VCH Family Practice Rounds

Anxiety and Depression

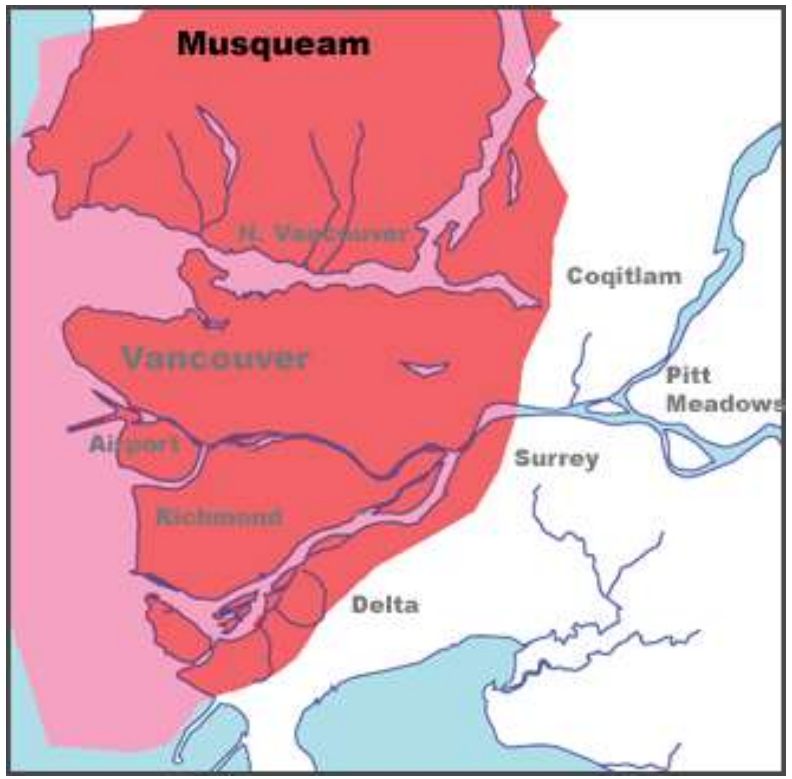
Beyond First Line Treatments

Dr. Ram Randhawa

January 25, 2022

We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam (xʷməθkʷəy̓əm), Squamish (Sḵwx̱wú7mesh) and Tsleil-Waututh (səlilwətaɬ) peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



disclosure & mitigation of bias

Dr. Randhawa has no affiliation, financial or otherwise, with a pharmaceutical, medical device, communications, or other for profit organization that is linked with this presentation.

This presentation will discuss the use of medications in the management of conditions for which those medications have not received regulatory approval in Canada ("off-label" use of medications). Any such off-label use will be clearly indicated.

recent antidepressants

1 2 3

vortioxetine (Trintellix): marketed as a "serotonin modulator and stimulator" – mechanisms include

serotonin re-uptake inhibition – antidepressant effect
5-HT1A agonist
5-HT1B partial agonist
5-HT1D antagonist
5-HT3 blockade – fewer gastrointestinal side effects, more potent effect
5-HT7 blockade – more potent antidepressant effect

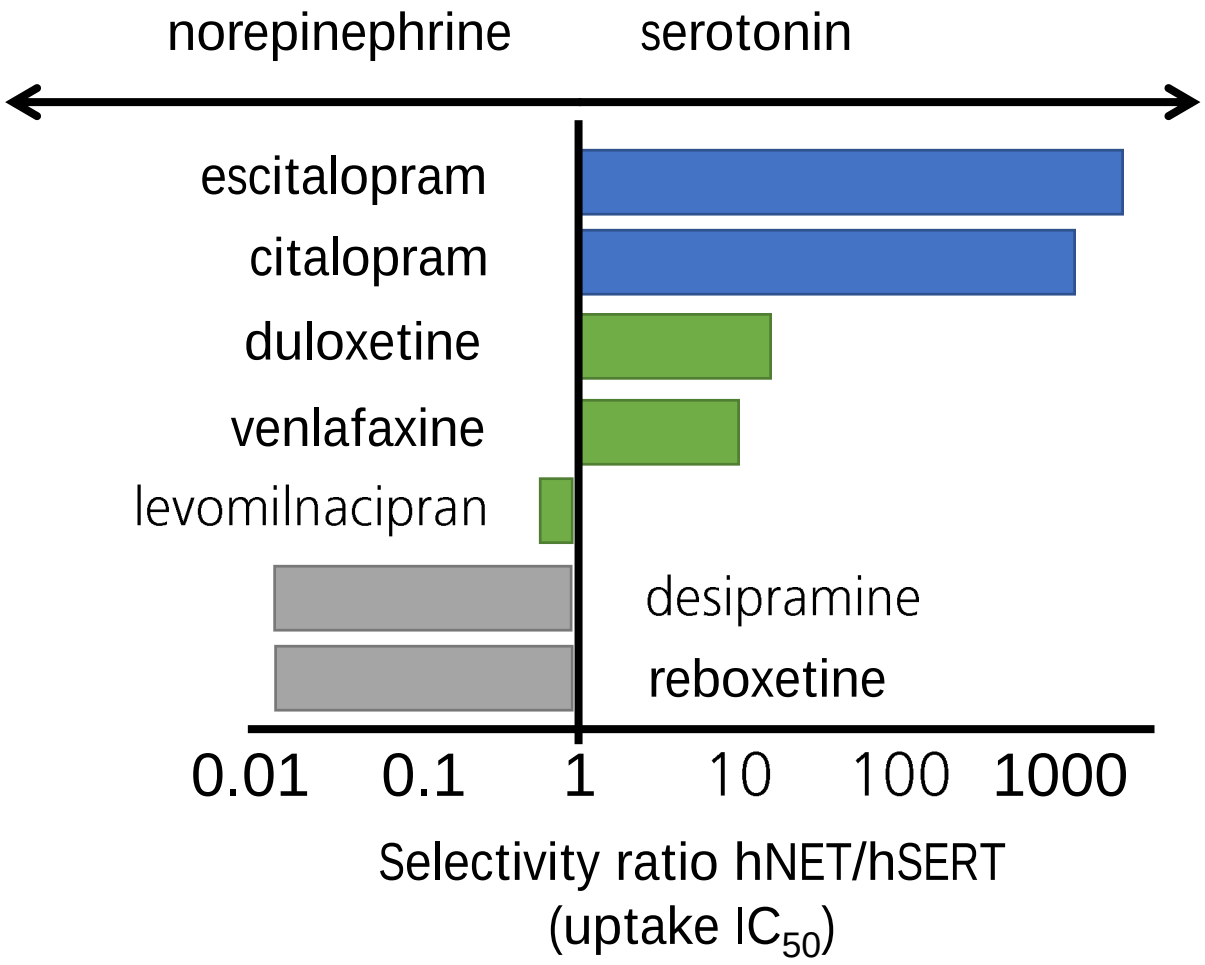
very few side effects other than nausea

recent antidepressants

vilazodone (Viibryd), available in the US since 2011, and marketed in Canada in January 2018; both an SSRI and a 5HT-1A partial agonist

few sexual side effects and no weight gain, but significant diarrhea and nausea.

recent antidepressants



Fetzima

levomilnacipram (Fetzima) approved by FDA in July 2013 and marketed in Canada in November 2015; similar to other SNRIs (venlafaxine, desvenlafaxine, duloxetine) but has a more "balanced" effect.

Auclair, A. L., Martel, J. C., Assié, M. B., Bardin, L., Heusler, P., Cussac, D., Marien, M., Newman-Tancredi, A., O'Connor, J. A., & Depoortère, R. (2013). Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety. *Neuropharmacology*, *70*, 338–347. https://doi.org/10.1016/j.neuropharm.2013.02.024

first and second line

large randomized controlled trials and/or meta-analyses

small randomized controlled trials and/or prospective studies

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder (Canadian Journal of Psychiatry, Vol 61 No 9, Sep 2016)

first line treatments for major depressive disorder

	daily cost
citalopram	0.28
escitalopram	0.50
fluoxetine	0.50
fluvoxamine	0.60
paroxetine	0.54
sertraline	0.24
bupropion	0.43
mirtazapine	0.68
venlafaxine	0.35
desvenlafaxine	2.89
duloxetine	1.17
vortioxetine	3.61

SSRIs have been the mainstay for the treatment of depression for more than 30 years, since Prozac was first approved by Health Canada in 1989

there is overwhelming evidence that they are effective in the treatment of depression and multiple other mental health conditions

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Wellbutrin was first approved in 1998 and is an NDRI – it is stimulating and provokes anxiety, but has been helpful in treating depression as well as various addictions and problems with attention and focus

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Remeron was approved in 2001 and is a "noradrenergic and selective serotonergic antidepressant" (NaSSA) – it is very sedating and stimulates appetite but is less likely to cause anxiety and may have fewer gastrointestinal side effects

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Effexor was approved in 1994 and was the first SNRI affecting both serotonin and norepinephrine re-uptake. Like Paxil, it is notorious for causing significant discontinuation syndrome, especially if stopped abruptly.

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Trintellix is the only "newer" antidepressant that has become a "first line" recommendation in the CANMAT guidelines.

Neither **Fetzima** (levomilnacipran) nor **Viibryd** (vilazodone) are recommended as first line treatments at this time.

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escitalopram	0.50	
fluoxetine	0.50	
fluvoxamine	0.60	
paroxetine	0.54	
sertraline	0.24	
bupropion	0.43	not covered (special authority: diagnosis depression)
mirtazapine	0.68	
venlafaxine	0.35	
desvenlafaxine	2.89	not covered
duloxetine	1.17	not covered (special authority: for neuropathic pain only)
vortioxetine	3.61	not covered (special authority: if failed 2 antidepressants)

desvenlafaxine, duloxetine, and vortioxetine are the most expensive of these medications

	MDD	GAD	SAD	panic	OCD	PTSD
citalopram						
escitalopram						
fluoxetine						
fluvoxamine						
paroxetine						
sertraline						
bupropion						
mirtazapine						
venlafaxine						
desvenlafaxine						
duloxetine						
vortioxetine						

	MDD	other indications (not necessarily from Health Canada)
citalopram		
escitalopram		
fluoxetine		bulimia, symptoms of menopause
fluvoxamine		
paroxetine		symptoms of menopause
sertraline		premenstrual dysphoric disorder
bupropion		seasonal prevention, smoking cessation (Zyban only)
mirtazapine		
venlafaxine		symptoms of menopause
desvenlafaxine		
duloxetine		pain, fibromyalgia, stress incontinence
vortioxetine		

selecting an antidepressant

patient preference and previous response

if an older medication was effective and well tolerated, it may be a better choice than something new

comorbidities

drug and food interactions

tolerability

efficacy

cost

selecting an antidepressant

patient preference and previous response

comorbidities

duloxetine is indicated for pain, fluoxetine for bulimia; vortioxetine may be better for cognition, and bupropion for ADHD type symptoms

drug and food interactions

tolerability

efficacy

cost

selecting an antidepressant

patient preference and previous response

comorbidities

drug and food interactions

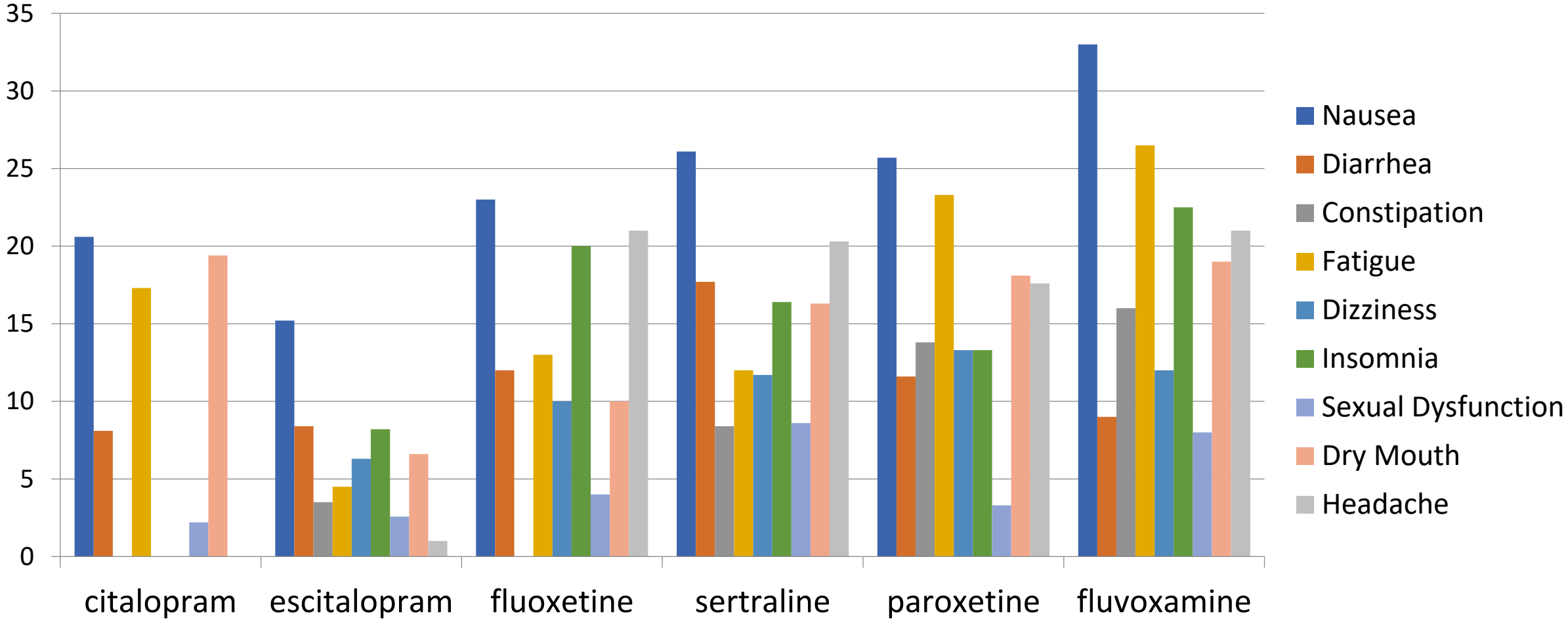
paroxetine and **fluoxetine** are more likely to have significant drug interactions; **sertraline** should be taken with food (if you're in Canada — if you are in the USA you can take it with or without food)

tolerability

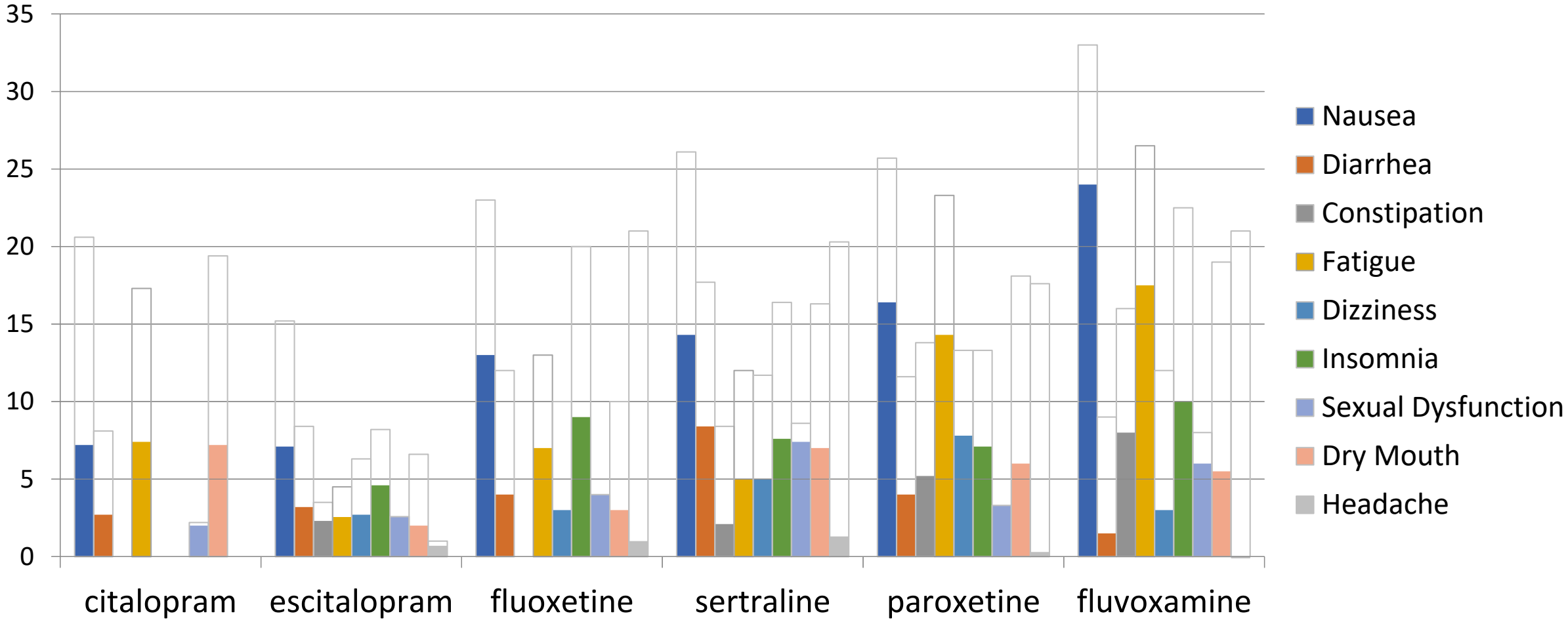
efficacy

cost

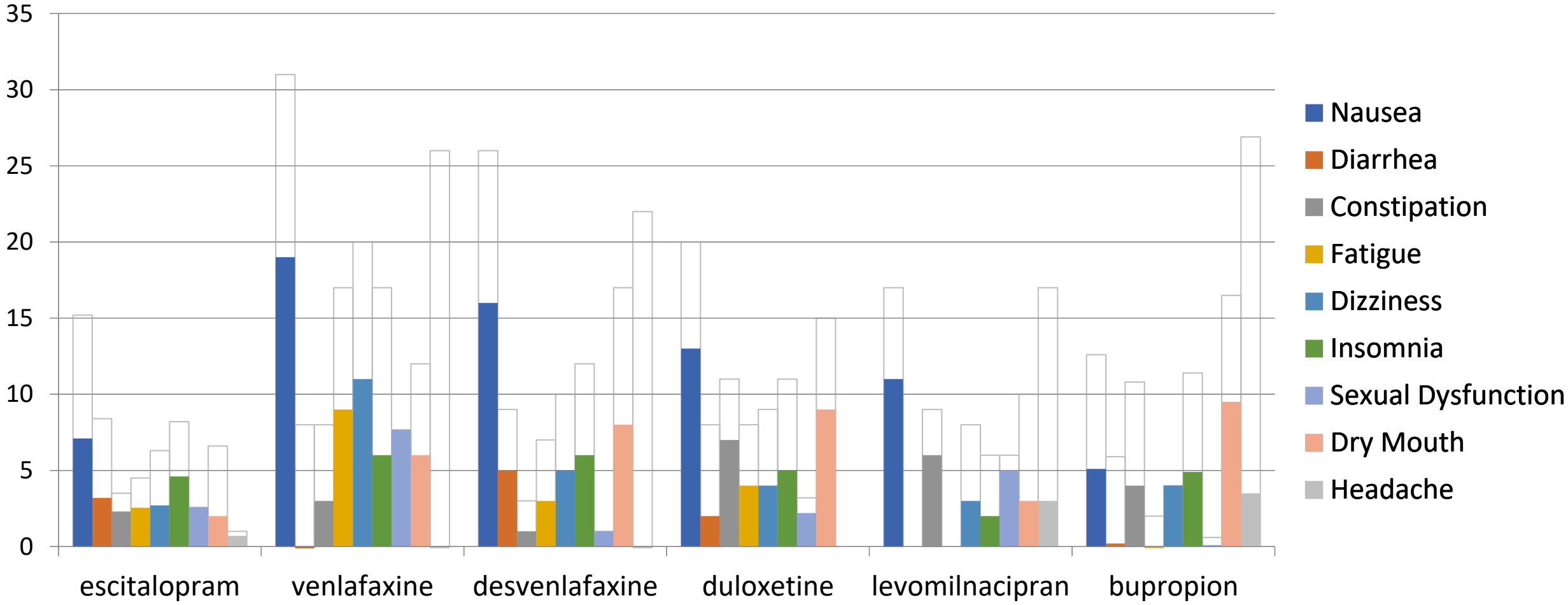
antidepressant side effects



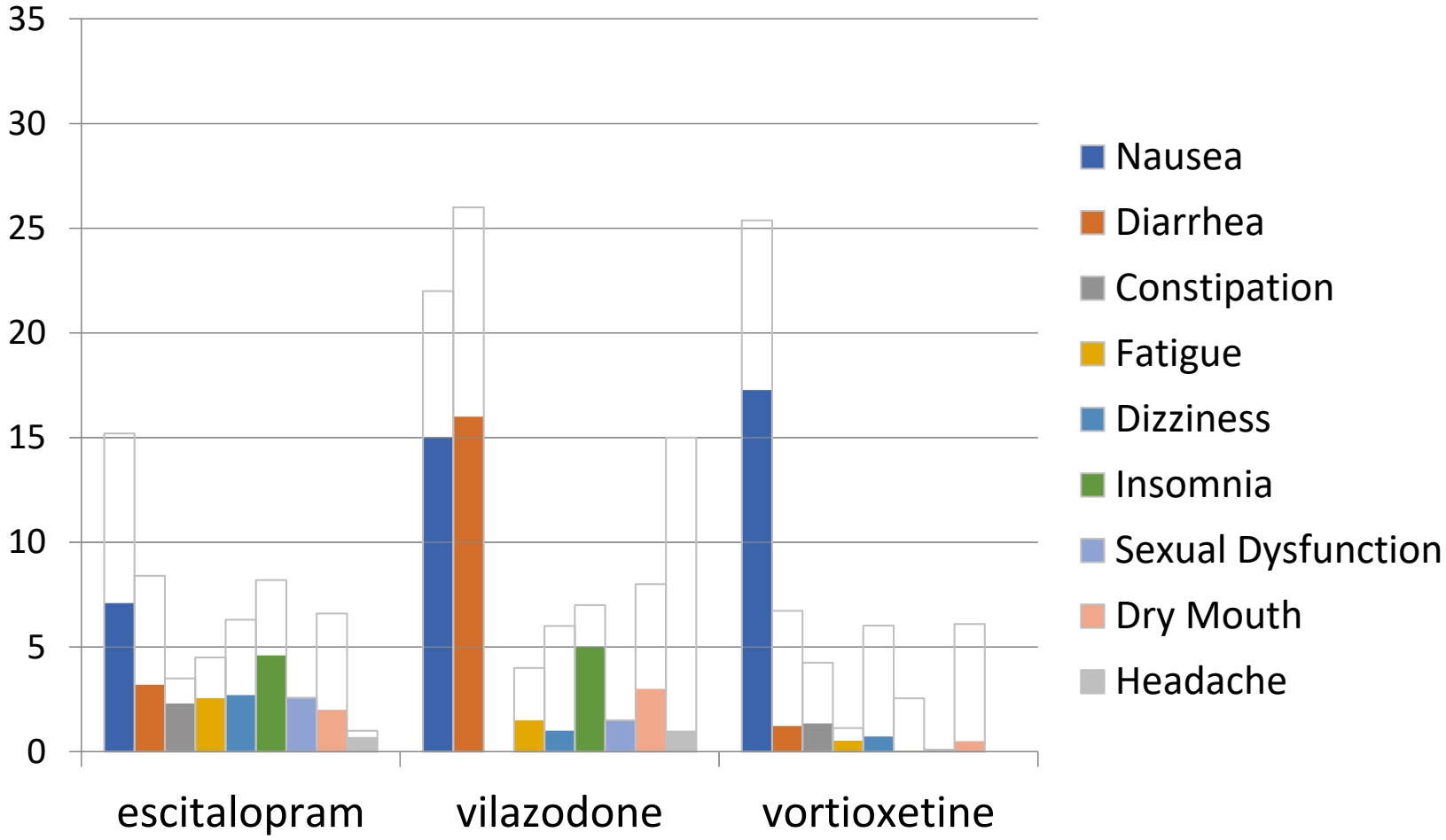
antidepressant side effects



antidepressant side effects



antidepressant side effects



antidepressant side effects

sexual side effects are reported in up to 70% of individuals on SSRIs (higher than the rate of 2% to 16% noted in clinical trials)

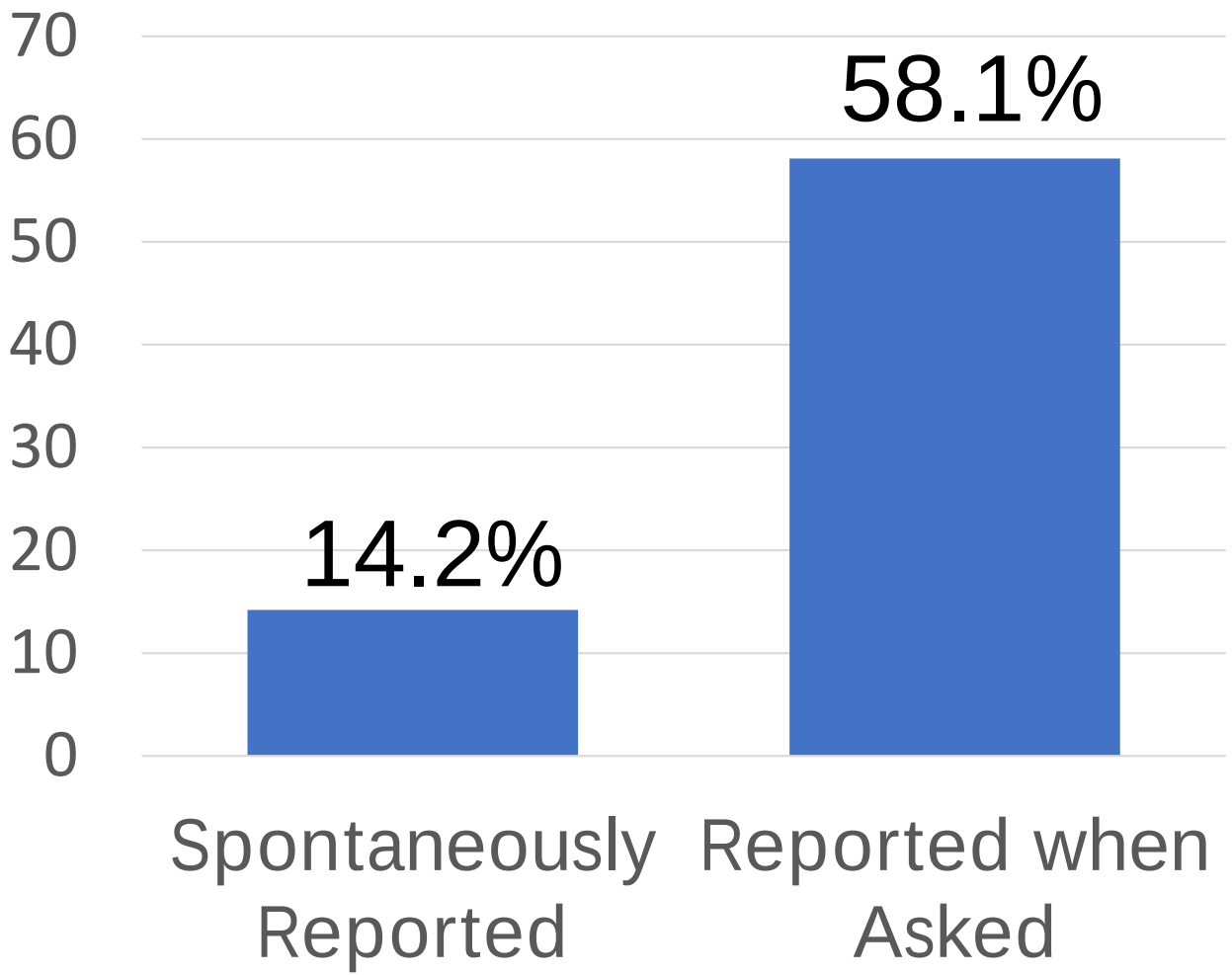
most common are decreased libido, erectile dysfunction, numbness, decreased lubrication, and difficulty with orgasm

a small but unknown percentage will have persistent post-SSRI sexual dysfunction

antidepressant side effects

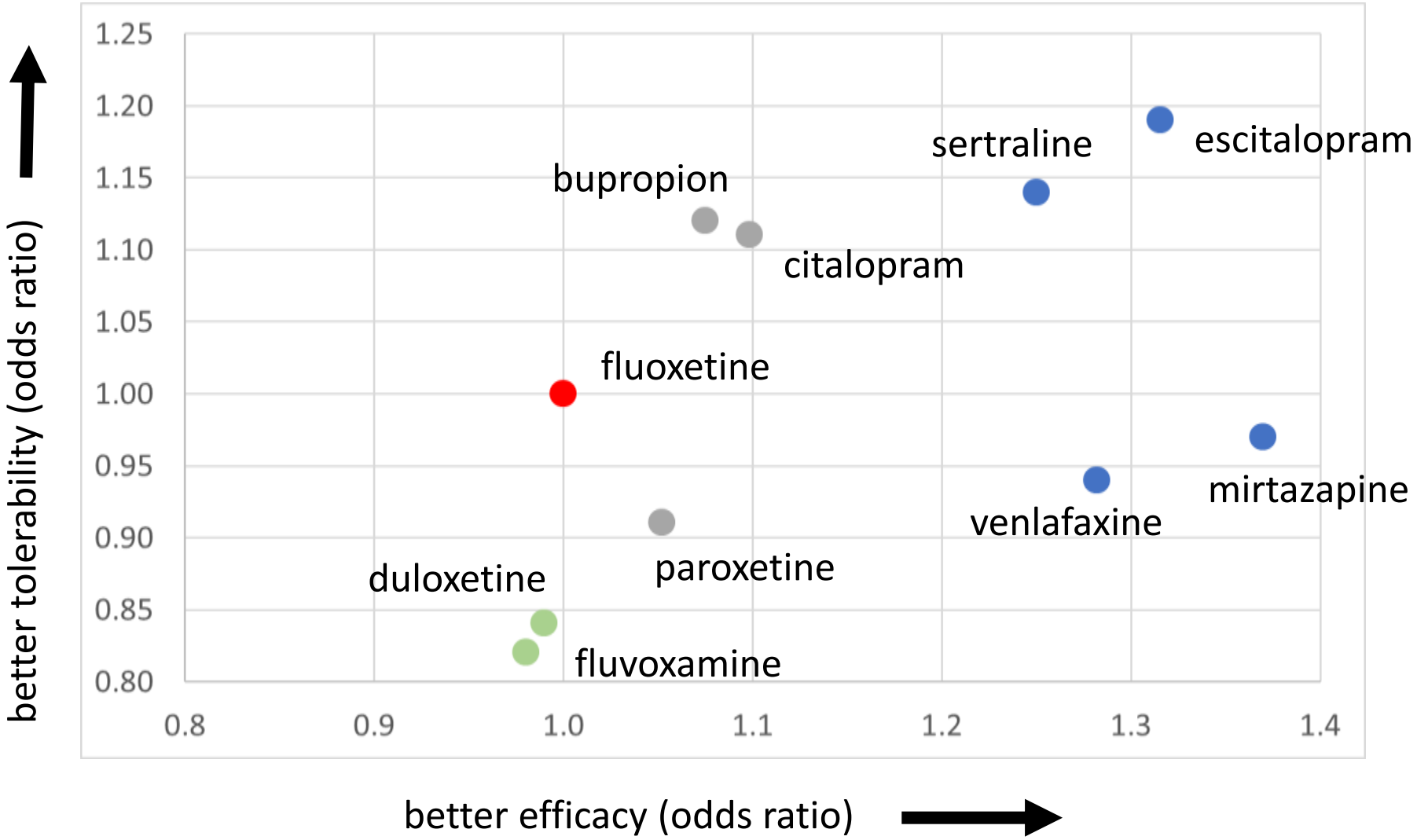
sexual side effects are reported more frequently with direct questioning

lower risk with bupropion, vortioxetine, vilazodone



Montejo-González AL, Llorca G, Izquierdo JA, Ledesma A, Bousoño M, Calcedo A, Carrasco JL, Ciudad J, Daniel E, De la Gandara J, Derecho J, Franco M, Gomez MJ, Macias JA, Martin T, Perez V, Sanchez JM, Sanchez S, Vicens E. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. J Sex Marital Ther. 1997 Fall;23(3):176-94. doi: 10.1080/00926239708403923.

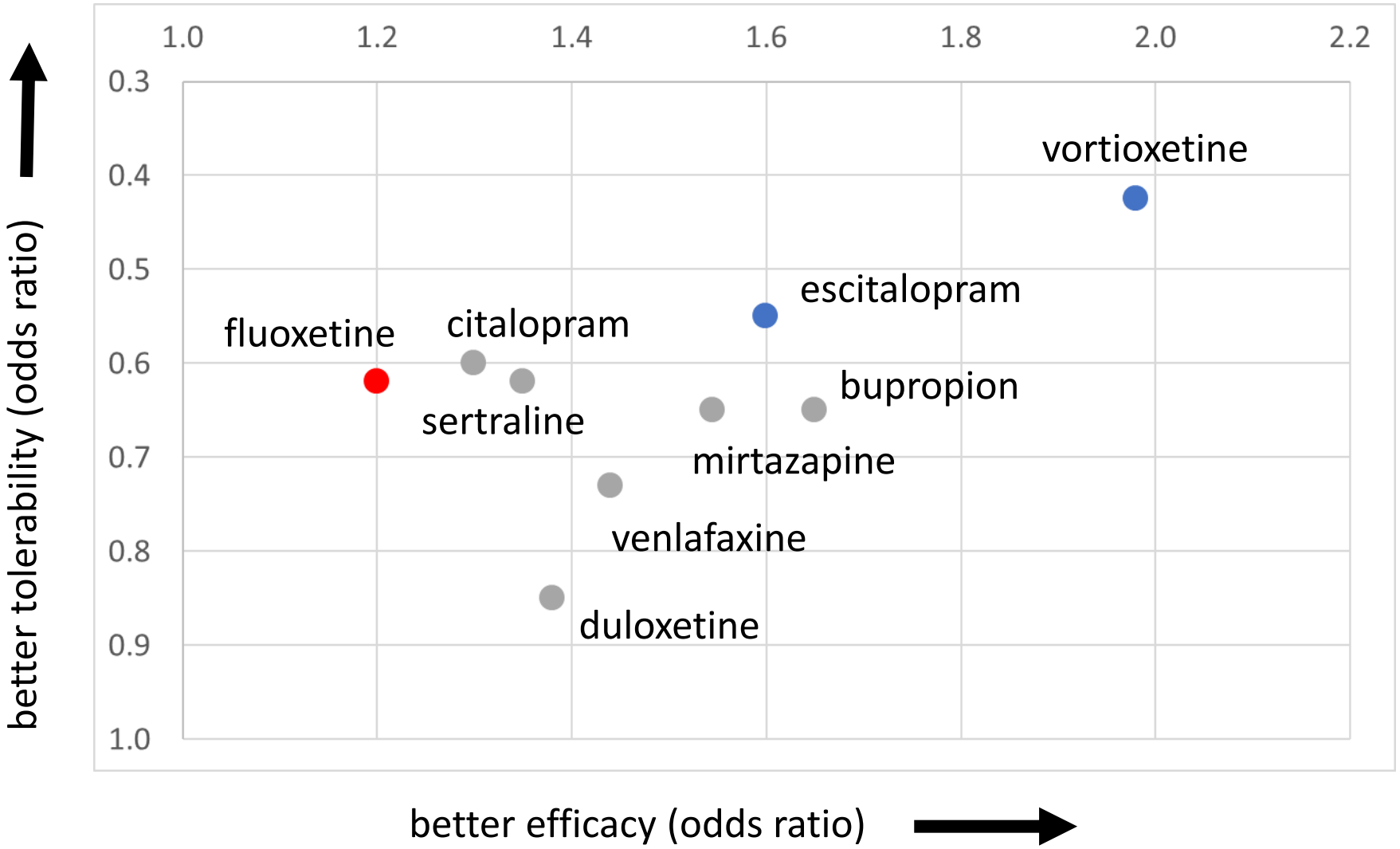
are some antidepressants better than others?



escitalopram, sertraline, venlafaxine, and mirtazapine have some evidence of slightly superior efficacy (5 to 6%) based on meta-analysis (2009)

Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, Watanabe N, Nakagawa A, Omori IM, McGuire H, Tansella M, Barbui C. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009 Feb 28;373(9665):746-58. doi: 10.1016/S0140-6736(09)60046-5.

are some antidepressants better than others?



in a similar but updated meta-analysis (2018) vortioxetine and escitalopram have some evidence of superior tolerability and efficacy

Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR. 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. Lancet. 2018 Apr 7;391(10128):1357-1366. doi: 10.1016/S0140-6736(17)32802-7.

are some antidepressants better than others?

individual variability in antidepressant response likely supersedes any trends to superior efficacy or tolerability that have been found in large population studies

assessing efficacy

determining whether an antidepressant has been helpful is often not as straightforward as we might expect

how do we tell when our first line treatment isn't working?

assessing efficacy

rating scales (QIDS-SR or PHQ-9) can be useful tools to supplement clinical judgement

improvement: > 20% reduction in scores
response: > 50% reduction in scores
remission: scores in "normal" range
0-5 for QIDS-SR or 0-4 for PHQ-9

Kudlow PA, McIntyre RS, Lam RW. Early switching strategies in antidepressant non-responders: current evidence and future research directions. CNS Drugs. 2014 Jul;28(7):601-9. doi: 10.1007/s40263-014-0171-5.

assessing efficacy

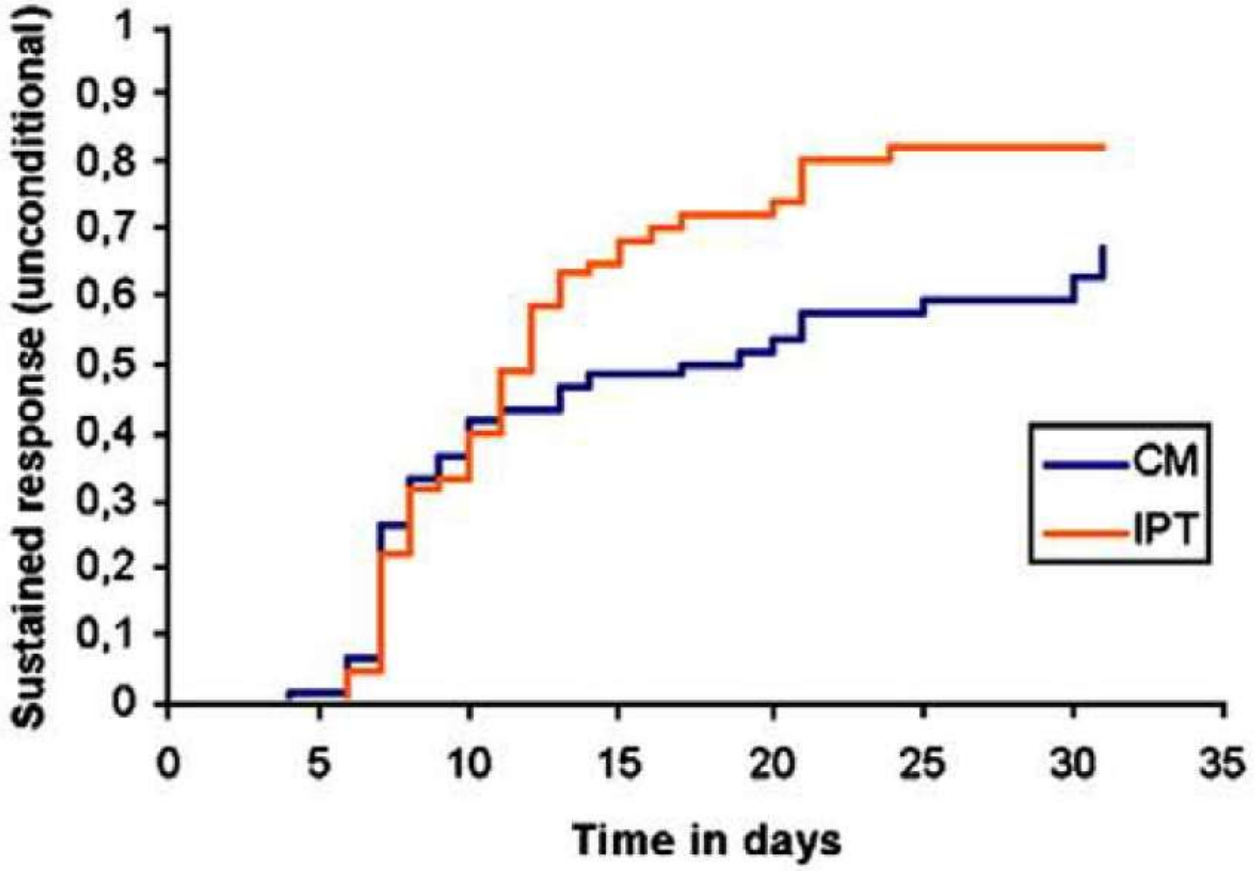
by 2 to 4 weeks we expect noticeable improvement (a 20% reduction in depression scales)

early improvement is a good sign – if there is no improvement by 2 weeks, the likelihood of improvement by 6 weeks is low; by 4 weeks, consider a new strategy

Kudlow PA, McIntyre RS, Lam RW. Early switching strategies in antidepressant non-responders: current evidence and future research directions. CNS Drugs. 2014 Jul;28(7):601-9. doi: 10.1007/s40263-014-0171-5.

assessing efficacy

some may report a therapeutic response within days of starting treatment – note that this does not necessarily imply a "placebo" effect



van Calker D, Zobel I, Dykierek P, Deimel CM, Kech S, Lieb K, Berger M, Schramm E. Time course of response to antidepressants: predictive value of early improvement and effect of additional psychotherapy. J Affect Disord. 2009 Apr;114(1-3):243-53. doi: 10.1016/j.jad.2008.07.023.

when first line treatments don’t work

- optimize the current medication
- switch to a different first line choice, or to a second line option
- add another medication
- try a neurostimulation intervention
- add psychotherapy

when first line treatments don’t work

optimize the current medication

has the patient been consistently compliant? can the dose be increased? can the timing be adjusted to enhance compliance?

Sequenced Treatment Alternatives for Resistant Depression (STAR*D)

1	citalopram 20 to 60 mg for 12 weeks	
2	switching to bupropion or venlafaxine or sertraline	adding on bupropion or buspirone or CBT
3	switching to mirtazapine or nortriptyline	adding on lithium or T3
4	switching to an MAOI	combining venlafaxine + mirtazapine

Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163:1905–1917.

Sequenced Treatment Alternatives for Resistant Depression (STAR*D)

for those who persevered with treatment, 67% eventually achieved remission – there were no significant differences between the different strategies

	remission rate	cumulative remission
step 1	36.8%	36.8%
step 2	30.6%	56.1%
step 3	13.7%	62.1%
step 4	13.0%	**67.0%**

Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163:1905–1917.

when first line treatments don't work

switch to a different first line choice, or to a second line option

in STAR*D response rates to citalopram were 33% and remission 47% – for those who did not respond, switching to a different first line medication led to remission in about 25%

bupropion	26%
sertraline	27%
venlafaxine	25%

when first line treatments don't work

add another medication for added effect

	daily cost	
aripiprazole	1.34	Abilify is indicated as an adjunct for depression
quetiapine	0.70	indicated if failed conventional antidepressant
risperidone	0.67	not indicated for depression
brexpiprazole	4.13	indicated as an adjunct for depression
olanzapine	0.77	not indicated for depression
bupropion	0.43	indicated for depression
lithium	0.57	not indicated for depression (mania only)
mirtazapine	0.68	indicated for depression
modafinil	1.42	not indicated for depression (narcolepsy, OSA, SWD)
liothyronine	3.10	not indicated for depression (hypothyroidism)

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when first line treatments don't work

add another medication for added effect

	daily cost	
aripiprazole	1.34	not covered (special authority
quetiapine	0.70	psychosis + drug failure)
risperidone	0.67	
brexpiprazole	4.13	not covered (special authority: psychosis + drug failure)
olanzapine	0.77	not covered (special authority: psychosis + drug failure)
bupropion	0.43	not covered (special authority: depression)
lithium	0.57	
mirtazapine	0.68	
modafinil	1.42	not covered (special authority: narcolepsy)
liothyronine	3.10	

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when first line treatments don't work
add another medication for added effect

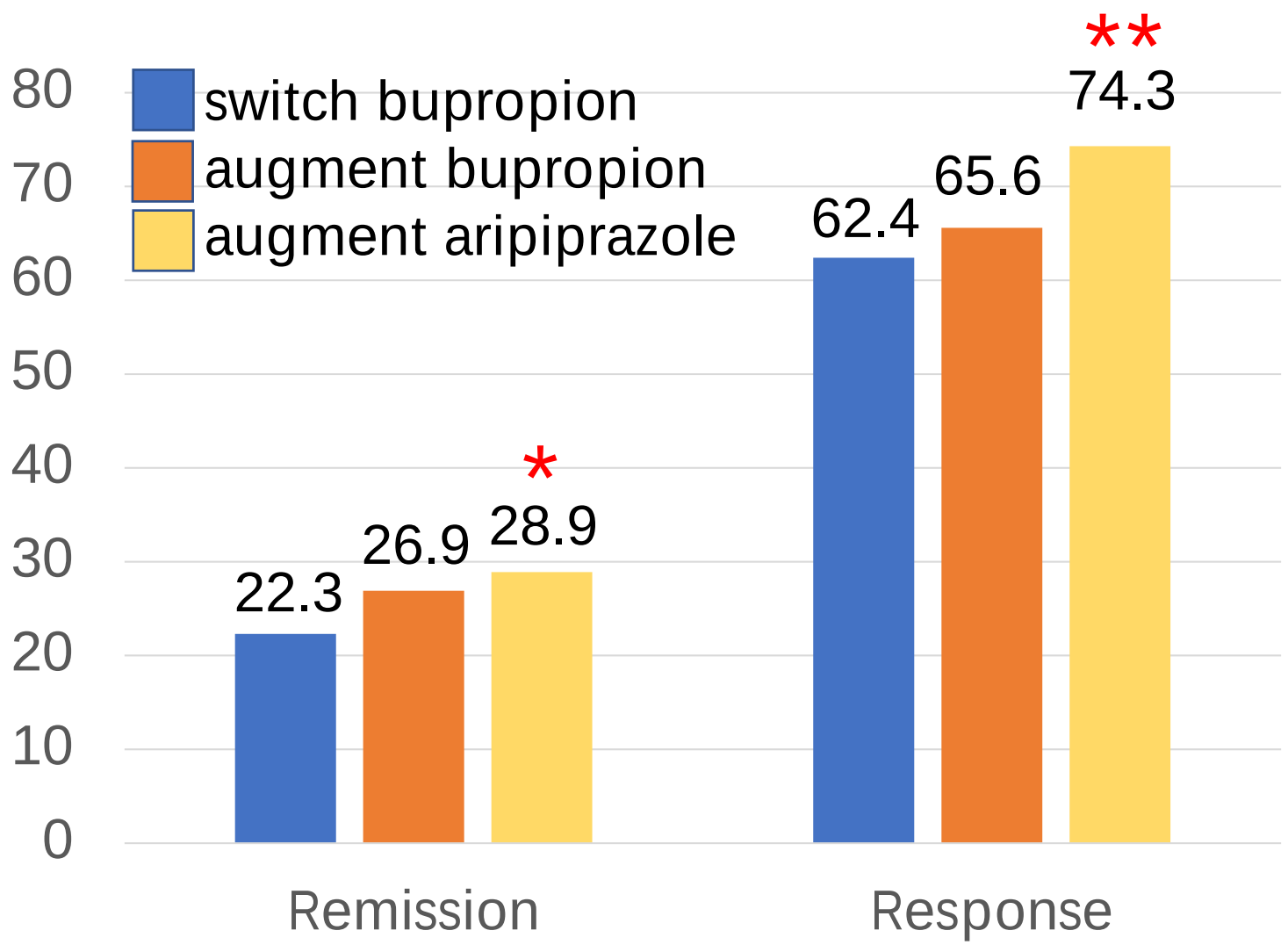
aripiprazole	2-5 mg (max 15 mg)	1st LINE
quetiapine	50 mg x 2d then 150 mg	
risperidone	0.25-3 mg	
brexpiprazole	1-3 mg	2nd LINE
olanzapine	5-10 mg	
bupropion	150-300 mg	
lithium	600-1200 mg	
mirtazapine	30-60 mg	
modafinil	100-400 mg	
liothyronine	25-50 mcg	

whether a medication has a formal indication for a given condition is a poor proxy for the scientific evidence supporting its use for that condition

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder (Canadian Journal of Psychiatry, Vol 61 No 9, Sep 2016)

switching vs. augmentation

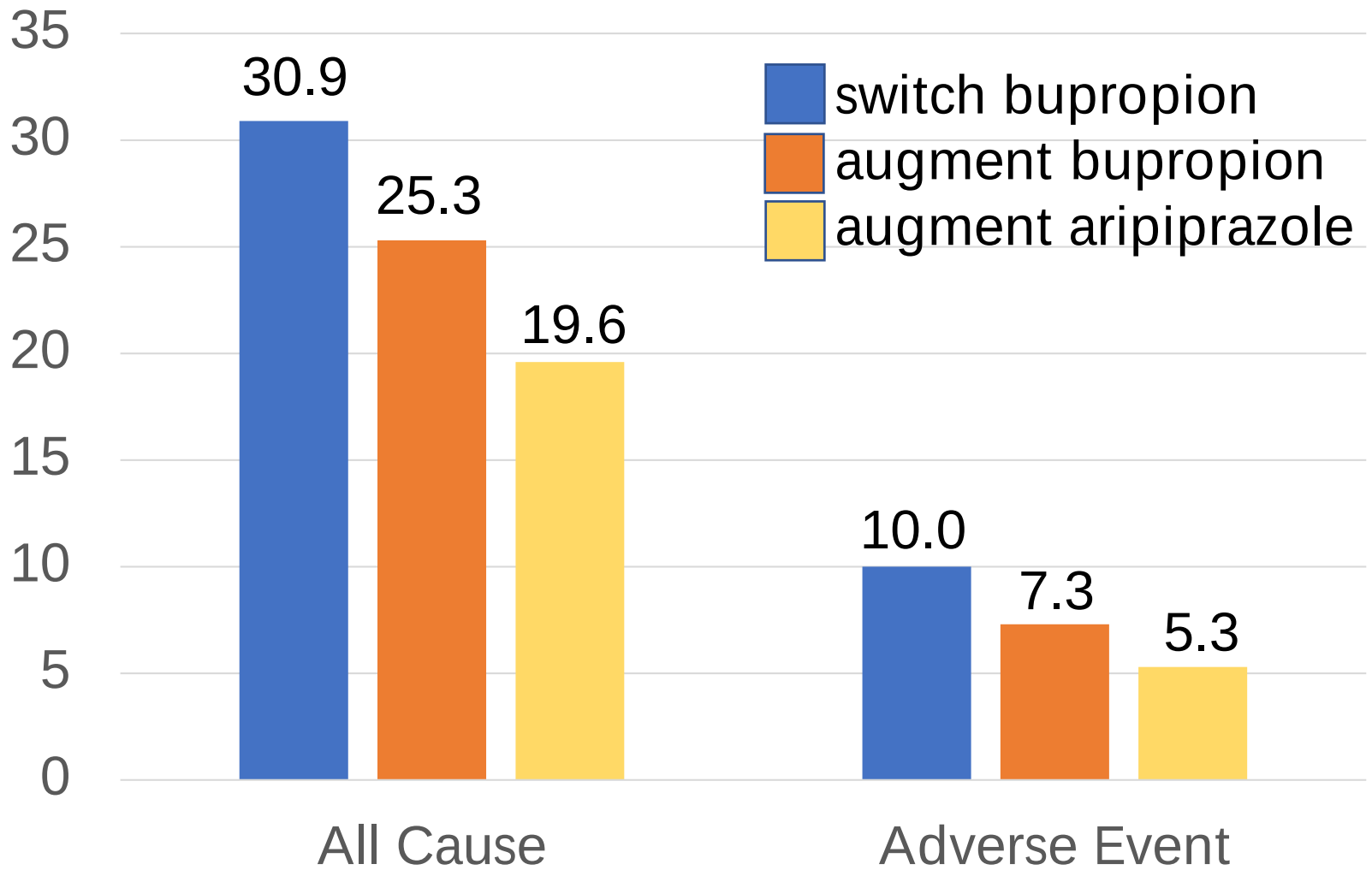
augmentation with aripiprazole was significantly better for response than either switching to bupropion or augmentation with bupropion



Mohamed S et al. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. JAMA. 2017 Jul 11;318(2):132-145. doi: 10.1001/jama.2017.8036.

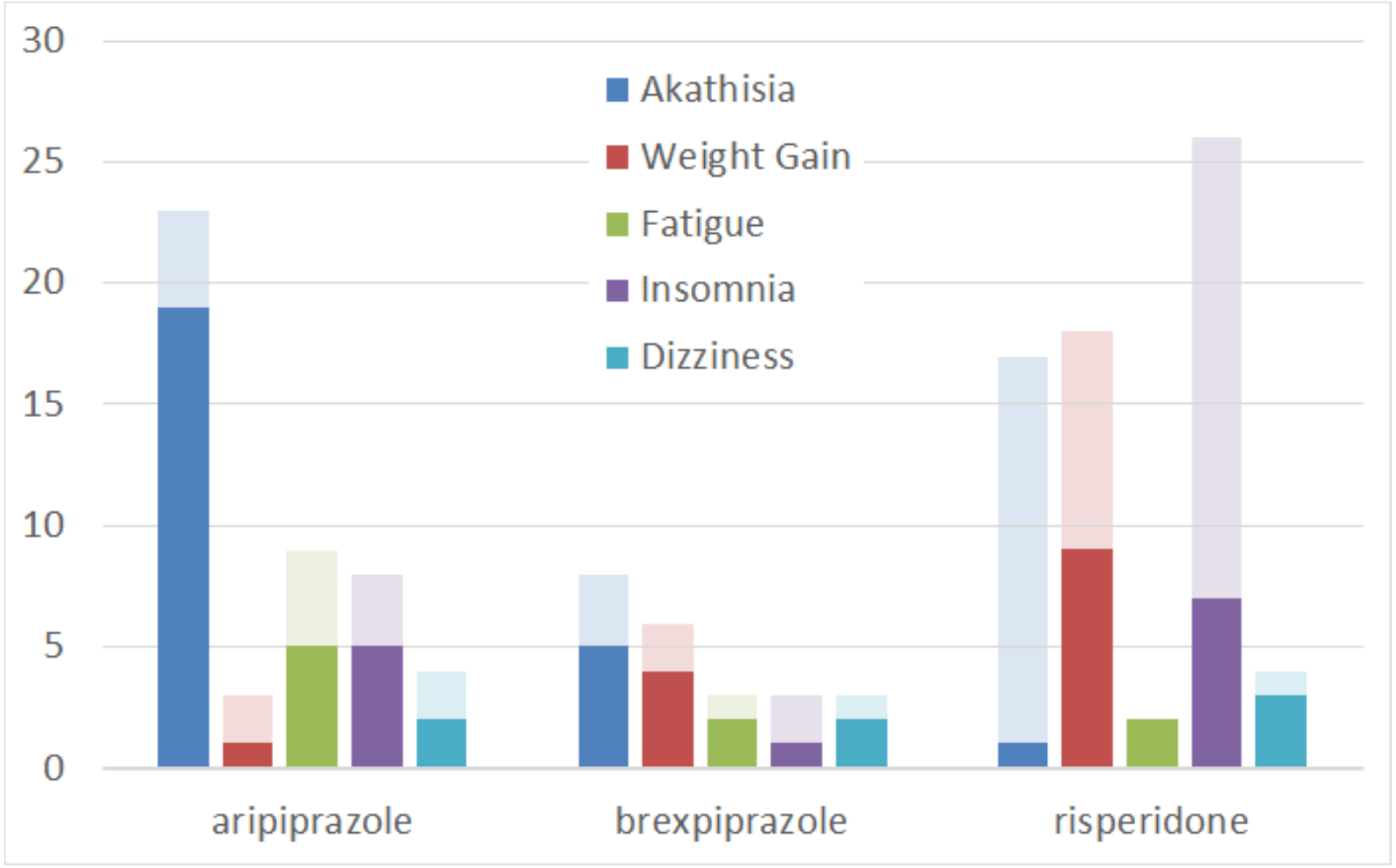
switching vs. augmentation

discontinuation rates were lower with aripiprazole; bupropion caused more anxiety, but aripiprazole cause fatigue, weight gain, and akathisia



side effects of antipsychotics

generally speaking, the newer atypical antipsychotics are well tolerated, especially at lower doses

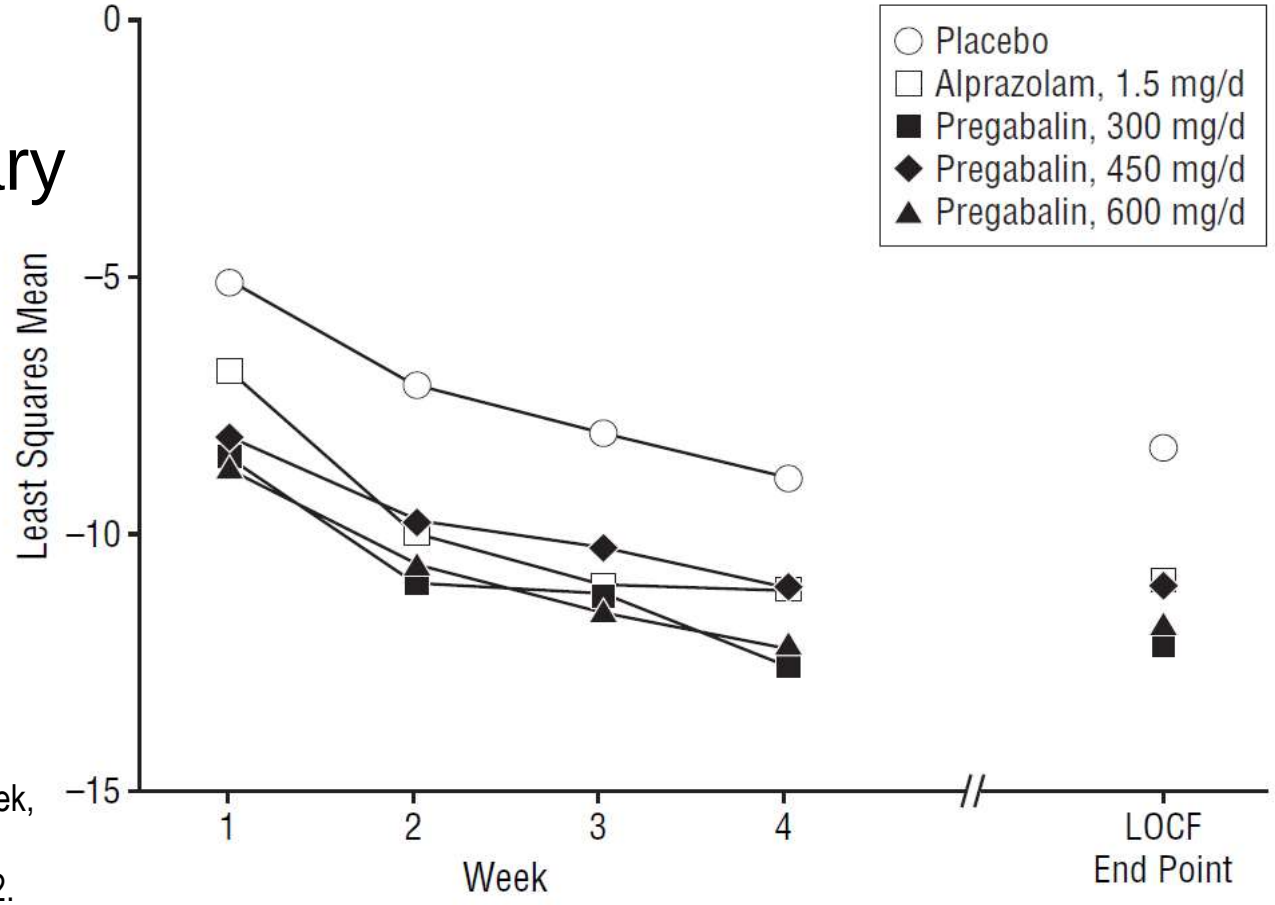


pregabalin and gabapentin

gabapentinoids bind to the $\alpha_2\delta$ subunit of voltage dependent calcium channels; they have no affinity for GABA receptors

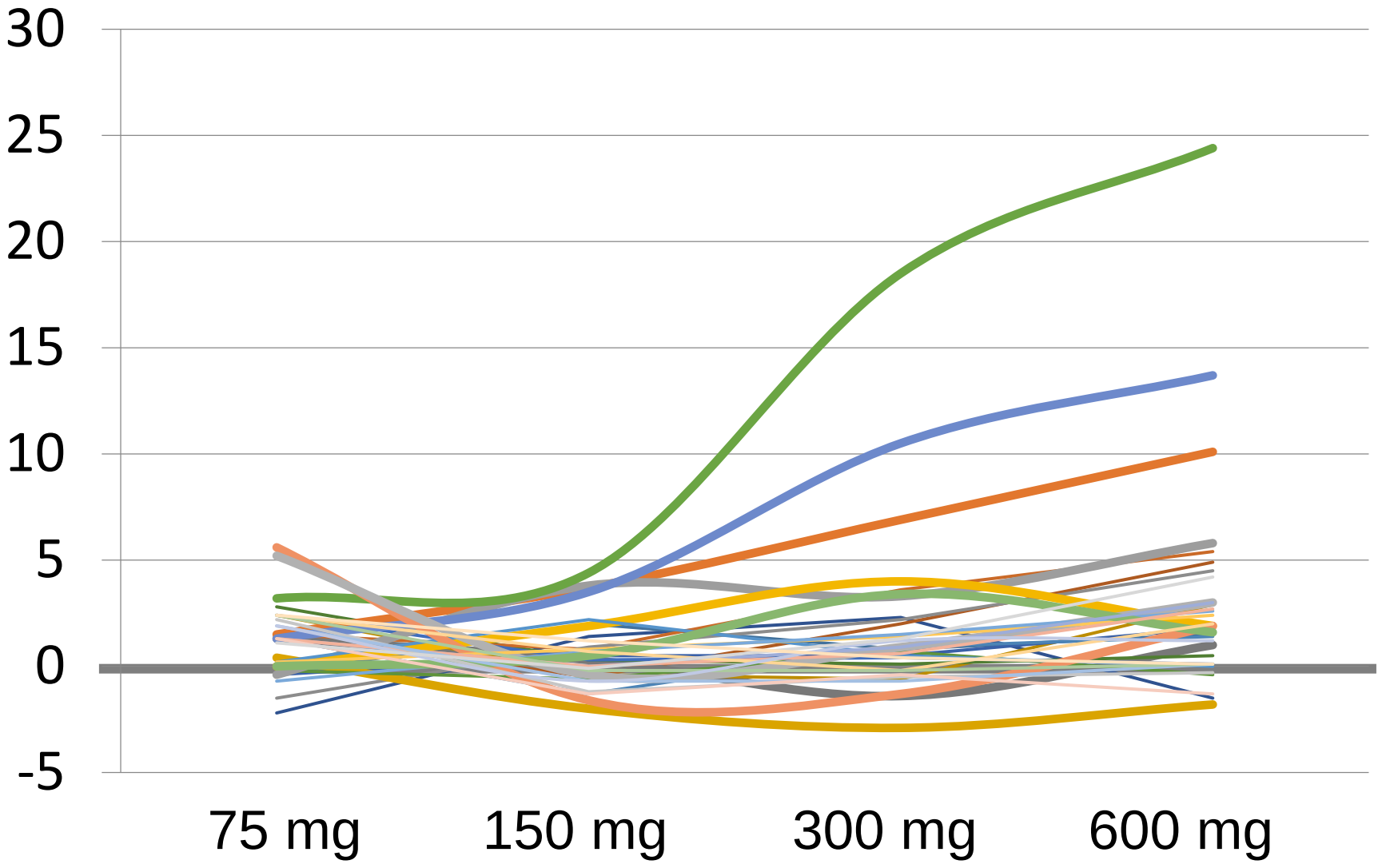
approved for the treatment of GAD in the British National Formulary

not approved by Health Canada for anxiety (for: diabetic peripheral neuropathy, post-herpetic neuralgia, fibromyalgia)



Rickels K et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry. 2005 Sep;62(9):1022-30. doi: 10.1001/archpsyc.62.9.1022.

pregabalin (Lyrica)



dizziness
somnolence
edema
weight gain
dry mouth
weakness
blurry vision

associated with severe constipation in some patients

transcranial magnetic stimulation

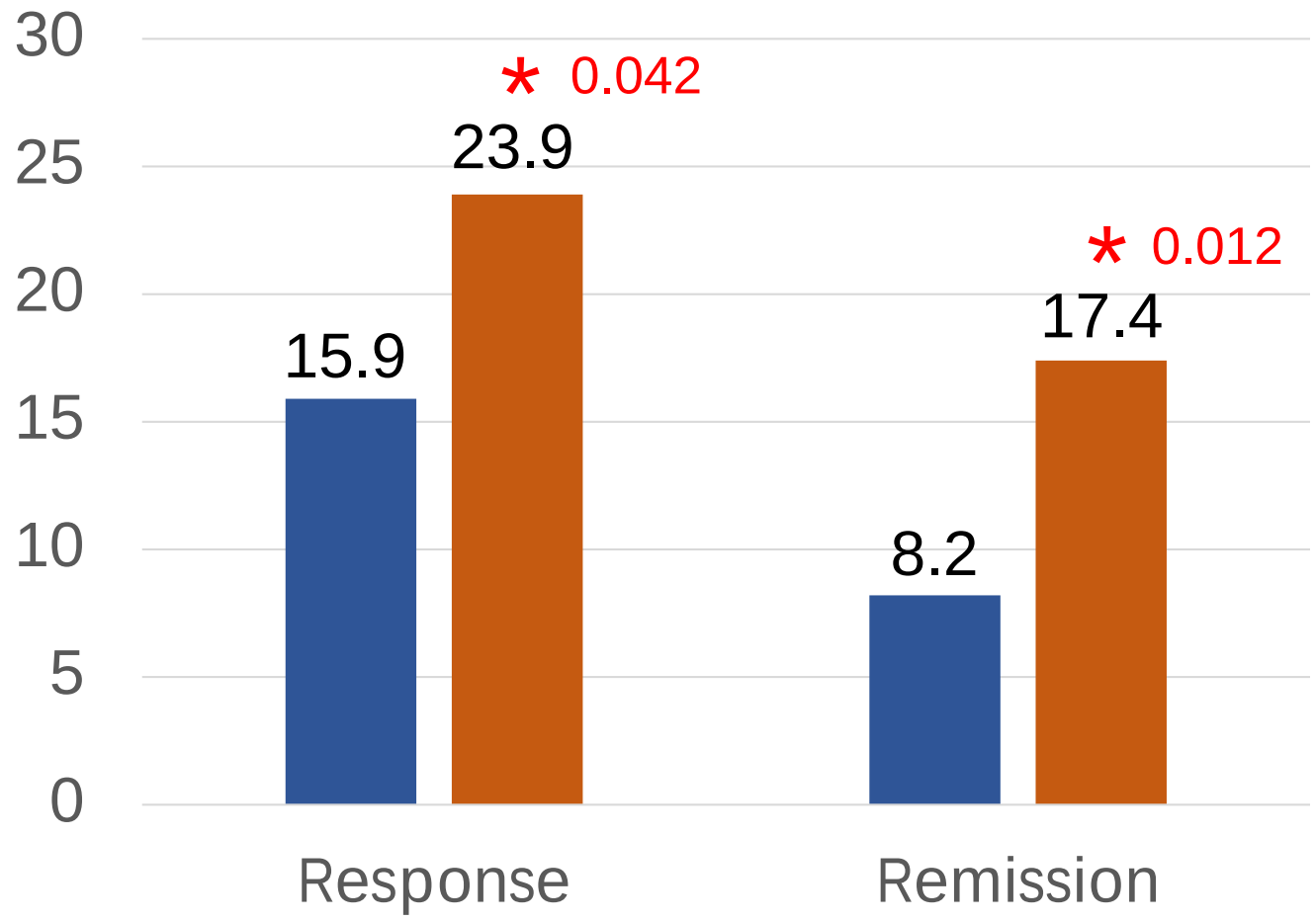
a non-invasive, non-convulsive neurostimulation therapy; treatment is daily (5 days a week) for 6 weeks

proven efficacy in a sham-controlled study of 300 patients with moderate to severe depression who had not responded to multiple anti-depressant trials

transcranial magnetic stimulation

approximately 24% of patients will respond within 6 weeks and approximately 17% will achieve remission

improvement usually begins by week 2 and is significant by week 4



transcranial magnetic stimulation

a full course of treatment at a private clinic costs approximately $3,000† – a similar course of treatment at the Non-Invasive Neurostimulation Therapies (NINET) lab at UBC is approximately $800†

† note: these costs are estimates based on indirect information gathered from patients over the past year and might be wildly inaccurate

https://ninet.med.ubc.ca/clinic/referral/

ketamine

can have a potent and rapid antidepressant effect – about 50% to 60% respond within 24 hours and 20% to 30% experience remission

most relapse within 10 days, but some experience a sustained response

twice weekly repeated infusions can be effective in maintaining response

ketamine

a course of 8 to 10 intravenous infusions is available privately for a cost of approximately $8,000†
intranasal esketamine is available for a cost of approximately $6,000 to $10,000†

† note: these costs are estimates based on indirect information gathered from patients over the past year and might be wildly inaccurate

psychotherapy

cognitive behavioral therapy (CBT) and mindfulness-based cognitive therapy (MBCT) are both 1st line treatments for depression

behavioral activation and interpersonal therapy (IPT) are 2nd line treatments

VCH Family Practice Rounds

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Dr. Ram Randhawa

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