Antidepressiva - Hur gör man?

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Depression

- Är en folksjukdom, med hög prevalens
- Är episodisk, > 50% recidiverande
- Obehandlad kan den pågå i över 6 mån
  - med ökad risk för recidiv
  - Ökad risk för kontinuerligt funktionsförlust
- Medelålder vid debut kring 30 års åldern

MDD Diagnostic Criteria: *DSM-5*

MDD diagnosis requires the presence of symptom 1, 2, or both and at least 5 of 9 total symptoms, which must persist for at least 2 weeks

1. Depressed mood for most of the day, nearly every day, based on self-report or observation of others
2. Markedly diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day
3. Significant weight loss when not dieting or weight gain (> 5% change in body weight in a month)
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day
8. Diminished ability to think or concentrate, or indecisiveness nearly every day
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. 2013.[12]

Table 8: Disability classes for the GBD study, with examples of long-term disease and injury sequelae falling in each class[a]

Disability class	Severity weights	Conditions[b]
I	0.00–0.02	Stunting due to malnutrition, schistosomiasis infection, long-term scarring due to burns (less than 20% of body)
II	0.02–0.12	Amputated finger, asthma case, edentulism, mastectomy, severe anaemia, stress incontinence
III	0.12–0.24	Angina, HIV not progressed to AIDS, infertility, alcohol dependence and problem use, low vision (<6/18, >3/60), rheumatoid arthritis
IV	0.24–0.36	Amputated arm, congestive heart failure, deafness, drug dependence, Parkinson disease, tuberculosis
V	0.36–0.50	Bipolar affective disorder, mild mental retardation, neurological sequelae of malaria, recto-vaginal fistula
VI	0.50–0.70	AIDS cases not on antiretroviral drugs, Alzheimer and other dementias, blindness, Down syndrome
VII	0.70–1.00	Active psychosis, severe depression, severe migraine, quadriplegia, terminal stage cancer

[a] Based on average severity weight globally for both sexes and all ages in the GBD 2004 update.

[b] Conditions are listed in the disability class for their global average weight. Most conditions will have distributions of severity spanning more than one disability class, potentially up to all seven.

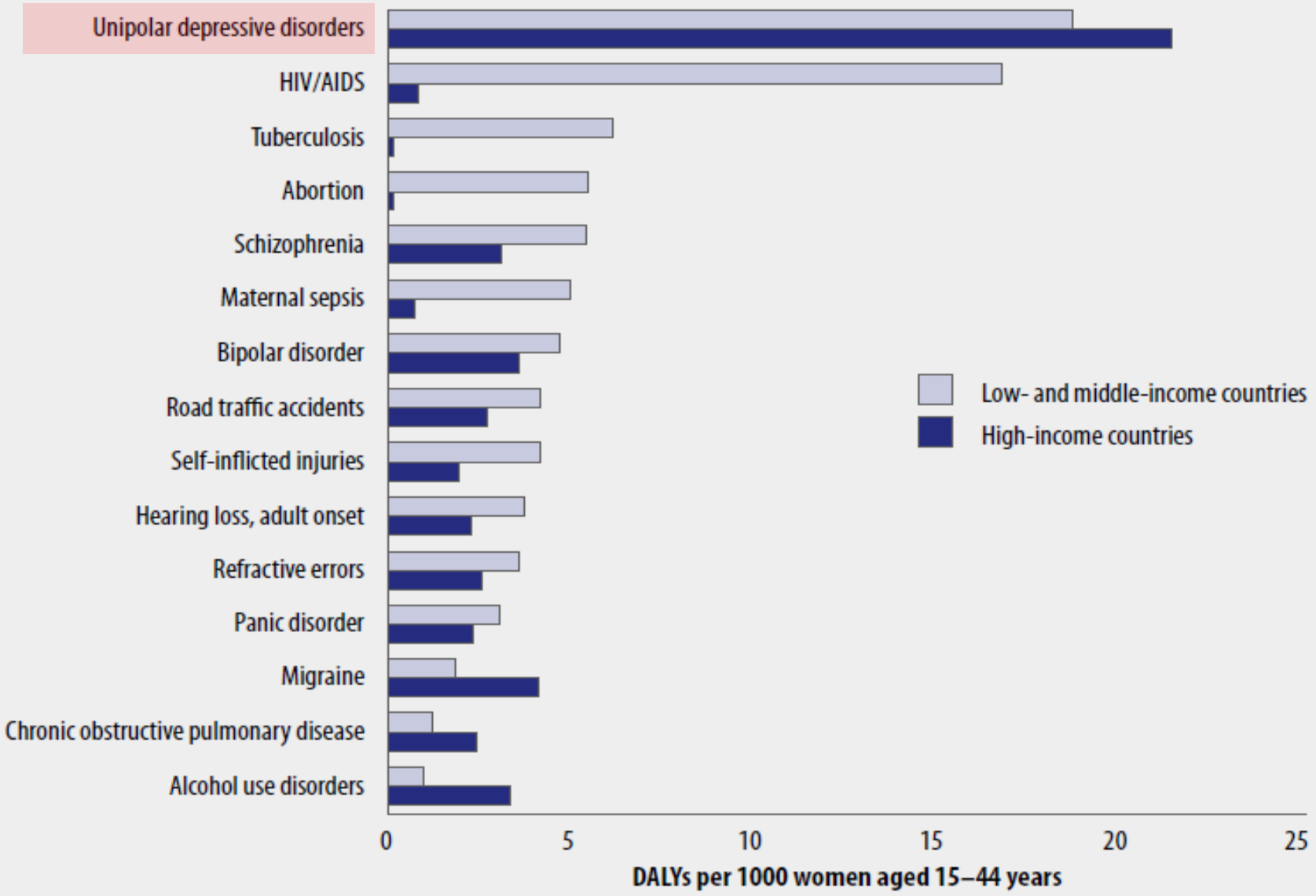
Table 13: Leading causes of burden of disease (DALYs), countries grouped by income, 2004

	Disease or injury	DALYs (millions)	Per cent of total DALYs		Disease or injury	DALYs (millions)	Per cent of total DALYs
	World				*Low-income countries*[a]		
1	Lower respiratory infections	94.5	6.2	1	Lower respiratory infections	76.9	9.3
2	Diarrhoeal diseases	72.8	4.8	2	Diarrhoeal diseases	59.2	7.2
3	Unipolar depressive disorders	65.5	4.3	3	HIV/AIDS	42.9	5.2
4	Ischaemic heart disease	62.6	4.1	4	Malaria	32.8	4.0
5	HIV/AIDS	58.5	3.8	5	Prematurity and low birth weight	32.1	3.9
6	Cerebrovascular disease	46.6	3.1	6	Neonatal infections and other[b]	31.4	3.8
7	Prematurity and low birth weight	44.3	2.9	7	Birth asphyxia and birth trauma	29.8	3.6
8	Birth asphyxia and birth trauma	41.7	2.7	8	Unipolar depressive disorders	26.5	3.2
9	Road traffic accidents	41.2	2.7	9	Ischaemic heart disease	26.0	3.1
10	Neonatal infections and other[b]	40.4	2.7	10	Tuberculosis	22.4	2.7
	Middle-income countries				*High-income countries*		
1	Unipolar depressive disorders	29.0	5.1	1	Unipolar depressive disorders	10.0	8.2
2	Ischaemic heart disease	28.9	5.0	2	Ischaemic heart disease	7.7	6.3
3	Cerebrovascular disease	27.5	4.8	3	Cerebrovascular disease	4.8	3.9
4	Road traffic accidents	21.4	3.7	4	Alzheimer and other dementias	4.4	3.6
5	Lower respiratory infections	16.3	2.8	5	Alcohol use disorders	4.2	3.4
6	COPD	16.1	2.8	6	Hearing loss, adult onset	4.2	3.4
7	HIV/AIDS	15.0	2.6	7	COPD	3.7	3.0
8	Alcohol use disorders	14.9	2.6	8	Diabetes mellitus	3.6	3.0
9	Refractive errors	13.7	2.4	9	Trachea, bronchus, lung cancers	3.6	3.0
10	Diarrhoeal diseases	13.1	2.3	10	Road traffic accidents	3.1	2.6

COPD, chronic obstructive pulmonary disease.

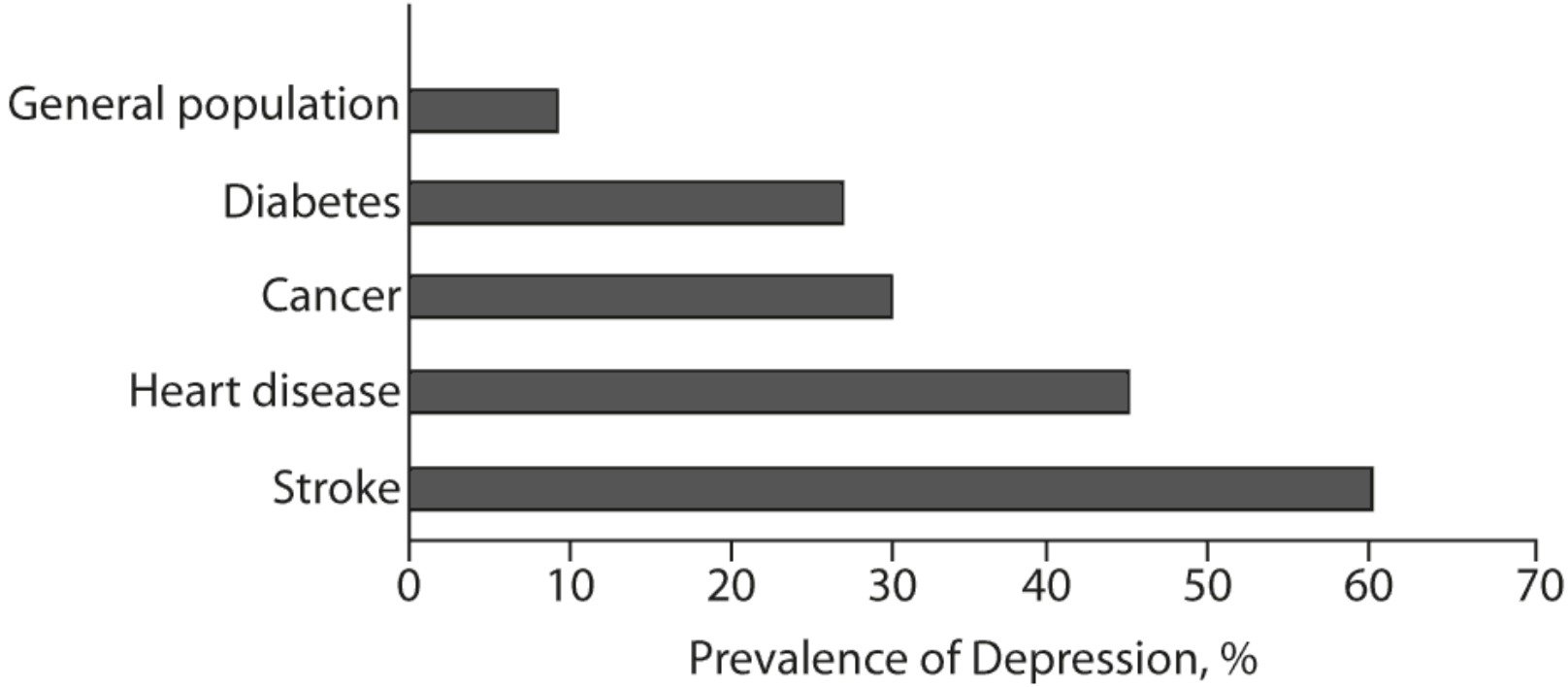
[a] Countries grouped by gross national income per capita (see Annex C, Table C2).
[b] This category also includes other non-infectious causes arising in the perinatal period apart from prematurity, low birth weight, birth trauma and asphyxia. These non-infectious causes are responsible for about 20% of DALYs shown in this category.

Figure 23: Leading causes of disease burden for women aged 15–44 years, high-income countries, and low- and middle-income countries, 2004



Depression and Chronic Diseases: It Is Time for a Synergistic Mental Health and Primary Care Approach

Figure 1. Prevalence of Depression in Major Chronic Illnesses



Voinov, Richie, Bailey. Prim Care Companion CNS Disord 2013;15(2):

Farmakoterapi – antidepressiva läkemedel

- 38 olika anti-depressiva
  - SSRI (citalopram, escitalopram, sertralin, osv)
  - NRI (reboxetin / Edronax)
  - SNRI (venlafaxin, duloxetin, TCA)
  - NDRI (bupropion)
  - Receptorantagonister (mirtazapin, mianserin)
  - Multimodala
    - Agomelatin: M1/M2 agonist & 5-HT2C antagonist
    - Vortioxetin: 5-HT återupttagshämmare, agonist på 5-HT1A, partiell agonist på 5-HT1B och antagonist på 5-HT3, 5-HT1D och 5-HT7)
  - Enzymhämare (Nardil, Parnate, Aurorix)

Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Cipriani et al. Lancet 2009; 373: 746–58*

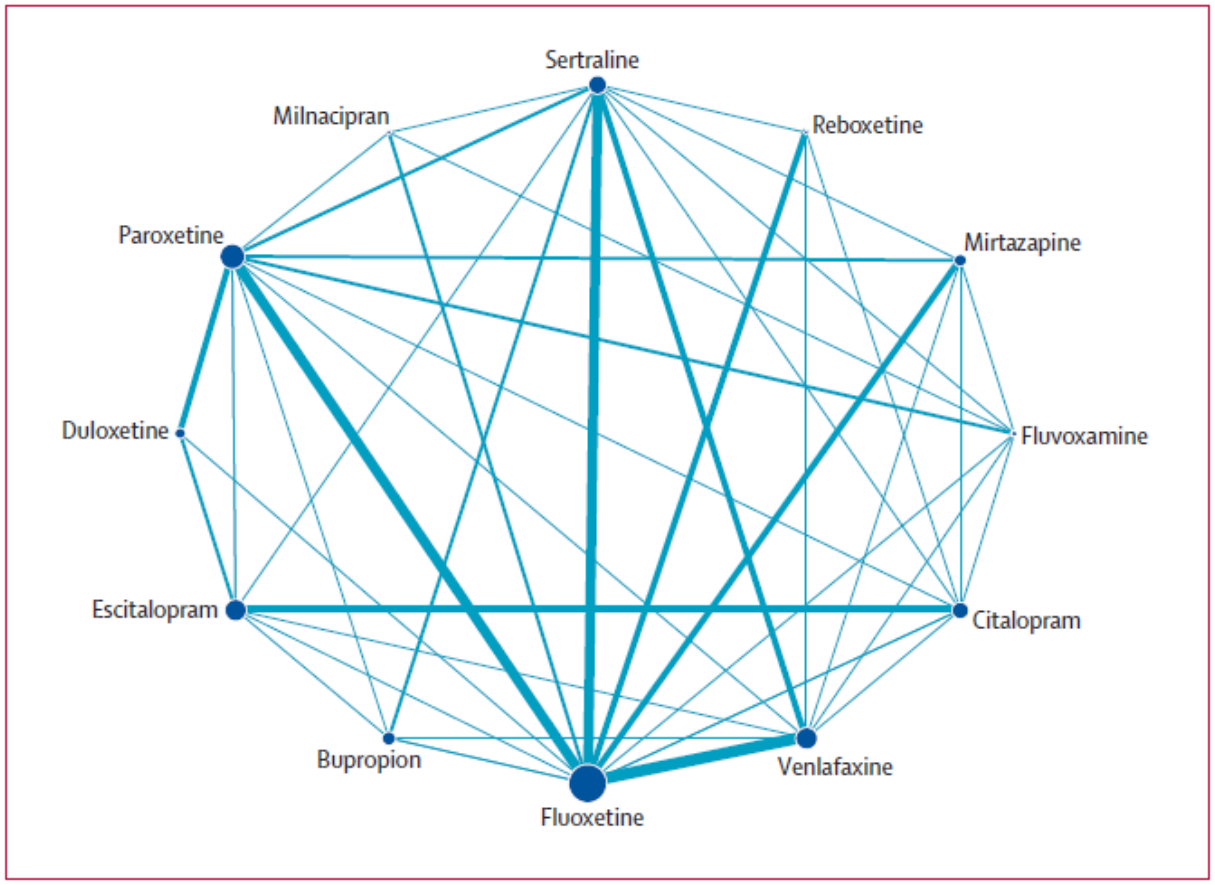


Figure 2: **Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)**

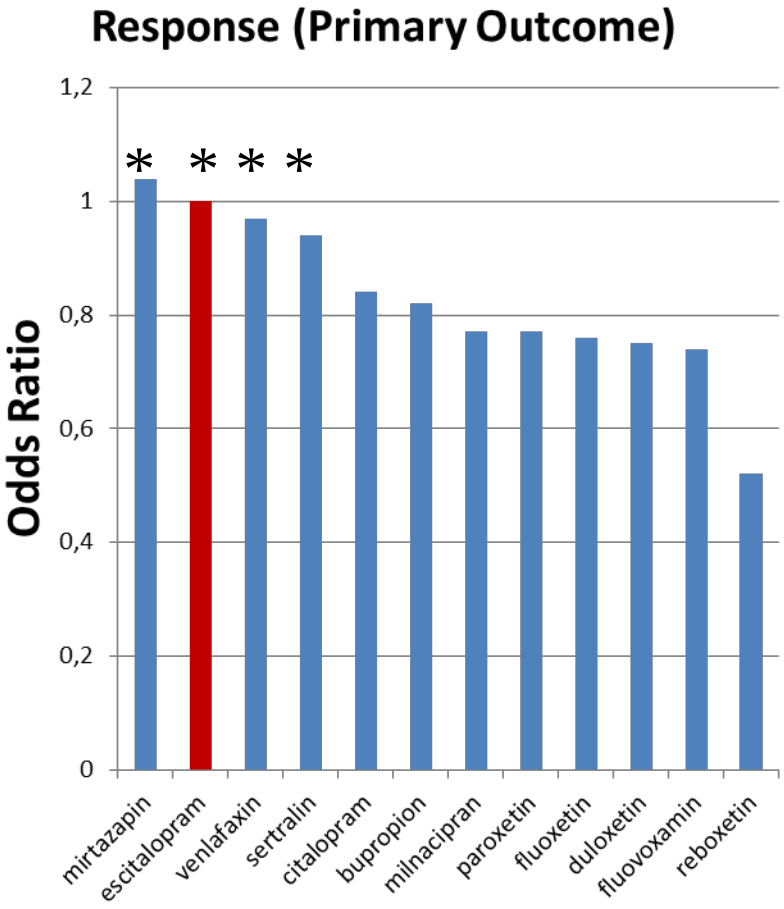
Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Cipriani et al. Lancet 2009; 373: 746–58*

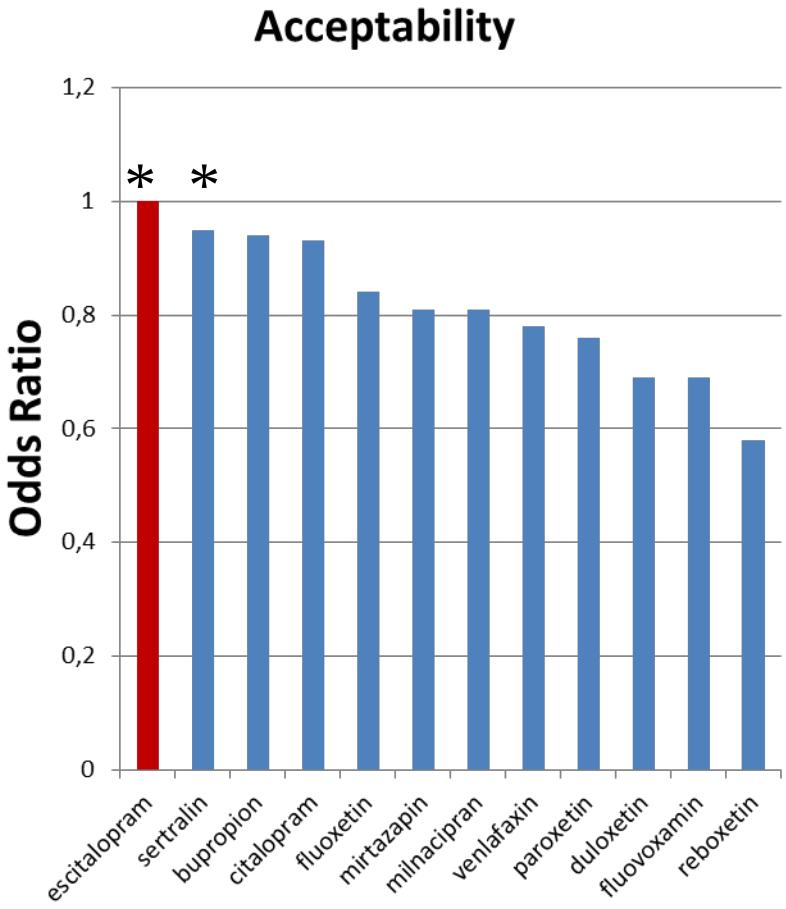
Efficacy (response rate) (95% CI) | Comparison | Acceptability (dropout rate) (95% CI)

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

Figure 3: Efficacy and acceptability of the 12 antidepressants

Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Cipriani et al. Lancet 2009; 373: 746–58*



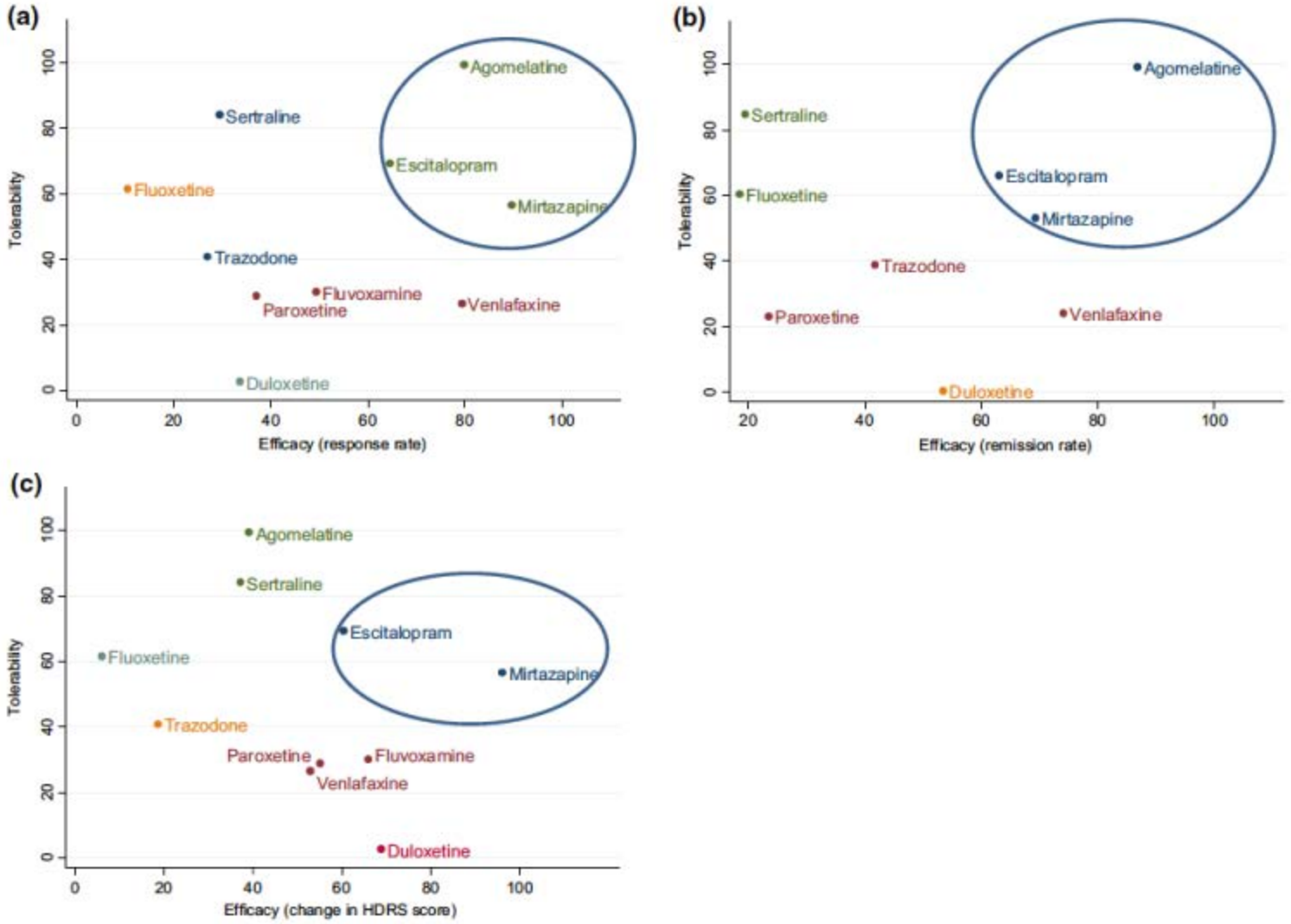


Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Cipriani et al. Lancet 2009; 373: 746–58*

- Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine , and reboxetine . Reboxetine was significantly less efficacious than all the other antidepressants tested.

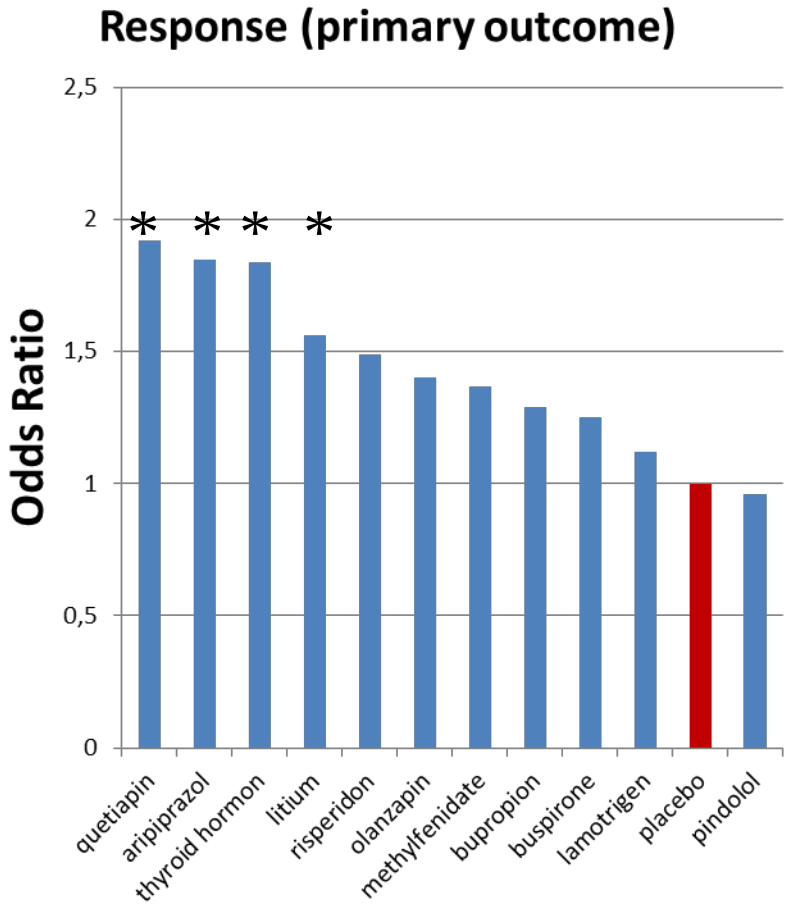
- Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine.

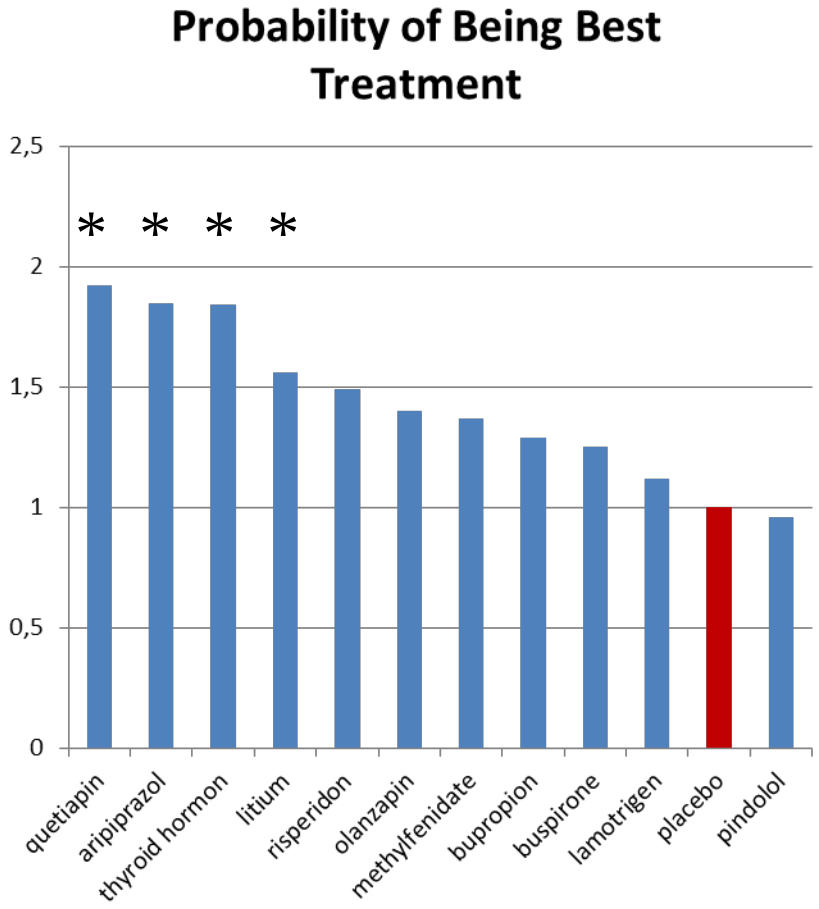
Network Meta-Analysis and Cost-Effectiveness Analysis of New Generation Antidepressants. Khoo et al., CNS Drugs (2015) 29:695–712



Comparative Efficacy, Acceptability, and Tolerability of Augmentation Agents in Treatment-Resistant Depression: Systemic Review and Network Analysis

Zhou et al., J Clin Psychiatry (2015) 76(4) e487-e498





Drug rank-ordered according to their overall probability of being the best treatment. Every drug was scored on a scale of 1-100 from the surface under the cumulative ranking curve (SUCAR) data

Are ADs Effective? A debate on their efficacy for the treatment of major depression in adults

Bschor, Kilarski (2016) Expert Review of Neurotherapeutics

- The efficacy of AD has been studied in thousands of RCTs
- AD are recommended in international guidelines
- Large meta-analyses have concluded that AD have significant, but modest effect when compared to placebo
- 75% of improvement is assumed to be due to placebo and the natural course of depression
- AD efficacy is overestimated by selective publishing, patient selection and insufficient blinding
- The placebo effect is beneficial and should not be dismissed as a disreputable mechanism of action of a given treatment.

Behandlings mål

- Remission och fullständigt återkomst av funktion
- Respons > 50% reduktion av symtom
- Partiell respons > 20% reduktion av symtom
- Icke-respons < 20% reduktion av symtom
- A meta-analysis showed that early improvement (ie, a 20% or greater improvement by week 2) is a highly sensitive predictor of remission at weeks 4 to 8.

Szegedi A, Jansen WT, van Willigenburg APP, et al. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *J Clin Psychiatry*. 2009;70(3):344–353

Global patterns of workplace productivity for people with depression: absenteeism and presenteeism costs across eight diverse countries.

Evans-Lacko S, Knapp M. Soc Psychiatry Psychiatr Epidemiol. 2016 Nov;51(11):1525-1537. Epub 2016 Sep 26.

Underdiagnos - underbehandling

- Among people in the US who had MDD in the previous 12 months, half received health care for the disorder. Treatment was adequate in only 42%, meaning that, of all people with MDD, only 22% received adequate treatment.

Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095–3105

Underdiagnos - underbehandling

- Använd skattningsskalor för screening och diagnostisk precision
- Använd i första hand självskattningsskalor såsom PHQ-9 alt MADRS-S, du sparar tid
- Använd strukturerad strategi för att optimera behandlingsutfall
- Använd skattningsskalor (PHQ-9, MADRS-S) för att följa upp behandlingsresultat och justera behandling för att uppnå remission

Kloka listan 2017

I första hand	**escitalopram, sertralin**
I andra hand	mirtazapin
Specialiserad vård	klomipramin
I tredje hand	tillägg av litium

Farmakologisk Behandling

- Vilka är de kritiska beslutsmoment?

När	Klinisk status	S-skalor	Plan
Vecka 0	Symtomatisk	PHQ-9 > 10 MADRS > 20	Initiera behandling, lägre dos inom det terapeutiska intervallet
Vecka 2	Remission	PHQ-9 < 5 MADRS < 12	Fortsätt med aktuell dos
	Partiellrespons		Gradvis öka dosen
	Besvärliga biverkningar		Fortsätt med aktuell dos, hantera biverkningarna Minska dosen, fortsätt i 2 veckor (Bytt till ett annat LM)
	Ingen respons		Gradvis öka dosen
	Besvärliga biverkningar		Minska dosen, fortsätt i 2 veckor (Bytt till ett annat LM)

När	Klinisk status	S-skalor	Plan
Vecka 4	Remission	+++	Fortsätt med aktuell dos
	Partiellrespons		Höja dosen Överväg att lägga till ett annat LM
	Besvärliga biverkningar		Fortsätt med aktuell dos, försök att hantera biverknigarna Bytt till ett annat LM
	Ingen respons		Öka dosen Bytt till ett annat LM
	Besvärliga biverkningar		Bytt till ett annat LM

När	Klinisk status	S-skalor	Plan
Vecka 6	Remission	+++	Fortsätt med aktuell dos
	Partiellrespons		Öka dosen Lägg till ett annat LM
	Besvärliga biverkningar		Fortsätt med aktuell dos, hantera biverknigarna Bytt till ett annat LM
	Ingen respons		Lägg till ett annat LM Bytt till ett annat LM
	Besvärliga biverkningar		Bytt till ett annat LM

När	Klinisk status	S-skalor	Plan
Vecka 9	Remission	+++	Fortsätt med aktuell dos
	Partiellrespons		Öka dosen Lägg till ett annat LM Bytt till ett annat LM
	Ingen respons el biverkningar		Bytt till ett annat LM
Vecka 12	Remission		Gå till nästa fas i behandlingen
	Partiellrespons		Bytt till ett annat LM (Öka dosen, utvärdera om 2 v)
	Ingen respons el biverkningar		Bytt till ett annat LM

LM	Startdos	Titrering	Måldos	Maxdos
Bupropion	150 mg	150 mg / 2v	300 mg	450 mg
Citalopram	20 mg	10 mg / 2v	20-40 mg	40 mg
Duloxetin	30 - 60 mg	30 mg / 2v	60 mg	120 mg
Escitalopram	10 mg	10 mg / 2v	10-20 mg	20 mg
Fluoxetin	20 mg	10-20 mg/ 2v	20-40 mg	60 mg
Mirtazapin	15 mg	15 mg / 1-2 v	30 mg	45 mg
Sertralin	50 mg	50 mg / 1-2 v	100-150 mg	200 mg
Venlafaxin	37,5 mg	75 mg / 1 -2v	150 mg	375 mg

Allvarliga biverkningar

- Serotonergt syndrom
- SIADH (SSRI)
- Krampanfall (bupropion, TCA)
- QTc förlängning (TCA, citalopram, escitalopram)
- Ökad blödningstid (SSRI)

Utsättningsbesvär

- Yrsel
- Illamående
- Irritabilitet
- Huvudvärk
- Ångest
- Influensa liknande symtombild

  - Trappa ner med c:a 25% / vecka
  - Kan ta upp till 2-3 månader
  - Informera patienten noggrant om förväntade utsättningsbesvär

SLUT