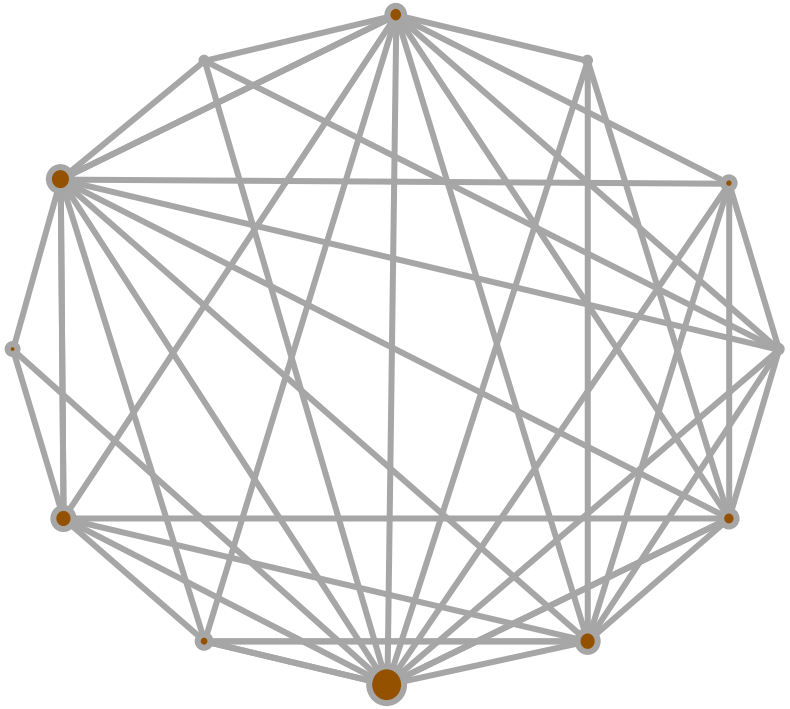
What a network of 500+ trials can tell us about antidepressants



Prof. Dr. Georgia Salanti

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University of Bern

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

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.

Lancet 2009; 373: 746–58

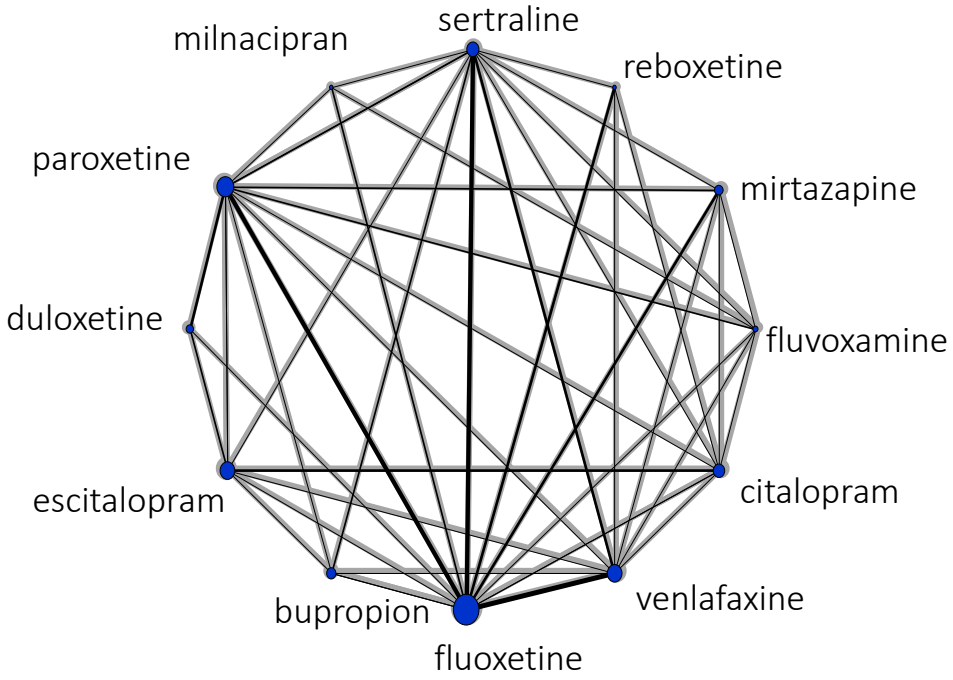
Andrea Cipriani

Toshi Furukawa

12 new generation antidepressants

117 RCTs (25 928 participants)

from 1991 to 2007



Statistical Methods in Medical Research 2008; **17**: 279–301

Evaluation of networks of randomized trials

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Randomized trials may be designed and interpreted as single experiments or they may be seen in the context of other similar or relevant evidence. The amount and complexity of available randomized evidence vary for different topics. Systematic reviews may be useful in identifying gaps in the existing randomized evidence, pointing to discrepancies between trials, and planning future trials. A new, promising, but also very much debated extension of systematic reviews, mixed treatment comparison (MTC) meta-analysis, has become increasingly popular recently. MTC meta-analysis may have value in interpreting the available randomized evidence from networks of trials and can rank many different treatments, going beyond focusing on simple pairwise-comparisons. Nevertheless, the evaluation of networks also presents special challenges and caveats. In this article, we review the statistical methodology for MTC meta-analysis. We discuss the concept of inconsistency and methods that have been proposed to evaluate it as well as the methodological gaps that remain. We introduce the concepts of network geometry and asymmetry, and propose metrics for the evaluation of the asymmetry. Finally, we discuss the implications of inconsistency, network geometry and asymmetry in informing the planning of future trials.

1 General considerations for networks of trials

The classic paradigm has been that randomized controlled trials (RCTs) should be designed, analysed and interpreted as single, isolated experiments. Every trial should start from equipoise, and ideally it should be adequately powered to answer the question of interest on its own.[1] However, equipoise is a contested term[2,3]. Moreover, in real practice, adequately powered trials are the rare exception. The average trial published currently still has a sample size of only 80 subjects and it is typically grossly underpowered.[4] For many questions of interest, several trials are being conducted–with same, similar or modestly dissimilar designs. There could be explicit scientific or marketing rationale for this multiplicity, or the multiplicity of trials may arise out of uncoordinated, diverse efforts of multiple teams of trialists and sponsors.[5]

Bayesian Network Meta-analysis

l,j,k random treatments

y_i the outcome of experiment i

θ_i the random effect

$$\begin{pmatrix} y_{1,l_1,j_1} \\ y_{2,l_2,j_2} \\ \vdots \\ y_{N,l_N,j_N} \end{pmatrix} \sim N\left(\begin{pmatrix} \theta_{1,l_1,j_1} \\ \theta_{2,l_2,j_2} \\ \vdots \\ \theta_{N,l_N,j_N} \end{pmatrix}, \Sigma \right) \quad \text{Likelihood}$$

$$\begin{pmatrix} \theta_{1,l_1,j_1} \\ \theta_{2,l_2,j_2} \\ \vdots \\ \theta_{N,l_N,j_N} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{1,l_1,j_1} \\ \mu_{2,l_2,j_2} \\ \vdots \\ \mu_{N,l_N,j_N} \end{pmatrix}, \begin{bmatrix} \tau_1^2 & c & c & c \\ c & \tau_2^2 & c & c \\ \vdots & \vdots & \ddots & \vdots \\ c & c & c & \tau_N^2 \end{bmatrix} \right) \quad \text{Random effects}$$

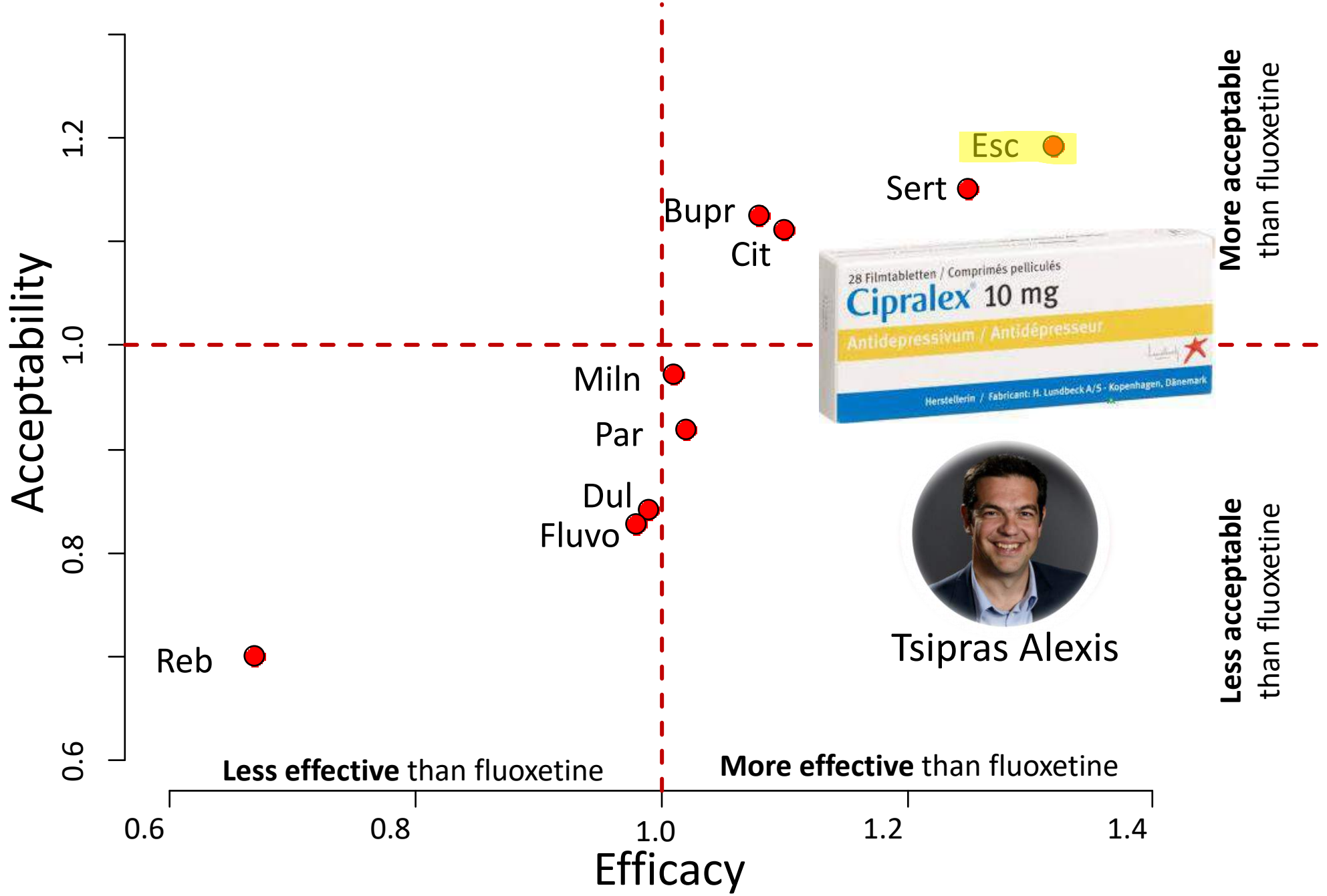
$$\mu_{lj} = \mu_{lk} + \mu_{kj} \quad \text{Consistency equations}$$

Create a league table

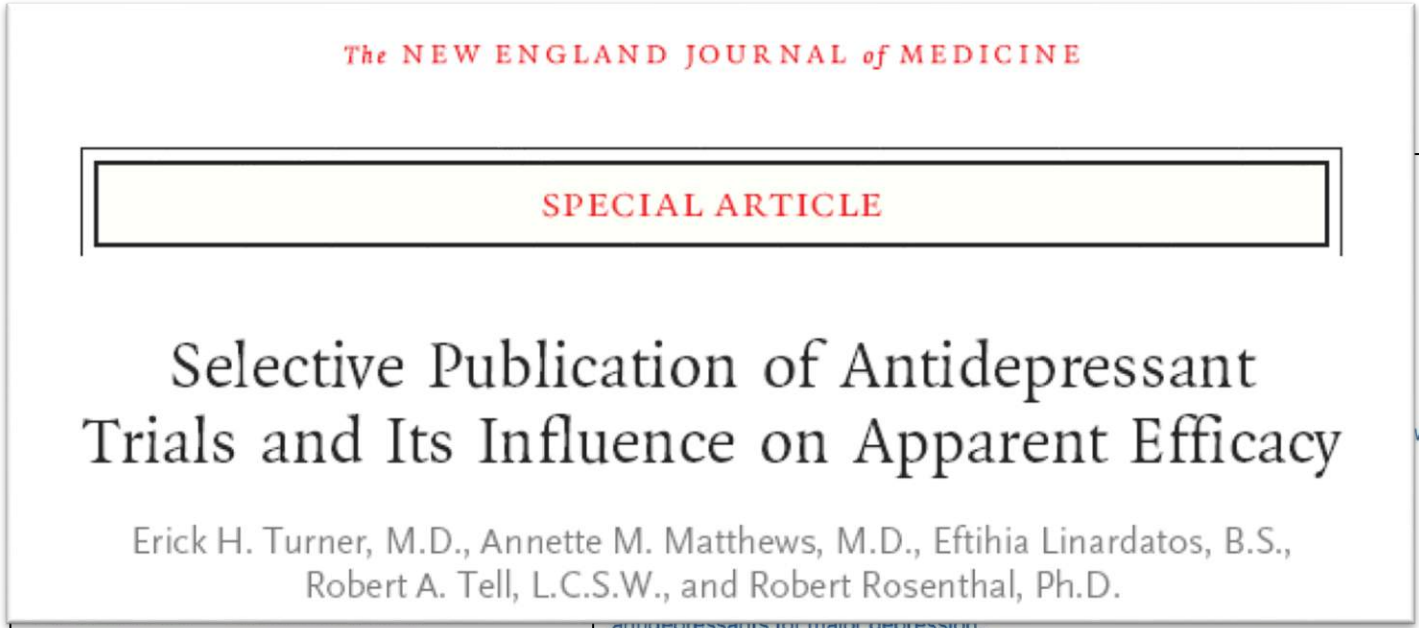
Efficacy (response rate) (95% CI) | Comparison | Acceptability (dropout rate) (95% CI)

BUP	1·00 (0·78–1·28)	0·75 (0·55–1·01)	1·06 (0·86–1·32)	0·89 (0·74–1·08)	0·73 (0·53–1·00)	0·87 (0·58–1·24)	0·87 (0·66–1·14)	0·81 (0·65–1·00)	**0·62** (0·45–0·86)	1·01 (0·82–1·27)	0·84 (0·68–1·02)
0·98 (0·78–1·23)	**CIT**	0·75 (0·55–1·02)	1·07 (0·86–1·31)	0·90 (0·73–1·09)	**0·73** (0·54–0·99)	0·87 (0·60–1·24)	0·87 (0·66–1·15)	0·81 (0·65–1·01)	**0·62** (0·45–0·84)	1·02 (0·81–1·28)	0·84 (0·67–1·06)
1·09 (0·83–1·43)	1·12 (0·87–1·44)	**DUL**	**1·43** (1·09–1·85)	1·19 (0·91–1·57)	0·98 (0·67–1·41)	1·16 (0·77–1·73)	1·16 (0·83–1·61)	1·08 (0·84–1·40)	0·83 (0·57–1·22)	**1·36** (1·01–1·83)	1·12 (0·84–1·50)
0·82 (0·67–1·01)	0·84 (0·70–1·01)	**0·75** (0·60–0·93)	**ESC**	0·84 (0·70–1·01)	**0·69** (0·50–0·94)	0·81 (0·55–1·15)	0·81 (0·62–1·07)	**0·76** (0·62–0·93)	**0·58** (0·43–0·81)	0·95 (0·77–1·19)	**0·78** (0·64–0·97)
1·08 (0·90–1·29)	1·10 (0·93–1·31)	0·99 (0·79–1·24)	**1·32** (1·12–1·55)	**FLU**	0·82 (0·62–1·07)	0·97 (0·69–1·32)	0·97 (0·77–1·21)	0·91 (0·79–1·05)	**0·70** (0·53–0·92)	1·14 (0·96–1·36)	0·94 (0·81–1·09)
1·10 (0·83–1·47)	1·13 (0·86–1·47)	1·01 (0·74–1·38)	**1·35** (1·02–1·76)	1·02 (0·81–1·30)	**FVX**	1·18 (0·76–1·75)	1·18 (0·87–1·61)	1·10 (0·84–1·47)	0·85 (0·57–1·26)	**1·38** (1·03–1·89)	1·14 (0·86–1·54)
1·07 (0·77–1·48)	1·09 (0·78–1·50)	0·97 (0·69–1·38)	1·30 (0·95–1·78)	0·99 (0·74–1·31)	0·97 (0·68–1·37)	**MIL**	0·99 (0·69–1·53)	0·94 (0·68–1·31)	0·72 (0·48–1·10)	1·17 (0·84–1·72)	0·97 (0·69–1·40)
0·79 (0·72–1·00)	0·80 (0·63–1·01)	**0·72** (0·54–0·94)	0·96 (0·76–1·19)	**0·73** (0·60–0·88)	**0·71** (0·55–0·92)	0·74 (0·53–1·01)	**MIR**	0·93 (0·75–1·17)	0·72 (0·51–1·03)	1·17 (0·91–1·51)	0·97 (0·76–1·23)
1·06 (0·87–1·30)	1·08 (0·90–1·30)	0·97 (0·78–1·20)	**1·30** (1·10–1·53)	0·98 (0·86–1·12)	0·96 (0·76–1·23)	1·00 (0·74–1·33)	**1·35** (1·11–1·64)	**PAR**	0·77 (0·56–1·05)	**1·25** (1·04–1·52)	1·03 (0·86–1·24)
1·60 (1·20–2·16)	**1·63** (1·25–2·14)	**1·46** (1·05–2·02)	**1·95** (1·47–2·59)	**1·48** (1·16–1·90)	**1·45** (1·03–2·02)	**1·50** (1·03–2·18)	**2·03** (1·52–2·78)	**1·50** (1·16–1·98)	**REB**	**1·63** (1·19–2·24)	1·34 (0·99–1·83)
0·87 (0·72–1·05)	0·88 (0·72–1·07)	0·79 (0·62–1·01)	1·06 (0·88–1·27)	**0·80** (0·69–0·93)	0·79 (0·61–1·01)	0·81 (0·60–1·11)	1·10 (0·90–1·36)	**0·82** (0·69–0·96)	**0·54** (0·41–0·71)	**SER**	0·82 (0·67–1·00)
0·85 (0·70–1·01)	0·86 (0·71–1·05)	**0·77** (0·60–0·99)	1·03 (0·86–1·24)	**0·78** (0·68–0·90)	**0·77** (0·59–0·99)	0·79 (0·58–1·08)	1·08 (0·87–1·33)	**0·79** (0·67–0·94)	**0·53** (0·40–0·69)	0·98 (0·82–1·16)	**VEN**

OR>1 means the treatment in top-left is better


Acceptability
1.2
1.0
0.8
0.6
Esc
Sert
Bupr
Cit
Miln
Par
Dul
Fluvo
Reb
28 Filmtabletten / Comprimés pelliculés
Cipralex 10 mg
Antidepressivum / Antidépresseur
Herstellerin / Fabricant: H. Lundbeck A/S - Kopenhagen, Dänemark
Tsipras Alexis
More acceptable than fluoxetine
Less acceptable than fluoxetine
Less effective than fluoxetine
More effective than fluoxetine
0.6
0.8
1.0
1.2
1.4
Efficacy

Criticism about excluding placebo-controlled trials
Why did you do it?



Ranking antidepressants.
Seyringer ME, Kasper S.
Lancet. 2009 May 23;373(9677):1760-1; author reply 1761-2.
PMID: 19465224 No abstract available.

Ranking antidepressants.
Gartlehner G, Gaynes BN, Hansen RA, Lohr KN.
Lancet. 2009 May 23;373(9677):1761; author reply 1761-2. do
PMID: 19465225 No abstract available.

antidepressants for major depression.
Usherwood T.
Evid Based Med. 2009 Oct;14(5):147. doi: 10.1136/ebm.14.5.147.
PMID: 19794022 No abstract available.

Review: clinically important differences between antidepressants.
McAllister-Williams RH.
Evid Based Ment Health. 2009 Nov;12(4):107. doi: 10.1136/ebmh.12.4.107.
PMID: 19854769 No abstract available.

Antidepressants for initial treatment of depression.
Darby-Stewart A, Dachs RJ, Graber MA.
Am Fam Physician. 2010 May 15;81(10):1205.
PMID: 20507044 No abstract available.

More data, more answers: picking the optimal antidepressant.
Parikh SV, Kennedy SH.
Lancet. 2018 Apr 7;391(10128):1333-1334. doi: 10.1016/S0140-6736(18)30421-5. Epub 2018 Feb 21.
PMID: 29477249 No abstract available.

Evidence on publication bias on antidepressants

- Turner et al found **73 studies** registered with the FDA used for the licensing of antidepressants drugs between 1987 and 2004 involving 12 drugs.
- **50 studies** of these 73 studies **were subsequently published in medical journals**
  - From the **38** FDA studies with **statistically significant** results only **one was not published**
  - from **the 36** FDA with **non-statistically significant** results only **33 were not published!**

Turner EH, Mathews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine.* 2008, **358**(3):252-260.

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.

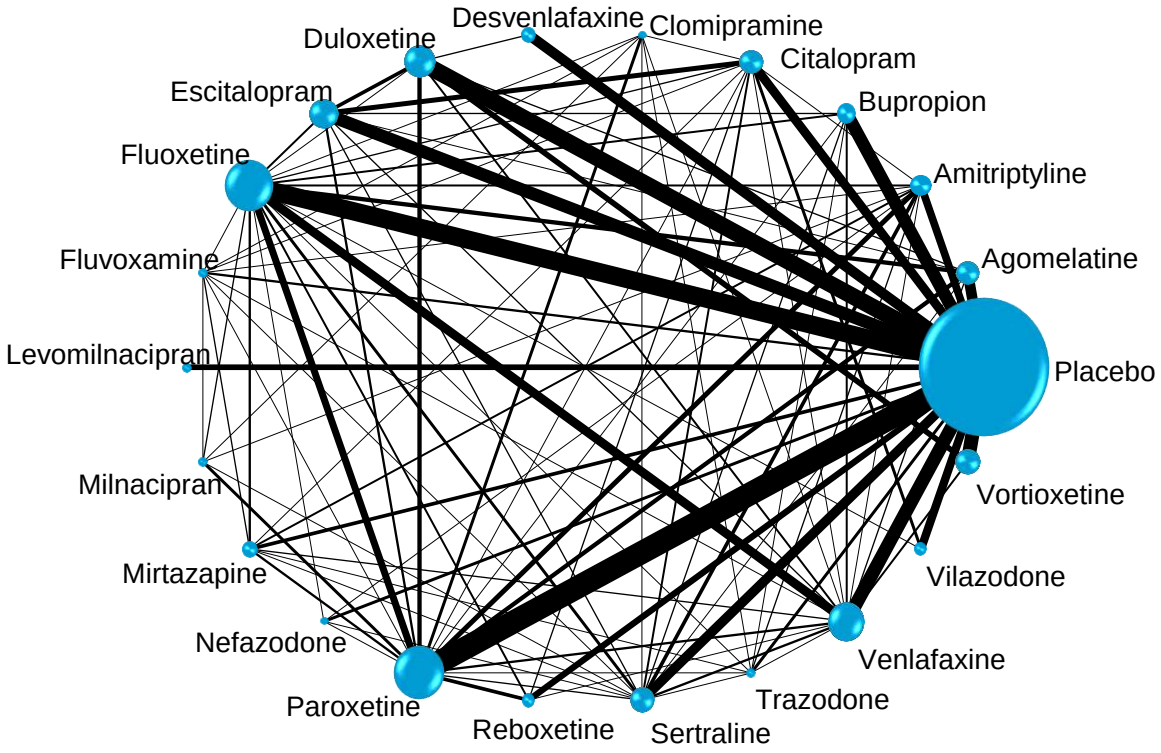
Cipriani, Furukawa, Salanti et al. Lancet 2018

21 antidepressants and placebo

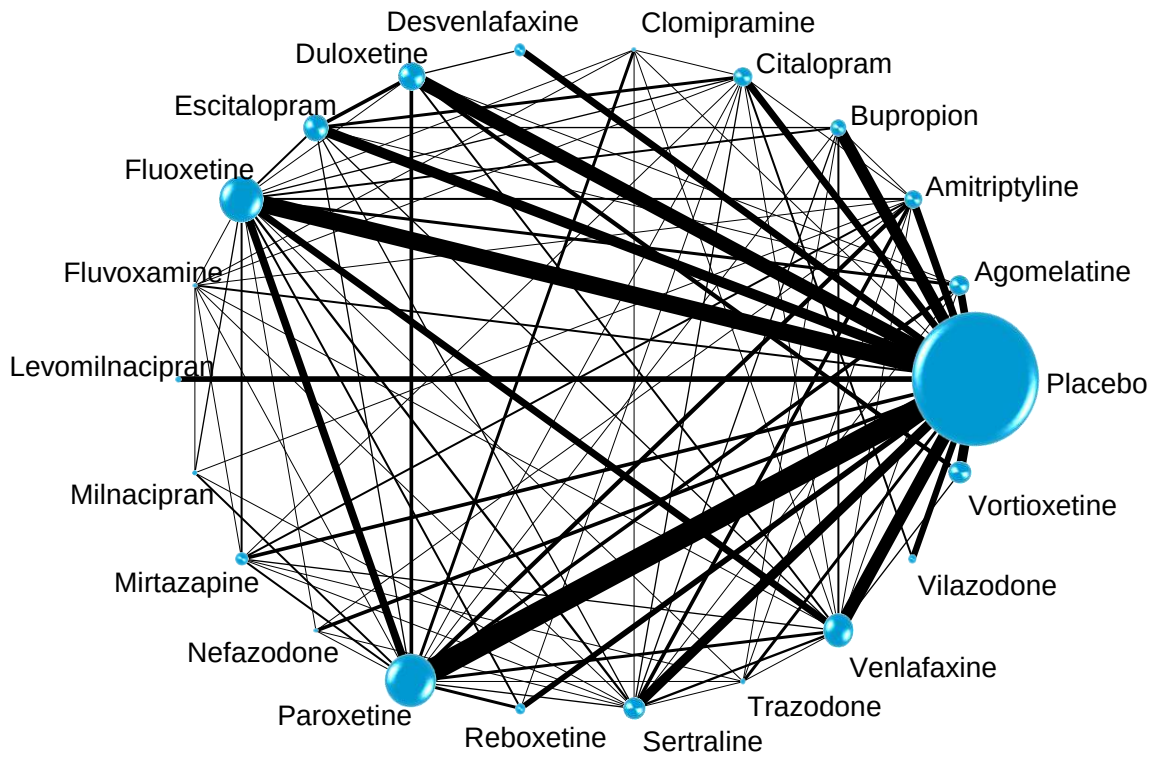
522 studies

302 placebo arms

Response

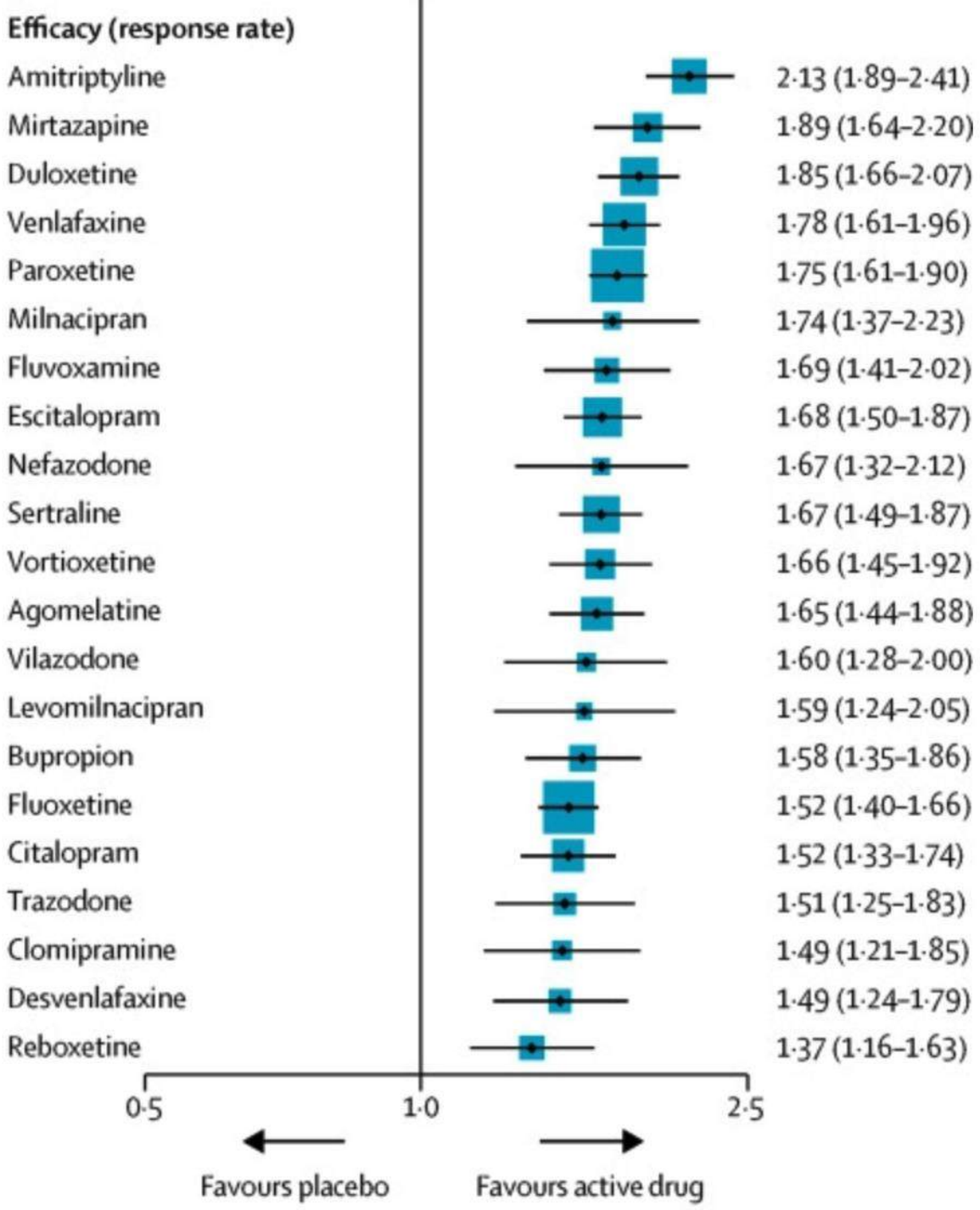


All-cause drop-outs



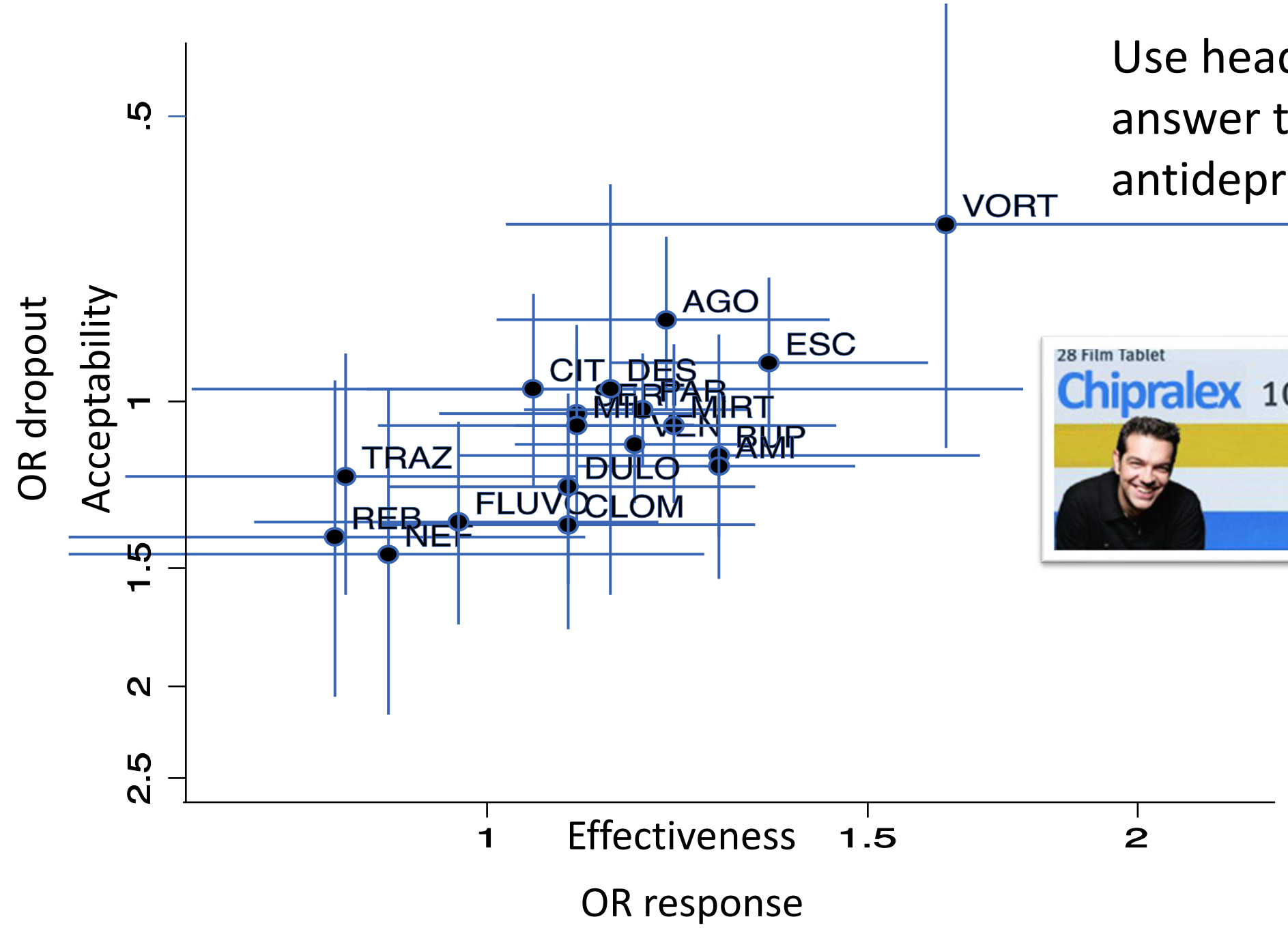
86 unpublished studies

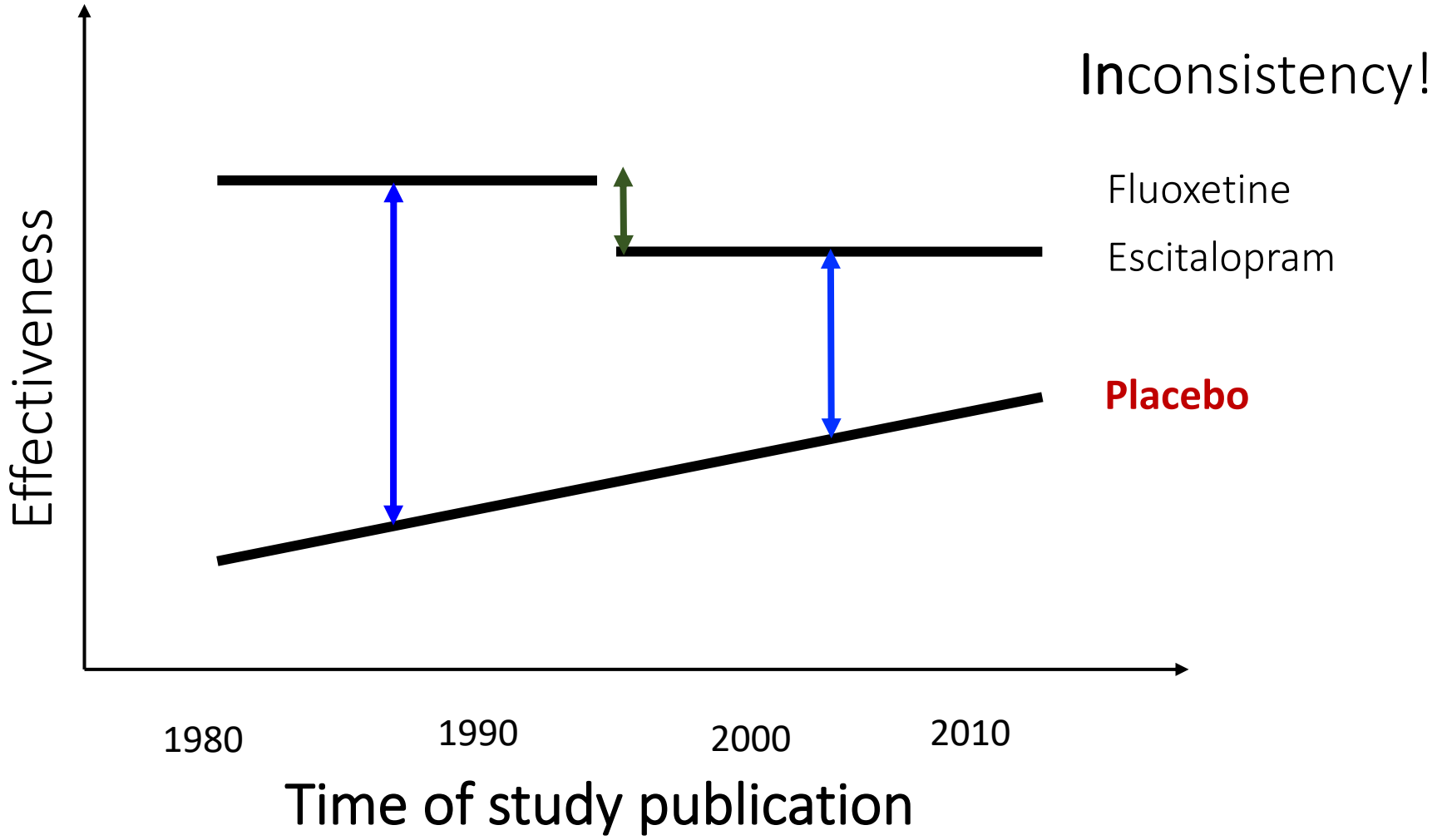
274 studies with published and unpublished data



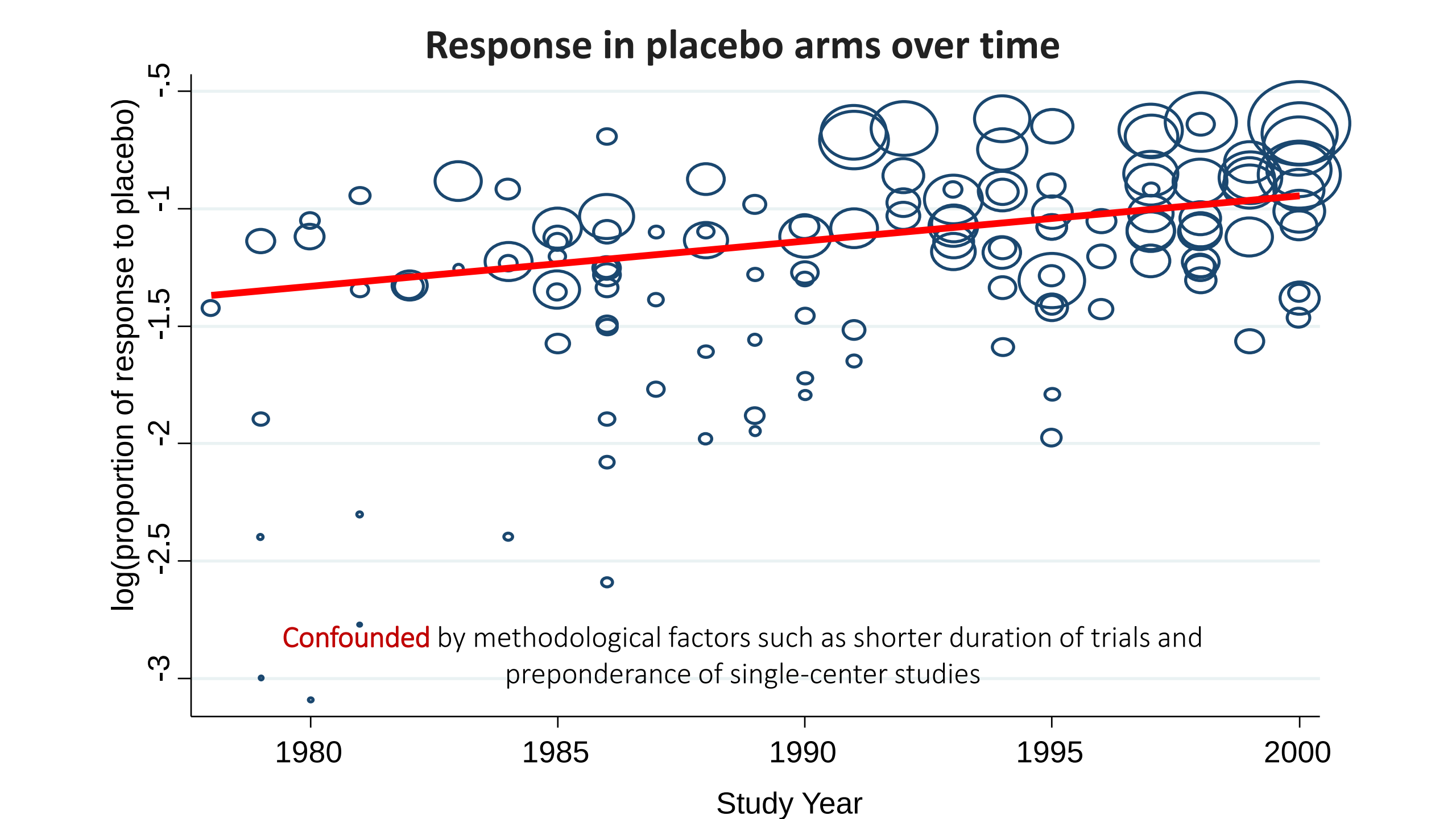
Use placebo-controlled trials to answer the question "do antidepressants work"?

Use head-to-head trials to answer the question “do antidepresants differ”?

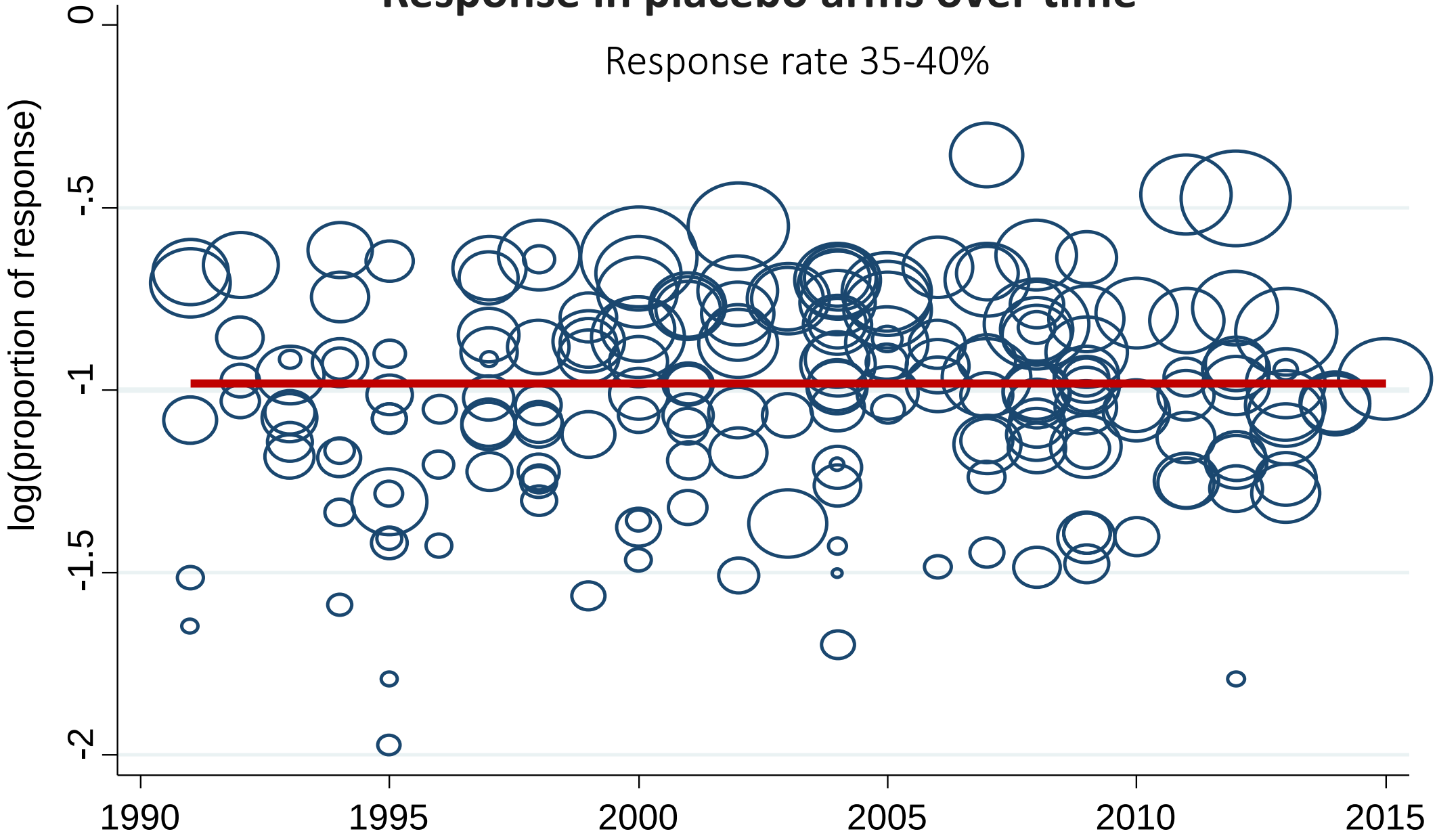




Walsh et al. *JAMA* 2002; 287: 1840–47.
Khan A et al. *CNS Neurosci Ther* 2010; 16: 217–26.

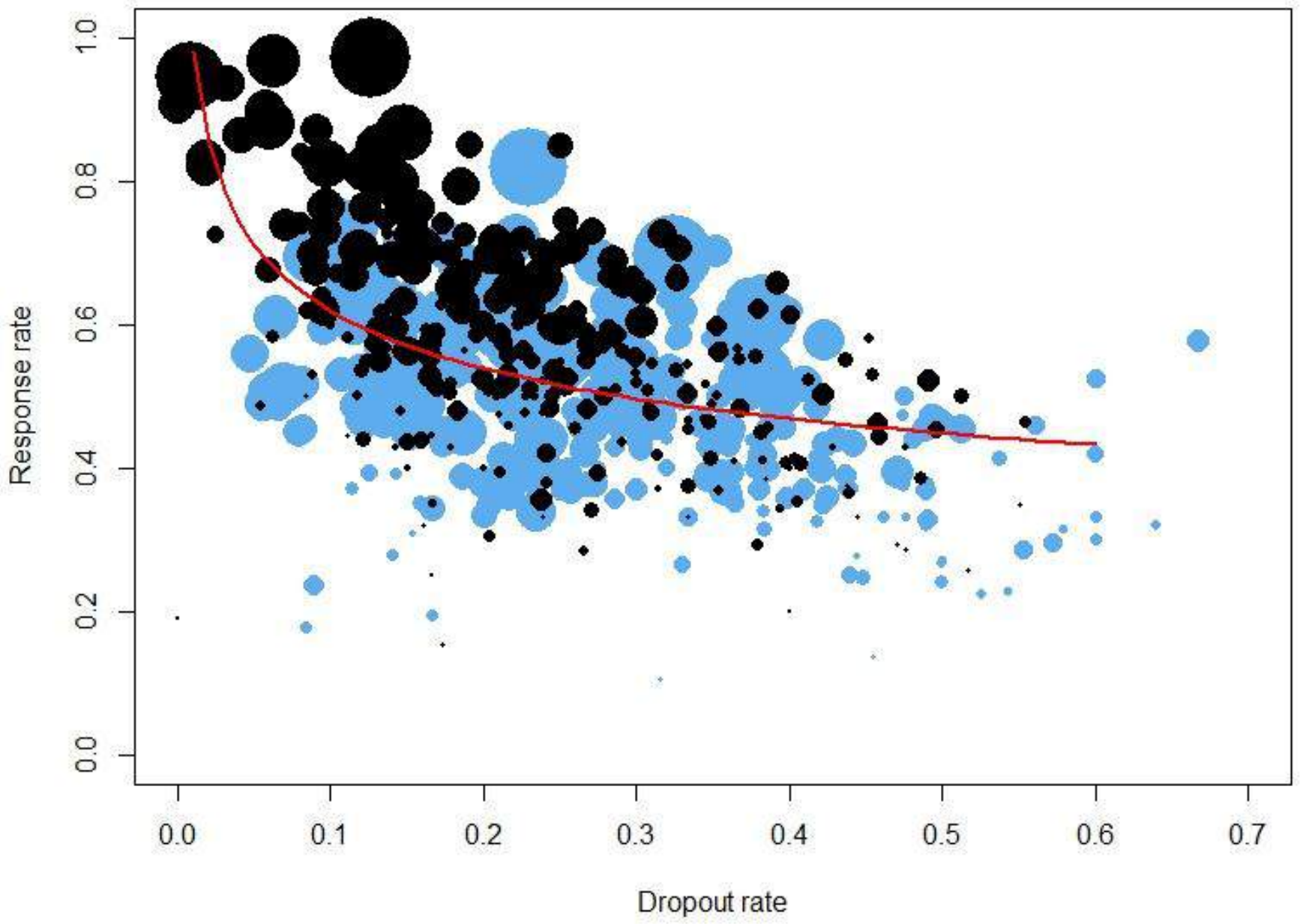

Response in placebo arms over time
log(proportion of response to placebo)
-.5
-1
-1.5
-2
-2.5
-3
1980
1985
1990
1995
2000
Study Year
Confounded by methodological factors such as shorter duration of trials and preponderance of single-center studies

Response in placebo arms over time



Furukawa TA et al. Lancet Psychiatry. 2016

Active arms from: placebo-controlled trials Head-to-head trials

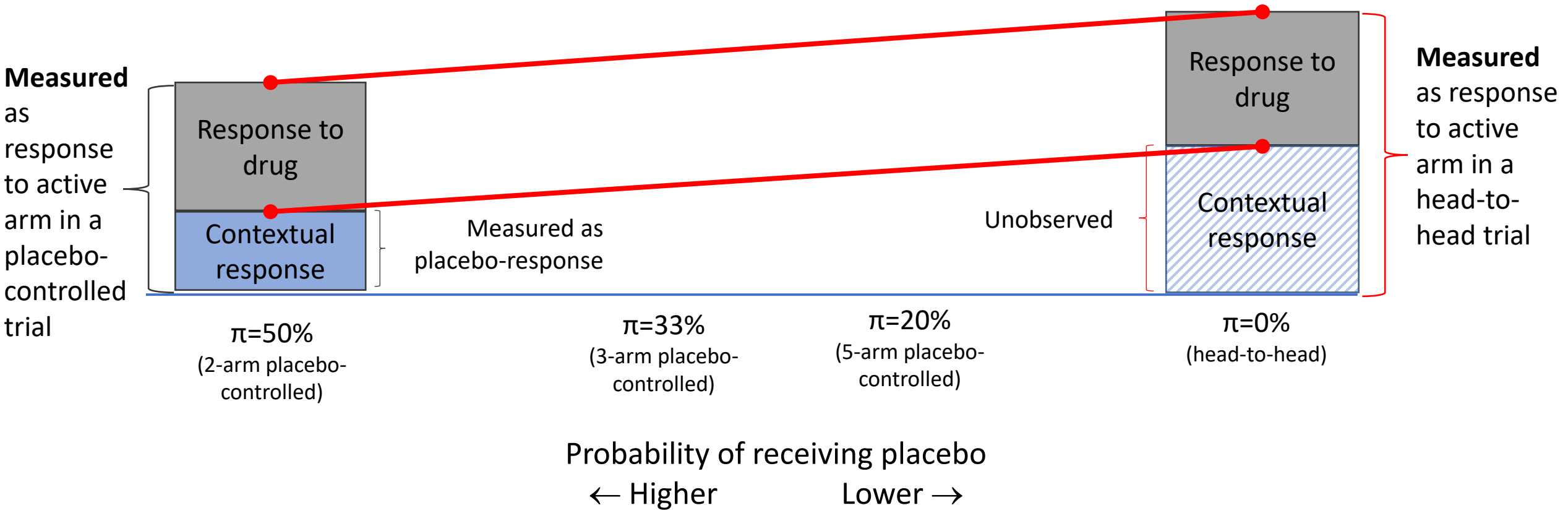


The response to antidepressants decreases and dropout increases when a placebo arm is included in the trial.

Salanti G at al. Int J Epidemiol. 2018

The limit of evidence synthesis

How to adjust for differential contextual response?
Impossible with the existing data!
We need an “unethical” trial



Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis

Toshi A Furukawa*, Andrea Cipriani*, Philip J Cowen, Stefan Leucht, Matthias Egger, Georgia Salanti

Summary

Background Depression is the single largest contributor to non-fatal health loss worldwide. Second-generation antidepressants are the first-line option for pharmacological management of depression. Optimising their use is crucial in reducing the burden of depression; however, debate about their dose dependency and their optimal target dose is ongoing. We have aimed to summarise the currently available best evidence to inform this clinical question.

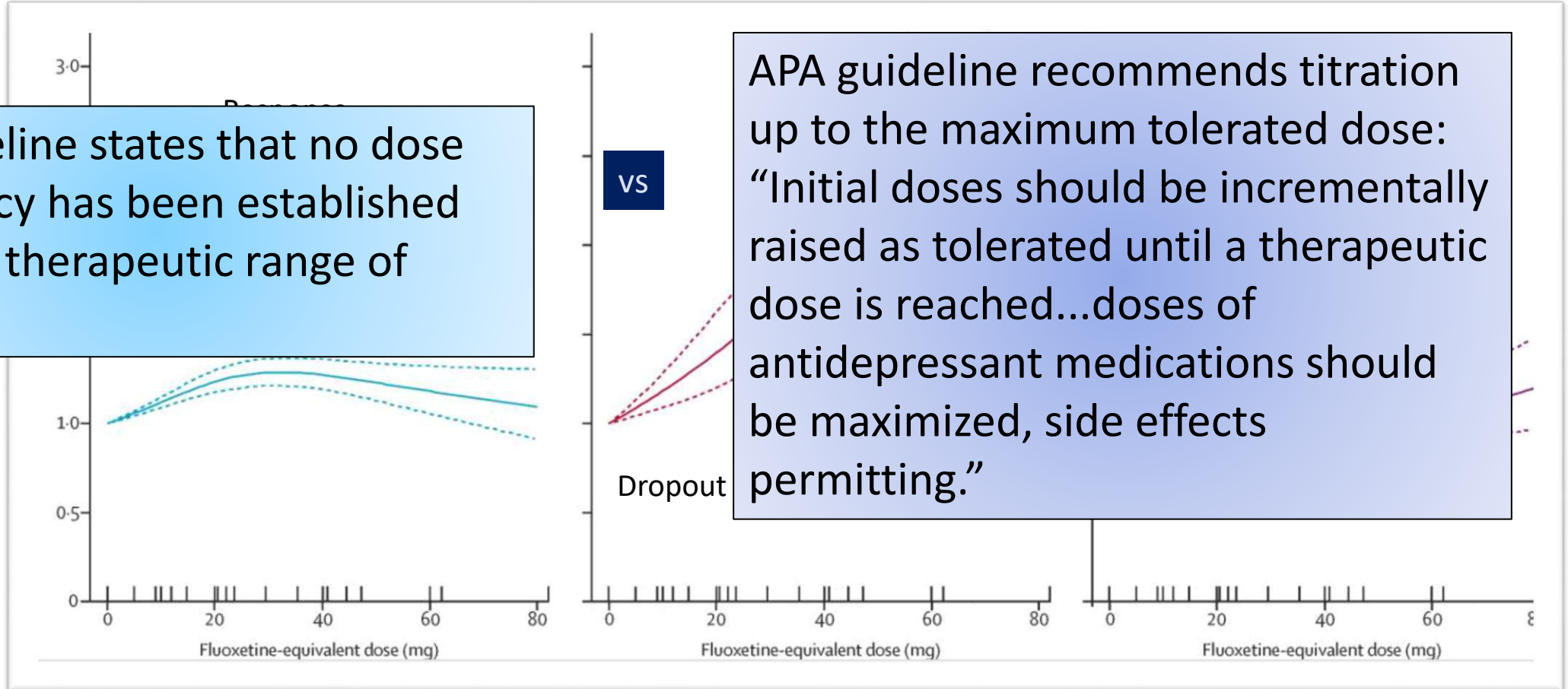
Lancet Psychiatry 2019; 6: 601–09

Published Online June 6, 2019 http://dx.doi.org/10.1016/

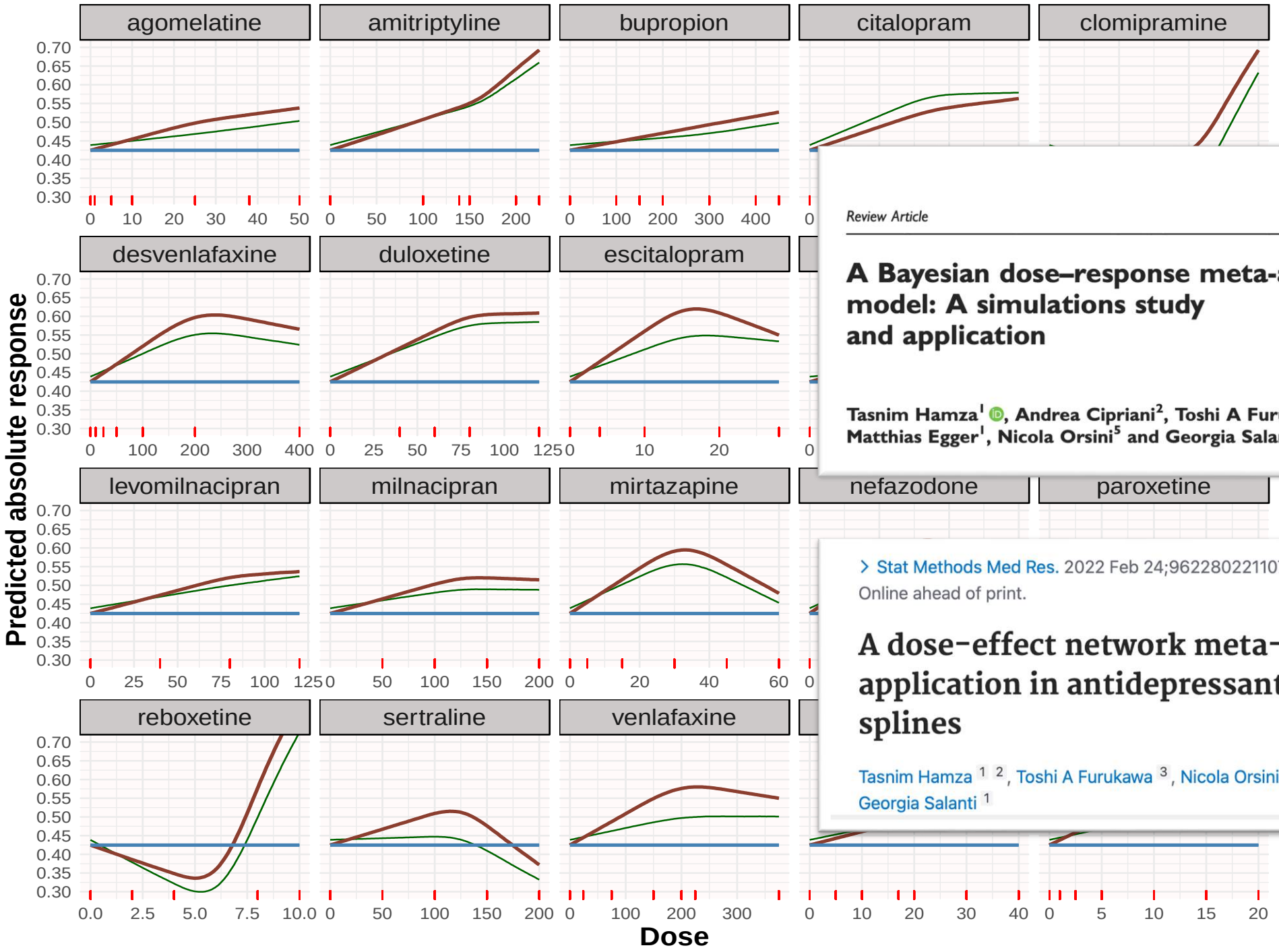
Lancet Psychiatry 2019; 6: 601–09

Dose-response meta-analysis of 77 studies: response increases up to 30 mg per day (fluoxetine equivalent) – dropout due to AE increases linearly

NICE guideline states that no dose dependency has been established within the therapeutic range of SSRIs



APA guideline recommends titration up to the maximum tolerated dose: "Initial doses should be incrementally raised as tolerated until a therapeutic dose is reached...doses of antidepressant medications should be maximized, side effects permitting."



Dose-response network meta-analysis

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

Review Article

Statistical Methods in Medical Research
2021, Vol. 30(5) 1358–1372

DOI: 10.1177/0962280220982643
journals.sagepub.com/home/smm
SAGE

A Bayesian dose–response meta-analysis model: A simulations study and application

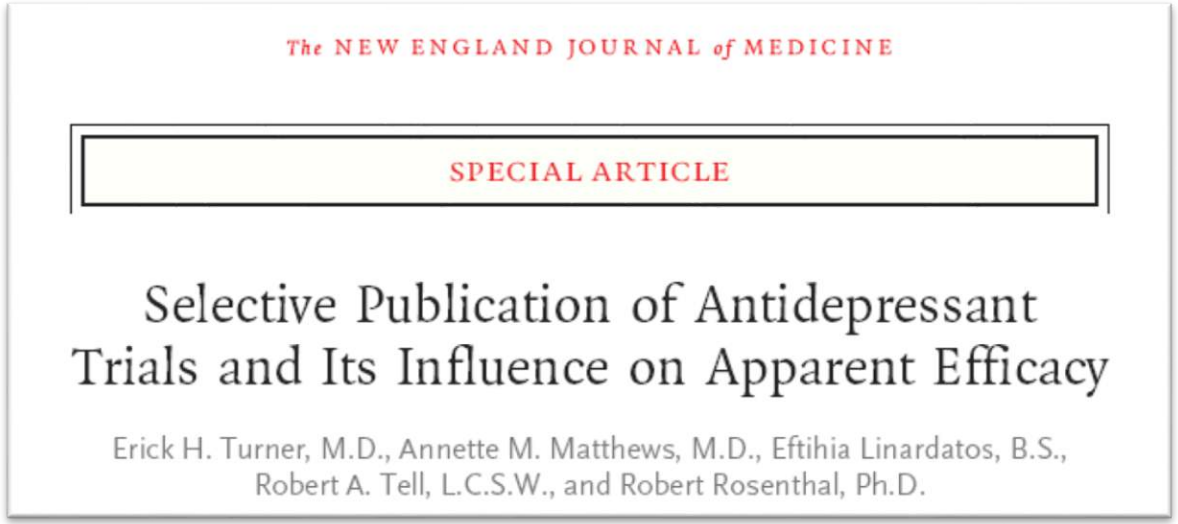
Tasnim Hamza[1], Andrea Cipriani[2], Toshi A Furukawa[3,4], Matthias Egger[1], Nicola Orsini[5] and Georgia Salanti[1]

› Stat Methods Med Res. 2022 Feb 24;9622802211070256. doi: 10.1177/09622802211070256.
Online ahead of print.

A dose-effect network meta-analysis model with application in antidepressants using restricted cubic splines

Tasnim Hamza [1 2], Toshi A Furukawa [3], Nicola Orsini [4], Andrea Cipriani [5], Cynthia P Iglesias [6], Georgia Salanti [1]

New trials are less subject to publication bias compared to older studies!



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

2009:

only 4 out of the 37 negative trials submitted to FDA were published **(11%)**

PLOS MEDICINE

RESEARCH ARTICLE

Selective publication of antidepressant trials and its influence on apparent efficacy: Updated comparisons and meta-analyses of newer versus older trials

Erick H. Turner[1,2]*, Andrea Cipriani[3,4,5], Toshi A. Furukawa[6], Georgia Salanti[7], Ymkje Anna de Vries[8,9]

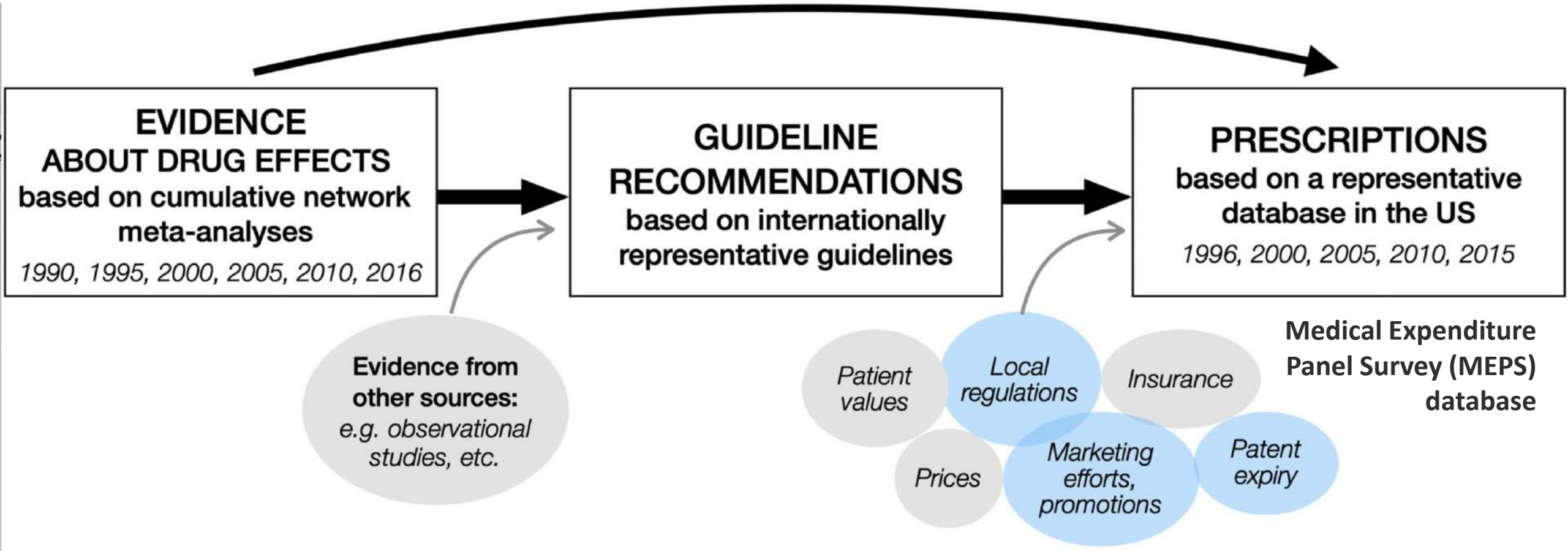
2022: new cohort of licensed drugs

30 trials submitted to FDA
15 negative trials submitted to FDA
7 **(47%)** of the positive trials submitted to FDA were published in the literature

Turner EH et al. PLOS Medicine 19(1): e1003886.

Is meta-analysis just a toy for statisticians and curious research psychiatrists?

In an ideal world….



Medical Expenditure Panel Survey (MEPS) database

Interactive Plots to Demonstrate the Evolution of Evidence for Antidepressants in the Acute Treatment of Major Depression

https://cinema.ispm.unibe.ch/shinies/GRISELDA/

The data used in this study comes from GRISELDA (Group of Researchers Investigating Specific Efficacy of individual Drugs for Acute depression) [1]. Double-blind RCTs of the acute phase treatment with **21 antidepressants** for adult patients (≥18 years old) with a primary diagnosis of **major depression** were **systematically** searched and included. About one in four trials included in the dataset comes from unpublished data, and two come from both published and unpublished sources.

In the **network meta-analysis,** we use two primary outcomes: efficacy and acceptability. **Efficacy** was measured by the response rate of the intervention, defined as the proportion of patients who showed 50% or greater reduction on a validated depression severity scales from baseline. **Acceptability** was measured by the all-cause discontinuation rate, defined as the proportion of patients who withdrew early due to any reasons.

[1] Cipriani A, Furukawa TA, Salanti G, et al, 2018. 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. Lancet 391, 1357-1366.

Scan me!

Choose the type of RCT you would like to synthesize: the reference drug will be placebo if all the trials are included, and the reference will be citalopram if only head-to-head trials are included.

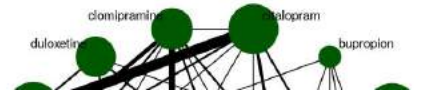
Choose the type of RCT

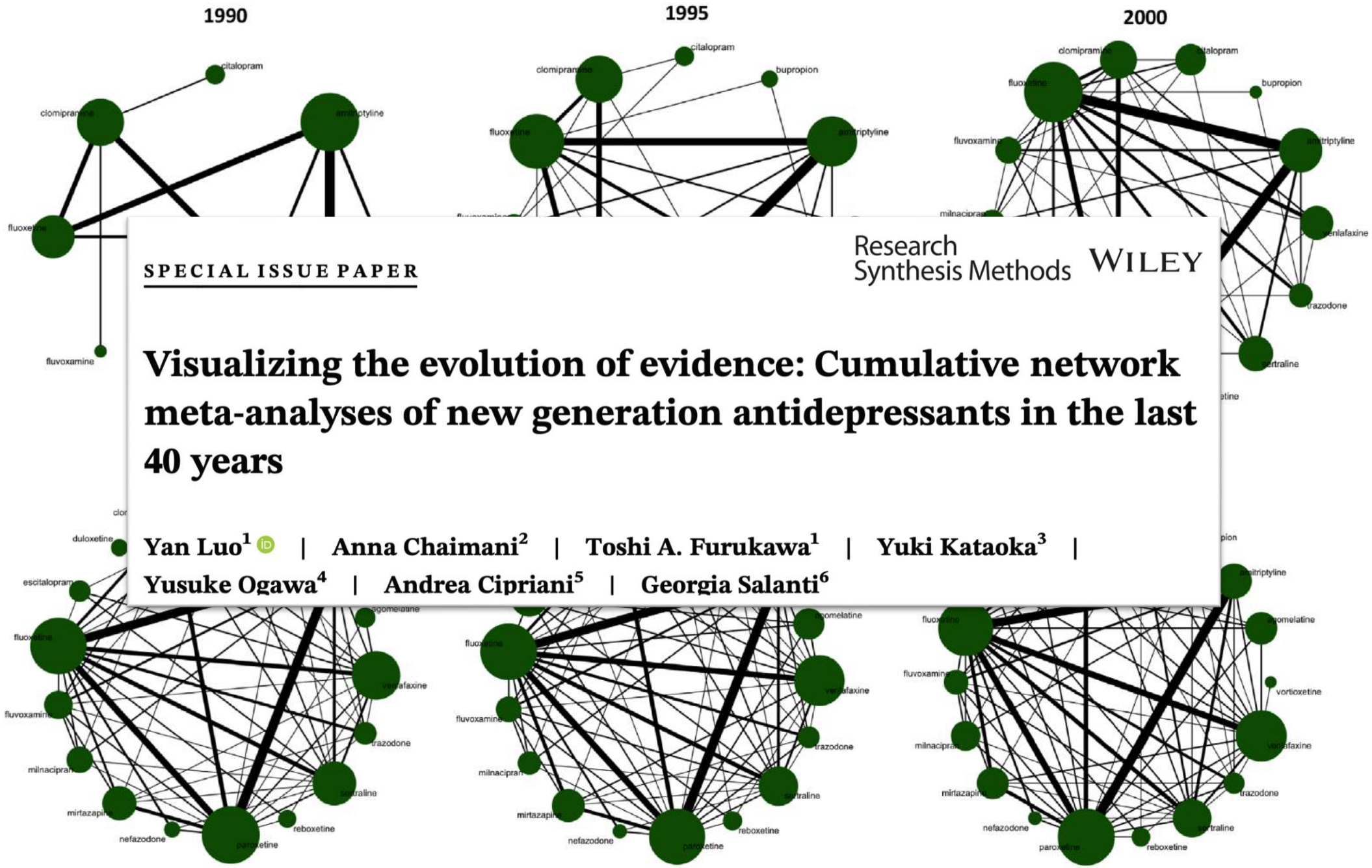
- Including placebo-controlled trials
- Only head-to-head trials

Choose the period of network meta-

Network Plots and Basic Information | 2 Dimensional Plots | Forest Plots | League Tables | Pairwise Comparisons | Funnel Plots | Evidence Evolution

The efficacy network:





SPECIAL ISSUE PAPER

Research Synthesis Methods WILEY

Visualizing the evolution of evidence: Cumulative network meta-analyses of new generation antidepressants in the last 40 years

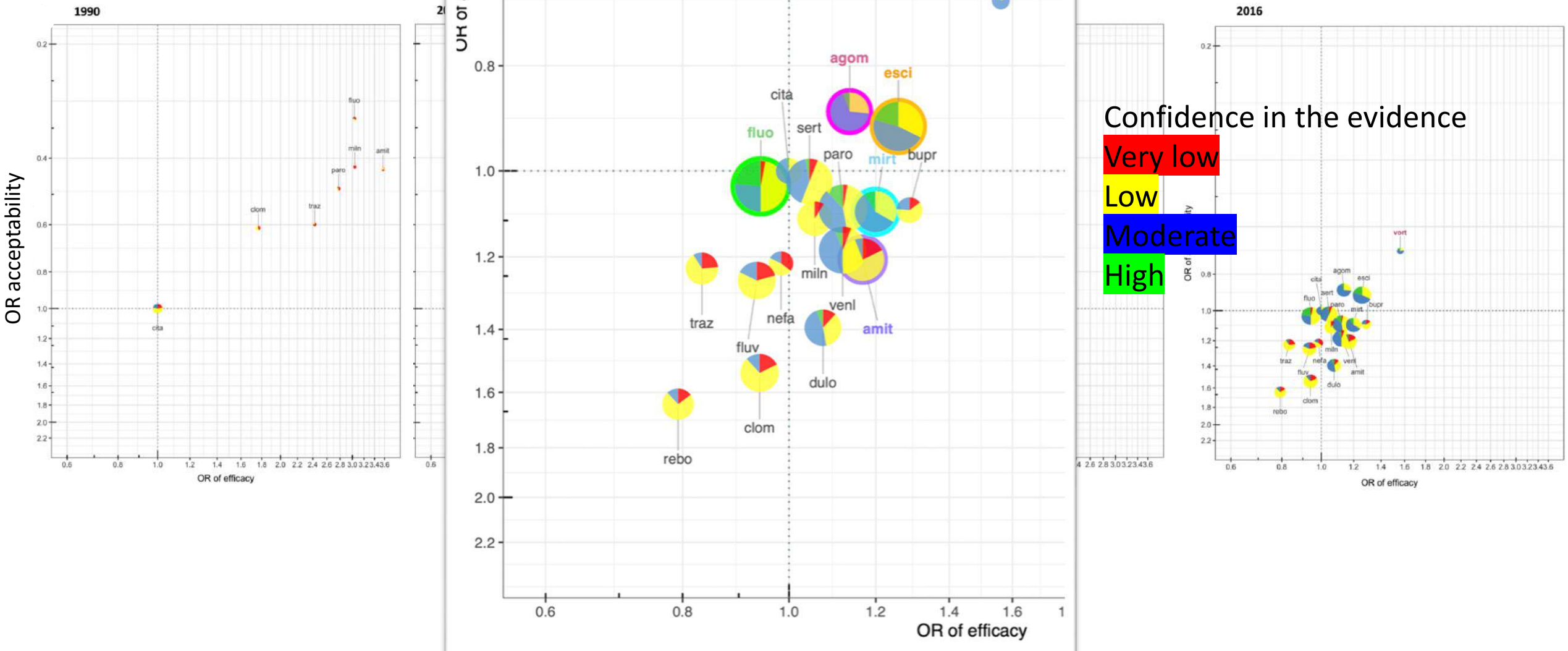
Yan Luo[1] | **Anna Chaimani**[2] | **Toshi A. Furukawa**[1] | **Yuki Kataoka**[3] | **Yusuke Ogawa**[4] | **Andrea Cipriani**[5] | **Georgia Salanti**[6]

Evolution of evidence on the effects of antidepressants with credibility judgement

ORs against citalopram

1990

2016



Guidelines do not fully reflect the evolving evidence

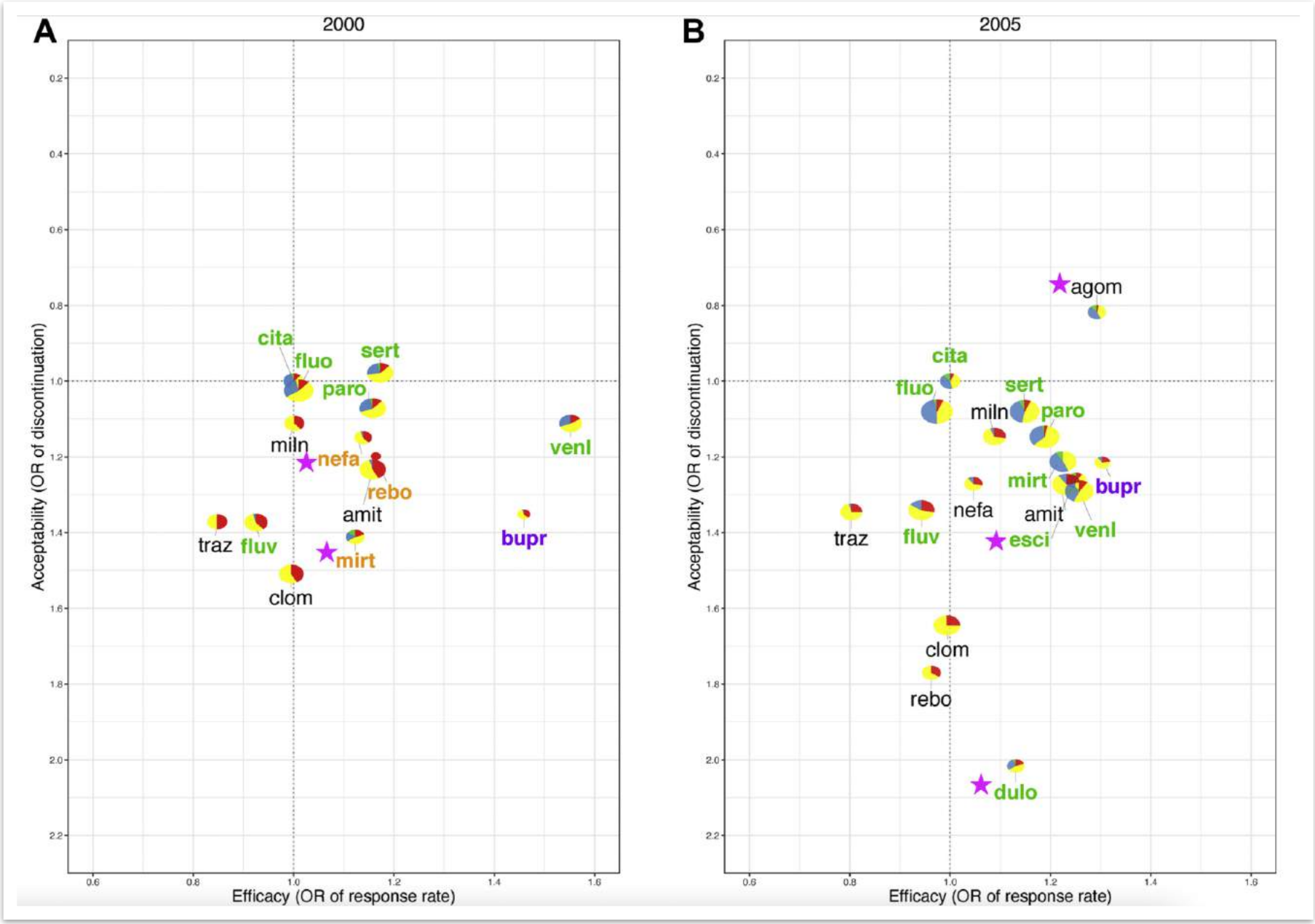
American Psychiatric Association

Agency for Health Care Policy and Research

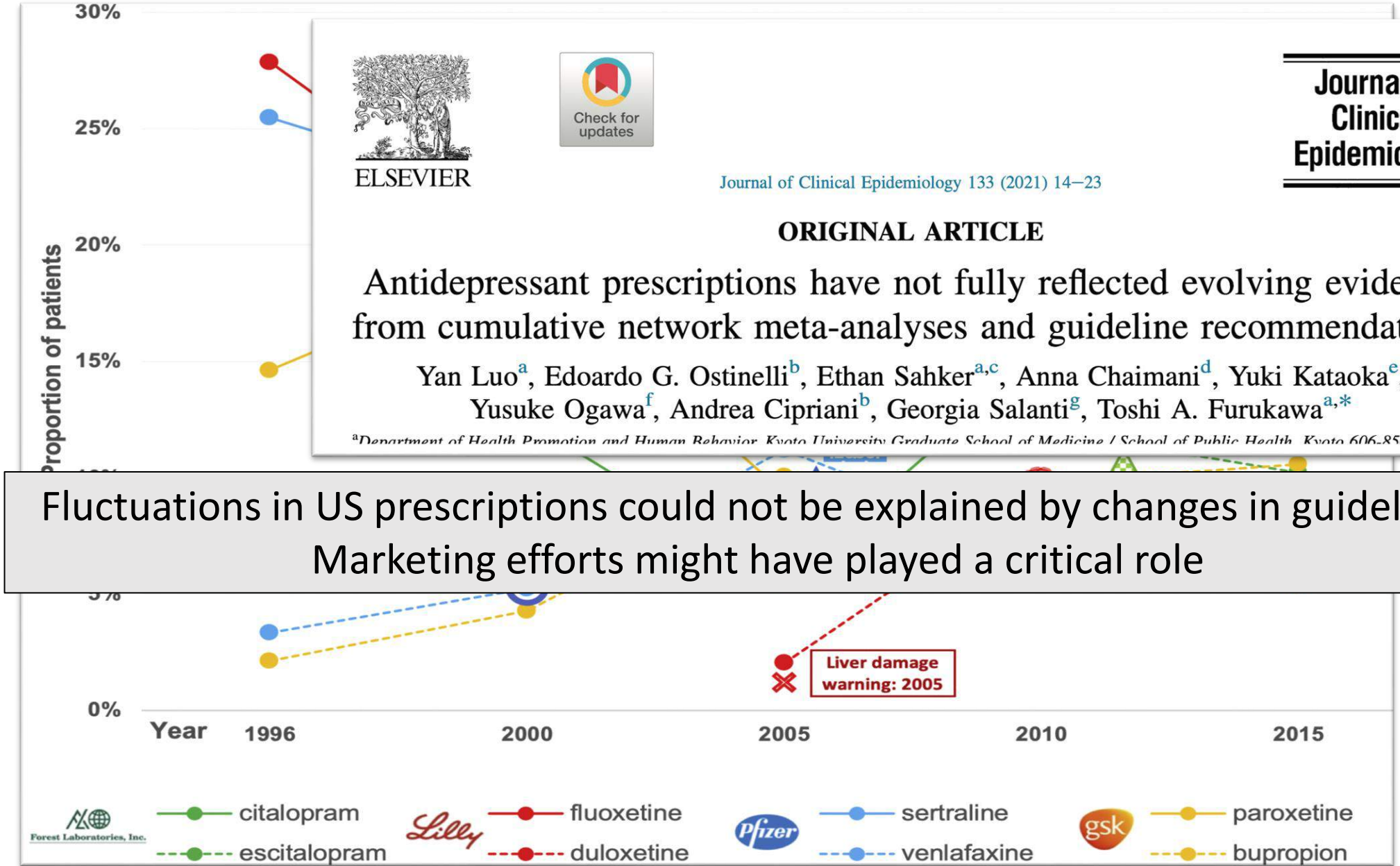
British Association for Psychopharmacology

NICE

Drug names labeled in green : recommended by more than two guidelines published within 5 years from the time of network meta-analyses



Prescription of 8 antidepressants recommended by APA



ELSEVIER

Check for updates

Journal of Clinical Epidemiology 133 (2021) 14–23

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Antidepressant prescriptions have not fully reflected evolving evidence from cumulative network meta-analyses and guideline recommendations

Yan Luo[a], Edoardo G. Ostinelli[b], Ethan Sahker[a,c], Anna Chaimani[d], Yuki Kataoka[e], Yusuke Ogawa[f], Andrea Cipriani[b], Georgia Salanti[g], Toshi A. Furukawa[a,*]

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Fluctuations in US prescriptions could not be explained by changes in guidelines
Marketing efforts might have played a critical role