Pharmacologic Treatment of Major Depressive Disorder – An Update

Murray Enns MD FRCPC
Professor, Department of Psychiatry
Medical Director, Operational Stress Injury Clinic,
Deer Lodge Centre

Declaration of Conflicts and Copyright Statement

- No conflicts of interest to declare

- *This copy is provided exclusively for research purposes and private study. Any use of the copy for a purpose other than research or private study may require the authorization of the copyright owner of the work in question. Responsibility regarding questions of copyright that may arise in the use of this copy is assumed by the recipient*

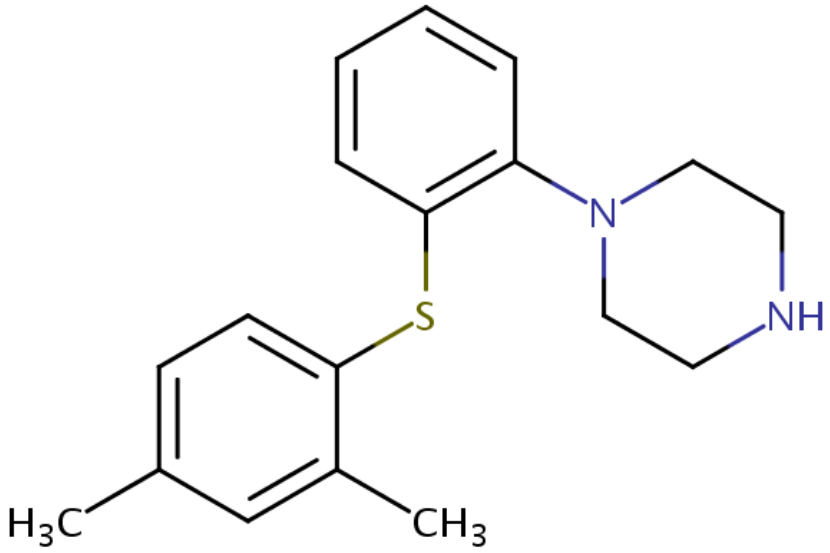
Learning Objectives

- To understand the place of newer antidepressant options in the treatment of major depressive disorder
- To use evidence based best practices for selecting an initial and subsequent antidepressant medications

Overview

- Review of newer antidepressants
  - Vortioxetine
  - Levomilnacipran
  - Vilazodone
- Findings from network meta-analyses
- Management of non-response

Vortioxetine = Trintellix ®



Vortioxetine – Pharmacodynamics

- Multi-modal: SSRI PLUS:
  - 5HT-1A agonist
  - 5HT-1B partial agonist
  - 5HT-1D, 5HT-3, 5HT-7 antagonist
- No other significant affinities for other receptors/transporters/enzymes

Vortioxetine - Pharmacokinetics

- Max plasma level: 7 – 8 hours
- No active metabolites
- Half-life: 57 hours; steady state 12 days
- Linear kinetics at clinically relevant doses

Gonda et al, Expert Opin Drug Discov 2018

Vortioxetine - drug interactions

- Metabolized by CYP-2D6
- Does not induce/inhibit P450 enzymes
- Strong 2D6 inhibitors raise level
  - e.g. bupropion
- Strong P450 inducers reduce level
  - e.g. rifampin, carbamazepine
- SSRI-like pharmacodynamic interactions

Chen et al, Clin Pharmacokinet 2018

Clinical use of vortioxetine

- Once-daily dosing, with or without food
- Dosing range 5 – 20 mg per day
- Usual starting dose of 10 mg per day
- 20 mg per day may be more effective*
  - *Only this dose differentiated from placebo in some US trials
- Positive maintenance therapy data available
- Abrupt discontinuation well tolerated

McIntyre, Neuropsychiatr Dis Treat 2017

Common adverse effects of vortioxetine

- Nausea (26 vs 9 %)
- Diarrhea (8 vs 6 %)
- Dry mouth (7 vs 6 %)
- Dizziness (7 vs 6 %)
- Constipation (5 vs 3 %)
- Vomiting (5 vs 1 %)

Vortioxetine and cognition

- Meta-analysis (9 RCTs) (vortioxetine, duloxetine, paroxetine, citalopram, sertraline, others)
- Antidepressants improved cognition: the most consistent and statistically significant findings (versus placebo):
  - SMD 0.16 for psychomotor speed (DSST)
  - SMD 0.24 for delayed recall (RAVLT)
- Vortioxetine had the largest pooled effect size for psychomotor speed - SMD 0.34

Rosenblat et al, Neuropsych Dis Treat 2015

Limitations

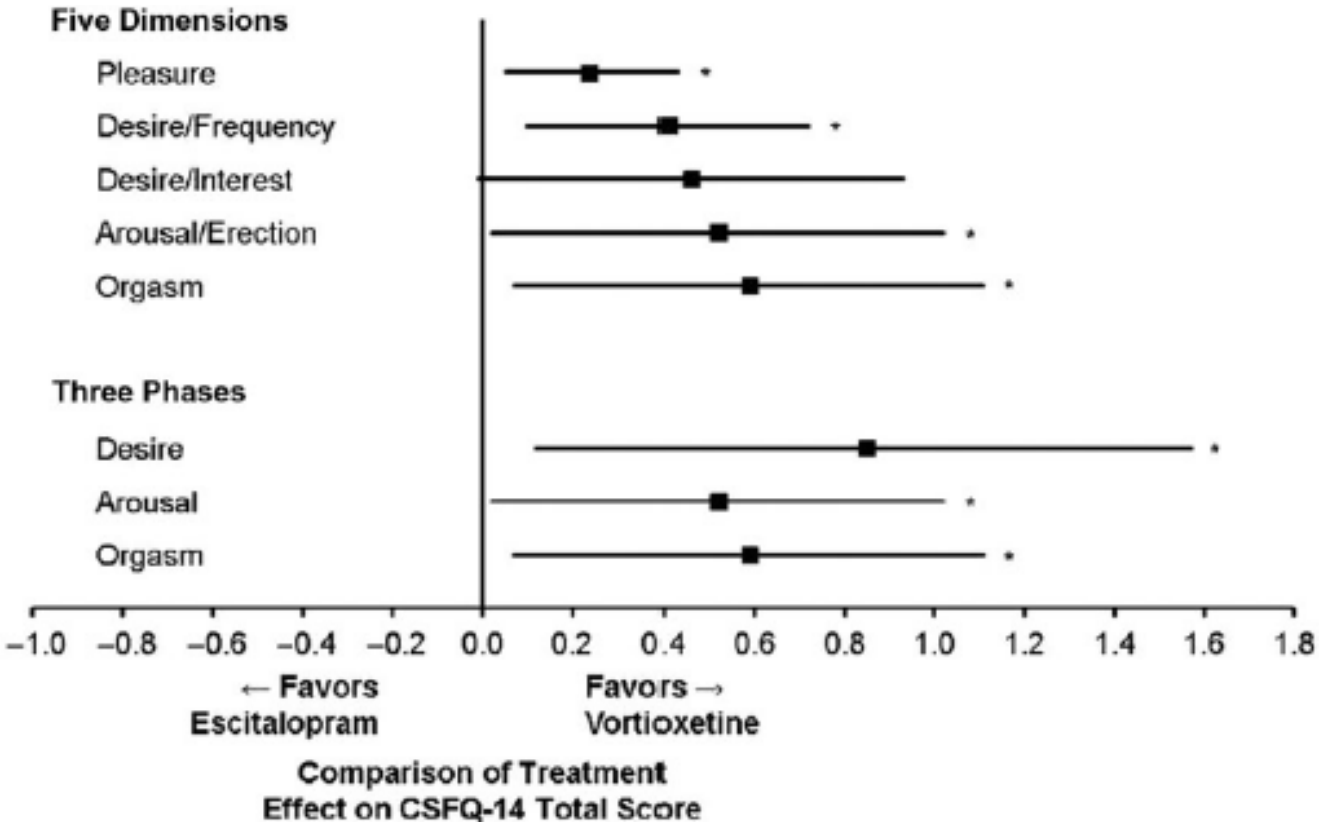
- Industry bias
- Many antidepressant agents not tested
- Heterogeneity of studies
- Uncertainty about the correlation between specific cognitive tests and functional outcomes

Vortioxetine and sexual dysfunction

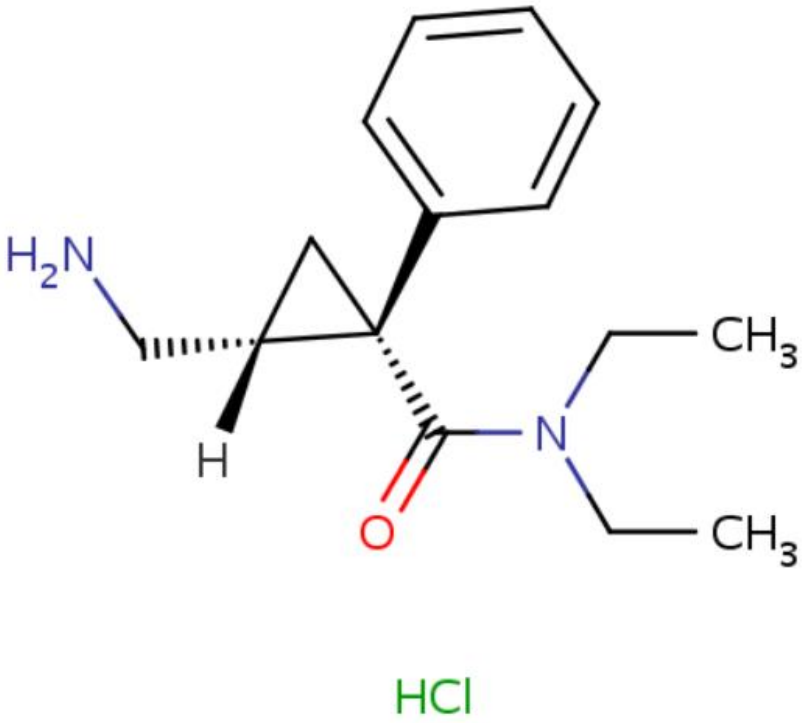
- Vortixetine appears to produce a low incidence of sexual dysfunction
- RCT evidence*: 447 subjects on SSRI/SNRI having sexual dysfunction (TESD) switched to escitalopram or vortioxetine
  - greater improvement with escitalopram in 4/5 domains of CSFQ-14 (see more…)
- New drug label (US) reflects an indication for vortioxetine in “treatment emergent sexual dysfunction”

*Jocobsen et al, J Sexual Med, 2015

Data from Jacobsen et al, 2015



Levomilnacipran ER = Fetzima ®



Note: Racemic “milnacipran” approved for fibromyalgia (US-FDA 2009).

Levomilnacipran ER - pharmacodynamics

- Levomilnacipran is the more active enantiomer of milnacipran
- Serotonin & noradrenaline reuptake inhibitor
- Reuptake inhibition NA > 5HT
  - (for venlafaxine, desvenlafaxine, duloxetine, the reverse holds, ie 5HT > NA reuptake inhibition)
- No other significant receptor affinities

Levomilnacipran ER - pharmacokinetics

- Max plasma level 6 to 8 hours
- No active metabolites
- Half-life: approx. 12 hours
- Linear kinetics at clinically relevant doses

Bruno et al, Curr Neuropharmacology, 2016

Levomilnacipran ER – drug interactions

- Metabolized by CYP-3A4
- Does not induce/inhibit P450 enzymes
- Renal excretion is important, so patients with renal impairment need dose reduction
- Susceptible to 3A4 inhibition
  - e.g. ketoconazole, clarithromycin, grapefruit
- SSRI and SNRI-like pharmacodynamic drug interactions

Scott, CNS Drugs, 2014

Clinical Use of levomilnacipran ER

- Once-daily dosing, with or without food
- Dosing range 20 – 120 mg per day
- Usual starting dose of 20 mg, increase to 40 mg in 2 days, then 40 mg increments
- Discontinuation by gradual dose reduction

Common adverse effects of levomilnacipran

- Nausea (17 vs 6 %)
- Constipation (9 vs 3 %)
- Sweating (9 vs 2 %)
- Increased heart rate (6 vs 1 %)
- Erectile dysfunction (6 vs 1 %)
- Palpitations (5 vs 1 %)

Levomilnacipran effect on motivation/energy

- RCT in MDD (N = 429) levomilnacipran vs placebo
- Measures: Motivation and Energy Inventory (MEI) and Sheehan Disability Scale (SDS)
- Levomilnacipran better than placebo in reducing reducing SDS and increasing MEI
- Increases in Motivation/Energy (MEI) explained the majority of improvement in Disability (SDS)… BUT

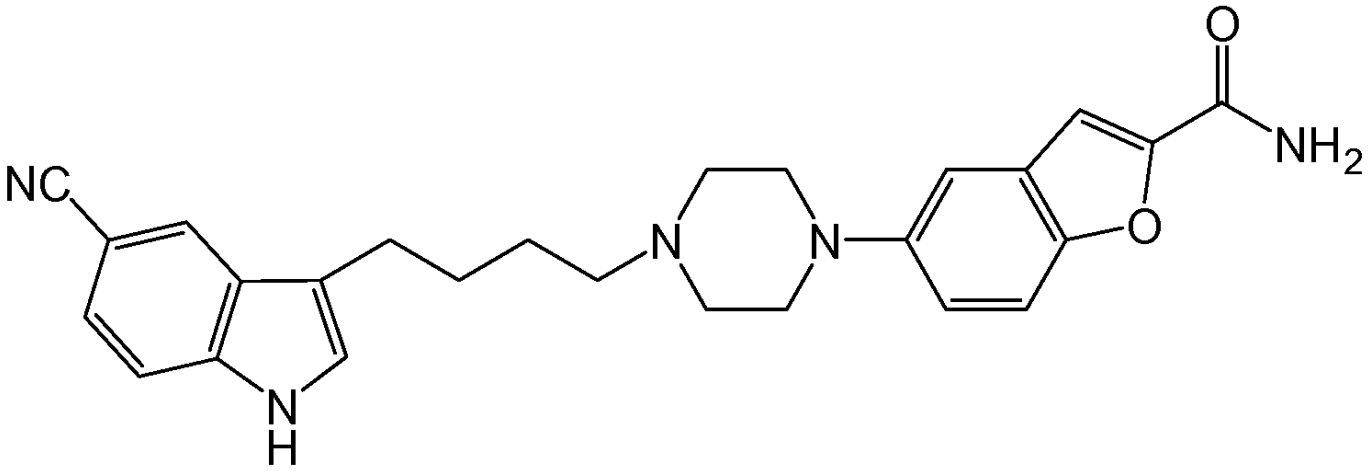
Thase et al, Int Clin Psychopharmacol 2016

Despite the credible concept…

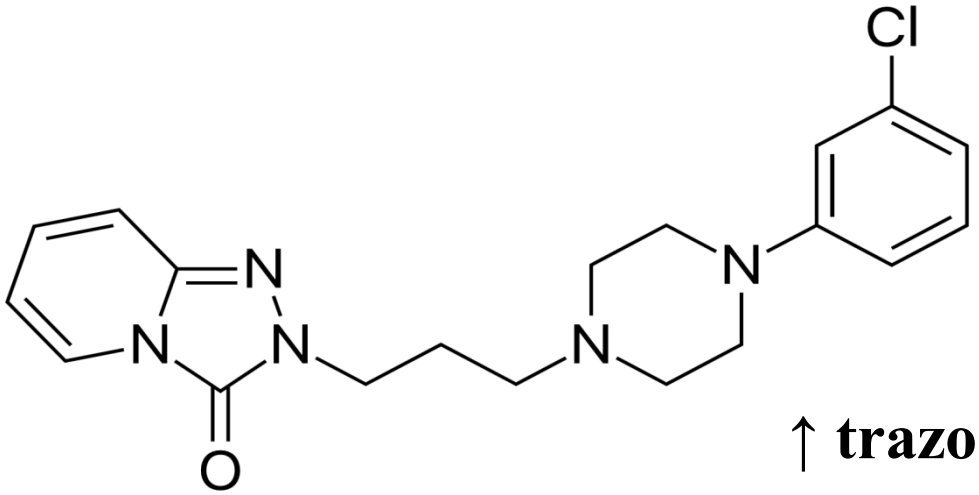
- Post-hoc analysis
- Industry sponsored trial
- Not replicated
- No active comparator medication

- Little weight can be placed on this finding

Vilazodone = Viibryd ®



↑ **vilazodone**



↑ **trazodone**

Vilazodone - Phamacodynamics

- Multi-modal: Potent SSRI PLUS:
  - 5HT-1A partial agonist
- 5HT-1A partial agonism is a shared effect with buspirone
- NOT very similar actions to trazodone (weak SSRI, 5HT-2A antagonist, anti-histamine)
- No affinity for DA or NA reuptake sites, no significant affinity for other 5HT receptors

Vilazodone - Pharmacokinetics

- Max plasma level: 4 – 5 hours
- Absorption strongly affected by food (+)
- Major metabolites are inactive
- Half-life: 24 hours
- Very highly protein bound (96-99%)

Stuivenga et al, Expert Opin Pharmacotherapy, 2018

Vilazodone – drug interactions

- Metabolized primarily by CYP-3A4
- Susceptible to 3A4 inhibition
  - e.g. ketoconazole, clarithromycin, grapefruit
- P450 - 3A4 inducers reduce levels
- May displace other highly protein-bound drugs (e.g. coumadin, phenytoin)
- SSRI-like pharmacodynamic drug interactions

Sahli et al, Exper Opin Drug Discovery, 2016

Clinical use of vilazodone

- Once-daily dosing WITH FOOD
- Target dose = 40 mg per day
- Initiate therapy at 10 mg, increase to 20 mg then 40 mg 7-day intervals (as tolerated)
- Gradual tapering recommended to D/C therapy
- Low incidence of sexual side effects

McIntyre, Neuropsychiatr Dis Treatment, 2017

Common adverse effects of vilazodone

- Diarrhea (28 vs 10 %)
- Nausea (24 vs 7 %)
- Headache (14 vs 14 %)
- Dry mouth (7 vs 5 %)
- Insomnia (6 vs 2 %)
- Somnolence (5 vs 2 %)
- Vomiting (5 vs 2 %)

Newer antidepressants: place in therapy?

- None are covered on MB Health Formulary
- All have drug costs significantly higher than comparators
- Adequate evidence of clinically meaningful advantages is mostly pending
- Vortioxetine and (probably) vilazodone have advantages pertaining to sexual adverse effects
- Other potential advantages are conjectural

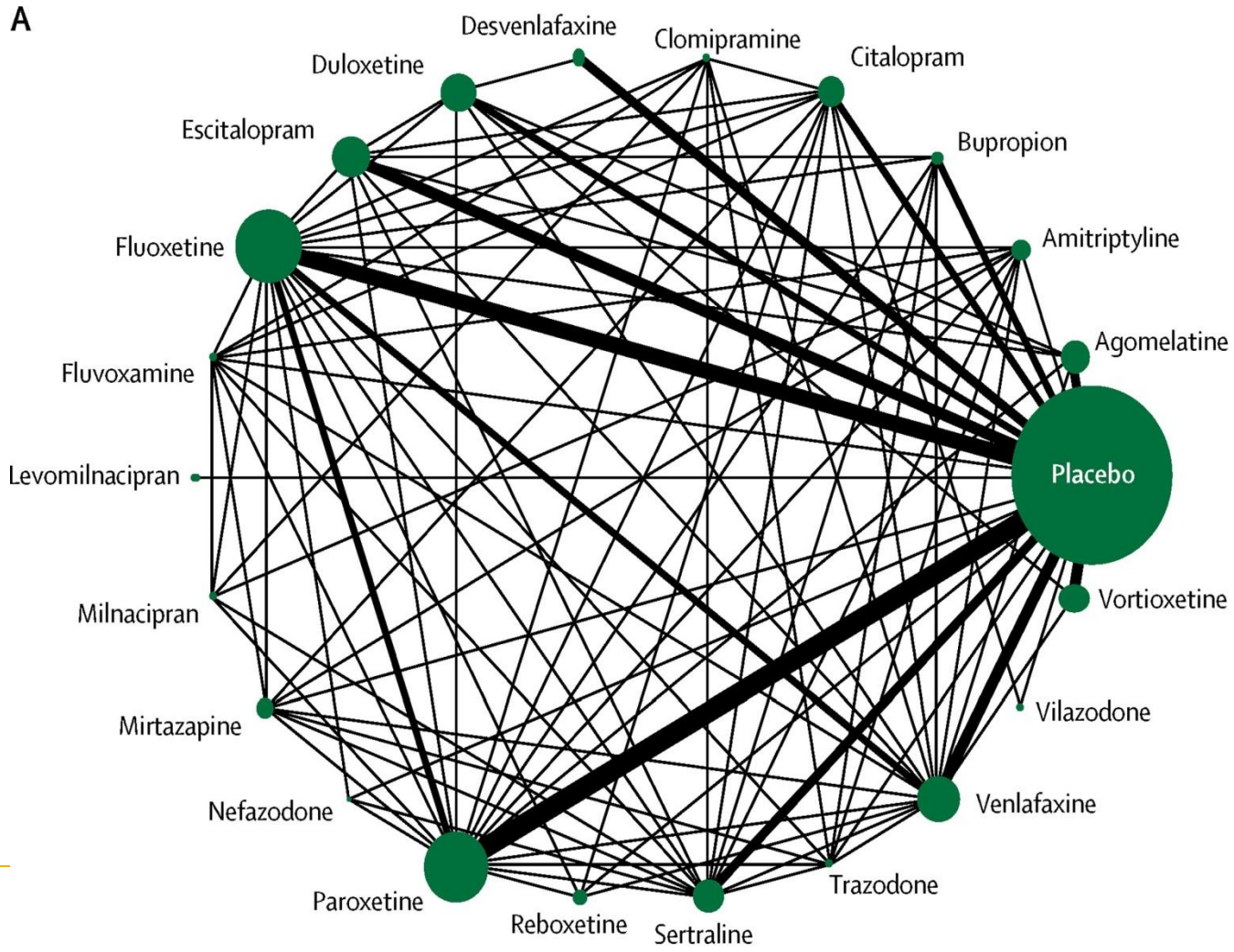
Are all antidepressants equally efficacious?

- Typical antidepressant RCTs are conducted against placebo or only one comparator
- The “best” evidence currently available is derived from meta-analysis, and contemporary guidelines use meta-analytic data extensively (e.g. CANMAT guidelines)
- “Network” meta-analysis increases available information by allowing both DIRECT and INDIRECT comparisons of agents AND making use of all available evidence

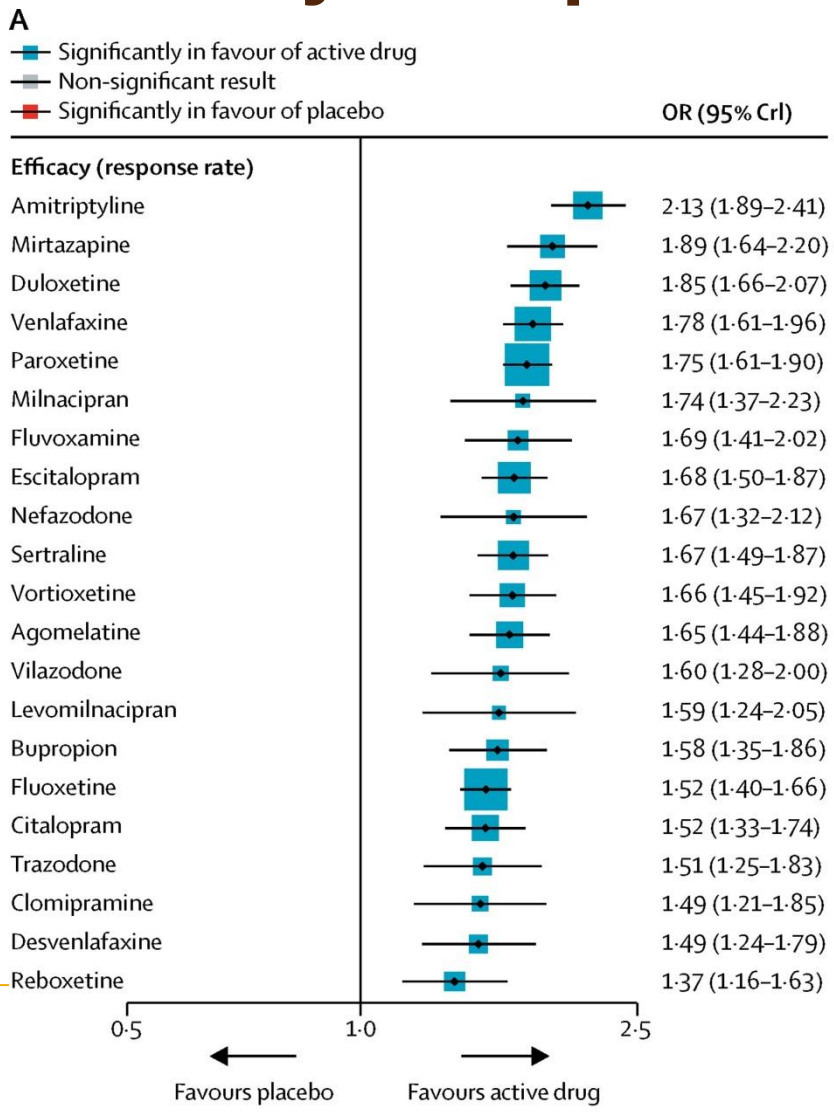
Cipriani et al, Lancet, April 2018: "Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for Major Depressive Disorder"

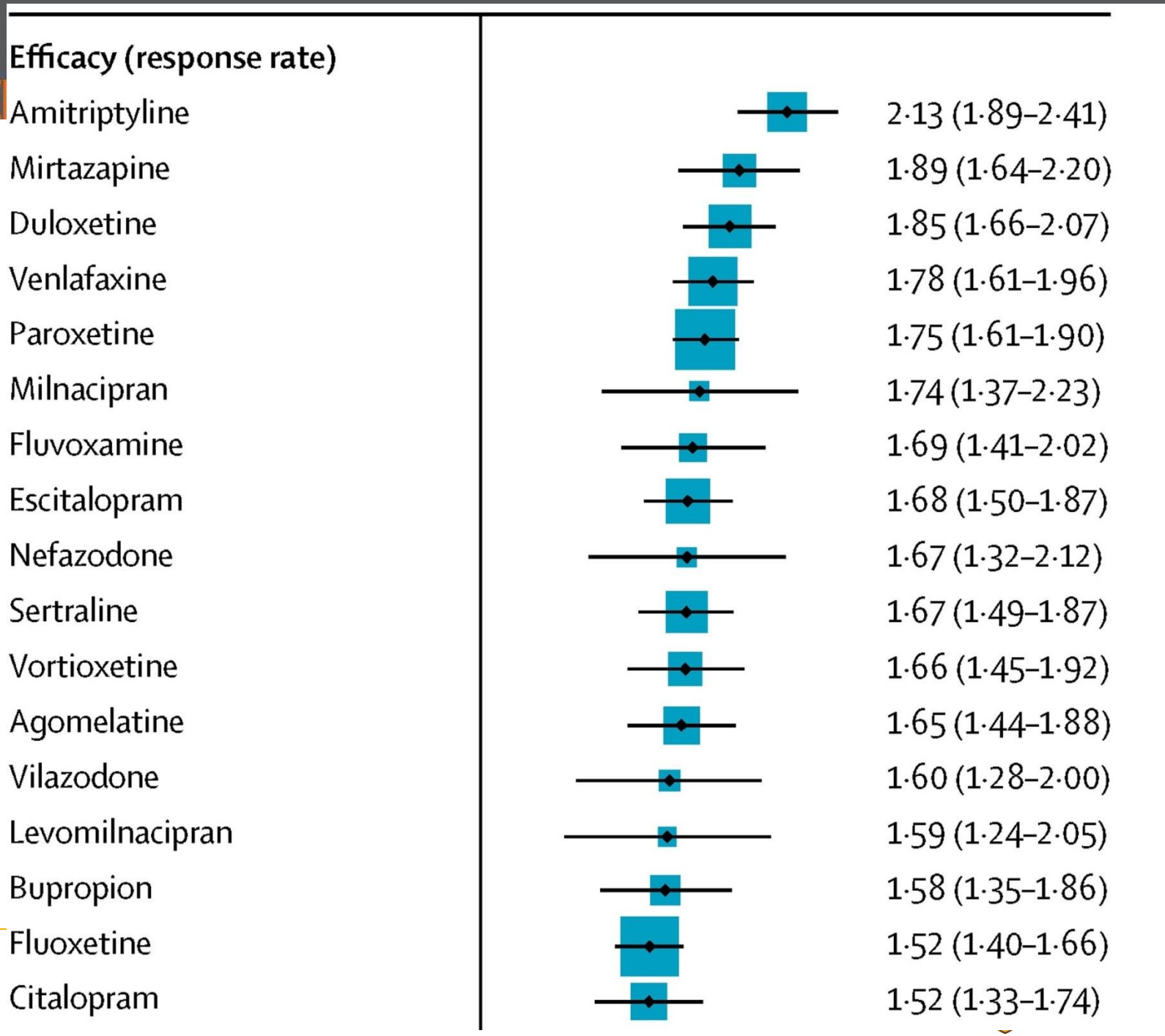
- Updated huge network meta-analysis
- 522 double-blinded clinical trials included
- 116,477 adult participants
- Mean age 44 years; 62% women
- 87,052 active medication; 29,425 placebo
- Median duration of treatment = 8 weeks
- 409/522 studies were pharma-funded

Network Efficacy Comparisons (Cipriani, 2018)

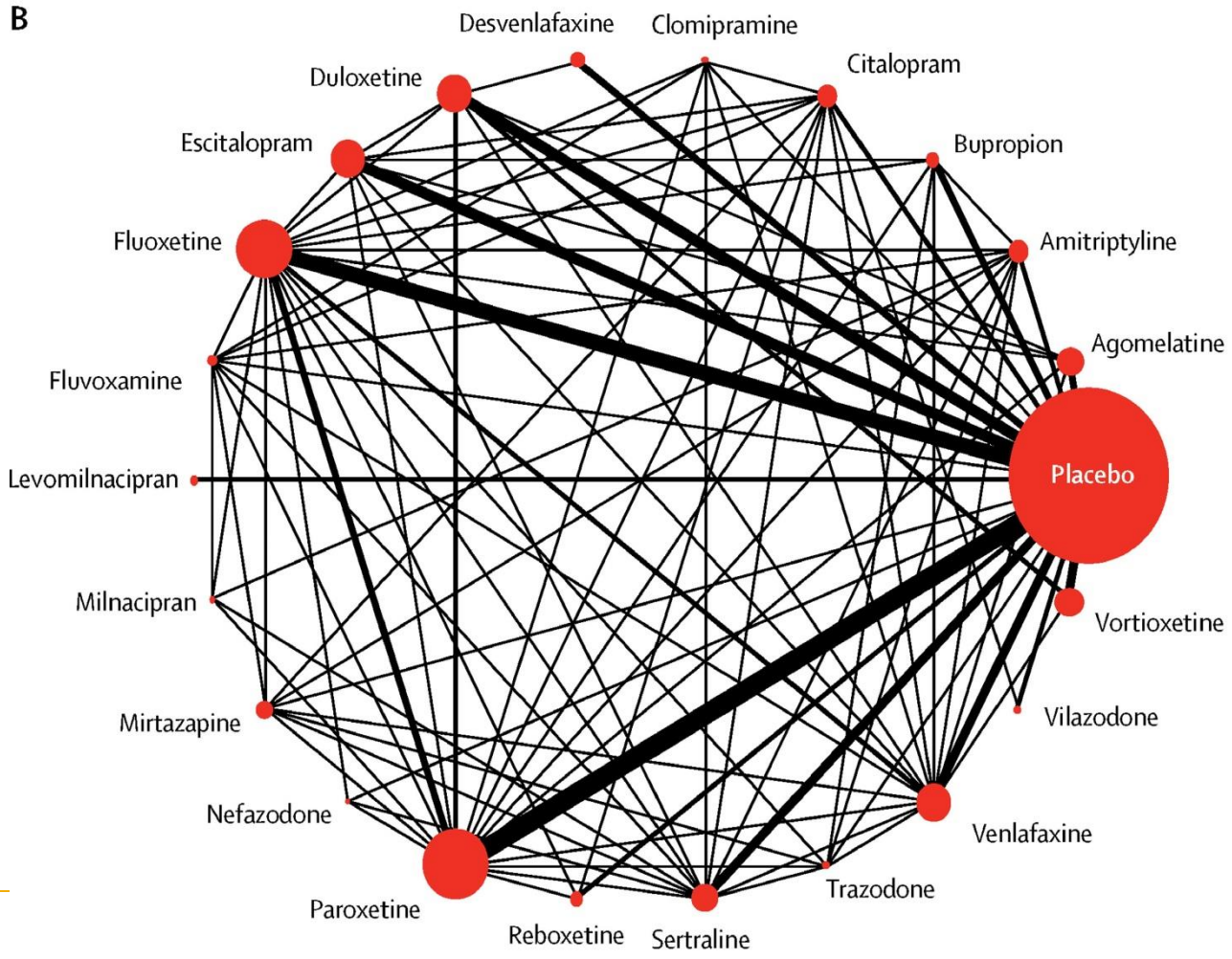


Results: Efficacy Comparisons

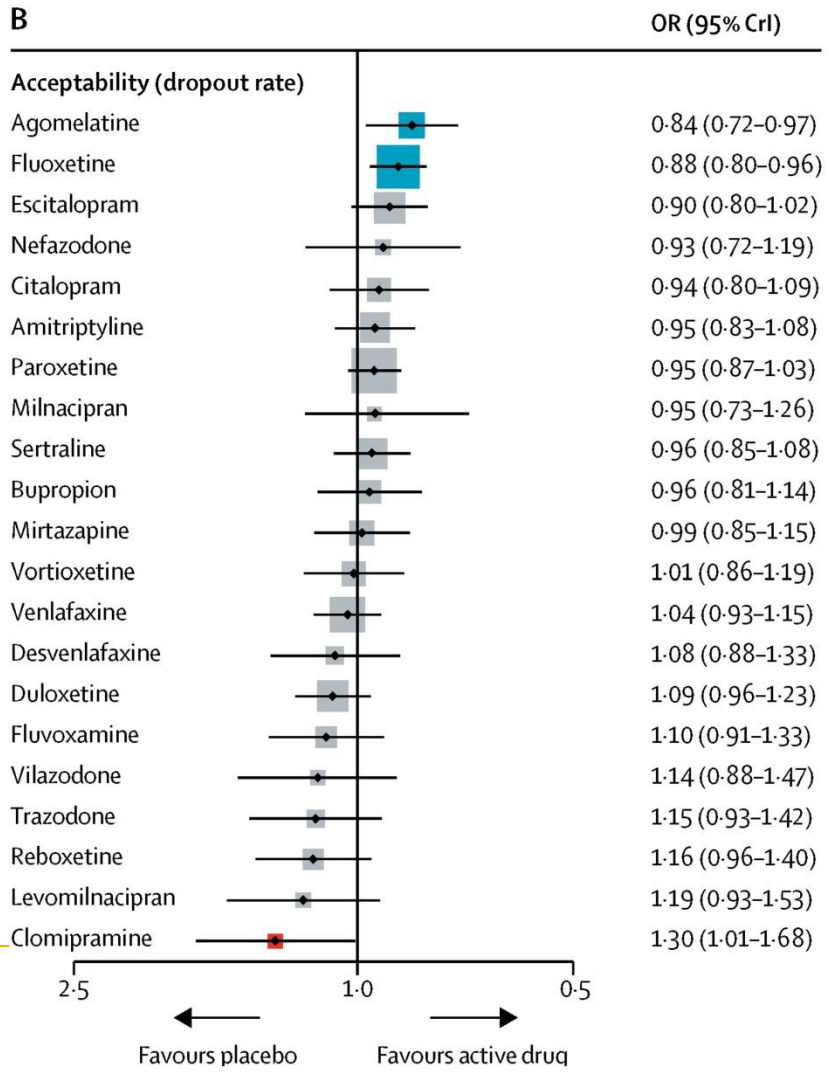


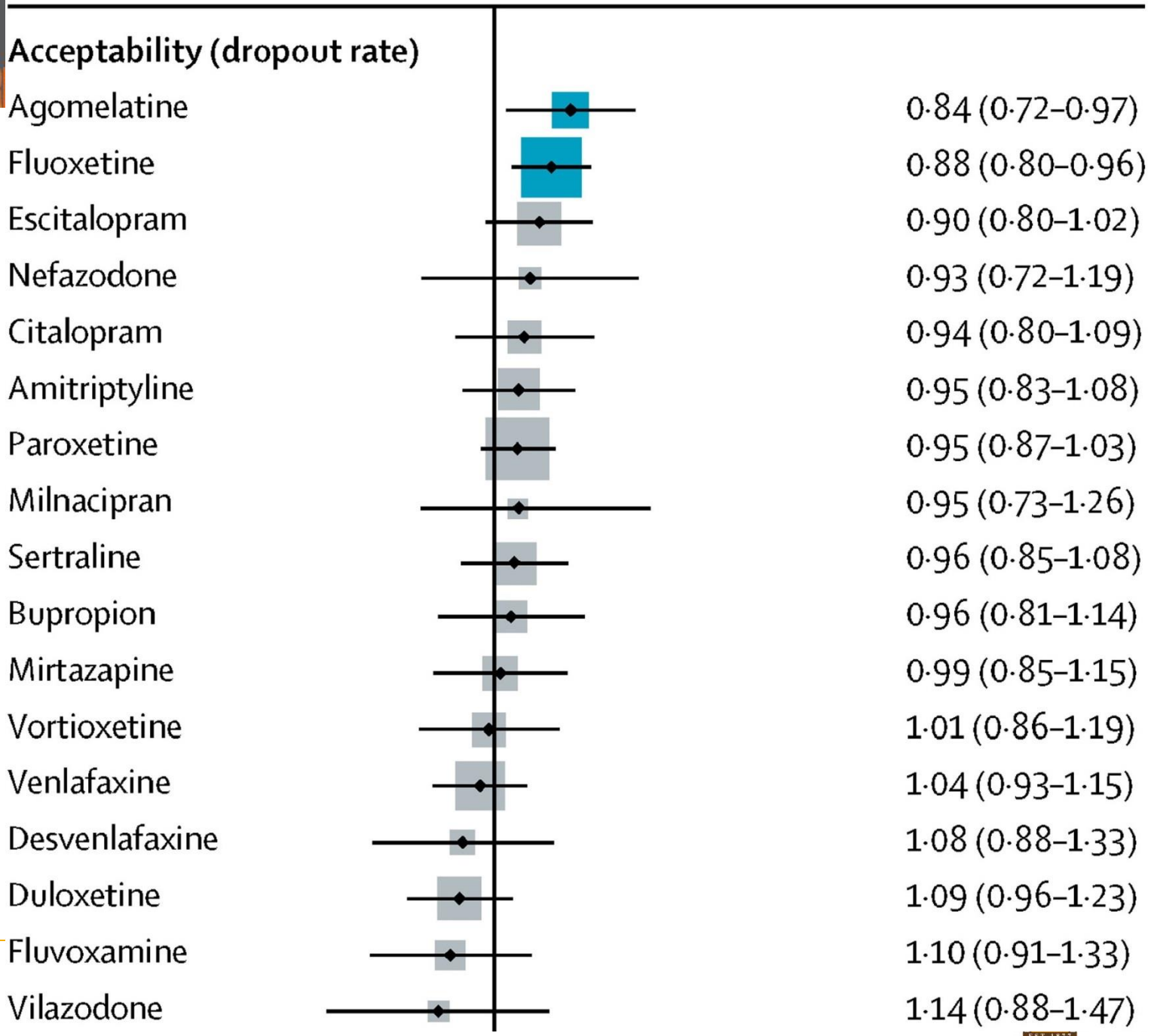

Efficacy (response rate)
Amitriptyline 2·13 (1·89–2·41)
Mirtazapine 1·89 (1·64–2·20)
Duloxetine 1·85 (1·66–2·07)
Venlafaxine 1·78 (1·61–1·96)
Paroxetine 1·75 (1·61–1·90)
Milnacipran 1·74 (1·37–2·23)
Fluvoxamine 1·69 (1·41–2·02)
Escitalopram 1·68 (1·50–1·87)
Nefazodone 1·67 (1·32–2·12)
Sertraline 1·67 (1·49–1·87)
Vortioxetine 1·66 (1·45–1·92)
Agomelatine 1·65 (1·44–1·88)
Vilazodone 1·60 (1·28–2·00)
Levomilnacipran 1·59 (1·24–2·05)
Bupropion 1·58 (1·35–1·86)
Fluoxetine 1·52 (1·40–1·66)
Citalopram 1·52 (1·33–1·74)

Network Acceptability Comparisons (Cipriani, 2018)



Results: Acceptability Comparisons




Acceptability (dropout rate)
Agomelatine 0·84 (0·72–0·97)
Fluoxetine 0·88 (0·80–0·96)
Escitalopram 0·90 (0·80–1·02)
Nefazodone 0·93 (0·72–1·19)
Citalopram 0·94 (0·80–1·09)
Amitriptyline 0·95 (0·83–1·08)
Paroxetine 0·95 (0·87–1·03)
Milnacipran 0·95 (0·73–1·26)
Sertraline 0·96 (0·85–1·08)
Bupropion 0·96 (0·81–1·14)
Mirtazapine 0·99 (0·85–1·15)
Vortioxetine 1·01 (0·86–1·19)
Venlafaxine 1·04 (0·93–1·15)
Desvenlafaxine 1·08 (0·88–1·33)
Duloxetine 1·09 (0·96–1·23)
Fluvoxamine 1·10 (0·91–1·33)
Vilazodone 1·14 (0·88–1·47)

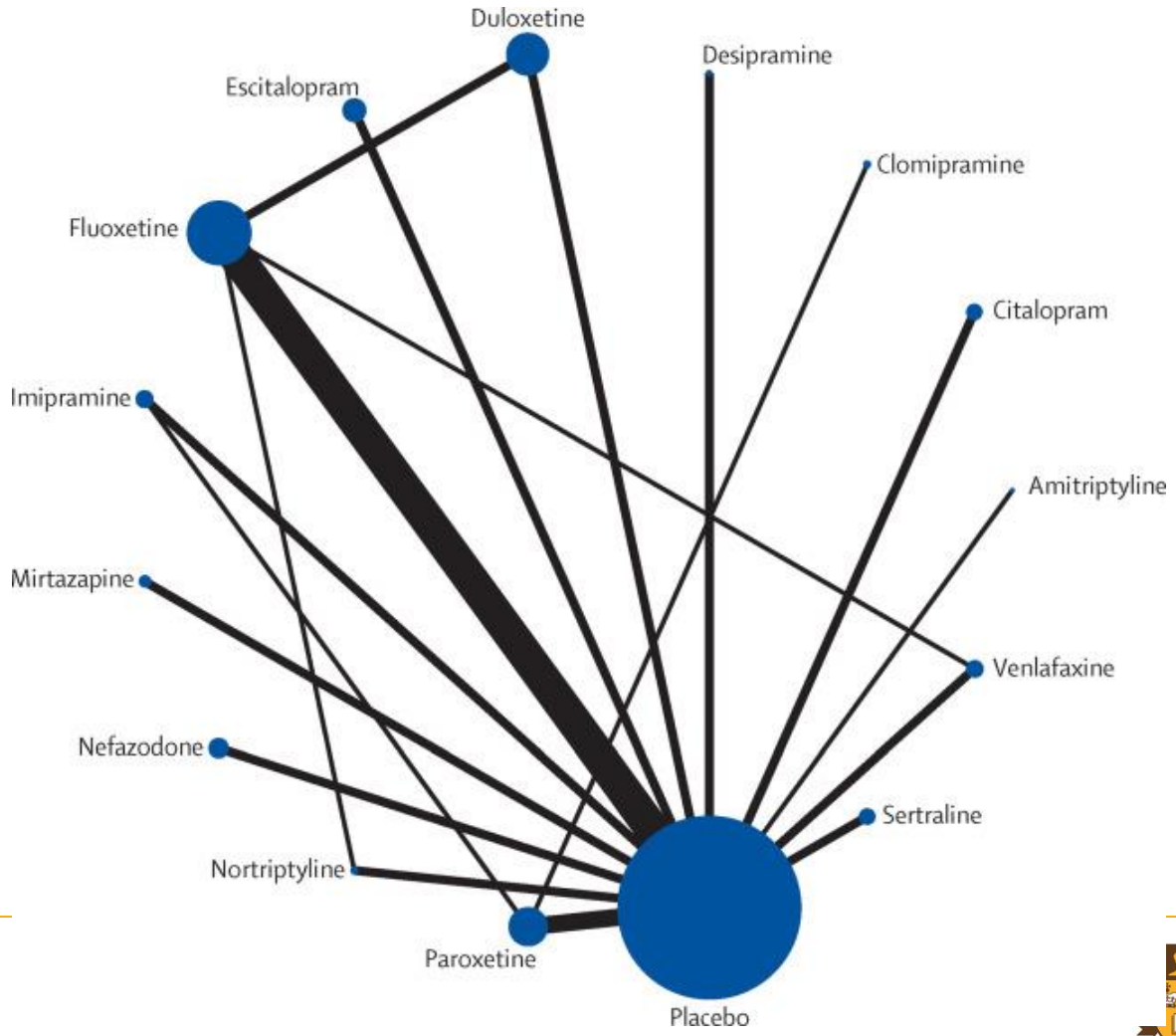
Efficacy and Acceptability in "Head to Head" Trials

- Superior efficacy – 7 agents: ***agomelatine***, amitriptyline, ***escitalopram***, mirtazapine, paroxetine, venlafaxine, ***vortioxetine***
  - Odds ratios ranging 1.19 to 1.96 vs other ADs
- Superior acceptability – ***agomelatine***, citalopram, ***escitalopram***, fluoxetine, sertraline, ***vortioxetine***
  - Odds ratios ranging 0.51 to 0.84 vs other ADs

Clinical application of results?

- In the absence of other considerations, may consider three (two) “best” overall
- Severity - may consider other highly efficacious agents (e.g. amitriptyline, venlafaxine, mirtazapine)
- Multiple intolerances – may consider other highly acceptable agents (e.g. sertraline, fluoxetine)
- Consider prior history of antidepressant response
- May consider specific side effect implications (e.g. weight gain, sedation, activation, insomnia)
- Consider co-morbidities and evidence base for efficacy in these concurrent conditions

What about children and adolescents?



Cipriani et al, Lancet, 2016

Summary of Network Meta Analysis for Child and Adolescent MDD

- Quality of evidence for most comparisons was low
- In terms of efficacy, only fluoxetine was better than placebo:
  (SMD −0·51, 95% CI −0·99 to −0·03)
- In terms of tolerability, fluoxetine was the best drug and imipramine the worst

Management of Incomplete or Non-Response

- Much weaker evidence base
- Incomplete or non-response to an initial antidepressant is common:
  - 1/3 remission
  - 1/3 meaningful improvement, not remission
  - 1/3 limited or no improvement

General Options for Incomplete or Non-Response

- Optimization of dose
- Switch to alternative treatment
- Augmentation (adding another Rx)
- Combination (adding another antidepressant)

What did STAR*D tell us about "next steps"?

- STAR*D = Sequences Treatment Alternatives to Relieve Depression
- Large, inclusive clinical trial, multiple stages, initial phase = Rx citalopram
- Equipoise stratified randomized design: mimics "real-world" practice…
- Measurement-based care (QIDS)
- Rx doses optimized at each step

Step 2 *switch therapy* in STAR*D

- (Citalopram discontinued & new Rx added; subjects tended to have less improvement with - or intolerance of - citalopram)
- Venlafaxine XR – remission rate 25.0%
- Bupropion SR – remission rate 25.5%
- Sertraline – remission rate 26.8%

Rush & Jain, Handb Exp Pharmacol, 2018

Step 2 *combination therapy* in STAR*D

- (Ongoing treatment with citalopram; most participants had had partial response)
- Buspirone added - remission rate 32.9%
- Bupropion SR added -remission rate 39.0%

Step 2 *cognitive behavior therapy* in STAR*D

- (CBT was available as a “switch” option OR as an “augmentation” option)
- Compared to medication switch options, CBT showed similar remission rates, CBT was better tolerated
- Compared to medication augmentation CBT showed similar remission rates, but medication augmentation had faster onset.

Thase et al, Am J Psychiatr, 2007

Cochrane Review, "Psychological Therapies for Treatment Resistant Depression" (Ijaz et al, 2018)

- Examined studies ADDING psychotx to "usual care" (antidepressant Rx) in adults
- Six trials (N=698) included; moderate quality evidence overall
- CBT(3); IPT(1); ST-dynamic(1); DBT(1)
- RR for remission 1.92 (CI 1.46 – 2.52)
- More serious adverse events (4.2% vs none) in "usual care" group (suicide attempt, hospitalization, exacerbation of depression)

And finally, a few newer TRD studies:

- **VAST-D**
  (VA Augmentation and Switching Treatments for Improving Depression Outcomes)
- **SUN☺D**
  (Strategic Use of New-Generation Antidepressants for Depression)
- **MIR**
  (Mirtazapine Added to SSRIs or SNRIs for Treatment Resistant Depression in Primary Care)

The VAST-D Randomized Clinical Trial

- US VA study of 1522 patients with MDD
- Non response to adequate antidepressant trial (dose, duration) – SSRI/SNRI/Mirtaz
- Randomized for 12 weeks in three groups:
  - Switch to BUPROPION (N = 511)
  - Augment with BUPROPION (N = 506)
  - Augment with ARIPIPRAZOLE (N = 505)
- Included a 24 week continuation phase

Mohamed et al, JAMA, 2017

VAST-D Participants

- Predominantly male (85%)
- Mean age 54 ± 12 years
- Predominantly chronic symptoms (median of 33 months)
- Mean of 2.3 ± 1.6 prior antidepressant treatments

VAST-D Summary of Efficacy Results

- Remission (QIDS-16 ≤ 5) at Week 12:
  - Bupropion switch – 22.3%
  - Bupropion augment – 26.9%
  - Aripiprazole augment – 28.9% (*p=.02 vs switch)

- Response (50% QIDS reduction) at Week 12:
  - Bupropion switch – 62.4%
  - Bupropion augment – 65.6%
  - Aripiprazole augment – 74.3% (p<.003 vs others)

VAST-D Summary of Adverse Effects
(focus on significant differences between groups)

Adverse effect	Bupropion switch	Bupropion augment	Aripiprazole augment
Nervousness	**24.3%**	**22.5%**	16.5%
Irritability	**6.3%**	**2.8%**	1.4%
Sedation	7.2%	7.9%	**14.5%**
Akathisia	4.3%	5.3%	**14.9%**
>7% weight gain (12 weeks)	2.3%	1.9%	**9.5%**
>7% weight gain (36 weeks)	5.2%	5.2%	**25.2%**

SUN☺D

(Kato et al, BMC Medicine, 2018)

- 2011 people, previously untreated MDD
- Step 1 – cluster randomized 48 clinics to titrate sertraline to EITHER 50 or 100 mg per day in the first three weeks
- Step 2 – randomize non-remitters to three groups (to week 9):
  - Continue sertraline
  - Add mirtazapine
  - Switch to mirtazapine

SUN☺D – Main outcomes

- Sertraline 50 vs 100 mg groups showed no difference in PHQ9 scores at week 9
- In comparison to continuing sertraline:
  - Addition of mirtazapine: PHQ-9 -0.99 points*
    and OR for remission = 1.80*
  - Switching to mirtazapine: PHQ-9 -1.01 points*
    and OR for remission = 1.51**

* $p < .001$; ** $p = .004$

MIR Trial

Kessler et al, British Medical Journal, 2018

- 480 adults, 70% women, with TRD in primary care practices
- All used an SSRI/SNRI for 6 weeks but had persisting depression (minimum BDI≥ 14), 2/3 were severely depressed
- Randomized to (added) Rx and followed up at 12, 24 and 52 weeks
  - placebo N = 239
  - mirtazapine 30 mg N = 241

MIR – main results (BDI scores)

Group	Baseline	Week 12	Week 24	Week 52
Mirtazapine	**31.5** (10.2)	**18.0** (12.3)	**17.3** (12.9)	**16.8** (12.7)
Placebo	**30.6** (9.6)	**19.7** (12.4)	**18.2** (12.6)	**16.7** (12.2)

Authors' conclusion:
"This study did not find evidence of a clinically important benefit of mirtazapine in addition to an SSRI/SNRI over placebo in TRD"

Summary

- New antidepressant treatment options have novel mechanisms and some potentially promising qualities, but are expensive, and not yet on MB Drug Formulary
- Meta-analytic data supports first-line use of escitalopram, vortioxetine, and *agomelatine,* unless other clinical considerations prevail
- Second line treatment options are varied and incompletely studied:
  - Switch when there has been no response
  - Consider augmentation/combination for partial responders
  - Consider psychotherapy options when available

- **QUESTIONS?**