What evidence is available to guide antidepressant choice?

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Liverpool

Synopsis

Question

- Does the recent Cipriani et al systematic review & meta-analysis[1] of antidepressant clinical trials enable better evidence-based choice of antidepressants?

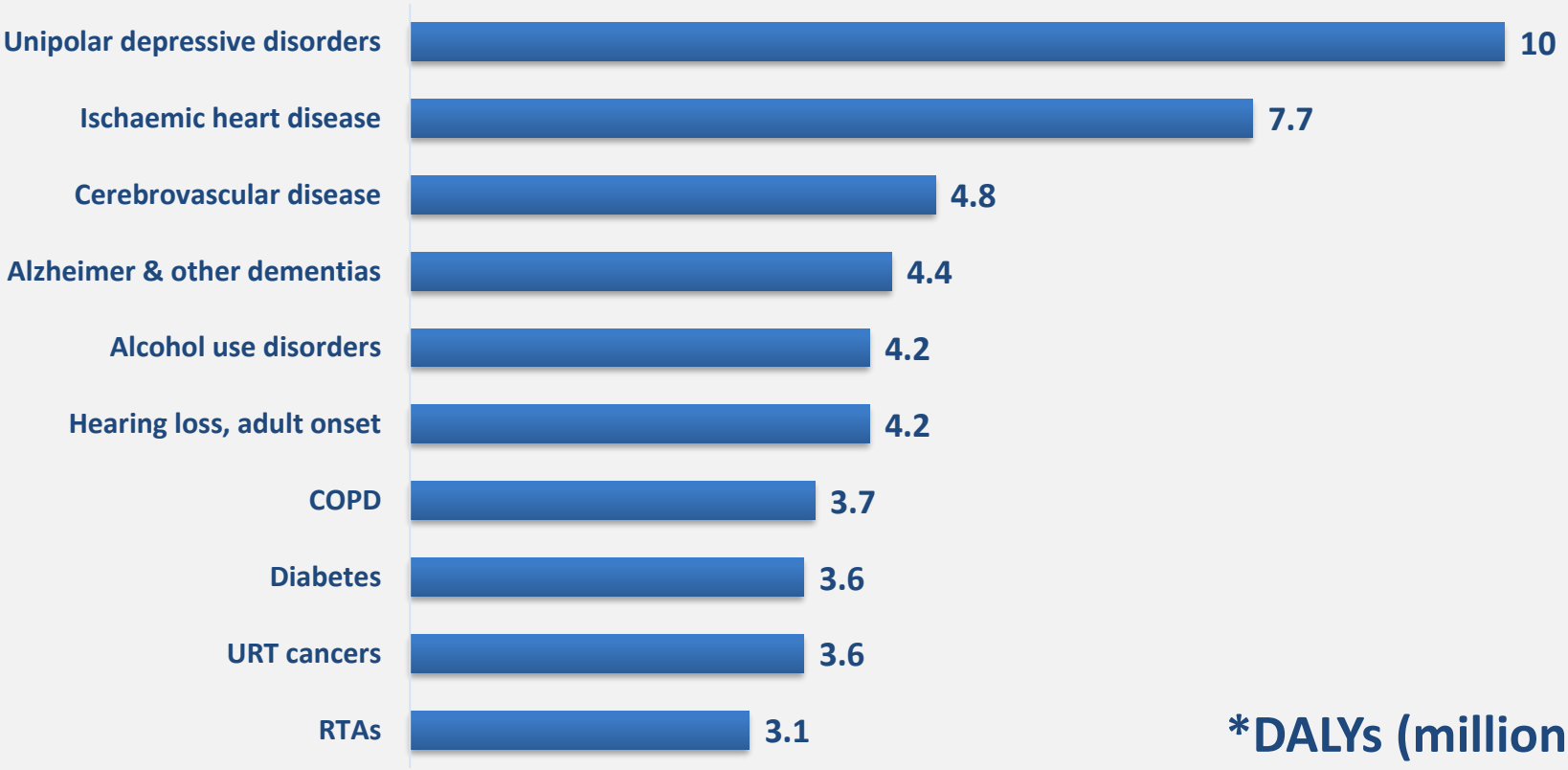
1. Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

Outline

- Context (1) – Burden of depression
- The Cipriani study
  - Method
  - Results
  - Interpretation
- Context (2) - Choosing an antidepressant
  - NICE guidelines
  - Population-based research
  - Technology appraisals

THE GLOBAL BURDEN OF DISEASE
2004 UPDATE

Burden of disease: leading causes of disability-adjusted life-years (high-income countries)



***DALYs (millions)**

World Health Organization

WHO. Global Burden of Disease 2004.
http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/ Accessed 18.12.2018

*Disability adjusted life years

Impact on health of Depression & other chronic diseases

- World Health Survey
- 60 countries
- 245,404 participants
- ICD-10 diagnosis of depression
- Other chronic diseases:
  - Angina
  - Arthritis
  - Asthma
  - Diabetes

- 18 health-related questions in 8 domains
  - vision, mobility, self-care, cognition, interpersonal activities, pain/discomfort, sleep & energy, affect

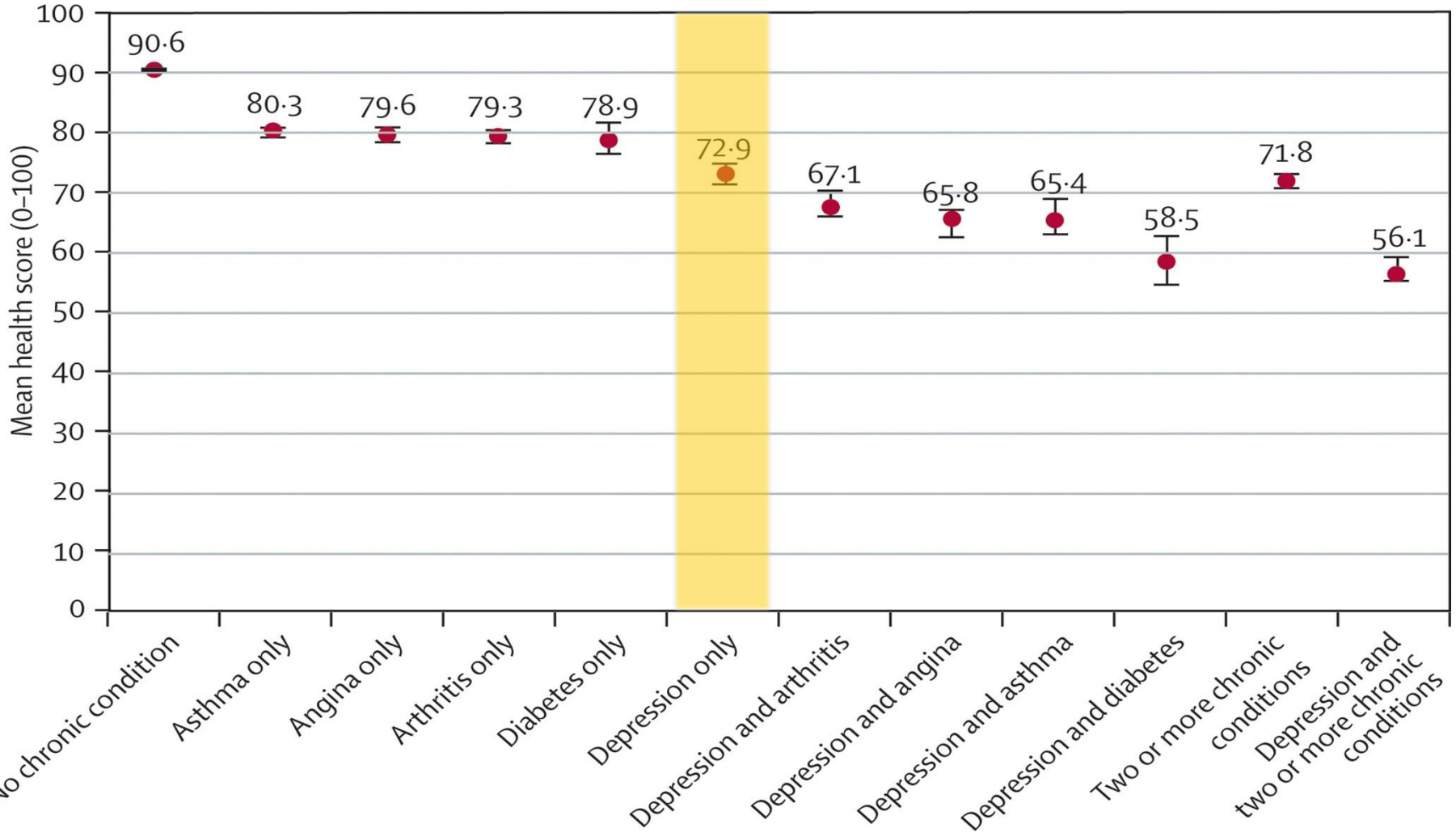
- 5-point scale
  - no difficulty or problem to extreme difficulty/inability

Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007;370:851-858

Depression

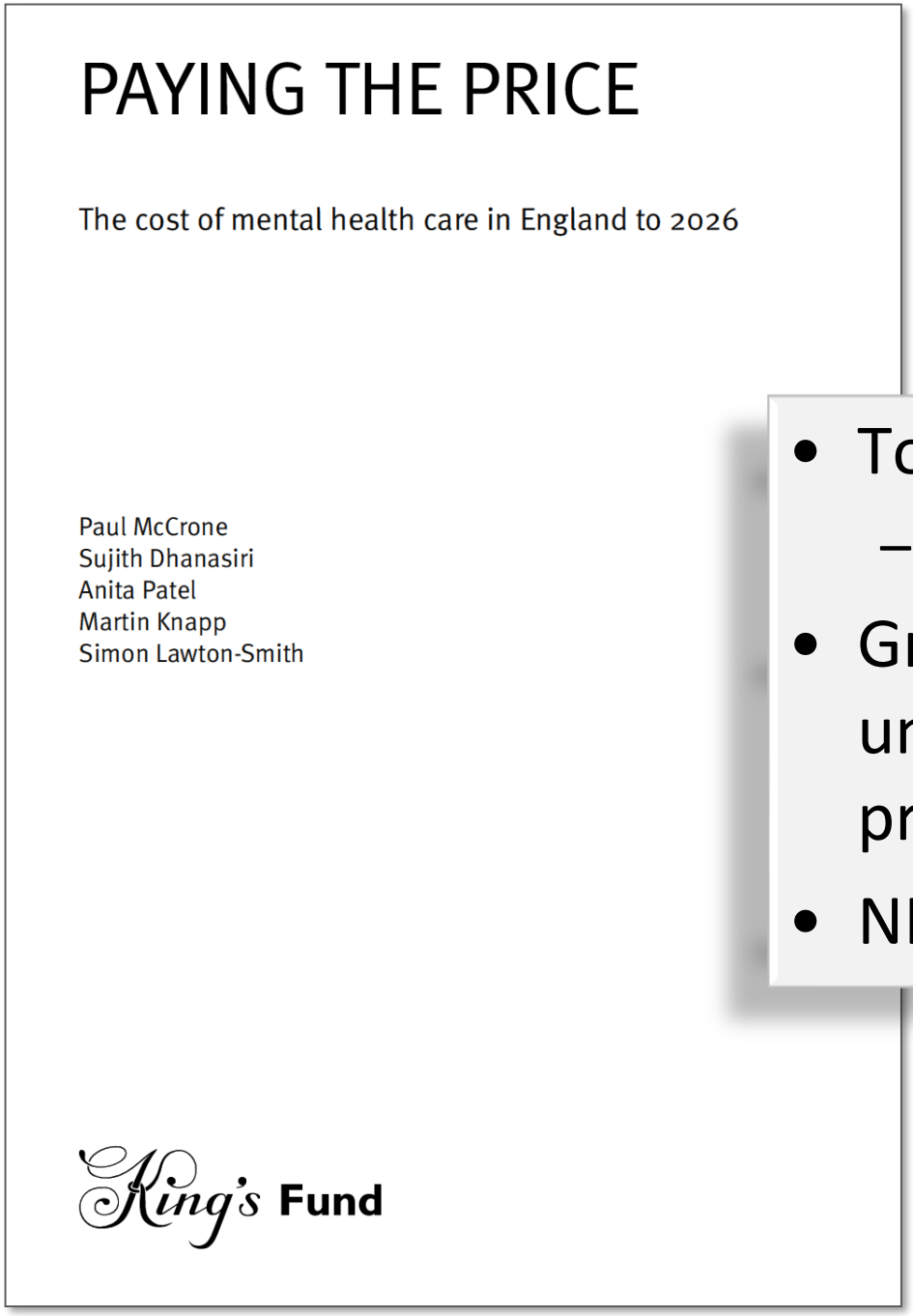
a. Greater impact on health than other chronic diseases

b. Comorbidity with other chronic illness: worst health scores of all disease states



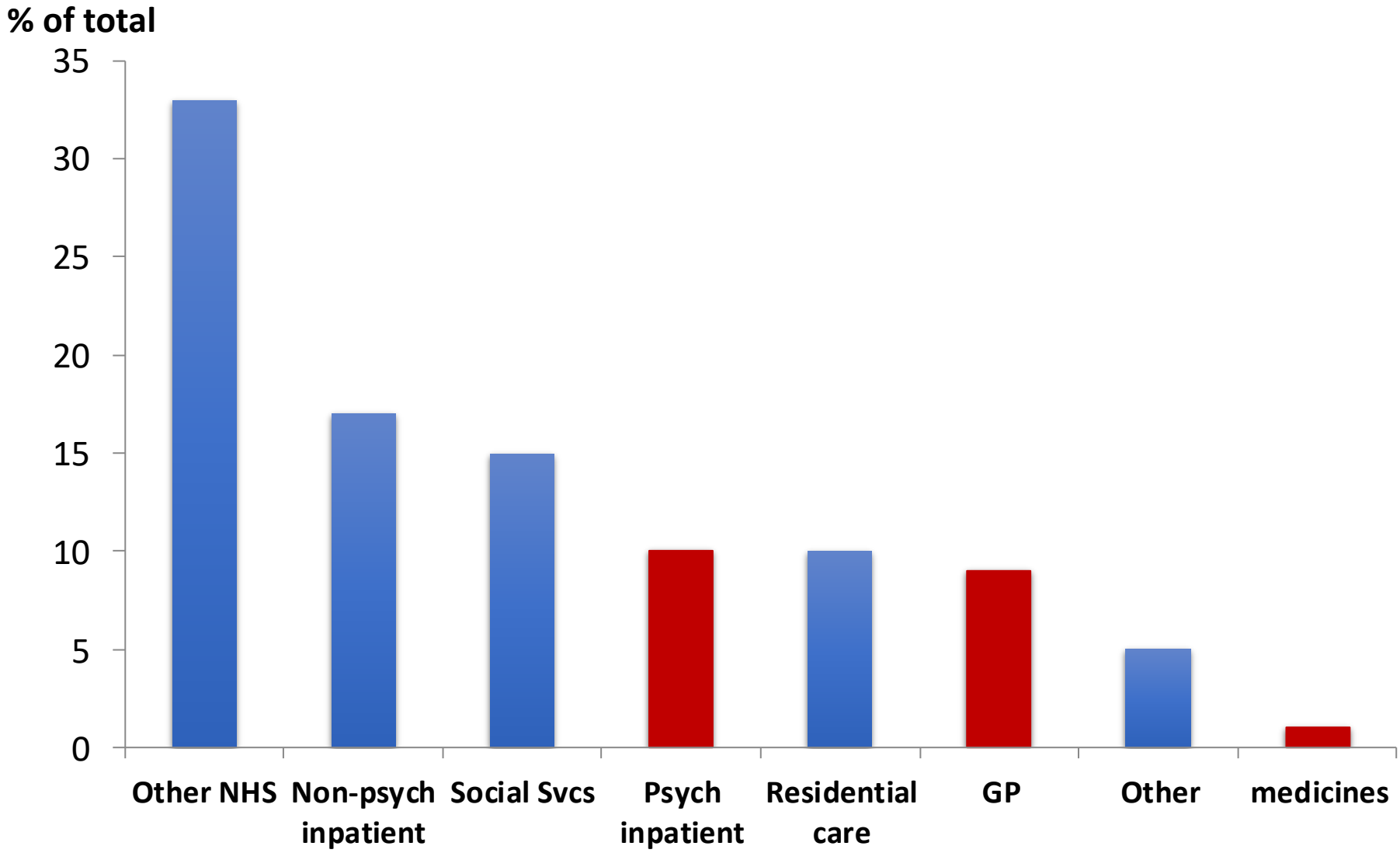
Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007;370:851-858

Economic Burden of Depression



- Total annual cost in England
  - **£8.6 billion** (2012 estimate)
- Greatest costs associated with unemployment & loss of productivity
- NHS costs approx **£1.8 billion**

Depression: Cost of Care



McCrone P, Dhanasiri S, Patel A, et al.
Paying the price: the cost of mental health care in England to 2026
London, King's Fund, 2008

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*

Lancet 2018; 391: 1357-1366

Drugs

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

Sarah Boseley *Health editor*

Wed 21 Feb 2018 23.30 GMT

▲ It is likely that in the UK alone 1 million more people a year should have access to either drugs or psychotherapy for depression, say experts. Photograph: Darron Cummings/AP

Antidepressants work - some more effectively than others - in treating depression, according to authors of a groundbreaking study which doctors hope will finally put to rest doubts about the controversial medicine.

Millions more people around the world should be prescribed pills or offered talking therapies, which work equally well for moderate to severe depression, say the doctors, noting that just one in six people receive proper treatment in the rich world - and one in 27 in the developing world.

most viewed


Yulia Skripal says she is recovering but disoriented


Live Russia will not accept findings of OPCW inquiry into Salisbury, ambassador signals - Politics live


Ex-Trump aide Paul Manafort approved 'black ops' to help Ukraine president


Alleged fraudster made €1m by 'recycling' bottles, German court hears


What's up PewdiePie? The troubling content of YouTube's biggest star

https://www.theguardian.com/science/2018/feb/21/the-drugs-do-work-antidepressants-are-effective-study-shows
Accessed 06.12.2018

More data, more answers: picking the optimal antidepressant

In an era of increasingly large datasets for health and emphasis on so-c
questions remain
do some antidepr
depression? And a
at least as measur
search of antidepre
2000 hits, but the
antidepressants are
is made particularly
40 antidepressants

Andrea Cipriani a
to these questions
Lancet in 2009, int
meta-analysis to ps
12 then newer antic
the rest. In that la
117 trials with nea
in *The Lancet*, Cipri
applying a similar

this latest paper, Cipriani and colleagues[2] carefully follow

". . . head-to-head efficacy comparisons of antidepressants disclosed seven agents (agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine) as distinctly more effective and four agents (fluoxetine, fluvoxamine, reboxetine, and trazodone) to be somewhat less effective than the other antidepressants."

"Although seven antidepressants had higher efficacy than the other antidepressants, after factoring in acceptability, three emerged as preferable: agomelatine, escitalopram, and vortioxetine. Three antidepressants had a poor profile of efficacy and acceptability: fluvoxamine, reboxetine, and trazodone."

"A direct clinical implication is that the three net efficacious antidepressants might be considered first choice, whereas the three less efficacious antidepressants might be avoided initially."

Parikh SV, Kennedy SH
Lancet 2018; 391: 1333-34

Study outline

Systematic review and network meta-analysis

- Cochrane Central Register of RCTs
- CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO
- Websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016.
- Placebo-controlled and head-to-head trials of 21 antidepressants in the acute treatment of adults (≥18 years) with major depressive disorder

RCT = randomised controlled trial

- 28 552 citations
- of these 522 RCTs included
- with 116 477 participants

Primary outcomes

- Efficacy (response rate)
  ≥50% improvement in symptom ratings
- Acceptability
  all-cause treatment discontinuations

- Outcomes measured as close as possible to 8 weeks from treatment initiation
- Odds ratios (ORs) estimated using pairwise and network meta-analysis

Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

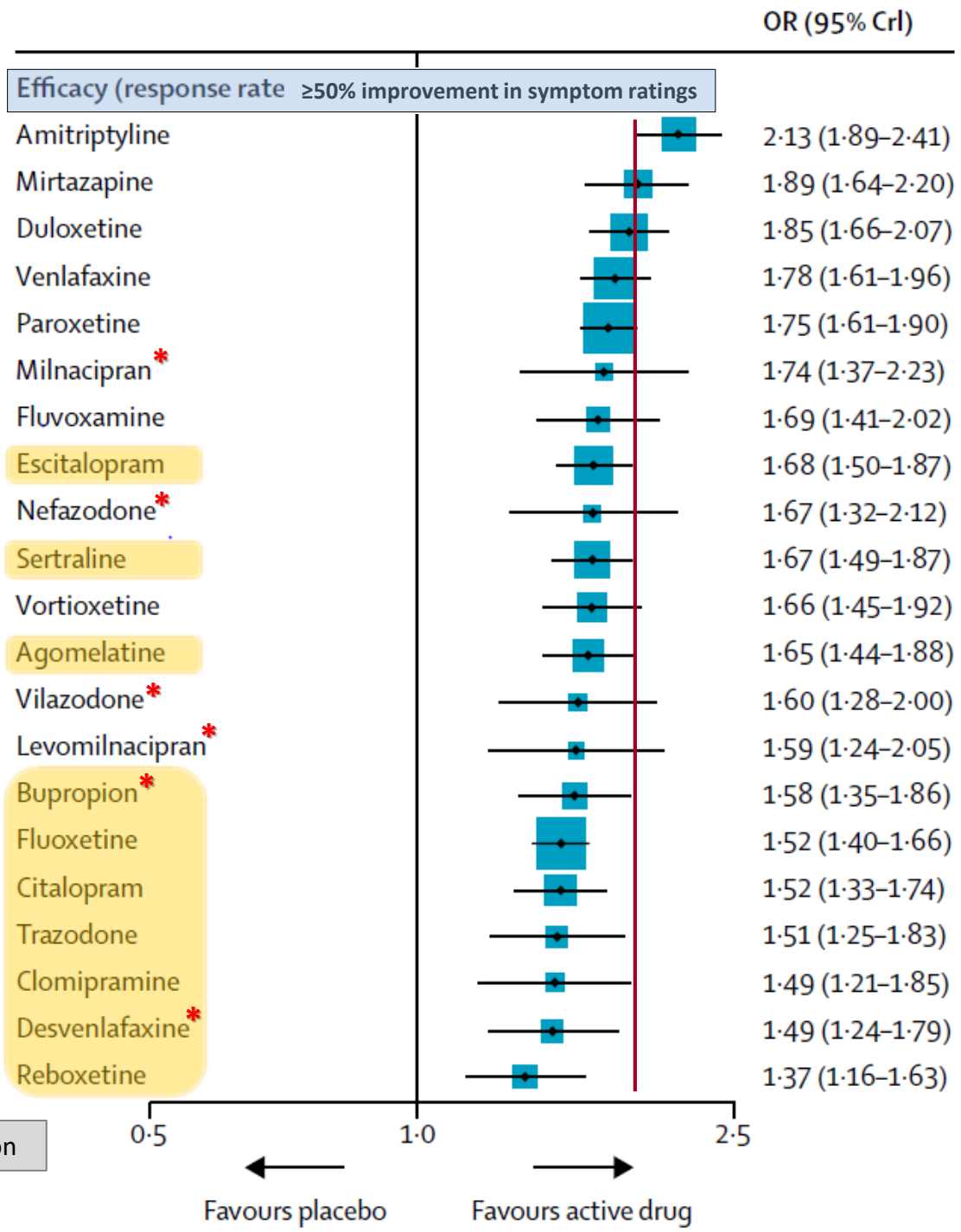
522 double-blind RCTs included in the network meta-analysis

- 23 agomelatine *vs* placebo or another active comparison
- 96 amitriptyline *vs* placebo or another active comparison
- *33 bupropion *vs* placebo or another active comparison
- 38 citalopram *vs* placebo or another active comparison
- 20 clomipramine *vs* placebo or another active comparison
- *9 desvenlafaxine *vs* placebo or another active comparison
- 30 duloxetine *vs* placebo or another active comparison
- 42 escitalopram *vs* placebo or another active comparison
- 117 fluoxetine *vs* placebo or another active comparison
- 32 fluvoxamine *vs* placebo or another active comparison
- *6 levomilnacipran *vs* placebo
- *10 milnacipran *vs* placebo or another active comparison
- 34 mirtazapine *vs* placebo or another active comparison
- *21 nefazodone *vs* placebo or another active comparison
- 114 paroxetine *vs* placebo or another active comparison
- 17 reboxetine *vs* placebo or another active comparison
- 54 sertraline *vs* placebo or another active comparison
- 26 trazodone *vs* placebo or another active comparison
- 68 venlafaxine *vs* placebo or another active comparison
- *9 vilazodone *vs* placebo or another active comparison
- 15 vortioxetine *vs* placebo or another active comparison

* Not licensed in the UK for the treatment of depression

Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

Forest plot of network meta-analysis of all trials for response rates vs placebo



Significantly in favour of active drug
Non-significant result
Significantly in favour of placebo

Lower response rate vs placebo than amitriptyline

Antidepressants compared with placebo.
OR=odds ratio. CrI=credible interval.

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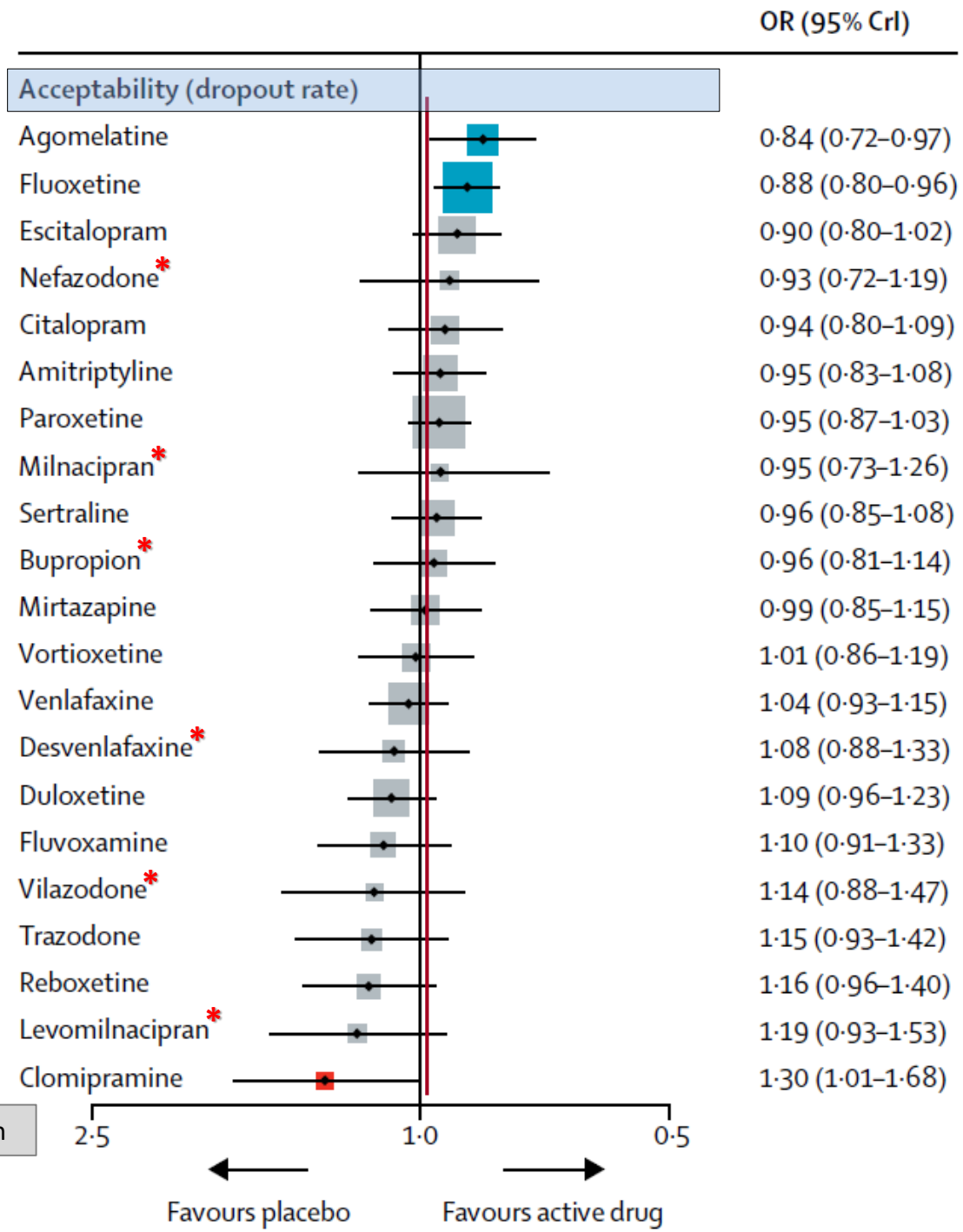
Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

Forest plot of network meta-analysis of all trials for drop-out rates vs placebo



Significantly in favour of active drug
Non-significant result
Significantly in favour of placebo

Antidepressants compared with placebo.
OR=odds ratio. CrI=credible interval.

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Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

Head-to-head comparisons for efficacy and acceptability

Efficacy (response rate) | Comparison | Acceptability (dropout rate)

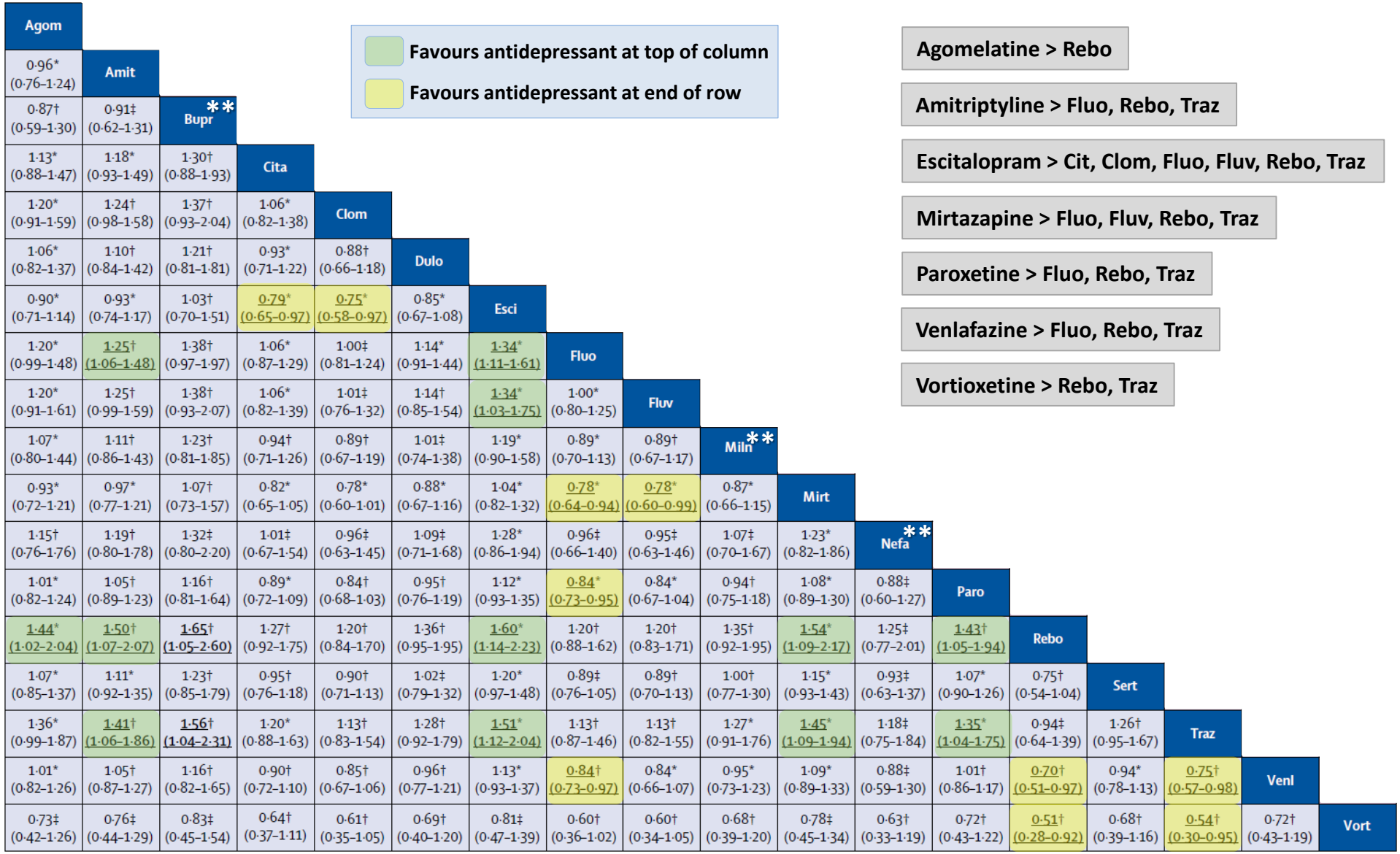
Agom	0·72* (0·55–0·92)	0·80* (0·54–1·15)	0·89* (0·66–1·19)	0·57* (0·42–0·77)	0·62† (0·47–0·82)	0·97* (0·74–1·27)	0·85† (0·68–1·05)	0·69† (0·51–0·97)	0·79* (0·58–1·09)	0·81* (0·61–1·05)	0·70* (0·44–1·14)	0·81* (0·65–1·00)	0·53* (0·36–0·80)	0·86* (0·66–1·13)	0·69* (0·48–0·98)	0·74† (0·58–0·92)	1·24† (0·71–2·19)
0·96* (0·76–1·24)	Amit	1·10‡ (0·78–1·58)	1·23* (0·94–1·64)	0·79† (0·60–1·05)	0·87† (0·66–1·15)	1·35* (1·05–1·74)	1·18† (0·99–1·42)	0·97† (0·74–1·24)	1·10† (0·84–1·45)	1·12* (0·89–1·42)	0·98‡ (0·62–1·55)	1·12† (0·95–1·34)	0·74† (0·51–1·10)	1·20* (0·97–1·47)	0·96‡ (0·70–1·31)	1·02† (0·83–1·26)	1·72† (1·00–3·05)
0·87† (0·59–1·30)	0·91‡ (0·62–1·31)	Bupr**	1·11‡ (0·76–1·67)	0·71† (0·49–1·07)	0·78† (0·53–1·18)	1·23* (0·84–1·80)	1·07‡ (0·76–1·50)	0·87‡ (0·59–1·30)	1·00‡ (0·66–1·49)	1·01† (0·70–1·47)	0·89‡ (0·51–1·54)	1·02‡ (0·73–1·43)	0·67† (0·42–1·08)	1·08‡ (0·75–1·56)	0·87‡ (0·57–1·30)	0·92‡ (0·66–1·30)	1·55† (0·85–2·94)
1·13* (0·88–1·47)	1·18* (0·93–1·49)	1·30† (0·88–1·93)	Cita	0·64† (0·47–0·87)	0·70* (0·51–0·95)	1·09* (0·85–1·42)	0·96* (0·76–1·21)	0·78* (0·57–1·06)	0·89* (0·64–1·23)	0·91† (0·68–1·21)	0·79‡ (0·49–1·32)	0·91* (0·71–1·17)	0·60† (0·41–0·87)	0·97‡ (0·74–1·25)	0·77* (0·53–1·13)	0·83† (0·64–1·07)	1·40† (0·78–2·48)
1·20* (0·91–1·59)	1·24† (0·98–1·58)	1·37† (0·93–2·04)	1·06* (0·82–1·38)	Clom	1·10† (0·80–1·51)	1·71* (1·27–2·29)	1·49† (1·16–1·90)	1·22† (0·88–1·67)	1·40† (1·00–1·92)	1·41* (1·05–1·91)	1·24‡ (0·76–2·00)	1·42† (1·12–1·79)	0·94‡ (0·62–1·41)	1·51† (1·15–1·96)	1·21† (0·83–1·73)	1·29† (0·99–1·67)	2·20† (1·22–3·90)
1·06* (0·82–1·37)	1·10† (0·84–1·42)	1·21† (0·81–1·81)	0·93* (0·71–1·22)	0·88† (0·66–1·18)	Dulo	1·56* (1·19–2·01)	1·37* (1·06–1·73)	1·12* (0·80–1·53)	1·28† (0·91–1·75)	1·30* (0·96–1·72)	1·13‡ (0·69–1·83)	1·30* (1·02–1·63)	0·86‡ (0·57–1·29)	1·38† (1·04–1·80)	1·10† (0·76–1·59)	1·18‡ (0·92–1·49)	1·99† (1·13–3·52)
0·90* (0·71–1·14)	0·93* (0·74–1·17)	1·03† (0·70–1·51)	0·79* (0·65–0·97)	0·75* (0·58–0·97)	0·85* (0·67–1·08)	Esci	0·87* (0·70–1·09)	0·71* (0·53–0·96)	0·81* (0·60–1·11)	0·83* (0·63–1·08)	0·72† (0·45–1·18)	0·83* (0·67–1·03)	0·55* (0·37–0·81)	0·88* (0·69–1·12)	0·70* (0·49–1·00)	0·75* (0·60–0·94)	1·27‡ (0·73–2·25)
1·20* (0·99–1·48)	1·25† (1·06–1·48)	1·38† (0·97–1·97)	1·06* (0·87–1·29)	1·00‡ (0·81–1·24)	1·14* (0·91–1·44)	1·34* (1·11–1·61)	Fluo	0·82* (0·64–1·04)	0·94* (0·72–1·20)	0·95* (0·77–1·16)	0·83† (0·54–1·30)	0·95* (0·83–1·09)	0·63† (0·44–0·90)	1·01† (0·84–1·21)	0·81* (0·60–1·09)	0·87† (0·74–1·01)	1·46† (0·85–2·53)
1·20* (0·91–1·61)	1·25† (0·99–1·59)	1·38† (0·93–2·07)	1·06* (0·82–1·39)	1·01‡ (0·76–1·32)	1·14† (0·85–1·54)	1·34* (1·03–1·75)	1·00* (0·80–1·25)	Fluv	1·14† (0·84–1·56)	1·16* (0·89–1·52)	1·01‡ (0·62–1·71)	1·16* (0·90–1·49)	0·77† (0·51–1·17)	1·23* (0·94–1·63)	0·99‡ (0·69–1·42)	1·06* (0·80–1·38)	1·78‡ (1·00–3·24)
1·07* (0·80–1·44)	1·11† (0·86–1·43)	1·23† (0·81–1·85)	0·94† (0·71–1·26)	0·89† (0·67–1·19)	1·01‡ (0·74–1·38)	1·19* (0·90–1·58)	0·89* (0·70–1·13)	0·89† (0·67–1·17)	Miln**	1·02† (0·75–1·37)	0·88‡ (0·54–1·44)	1·02‡ (0·80–1·31)	0·67† (0·45–1·03)	1·08* (0·82–1·44)	0·86* (0·60–1·25)	0·93* (0·71–1·22)	1·56† (0·89–2·84)
0·93* (0·72–1·21)	0·97* (0·77–1·21)	1·07† (0·73–1·57)	0·82* (0·65–1·05)	0·78* (0·60–1·01)	0·88* (0·67–1·16)	1·04* (0·82–1·32)	0·78* (0·64–0·94)	0·78* (0·60–0·99)	0·87* (0·66–1·15)	Mirt	0·87† (0·55–1·41)	1·00* (0·82–1·23)	0·66* (0·45–0·99)	1·06* (0·84–1·35)	0·85* (0·62–1·18)	0·91* (0·73–1·13)	1·53† (0·89–2·72)
1·15† (0·76–1·76)	1·19† (0·80–1·78)	1·32‡ (0·80–2·20)	1·01‡ (0·67–1·54)	0·96‡ (0·63–1·45)	1·09‡ (0·71–1·68)	1·28* (0·86–1·94)	0·96‡ (0·66–1·40)	0·95‡ (0·63–1·46)	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	Nefa**	1·15‡ (0·74–1·78)	0·75‡ (0·43–1·32)	1·23† (0·77–1·90)	0·98‡ (0·57–1·64)	1·04‡ (0·66–1·65)	1·76† (0·90–3·56)
1·01* (0·82–1·24)	1·05† (0·89–1·23)	1·16† (0·81–1·64)	0·89* (0·72–1·09)	0·84† (0·68–1·03)	0·95† (0·76–1·19)	1·12* (0·93–1·35)	0·84* (0·73–0·95)	0·84* (0·67–1·04)	0·94† (0·75–1·18)	1·08* (0·89–1·30)	0·88‡ (0·60–1·27)	Paro	0·66† (0·46–0·94)	1·06* (0·88–1·28)	0·85† (0·63–1·15)	0·91* (0·77–1·07)	1·53† (0·90–2·66)
1·44* (1·02–2·04)	1·50† (1·07–2·07)	1·65† (1·05–2·60)	1·27† (0·92–1·75)	1·20† (0·84–1·70)	1·36† (0·95–1·95)	1·60* (1·14–2·23)	1·20† (0·88–1·62)	1·20† (0·83–1·71)	1·35† (0·92–1·95)	1·54* (1·09–2·17)	1·25‡ (0·77–2·01)	1·43† (1·05–1·94)	Rebo	1·61† (1·09–2·34)	1·29† (0·81–2·01)	1·38† (0·94–1·99)	2·32† (1·24–4·41)
1·07* (0·85–1·37)	1·11* (0·92–1·35)	1·23† (0·85–1·79)	0·95† (0·76–1·18)	0·90† (0·71–1·13)	1·02‡ (0·79–1·32)	1·20* (0·97–1·48)	0·89‡ (0·76–1·05)	0·89† (0·70–1·13)	1·00† (0·77–1·30)	1·15* (0·93–1·43)	0·93‡ (0·63–1·37)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	Sert	0·80* (0·58–1·11)	0·86* (0·70–1·05)	1·45† (0·84–2·54)
1·36* (0·99–1·87)	1·41† (1·06–1·86)	1·56† (1·04–2·31)	1·20* (0·88–1·63)	1·13† (0·83–1·54)	1·28† (0·92–1·79)	1·51* (1·12–2·04)	1·13† (0·87–1·46)	1·13† (0·82–1·55)	1·27* (0·91–1·76)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	1·26† (0·95–1·67)	Traz	1·07‡ (0·77–1·47)	1·80† (0·98–3·38)
1·01* (0·82–1·26)	1·05† (0·87–1·27)	1·16† (0·82–1·65)	0·90† (0·72–1·10)	0·85† (0·67–1·06)	0·96† (0·77–1·21)	1·13* (0·93–1·37)	0·84† (0·73–0·97)	0·84* (0·66–1·07)	0·95* (0·73–1·23)	1·09* (0·89–1·33)	0·88‡ (0·59–1·30)	1·01† (0·86–1·17)	0·70† (0·51–0·97)	0·94* (0·78–1·13)	0·75† (0·57–0·98)	Venl	1·69† (1·01–2·86)
0·73‡ (0·42–1·26)	0·76‡ (0·44–1·29)	0·83‡ (0·45–1·54)	0·64† (0·37–1·11)	0·61† (0·35–1·05)	0·69† (0·40–1·20)	0·81‡ (0·47–1·39)	0·60† (0·36–1·02)	0·60† (0·34–1·05)	0·68† (0·39–1·20)	0·78‡ (0·45–1·34)	0·63† (0·33–1·19)	0·72† (0·43–1·22)	0·51† (0·28–0·92)	0·68† (0·39–1·16)	0·54† (0·30–0·95)	0·72† (0·43–1·19)	Vort

Data are ORs (95% CrI) in the column-defining treatment compared with the row-defining treatment.
For efficacy, ORs higher than 1 favour the column-defining treatment (ie, the first in alphabetical order).
For acceptability, ORs lower than 1 favour the first drug in alphabetical order.
*Moderate quality of evidence. †Low quality of evidence. ‡Very low quality of evidence

** Not licensed for the treatment of depression in the UK

Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

Head-to-head comparisons for efficacy



	Agom	Amit	Bupr**	Cita	Clom	Dulo	Esci	Fluo	Fluv	Miln**	Mirt	Nefa**	Paro	Rebo	Sert	Traz	Venl	Vort
Agom		0·96* (0·76–1·24)	0·87† (0·59–1·30)	1·13* (0·88–1·47)	1·20* (0·91–1·59)	1·06* (0·82–1·37)	0·90* (0·71–1·14)	1·20* (0·99–1·48)	1·20* (0·91–1·61)	1·07* (0·80–1·44)	0·93* (0·72–1·21)	1·15† (0·76–1·76)	1·01* (0·82–1·24)	1·44* (1·02–2·04)	1·07* (0·85–1·37)	1·36* (0·99–1·87)	1·01* (0·82–1·26)	0·73‡ (0·42–1·26)
Amit	0·91‡ (0·62–1·31)		1·18* (0·93–1·49)	1·24† (0·98–1·58)	1·10† (0·84–1·42)	0·93* (0·74–1·17)	1·25† (1·06–1·48)	1·25† (0·99–1·59)	1·11† (0·86–1·43)	0·97* (0·77–1·21)	1·19† (0·80–1·78)	1·05† (0·89–1·23)	1·50† (1·07–2·07)	1·11* (0·92–1·35)	1·41† (1·06–1·86)	1·05† (0·87–1·27)	0·76‡ (0·44–1·29)
Bupr**	1·30† (0·88–1·93)	1·37† (0·93–2·04)		1·06* (0·82–1·38)	0·88† (0·66–1·18)	0·85* (0·67–1·08)	1·03† (0·70–1·51)	1·38† (0·97–1·97)	1·38† (0·93–2·07)	1·23† (0·81–1·85)	1·07† (0·73–1·57)	1·32‡ (0·80–2·20)	1·16† (0·81–1·64)	1·65† (1·05–2·60)	1·23† (0·85–1·79)	1·56† (1·04–2·31)	1·16† (0·82–1·65)	0·83‡ (0·45–1·54)
Cita	1·06* (0·82–1·38)	1·21† (0·81–1·81)	0·93* (0·71–1·22)		0·93* (0·71–1·22)	1·14* (0·91–1·44)	1·34* (1·11–1·61)	1·06* (0·87–1·29)	1·06* (0·82–1·39)	0·94† (0·71–1·26)	0·82* (0·65–1·05)	1·01‡ (0·67–1·54)	0·89* (0·67–1·04)	1·27† (0·92–1·75)	0·95† (0·76–1·18)	1·20* (0·88–1·63)	0·90† (0·72–1·10)	0·64† (0·37–1·11)
Clom	1·00‡ (0·81–1·24)	1·14* (0·91–1·44)	1·34* (1·11–1·61)	1·00‡ (0·81–1·24)		1·01‡ (0·76–1·32)	1·14† (0·85–1·54)	1·00‡ (0·81–1·24)	1·01‡ (0·76–1·32)	0·89† (0·67–1·19)	0·78* (0·60–1·01)	0·96‡ (0·63–1·45)	0·84† (0·68–1·03)	1·20† (0·84–1·70)	0·90† (0·71–1·13)	1·13† (0·83–1·54)	0·85† (0·67–1·06)	0·61† (0·35–1·05)
Dulo	1·14* (0·91–1·44)	1·34* (1·11–1·61)	1·00* (0·80–1·25)	1·14† (0·85–1·54)	1·01‡ (0·74–1·38)		1·19* (0·90–1·58)	0·89* (0·70–1·13)	0·89† (0·67–1·17)	0·88* (0·67–1·16)	1·04* (0·82–1·32)	0·96‡ (0·66–1·40)	0·84* (0·67–1·04)	1·20† (0·88–1·62)	0·89‡ (0·76–1·05)	1·13† (0·87–1·46)	0·84* (0·66–1·07)	0·60† (0·36–1·02)
Esci	1·34* (1·11–1·61)	1·34* (1·03–1·75)	1·14† (0·85–1·54)	1·01‡ (0·74–1·38)	1·19* (0·90–1·58)		0·78* (0·64–0·94)	0·78* (0·60–0·99)	0·87* (0·66–1·15)	1·04* (0·82–1·32)	0·96‡ (0·66–1·40)	0·95‡ (0·63–1·46)	0·94† (0·75–1·18)	1·35† (0·92–1·95)	1·00† (0·77–1·30)	1·27* (0·91–1·76)	0·95* (0·73–1·23)	0·68† (0·39–1·20)
Fluo	1·00* (0·80–1·25)	0·89* (0·70–1·13)	0·89† (0·67–1·17)	0·87* (0·66–1·15)	1·23* (0·82–1·86)	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	1·08* (0·89–1·30)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·78‡ (0·45–1·34)
Fluv	0·89† (0·67–1·17)	0·87* (0·66–1·15)	1·23* (0·82–1·86)	1·08* (0·89–1·30)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·63† (0·33–1·19)
Miln**	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·54† (0·30–0·95)	0·68† (0·39–1·16)	0·72† (0·43–1·19)
Mirt	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·54† (0·30–0·95)	0·68† (0·39–1·16)	0·72† (0·43–1·19)
Nefa**	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·54† (0·30–0·95)	0·68† (0·39–1·16)	0·72† (0·43–1·19)
Paro	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·54† (0·30–0·95)	0·68† (0·39–1·16)	0·72† (0·43–1·19)
Rebo	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·54† (0·30–0·95)	0·68† (0·39–1·16)	0·72† (0·43–1·19)
Sert	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·54† (0·30–0·95)	0·68† (0·39–1·16)	0·72† (0·43–1·19)
Traz	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·54† (0·30–0·95)	0·68† (0·39–1·16)	0·72† (0·43–1·19)
Venl	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·54† (0·30–0·95)	0·68† (0·39–1·16)	0·72† (0·43–1·19)
Vort	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	0·88‡ (0·60–1·27)	1·25‡ (0·77–2·01)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	1·26† (0·95–1·67)	1·45* (1·09–1·94)	1·18‡ (0·75–1·84)	1·35* (1·04–1·75)	0·94‡ (0·64–1·39)	0·75† (0·57–0·98)	0·94* (0·78–1·13)	0·70† (0·51–0·97)	0·51† (0·28–0·92)	0·54† (0·30–0·95)	0·68† (0·39–1·16)	0·72† (0·43–1·19)

Favours antidepressant at top of column

Favours antidepressant at end of row

Agomelatine > Rebo

Amitriptyline > Fluo, Rebo, Traz

Escitalopram > Cit, Clom, Fluo, Fluv, Rebo, Traz

Mirtazapine > Fluo, Fluv, Rebo, Traz

Paroxetine > Fluo, Rebo, Traz

Venlafazine > Fluo, Rebo, Traz

Vortioxetine > Rebo, Traz

Data are ORs (95% CrI) in the column-defining treatment compared with the row-defining treatment.
For efficacy, ORs higher than 1 favour the column-defining treatment (ie, the first in alphabetical order).
For acceptability, ORs lower than 1 favour the first drug in alphabetical order.
*Moderate quality of evidence. †Low quality of evidence. ‡Very low quality of evidence

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Head-to-head comparisons for acceptability

	Agom	Amit	Bupr**	Cita	Clom	Dulo	Esci	Fluo	Fluv	Miln**	Mirt	Nefa**	Paro	Rebo	Sert	Traz	Venl	Vort
Agom		0·72* (0·55–0·92)	0·80* (0·54–1·15)	0·89* (0·66–1·19)	0·57* (0·42–0·77)	0·62† (0·47–0·82)	0·97* (0·74–1·27)	0·85† (0·68–1·05)	0·69† (0·51–0·97)	0·79* (0·58–1·09)	0·81* (0·61–1·05)	0·70* (0·44–1·14)	0·81* (0·65–1·00)	0·53* (0·36–0·80)	0·86* (0·66–1·13)	0·69* (0·48–0·98)	0·74† (0·58–0·92)	1·24† (0·71–2·19)
Amit			1·10‡ (0·78–1·58)	1·23* (0·94–1·64)	0·79† (0·60–1·05)	0·87† (0·66–1·15)	1·35* (1·05–1·74)	1·18† (0·99–1·42)	0·97† (0·74–1·24)	1·10† (0·84–1·45)	1·12* (0·89–1·42)	0·98‡ (0·62–1·55)	1·12† (0·95–1·34)	0·74† (0·51–1·10)	1·20* (0·97–1·47)	0·96‡ (0·70–1·31)	1·02† (0·83–1·26)	1·72† (1·00–3·05)
Bupr**				1·11‡ (0·76–1·67)	0·71† (0·49–1·07)	0·78† (0·53–1·18)	1·23* (0·84–1·80)	1·07‡ (0·76–1·50)	0·87‡ (0·59–1·30)	1·00‡ (0·66–1·49)	1·01† (0·70–1·47)	0·89‡ (0·51–1·54)	1·02‡ (0·73–1·43)	0·67† (0·42–1·08)	1·08‡ (0·75–1·56)	0·87‡ (0·57–1·30)	0·92‡ (0·66–1·30)	1·55† (0·85–2·94)
Cita					0·64† (0·47–0·87)	0·70* (0·51–0·95)	1·09* (0·85–1·42)	0·96* (0·76–1·21)	0·78* (0·57–1·06)	0·89* (0·64–1·23)	0·91† (0·68–1·21)	0·79‡ (0·49–1·32)	0·91* (0·71–1·17)	0·60† (0·41–0·87)	0·97‡ (0·74–1·25)	0·77* (0·53–1·13)	0·83† (0·64–1·07)	1·40† (0·78–2·48)
Clom						1·10† (0·80–1·51)	1·71* (1·27–2·29)	1·49† (1·16–1·90)	1·22† (0·88–1·67)	1·40† (1·00–1·92)	1·41* (1·05–1·91)	1·24‡ (0·76–2·00)	1·42† (1·12–1·79)	0·94‡ (0·62–1·41)	1·51† (1·15–1·96)	1·21† (0·83–1·73)	1·29† (0·99–1·67)	2·20† (1·22–3·90)
Dulo							1·56* (1·19–2·01)	1·37* (1·06–1·73)	1·12* (0·80–1·53)	1·28† (0·91–1·75)	1·30* (0·96–1·72)	1·13‡ (0·69–1·83)	1·30* (1·02–1·63)	0·86‡ (0·57–1·29)	1·38† (1·04–1·80)	1·10† (0·76–1·59)	1·18‡ (0·92–1·49)	1·99† (1·13–3·52)
Esci								0·87* (0·70–1·09)	0·71* (0·53–0·96)	0·81* (0·60–1·11)	0·83* (0·63–1·08)	0·72† (0·45–1·18)	0·83* (0·67–1·03)	0·55* (0·37–0·81)	0·88* (0·69–1·12)	0·70* (0·49–1·00)	0·75* (0·60–0·94)	1·27‡ (0·73–2·25)
Fluo									0·82* (0·64–1·04)	0·94* (0·72–1·20)	0·95* (0·77–1·16)	0·83† (0·54–1·30)	0·95* (0·83–1·09)	0·63† (0·44–0·90)	1·01† (0·84–1·21)	0·81* (0·60–1·09)	0·87† (0·74–1·01)	1·46† (0·85–2·53)
Fluv										1·14† (0·84–1·56)	1·16* (0·89–1·52)	1·01‡ (0·62–1·71)	1·16* (0·90–1·49)	0·77† (0·51–1·17)	1·23* (0·94–1·63)	0·99‡ (0·69–1·42)	1·06* (0·80–1·38)	1·78‡ (1·00–3·24)
Miln**											1·02† (0·75–1·37)	0·88‡ (0·54–1·44)	1·02‡ (0·80–1·31)	0·67† (0·45–1·03)	1·08* (0·82–1·44)	0·86* (0·60–1·25)	0·93* (0·71–1·22)	1·56† (0·89–2·84)
Mirt												0·87† (0·55–1·41)	1·00* (0·82–1·23)	0·66* (0·45–0·99)	1·06* (0·84–1·35)	0·85* (0·62–1·18)	0·91* (0·73–1·13)	1·53† (0·89–2·72)
Nefa**													1·15‡ (0·74–1·78)	0·75‡ (0·43–1·32)	1·23† (0·77–1·90)	0·98‡ (0·57–1·64)	1·04‡ (0·66–1·65)	1·76† (0·90–3·56)
Paro														0·66† (0·46–0·94)	1·06* (0·88–1·28)	0·85† (0·63–1·15)	0·91* (0·77–1·07)	1·53† (0·90–2·66)
Rebo															1·61† (1·09–2·34)	1·29† (0·81–2·01)	1·38† (0·94–1·99)	2·32† (1·24–4·41)
Sert																0·80* (0·58–1·11)	0·86* (0·70–1·05)	1·45† (0·84–2·54)
Traz																	1·07‡ (0·77–1·47)	1·80† (0·98–3·38)
Venl																		1·69† (1·01–2·86)
Vort																		

Agomelatine > Amit, Clom, Dulo, Fluv, Rebo, Traz, Venl

Citalopram > Clom, Dulo, Rebo

Escitalopram > Amit, Clom, Dulo, Fluv, Rebo, Venl

Fluoxetine > Clom, Dulo, Rebo

Mirtazapine > Clom, Rebo

Paroxetine > Clom, Dulo, Rebo

Sertraline > Clom, Dulo, Rebo

Vortioxetine > Amit, Clom, Dulo, Fluv, Rebo, Venl

Favours antidepressant at bottom of column

Favours antidepressant at end of row

Data are ORs (95% CrI) in the column-defining treatment compared with the row-defining treatment.
For efficacy, ORs higher than 1 favour the column-defining treatment (ie, the first in alphabetical order).
For acceptability, ORs lower than 1 favour the first drug in alphabetical order.
*Moderate quality of evidence. †Low quality of evidence. ‡Very low quality of evidence

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Choice of initial antidepressant? Differences in efficacy?

Vs placebo

- Amitriptyline greatest numerical separation from placebo
- Not significantly different from amitriptyline:
  - Duloxetine
  - Mirtazapine
  - Nefazodone*
  - Paroxetine
  - Venlafaxine
  - Vortioxetine

* Not licensed in the UK

Head-to head

More effective:

1. Agomelatine
2. Amitriptyline
3. Escitalopram
4. Mirtazapine
5. Paroxetine
6. Venlafaxine
7. Vortioxetine

(ORs between 1·19 and 1·96)

Least efficacious:

1. Fluoxetine
2. Fluvoxamine
3. Reboxetine
4. Trazodone

(ORs between 0·51 and 0·84)

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Choice of initial antidepressant? Differences in acceptability?

Vs placebo

- Favours active drug compared to placebo
  - Agomelatine & Fluoxetine
- Inferior to placebo
  - Clomipramine
- No different from placebo
  - All others

Head-to head

More tolerable:

1. Agomelatine
2. Citalopram
3. Escitalopram
4. Fluoxetine
5. Sertraline
6. Vortioxetine

(ORs between 0.43 and 0.77)

Highest drop-out rates:

1. Amitriptyline
2. Clomipramine
3. Duloxetine
4. Fluvoxamine
5. Reboxetine
6. Trazodone
7. Venlafaxine

(ORs between 1.30 and 2.32)

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Summary of efficacy & acceptability

(antidepressants in clinical use in UK)

	Efficacy Vs Placebo	Head-to-head more effective?	Acceptability vs placebo	Head-to-head more tolerable?	Initial choice?
Agomelatine	☑	☑	☑	☑	☑
Amitriptyline	☑	☑	no different	✖	
Citalopram	☑	-	no different	☑	
Clomipramine	☑	-	✖	✖	
Duloxetine	☑	-	no different	✖	
Escitalopram	☑	☑	no different	☑	☑
Fluoxetine	☑	✖	☑	☑	
Fluvoxamine	☑	✖	no different	✖	
Mirtazapine	☑	☑	no different	-	
Paroxetine	☑	☑	no different	-	
Reboxitine	☑	✖	no different	✖	
Sertraline	☑	-	no different	☑	
Trazodone	☑	✖	no different	✖	
Venlafaxine	☑	☑	no different	✖	
Vortioxetine	☑	☑	no different	☑	☑

☑ = Higher response rates or lower drop-out rates compared with other antidepressants or placebo

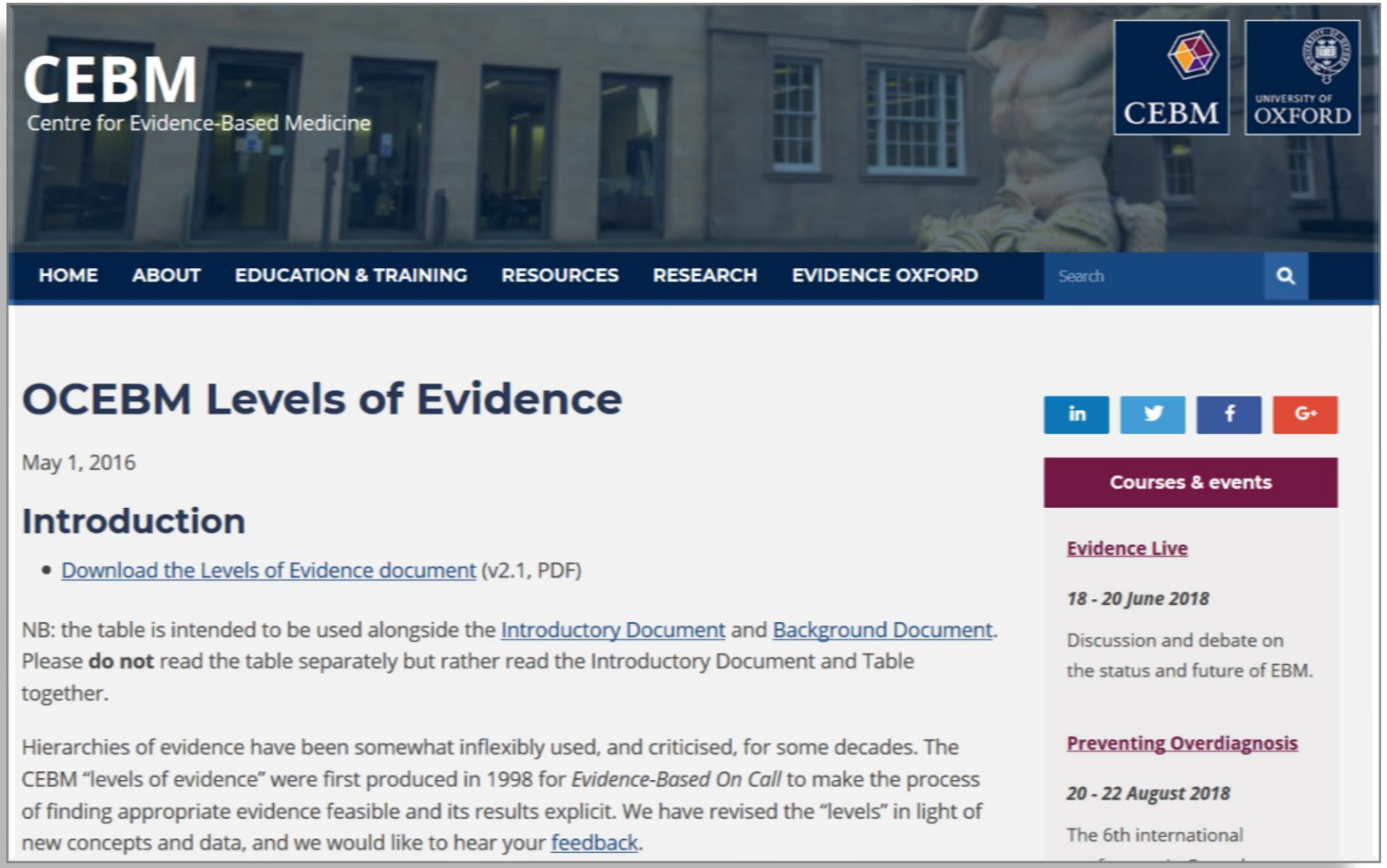
✖ = Lower response rates or higher drop-out rates compared with other antidepressants or placebo

Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

“ . . . the findings from this network meta-analysis represent the most comprehensive currently available evidence base to guide the initial choice about pharmacological treatment for acute major depressive disorder in adults.”

Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

How strong is this evidence?



https://www.cebm.net/2016/05/ocebm-levels-of-evidence/ accessed 08.12.2018

How strong is this evidence?

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

https://www.cebm.net/2016/05/ocebm-levels-of-evidence/ accessed 06.04.2018

NICE National Institute for Health and Care Excellence

NICE guideline

Choice of initial antidepressant

Depression in adults: recognition and management

Clinical guideline
Published: 28 October 2009
nice.org.uk/guidance/cg90

When an antidepressant is to be prescribed, it should normally be an SSRI in a generic form because SSRIs are equally effective as other antidepressants and have a favourable risk–benefit ratio.

NICE Guideline accessed 18.12.18

The guideline is in the process of being updated.
A revised version is expected December 2019

Summary of efficacy & acceptability

(antidepressants in clinical use in UK)

	Efficacy Vs Placebo	Head-to-head more effective?	Acceptability vs placebo	Head-to-head more tolerable?	Initial choice?
Agomelatine	☑	☑	☑	☑	☑
Amitriptyline	☑	☑	no different	✖	
Citalopram	☑	-	no different	☑	
Clomipramine	☑	-	✖	✖	
Duloxetine	☑	-	no different	✖	
Escitalopram	☑	☑	no different	☑	☑
Fluoxetine	☑	✖	☑	☑	
Fluvoxamine	☑	✖	no different	✖	
Mirtazapine	☑	☑	no different	-	
Paroxetine	☑	☑	no different	-	
Reboxitine	☑	✖	no different	✖	
Sertraline	☑	-	no different	☑	
Trazodone	☑	✖	no different	✖	
Venlafaxine	☑	☑	no different	✖	
Vortioxetine	☑	☑	no different	☑	☑

☑ = Higher response rates or lower drop-out rates compared with other antidepressants or placebo

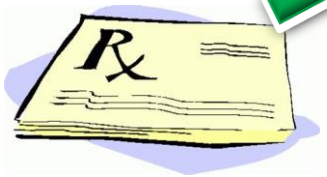
✖ = Lower response rates or higher drop-out rates compared with other antidepressants or placebo

Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

Typical patient pathway?

Moderate-severe depression

Seen by GP



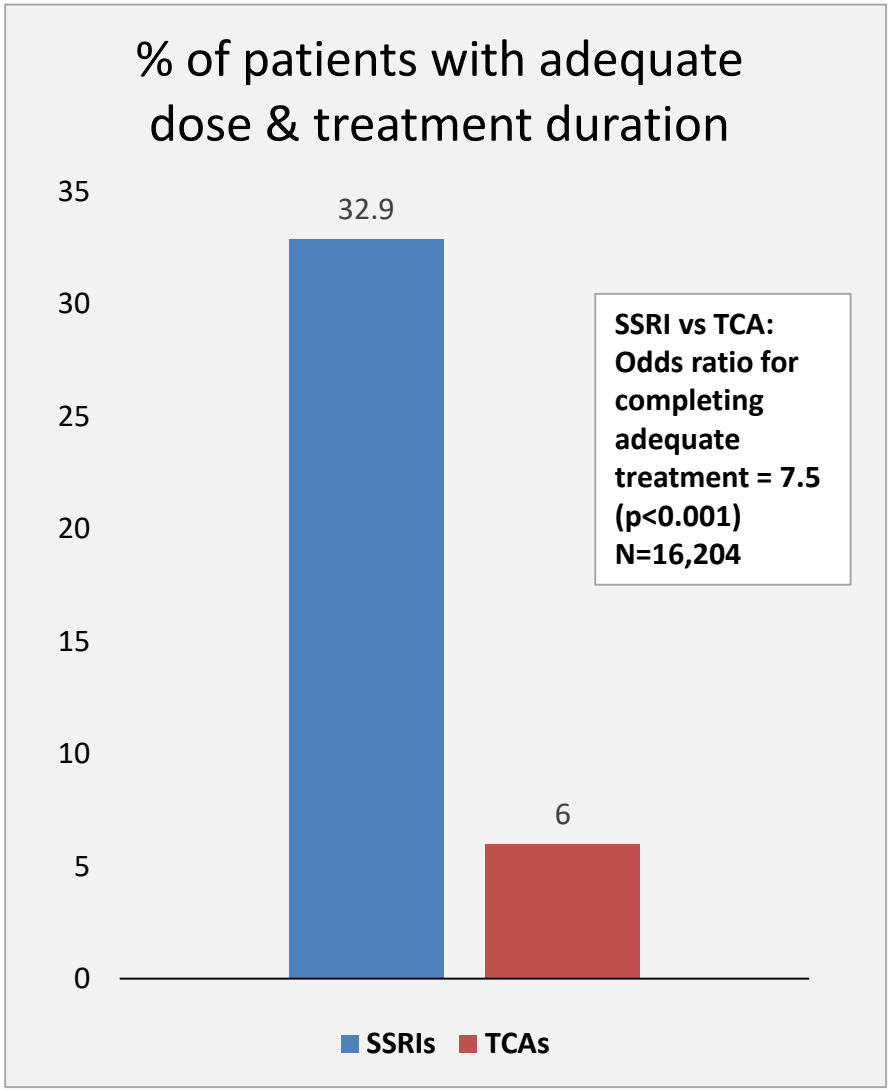
Antidepressant prescribed

Dispensed in pharmacy

Response & recovery

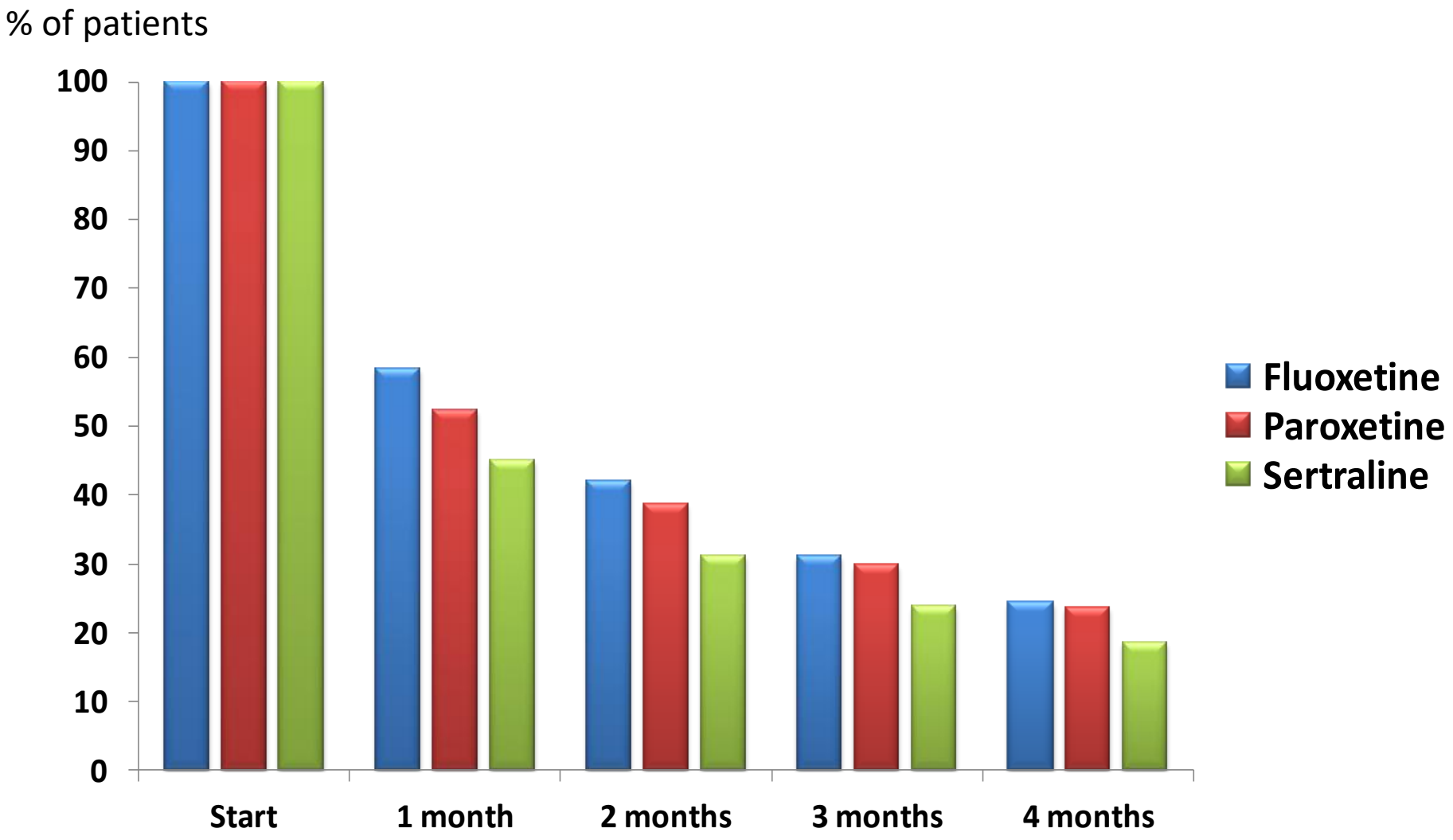
Antidepressants: adequacy of dose & duration of treatment in UK

- Large naturalistic study
- New episodes of depression treated in primary care
- Initial treatment with
  - TCA
    - Amitriptyline, Dosulepin, Imipramine, Lofepramine
  - SSRI
    - Fluoxetine, Paroxetine, Sertraline
- Outcome measure
  - Whether patients received 'adequate' treatment
    - 120 days continuous treatment at an adequate dose within 6 months of initiation



Dunn RL, Donoghue JM, Ozminkowski RJ et al.
Longitudinal patterns of antidepressant prescribing in primary care in the UK: comparison with treatment guidelines
J Psychopharmacol 1999;13:136-43

Treatment duration with SSRIs



Donoghue JM
Selective serotonin reuptake inhibitor use in primary care: a five-year naturalistic study
Clin Drug Invest 1998;16:453-462

BMJ

RESEARCH

1993-2005

Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database

Michael Moore, senior lecturer,[1]
A Mullee, director, research des
professor of primary medical ca

[1]University of Southampton, Aldermoor Health Centre, Southampton SO16 5ST
[2]Public Health Sciences and Medical Statistics, University of Southampton, Southampton SO16 6YD
[3]Division of Medical Education, School of Medicine, University of Southampton, Southampton SO16 7PX
Correspondence to: Michael Moore
mvm198@soton.ac.uk

Cite this as: *BMJ* 2009;339:b3999
doi:10.1136/bmj.b3999

ABSTRACT

Objective To explore the reasons b
increase in antidepressant prescrib
Kingdom.

Design Detailed retrospective anal
practitioner consultations and anti
prescribing.

Data source Data were obtained fro
research database, which contains
records of over 3 million patients r
Data were extracted for all new inc
depression between 1993 and 200

Review methods Detailed analysis
consultations and antidepressant
restricted to 170 practices that wer
the full duration of the study.

Results In total, 189 851 people w
practice research database experie
episode of depression between 19
150 825 (79.4%) received a prescr
antidepressants in the first year of
proportion remained stable across
examined. The incidence of new ca
in young women but fell slightly in
overall incidence increased then d
7.83 cases per 1000 patient years
2005, women: 15.83 cases per 10
1993 to 10.06 in 2005). Antidepre
nearly doubled during the study pe
number of prescriptions issued pe
from 2.8 in 1993 to 5.6 in 2004. Th
antidepressant prescriptions were
treatment or as intermittent treatm
multiple episodes of depression.

Conclusions The rise in antidepres
mainly explained by small changes
patients receiving long term treatm
guidelines have focused on antide
appropriate targeting of antidepressants. To address the
costly rise in antidepressant prescribing, future research
and guidance needs to concentrate on appropriate long

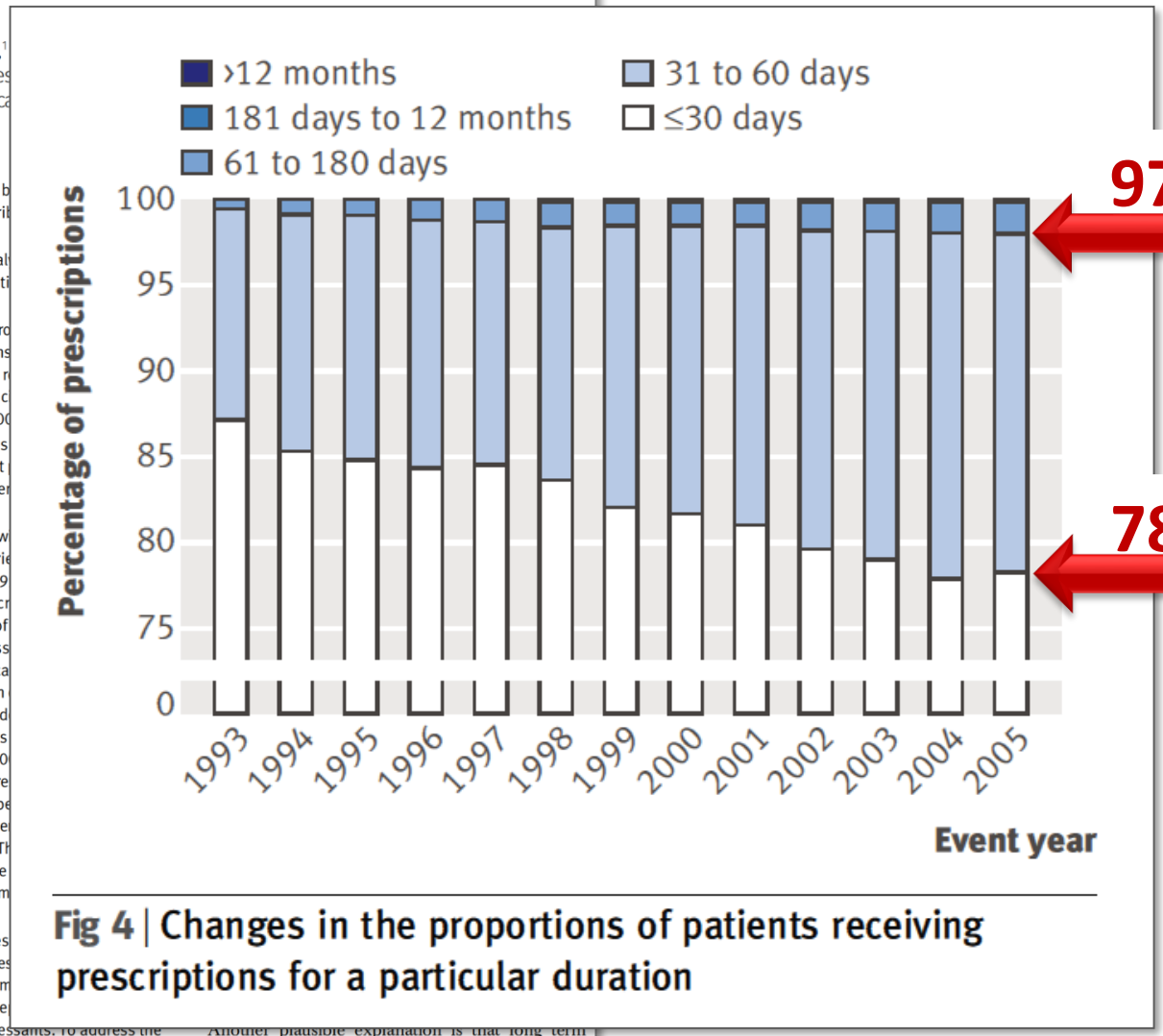


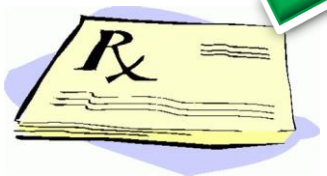
Fig 4 | Changes in the proportions of patients receiving prescriptions for a particular duration

Another plausible explanation is that long term repeat prescribing of antidepressants has increased in recent years. A cross sectional survey of general

Typical patient pathway?

Moderate-severe depression

Seen by GP



Antidepressant prescribed

Dispensed in pharmacy

Response & recovery?

Majority stop treatment too soon

- 1 in 5 sufferers do not recover fully from the first episode
- 70-80% suffer at least one recurrence of the illness

CHALLENGING THINKING IN THE MANAGEMENT OF DEPRESSION

‘You can’t solve problems using the same thinking that created them.’

Albert Einstein

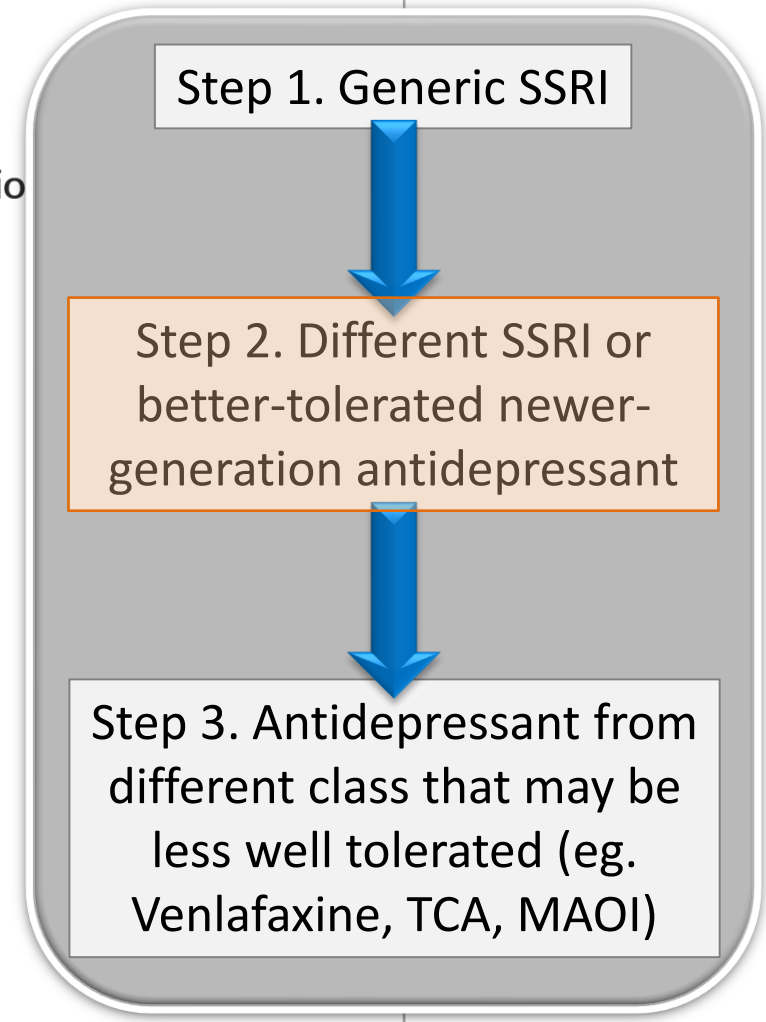
Sequencing antidepressants after initial inadequate response

NICE National Institute for Health and Care Excellence

NICE guideline

Depression in adults: recognitio
management

Clinical guideline
Published: 28 October 2009
nice.org.uk/guidance/cg90



Summary of efficacy & acceptability

(antidepressants in clinical use in UK)

	Efficacy Vs Placebo	Head-to-head more effective?	Acceptability vs placebo	Head-to-head more tolerable?	Initial choice?
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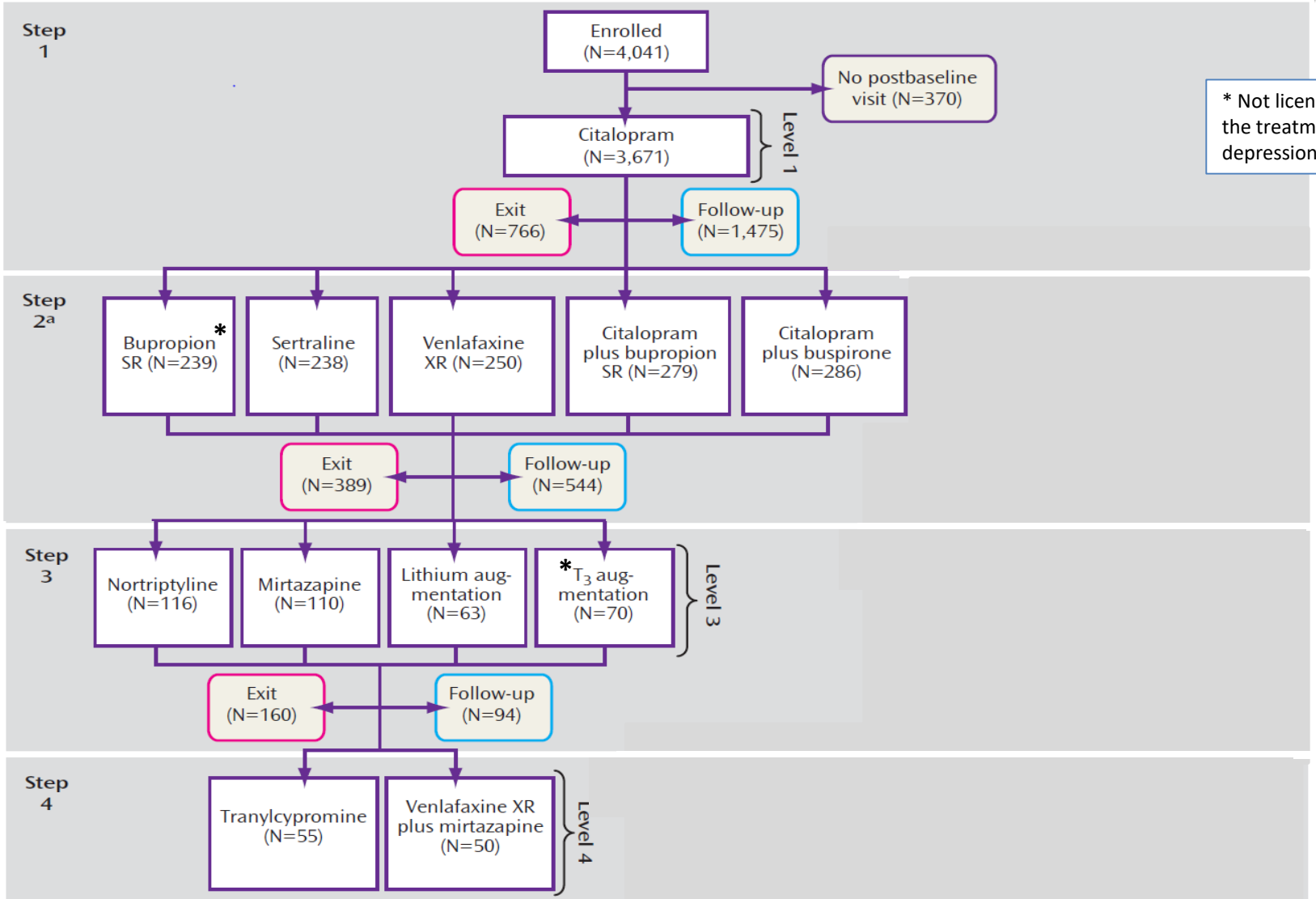
☑ = Higher response rates or lower drop-out rates compared with other antidepressants or placebo

✖ = Lower response rates or higher drop-out rates compared with other antidepressants or placebo

Cipriani A, et al. ***Lancet*** 2018; 391: 1357-1366

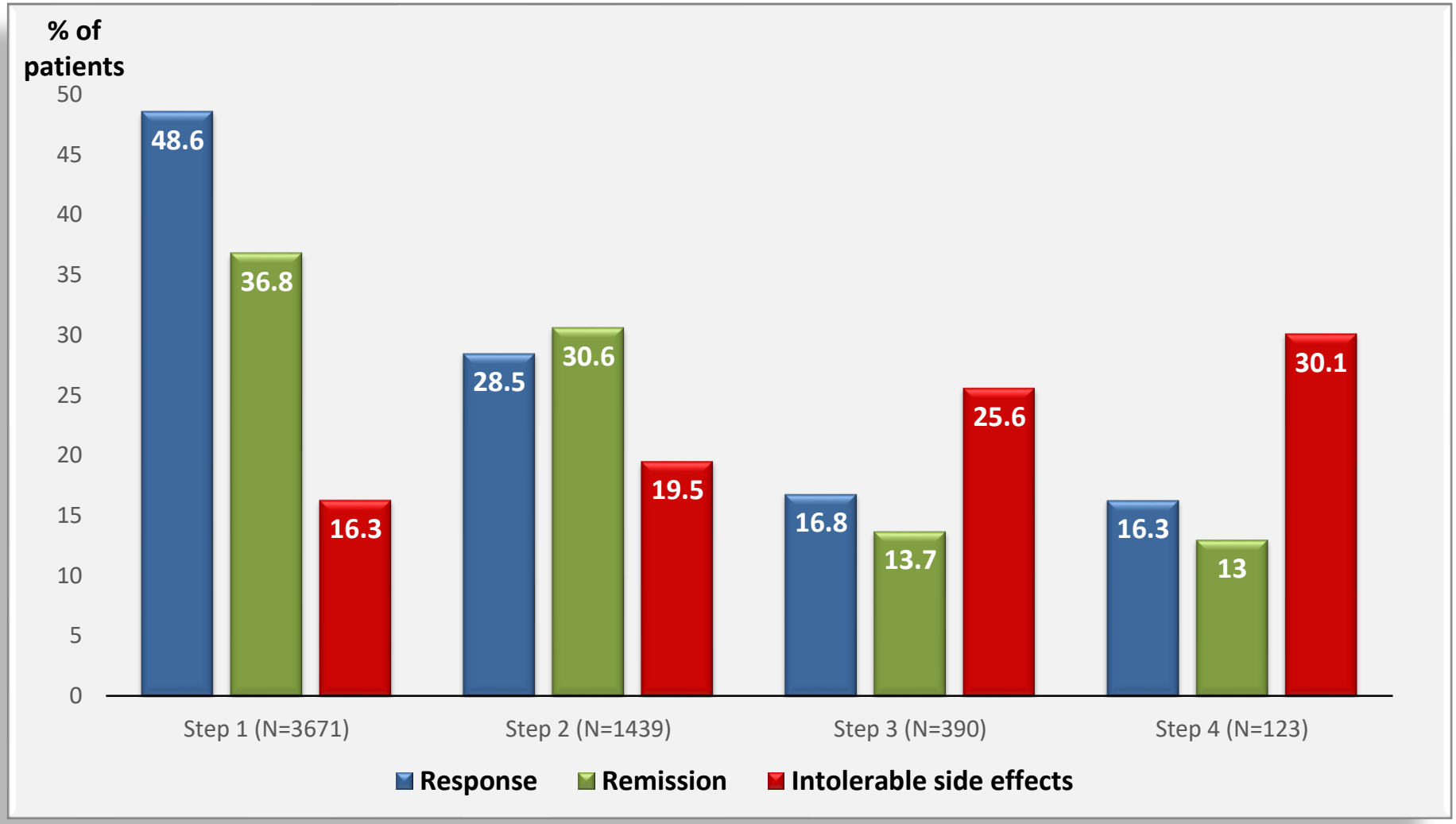
Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial



* Not licensed in the treatment of depression in UK

Rush AJ et al. Am J Psychiatry 2006; 163:1905–1917

STAR*D. With each treatment step: response and remission reduce, AEs increase



Rush AJ, Trivedi MH, Wisniewski SR et al.
Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D Report
Am J Psychiatry 2006; 163:1905–1917

If a patient doesn’t respond to,
or can’t tolerate initial and subsequent
antidepressant treatment . . .

What next?

Sequencing antidepressants after initial inadequate response

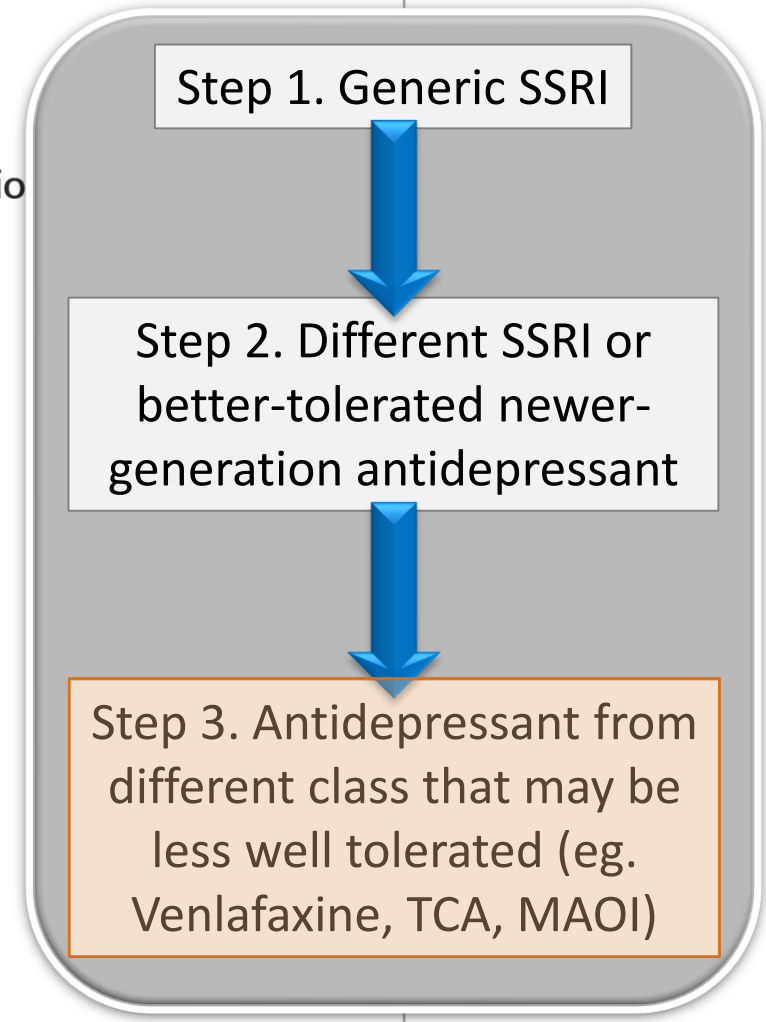
2009

NICE National Institute for Health and Care Excellence

NICE guideline

Depression in adults: recognitio
management

Clinical guideline
Published: 28 October 2009
nice.org.uk/guidance/cg90



NICE National Institute for Health and Care Excellence

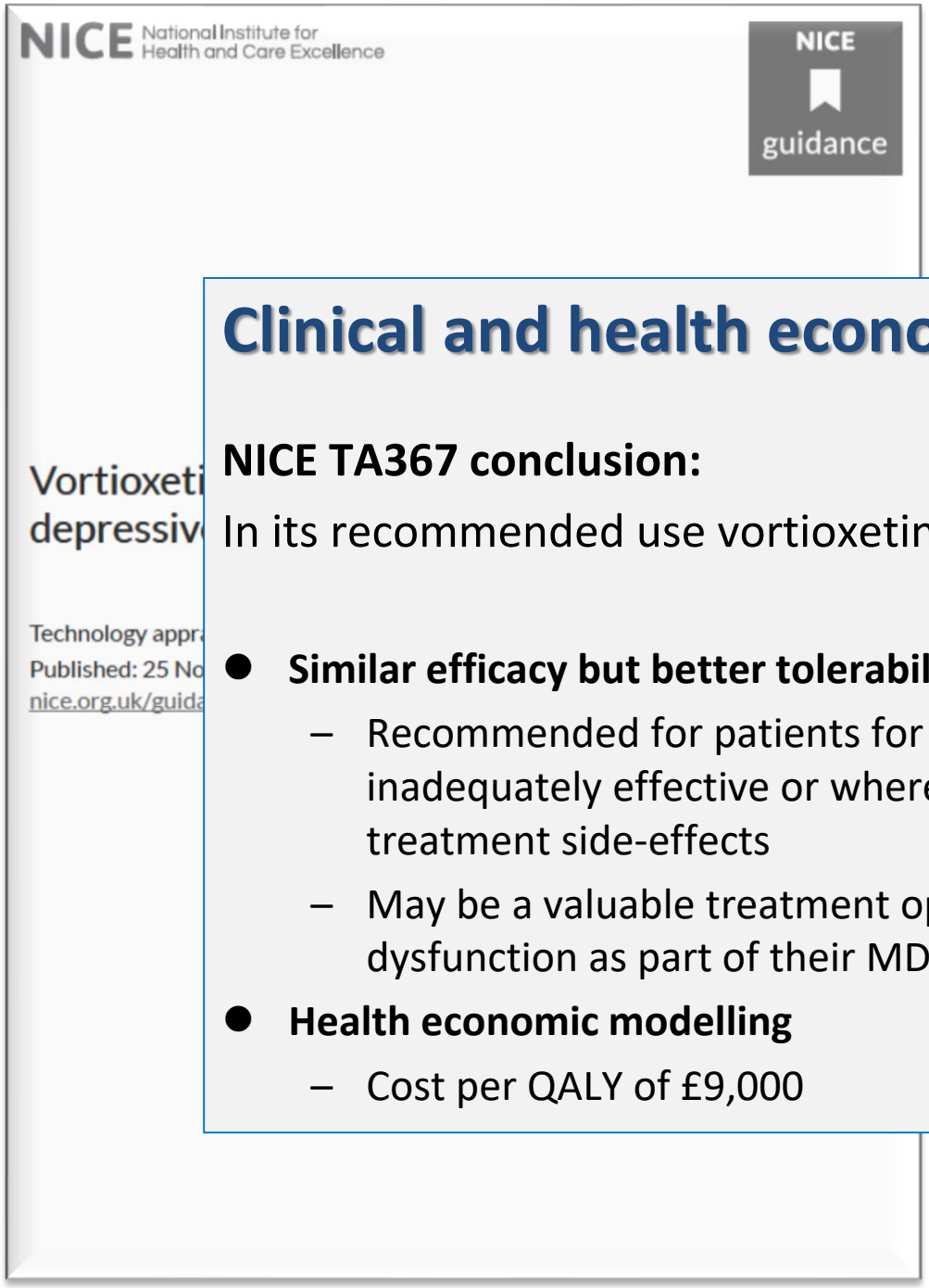
NICE guidance

Vortioxetine for treating major depressive episodes

Technology appraisal guidance
Published: 25 November 2015
nice.org.uk/guidance/ta367

2015

"Vortioxetine is recommended as an option for treating major depressive episodes in adults whose condition has responded inadequately to 2 antidepressants within the current episode."



Clinical and health economic data

NICE TA367 conclusion:

In its recommended use vortioxetine is both clinically- and cost-effective

- **Similar efficacy but better tolerability profile than other antidepressants**
  - Recommended for patients for whom previous treatments are inadequately effective or where they are unable to tolerate the treatment side-effects
  - May be a valuable treatment option for people experiencing cognitive dysfunction as part of their MDE
- **Health economic modelling**
  - Cost per QALY of £9,000

Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox
NHS SCOTLAND

2016

vortioxetine 5mg, 10mg, 20mg film-coated tablet (Brintellix®)

SMC No. (1158/16)

Lundbeck Ltd.

10 June 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

vortioxetine 5mg, 10mg, 20mg film-coated tablet (Brintellix®) is accepted for restricted use within NHS Scotland.

Indication under review: the treatment of major depressive episodes in adults.

SMC restriction: patients who have experienced an inadequate response (either due to lack of adequate efficacy and/or safety concerns/intolerability) to two or more previous antidepressants.

In two phase III, randomised, double-blind studies in adults with major depressive disorder, vortioxetine was non-inferior to two alternative antidepressants at reducing the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to week 8.

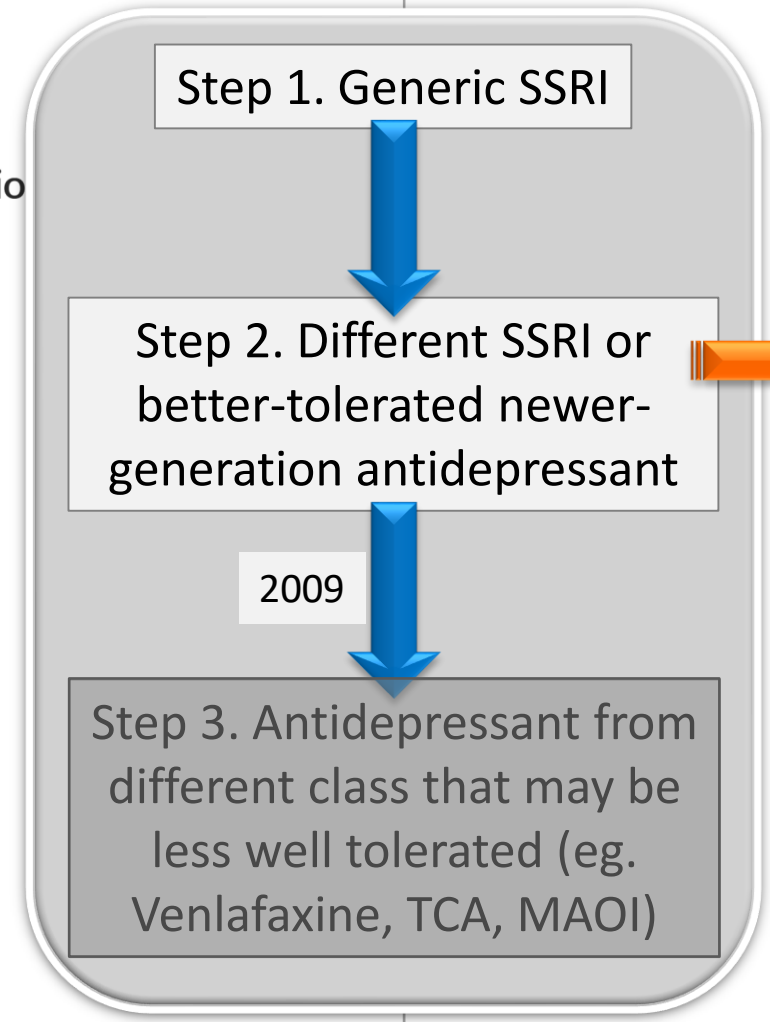
Sequencing antidepressants after initial inadequate response

NICE National Institute for Health and Care Excellence

NICE guideline

Depression in adults: recognitio
management

Clinical guideline
Published: 28 October 2009
nice.org.uk/guidance/cg90



Step 3: (2015/16)

NICE TA367

SMC 1158/16

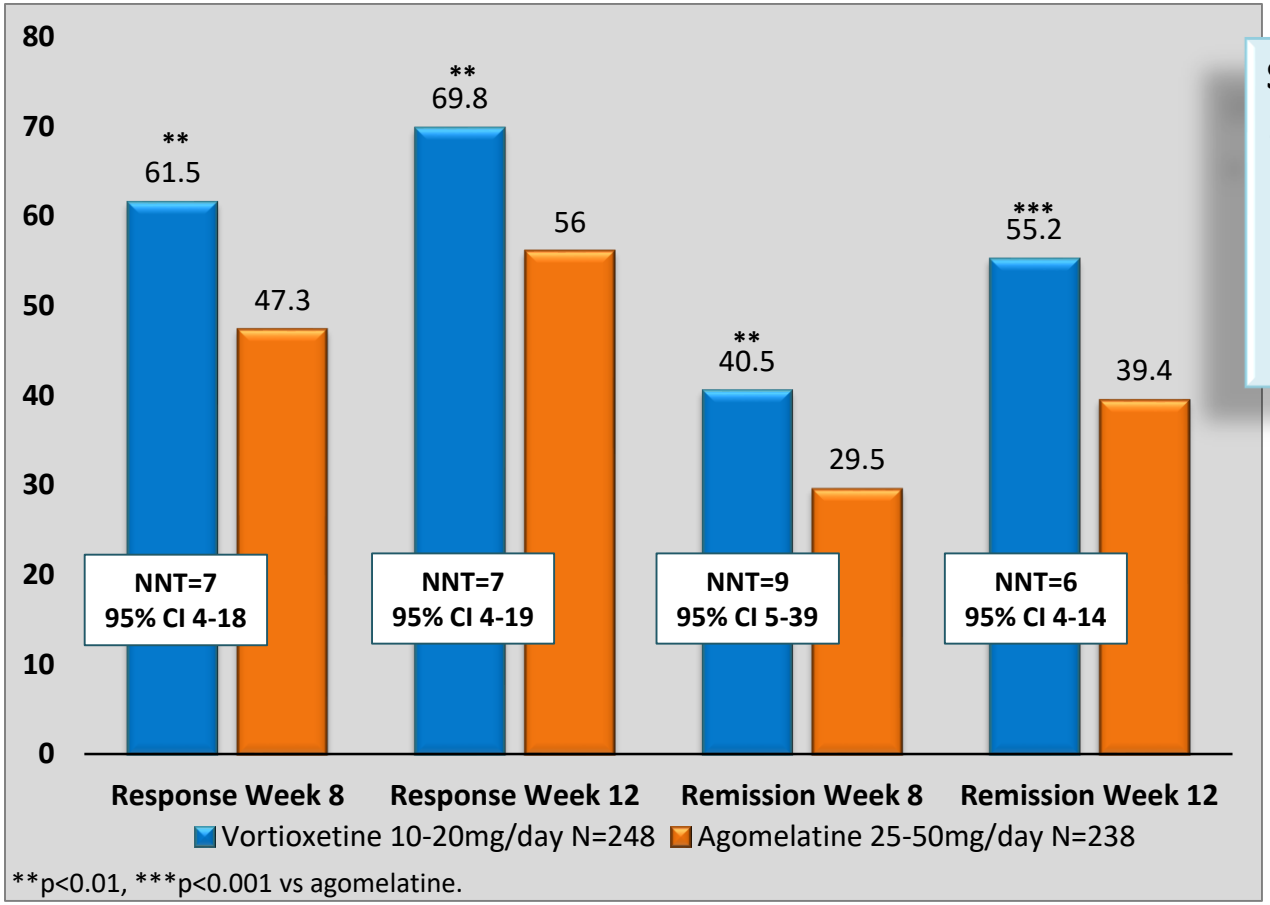
Vortioxetine

" . . . in adults whose condition has responded inadequately to 2 antidepressants within the current episode."

Vortioxetine in patients with suboptimal response to initial SSRI or SNRI

12-week double-blind study in patients treated with vortioxetine or agomelatine[1]

MADRS response and remission rates; FAS, LOCF at Week 8 and Week 12



STAR*D study:

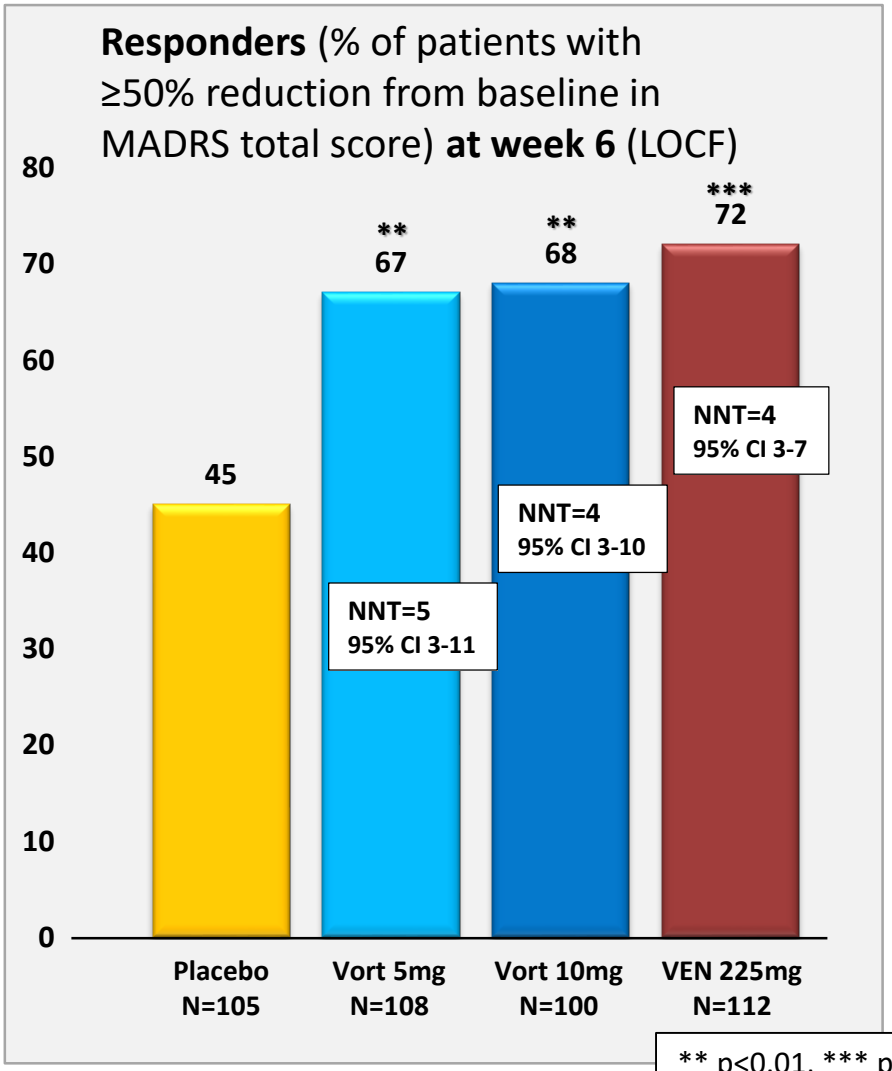
- 30.6% of patients achieved remission at week 5-7 (QUIDS-SR16≤5) after switching to a second antidepressant[2]

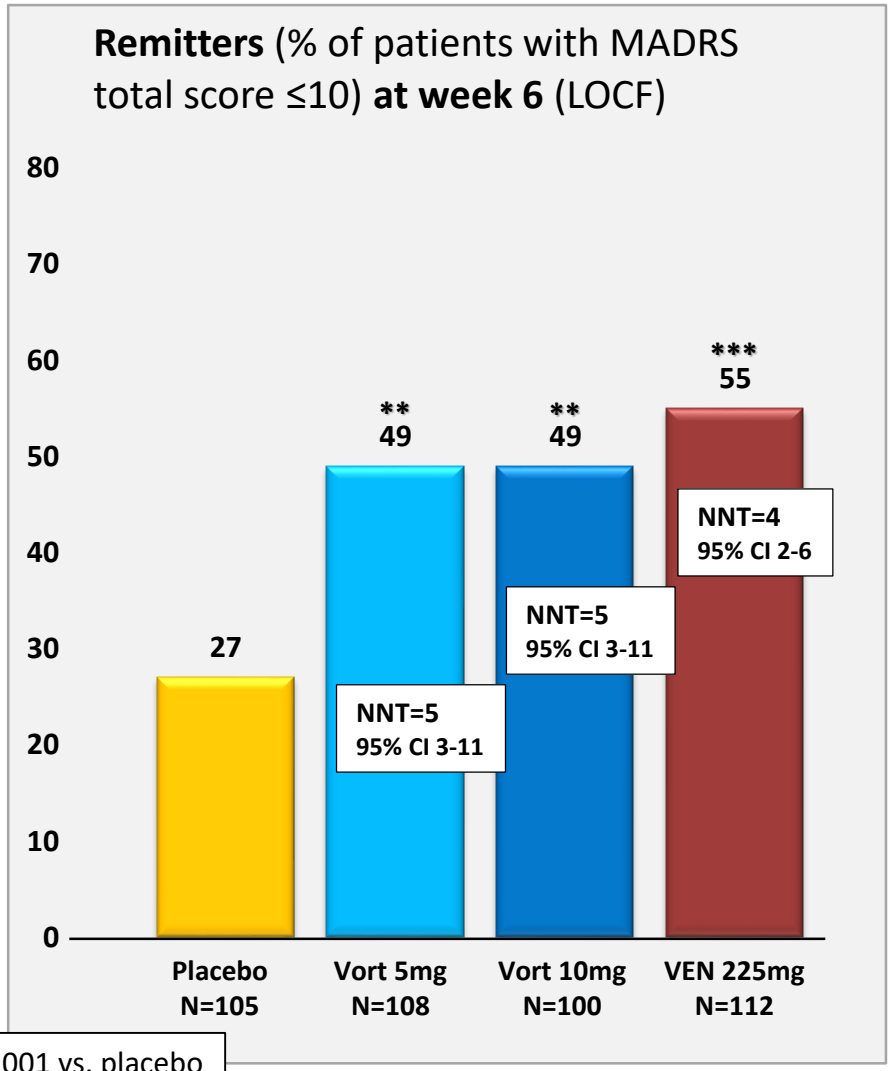
Response defined as ≥50% improvement from baseline in MADRS total score; remission defined as MADRS total score ≤10; response and remission were analysed using logistic regression (FAS, LOCF)

1. Montgomery et al. Hum Psychopharmacol Clin Exp 2014;29(5):470–482
2. Rush et al. American Journal of Psychiatry 2006;163(11):1905–1917

Vortioxetine in the treatment of severe depression

(baseline MADRS score ≥30)





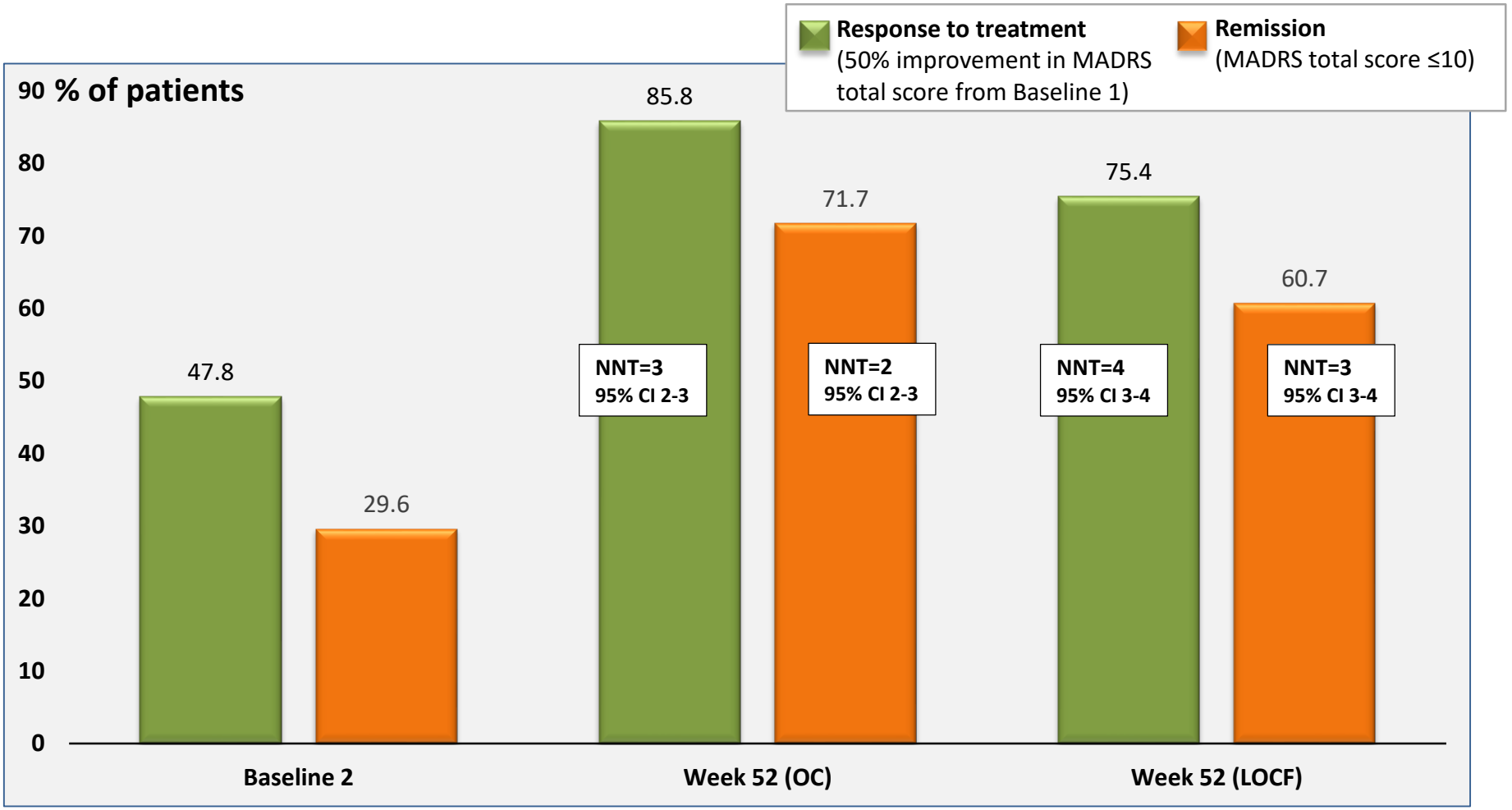
** p<0.01, *** p<0.001 vs. placebo

Venlafaxine (VEN) was included as an active reference for assay sensitivity. No comparison with vortioxetine can be inferred.

NNTs calculated vs placebo.

Alvarez E, Perez V, Dragheim M et al.
A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder
Int J Neuropsychopharmacol 2012;15(5):589–600

Effectiveness of vortioxetine is maintained with continuous treatment over 52 weeks*



*As assessed by MADRS. Mean MADRS total scores for patients previously treated with vortioxetine 5-20 mg/day in 6- to 8-week randomised controlled trials who continued treatment in an open-label extension study (n=1230).

Baseline 1 = randomisation to RCT
Baseline 2 = end of RCT & continuation into extension study
NNT calculated for effect of staying in treatment to week 52

Vieta E, Loft H, Florea I.
Effectiveness of long-term vortioxetine treatment of patients with major depressive disorder
Eur Neurospsychopharmacol 2017; 27: 877-84

Side effects are an important cause of premature treatment discontinuation

The majority of patients treated with antidepressants experience at least one problematic / unpleasant side effect[1]

- Side effects often create barriers to achieving remission, and add difficulties in the prevention of relapse and recurrence

As many as one quarter of patients discontinue their antidepressants due to difficult-to-tolerate side effects[1]

- Others may continue on antidepressant therapy, but experience diminished quality of life related to side effects

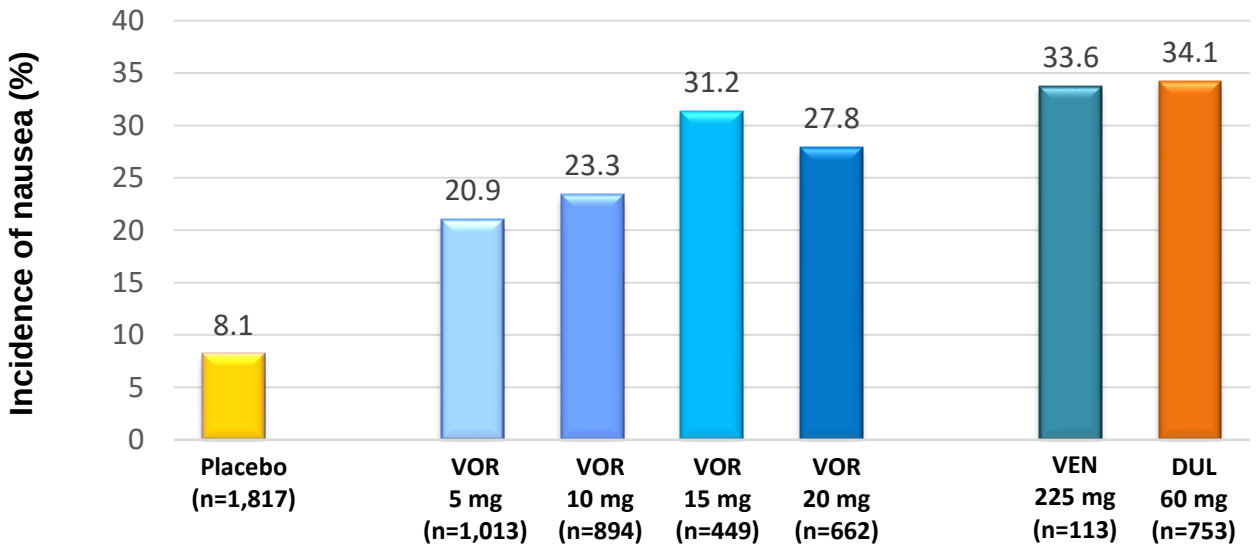
A study by Hu et al (2004) found that 33% of patients discontinued antidepressant treatment within 105 days[2]

- The most often cited reason for treatment discontinuation was adverse events (36%)[1,2]
- The presence of multiple side effects, or side effects deemed 'extremely bothersome,' significantly increased the odds of discontinuation[1,2]

1. Kelly et al. Dialogues Clin Neurosci 2008;10(4):409–418
2. Hu et al. J Clin Psychiatry 2004;65(7):959–965

Vortioxetine: nausea is very common but transient (median duration 9–16 days)[1]

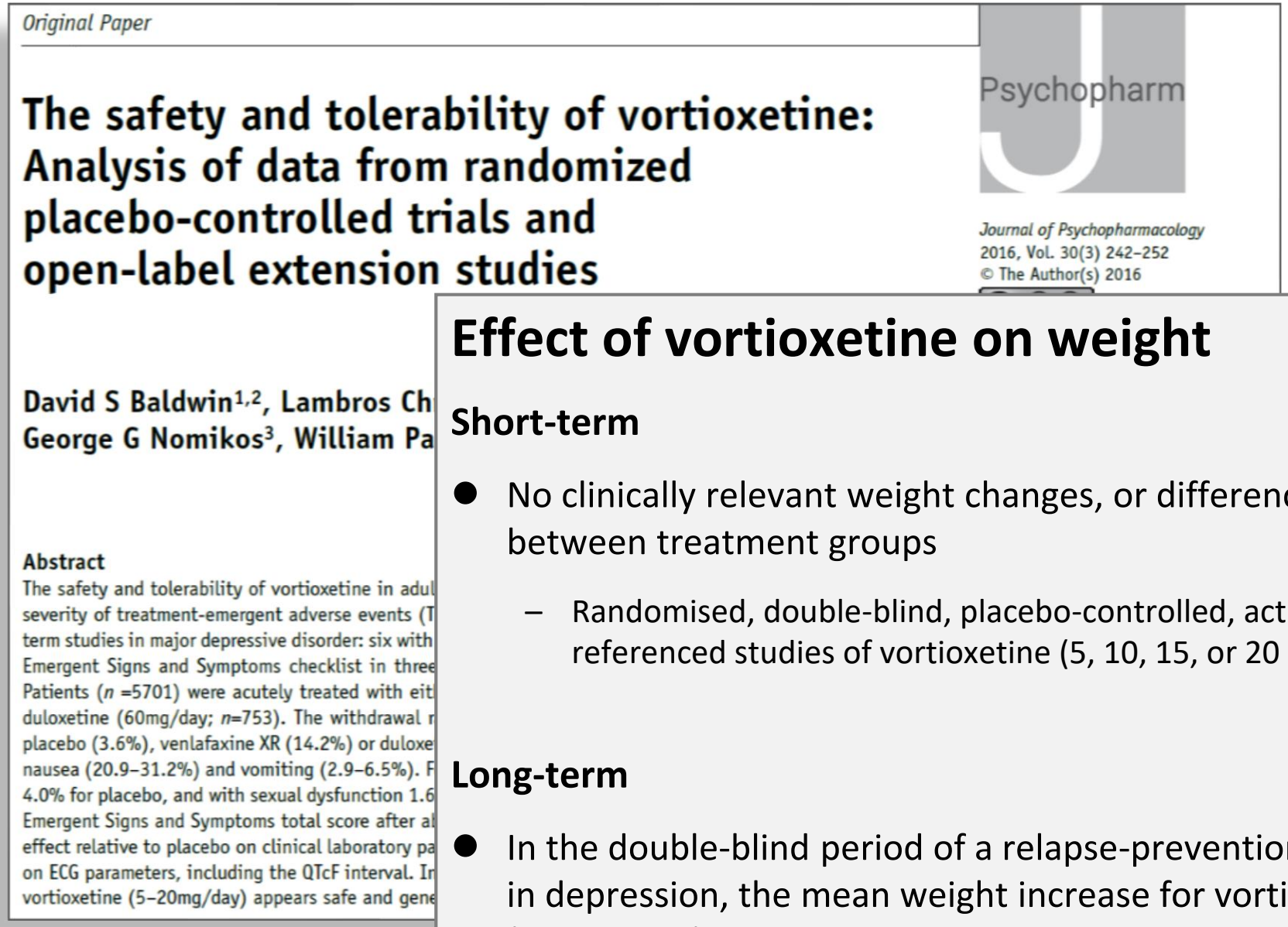
Incidence of nausea reported as a TEAE in short-term clinical trials[1]



- Nausea with vortioxetine (VOR) typically occurs within the first 2 weeks, is usually mild to moderate, transient, and does not generally lead to treatment discontinuation[2]

Duloxetine (DUL) and Venlafaxine (VEN) were included as active references for assay sensitivity and no comparison with vortioxetine can be inferred.

1. Baldwin et al. J Psychopharmacology 2016; 20(3): 242-252
2. Vortioxetine SmPC Accessed 8.12.18



Original Paper

The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies

Psychopharm

Journal of Psychopharmacology
2016, Vol. 30(3) 242–252

David S Baldwin[1,2], Lambros Ch
George G Nomikos[3], William Pa

Abstract

The safety and tolerability of vortioxetine in adul
severity of treatment-emergent adverse events (T
term studies in major depressive disorder: six with
Emergent Signs and Symptoms checklist in three
Patients (*n* =5701) were acutely treated with eit
duloxetine (60mg/day; *n*=753). The withdrawal r
placebo (3.6%), venlafaxine XR (14.2%) or duloxe
nausea (20.9–31.2%) and vomiting (2.9–6.5%). F
4.0% for placebo, and with sexual dysfunction 1.6
Emergent Signs and Symptoms total score after a
effect relative to placebo on clinical laboratory pa
on ECG parameters, including the QTcF interval. In
vortioxetine (5–20mg/day) appears safe and gene

Effect of vortioxetine on weight

Short-term

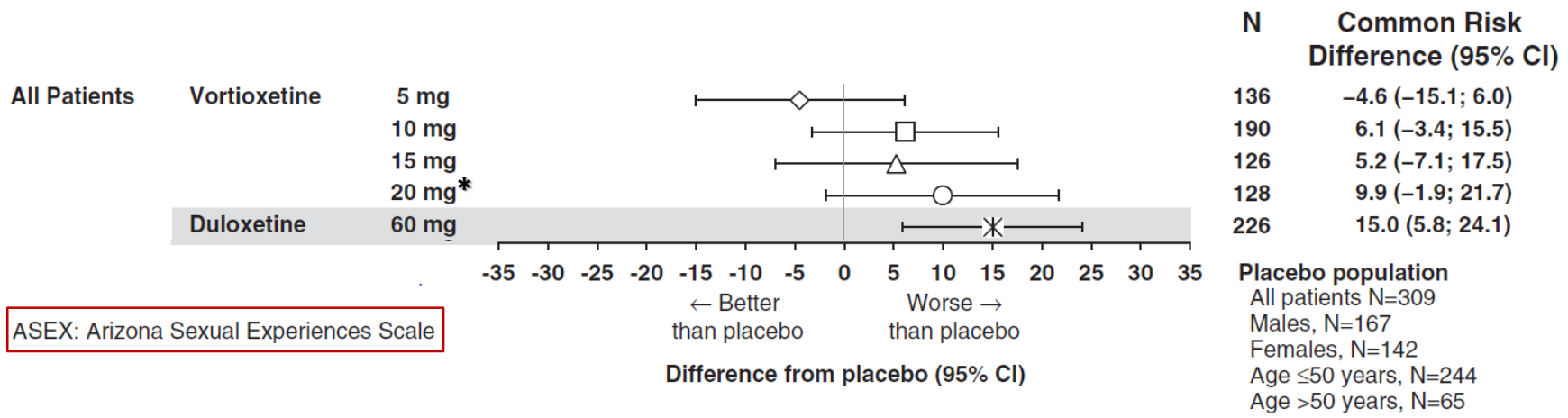
- No clinically relevant weight changes, or differences between treatment groups
  - Randomised, double-blind, placebo-controlled, active-referenced studies of vortioxetine (5, 10, 15, or 20 mg/day)

Long-term

- In the double-blind period of a relapse-prevention study in depression, the mean weight increase for vortioxetine (0.7 - 0.8 kg) was similar to placebo

Vortioxetine: sexual dysfunction similar to placebo at 5mg, 10mg and 15mg doses

Common risk difference of treatment-emergent sexual dysfunction in patients without sexual dysfunction at baseline: a pooled analysis of 7 short-term vortioxetine trials (6 in MDD, 1 in generalized anxiety disorder)



Duloxetine was included as an active reference for assay sensitivity and no comparison with vortioxetine can be inferred.

Jacobsen PL, Mahableshwarkar AR, Palo WA et al.
Treatment-emergent sexual dysfunction in randomized trials of vortioxetine for major depressive disorder or generalized anxiety disorder: a pooled analysis.
CNS Spectrums 2016; 21: 367–378.

Sexual dysfunction (TEAE reports)

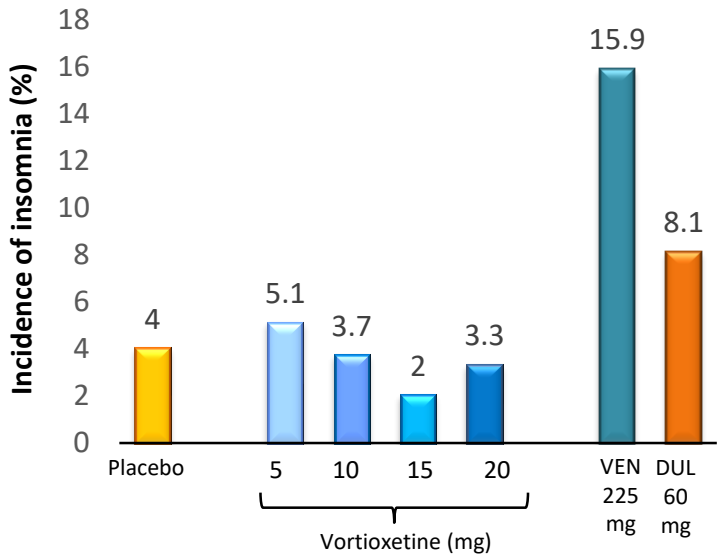
Sexual dysfunction during treatment with vortioxetine was low and similar to that in the placebo group (1.6-1.8% vs 1.0%)

Baldwin DS, Chrones L, Florea I, et al.
The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies.
Journal of Psychopharmacology 2016;30:242–252

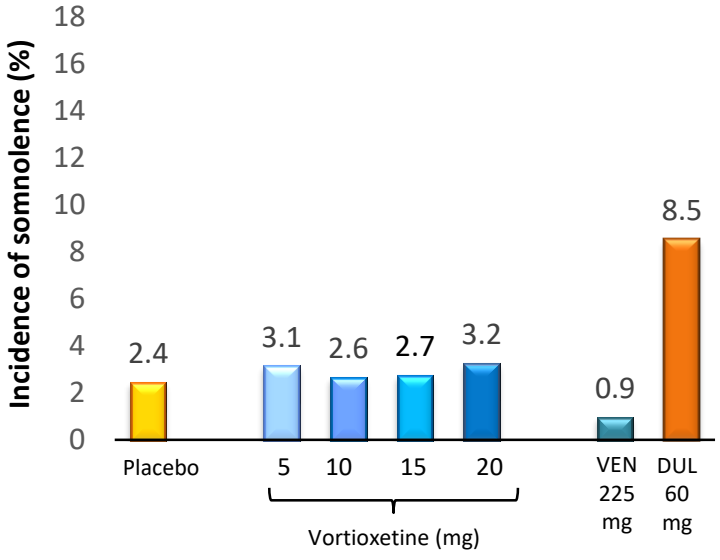
*The 20mg/day dose was associated with an increase in the incidence of treatment-emergent sexual dysfunction compared with placebo (14.2%, 95% CI [1.4, 27]; NNH=7, 95% CI 4-23)
15mg tablet is not available in the UK

Vortioxetine: incidence of sleep disturbance no different from placebo

Incidence of insomnia reported as a TEAE in short-term clinical trials[1]



Incidence of somnolence reported as a TEAE in short-term clinical trials[1]



Placebo n=1,817; vortioxetine: 5 mg n=1,1013, 10 mg n=894, 15 mg n=449, 20 mg n=662; venlafaxine n = 113; duloxetine n=753[1]

Duloxetine (DUL) and Venlafaxine (VEN) were included as active references for assay sensitivity and no comparison with vortioxetine can be inferred.

Baldwin DS, Chrones L, Florea I, et al.
The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies.
Journal of Psychopharmacology 2016;30:242–252

TEAEs of ≥5% incidence in any treatment group in 11 short-term studies in adult patients with depression

Preferred term for TEAE	Placebo (n=1,817)	Vortioxetine 5 mg (n=1,013)	Vortioxetine 10 mg (n=894)	Vortioxetine 15 mg (n=449)	Vortioxetine 20 mg (n=662)	Venlafaxine 225 mg (n=113)	Duloxetine 60 mg (n=753)
% patients with TEAEs	**58**	**65**	**61**	**69**	**65**	**75**	**76**
Nausea	8	21	23	**NNH=5**; 95% CI 4-6	28	34	34
Headache	13	14	13	15	**Infinity**	13	28	13
Dry mouth	6	7	6	**NNH=100**; 95% CI 32-infinity		7	17	17
Dizziness	6	6	5	7	**Infinity**	6	10	12
Diarrhoea	5	7	6	**NNH=100**; 95% CI 33-infinity		6	4	9
Vomiting	1	3	4	**NNH=25**; 95% CI 19-36		5	4	4
Insomnia[a]	4	5	4	**NNT=100**; 95% CI 37-infinity		3	16	8
Constipation	3	3	4	**NNH=100**; 95% CI 39-infinity		4	10	10
Somnolence	2	3	3	3	3	1	9
Fatigue	3	3	3	4	2	10	8
Decreased appetite	1	2	1	1	2	1	7
Sexual dysfunction[b]	1	2	2	2	2	12	5
Hyperhidrosis	2	2	2	2	1	15	7

- Duloxetine and Venlafaxine were included as active references for assay sensitivity. No comparison with vortioxetine can be inferred.
- TEAEs above the red line occur with a frequency ≥5% for vortioxetine
- TEAEs below the red line occur with a frequency ≥5% for duloxetine or venlafaxine

NNHs calculated for vortioxetine 20mg vs placebo

[a] Includes the preferred terms: insomnia, initial insomnia, middle insomnia, hyposomnia, sleep disorder, dyssomnia, poor quality sleep, and terminal insomnia.
[b] Includes the preferred terms: libido decreased, ejaculation delayed, ejaculation disorder, orgasm abnormal, anorgasmia, disturbance in sexual arousal, ejaculation failure, erectile dysfunction, loss of libido, orgasmic sensation decreased, sexual dysfunction, and vulvovaginal dryness.
Always refer to product SMPC for complete list of adverse events

Baldwin et al. Journal of Psychopharmacology 2016;30 (3):242-252

Vortioxetine

- Effective in acute depressive episode
- Effective in patients with sub-optimal response to SSRI or SNRI
- Effective in severe depression
- Effectiveness maintained long-term
- Improves cognitive function

Relatively low burden of adverse effects

- Nausea very common (NNH=5 vs placebo) but transient
- Sexual dysfunction
- Weight gain
- Sleep disturbance

Similar to placebo

- Other AEs no different from placebo

Recommended by NICE & SMC as 3rd-line treatment

Summary

- Depression causes single greatest burden of disease in high-income countries[1]
- High cost to England economy
  - Costs of medicines a small fraction of this[2]
- Current recommendations & treatment approaches do not deliver desired outcomes
- Cipriani findings change the evidence base for choice of initial antidepressant
- Many patients discontinue treatment prematurely
  - Adverse effects often cited as main reason
- Uncertainty about sequencing after non-response or inability to tolerate initial antidepressant

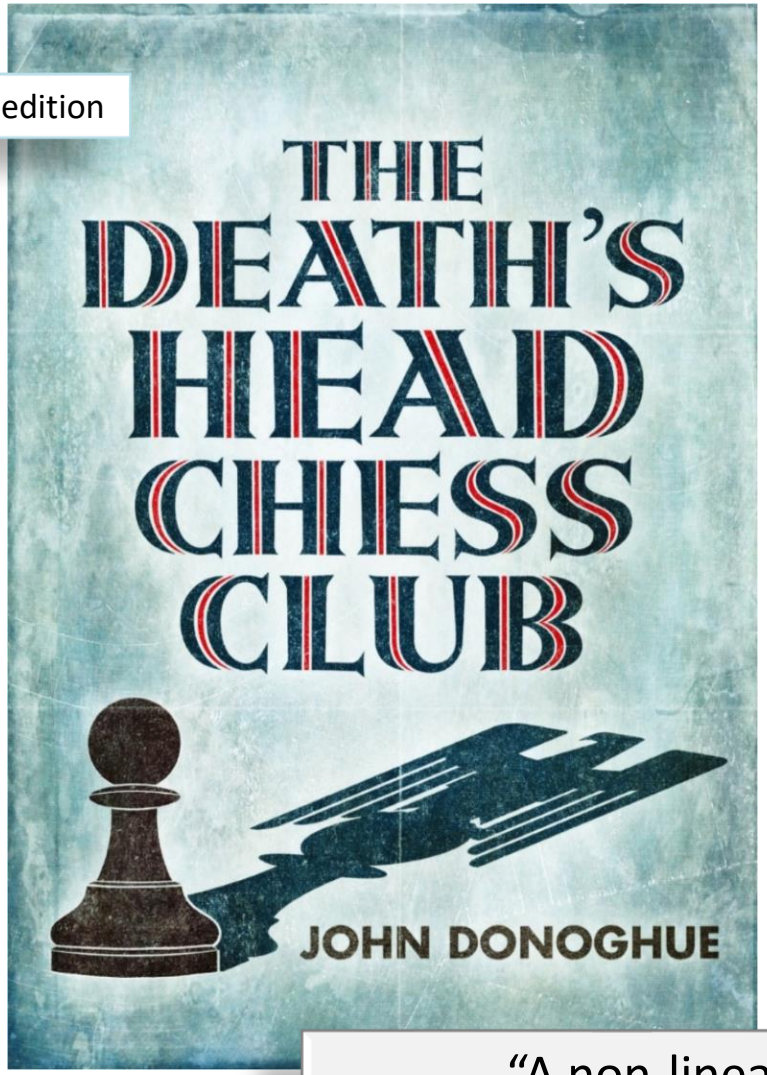
1. WHO. Global Burden of Disease 2004. http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/ Accessed on 8.12.18

2. McCrone P, Dhanasiri S, Patel A, et al. Paying the price: the cost of mental health care in England to 2026. London, King's Fund, 2008

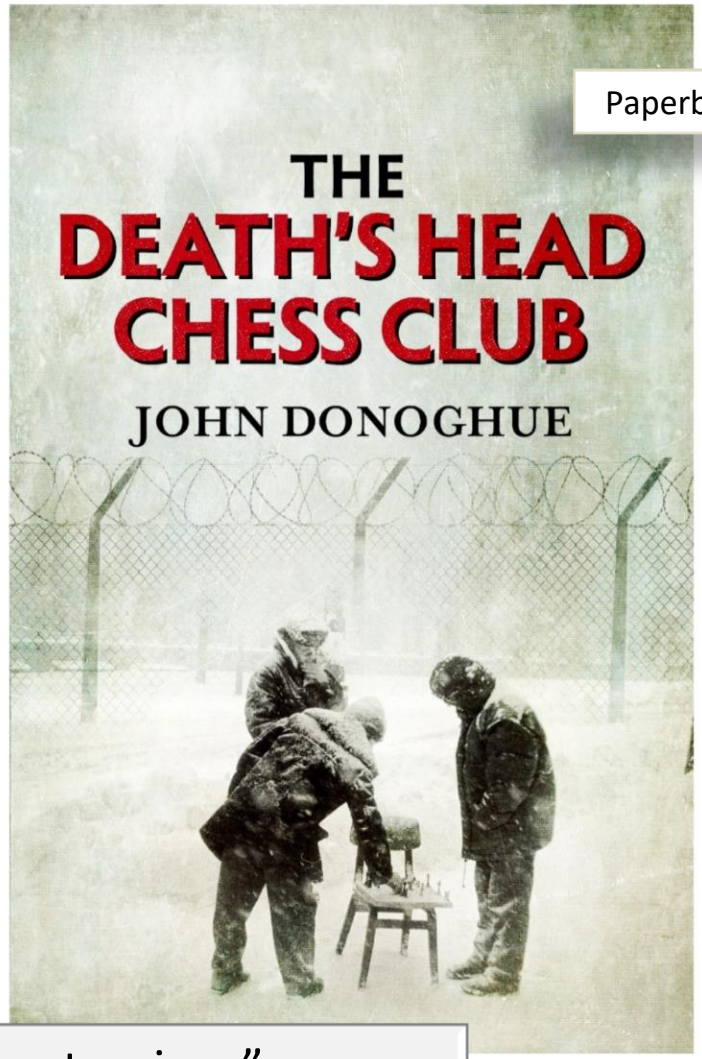
Thank you

www.mentalmeds.co.uk

First edition



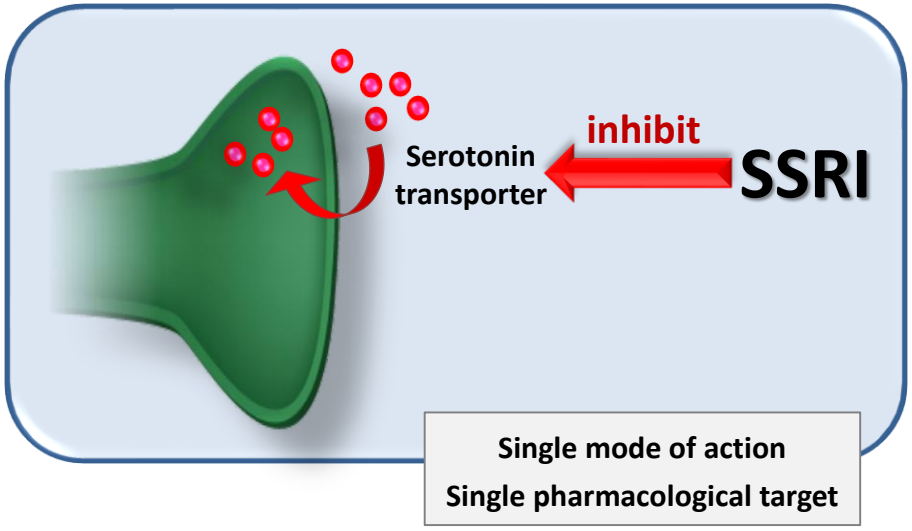
Paperback

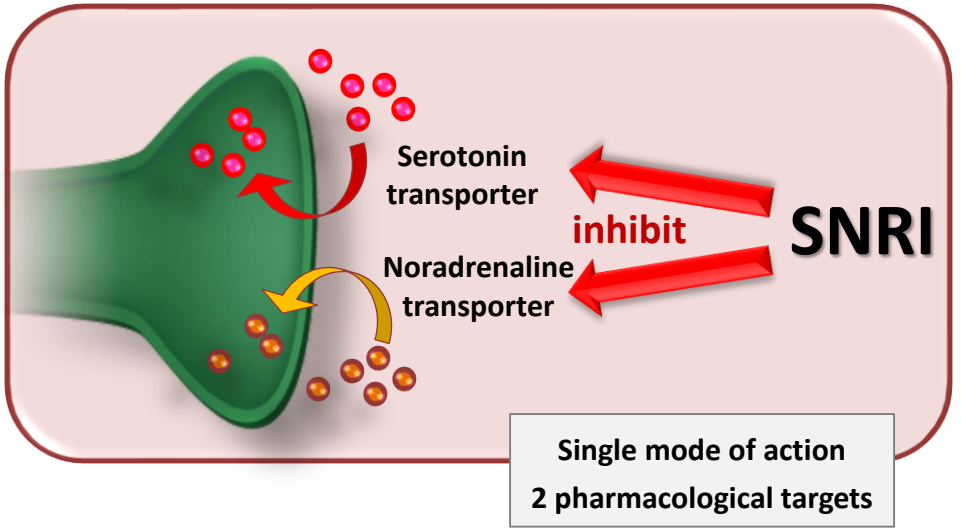


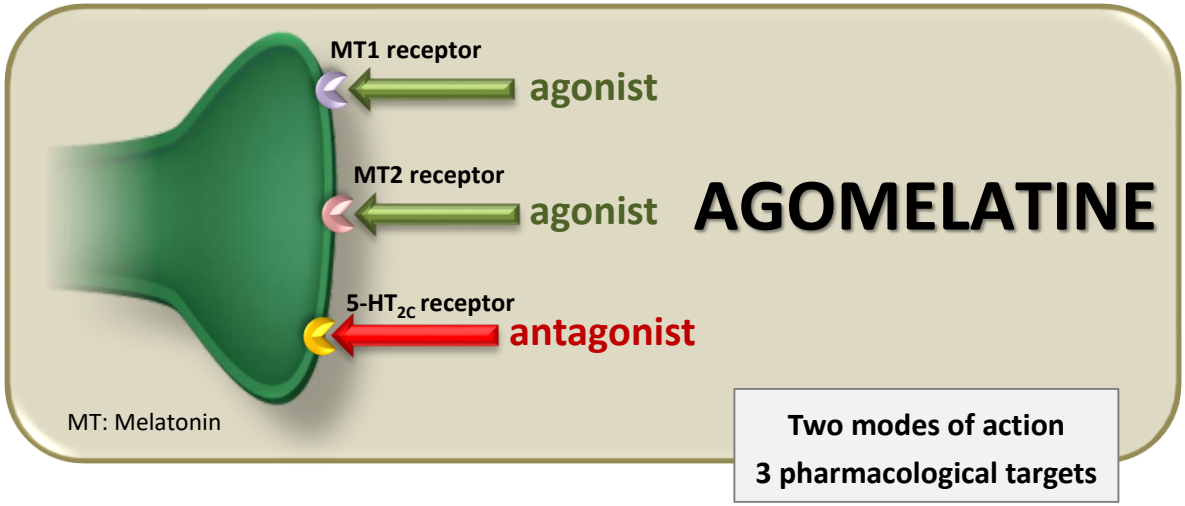
"A non-linear masterpiece"
New York Book Journal

Winner of the Waverton Good Read Award 2016

Modes of action of antidepressants

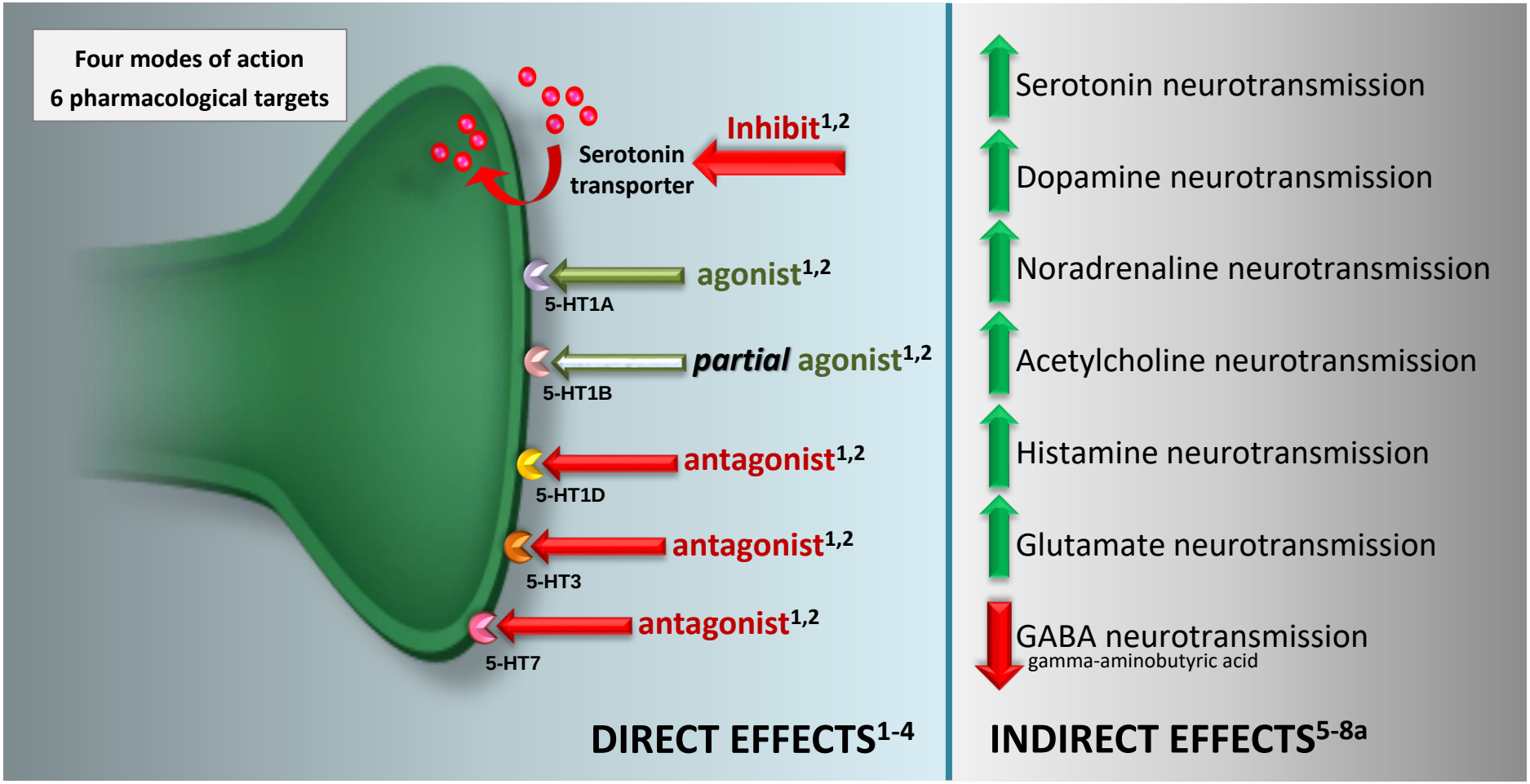






Nutt D. J Psychopharmacol 2009;23:343-5
Fornaro et al. Curr Neuropharmacol 2010;8:287-304
Westrich et al. Int J Psychiatry Clin Pract 2012;16(Suppl 1):47,abs P71

Vortioxetine: A multimodal antidepressant



1. Bang-Anderson et al. J Med Chem 2011;54(9):3206–3221
2. Mørk et al. JPET 2012; 340 (3): 666–675
3. Vortioxetine SmPC
4. Westrich et al. Poster at IFMAD 2012
5. Mørk et al. Poster at ECNP 2011
6. Mørk et al. Poster at SOBP 2011
7. Pehrson et al. Poster at ECNP 2013
8. Mørk et al. Poster at APA 2013

[a]In the forebrain. The precise contribution of individual targets to the observed pharmacodynamic profile remains unclear. Caution should be applied when extrapolating findings from animal studies to humans.