From Evidence to Everyday Practice: The effects of antidepressants on cardiac, metabolic and other physiological parameters

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Background

Antidepressants are among the most commonly prescribed drugs in high-income countries (OECD, 2023).

Physiological and metabolic effects of psychotropics are clinically important (Correll et al., 2015)

Cardiometabolic disease is a leading contributor to reduced life expectancy in people with mental illness (Gardner-Sood et al., 2015)

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The *Lancet Psychiatry* Commission: a blueprint for protecting physical health in people with mental illness

Joseph Firth, PhD [a,b,e] · Najma Siddiqi, PhD [h,i,*] · Ai Koyanagi, MD [j,k,l,*] · Dan Siskind, PhD [m,n,*] · Simon Rosenbaum, PhD [p,*] · Prof Cherrie Galletly, MD [r,s,an,*] · Stephanie Allan, MA [t] · Constanza Caneo, MD [u] · Rebekah Carney, PhD [b,v] · Prof Andre F Carvalho, MD [x,y] · Mary Lou Chatterton, PharmD [z] · Prof Christoph U Correll, MD [ab,ac,ad] · Prof Jackie Curtis, MBBS [p,av] · Fiona Gaughran, MD [ae,ag] · Adrian Heald, DM [c,ah,ai] · Erin Hoare, PhD [aa] · Sarah E Jackson, PhD [aj] · Prof Steve Kisely, DMedRes [n,ak] · Prof Karina Lovell, PhD [d,al] · Prof Mario Maj, MD [am] · Prof Patrick D McGorry, MD [e,f] · Prof Cathrine Mihalopoulos, PhD [z] · Hannah Myles, MBBS [an] · Brian O'Donoghue, PhD [e,f] · Toby Pillinger, MRCP [ae,ag,ao,ap] · Prof Jerome Sarris, PhD [a,g,aq] · Prof Felipe B Schuch, PhD [ar] · David Shiers, MBChB [b,w] · Lee Smith, PhD [as] · Marco Solmi, MD [at] · Shuichi Suetani, MD [m,o,au] · Johanna Taylor, PhD [h] · Scott B Teasdale, PhD [p,av] · Prof Graham Thornicroft, PhD [af] · John Torous, MD [aw] · Prof Tim Usherwood, MD [q,ax] · Prof Davy Vancampfort, PhD [ay,az] · Nicola Veronese, MD [ba] · Prof Philip B Ward, PhD [p,bb] · Prof Alison R Yung, MD [b,e,f] · Prof Eoin Killackey, DPsych [e,f,†] · Brendon Stubbs, PhD [ae,ag,†] Show less

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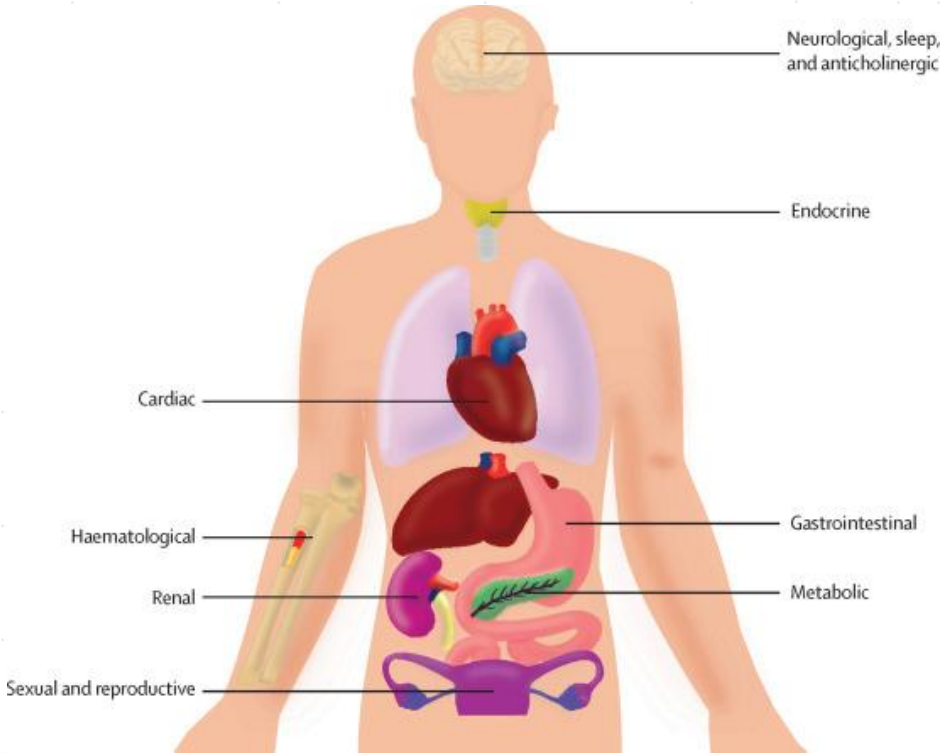
Holistic prevention and management of physical health side-effects of psychotropic medication: second report of the *Lancet Psychiatry* Physical Health Commission

Sean Halstead, MD [a,b] · Chloe X Yap, PhD [a,b,c,d] · Nicola Warren, PhD [a,b] · Sri Mahavir Agarwal, MD PhD [e,f,g,h] · Bodyl A Brand, PhD [d] · Sherry Kit Wa Chan, MD [k] · Prof Andrea Cipriani, MD PhD [d,l,m] · Prof Christoph U Correll, MD [n,o,p,q,r] · Nicolas Crossley, PhD [s] · Enrico D'Ambrosio, PhD [t,u] · Prof Robin Emsley, DMed [v] · Joseph Firth, PhD [w,x] · Prof Fiona Gaughran, MD [u,y] · Siobhan Gee, PhD [y,z] · Prof Margaret Hahn, MD PhD [e,g,h,i,j,aa] · Prof Joseph F Hayes, PhD [ab,ac] · Adrian Heald, DM [ad,ae] · Prof Oliver D Howes, DM [u] · Prof John M Kane, MD [o] · Maria Kapi, PhD [y,af] · Prof Stefan Leucht, MD [r,ag] · Nicholas Meyer, PhD [ah,ai] · Prof Brian O'Donoghue, PhD [aj] · Emmanuel Okeke, BSc [y] · Benjamin I Perry, PhD [ak,al] · Marco Solmi, MD PhD [q,am,an,ao] · Prof Iris E Sommer [ap] · Vivek Srivastava, MD FRCP [aq,ar,as] · Heidi Taipale, PhD [at,au] · Prof David Taylor, PhD [af] · Prof Jari Tiihonen, MD PhD [at,au,av] · Prof Allan H Young, FRCPsych [aw] · the Lancet Psychiatry Physical Health Commission Consortium [*] · Robert A McCutcheon, PhD [d,m,†,u] · Prof Dan Siskind, PhD [a,b,†] · Toby Pillinger, PhD [u,y,†] Show less



2019

- Exposed scale of premature mortality & cardiometabolic disease in mental illness
- Identified modifiable risks (smoking, inactivity, poor diet, sleep)
- Called for screening, lifestyle interventions & integrated care

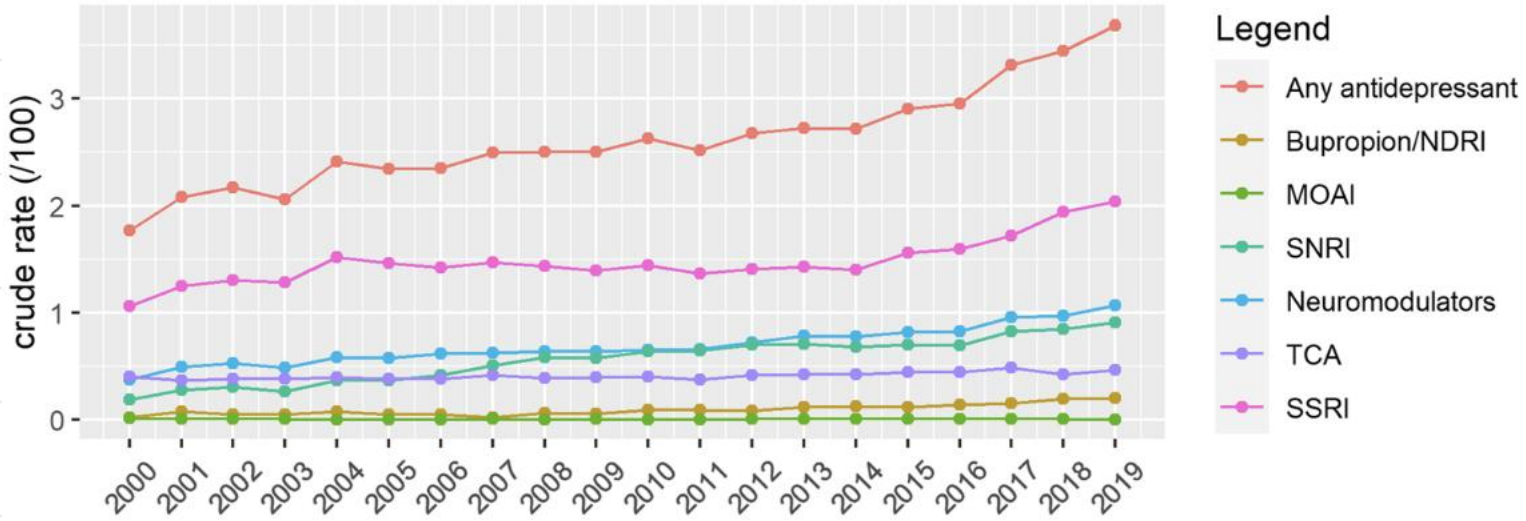
2025

- Systems-based synthesis of psychotropic side-effects (cardiometabolic, cardiac, neuro, endocrine, etc.)
- Patient-centred: lived experience, shared decision-making
- Digital tools (e.g., side-effect ranking heatmaps) to guide prescribing

RESEARCH Open Access

Trends in the epidemiology of depression and comorbidities from 2000 to 2019 in Belgium

Roosje Walrave[1†], Simon Gabriël Beerten[1*†], Pavlos Mamouris[1], Kristien Coteur[1], Marc Van Nuland[1], Gijs Van Pottelbergh[1], Lidia Casas[2,3] and Bert Vaes[1]

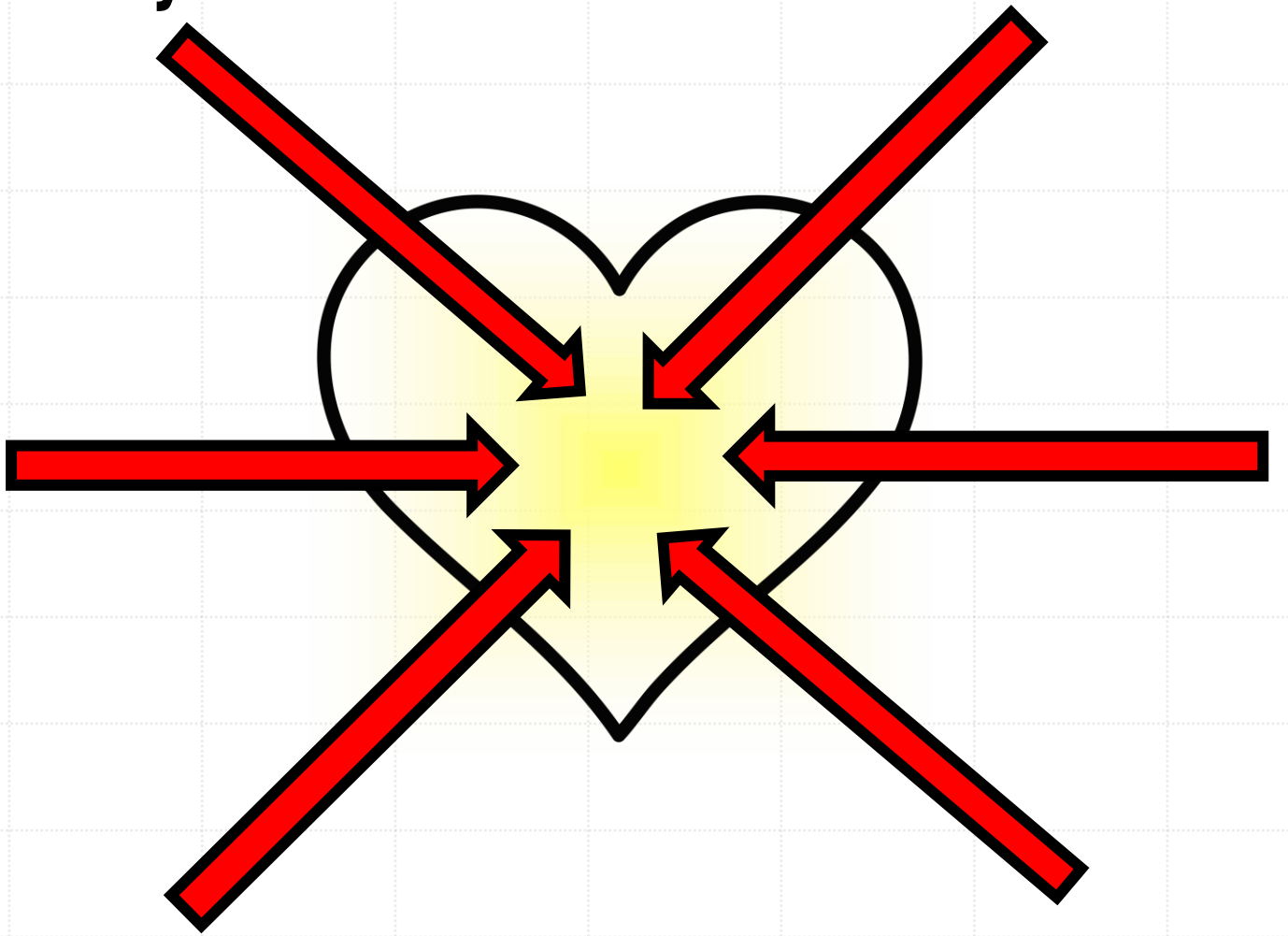


- 538,299 patients from family practice registration network in Flanders
- Increasing trend in incidence of depression
- Increasing trend in antidepressant use in depression and across all patients in primary care registry

- **1.8 chronic diseases per patient with depression**
- **Hypertension most prevalent somatic co-morbidity (14.6%)**
- **Diabetes mellitus rates 3.5% -> 6.7%**

Lifestyle

Illness



Antidepressants

Intrinsic risk?

Less likely to seek help

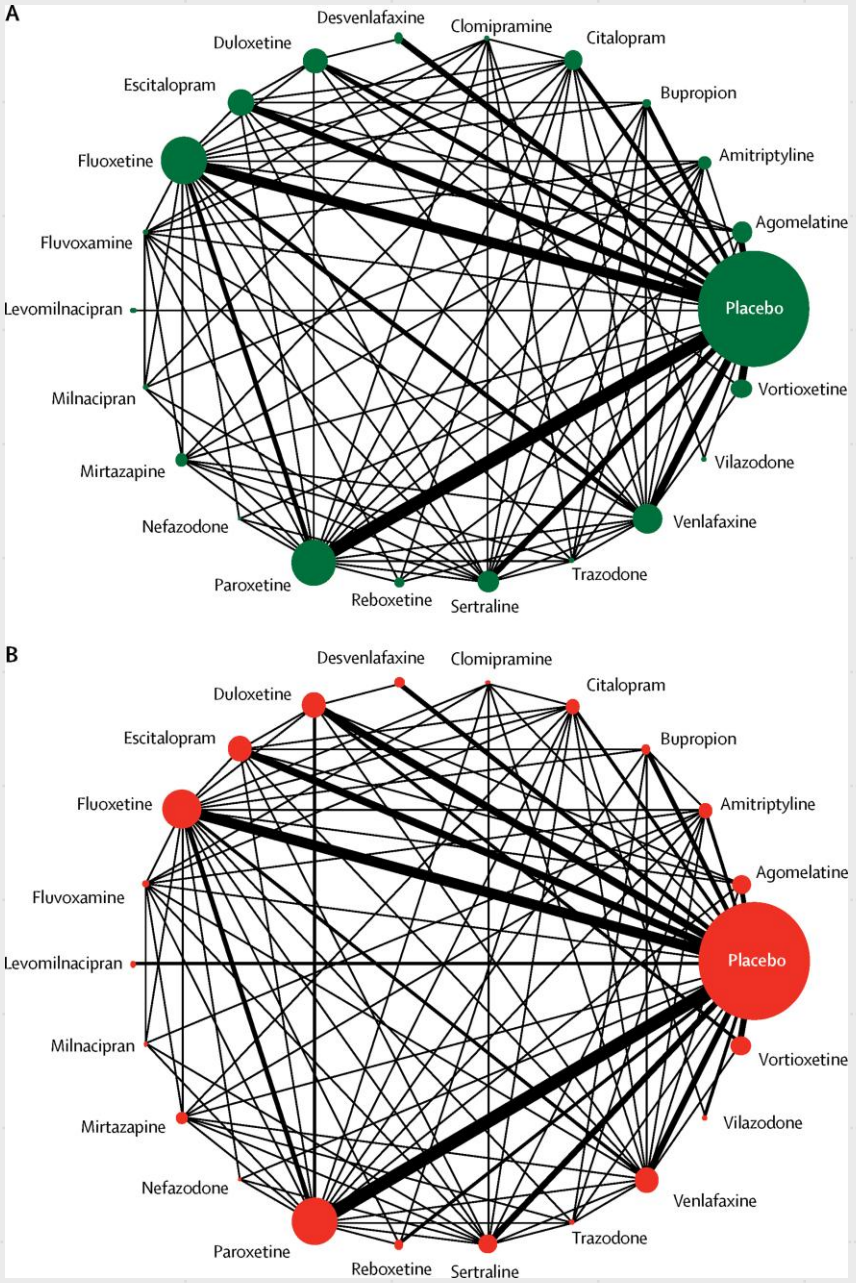
Less likely to get help

What do we actually know about the physiological effects of antidepressants?

- Antidepressants are among the most prescribed drugs in Europe, yet prescribers lack comparative safety data
- **Evidence is fragmented and difficult to integrate into prescribing decisions**
  - Clinical trials typically focus on efficacy, with side-effect data inconsistently reported.
- **Comparative evidence is needed**

Network meta-analysis:

Synthesis of direct and indirect evidence to rank comparative effects of interventions against each other

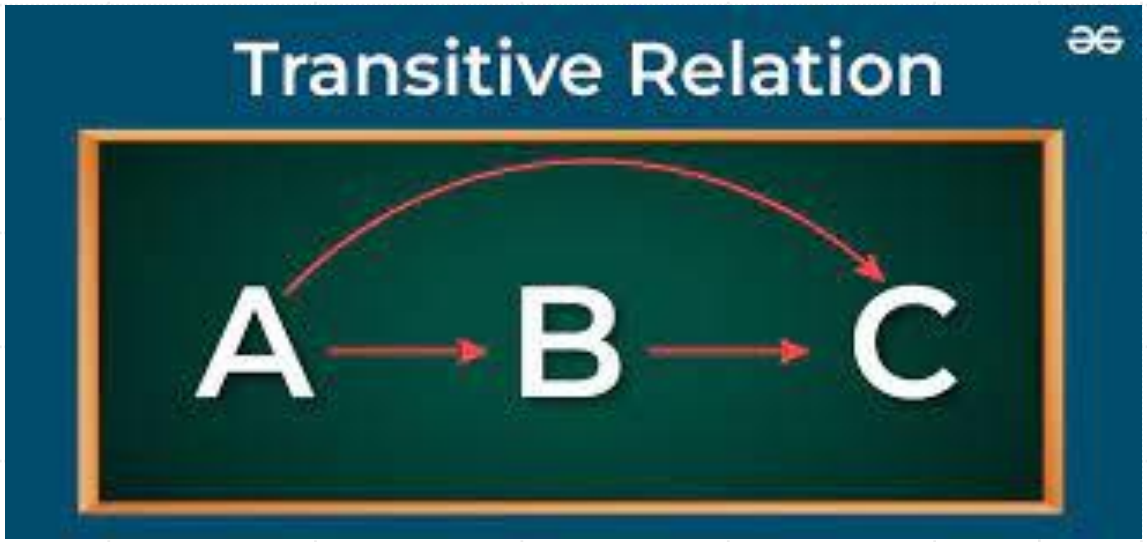


(Cipriani et al., 2018).

Transitivity in Network Meta-Analysis

- **Definition**
  - Assumption that patients included in different trials could, in principle, be randomly assigned to any of the treatments in the network.

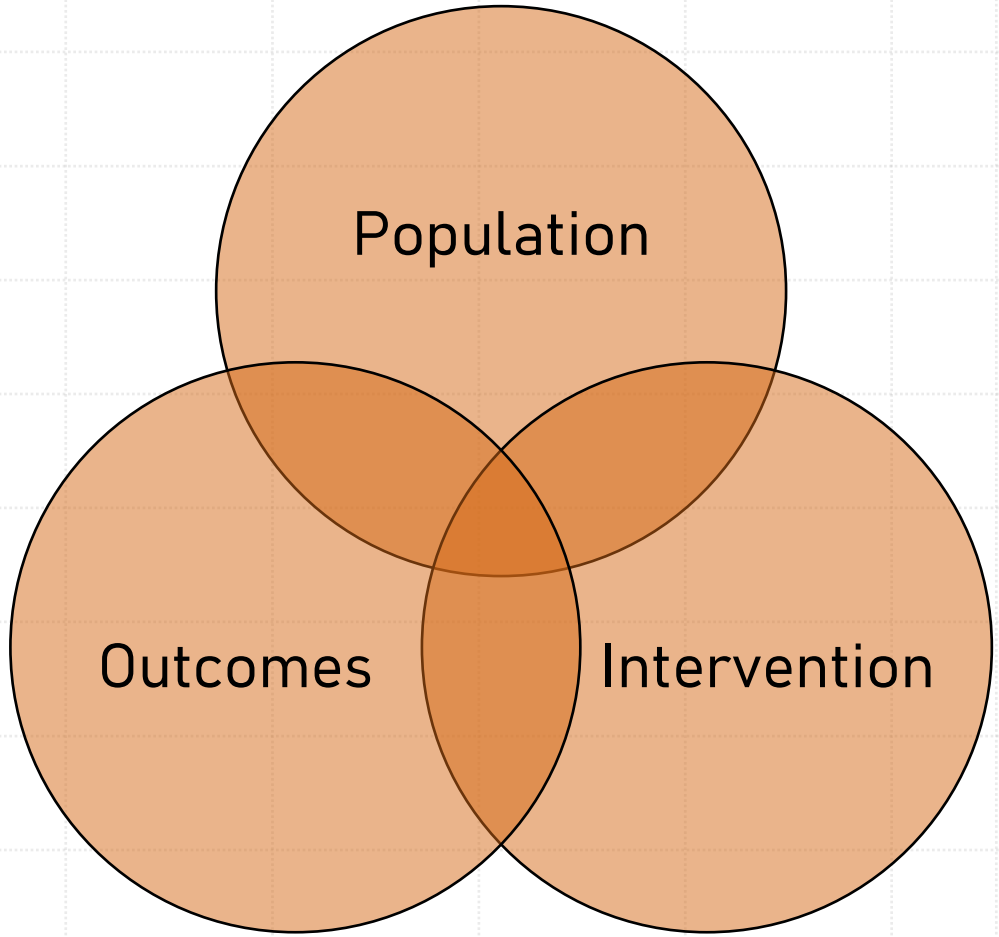
- **Why It Matters**
  - Enables valid *indirect comparisons* (e.g., if Drug A vs B and Drug B vs C are studied, we can infer A vs C).



Without transitivity, treatment rankings may be biased.

Key assumptions for transitivity

- **Similarity of study populations**
  - Age, sex, illness severity, comorbidities, treatment resistance.
- **Similarity of interventions**
  - Drug doses, formulations, co-prescriptions, treatment duration.
- **Similarity of outcomes**
  - Consistent measurement methods, follow-up times, definitions of endpoints.
- **Even distribution of effect modifiers**
  - No treatment is only studied in patients with particular characteristics (e.g., high BMI, resistant depression).



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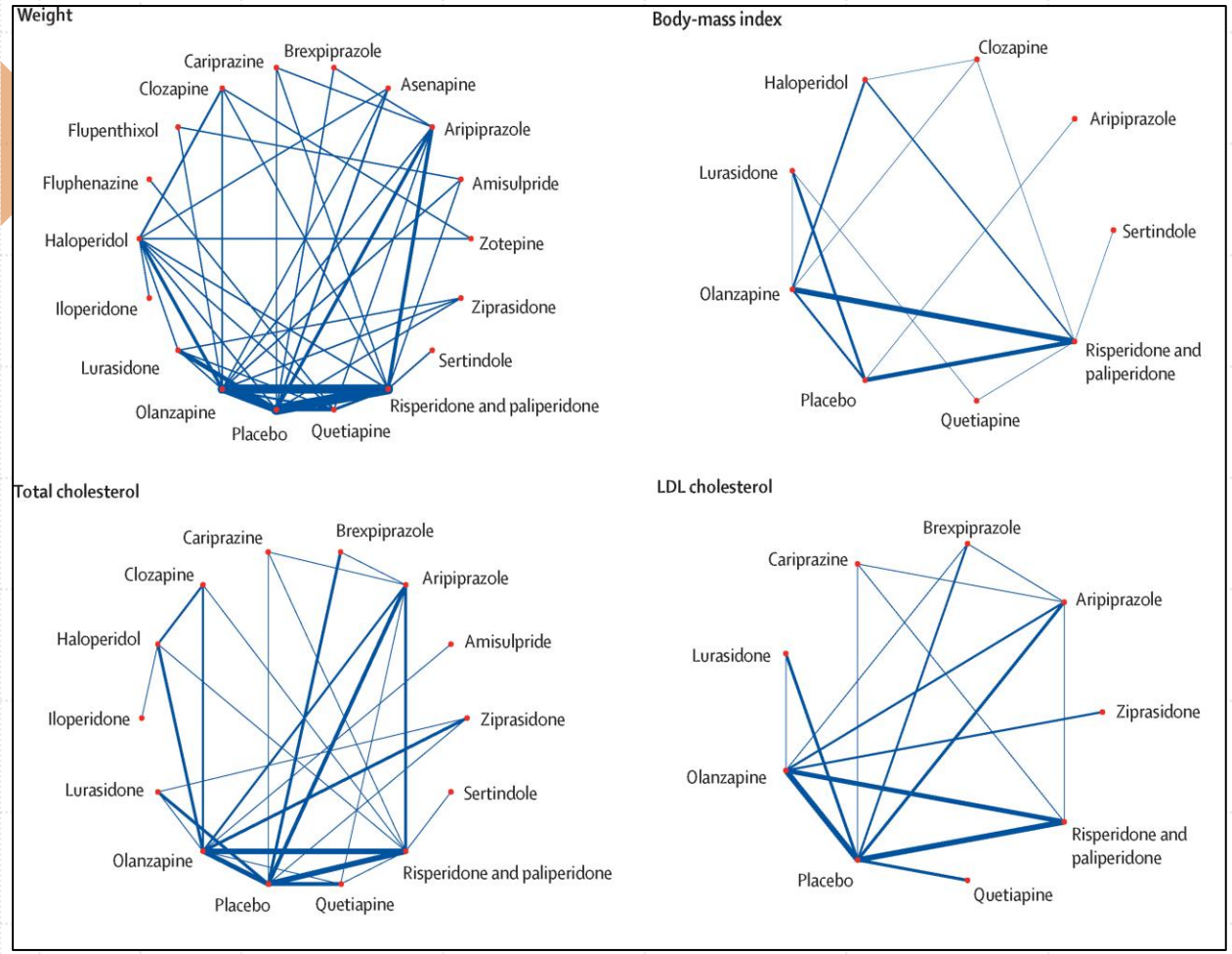
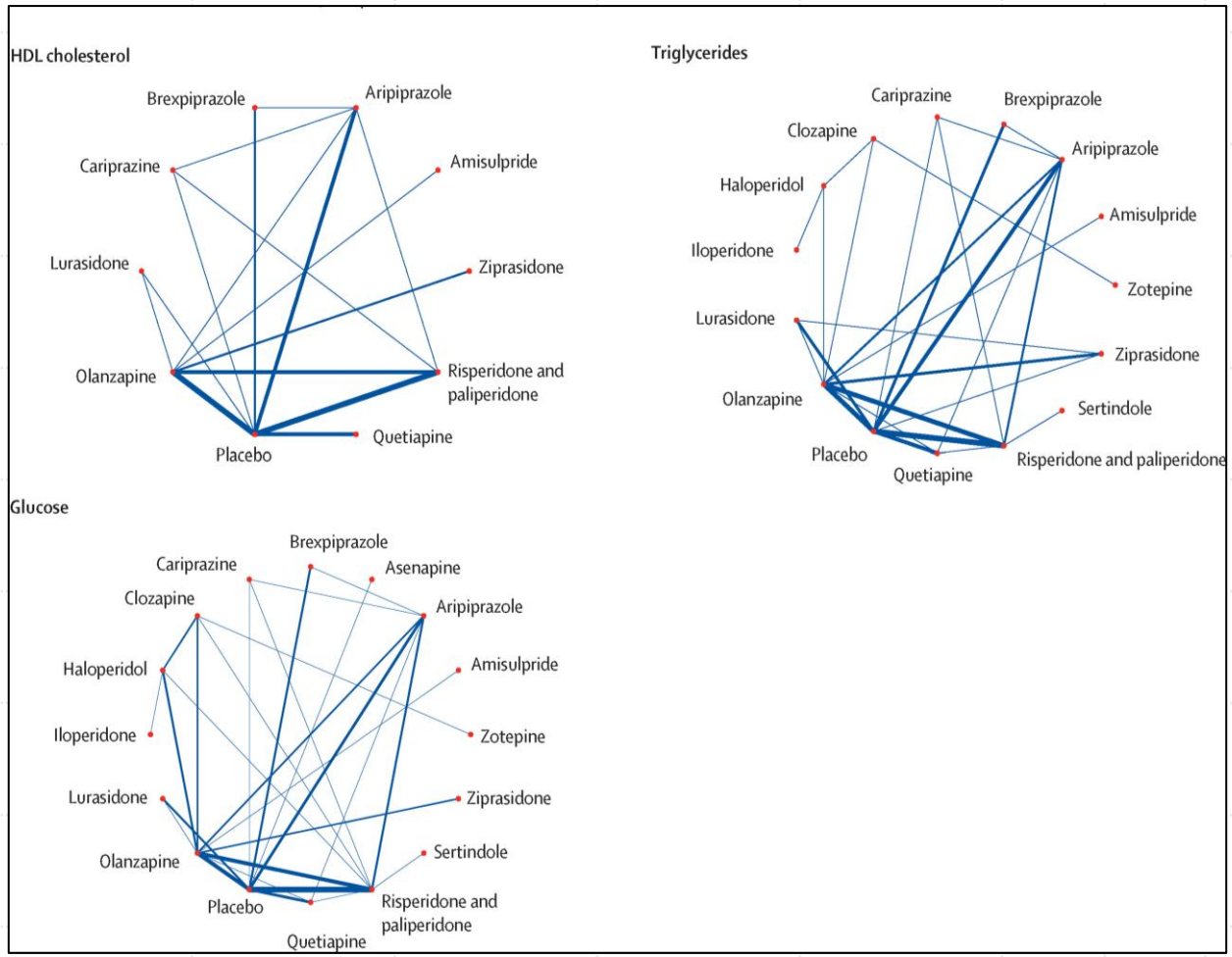
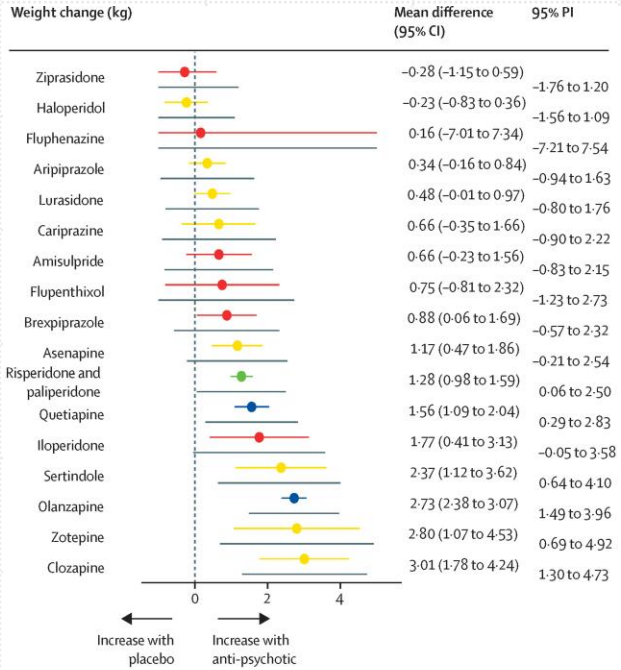
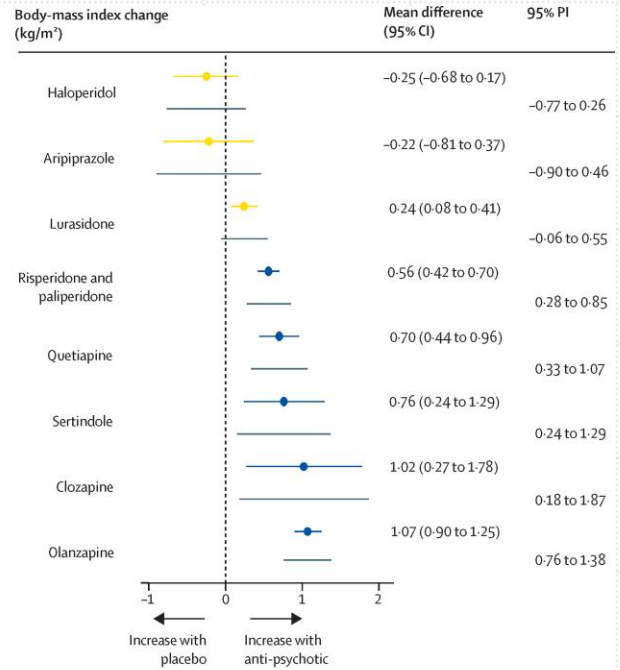
Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis

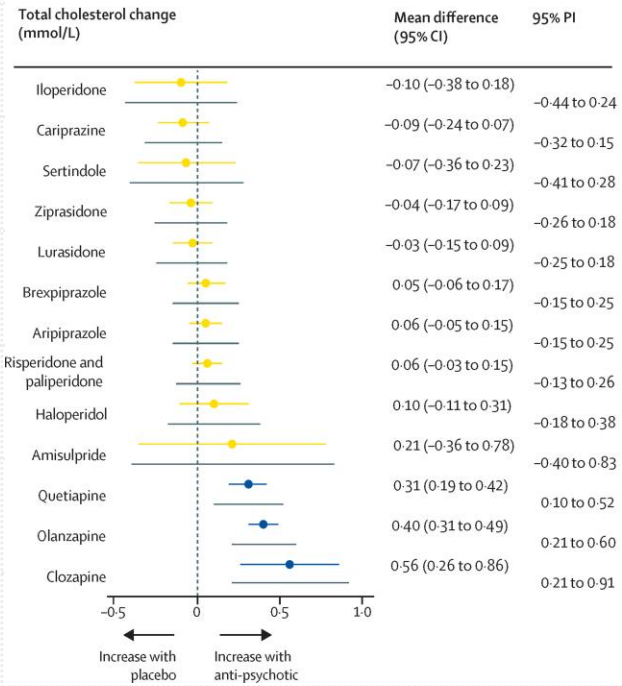
Toby Pillinger, MRCP [a,b,†] · Robert A McCutcheon, MRCPsych [a,b,†] · Luke Vano, MD [a,b] · Yuya Mizuno, MRCPsych [a,b,c] · Atheeshaan Arumuham, MD [a,b] · Guy Hindley, MD [a,b] · Katherine Beck, MRCPsych [a,b] · Sridhar Natesan, PhD [a,b] · Orestis Efthimiou, PhD [d] · Prof Andrea Cipriani, PhD [e,f] · Prof Oliver D Howes, MRCPsych [a,b] Show less

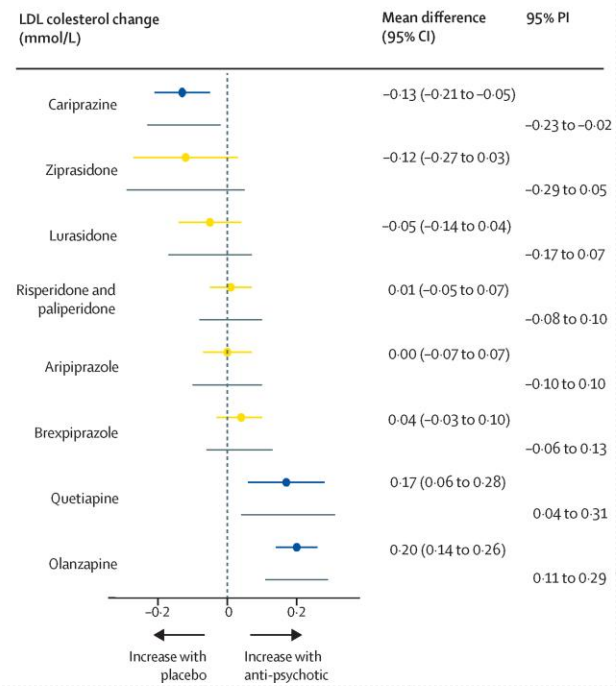

Weight
Cariprazine
Brexpiprazole
Clozapine
Asenapine
Flupenthixol
Aripiprazole
Fluphenazine
Amisulpride
Haloperidol
Zotepine
Iloperidone
Ziprasidone
Lurasidone
Sertindole
Olanzapine
Risperidone and paliperidone
Placebo
Quetiapine
Body-mass index
Clozapine
Haloperidol
Aripiprazole
Lurasidone
Sertindole
Olanzapine
Risperidone and paliperidone
Placebo
Quetiapine
Total cholesterol
Cariprazine
Brexpiprazole
Clozapine
Aripiprazole
Haloperidol
Amisulpride
Iloperidone
Ziprasidone
Lurasidone
Sertindole
Olanzapine
Risperidone and paliperidone
Placebo
Quetiapine
LDL cholesterol
Brexpiprazole
Cariprazine
Aripiprazole
Lurasidone
Ziprasidone
Olanzapine
Risperidone and paliperidone
Placebo
Quetiapine

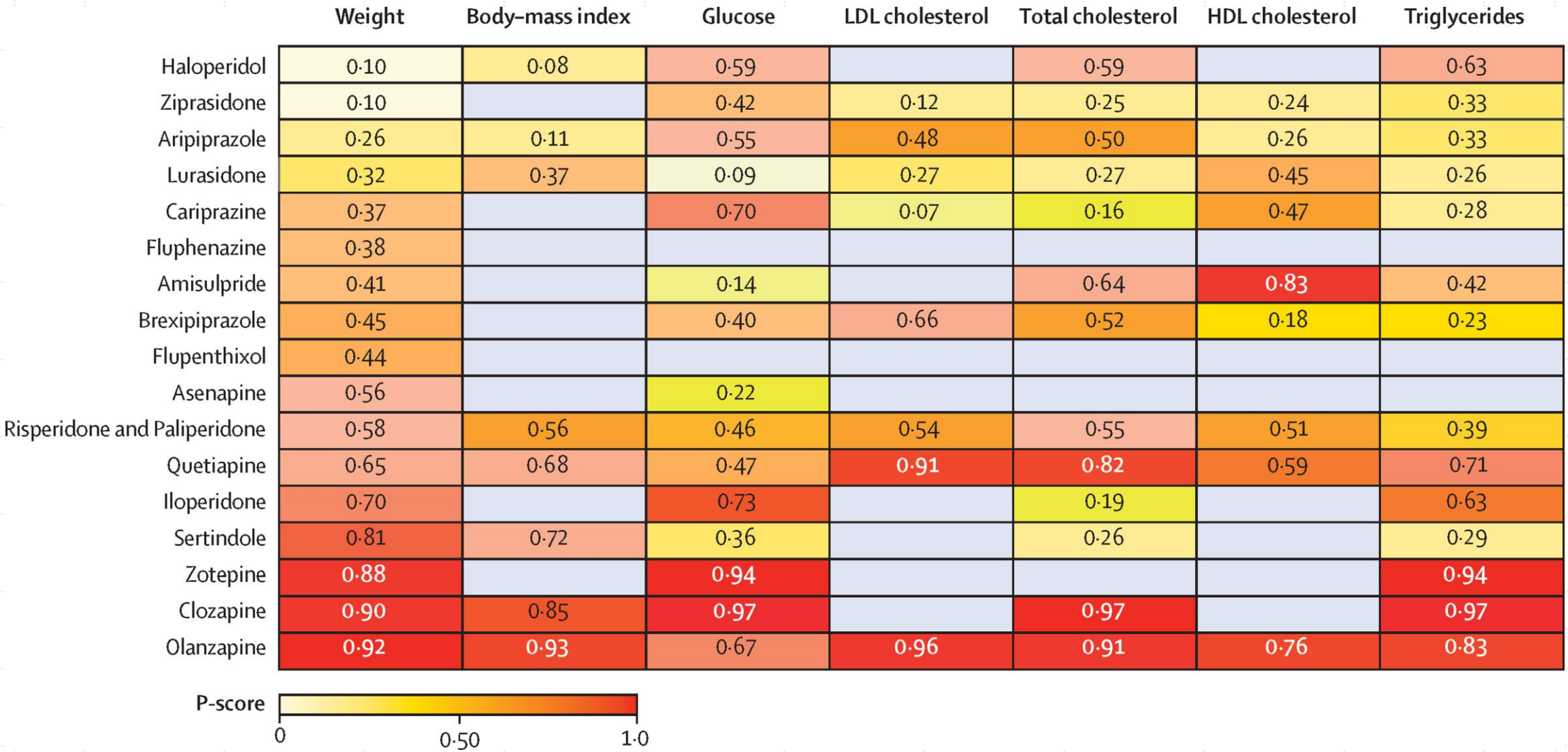

HDL cholesterol
Brexpiprazole
Aripiprazole
Cariprazine
Amisulpride
Lurasidone
Ziprasidone
Olanzapine
Risperidone and paliperidone
Placebo
Quetiapine
Triglycerides
Cariprazine
Brexpiprazole
Clozapine
Aripiprazole
Haloperidol
Amisulpride
Iloperidone
Zotepine
Lurasidone
Ziprasidone
Olanzapine
Sertindole
Placebo
Risperidone and paliperidone
Quetiapine
Glucose
Brexpiprazole
Cariprazine
Asenapine
Clozapine
Aripiprazole
Amisulpride
Haloperidol
Iloperidone
Zotepine
Lurasidone
Ziprasidone
Olanzapine
Sertindole
Placebo
Risperidone and paliperidone
Quetiapine

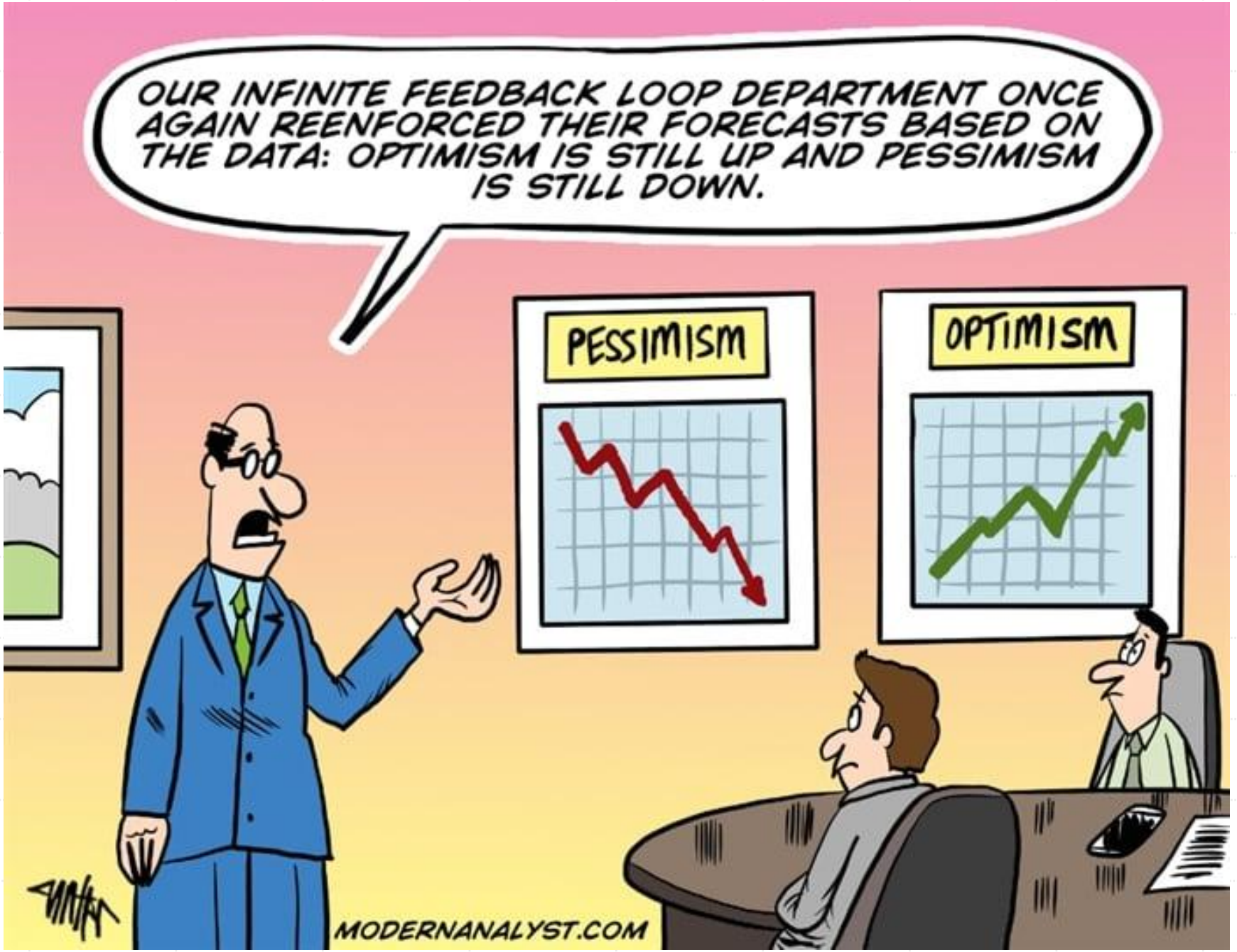

Weight change (kg)
Mean difference (95% CI)
95% PI
Ziprasidone
Haloperidol
Fluphenazine
Aripiprazole
Lurasidone
Cariprazine
Amisulpride
Flupenthixol
Brexpiprazole
Asenapine
Risperidone and paliperidone
Quetiapine
Iloperidone
Sertindole
Olanzapine
Zotepine
Clozapine
−0·28 (−1·15 to 0·59)
−0·23 (−0·83 to 0·36)
0·16 (−7·01 to 7·34)
0·34 (−0·16 to 0·84)
0·48 (−0·01 to 0·97)
0·66 (−0·35 to 1·66)
0·66 (−0·23 to 1·56)
0·75 (−0·81 to 2·32)
0·88 (0·06 to 1·69)
1·17 (0·47 to 1·86)
1·28 (0·98 to 1·59)
1·56 (1·09 to 2·04)
1·77 (0·41 to 3·13)
2·37 (1·12 to 3·62)
2·73 (2·38 to 3·07)
2·80 (1·07 to 4·53)
3·01 (1·78 to 4·24)
−1·76 to 1·20
−1·56 to 1·09
−7·21 to 7·54
−0·94 to 1·63
−0·80 to 1·76
−0·90 to 2·22
−0·83 to 2·15
−1·23 to 2·73
−0·57 to 2·32
−0·21 to 2·54
0·06 to 2·50
0·29 to 2·83
−0·05 to 3·58
0·64 to 4·10
1·49 to 3·96
0·69 to 4·92
1·30 to 4·73
0
2
4
Increase with placebo
Increase with anti-psychotic


Body-mass index change (kg/m²)
Mean difference (95% CI)
95% PI
Haloperidol
Aripiprazole
Lurasidone
Risperidone and paliperidone
Quetiapine
Sertindole
Clozapine
Olanzapine
−0·25 (−0·68 to 0·17)
−0·22 (−0·81 to 0·37)
0·24 (0·08 to 0·41)
0·56 (0·42 to 0·70)
0·70 (0·44 to 0·96)
0·76 (0·24 to 1·29)
1·02 (0·27 to 1·78)
1·07 (0·90 to 1·25)
−0·77 to 0·26
−0·90 to 0·46
−0·06 to 0·55
0·28 to 0·85
0·33 to 1·07
0·24 to 1·29
0·18 to 1·87
0·76 to 1·38
−1
0
1
2
Increase with placebo
Increase with anti-psychotic


Total cholesterol change (mmol/L)
Mean difference (95% CI)
95% PI
Iloperidone
Cariprazine
Sertindole
Ziprasidone
Lurasidone
Brexpiprazole
Aripiprazole
Risperidone and paliperidone
Haloperidol
Amisulpride
Quetiapine
Olanzapine
Clozapine
−0·10 (−0·38 to 0·18)
−0·09 (−0·24 to 0·07)
−0·07 (−0·36 to 0·23)
−0·04 (−0·17 to 0·09)
−0·03 (−0·15 to 0·09)
0·05 (−0·06 to 0·17)
0·06 (−0·05 to 0·15)
0·06 (−0·03 to 0·15)
0·10 (−0·11 to 0·31)
0·21 (−0·36 to 0·78)
0·31 (0·19 to 0·42)
0·40 (0·31 to 0·49)
0·56 (0·26 to 0·86)
−0·44 to 0·24
−0·32 to 0·15
−0·41 to 0·28
−0·26 to 0·18
−0·25 to 0·18
−0·15 to 0·25
−0·15 to 0·25
−0·13 to 0·26
−0·18 to 0·38
−0·40 to 0·83
0·10 to 0·52
0·21 to 0·60
0·21 to 0·91
−0·5
0
0·5
1·0
Increase with placebo
Increase with anti-psychotic


LDL colesterol change (mmol/L)
Mean difference (95% CI)
95% PI
Cariprazine
Ziprasidone
Lurasidone
Risperidone and paliperidone
Aripiprazole
Brexpiprazole
Quetiapine
Olanzapine
−0·13 (−0·21 to −0·05)
−0·12 (−0·27 to 0·03)
−0·05 (−0·14 to 0·04)
0·01 (−0·05 to 0·07)
0·00 (−0·07 to 0·07)
0·04 (−0·03 to 0·10)
0·17 (0·06 to 0·28)
0·20 (0·14 to 0·26)
−0·23 to −0·02
−0·29 to 0·05
−0·17 to 0·07
−0·08 to 0·10
−0·10 to 0·10
−0·06 to 0·13
0·04 to 0·31
0·11 to 0·29
−0·2
0
0·2
Increase with placebo
Increase with anti-psychotic


Weight
Body–mass index
Glucose
LDL cholesterol
Total cholesterol
HDL cholesterol
Triglycerides
Haloperidol 0·10 0·08 0·59 0·59 0·63
Ziprasidone 0·10 0·42 0·12 0·25 0·24 0·33
Aripiprazole 0·26 0·11 0·55 0·48 0·50 0·26 0·33
Lurasidone 0·32 0·37 0·09 0·27 0·27 0·45 0·26
Cariprazine 0·37 0·70 0·07 0·16 0·47 0·28
Fluphenazine 0·38
Amisulpride 0·41 0·14 0·64 0·83 0·42
Brexipiprazole 0·45 0·40 0·66 0·52 0·18 0·23
Flupenthixol 0·44
Asenapine 0·56 0·22
Risperidone and Paliperidone 0·58 0·56 0·46 0·54 0·55 0·51 0·39
Quetiapine 0·65 0·68 0·47 0·91 0·82 0·59 0·71
Iloperidone 0·70 0·73 0·19 0·63
Sertindole 0·81 0·72 0·36 0·26 0·29
Zotepine 0·88 0·94 0·94
Clozapine 0·90 0·85 0·97 0·97 0·97
Olanzapine 0·92 0·93 0·67 0·96 0·91 0·76 0·83
P-score
0
0·50
1·0


OUR INFINITE FEEDBACK LOOP DEPARTMENT ONCE AGAIN REENFORCED THEIR FORECASTS BASED ON THE DATA: OPTIMISM IS STILL UP AND PESSIMISM IS STILL DOWN.
PESSIMISM
OPTIMISM
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Antipsychotics – key “take-aways”

Marked variation between antipsychotics:

Clozapine and olanzapine caused the greatest weight, lipid, and glucose disturbances, while aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone showed the most benign metabolic profiles

Predictors of higher risk:

Male sex, higher baseline weight, and non-white ethnicity predicted greater susceptibility to antipsychotic-induced metabolic dysregulation

Implications for prescribing:

Choice of antipsychotic should balance efficacy with metabolic risk, particularly in patients with comorbidities. Updated treatment guidelines are warranted to incorporate these differences

… what about antidepressants?

Choosing between sertraline and mirtazapine may have very different implications for a patient with obesity and hypertension

…why does it matter?

- **Physiological effects directly influence morbidity and mortality**
  - Antidepressants can affect weight, blood pressure, glucose, and lipids
- **Evidence remains fragmented and under-reported**
  - ***Example: A prescriber choosing between two SSRIs has little comparative evidence on which causes more sustained weight gain.***
- **No prior comparative ranking available**
  - Unlike antipsychotics, antidepressants have not been systematically ranked by their physiological impact.

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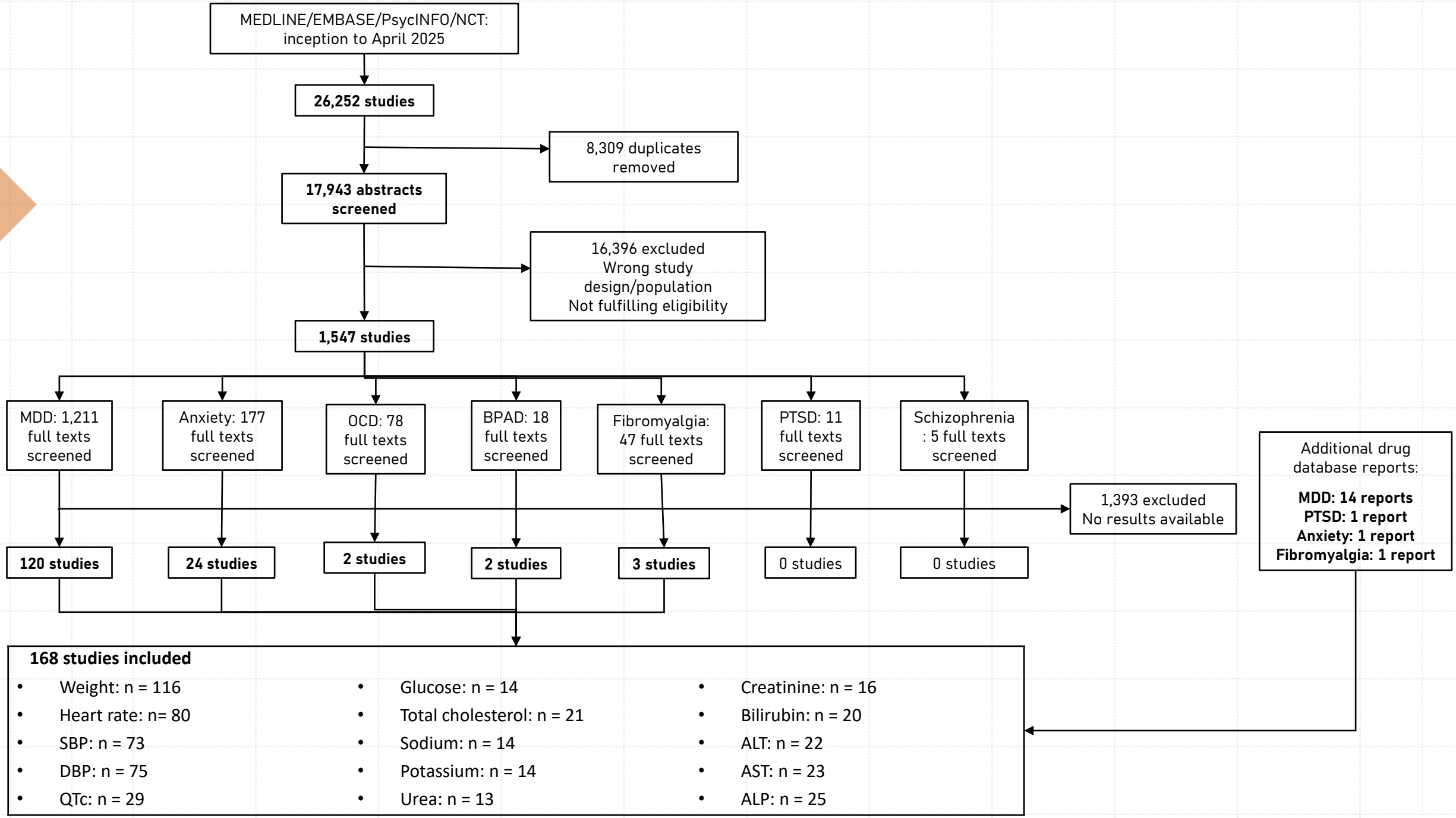
The effects of antidepressants on cardiometabolic and other physiological parameters: a systematic review and network meta-analysis

Toby Pillinger, Atheeshaan Arumuhan*, Robert A McCutcheon, Enrico D'Ambrosio, Georgios Basdanis, Marco Branco, Richard Carr, Valeria Finelli, Toshi A Furukawa, Siobhan Gee, Adrian Heald, Sameer Jauhar, Zihan Ma, Valentina Mancini, Calum Moulton, Georgia Salanti, David M Taylor, Anneka Tomlinson, Allan H Young, Orestis Efthimiou†, Oliver D Howes†, Andrea Ciprianit†*

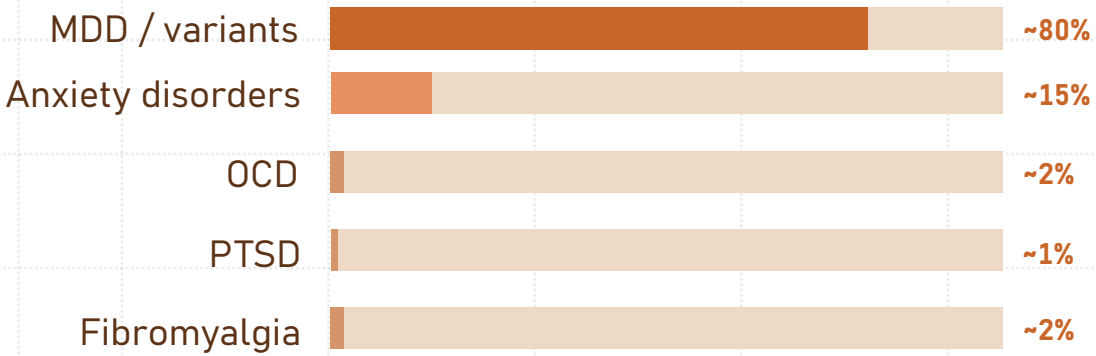
Drug class	Drugs included in NMA	Key metabolic receptor mechanism
SSRIs Selective serotonin reuptake inhibitors	Fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine	5-HT reuptake inhibition
SNRIs Serotonin-noradrenaline reuptake inhibitors	Venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran	5-HT + NE reuptake inhibition; NE activity drives haemodynamic effects
TCAs Tricyclic antidepressants	Amitriptyline, imipramine, nortriptyline, clomipramine, doxepin, maprotiline, desipramine, trimipramine	H1 antagonism (weight); NE reuptake (HR, BP); M3 muscarinic (glucose); α1 (BP)
NaSSAs Noradrenergic & specific serotonergic	Mirtazapine, mianserin	H1 + 5-HT2C antagonism; most potent histaminergic blockade of all classes
MAOIs / RIMAs Monoamine oxidase inhibitors	Phenelzine (irreversible); moclobemide (RIMA); selegiline (MAO-B)	MAO inhibition → ↑ monoamine availability; moclobemide: reversible, selective MAO-A
Melatonergic / NDRI / Other Agomelatine, bupropion, trazodone, reboxetine, vilazodone, vortioxetine	**Agomelatine** MT1/MT2 agonist + 5-HT2C antagonist **Bupropion** NE + DA reuptake inhibitor	Agomelatine: no monoamine reuptake; weight loss via 5-HT2C antagonism. Bupropion: DA/NE reuptake → appetite suppression


MEDLINE/EMBASE/PsycINFO/NCT: inception to April 2025
26,252 studies
8,309 duplicates removed
17,943 abstracts screened
16,396 excluded Wrong study design/population Not fulfilling eligibility
1,547 studies
MDD: 1,211 full texts screened
Anxiety: 177 full texts screened
OCD: 78 full texts screened
BPAD: 18 full texts screened
Fibromyalgia: 47 full texts screened
PTSD: 11 full texts screened
Schizophrenia : 5 full texts screened
1,393 excluded No results available
120 studies
24 studies
2 studies
2 studies
3 studies
0 studies
0 studies
Additional drug database reports:
MDD: 14 reports
PTSD: 1 report
Anxiety: 1 report
Fibromyalgia: 1 report
168 studies included
Weight: n = 116
Heart rate: n= 80
SBP: n = 73
DBP: n = 75
QTc: n = 29
Glucose: n = 14
Total cholesterol: n = 21
Sodium: n = 14
Potassium: n = 14
Urea: n = 13
Creatinine: n = 16
Bilirubin: n = 20
ALT: n = 22
AST: n = 23
ALP: n = 25

Study population

TOTAL PARTICIPANTS	STUDIES INCLUDED	ANTIDEPRESSANTS	MEAN AGE
58,534	**168**	**30**	**44.7 yrs**
41,937 treated · 16,597 placebo	151 RCTs · 17 FDA reports	all vs placebo	SD 15.8

Diagnosis breakdown (by study count)



Sex

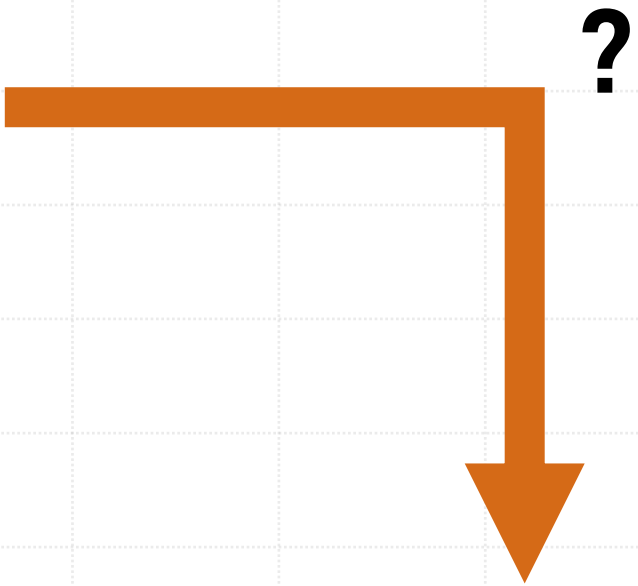
Ethnicity (reported data)

Treatment duration

8 weeks median

IQR 6.0–8.5 · range 3–12 weeks

Pan-diagnostic



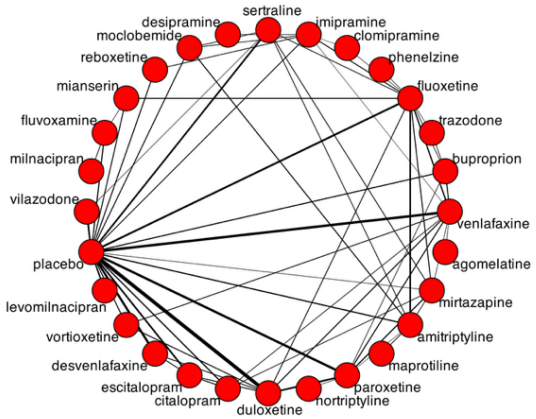
Transitivity

- The outcomes (weight, blood pressure, glucose, liver enzymes, etc.) are **physiological parameters**, not psychiatric symptom scores.
  - These are less likely to be strongly modified by diagnosis compared to drug pharmacology.

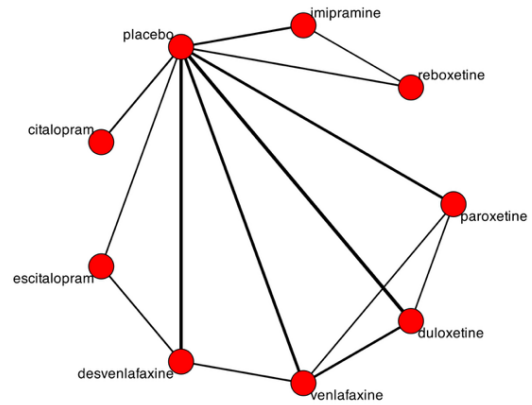
- The included trials were all **acute-phase monotherapy RCTs** (median 8 weeks), reducing variability in treatment context.

- The main effect modifiers for these physiological outcomes are **age, sex, and baseline weight**, not diagnosis per se. These were checked for balance.

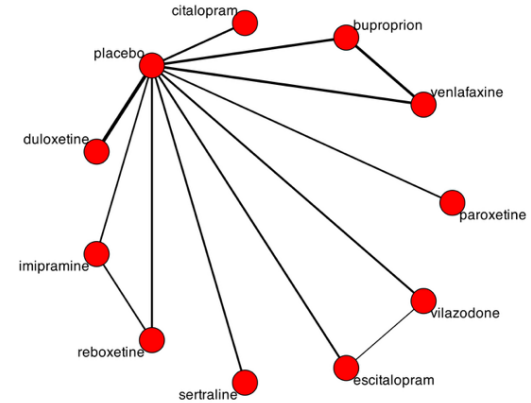
Weight



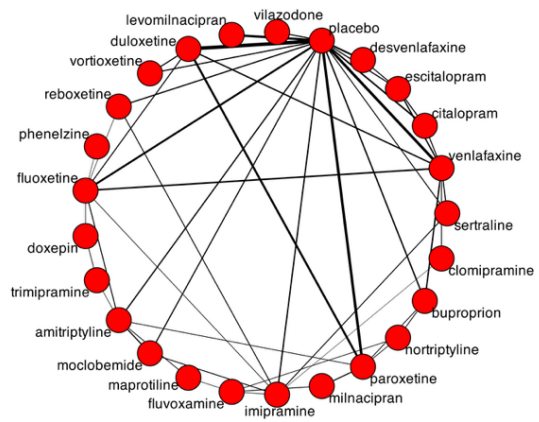
Total cholesterol



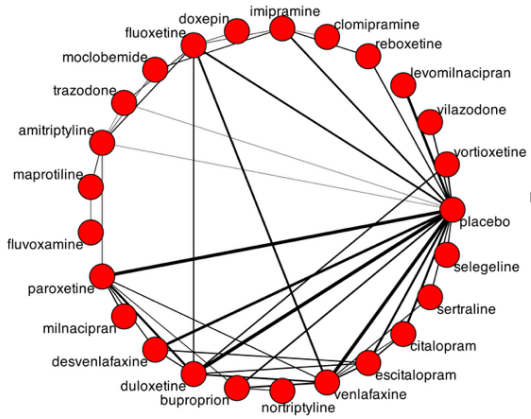
Glucose



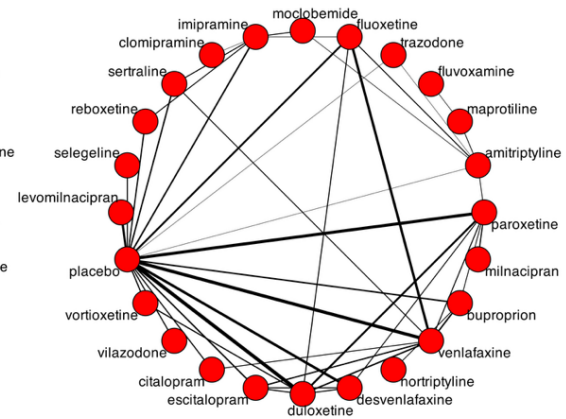
Heart rate



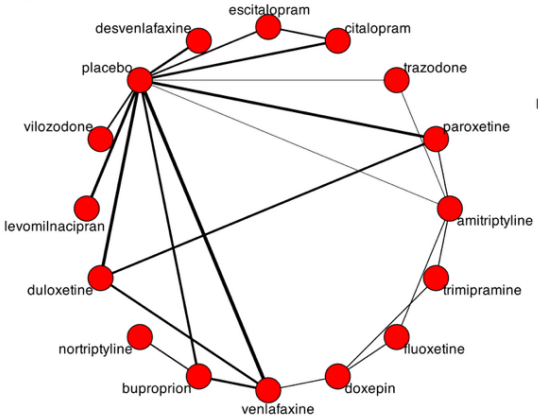
Systolic blood pressure



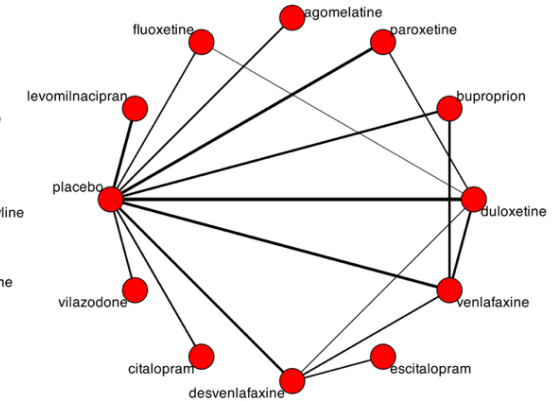
Diastolic blood pressure



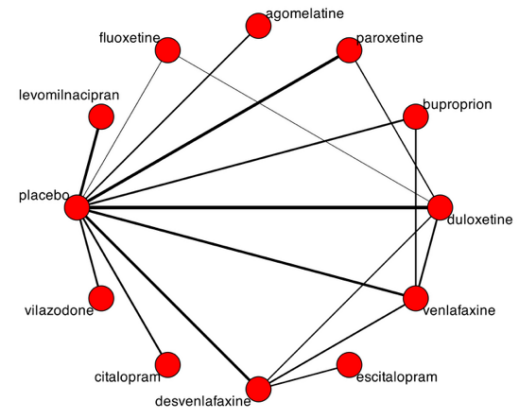
QTc interval

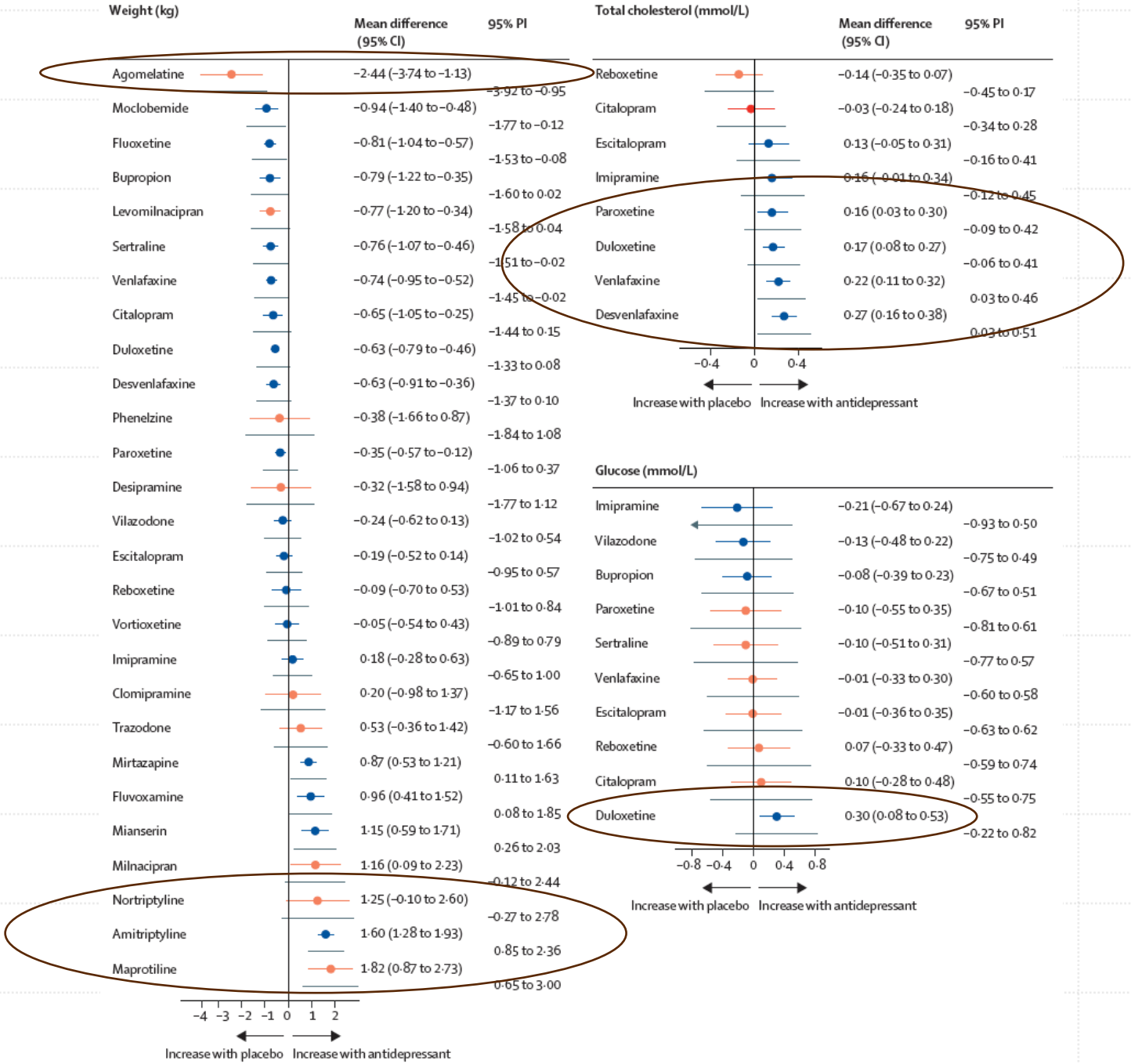


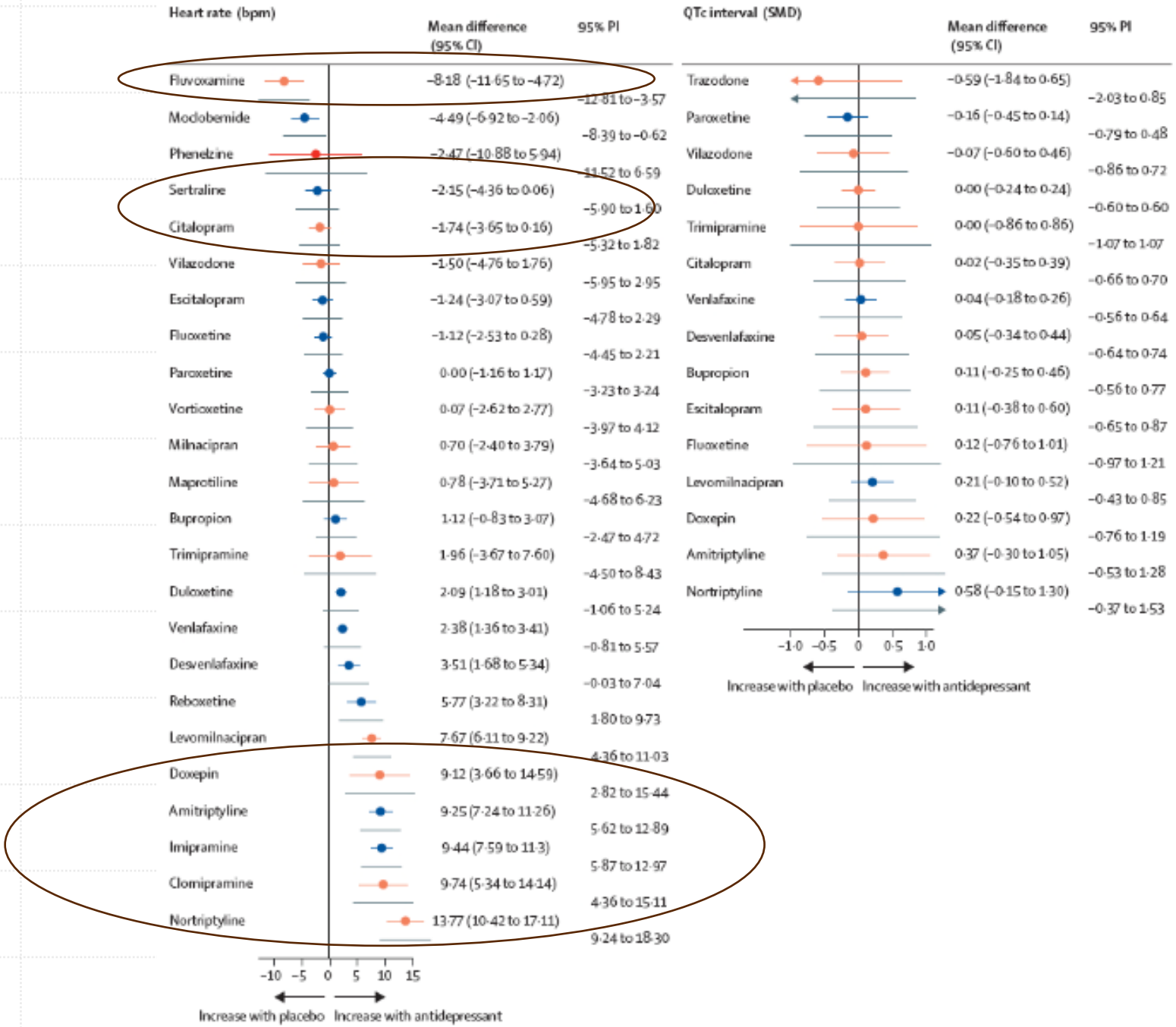
Aspartate transferase

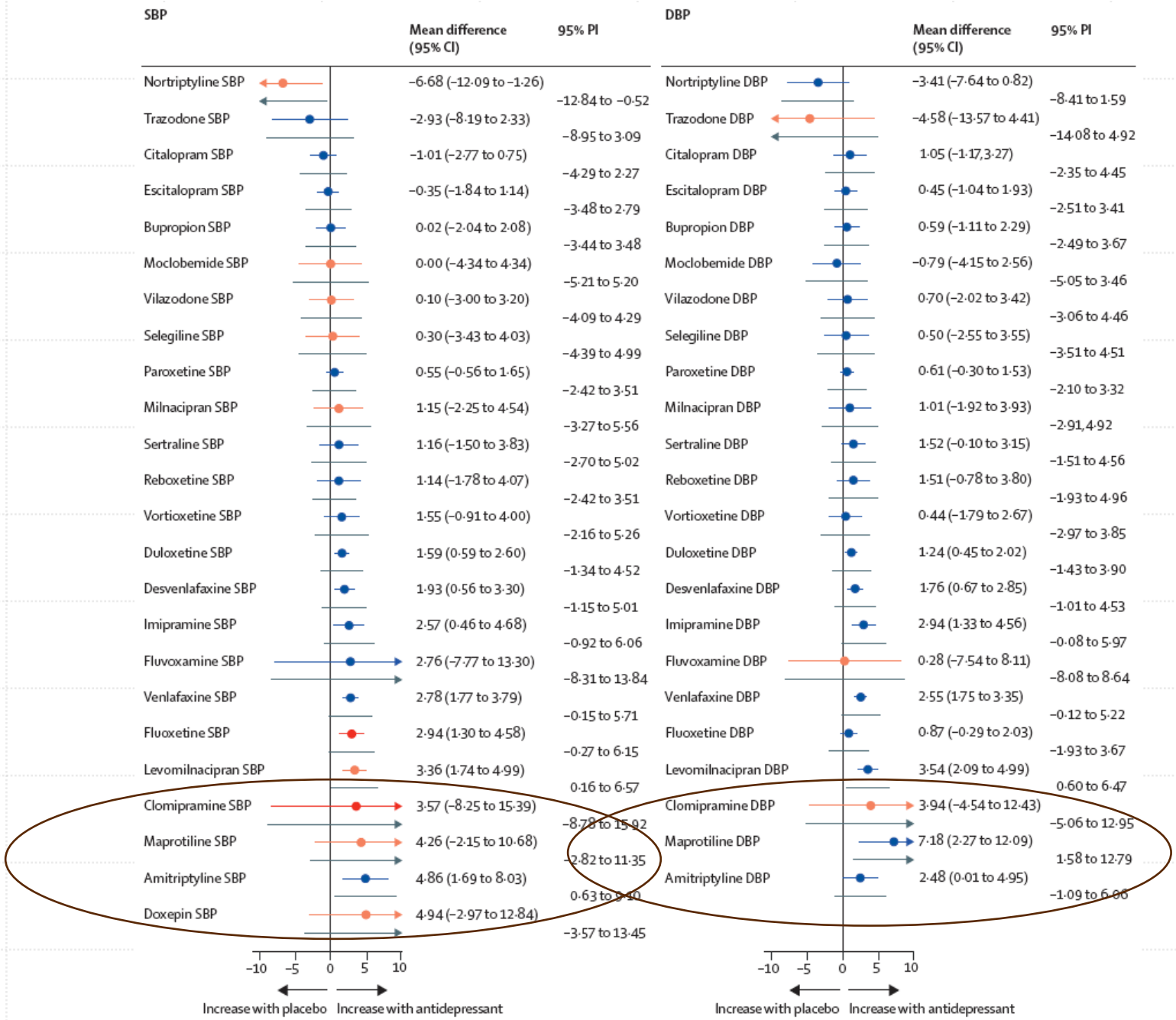


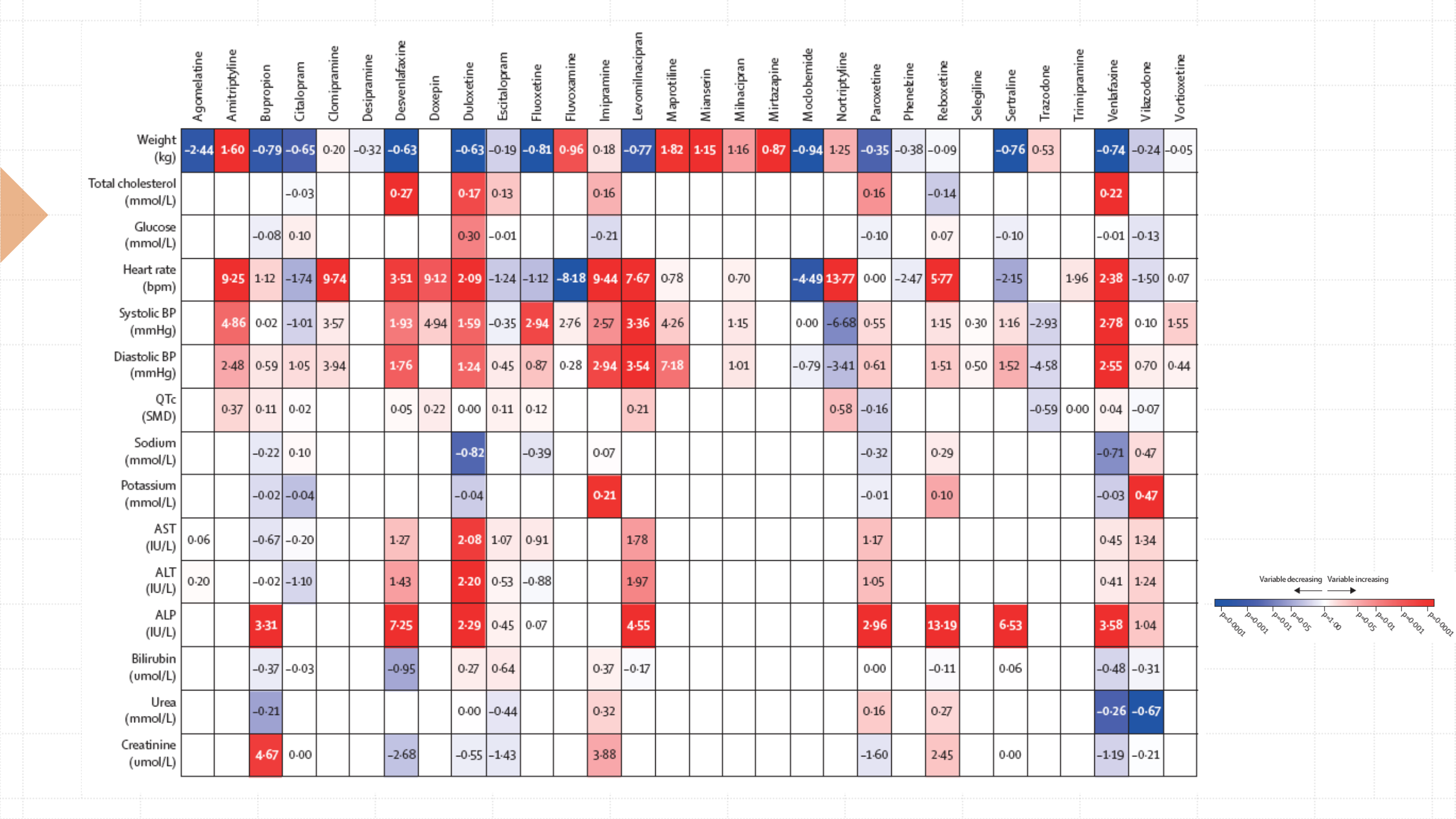
Alanine transaminase




Weight (kg)
Mean difference (95% CI)
95% PI
Agomelatine −2·44 (−3·74 to −1·13) −3·92 to −0·95
Moclobemide −0·94 (−1·40 to −0·48) −1·77 to −0·12
Fluoxetine −0·81 (−1·04 to −0·57) −1·53 to −0·08
Bupropion −0·79 (−1·22 to −0·35) −1·60 to 0·02
Levomilnacipran −0·77 (−1·20 to −0·34) −1·58 to 0·04
Sertraline −0·76 (−1·07 to −0·46) −1·51 to −0·02
Venlafaxine −0·74 (−0·95 to −0·52) −1·45 to −0·02
Citalopram −0·65 (−1·05 to −0·25) −1·44 to 0·15
Duloxetine −0·63 (−0·79 to −0·46) −1·33 to 0·08
Desvenlafaxine −0·63 (−0·91 to −0·36) −1·37 to 0·10
Phenelzine −0·38 (−1·66 to 0·87) −1·84 to 1·08
Paroxetine −0·35 (−0·57 to −0·12) −1·06 to 0·37
Desipramine −0·32 (−1·58 to 0·94) −1·77 to 1·12
Vilazodone −0·24 (−0·62 to 0·13) −1·02 to 0·54
Escitalopram −0·19 (−0·52 to 0·14) −0·95 to 0·57
Reboxetine −0·09 (−0·70 to 0·53) −1·01 to 0·84
Vortioxetine −0·05 (−0·54 to 0·43) −0·89 to 0·79
Imipramine 0·18 (−0·28 to 0·63) −0·65 to 1·00
Clomipramine 0·20 (−0·98 to 1·37) −1·17 to 1·56
Trazodone 0·53 (−0·36 to 1·42) −0·60 to 1·66
Mirtazapine 0·87 (0·53 to 1·21) 0·11 to 1·63
Fluvoxamine 0·96 (0·41 to 1·52) 0·08 to 1·85
Mianserin 1·15 (0·59 to 1·71) 0·26 to 2·03
Milnacipran 1·16 (0·09 to 2·23) −0·12 to 2·44
Nortriptyline 1·25 (−0·10 to 2·60) −0·27 to 2·78
Amitriptyline 1·60 (1·28 to 1·93) 0·85 to 2·36
Maprotiline 1·82 (0·87 to 2·73) 0·65 to 3·00
−4 −3 −2 −1 0 1 2
Increase with placebo
Increase with antidepressant
Total cholesterol (mmol/L)
Mean difference (95% CI)
95% PI
Reboxetine −0·14 (−0·35 to 0·07) −0·45 to 0·17
Citalopram −0·03 (−0·24 to 0·18) −0·34 to 0·28
Escitalopram 0·13 (−0·05 to 0·31) −0·16 to 0·41
Imipramine 0·16 (−0·01 to 0·34) −0·12 to 0·45
Paroxetine 0·16 (0·03 to 0·30) −0·09 to 0·42
Duloxetine 0·17 (0·08 to 0·27) −0·06 to 0·41
Venlafaxine 0·22 (0·11 to 0·32) 0·03 to 0·46
Desvenlafaxine 0·27 (0·16 to 0·38) 0·03 to 0·51
−0·4 0 0·4
Increase with placebo
Increase with antidepressant
Glucose (mmol/L)
Imipramine −0·21 (−0·67 to 0·24) −0·93 to 0·50
Vilazodone −0·13 (−0·48 to 0·22) −0·75 to 0·49
Bupropion −0·08 (−0·39 to 0·23) −0·67 to 0·51
Paroxetine −0·10 (−0·55 to 0·35) −0·81 to 0·61
Sertraline −0·10 (−0·51 to 0·31) −0·77 to 0·57
Venlafaxine −0·01 (−0·33 to 0·30) −0·60 to 0·58
Escitalopram −0·01 (−0·36 to 0·35) −0·63 to 0·62
Reboxetine 0·07 (−0·33 to 0·47) −0·59 to 0·74
Citalopram 0·10 (−0·28 to 0·48) −0·55 to 0·75
Duloxetine 0·30 (0·08 to 0·53) −0·22 to 0·82
−0·8 −0·4 0 0·4 0·8
Increase with placebo
Increase with antidepressant


Heart rate (bpm)
Mean difference (95% CI)
95% PI
Fluvoxamine −8·18 (−11·65 to −4·72) −12·81 to −3·57
Moclobemide −4·49 (−6·92 to −2·06) −8·39 to −0·62
Phenelzine −2·47 (−10·88 to 5·94) −11·52 to 6·59
Sertraline −2·15 (−4·36 to 0·06) −5·90 to 1·60
Citalopram −1·74 (−3·65 to 0·16) −5·32 to 1·82
Vilazodone −1·50 (−4·76 to 1·76) −5·95 to 2·95
Escitalopram −1·24 (−3·07 to 0·59) −4·78 to 2·29
Fluoxetine −1·12 (−2·53 to 0·28) −4·45 to 2·21
Paroxetine 0·00 (−1·16 to 1·17) −3·23 to 3·24
Vortioxetine 0·07 (−2·62 to 2·77) −3·97 to 4·12
Milnacipran 0·70 (−2·40 to 3·79) −3·64 to 5·03
Maprotiline 0·78 (−3·71 to 5·27) −4·68 to 6·23
Bupropion 1·12 (−0·83 to 3·07) −2·47 to 4·72
Trimipramine 1·96 (−3·67 to 7·60) −4·50 to 8·43
Duloxetine 2·09 (1·18 to 3·01) −1·06 to 5·24
Venlafaxine 2·38 (1·36 to 3·41) −0·81 to 5·57
Desvenlafaxine 3·51 (1·68 to 5·34) −0·03 to 7·04
Reboxetine 5·77 (3·22 to 8·31) 1·80 to 9·73
Levomilnacipran 7·67 (6·11 to 9·22) 4·36 to 11·03
Doxepin 9·12 (3·66 to 14·59) 2·82 to 15·44
Amitriptyline 9·25 (7·24 to 11·26) 5·62 to 12·89
Imipramine 9·44 (7·59 to 11·3) 5·87 to 12·97
Clomipramine 9·74 (5·34 to 14·14) 4·36 to 15·11
Nortriptyline 13·77 (10·42 to 17·11) 9·24 to 18·30
−10 −5 0 5 10 15
Increase with placebo
Increase with antidepressant
QTc interval (SMD)
Mean difference (95% CI)
95% PI
Trazodone −0·59 (−1·84 to 0·65) −2·03 to 0·85
Paroxetine −0·16 (−0·45 to 0·14) −0·79 to 0·48
Vilazodone −0·07 (−0·60 to 0·46) −0·86 to 0·72
Duloxetine 0·00 (−0·24 to 0·24) −0·60 to 0·60
Trimipramine 0·00 (−0·86 to 0·86) −1·07 to 1·07
Citalopram 0·02 (−0·35 to 0·39) −0·66 to 0·70
Venlafaxine 0·04 (−0·18 to 0·26) −0·56 to 0·64
Desvenlafaxine 0·05 (−0·34 to 0·44) −0·64 to 0·74
Bupropion 0·11 (−0·25 to 0·46) −0·56 to 0·77
Escitalopram 0·11 (−0·38 to 0·60) −0·65 to 0·87
Fluoxetine 0·12 (−0·76 to 1·01) −0·97 to 1·21
Levomilnacipran 0·21 (−0·10 to 0·52) −0·43 to 0·85
Doxepin 0·22 (−0·54 to 0·97) −0·76 to 1·19
Amitriptyline 0·37 (−0·30 to 1·05) −0·53 to 1·28
Nortriptyline 0·58 (−0·15 to 1·30) −0·37 to 1·53
−1·0 −0·5 0 0·5 1·0
Increase with placebo
Increase with antidepressant


SBP
Mean difference (95% CI)
95% PI
Nortriptyline SBP
−6·68 (−12·09 to −1·26)
−12·84 to −0·52
Trazodone SBP
−2·93 (−8·19 to 2·33)
−8·95 to 3·09
Citalopram SBP
−1·01 (−2·77 to 0·75)
−4·29 to 2·27
Escitalopram SBP
−0·35 (−1·84 to 1·14)
−3·48 to 2·79
Bupropion SBP
0·02 (−2·04 to 2·08)
−3·44 to 3·48
Moclobemide SBP
0·00 (−4·34 to 4·34)
−5·21 to 5·20
Vilazodone SBP
0·10 (−3·00 to 3·20)
−4·09 to 4·29
Selegiline SBP
0·30 (−3·43 to 4·03)
−4·39 to 4·99
Paroxetine SBP
0·55 (−0·56 to 1·65)
−2·42 to 3·51
Milnacipran SBP
1·15 (−2·25 to 4·54)
−3·27 to 5·56
Sertraline SBP
1·16 (−1·50 to 3·83)
−2·70 to 5·02
Reboxetine SBP
1·14 (−1·78 to 4·07)
−2·42 to 3·51
Vortioxetine SBP
1·55 (−0·91 to 4·00)
−2·16 to 5·26
Duloxetine SBP
1·59 (0·59 to 2·60)
−1·34 to 4·52
Desvenlafaxine SBP
1·93 (0·56 to 3·30)
−1·15 to 5·01
Imipramine SBP
2·57 (0·46 to 4·68)
−0·92 to 6·06
Fluvoxamine SBP
2·76 (−7·77 to 13·30)
−8·31 to 13·84
Venlafaxine SBP
2·78 (1·77 to 3·79)
−0·15 to 5·71
Fluoxetine SBP
2·94 (1·30 to 4·58)
−0·27 to 6·15
Levomilnacipran SBP
3·36 (1·74 to 4·99)
0·16 to 6·57
Clomipramine SBP
3·57 (−8·25 to 15·39)
−8·78 to 15·92
Maprotiline SBP
4·26 (−2·15 to 10·68)
−2·82 to 11·35
Amitriptyline SBP
4·86 (1·69 to 8·03)
0·63 to 9·10
Doxepin SBP
4·94 (−2·97 to 12·84)
−3·57 to 13·45
−10 −5 0 5 10
Increase with placebo
Increase with antidepressant
DBP
Mean difference (95% CI)
95% PI
Nortriptyline DBP
−3·41 (−7·64 to 0·82)
−8·41 to 1·59
Trazodone DBP
−4·58 (−13·57 to 4·41)
−14·08 to 4·92
Citalopram DBP
1·05 (−1·17,3·27)
−2·35 to 4·45
Escitalopram DBP
0·45 (−1·04 to 1·93)
−2·51 to 3·41
Bupropion DBP
0·59 (−1·11 to 2·29)
−2·49 to 3·67
Moclobemide DBP
−0·79 (−4·15 to 2·56)
−5·05 to 3·46
Vilazodone DBP
0·70 (−2·02 to 3·42)
−3·06 to 4·46
Selegiline DBP
0·50 (−2·55 to 3·55)
−3·51 to 4·51
Paroxetine DBP
0·61 (−0·30 to 1·53)
−2·10 to 3·32
Milnacipran DBP
1·01 (−1·92 to 3·93)
−2·91,4·92
Sertraline DBP
1·52 (−0·10 to 3·15)
−1·51 to 4·56
Reboxetine DBP
1·51 (−0·78 to 3·80)
−1·93 to 4·96
Vortioxetine DBP
0·44 (−1·79 to 2·67)
−2·97 to 3·85
Duloxetine DBP
1·24 (0·45 to 2·02)
−1·43 to 3·90
Desvenlafaxine DBP
1·76 (0·67 to 2·85)
−1·01 to 4·53
Imipramine DBP
2·94 (1·33 to 4·56)
−0·08 to 5·97
Fluvoxamine DBP
0·28 (−7·54 to 8·11)
−8·08 to 8·64
Venlafaxine DBP
2·55 (1·75 to 3·35)
−0·12 to 5·22
Fluoxetine DBP
0·87 (−0·29 to 2·03)
−1·93 to 3·67
Levomilnacipran DBP
3·54 (2·09 to 4·99)
0·60 to 6·47
Clomipramine DBP
3·94 (−4·54 to 12·43)
−5·06 to 12·95
Maprotiline DBP
7·18 (2·27 to 12·09)
1·58 to 12·79
Amitriptyline DBP
2·48 (0·01 to 4·95)
−1·09 to 6·06
−10 −5 0 5 10
Increase with placebo
Increase with antidepressant


Agomelatine
Amitriptyline
Bupropion
Citalopram
Clomipramine
Desipramine
Desvenlafaxine
Doxepin
Duloxetine
Escitalopram
Fluoxetine
Fluvoxamine
Imipramine
Levomilnacipran
Maprotiline
Mianserin
Milnacipran
Mirtazapine
Moclobemide
Nortriptyline
Paroxetine
Phenelzine
Reboxetine
Selegiline
Sertraline
Trazodone
Trimipramine
Venlafaxine
Vilazodone
Vortioxetine
Weight (kg)
Total cholesterol (mmol/L)
Glucose (mmol/L)
Heart rate (bpm)
Systolic BP (mmHg)
Diastolic BP (mmHg)
QTc (SMD)
Sodium (mmol/L)
Potassium (mmol/L)
AST (IU/L)
ALT (IU/L)
ALP (IU/L)
Bilirubin (umol/L)
Urea (mmol/L)
Creatinine (umol/L)
Variable decreasing
Variable increasing
p=0·0001
p=0·001
p=0·01
p=0·05
p=1·00
p=0·05
p=0·01
p=0·001
p=0·0001

Considerations

- **Why continuous outcomes?**
  - Consistent categorical **thresholds** (e.g., QTc >500 ms) are rarely reported in RCTs. Continuous measures allow estimation of how many patients might cross clinically relevant cut-offs.
- **Risk is incremental, not binary:**
  - Biological risk rises gradually, not abruptly at fixed cut-offs. Modeling continuous changes better reflects real-world risk.
- **Population impact:**
  - Even small cardiometabolic changes can have major effects at scale due to widespread antidepressant use.
- **Weight gain drivers:**
  - Most evident with drugs antagonising **H1 and 5-HT2C receptors** (e.g., mirtazapine, tricyclics), consistent with pharmacology.

Limitations – what about QT prolongation and hyponatraemia?

- **RCT vs real-world discrepancy:**
  - NMA found minimal QTc or sodium changes, but large registry studies link citalopram to highest hyponatraemia and TdP risk.
- **Why the difference?**
  - RCTs: younger, healthier, monotherapy, short-term → underestimates risk.
    Observational: older, comorbid, polypharmacy → higher risk but more confounding.
- **Clinical message:**
  - Combine RCT and real-world data for decision-making; short-term trial data ≠ long-term safety.

Clinical Relevance

- **Population-level impact:**
  - Even small changes in weight, heart rate, or blood pressure can significantly affect cardiovascular risk when scaled to millions of patients.
- **Risk estimates:**
  - +1 kg weight → **+3% CVD risk**
  - +1 bpm HR → **+3% all-cause mortality** (men >50)
  - +1 mmHg SBP → **+1% stroke death risk**
- **Example:**
  - 8 weeks of **amitriptyline** (+1.5 kg, +9 bpm, +5 mmHg SBP) could meaningfully increase long-term cardiovascular risk.

Future directions

- **Long-term safety:**
  - Investigate whether short-term physiological changes (e.g., HR, BP, weight) persist during maintenance therapy.
- **Broader outcomes:**
  - Include other clinically relevant adverse effects (sexual dysfunction, emotional blunting, GI symptoms) alongside physiological measures.
- **Digital decision tools:**
  - Develop and validate tools incorporating these findings for personalized prescribing and shared decision-making.
  - **Psymatik.com**

THANK YOU

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Prof Andrea Cipriani

Psychiatric Imaging Group