Psychiatric Medications: What you need to know

Lindsay J. McCoy, Pharm.D., BCPP

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Disclosures

- Lindsay McCoy has nothing to disclose.

Objectives

- Discuss the prescribing considerations with recently approved drug therapies in the treatment of mood disorders.
- Recognize and manage potential drug-drug and drug-disease interactions.

Atypical Antipsychotics

Aripiprazole

Brexpiprazole

Cariprazine

Lurasidone

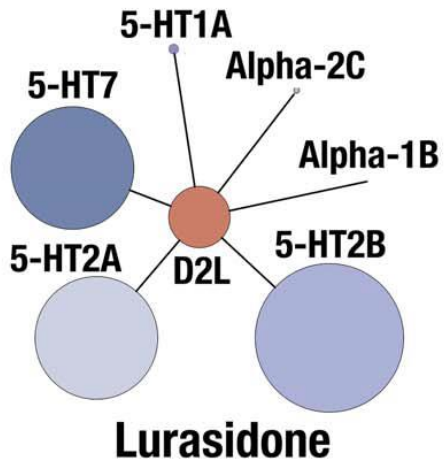
Comparing binding profiles

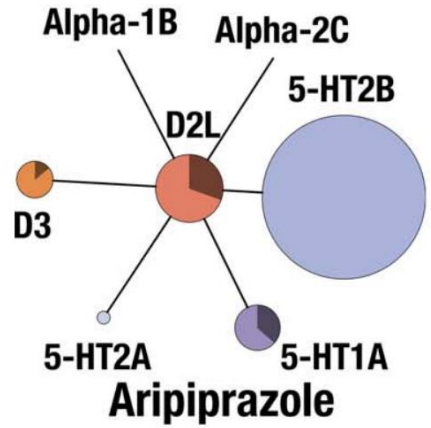
Table 2. Binding affinities of aripiprazole, brexpiprazole, cariprazine, and the clinical properties of the receptors.

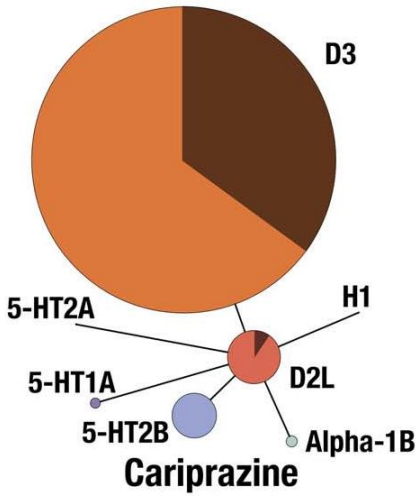
	Aripiprazole	Brexpiprazole	Cariprazine	Therapeutic effects	Adverse effects
D_2	0.34	0.30	0.49	Antipsychotic	EPS, tardive dyskinesia, akathesia, NMS hyperprolactinemia
D_3	0.8	1.1	0.085	Antipsychotic (including negative symptoms), antimanic, antidepressant	
5-HT_{1A}	1.7	0.12	2.6	Antidepressant, anxiolytic	
5-HT_{2A}	3.4	0.47	18.8	Anti-EPS	
5-HT_{2C}	15	34	134	Antidepressant	
5-HT_7	29	3.7	111	Antidepressant	
H_1	61	19	23.2	Anxiolytic, anti-insomnia	Weight gain sedation
M_1	>1000	>1000	>1000	Opposes EPS	Xerostomia, constipation, blurry vision, cognitive dysfunction, falls (e.g. older adults)
α_1	57	3.8	155	Antihypertensive	Sedation, orthostasis

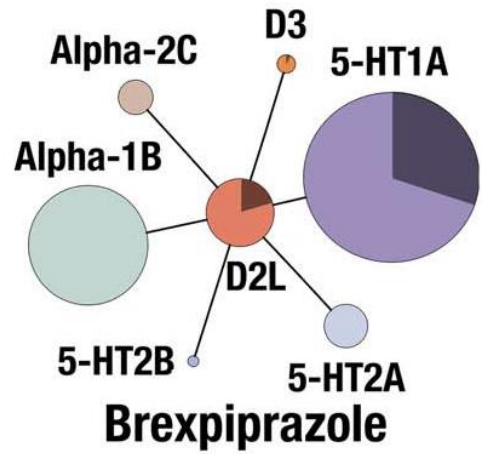
Comparing the three partial D_2 agonists:
(1) Aripiprazole has the greatest affinity for 5-HT_{2C}R; it has the weakest affinity for H_1R. Theoretically, this suggests it may be less associated with metabolic symptoms and perhaps elevate monoamines for better antidepressant effects, therapeutically speaking. It may be the least sedating.
(2) Brexpiprazole shows the greatest affinity for D_2R, 5-HT_{1A}R, 5-HT_{2A}R, 5-HT_7R, H_1R, and α_1R; it has the weakest affinity for D_3R. This suggests the possibility that it can both inhibit and enhance dopamine activity to a higher degree, treating either psychosis or depression. The serotonin modulation is highly suggestive of antidepressant activity.
(3) Cariprazine shows the greatest affinity for D_3R; it is the weakest in affinity for D_2R, 5-HT_{1A}R, 5-HT_{2A}R, 5-HT_7R, and α_1R. This may promote a fair amount of dopamine activity and act as an antidepressant. The serotonin modulation is highly suggestive of antidepressant activity.
EPS, extrapyramidal symptoms; NMS, neuroleptic malignant syndrome.

Frankel, J. S., & Schwartz, T. L. (2017). Brexpiprazole and cariprazine: distinguishing two new atypical antipsychotics from the original dopamine stabilizer aripiprazole. Therapeutic Advances in Psychopharmacology, 29–41. https://doi.org/10.1177/2045125316672136









Stephen R. Saklad (2017) Graphic representation of pharmacology: Development of an alternative model. Mental Health Clinician: September 2017, Vol. 7, No. 5, pp. 201-206.

Aripiprazole

- Indications/dosing (adult):
  - Schizophrenia – 10-15 mg/day (max 30mg)
  - Bipolar mania – monotherapy – 15 mg/day (max 30mg)
  - Bipolar mania – adjunct to lithium or valproate – 15 mg/day (max 30mg)
  - Major depressive disorder – adjunct to antidepressant – 5-10 mg/day (max 15mg)
- Common side effects: akathisia, tremor, extrapyramidal symptoms, somnolence, insomnia
- Mechanism of action: D2 and 5-HT_{1A} partial agonist; 5-HT_{2A} antagonist

Abilify(R) [package insert]. Rockville, MD: Otsuka America Pharmaceutical; 2014

Aripiprazole [drug interactions]

Strong CYP450 2D6 and 3A4 inhibitors	Reduce usual dose by half
Strong CYP450 3A4 inducers	Double usual dose over 1-2 weeks
Known 2D6 poor metabolizers	Reduce usual dose by half
Antihypertensive medications	Monitor BP closely; adjust if necessary
Benzodiazepines	Monitor sedation, BP; adjust if necessary
Known 2D6 poor metabolizer AND 3A4 inhibitor	Reduce usual dose to ¼
Strong 3A4 inhibitor with 2D6 inhibitor	Reduce usual dose to ¼

Brexpiprazole

- Indications/dosing (adult):
  - Adjunct to antidepressant in MDD: 2 mg/day (max 3 mg)
  - Schizophrenia: 2-4 mg/day (max 4mg)
- Mechanism of action: D2 and 5-HT_{1A} partial agonist; 5-HT_{2A} antagonist
- Most common side effects: akathisia, increased weight
- Drug interactions:
  - CYP450 2D6 and 3A4 inhibitors/inducers
  - CYP450 2D6 poor metabolizers

Brexpiprazole [Drug Interactions]

Strong CYP450 2D6 OR 3A4 inhibitors	Reduce usual dose by half
Strong CYP450 3A4 inducers	Double usual dose and adjust based on response
Known 2D6 poor metabolizer AND strong/moderate 3A4 inhibitor	Reduce usual dose to ¼
Strong/moderate 3A4 AND strong/moderate 2D6 inhibitor	Reduce usual dose to ¼

Cariprazine

- Indications:
  - Schizophrenia – 1.5 - 6 mg/day (max 6 mg/day)
  - Acute manic or mixed episodes associated with bipolar I disorder – 3 – 6 mg/day (max 6 mg/day)
- Common side effects: extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, restlessness
- Mechanism of action: D2 and 5-HT_{1A} partial agonist; 5-HT_{2A} antagonist
- Drug interactions: CYP450 3A4 inhibitors/inducers

Vraylar® [package insert]. Madison, NJ: Allergan; 2018

Cariprazine

- Positive outcomes vs placebo for
  - Schizophrenia
  - Bipolar (mania and depression)
  - Major Depressive Disorder
- High rates of akathisia (2.8% to 22.3%)
- Low rates of metabolic disturbances

Campbell R.H., Diduch M., Gardner K.N., Thomas C. Review of cariprazine in management of psychiatric illness. Ment. Health Clin. 2017;7:221–229. doi: 10.9740/mhc.2017.09.221.

Lurasidone

- Indications:
  - Schizophrenia – 40 – 160 mg/day
  - Depressive episode associated with Bipolar I Disorder (bipolar depression), monotherapy or adjunctive therapy with lithium or valproate – 20 – 120 mg/day
- Common side effects: Somnolence, akathisia, extrapyramidal symptoms
- Mechanism of Action: D2 and 5-HT_{2A} antagonist

Latuda®[package insert]. Marlborough, MA: Sunovion; 2018.

Lurasidone [Drug Interactions]

- Avoid use with **strong** CYP450 3A4 inhibitors and inducers
- Reduce dose by half with **moderate** CYP450 3A4 inhibitors and inducers

Atypical Antipsychotics [Metabolic Adverse Effects]

Table 5. Summary of potential for metabolic adverse effects with atypical antipsychotics.[1-13]

	Weight gain	Acute Hyperglycemia/ Diabetes	Worsening lipid profile
Clozapine (Clozaril®)	High	High*	High
Olanzapine (Zyprexa®)	High	High*	High
Quetiapine (Seroquel®)	Moderate	Moderate*	Moderate
Risperidone (Risperdal®)	Moderate	Low to moderate*	Low to moderate
Iloperidone (Fanapt®)	Moderate	Low/NR	Low/NR
Asenapine (Saphris®)	Low	Low/NR	Low/NR
Paliperidone (Invega®)	Low	Low/NR	Low/NR
Lurasidone (Latuda®)	Low	Low/NR	Low/NR
Aripiprazole (Abilify®)	Low	Low*	Low
Ziprasidone (Geodon®)	Low	Low*	Low
Cariprazine (Vraylar®)	Low	Low	Low

NR = not reported
*Agents with existing case reports of acute hyperglycemia

https://doi.org/10.9740/mhc.n166834
Vraylar® [package insert]. Madison, NJ: Allergan; 2018

Antidepressants

Vortioxetine

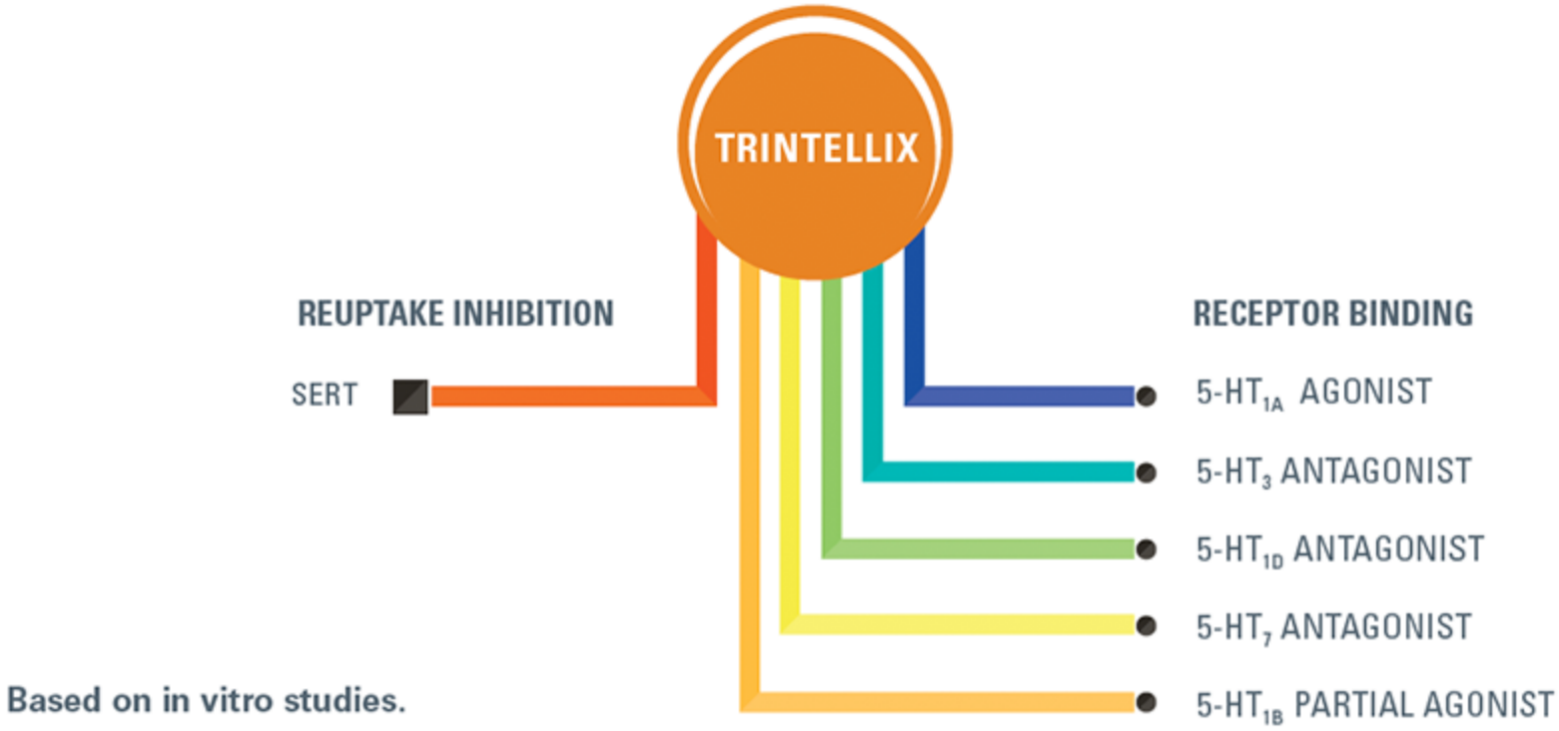
Vilazodone

Vortioxetine

- Indicated for the treatment of major depressive disorder
- Mechanism of action…….

Trintellix® [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2017.

Vortioxetine (Mechanism of action)



The clinical relevance of the pharmacologic activity is unknown.

https://www.trintellixhcp.com/clinical-pharmacology

Vortioxetine [Key Points]

- Dose: 5 to 20 mg daily
- Side effects: **Nausea**, headache, diarrhea, dry mouth
- Major drug interactions:
  - Strong CYP450 2D6 inhibitors
    - Bupropion
    - Fluoxetine
    - Paroxetine

    } Reduce dose by half
  - CYP Inducers: consider dose increase, max 3 times original dose
- Poor 2D6 metabolizers: max 10mg/day

Vilazodone

- Indicated in the treatment of major depressive disorder
- Mechanism of action:
  - Selective inhibition of serotonin reuptake
  - 5-HT_{1A} partial agonist

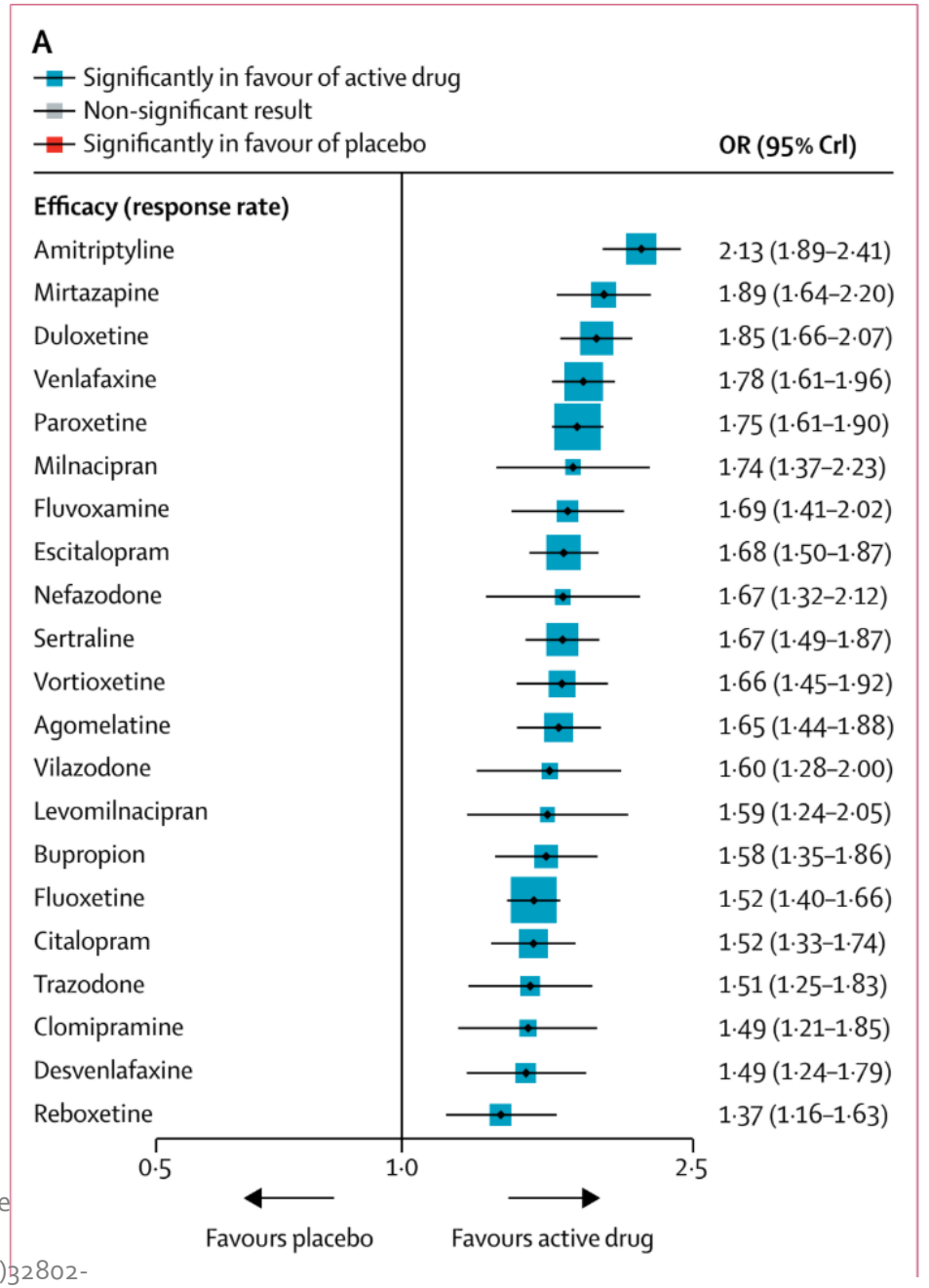
Vilazodone®[package insert]. New Haven, CT: Trovis Pharmaceuticals LCC; 2011.

Vilazodone [Key Points]

- Recommended dose: 40mg daily
  - Initial titration: 10mg x 7 days, then 20mg x 7 days, then 40mg daily
  - Take with food
- Side effects: Diarrhea, nausea, dry mouth, vomiting
- Drug interactions:
  - CYP450 3A4 inhibitors: reduce dose to max 20mg daily
  - CYP450 inducers: not studied for package insert
    - May be prudent to increase dose to 80 mg daily

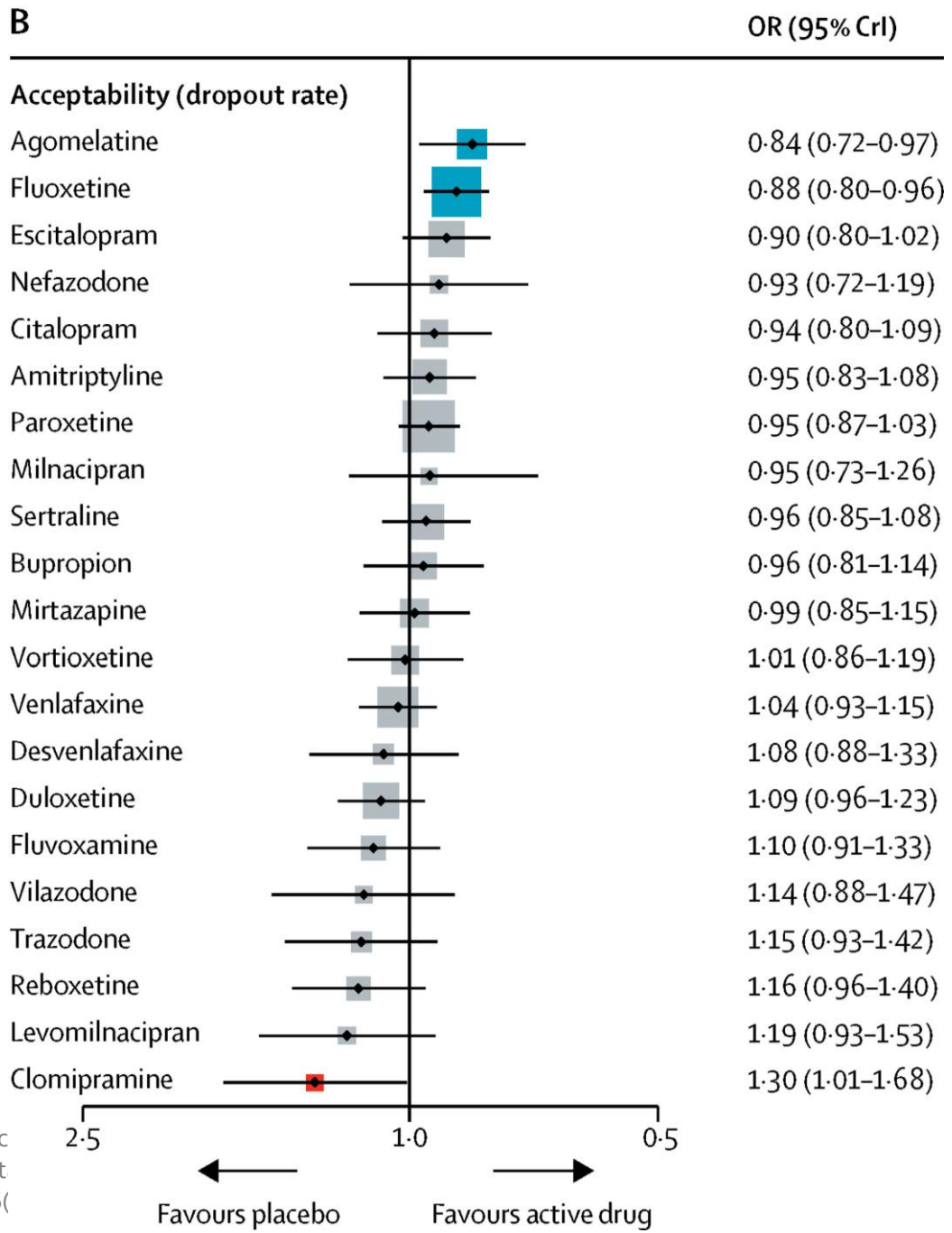
Vilazodone®[package insert]. New Haven, CT: Trovis Pharmaceuticals LCC; 2011.

Comparative Efficacy of 21 Anti-depressants



Cipriani et al. 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. The Lancet 2018;391(10128):1357-1366. DOI: https://doi.org/10.1016/S0140-6736(17)32802-7

Comparative Acceptability of 21 Anti-depressants



Cipriani et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the ac
treatment of adults with major depressive disorder: a systematic review and network met
analysis. The Lancet 2018;391(10128):1357-1366. DOI: https://doi.org/10.1016/S0140-6736(

Comparative Efficacy of 21 Anti-depressants

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

Cipriani et al. 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. The Lancet 2018;391(10128):1357-1366. DOI: https://doi.org/10.1016/S0140-6736(17)32802-7`

"Drugs are reported in alphabetical order. 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. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored. "

- A 37 yo F with Major Depressive Disorder is currently stabilized on sertraline 100mg daily and aripiprazole 10mg daily. She begins to complain about sexual side effects and would like to switch to bupropion. Which of the following is correct:
  - A. Discontinue sertraline and start bupropion at the patient's request.
  - B. Discontinue both sertraline and aripiprazole to start bupropion.
  - C. Cross titrate sertraline and bupropion to reduce side effects; make no changes to aripiprazole
  - D. Cross titrate sertraline and bupropion to reduce side effects and reduce the dose of her aripiprazole by half

- One potential benefit of D2 partial agonists (such as aripiprazole, brexpiprazole, and cariprazine) over other atypical antipsychotics is:
  - A. Reduced drug interactions
  - B. Reduced risk of akathisia
  - C. Reduced risk of metabolic side effects
  - D. Increased efficacy

- A 32 yo M with history of irritable bowel syndrome presents with a new diagnosis of depression. Which of the following would be the **least** appropriate initial treatment option?
  - A. Citalopram 20 mg daily
  - B. Bupropion SR 100 mg daily
  - C. Vilazodone 20 mg daily
  - D. Escitalopram 10 mg daily