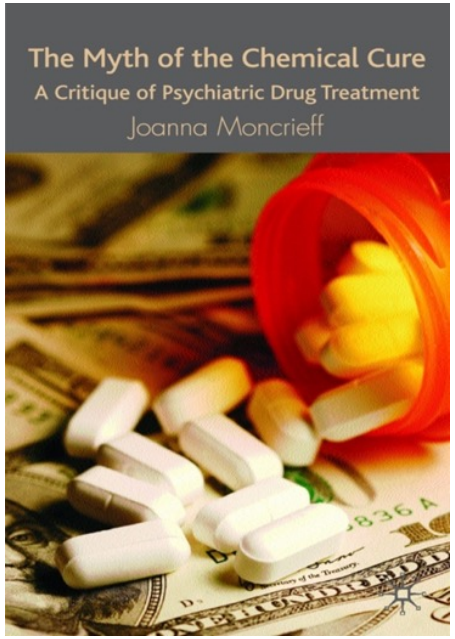
- There is evidence that antidepressants increase the risk of suicidal behaviour in young people but not adults. It is still rare.

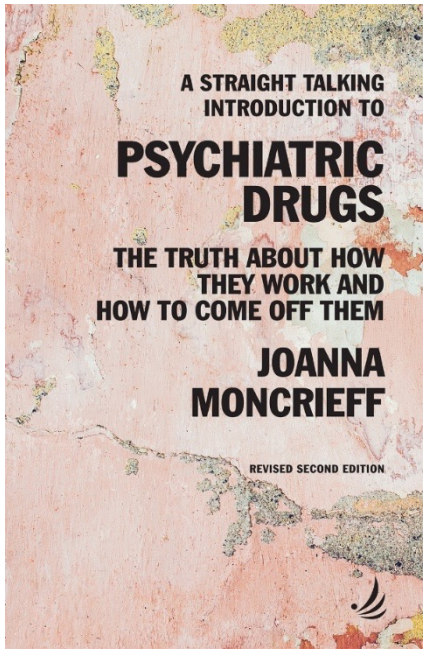
How have we misunderstood psychiatric drug treatment so badly?

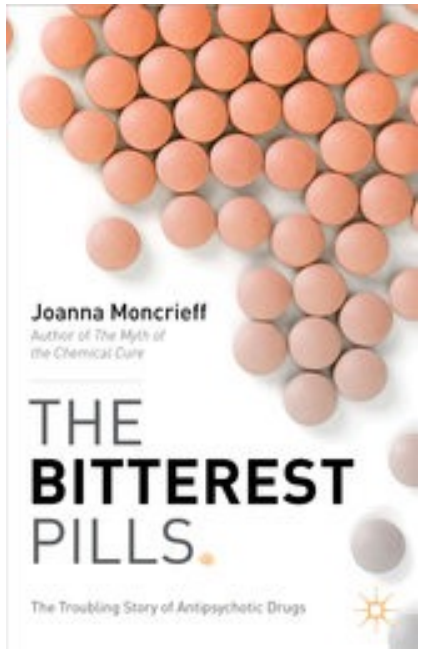
PROFESSIONAL INTERESTS

PHARMACEUTICAL INDUSTRY

INSECURITY AND DESPERATION


The Myth of the Chemical Cure
A Critique of Psychiatric Drug Treatment
Joanna Moncrieff


A STRAIGHT TALKING INTRODUCTION TO
PSYCHIATRIC DRUGS
THE TRUTH ABOUT HOW THEY WORK AND HOW TO COME OFF THEM
JOANNA MONCRIEFF
REVISED SECOND EDITION


Joanna Moncrieff
Author of The Myth of the Chemical Cure
THE BITTEREST PILLS
The Troubling Story of Antipsychotic Drugs