High Dose
Psychiatry

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Disclosures
None

Feb 2025

Antipsychotics

High-dose Treatment with Neuroleptics in the Acute Phase of Mental Disease

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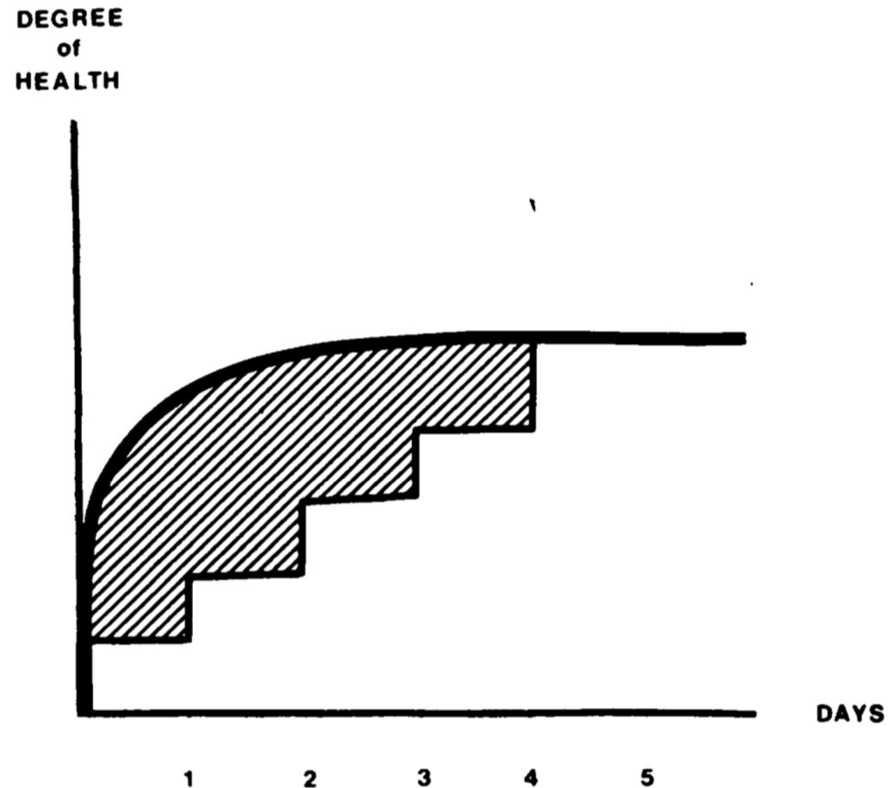


Fig 1 *Schematic drawing of the titration (steps) and the high-dose treatment approach. The striped area represents the social availability gain*

High Dose Antipsychotics

10-20 times usual doses

Early claims

"Many psychotic patients... have nothing to lose, but much to gain, by receiving aggressive pharmacologic treatment."

Ketai R, Hosp Community Psychiatry. 1976;27(1):37-39

"If a high dose is given from the beginning, no extrapyramidal side-effects may occur"

Dencker SJ. Proc R Soc Med. 1976;69 suppl 1(Suppl 1):32-34.

1988. Ross Baldessarini and colleagues.

Analysis of 33 randomized trials.

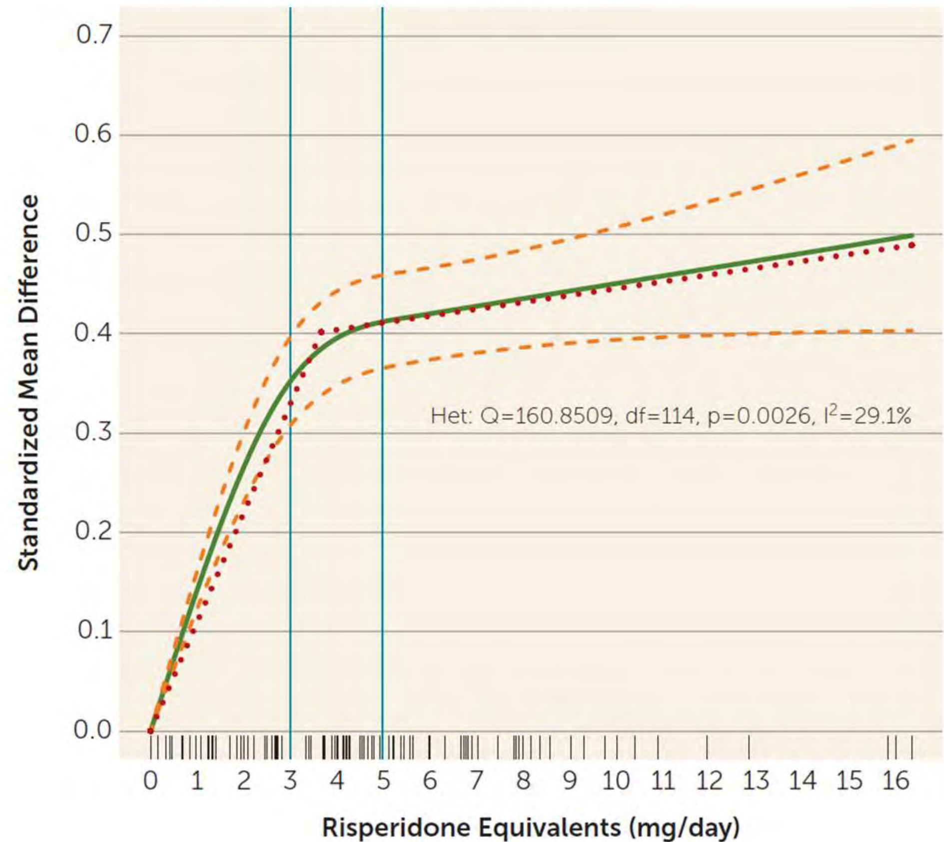
No benefit with high dose antipsychotics, but greater risk of EPS.

Baldessarini RJ et al. Arch Gen Psychiatry. 1988;45(1):79-91

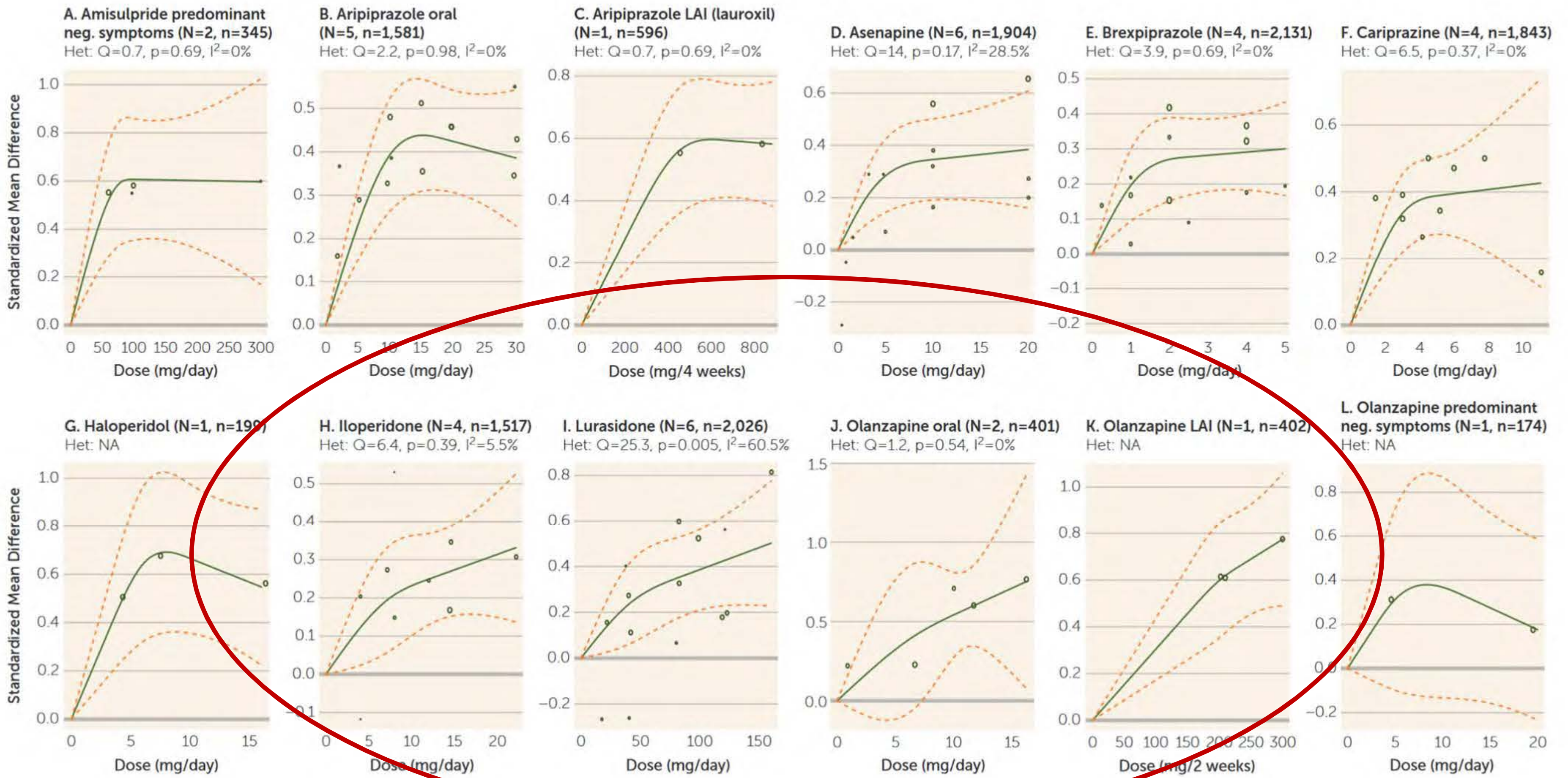
Second Generation Antipsychotics in Schizophrenia

Response peaks at
3.7 mg risperidone equivalents

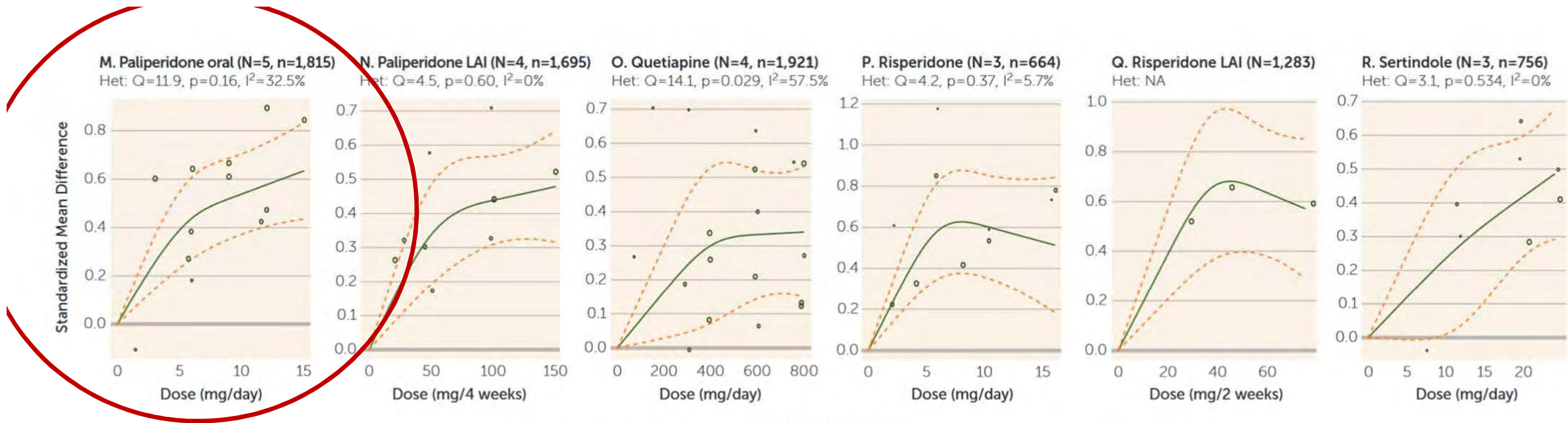
FIGURE 3. Dose-response curve across antipsychotic drugs, with doses converted to risperidone equivalents[a]



68 RCTs in Leucht S et al, Am J Psychiatry. 2020;177(4):342-353.

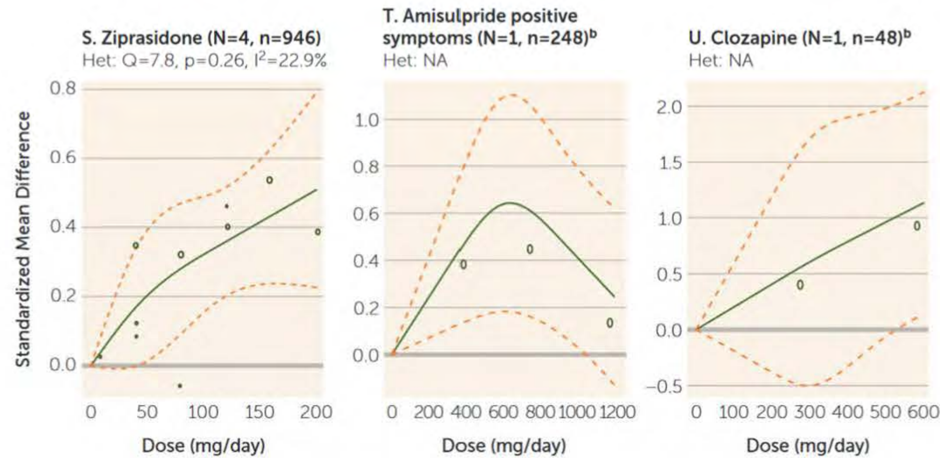


Leucht S et al, Am J Psychiatry. 2020;177(4):342-353.



Possibly Linear (no plateau):

1. Olanzapine > 15 mg
2. Paliperidone > 15 mg
3. Lurasidone > 160 mg
4. Illoperidone > 20 mg



Looks linear, but not:

1. *Ziprasidone:* No benefit for 320mg vs 160mg
2. *Clozapine:* Only 1 study
3. *Sertindole:* Linear disappeared on sensitivity analysis

Leucht S et al, Am J Psychiatry. 2020;177(4):342-353.

Max Dose

Antipsychotic	95% effective dose	Plateau?
Aripiprazole	11.5 mg	
Asenapine	15 mg	
Brexpiprazole	3.4 mg	
Haloperidol	6.3 mg	
Iloperidone	20.1 mg	No
Lurasidone	147 mg	No
Olanzapine	15.2 mg	No
Paliperidone	13.4 mg	No
Quetiapine	482 mg	
Risperidone	6.3 mg	
Ziprasidone	186 mg	

Leucht S et al, Am J Psychiatry. 2020;177(4):342-353.

Olanzapine Exception

High dose olanzapine (25-50 mg) equaled switch to clozapine in 3/4 small randomized trials of treatment resistant schizophrenia

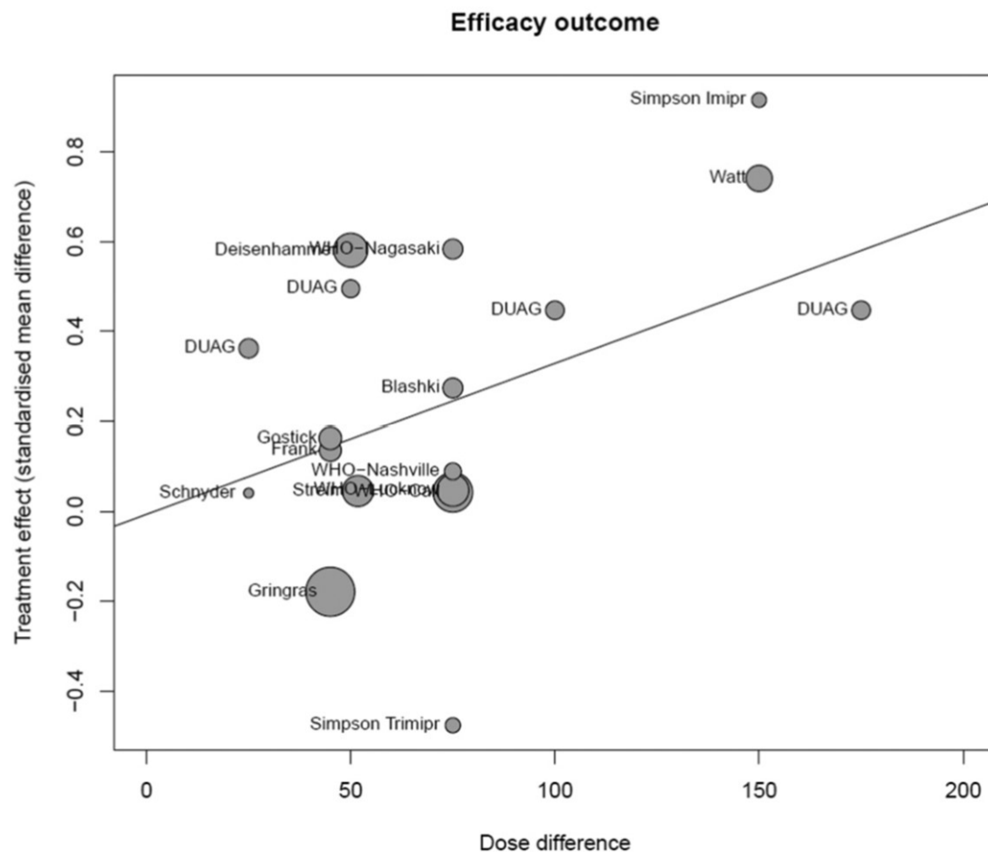
Gannon L et al, Ther Adv Psychopharmacol. 2023;13:20451253231168788

Antidepressants

Tricyclic Dose Response

Every increase of 100 mg imipramine equivalents = 0.34 effect size difference

Imipramine 100 mg =
Amitriptyline, desipramine, doxepine 100 mg =
Amoxapine 167 mg =
Clomipramine, maprotiline 83 mg =
Nortriptyline 74 mg =
Protriptyline 19 mg =
Trimipramine 85 mg



15 RCTs of fixed dose comparisons. Baethge C et al. J Affect Disord. 2022;307:191-198.

Antidepressants

Plasma levels established only for tricyclics

	Level ng/ml	Notes
Amitriptyline	90-140	Linear response
Nortriptyline	60-150	Best studied. Bell-shaped curve.
Imipramine	175-250	Linear response
Desipramine	120-350	Linear response

Baldessarini, RJ. Chemotherapy in Psychiatry, 3rd ed (2013)

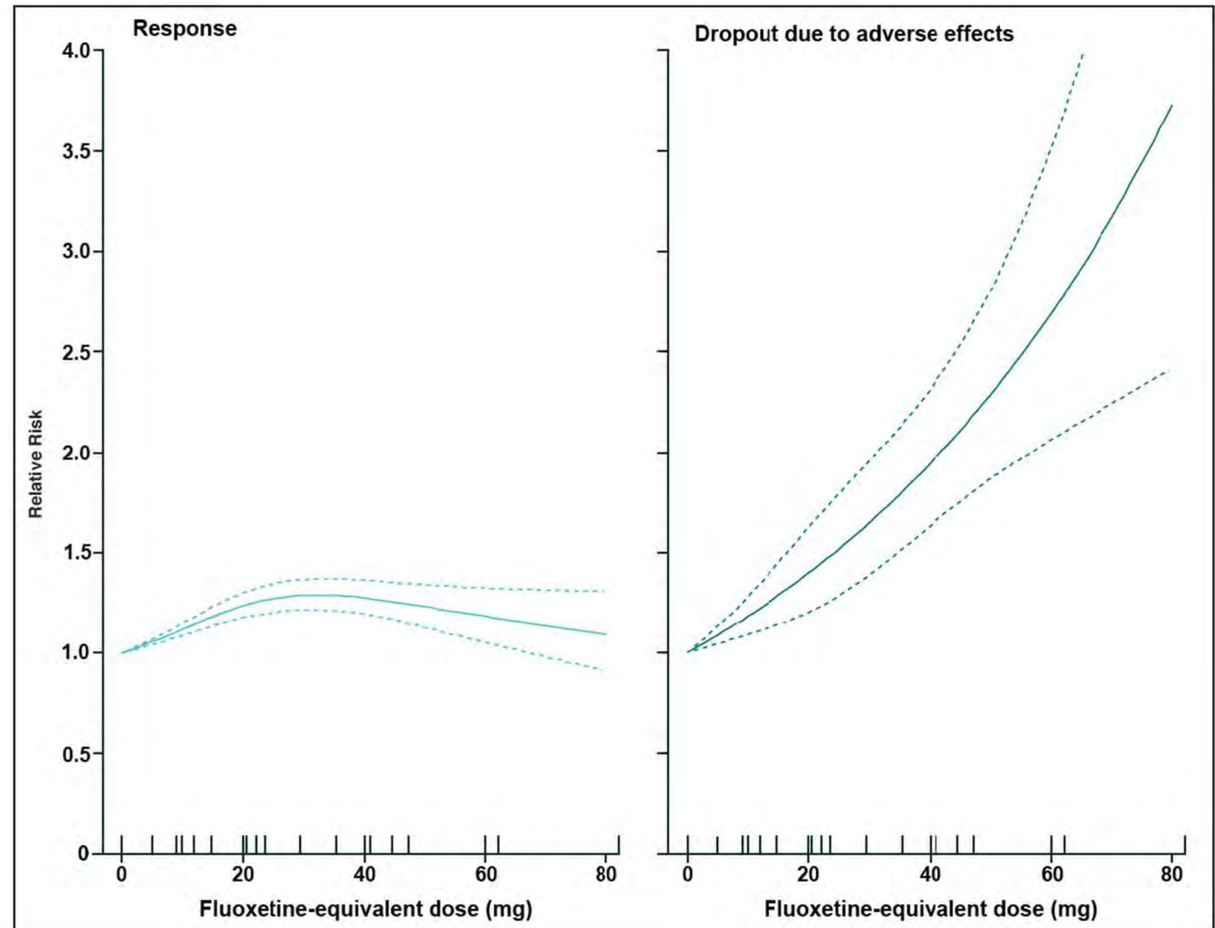
MAOIs

- Tranylcypromine 90-130 mg in TRD (case reports)
- Additional risk = orthostasis (Rx glucocortisone 0.1 to 0.2 mg/d or abdominal binders)
- EMSAM: no dose-resp data, but ½ reached 12mg in trials

Amsterdam JD, Berwish NJ. Pharmacopsychiatry. 1989;22(1):21-25. Guze BH. J Clin Psychiatry. 1987;48(1):31-32. Asnis GM, Henderson MA. Neuropsychiatr Dis Treat. 2014;10:1911-1923

SSRI Dose-Response

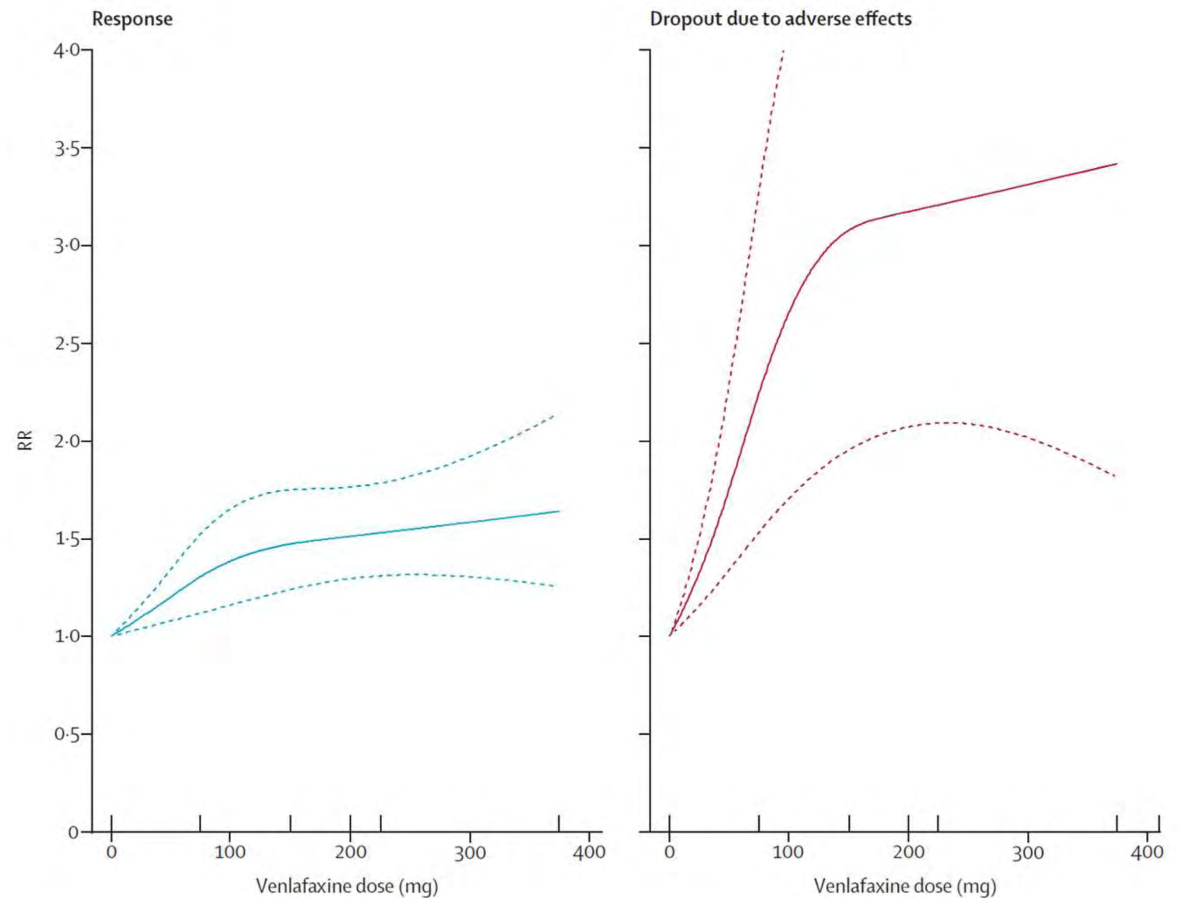
Peak benefits at 20-40 mg fluoxetine equivents



99 fixed-dose groups. Furukawa TA et al. Lancet Psychiatry. 2019;6(7):601-609.

Venlafaxine Dose-Response

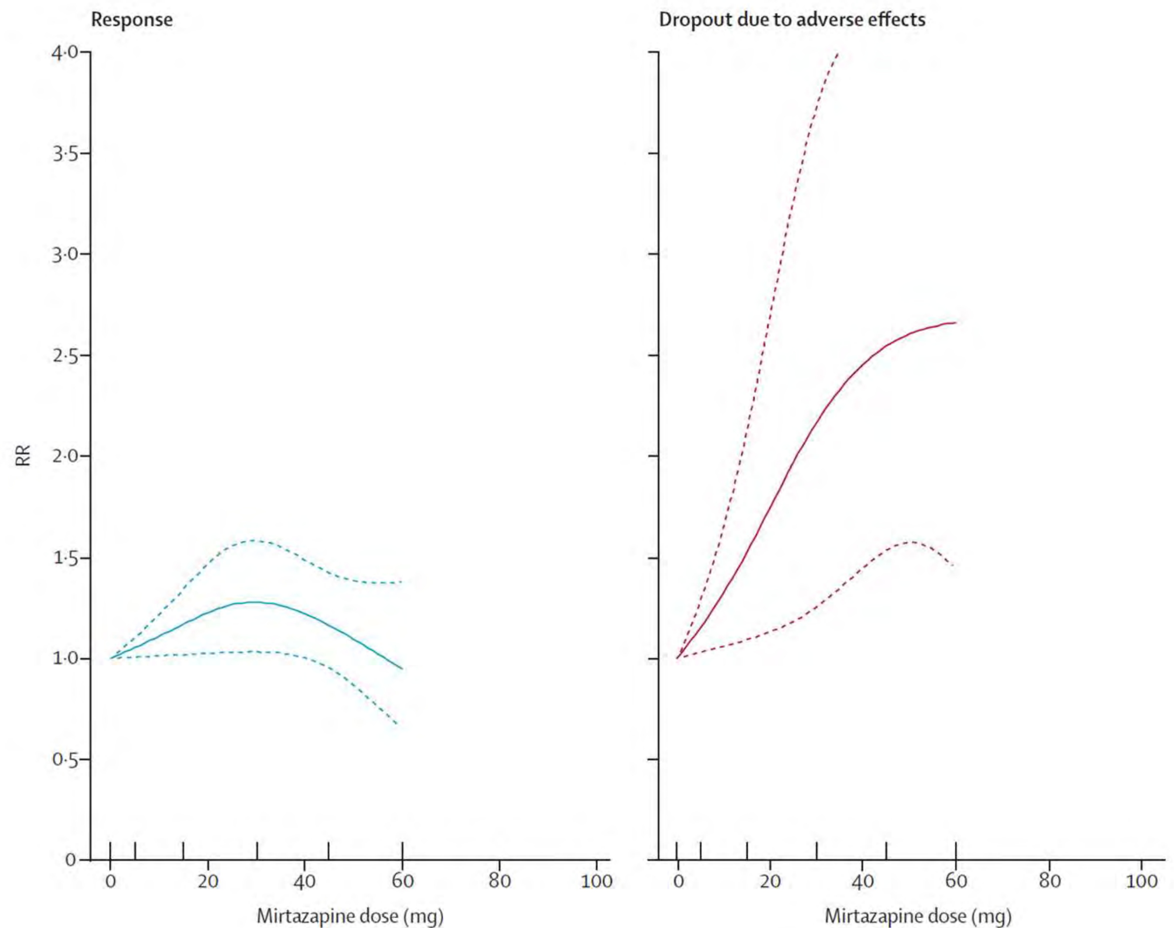
Peak effects at 75-150 mg followed by modest increase



17 fixed-dose groups. Furukawa TA et al. Lancet Psychiatry. 2019;6(7):601-609.

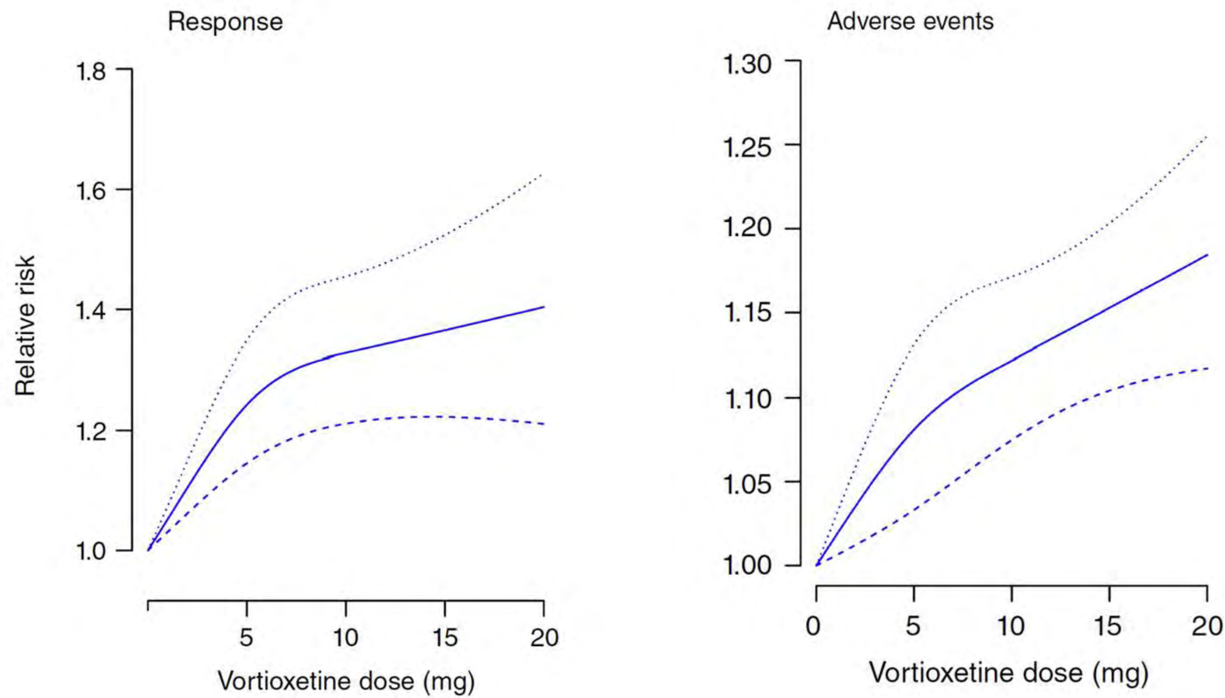
Mirtazapine Dose-Response

Peak effects at 15-30 mg followed by worsening



11 fixed-dose groups. Furukawa TA et al. Lancet Psychiatry. 2019;6(7):601-609.

Vortioxetine Dose-Response

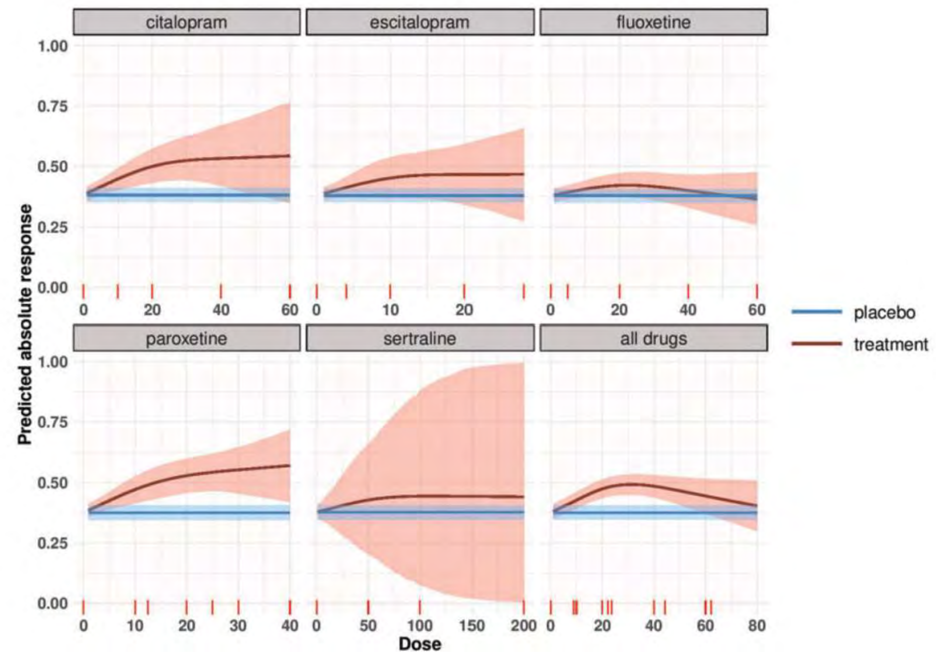


5 mg = 50% effective dose
18 mg = 95% effective dose

Meta-analysis of 16 trials, Yang X et al, Psychiatry Clin Neurosci, July 3, 2024

SSRI Dose-Response

Similar pleateau effect across SSRIs



Metaanalysis of 60 trials. Hamza T et al. Stat Methods Med Res. 2021;30(5):1358-1372.

Dose-Response by Class

Linear for tricyclics, reboxetine and – within normal dosing range – SNRIs and vortioxetine

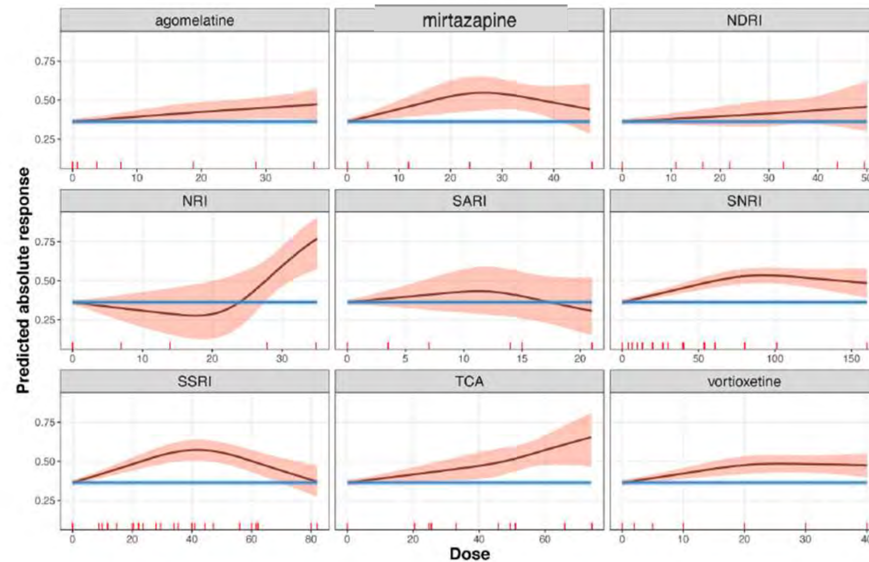


Figure 4. Dose-effect network meta-analysis summary curve for each of the 9 drug classes (see Appendix Table 1). The blue line depicts the effect estimated from all placebo arms in the network (36.2%) and its 95% credible region. The red line represents the absolute response to each drug class (estimated from model M5) and the shaded area is its 95% credible region.

Network metaanalysis of 120 trials. Hamza T et al, Stat Methods Med Res, 2/2022.

Antidepressant Dose-Response

Dose-response for amitriptyline, clomipramine, reboxetine…

venlafaxine (to 225 mg), desvenlafaxine (to 200 mg)

Network metaanalysis of 120 trials. Hamza T et al, Stat Methods Med Res, 2/2022.

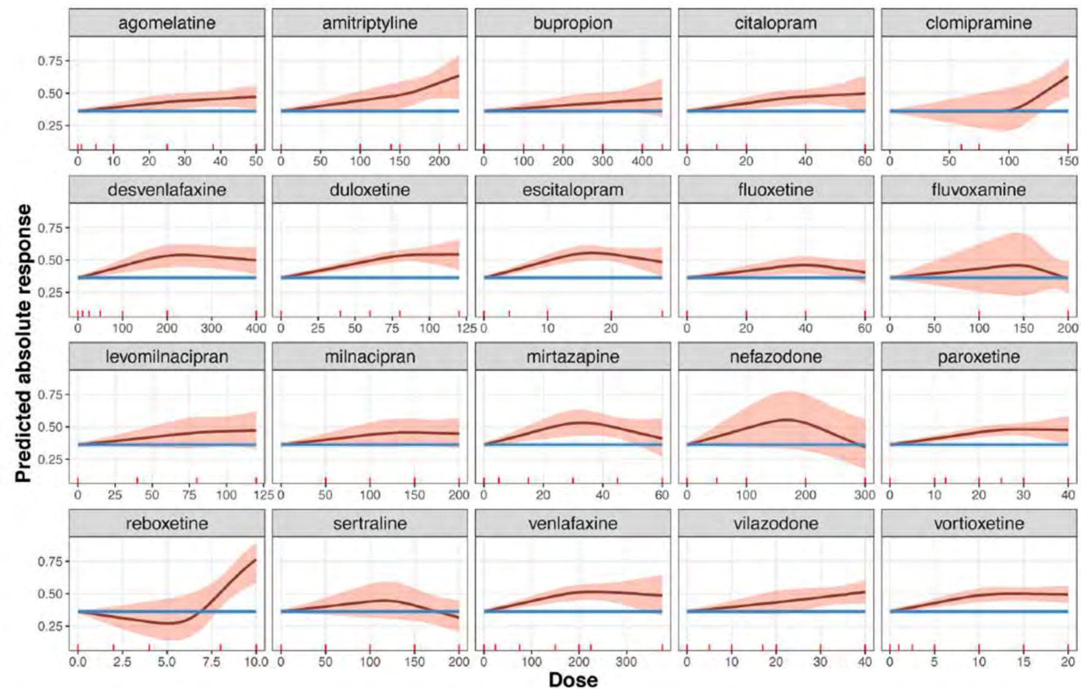
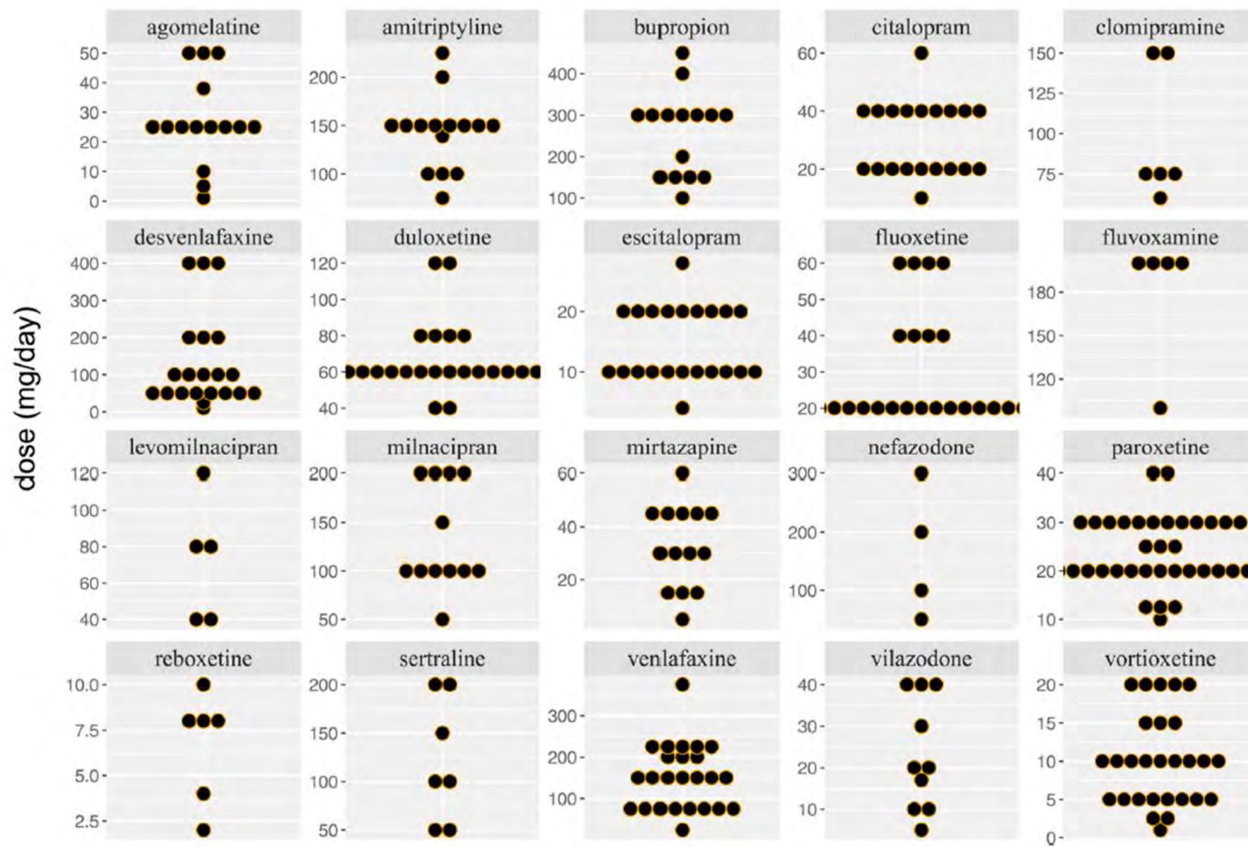


Figure 2. Dose–effect network meta-analysis summary curve for each antidepressant. The blue line depicts the effect estimated from all placebo arms in the network (36.2%) with its 95% credible region. The red line represents the absolute response to each antidepressant (estimated from model M1) and the shaded area is its 95% credible region.

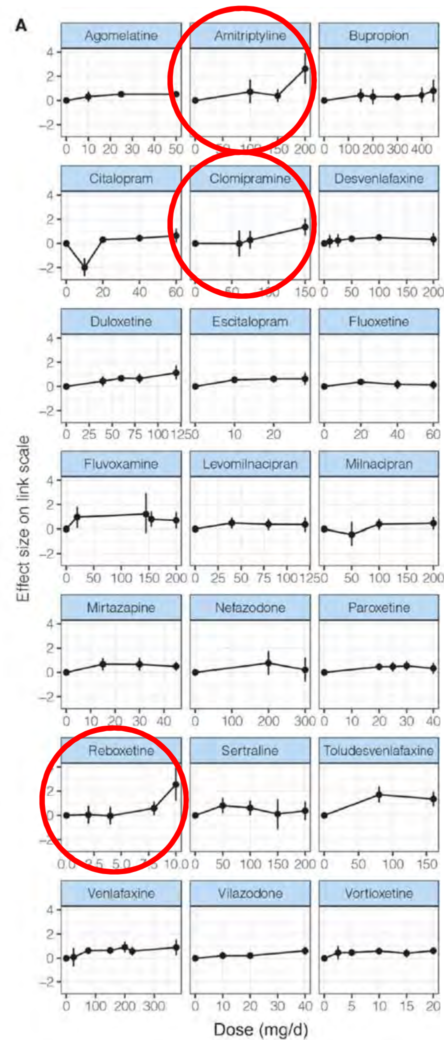


Dose distribution of 21 antidepressants in 120 trials

Network metaanalysis of 120 trials. Hamza T et al, Stat Methods Med Res, 2/2022.

Confirmation: Antidepressant Dose-Response

Linear increase: Amitriptyline, clomipramine, reboxetine



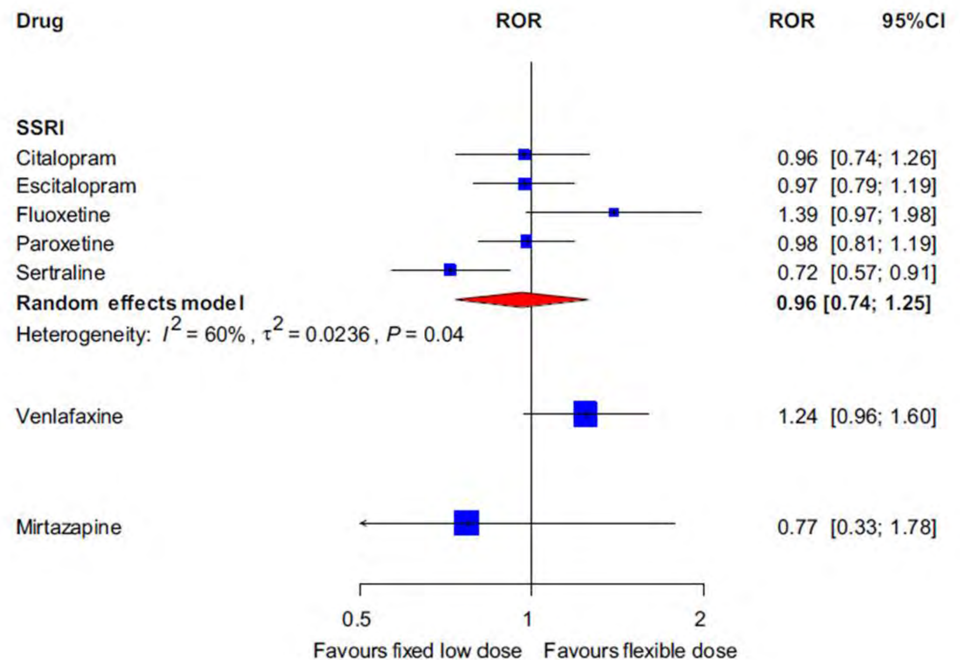
Network meta-analysis of 160 trials: Zhou S et al, Chin Med J (Engl), June 2024.

Umbrella review of 39 SSRI dose-response analyses: Johnson CF, et al. BMJ Med. 2022 Dec 1;1(1):e000017.

Raise the dose or give it more time?

No benefit with titrating up for SSRIs or mirtazapine.

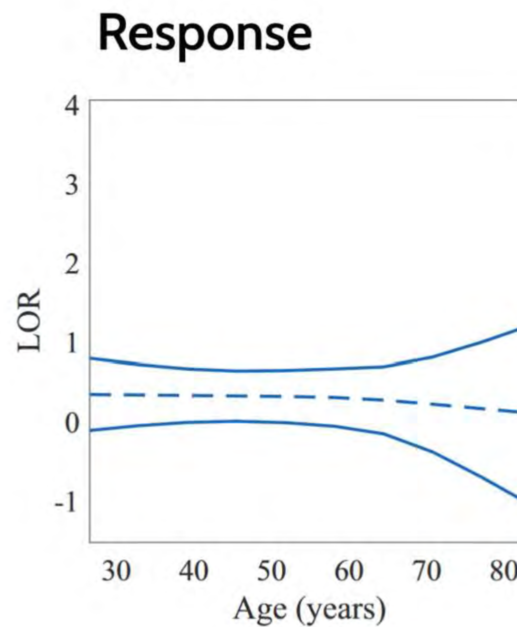
Benefit for raising venlafaxine up from 75 to 150 mg.

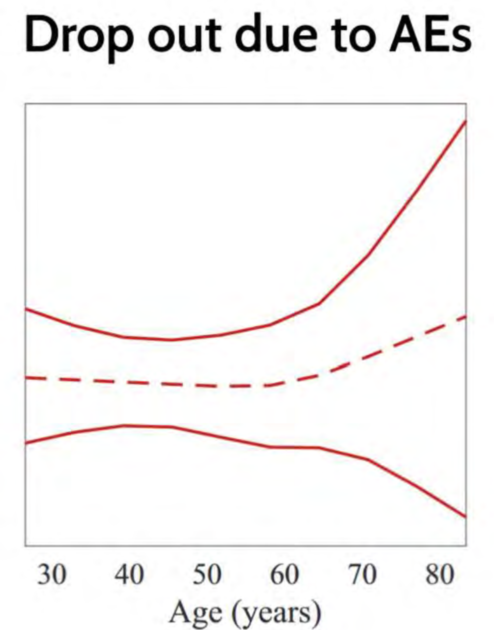


Metaanalysis of 123 trials. Furukawa TA et al, Acta Psychiatr Scand. 2020;141(5):401-409.

Re-analyzed by Age

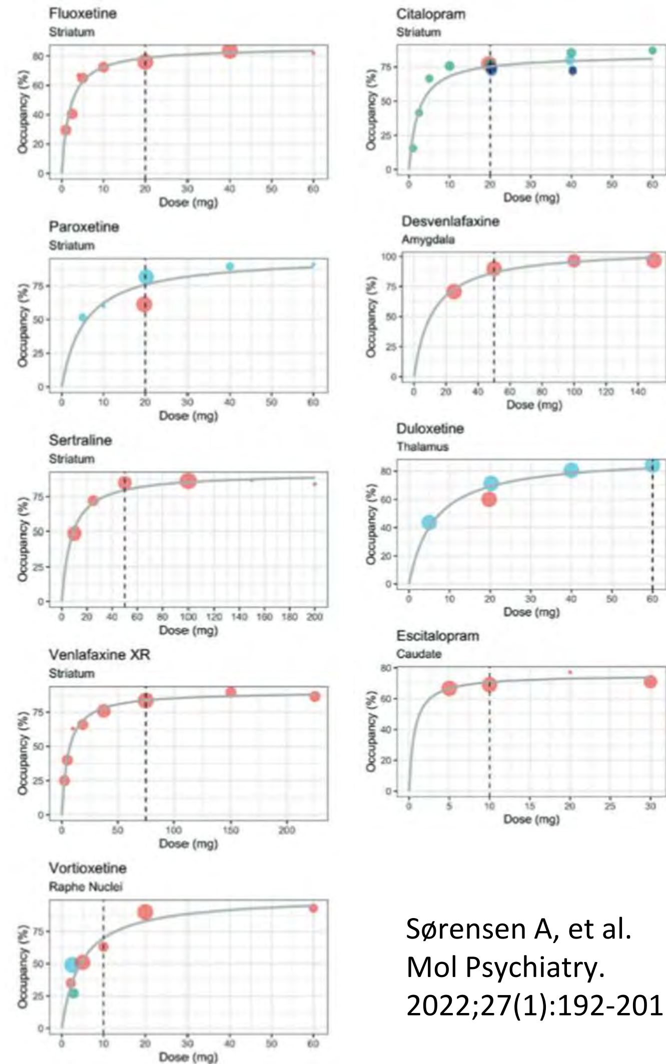
Slightly lower response, much higher adverse effects after age 60-70





Holper L. EClinicalMedicine. 2020;18:100219

For SSRIs and SNRIs, minimum effective antidepressant dose = 80% occupancy at serotonin transporter



Sørensen A, et al.
Mol Psychiatry.
2022;27(1):192-201

Desvenlafaxine

- Serum levels impacted by UGT1A1 in liver
- CNS levels impacted by p-glycoprotein transporter genes: ABCB1 and ABCC1
- 15% require higher doses (150-200 mg), based on study of 119 using CNSDose pharmacogenetic panel
- CNSDose informs dosing, and is the only pharmacogenomic panel with a positive, double-blind RCT (NNT = 3)

Bousman CA, et al. Pharmacogenet Genomics. 2017;27(1):1-6.
Singh AB. Clin Psychopharmacol Neurosci. 2015;13(2):150-156.

Trazodone

- Its metabolite m-chlorophenylpiperazine (mCPP) is a serotonin agonist and illicit substance
- Rapid rise in mCPP = dysphoria, psychosis, suicidality
- Watch for CYP-2D6 inhibitors that raise mCPP:
  - Fluoxetine, paroxetine, sertraline (>150mg), bupropion, duloxetine, tricyclics

Shamseddeen W et al J Child Adolesc Psychopharmacol 2019 Aug;29(7):573
Lavigne JE et al J Gen Intern Med. 2019;34(8):1554-1563

A new light from a trusted source

New
Desyrel®
(Trazodone HCl)

Not a tricyclic.
Not a tetracyclic.
Watch for the light.

Trazodone

- For depression, slow titration improves outcomes
- Start 50 mg, raise every 3-7 days to 150-300mg

Debattista C and Schatzberg A, Manual of Clinical Psychopharmacology, 10th Edition, 2024

Antidepressant Dosing

Antidepressant	Optimal dose (mg/d)	FDA max	Equivalent to fluoxetine 40
Citalopram	20-40	60	? 36
Escitalopram	10-20	20	18
Fluoxetine	20-40	80	40
Fluvoxamine	100-150	? (300 ocd)	143
Paroxetine	20-30	50	34
Sertraline	50-100	200	99
Duloxetine	40-60	120	? 60
Desvenlafaxine	50-200	400	? 100
Venlafaxine	75-150	225	149
Bupropion	150-300	450	349
Mirtazapine	15-30	45	51
Nefazodone	? 300-600	600	535
Trazodone	? 150-300	600	401
Vilazodone	10-20	20	? 20
Vortioxetine	20-40	40	? 40

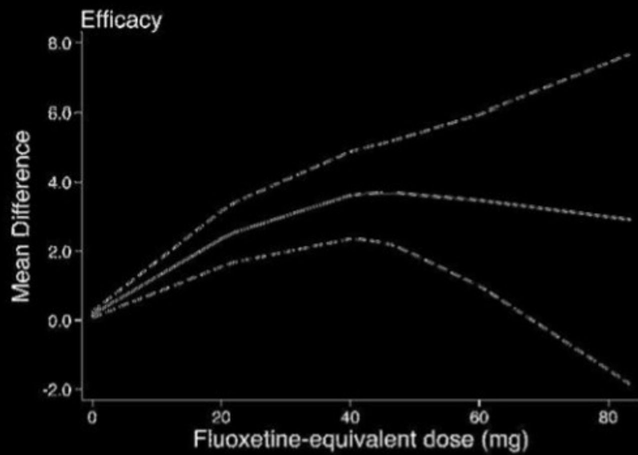
Tricyclic	Equiv to fluoxetine 40
Amitriptyline	122
Desipramine	196
Doxepin	140
Imipramine	137
Nortriptyline	101
Clomipramine	116

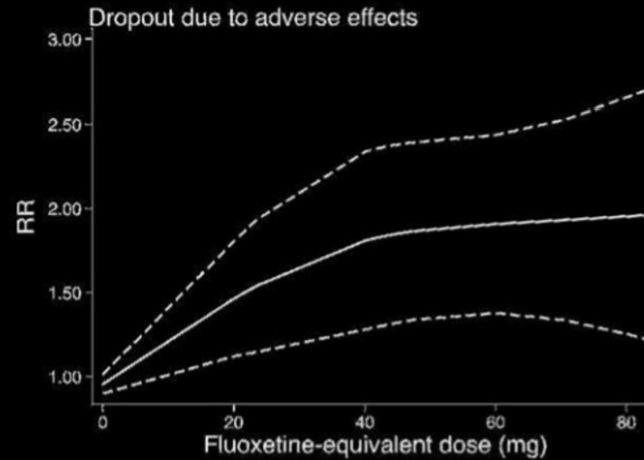
Hayasaka Y et al, J Affect Disord. 2015;180:179-184;
Furukawa TA et al. Lancet Psychiatry. 2019;6(7):601-609.

For meds with ?, we lack dose-response data.

SSRI Dose Response in OCD

Efficacy | **Dropout due to adverse effects**





Xu J et al, Front Psychiatry. 2021;12:717999; based on 11 trials

Clomipramine

- Highly serotonergic, but not a high risk of serotonin syndrome
- High level = seizures, cardiac conduction delay
- Keep below 500 ng/ml
  (clomipramine + norclomipramine 12 hr after dose)
- Caution: 2D6, 2C19, 1A2 inhibitors

Grapefruit, bupropion, CBD, duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline (≥ 150 mg/day)

Mood Stabilizers

Now approved ages 7 and up

Lithium

Depression/maintenance: 0.6-0.8 mmol/L

Acute mania: 0.8-1.2 mmol/L

Elderly: lower target level by ~30%

May spare kidneys by keeping < 0.8 mmol/L

Clos S et al, Lancet Psychiatry. 2015;2(12):1075-1083

Lamotrigine

Effective dose: 50-200 mg

In large trial, 200 = 400 mg (trends of superiority for 200 mg)

Cognition improves at 50-150 mg, can worsen in higher dose (word finding problems)

When to use higher doses (200-400): 3rd trimester, on HRT or carbamazepine

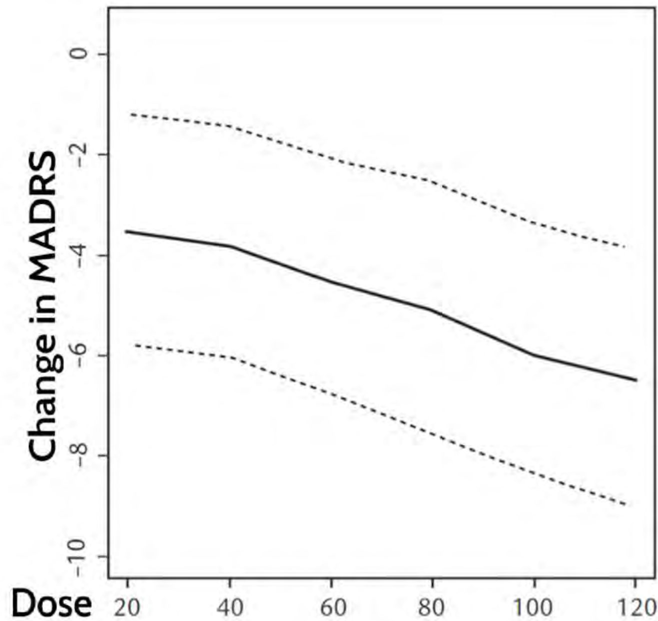
Calabrese JR et al, J Clin Psychiatry. 2003;64(9):1013-1024

Lamotrigine Dosing

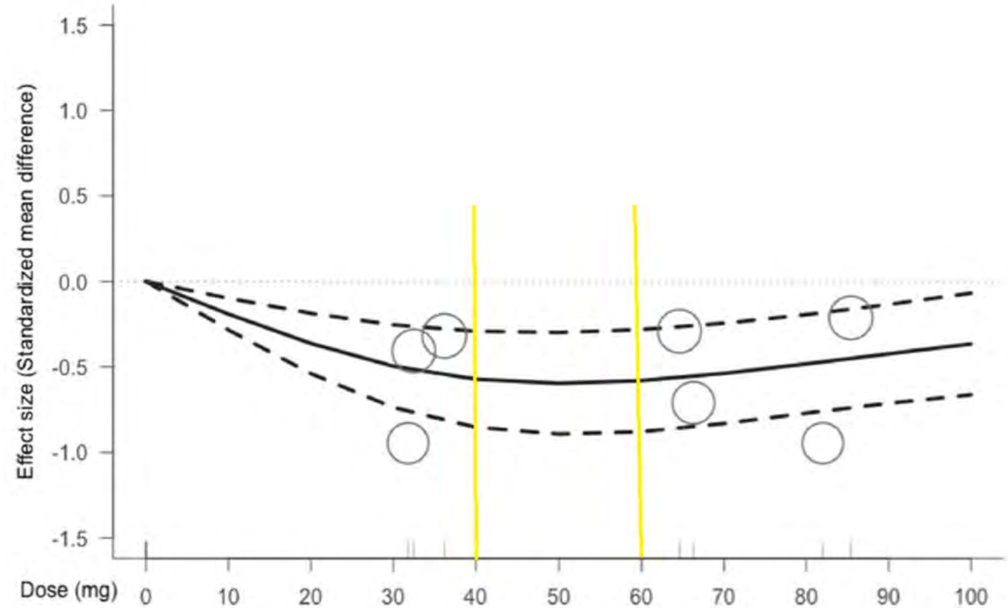
Population	Target dose	Titration
General	50-200 mg/day	25 mg qd x14 days, 50 mg qd x14 days, then increase by 50 mg/day every 1-2 weeks.
Women on estrogen-containing oral contraceptives	100-400 mg/day	Same as general
Children and adolescents (age < 18)*	0.85-3.5 mg/kg	See prescribing guidelines for weight-based titrations in children 12 and under. I recommend following these for adolescents under age 18 as well.
Geriatrics (age ≥ 65)	40-175 mg/day	Same as general
Pregnancy	100-400 mg/day in third trimester, but varies widely (best to check the serum level before pregnancy and again in second and third trimesters).	Same as general
On valproic acid	25-100 mg/day	25 mg qod x14 days, 25 mg qd x14 days, then increase by 25-50 mg/day every 1-2 weeks.
On carbamazepine, phenytoin, phenobarbital, or primidone	100-400 mg/day	50 mg qd x14 days, 100 mg qd x14 days, then increase by 100 mg/day every 1-2 weeks.
On topiramate	40-175 mg/day	Same as general
Genetic variations at UGT1A4	Unknown. Some guides suggest raising the dose by 135-180% for rapid metabolizers and lowering by 30-70% for slow metabolizers.	Unknown

*Lamotrigine is not FDA-approved in patients under age 18 with bipolar disorder, but it is approved for childhood epilepsy. Children need slower titration because they are at increased risk for a rash.

Lurasidone in Bipolar Depression



Flexible-dose

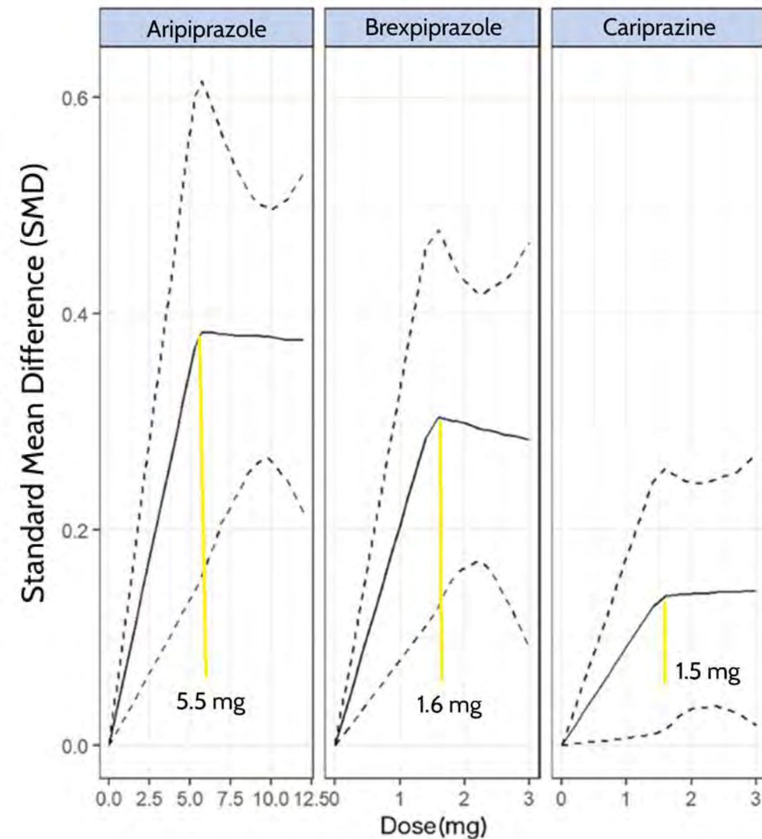


Fixed-dose analysis

Chapel S et al. Clin Ther. 2016;38(1):4-15; Lin YW et al, BMJ Ment Health 2024, 27(1):e301165

D3 Partial Agonists in Unipolar Depression

Optimal dose at aripiprazole 5.5 mg, brexpiprazole 1.6 mg, and cariprazine 1.5 mg



Network metaanalysis of 16 trials

Terao I, Kodama W. J Clin Psychopharmacol. 2024, 44(4):413-417.

Quetiapine

GAD: 150 mg

OCD: 200-300 mg

Major Depression: 150-300 mg

Bipolar Dep: 300 mg

Mania: 600 mg

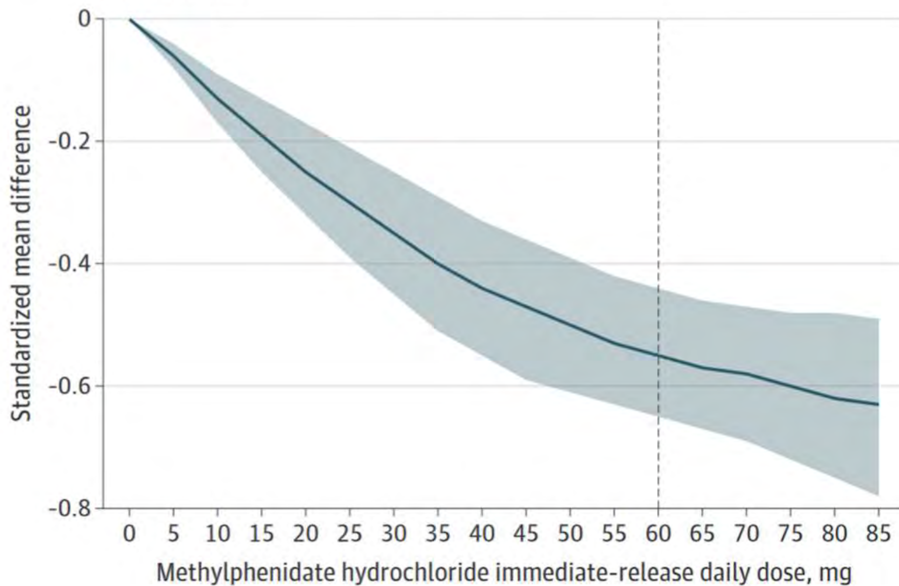
Schizophrenia: 500-600 mg

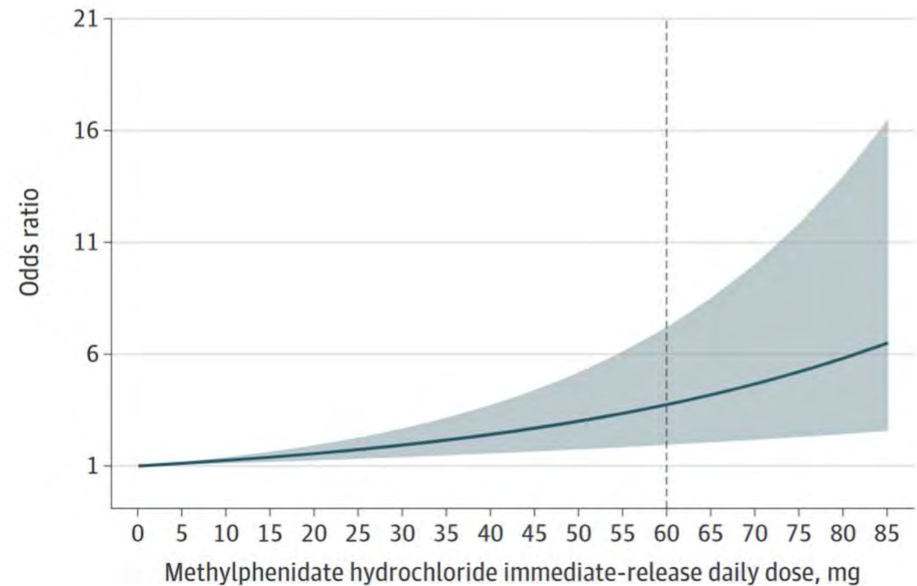
Lamotrigine may lower quetiapine 30%

Zhornitsky S et al, Int Clin Psychopharmacol. 2011;26(4):183-192

Stimulants

Methylphenidate dose-response

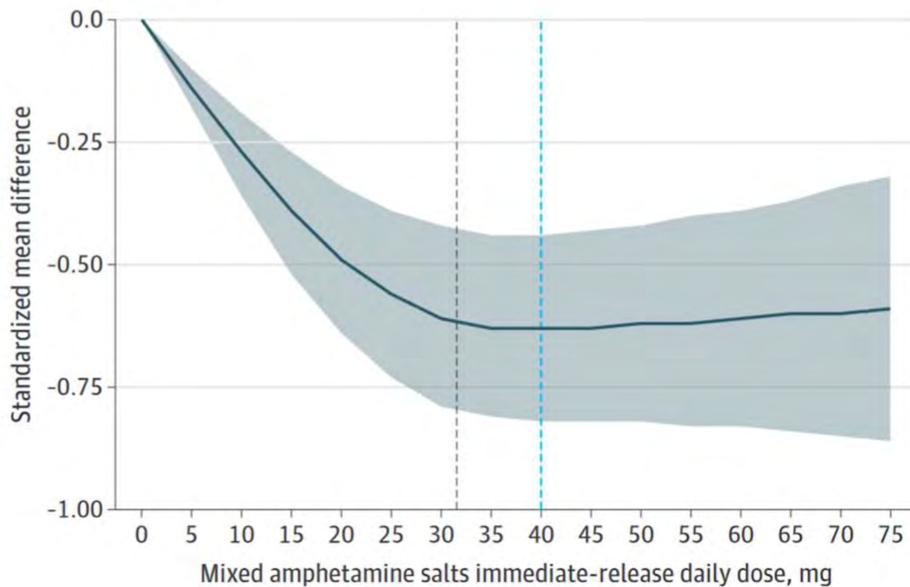


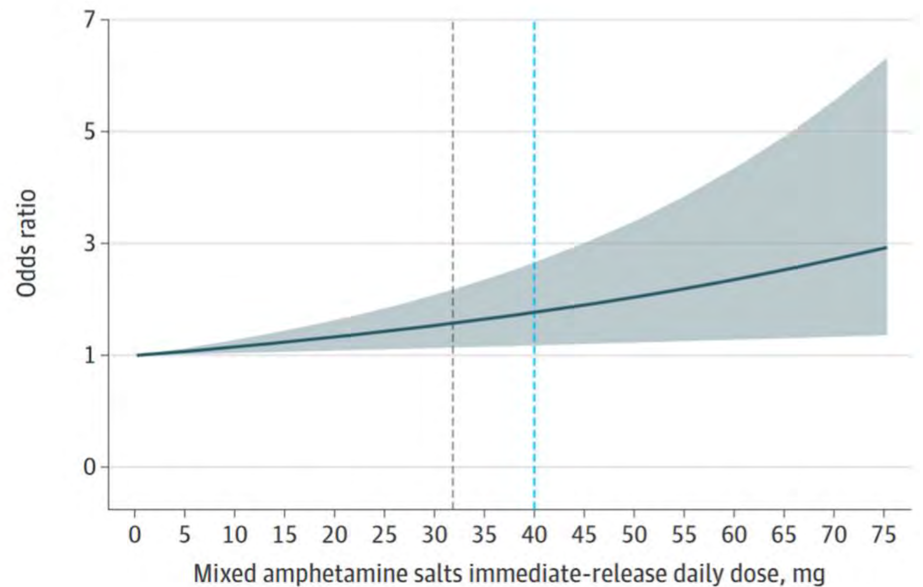


60 mg = Maximium risk:benefit

Farhat LC, et al. JAMA Psychiatry. 2024;81(2):157-166

Amphetamine dose-response





Risk-benefit max at 30-35 mg Adderall (=25-30 dextroamphetamine, 70-80 Vyvanse)

Farhat LC, et al. JAMA Psychiatry. 2024;81(2):157-166

High dose stimulants

In narcolepsy, over 120 mg/day of either stimulant associated with higher risk of (n=112)…

Psychosis (12x)

Psychiatric hospitalization (3x)

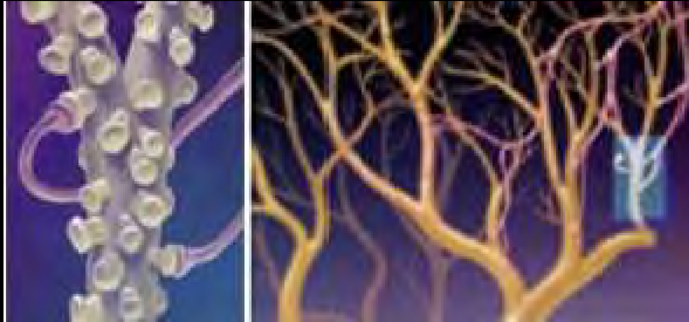
Substance abuse (4x)

Possibly suicide (5x)

In hospitalized patients (n=4122), 3-5x increase risk of psychosis/mania with amphetamine Rx (esp > 30 mg dextroamphetamine).

No difference for Rx methylphenidate.

Auger RR, Sleep 2005; Moran LV et al Am J Psychiatry 2024;181(10):901-909



Neurotoxicity

High dose amphetamine -->

Dopamine elevation in cytoplasm -->

Oxidative stress and inflammation -->

Damaged dopamine nerve terminals in hippocampus and cerebral cortex

Older brains have…

More toxicity from methamphetamine

Higher amphetamine levels in CNS (2-fold higher compared to younger)

[in animal studies]

Berman SM, Mol Psychiatry 2009

High dose stimulants

Think twice before going above….

Amphetamines

- Mixed amphetamines (Adderall) 35 mg
- Dextroamphetamine 30 mg
- Lisdexamfetamine (Vyvanse) 80 mg

Methylphenidates

- Methylphenidate 60 mg
- Dexmethylphenidate 30 mg

Questions?
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