노인 인지저하에서 Vortioxetine 처방

순천향 의대 신경과
양 영 순

Depression has many symptoms

Emotional

Sadness
Anxiety
Irritability
Lack of enjoyment
Suicidal ideation
Hopelessness
Guilt

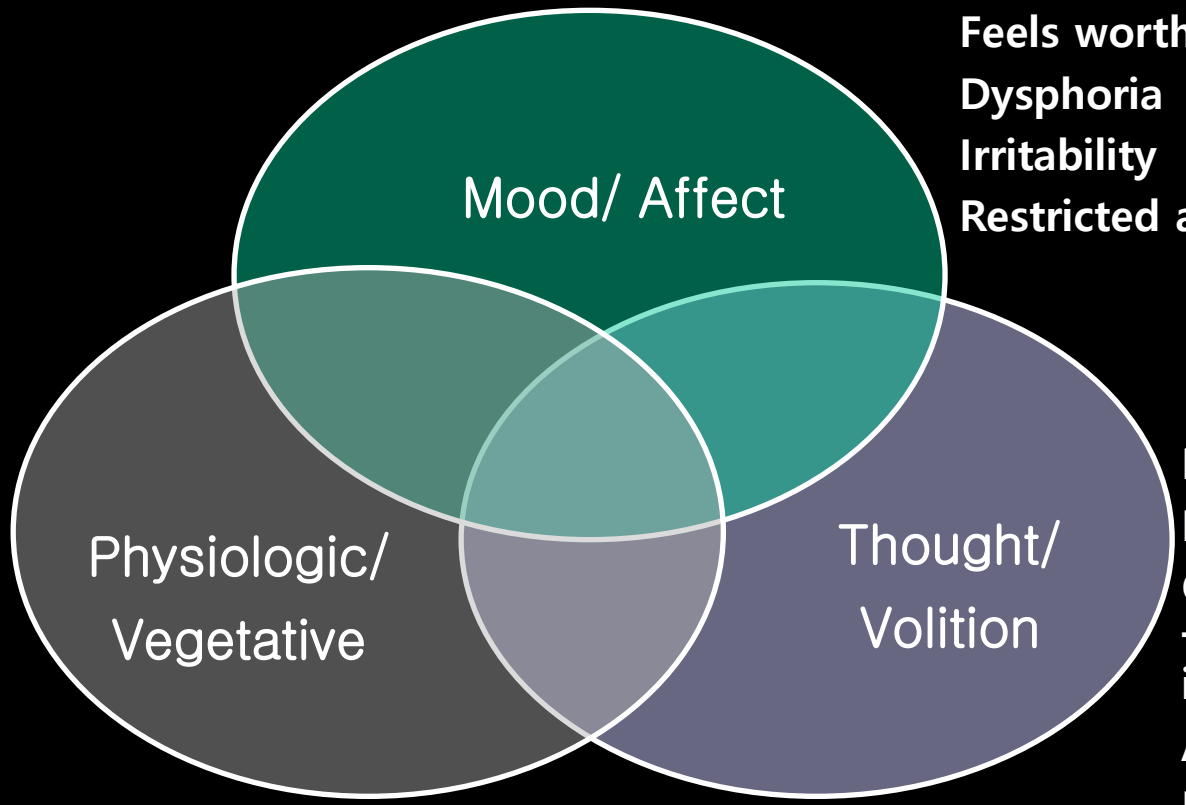
Cognitive

Difficulties with:
Attention and concentration
Short- and long-term memory
Decision making
Planning and organisation
Mental sharpness
Word-finding
Thinking speed
Judgement

Physical

Fatigue
Eating changes
Insomnia
Headaches
Stomach problems
Chest pain

Major Categories of Depression Symptomatology

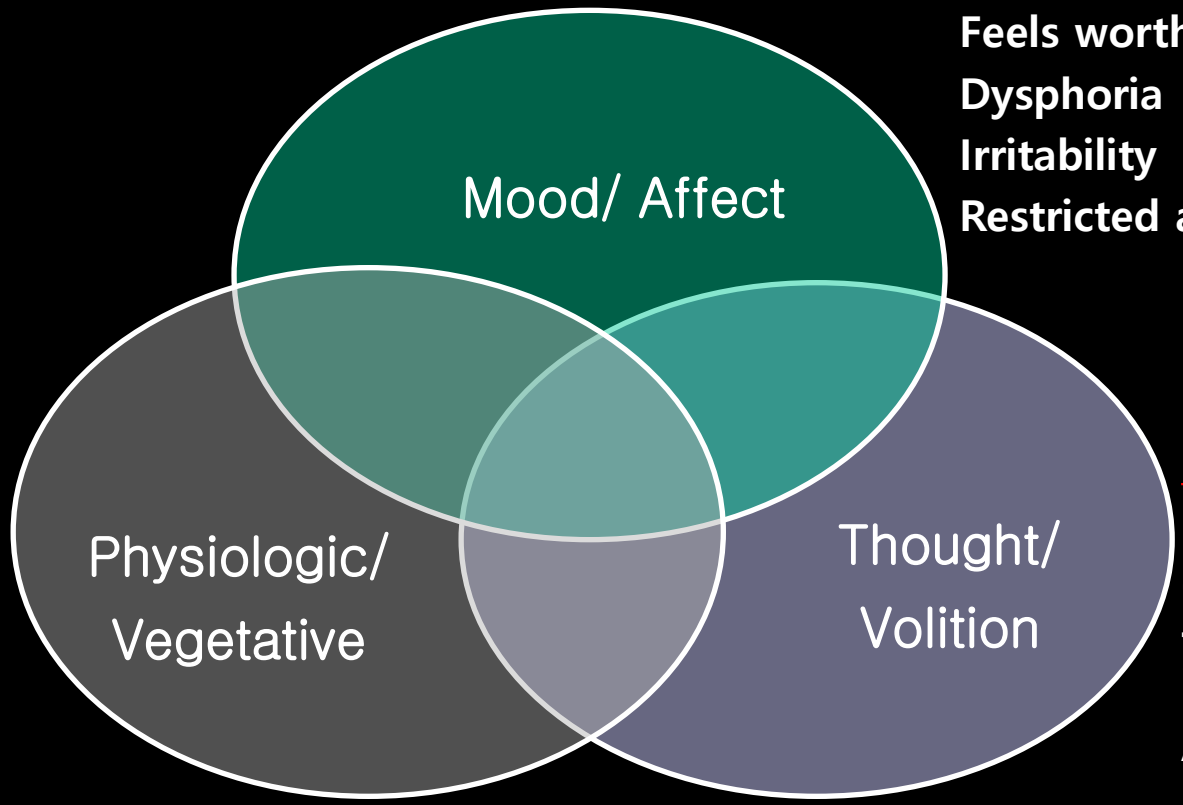


Depressive mood
Feels worthless/ guilt
Dysphoria
Irritability
Restricted affect

Loss/ change of appetite
Insomnia/ hypersomnia
Psychomotor agitation/ retardation
Loss of libido
Somatic symptoms

Loss of interest
Loss of energy
Cognitive impairment
Thoughts of death/ suicidal ideation
Apathy
Delusion /hallucination

Major Categories of Depression Symptomatology



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Major Depressive Episode: DSM-IV

> 5 including 1 or 2, > 2 weeks

1. ***Depressed mood***
2. ***Loss of interest***
3. Loss or change of appetite
4. Insomnia/ hypersomnia
5. Psychomotor agitation/ retardation
6. Loss of energy
7. Feeling of worthlessness/ guilt
8. Cognitive impairment
9. Recurrent thoughts of death/ suicidal ideation

Diagnostic criteria for Major Depressive Episode:(DSM-5)

A. **Five (or more)** of the following symptoms have been present during the same 2- week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. **Depressed mood** most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
2. **Markedly diminished interest or pleasure** in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. **Significant weight lo**ss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
4. **Insomnia or hypersomnia** nearly every day.
5. **Psychomotor agitation or retardation** nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
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 (not merely self-reproach or guilt about being sick).
8. **Diminished ability to think or concentrate**, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of **death** (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically **significant distress or impairment** in social, occupational or other important areas of functioning.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

DSM-5 Major Depressive Disorder

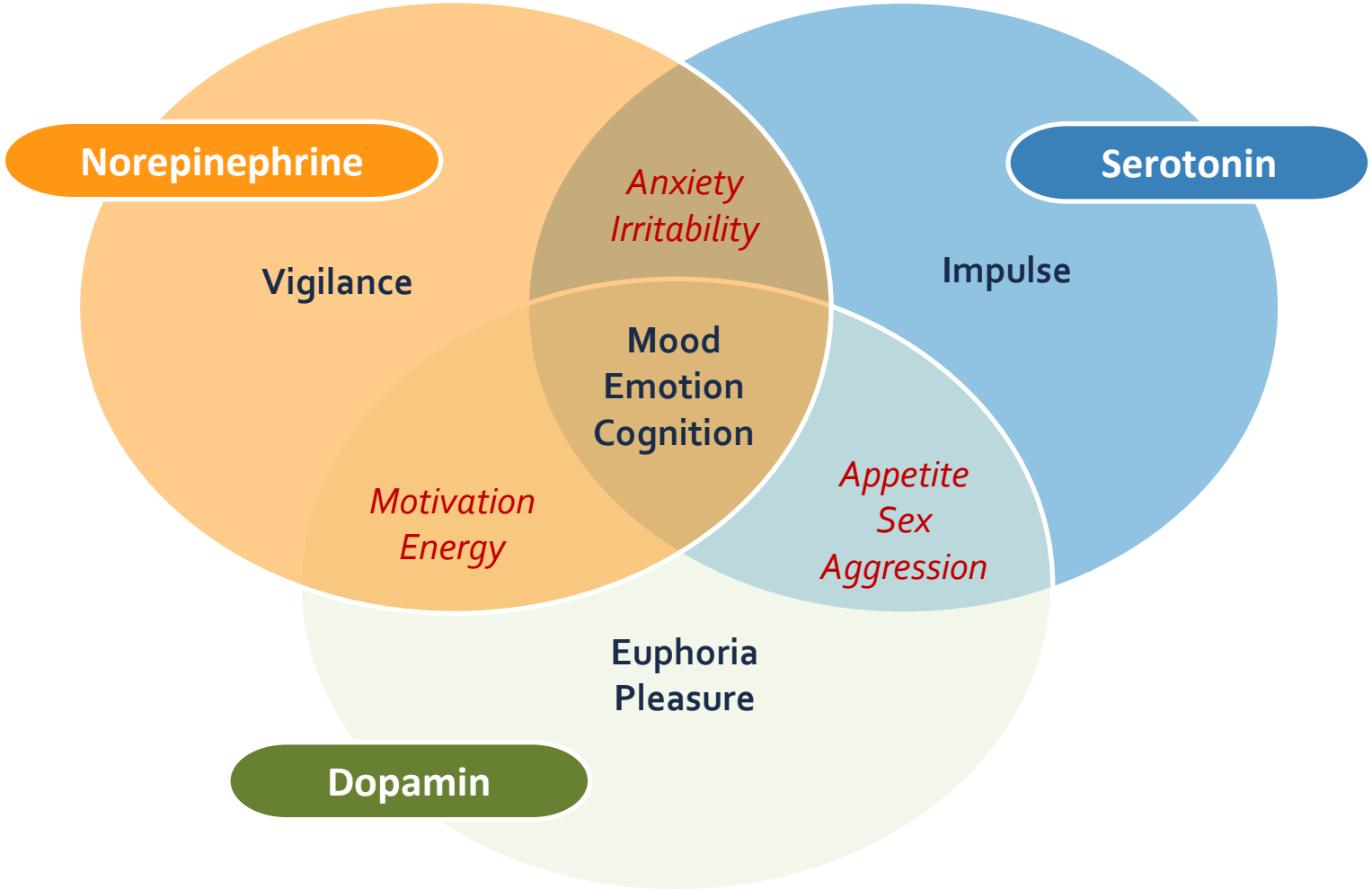
A. 다음 9가지의 증상 중 5가지 이상이 최소 2주 이상 거의 매일 지속되어야 한다. 최소한 한 가지 증상은 **우울한 기분 또는 흥미나 쾌락의 상실**이어야 한다.

1. 거의 하루 종일 우울한 기분이 거의 매일 이어지며, 이는 주관적 느낌 (예컨대 슬픔, 공허감, 아무런 희망이 없음)이나 객관적 관찰 소견(예컨대, 자주 눈물을 흘림)으로 확인된다.
2. 거의 하루 종일 거의 모든 활동에 대한 흥미나 즐거움 감소된 상태가 거의 매일 이어짐.
3. 체중 또는 식욕의 심한 감소나 증가
4. 거의 매일 반복되는 불면이나 과수면
5. 정신운동의 초조 (예: 안절부절 못함) 또는 지체 (예: 생각이나 행동이 평소보다 느려짐)
6. 거의 매일 반복되는 피로감 또는 활력 상실
7. 무가치감, 또는 지나치거나 부적절한 죄책감이 거의 매일 지속됨.
8. 사고력 또는 집중력의 감퇴, 결정을 못 내리는 우유부단함이 심해져 거의 매일 지속됨.
9. 죽음에 대한 생각이 되풀이되어 떠오르거나, 특정한 계획이 없는 자살 사고가 반복되거나, 자살을 시도하거나, 구체적인 자살 계획을 세움.

B. 임상적으로 의미 있는 고통이나 **대인관계, 직업을 포함한 주요 영역의 기능 저하**를 일으킴.

C. 약물 등 섭취 물질이나 질병으로 인해 야기된 생리적 효과로 인한 것이 아니어야 함.

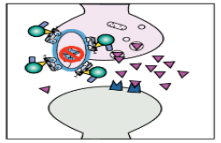
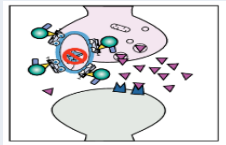
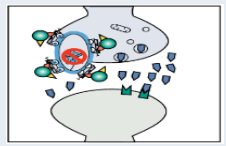
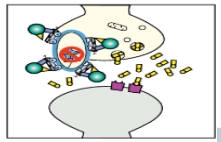
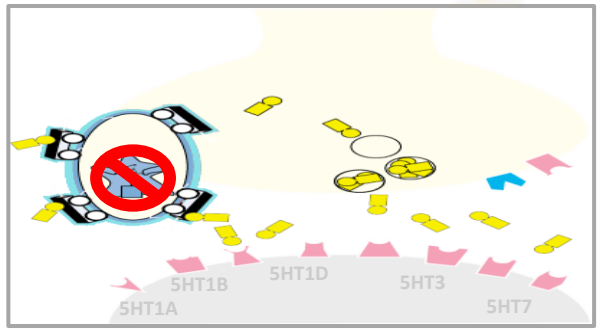
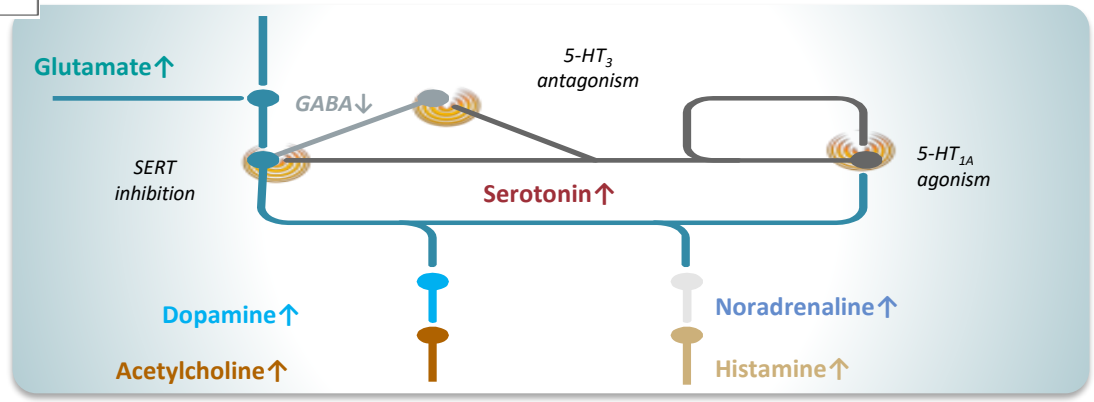
Neurotransmitter(NT) in Depression



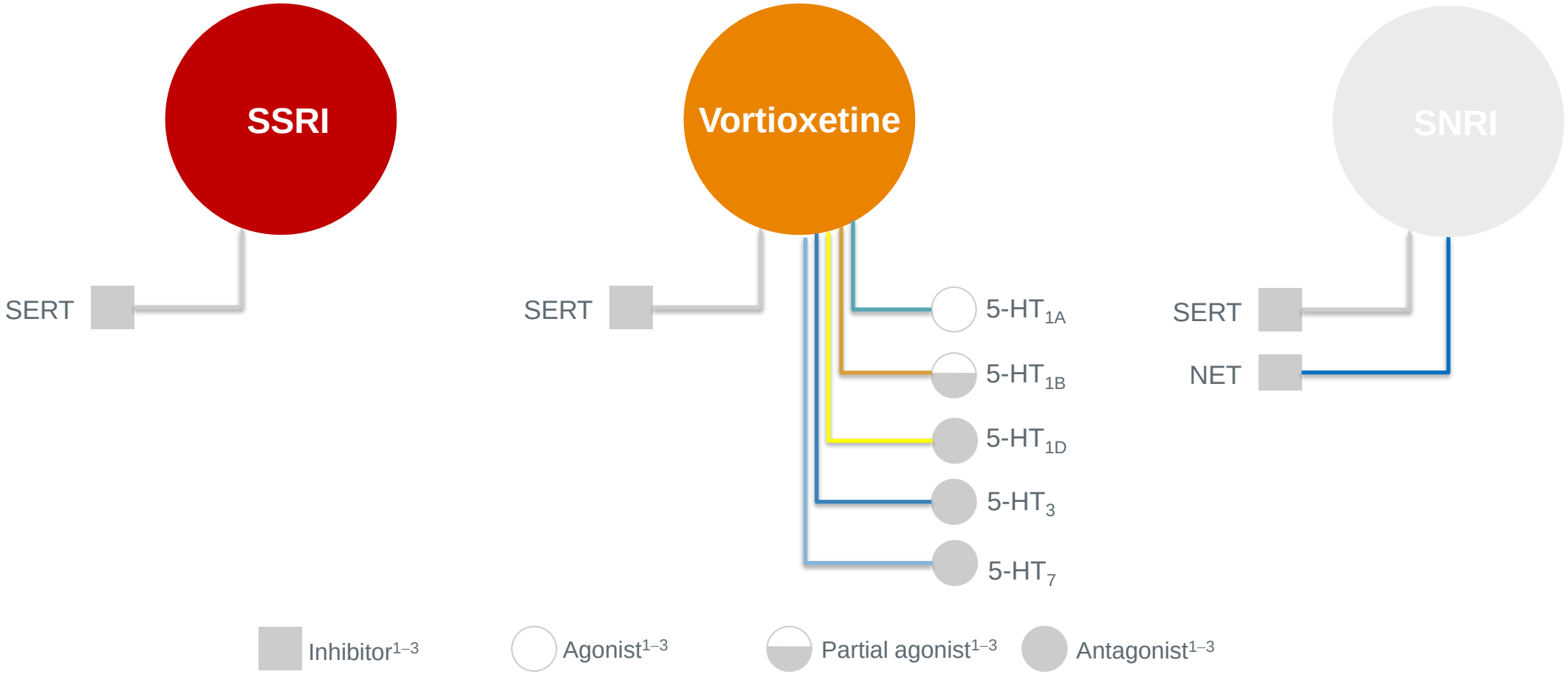
Reproduced from Healy and McMonagle. J Clin Psychiatry. 2000

Classification		Drugs
TCA	Tricyclic Antidepressants	Amitryptiline / Clomipramine / Imipramine / Desipramine / Nortriptyline
MAOI	Monoamine Oxidase Inhibitor	Phenelzine / Isocarboxazid
RIMA	Reversible inhibitor of MAO-A	Moclobemide
SSRI	Selective Serotonin Reuptake Inhibitor	Fluoxetine / Fluvoxamine / Paroxetine / Sertraline / Citalopram / Escitalopram
SARI	Serotonin Antagonist/Reuptake Inhibitor	Trazodone / Nefazodone
SPARI	Serotonin Partial Agonist/Reuptake Inhibitor	Vilazodone
SNRI	Serotonin Norepinephrine Reuptake Inhibitor	Venlafaxine / Desvenlafaxine / Duloxetine / Milnacipran
NRI	(Selective) Norepinephrine Reuptake Inhibitor	Reboxetine / Evidoxetine / Atomexetine
NaSSA	Noradrenergic and specific serotonergic antidepressant	Mirtazapine / Mianserin
NDRI	Norepinephrine Dopamine Reuptake Inhibitor	Bupropion
SNDRI	Serotonin-Norepinephrine-Dopamine Reuptake Inhibitor	Amitifadine
New ATDs	Melatonergic Antidepressant	Agomelatine
	Serotonin Modulator and Stimulator	Vortioxetine
	NMDA Blockade	Ketamine? Dextromethorphan?
Herbal ATDs	Herbal Antidepressant	St. John's wort ext.

Comparison of AD's Mechanism

	Classification	Examples	Mechanism	Indirect Effect
SSRI	**Selective Serotonin Reuptake Inhibitor**	Fluoxetine/Fluvoxamine /Paroxetine/Sertraline/Citalopram/Escitalopram		**5HT↑**
SNRI	**Serotonin Norepinephrine Reuptake Inhibitor**	Duloxetine/Venlafaxine/ Desvenlafaxine	 	**5HT↑ & NE ↑**
NDRI	**Norepinephrine Dopamine Reuptake Inhibitor**	Bupropion	 	**NE ↑ & DA ↑**
Multi-modal	**Serotonin Modulator and Stimulator**	Vortioxetine	  	**5HT↑ & NE, DA, Ach, His↑**

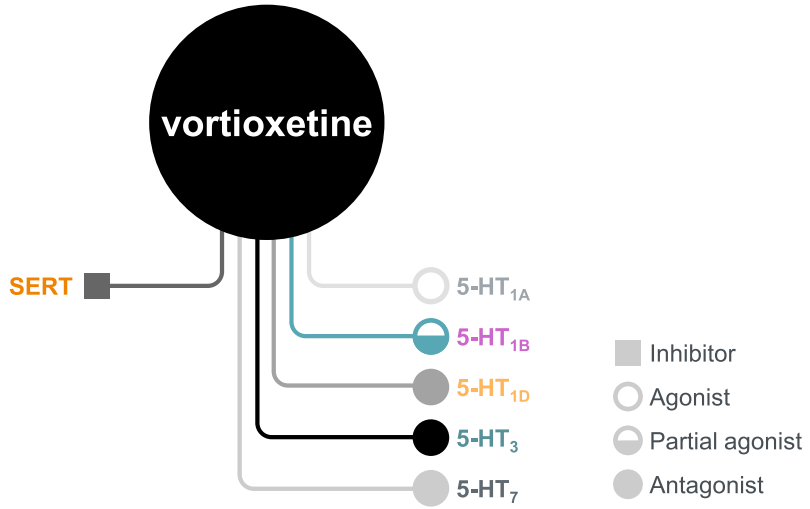
항우울제의 작용 기전 비교



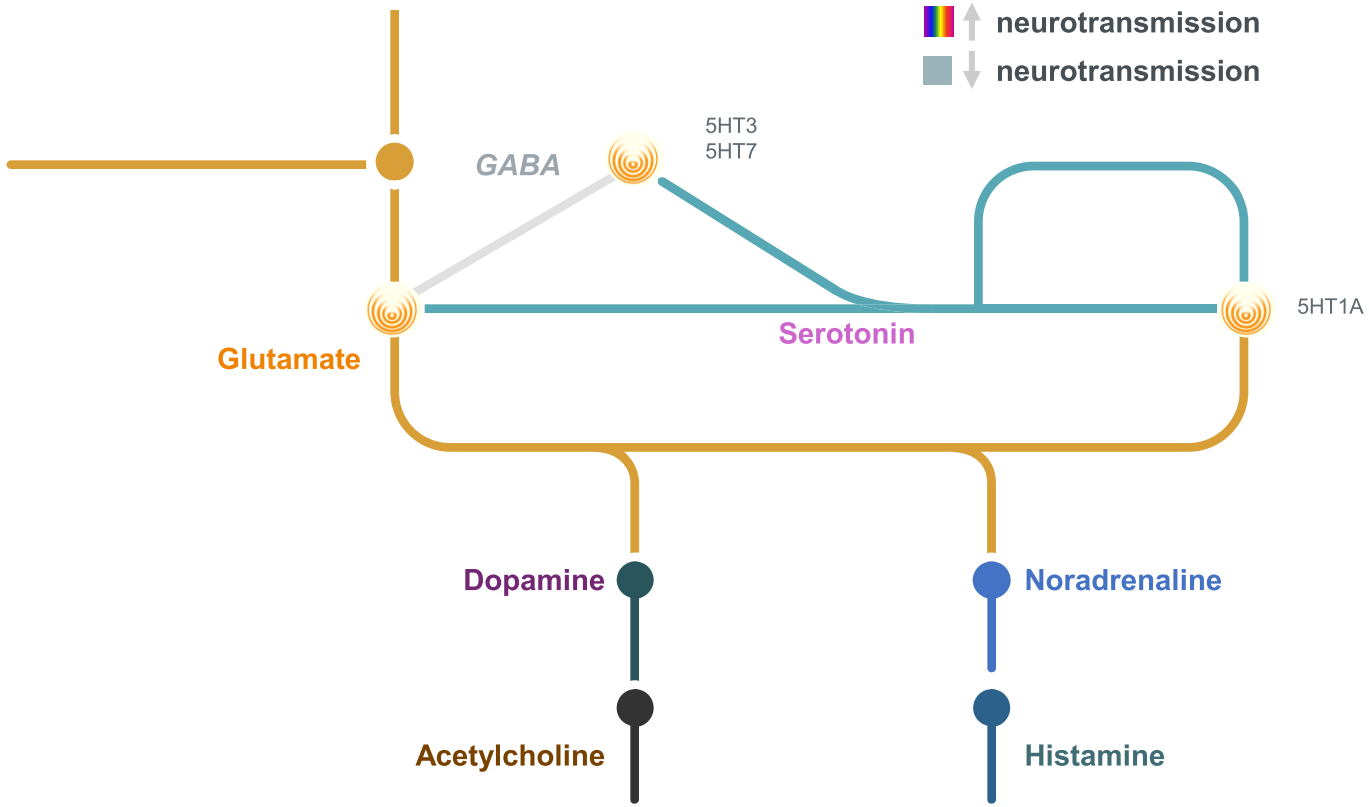
The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly. HT = hydroxytryptamine; NET = norepinephrine transporter; MDD = major depressive disorder; SERT = serotonin reuptake transporter; SNRI = serotonin–noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Created from 1. Bang-Andersen B, et al. J Med Chem. 2011;54:3206–21; 2. Sanchez C, et al. Pharmacol Ther. 2015;145:43–57; 3. Brintellix® (vortioxetine) Summary of Product Characteristics 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/brintellix-epar-product-information_en.pdf [Accessed May 2022].

Consequences of vortioxetine (Neurotransmission in preclinical models)



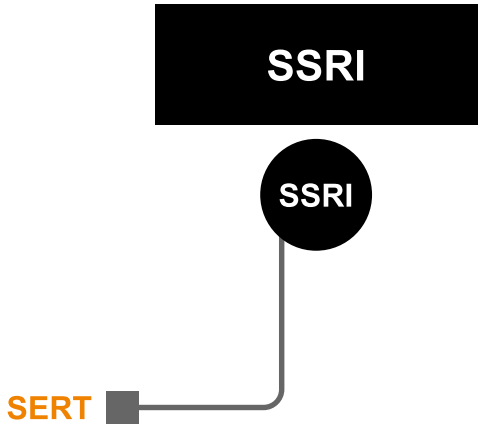
Vortioxetine's multimodal pharmacology exerts distinct effects across neural pathways associated with mood and cognition, including enhanced glutamate signaling



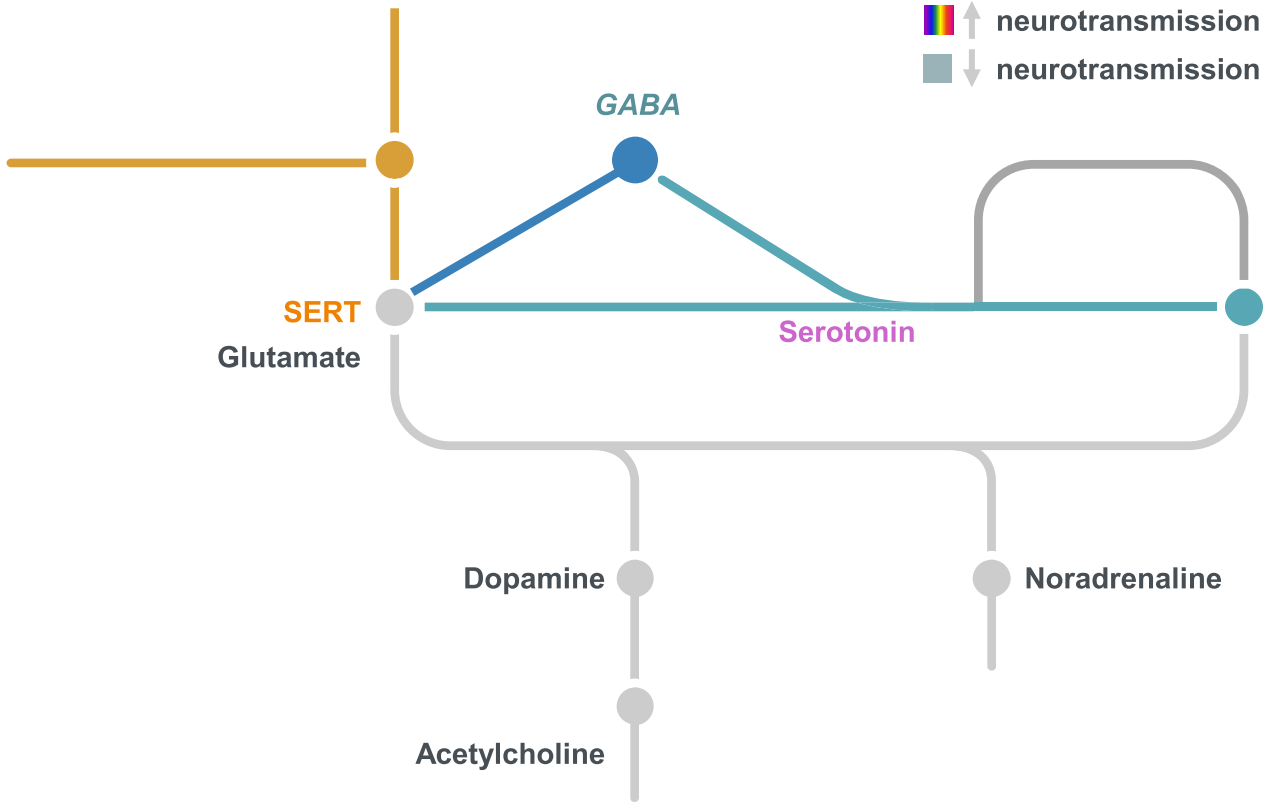
NB. The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to humans.

5-HT, serotonin; GABA, gamma-aminobutyric acid; SSRI, selective serotonin reuptake inhibitor; VOR, vortioxetine.

Sanchez *et al. Pharmacol Ther*. 2015 Jan;145:43-57; Pehrson *et al. CNS Spectr*. 2014 Apr; 19(2): 121–133.



SSRIs cause a global elevation in 5-HT levels, and the indiscriminate activation of 5-HT receptors that dampens downstream neurotransmission

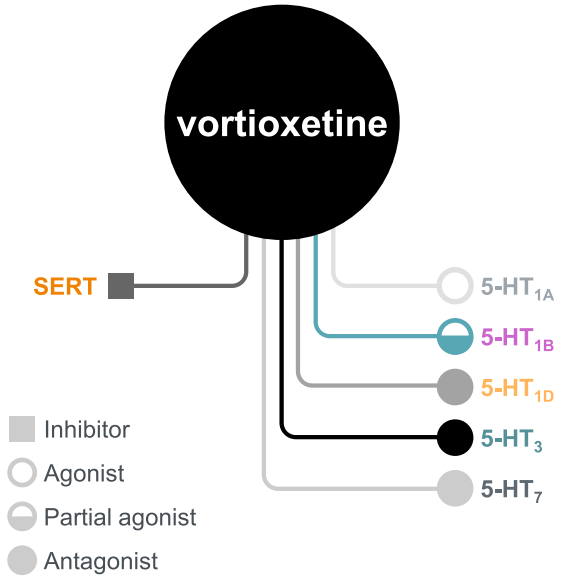


NB. The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to humans

1. Mansari *et al*. CNS Neurosci Ther. 2010 Jun;16(3):e1-17; 2. West *et al*. Int J Neuropsychopharmacol. 2011 Mar; 14(2): 201–210;
3. Szabo *et al*. Neuropsychopharmacology. 2001 Dec;25(6):845-57; 4. Kawahara *et al*. Psychopharmacology (Berl). 2007 Sep;194(1):73-81;
5. Dremencov *et al*. J Psychiatry Neurosci. 2009 May;34(3):223-9; 6. Degroot & Nomikos. Curr Opin Pharmacol. 2007 Feb;7(1):62-8;
7. Jackson *et al*. Brain Res. 1988 Aug 9;457(2):259-66; 8. Komlósi *et al*. J Neurosci. 2012 Nov 14;32(46):16369-78.

MOA of Brintellix®

Pharmacological profile (Receptor modulation & Reuptake inhibition)



[a]In the forebrain
SERT, serotonin transporter;
GABA, gamma-aminobutyric acid

Receptor activity

Reuptake inhibition

Neurotransmitter system modulation

Direct effects

- 5-HT$_3$ antagonist
- 5-HT$_7$ antagonist
- 5-HT$_{1D}$ antagonist
- 5-HT$_{1B}$ partial agonist
- 5-HT$_{1A}$ agonist
- SERT inhibitor

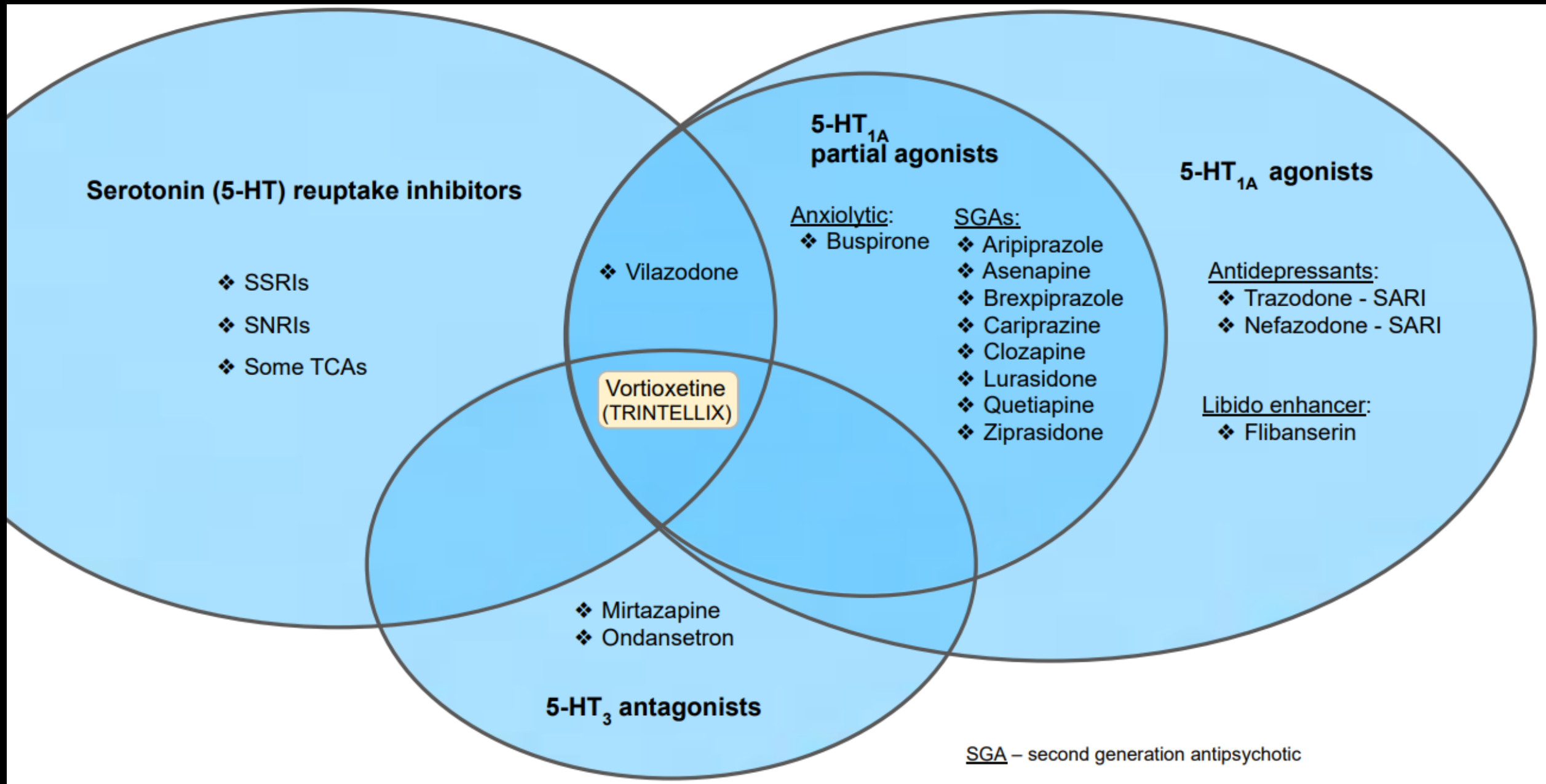
Indirect effects[a]

- ↑ serotonin neurotransmission
- ↑ dopamine neurotransmission
- ↑ noradrenaline neurotransmission
- ↑ acetylcholine neurotransmission
- ↑ histamine neurotransmission
- ↓ GABA neurotransmission
- ↑ glutamate neurotransmission

Observed clinical effects

↑ mood | ↑ cognition | ↓ sexual dysfunction | ↓ insomnia | ↓ anxiety

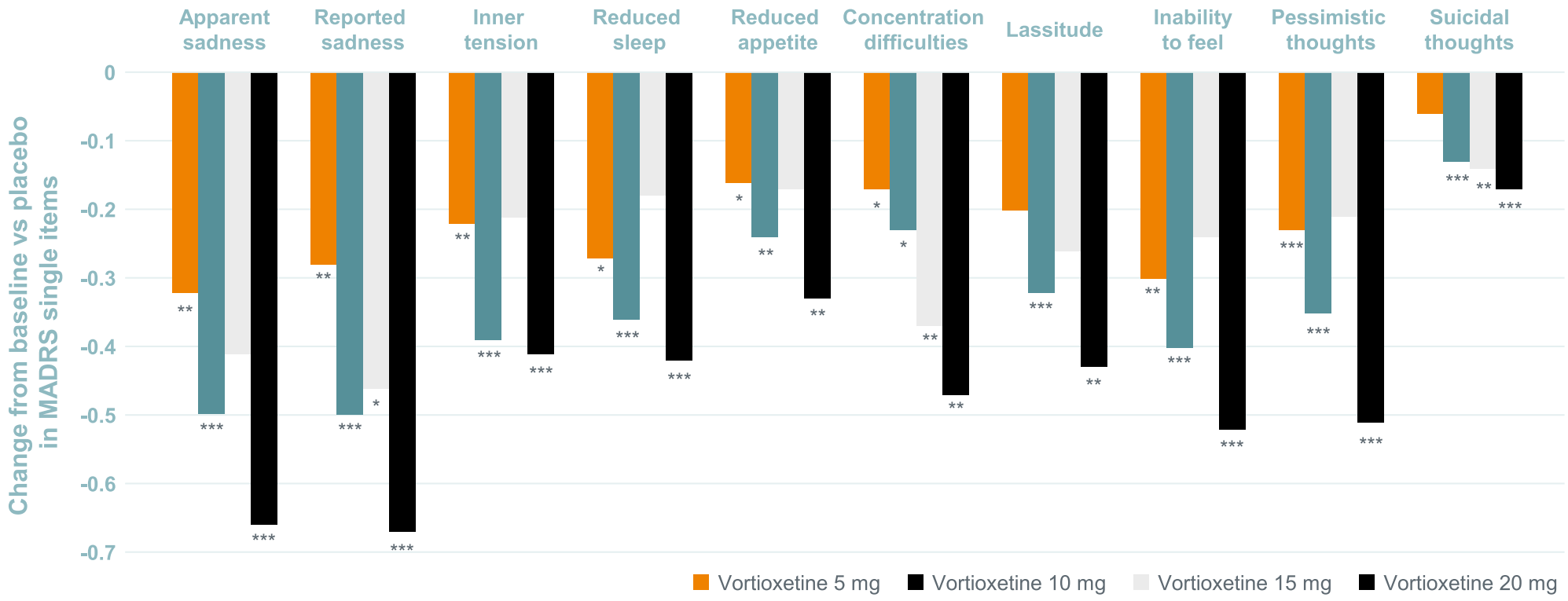
Bang-Andersen *et al. J Med Chem* 2011;54:3206-3221; Mørk *et al. Eur Neuropsychopharmacol* 2011;21(Suppl 3):S407; Mørk *et al. Pharmacol Biochem Behav*. 2013 Apr;105:41-50; Pehrson *et al. Eur Neuropsychopharmacol*. 2013 Feb;23(2):133-45.


Serotonin (5-HT) reuptake inhibitors
❖ SSRIs
❖ SNRIs
❖ Some TCAs
5-HT1A partial agonists
Anxiolytic:
❖ Buspirone
SGAs:
❖ Aripiprazole
❖ Asenapine
❖ Brexpiprazole
❖ Cariprazine
❖ Clozapine
❖ Lurasidone
❖ Quetiapine
❖ Ziprasidone
5-HT1A agonists
Antidepressants:
❖ Trazodone - SARI
❖ Nefazodone - SARI
Libido enhancer:
❖ Flibanserin
❖ Vilazodone
Vortioxetine (TRINTELLIX)
❖ Mirtazapine
❖ Ondansetron
5-HT3 antagonists
SGA – second generation antipsychotic

Efficacy of Brintellix®

Vortioxetine improves all items of MADRS

Meta-analysis of change from baseline in MADRS single items at Week 6/8, difference from placebo – 11 short-term studies in adults (FAS, MMRM)

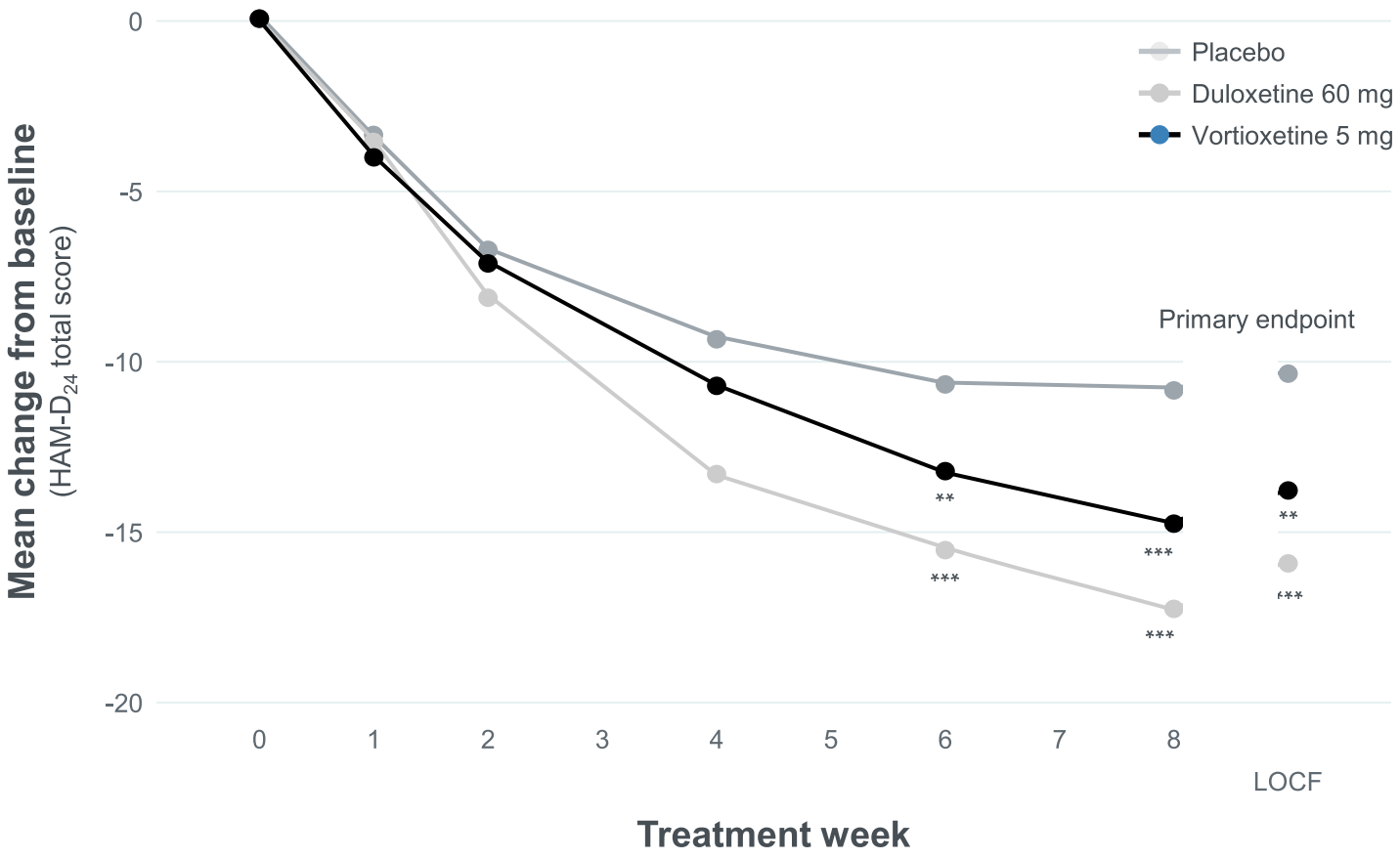


*p<0.05, **p<0.01, ***p≤0.001 vs placebo; Meta-analysis includes 11 studies: HLu 11492A, HLu 11984A, TAK 305, HLu 13267A, TAK 315, TAK 316, TAK 303, TAK 304, TAK 317, HLu 14122A, and CCT-002
FAS=full analysis set; MMRM=mixed model for repeated measures

Thase *et al., Eur Neuropsychopharmacol.* 2016 Jun;26(6):979-93.

Efficacy of Brintellix®

Efficacy was significant in elderly patients



Discontinuation rate due to AEs

Placebo	Vortioxetine	Duloxetine
2.8%	5.8% (*p*=0.2605)	*9.9% (*p*=0.016)

- 8-week placebo-controlled study in patients aged ≥65 years
  - Mean change from baseline in HAMD24 score by visit (FAS, MMRM; endpoint LOCF)
    **p<0.01, ***p<0.001 vs placebo; nominal p-values for MMRM

Katona C, *et al*. Int Clin Psychopharmacol 2012;27(4):215-223.

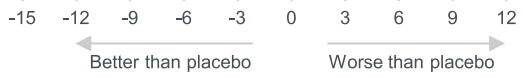
Efficacy of Brintellix®

Efficacy was comparable in patients aged 55 or older

Mean change from baseline in MADRS total score by visit in patients with severe depression

(FAS, OC, ANCOVA; endpoint LOCF)

NCT Identifier	VOR dose	N	Difference (±SE)	Standardized Effect size	*P*-value
NCT00839423	5 mg	19	-6.60 (2.67)	-0.87	0.017
	10 mg	22	-7.35 (2.54)	-0.99	0.006
NCT00635219	5 mg	26	-0.98 (2.56)	-0.11	0.703
	10 mg	32	-0.59 (2.51)	-0.06	0.814
NCT00735709	5 mg	36	-5.84 (1.74)	-0.77	0.001
	10 mg	32	-5.46 (1.76)	-0.73	0.002
NCT01140906	15 mg	40	-4.61 (1.68)	-0.60	0.007
	20 mg	32	-7.02 (1.80)	-0.90	<0.001
NCT01153009	15 mg	18	-3.69 (2.96)	-0.40	0.217
	20 mg	15	-6.26 (3.22)	-0.66	0.056
NCT01163266	10 mg	25	-1.96 (2.69)	-0.20	0.468
	20 mg	29	-0.78 (2.63)	-0.08	0.767
NCT00672958	5 mg	49	0.64 (2.22)	0.06	0.775
NCT00672620	5 mg	27	-0.50 (2.19)	-0.06	0.821
NCT01179516	10 mg	27	1.69 (2.57)	0.17	0.512
	15 mg	32	4.54 (2.44)	0.45	0.067
NCT01255787	5 mg	30	1.77 (2.38)	0.19	0.460
	10 mg	34	-1.71 (2.31)	-0.18	0.462
	20 mg	33	0.42 (2.33)	0.05	0.857
NCT00811252	5 mg	137	-4.74 (1.04)	-0.56	<0.001
NCT01422213	10 mg	50	-3.16 (1.70)	-0.37	0.065
	20 mg	56	-8.62 (1.67)	-1.00	<0.001
Meta-analysis	5 mg	324	-2.56 (1.22)	-0.17	0.035
	10 mg	222	-2.87 (1.07)	-0.25	0.007
	15 mg	90	-1.32 (2.99)	-0.06	0.658
	20 mg	165	-4.65 (1.86)	-0.27	0.012



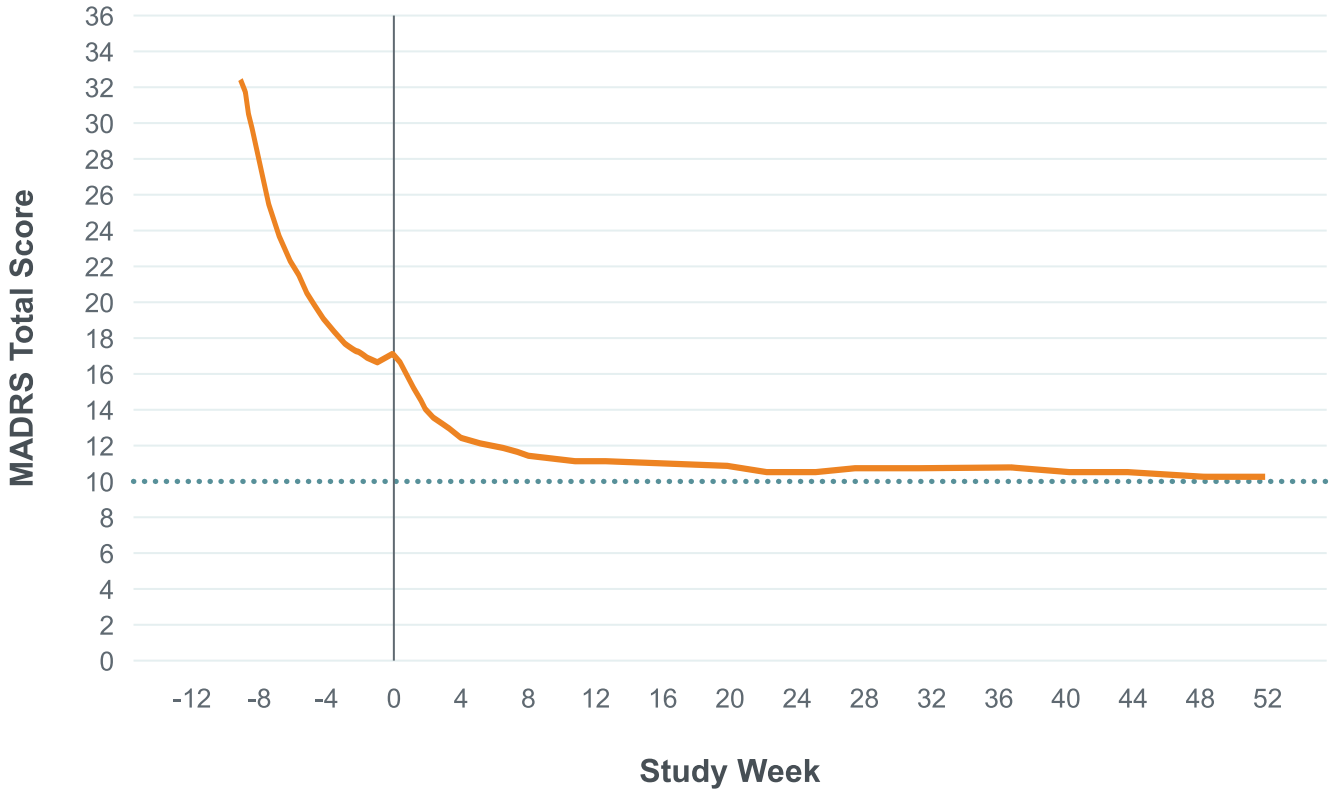
- 1,508 patients (mean age = 62.4 years; range, 55–88 years) were included.
- **Vortioxetine 5–20 mg/day is efficacious and well tolerated in MDD patients aged ≥55 years**, a group that is often comorbid with other conditions and treated with other medications.

Nomikos *et al.*, CNS Spectr. 2017 Aug;22(4):348-362.

Efficacy of Brintellix®

Long-term Efficacy in extention (52 week) studies

Mean MADRS total score by visit (FAS, LOCF)



- 6-8 week, randomised, double-blind, placebo-controlled trial of vortioxetine in adults (<65 yrs) with MDD, and long-term (52-week) extension

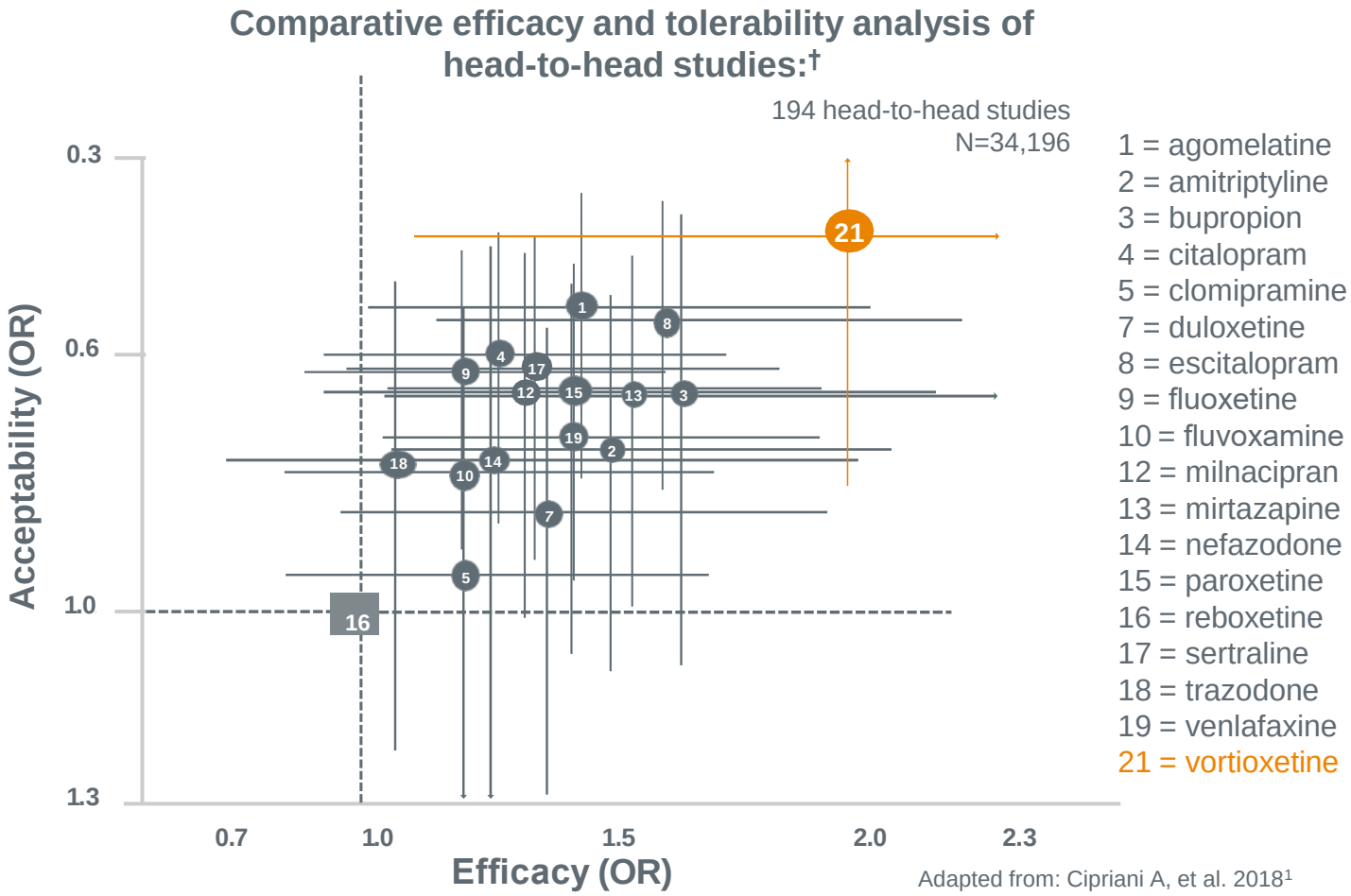
Mean MADRS total scores for patients previously treated with vortioxetine 5-20 mg/day in 6- to 8-week randomized controlled trials who continued treatment in an open label extension study **(N=1,230);** (LOCF). The vertical line represents Baseline Ⅱ (start of treatment in the extension study). The horizontal dashed black line indicates the cut point for remission (defined as MARDS total score ≤ 10).

Vieta *et al. Eur Neuropsychopharmacol.* 2017 Sep;27(9):877-884.

Comparative Efficacy & Tolerability

Antidepressants for the acute treatment of MDD

- A large network meta-analysis including 522 trials and 116,477 patients compared 21 antidepressants in the acute treatment of MDD in adults
- All antidepressants were shown to be **more effective than placebo**
- Considering placebo-controlled and head-to-head studies, **vortioxetine showed similar efficacy* and acceptability** as most other antidepressants**

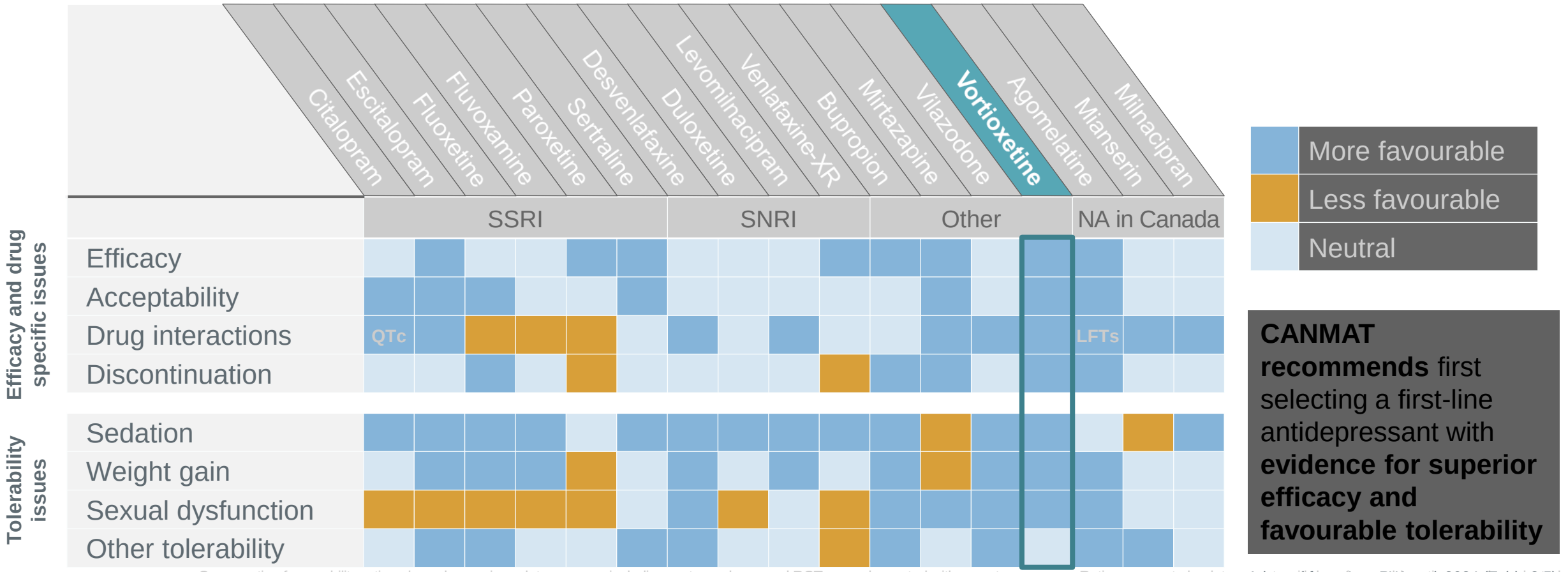


Adapted from: Cipriani A, et al. 2018[1]

HAM-D = Hamilton Depression Rating Scale; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale.*Antidepressive response was defined by a reduction of ≥50% of the total score on a standardised observer-rating scale for depression (HAM-D or MADRS). **Acceptability was defined based on all-cause discontinuation of the treatments. LOCF data are reported as OR in comparison with reboxetine, which is the reference drug. †A network meta-analysis of only head-to-head studies included a single direct study comparison of vortioxetine at a dose of 10 mg/day and venlafaxine at a dose of 150 mg/day. The error bars, indicating 95% credibility intervals, reflect limited data for Brintellix® (vortioxetine) in this network meta-analysis. **Registration status may differ from country to country**.

1. Cipriani A, et al. Lancet. 2018;391:1357-1366.

CANMAT 2023 guidelines provide comparative favourability ratings for first-line antidepressants on efficacy and tolerability



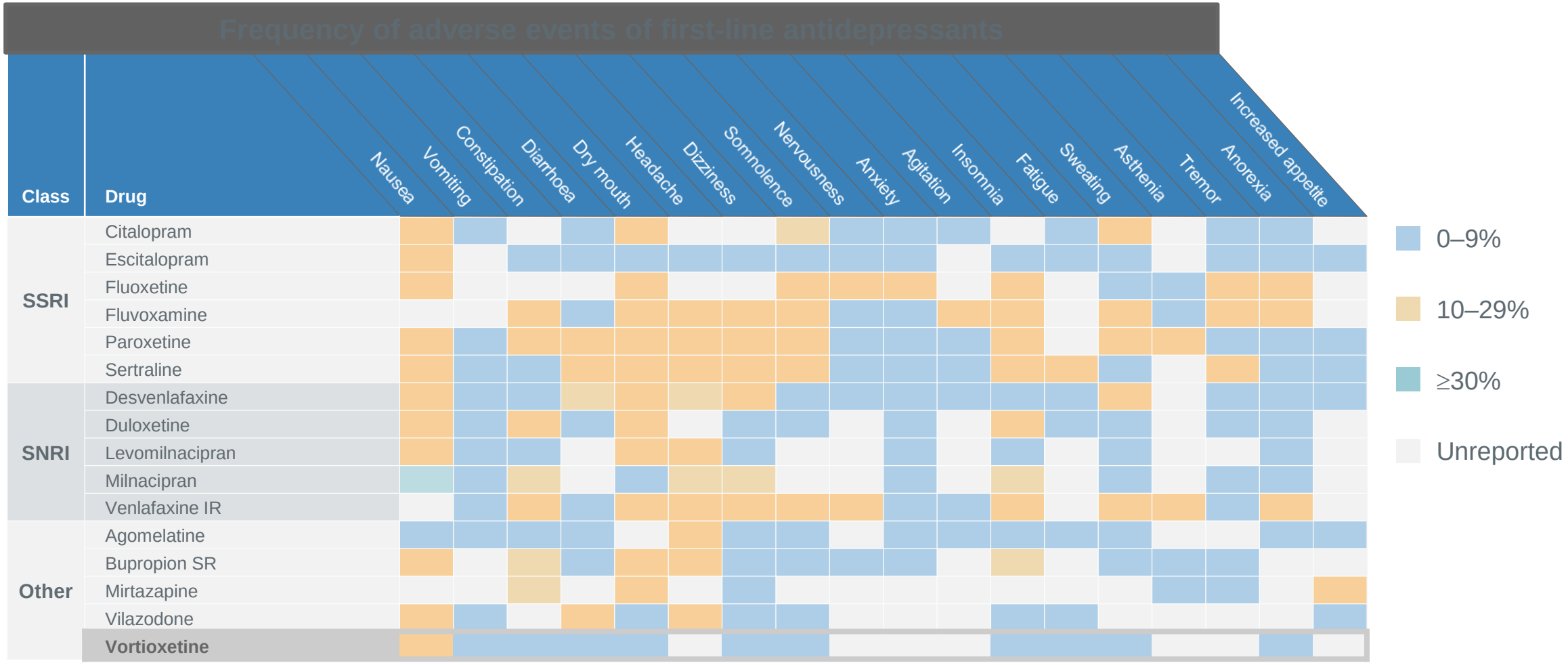
CANMAT recommends first selecting a first-line antidepressant with **evidence for superior efficacy and favourable tolerability**

Adapted from: Lam RW, et al. 2024 (Table 3.5)

Comparative favourability ratings based on various data sources, including meta-analyses and RCTs, supplemented with expert consensus. Ratings are not absolute; [illegible]. Clear squares do not imply intermediate favourability. Efficacy refers to response rates in meta-analyses. Acceptability refers to all-cause discontinuation rates in meta-analyses. Drug Interactions include clinically significant interactions. Discontinuation refers to potential for discontinuation effects. 'Other tolerability' refers to side effects other than sedation, weight gain, and sexual dysfunction. **Registration status may differ from country to country**. Abbreviated vortioxetine prescribing information can be found at the end of this slide deck. CANMAT = Canadian Network for Mood and Anxiety Treatments; LFTs = recommended monitoring of liver function tests; NA = not available; QTc = recommended monitoring for prolongation of QTc interval; RCT = randomised controlled trial; SNRI = serotonin-noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

CANMAT guidelines: Lam RW, et al. Can J Psychiatry. 2024;69:641-687.

CANMAT 2023 guidelines show that the prevalence of adverse events varies across first-line antidepressants



Adapted from: Lam RW, et al. 2024 (Table 3.4)

Based on unadjusted rates from product monographs. **Registration status may differ from country to country**. Abbreviated vortioxetine prescribing information can be found at the end of this slide deck.

CANMAT = Canadian Network for Mood and Anxiety Treatments; IR, immediate release; SNRI = serotonin-norepinephrine reuptake inhibitor; SR, sustained release; SSRI = selective serotonin reuptake inhibitor.

CANMAT guidelines. Lam RW, et al. Can J Psychiatry. 2024;69:641-687.

CANMAT 2023 Guidelines keep recommending Vortioxetine as first-line therapy for MDD

The first choice of an antidepressant can be any of the first-line antidepressants, taking into account efficacy, potential for adverse effects, clinical presentation, cost, and patient preference

Summary Recommendations for Antidepressants

Line of treatment	Antidepressant	Daily dose[1]	Mechanism	Level of Evidence
First line	Citalopram	20 - 40 mg	SSRI	●
	Escitalopram	10 - 20 mg	SSRI	●
	Fluoxetine	20 - 60 mg	SSRI	●
	Fluvoxamine	100 - 300 mg	SSRI	●
	Paroxetine	20 - 50 mg	SSRI	●
	Sertraline	50 - 200 mg	SSRI	●
	Desvenlafaxine	50 - 100 mg	SNRI	●
	Duloxetine	60 - 120 mg	SNRI	●
	Levomilnacipran*	40 - 120 mg	SNRI	●
	Venlafaxine-XR	75 - 225 mg	SNRI	●
	Bupropion	150 - 450 mg[2]	NDRI	●
	Mirtazapine	30 - 60 mg	α_2 antagonist; 5 - HT2 antagonist	●
	Vilazodone*	20 - 40 mg	SRI; 5 - HT1A agonist	●
	Vortioxetine	**10 - 20 mg**	**SRI; 5 - HT1A, 5 - HT1B agonist; 5 - HT1D, 5 - HT3A, 5 - HT7 antagonist**	●
	Agomelatine#	25 - 50 mg	MT1, MT2 agonist; 5 - HT2 antagonist	●
	Mianserin#	30 - 90 mg	α_2 antagonist; 5 - HT2 antagonist	●
	Milnacipran#	50 - 200 mg	SNRI	●

● Level 1; ◔ Level 2; ◑ Level 3; ◕ Level 4;

[1]Dose ranges are taken from product monographs; in clinical care, doses below and above the range may be used. [2]Daily doses above 300 mg should be given in divided doses.
*Starred items indicate changes since CANMAT 2016 guidelines, based on updated evidence.

CANMAT = Canadian Network for Mood and Anxiety Treatments; SNRI=serotonin-norepinephrine reuptake inhibitor; SRI=serotonin reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; MT=melatonin receptor; 5-HT=5-hydroxytryptamine receptor; α1 =alpha-1 adrenergic receptor; α2=alpha-2 adrenergic receptor; MDD=Major Depressive Disorder

1. Lam RW, *et al*. Can J Psychiatry. 2024 Sep;69(9):641-687.

Cognitive symptoms are common in MDD and Vortioxetine may have superior efficacy for cognitive dysfunction than SSRIs

Summary Medication Recommendations for DSM–5-TR Episode Specifiers and Symptom Dimensions

Line of treatment	DSM-5-TR episode specifiers				Symptom dimensions		
	• Anxious distress • Atypical features • Melancholic features	• Mixed Features	• Psychotic features	• Catatonic features	• **Cognitive Dysfunction**	• Sleep disturbance	• Somatic symptoms
First line	Any first-line antidepressant from Table 3.3 ●	Any first-line antidepressant* from Table 3.3 ●	Any first-line antidepressant from Table 3.3 + atypical antipsychotic ●	Benzodiazepine and any first-line antidepressant from Table 3.3 ◔	**Vortioxetine** ●	Agomelatine† ●	Duloxetine (pain) Bupropion (fatigue)
Second line	Any second-line antidepressant from Table 3.3 ●	Lurasidone** ◔			Bupropion ◔ Duloxetine ◔ SSRIs** ◔	Mirtazapine ◔ Quetiapine-XR ◔ Trazodone ◔	Duloxetine** (fatigue) ◔ Other SNRIs (pain) ◔ SSRIs** (fatigue) ◔

● Level 1; ◔ Level 2; ◐ Level 3; ◴ Level 4;

* When initiating medications, monitor for activating side effects (e.g., agitation, increase in suicidal ideation) and potential switch to (hypo)mania.
** Comparisons only with placebo.
†Not available in Canada

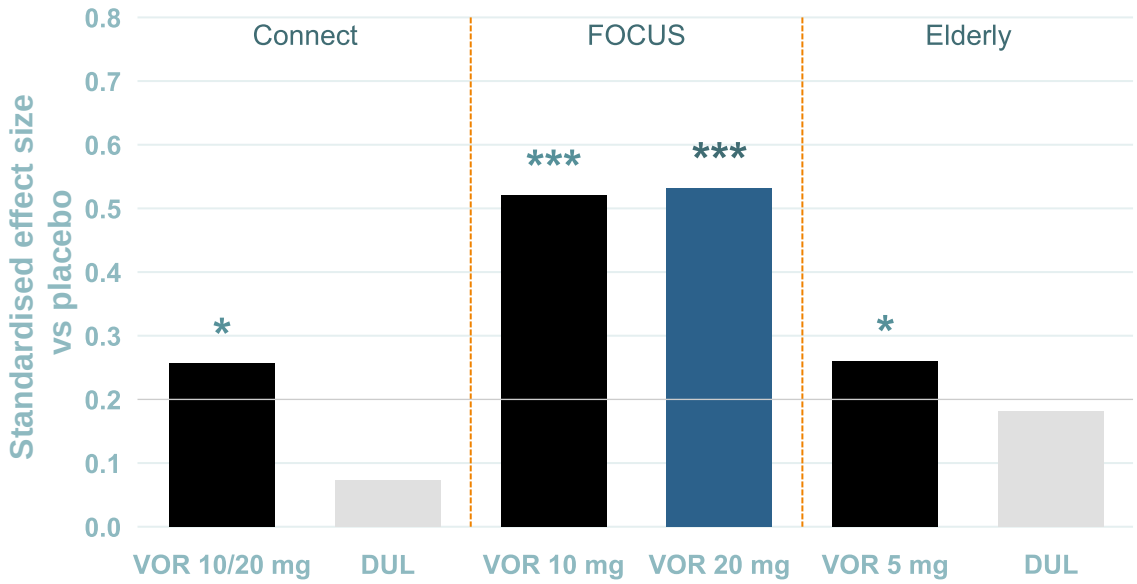
SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor, MDD=Major Depressive Disorder

1, Lam RW, *et al*. Can J Psychiatry. 2024 Sep;69(9):641-687.

Brintellix® improves cognitive performance in MDD, as measured by DSST in 3 clinical trials

DSST – Replication: Number of correct symbols, change from baseline at Week 8

(FAS, ANCOVA, LOCF, path analysis; $^{*}p<0.05$, $^{***}p<0.001$)



All 3 studies were 8-week placebo-controlled and included subjects with moderate to severe MDD (MADRS≥26)

	ELDERLY	FOCUS	CONNECT
Subjects, N	453	602	602
Primary endpoint	Depression	Cognitive dysfunction	Cognitive dysfunction
Age	≥65 years	18-65 years	18-65 years
Vortioxetine	5 mg	10 and 20 mg	10/20 mg
Region	EU/CA/US	EU/US/RoW	EU/US
Active reference	Duloxetine	–	Duloxetine

✓ **DSST measures executive functioning, working memory, attention and speed of processing.**

✓ **The effect of vortioxetine on DSST performance is to a large degree independent of the improvement in general depressive symptoms**

(measured by MADRS / HAMD24)

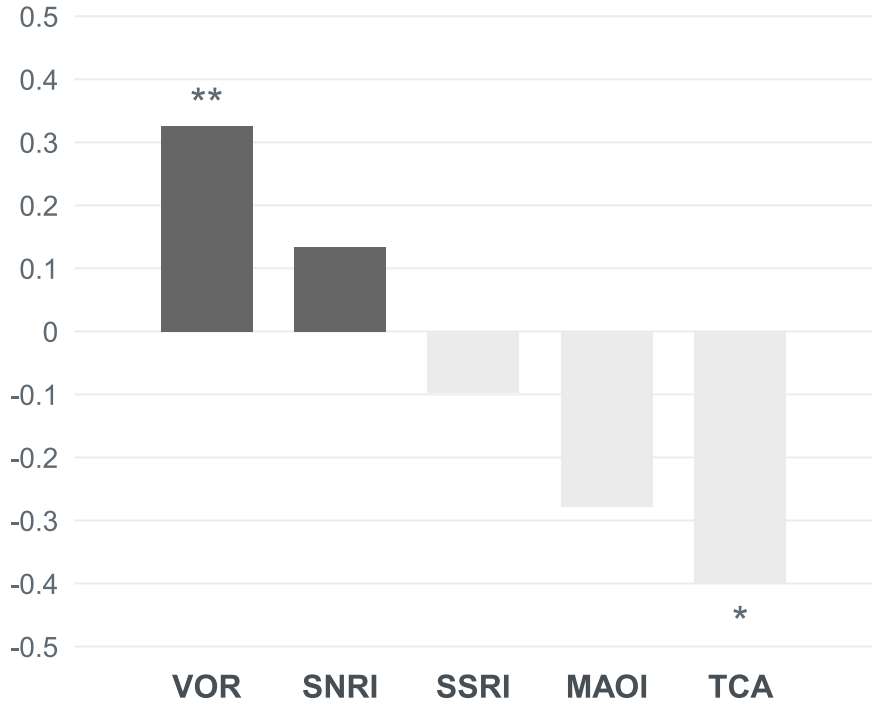
Mahableshwarkar. *Neuropsychopharmacology*. 2015 Jul;40(8):2025-37.; McIntyre. *Int J Neuropsychopharmacol*. 2014 Oct;17(10):1557-67.; Katona. *Int Clin Psychopharmacol*. 2012 Jul;27(4):215-23.

Efficacy of Brintellix® to cognitive dysfunction in MDD

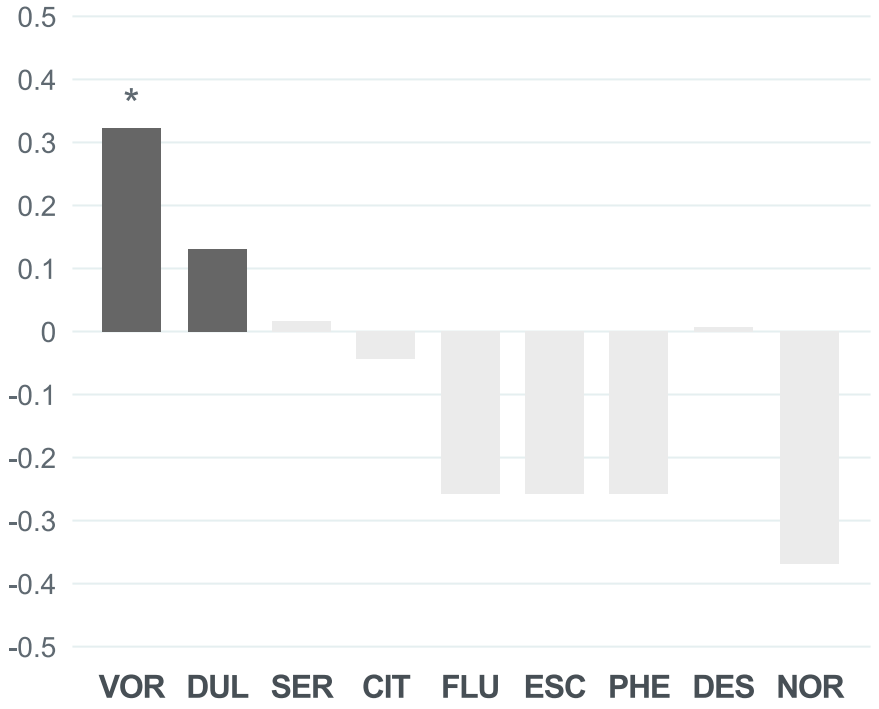
Comparative efficacy of antidepressants to cognitive dysfunction

Standardized effect size, relative to placebo

a By-class analysis



b By-treatment analysis

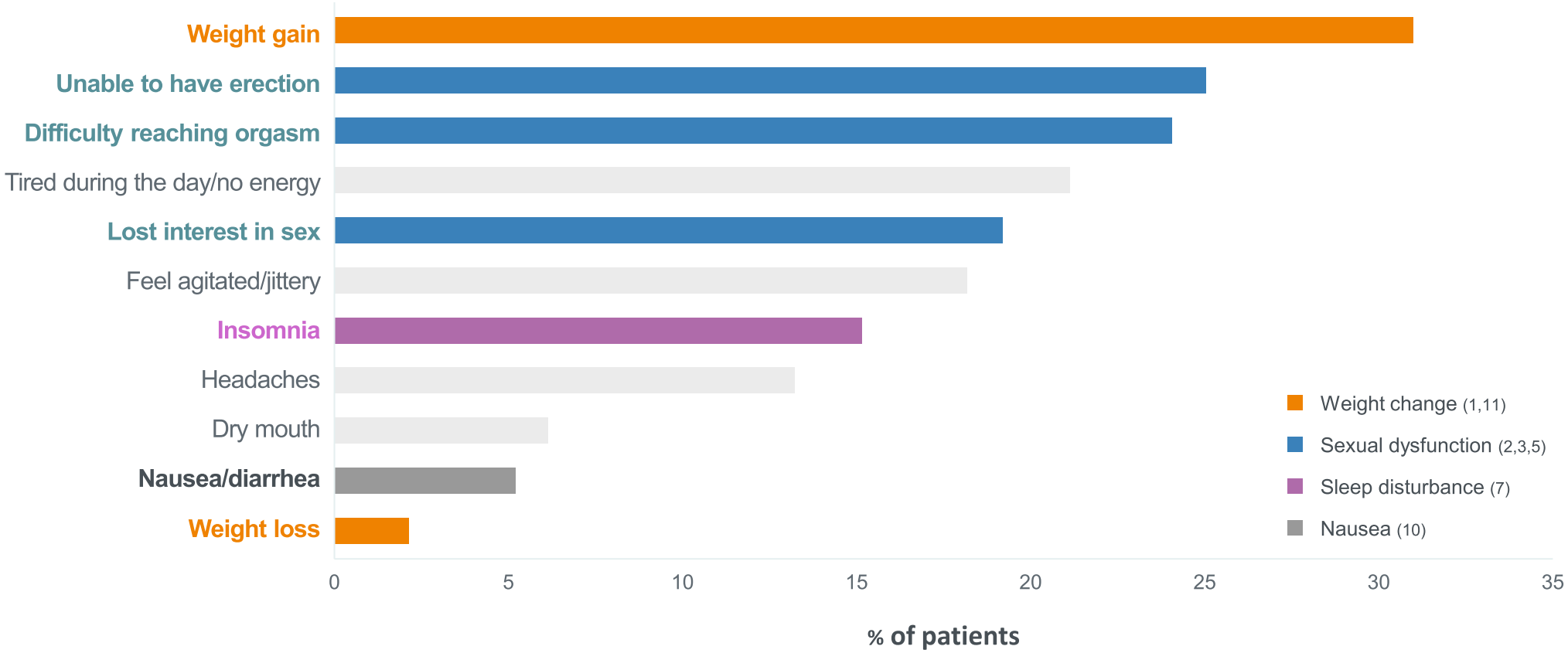


Standardized mean difference vs placebo (a) by-class analysis and (b) by-treatment analysis. Abbreviations: CIT. citalopram; DES, desipramine; DUL, duloxetine; ESC, escitalopram; FLU, fluoxetine; MOAI, monoam-ine-oxidase inhibitor; NOR, nortriptyline; PHE, phenelzine; SER, sertraline; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressnats; VOR, vortioxetine. $^{*}P<.05$; $^{**}P<.01$

Baune *et al*. Int J Neuropsychopharmacol. 2018 Feb 1;21(2):97-107.

Antidepressant-Related Adverse Effects Impacting Treatment Compliance

Frequency of Adverse effects reported as “extremely difficult to live with”



Ashton *et al. Curr Ther Res Clin Exp*. 2005 Mar;66(2):96-106.

Tolerability of Brintellix®

Vortioxetine is a well-tolerated antidepressant

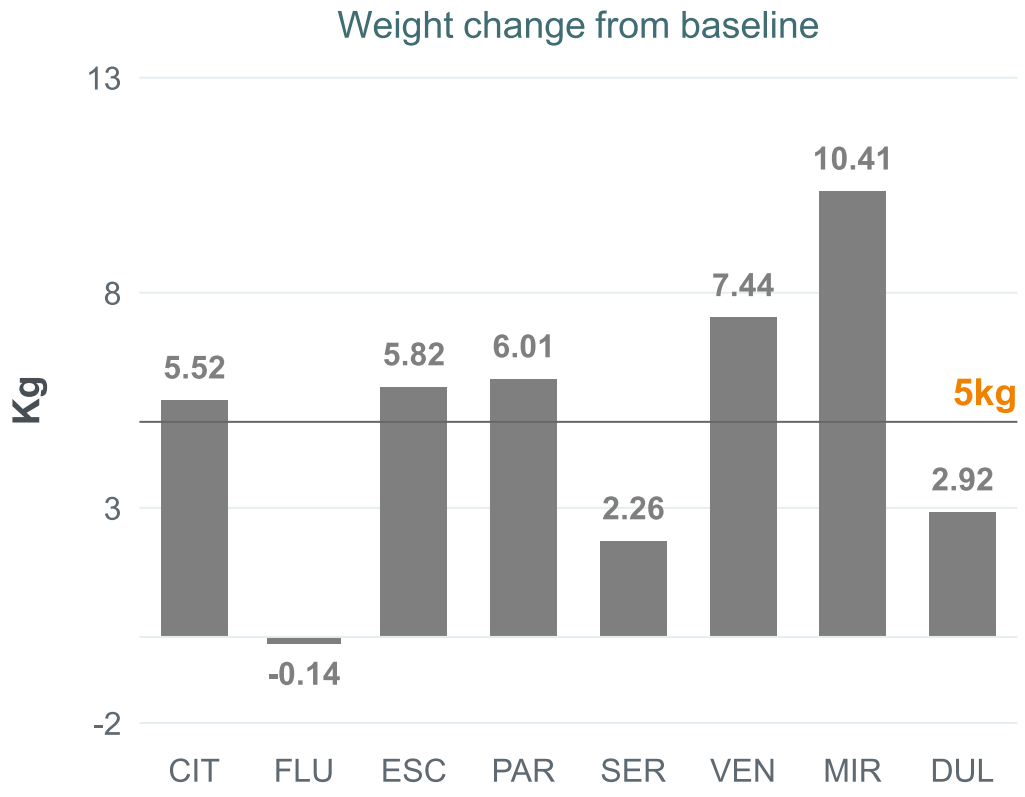
Several adverse events remain with current therapies, which may lead to discontinuation and thus a higher risk of relapse / lower chance of remission

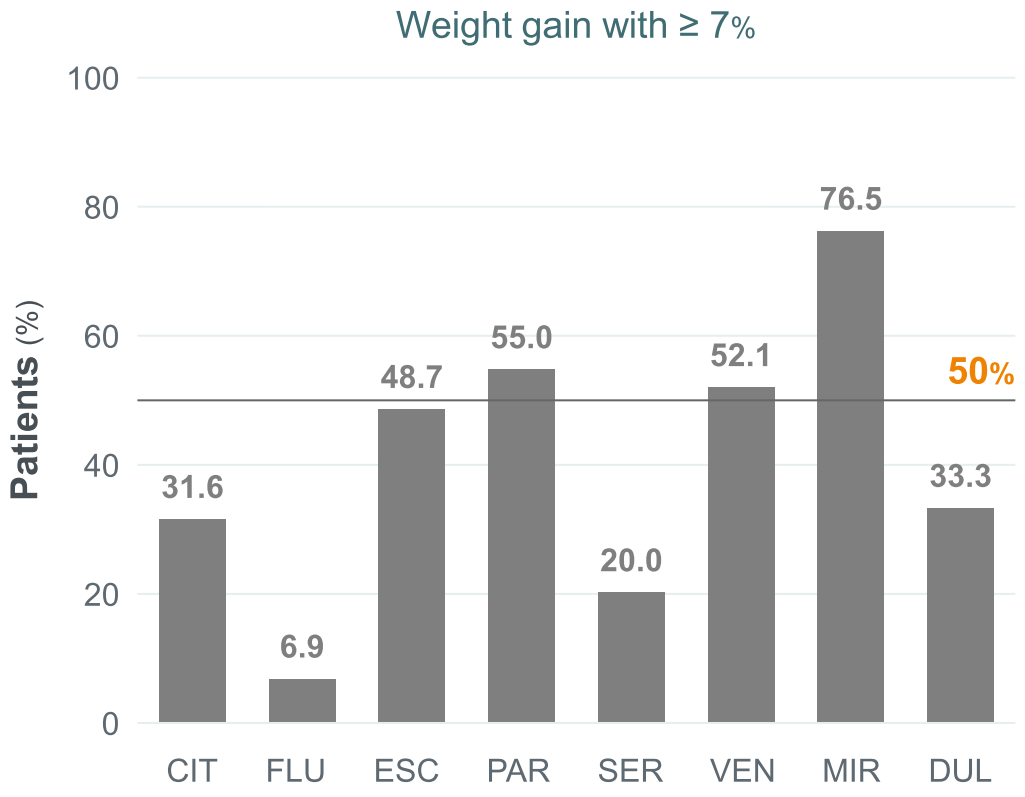
Side effect	Addressed in Brintellix® (vortioxetine) clinical trials	Outcome
Sleep disturbance (insomnia and somnolence)	AE	Placebo-level insomnia and somnolence
Weight gain	Weight assessed	Weight neutral in the short- and long-term
Sexual dysfunction	AE, ASEX	Placebo-level sexual side effects (5 mg and 10 mg dose)
Discontinuation symptoms	DESS	No discontinuation symptoms

Bull 2002; Kelly 2008; Cassano 2004; Masand 2003; Lin 1995; Rosenburg 2003; H. Lundbeck A/S; Alvarez 2012; Katona 2012; Baldwin 2012; Henigsberg 2012; Boulenger 2012; Vortioxetine SPC

Weight gain effects of antidepressants

Several antidepressant affect to weight gain

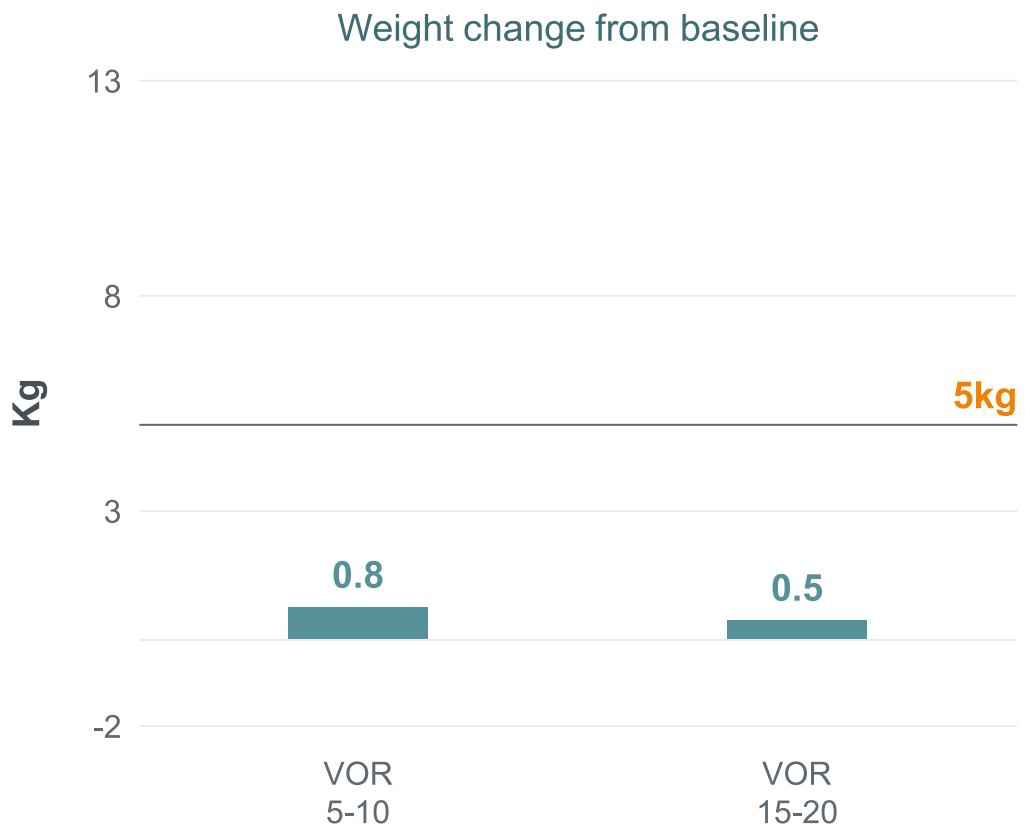


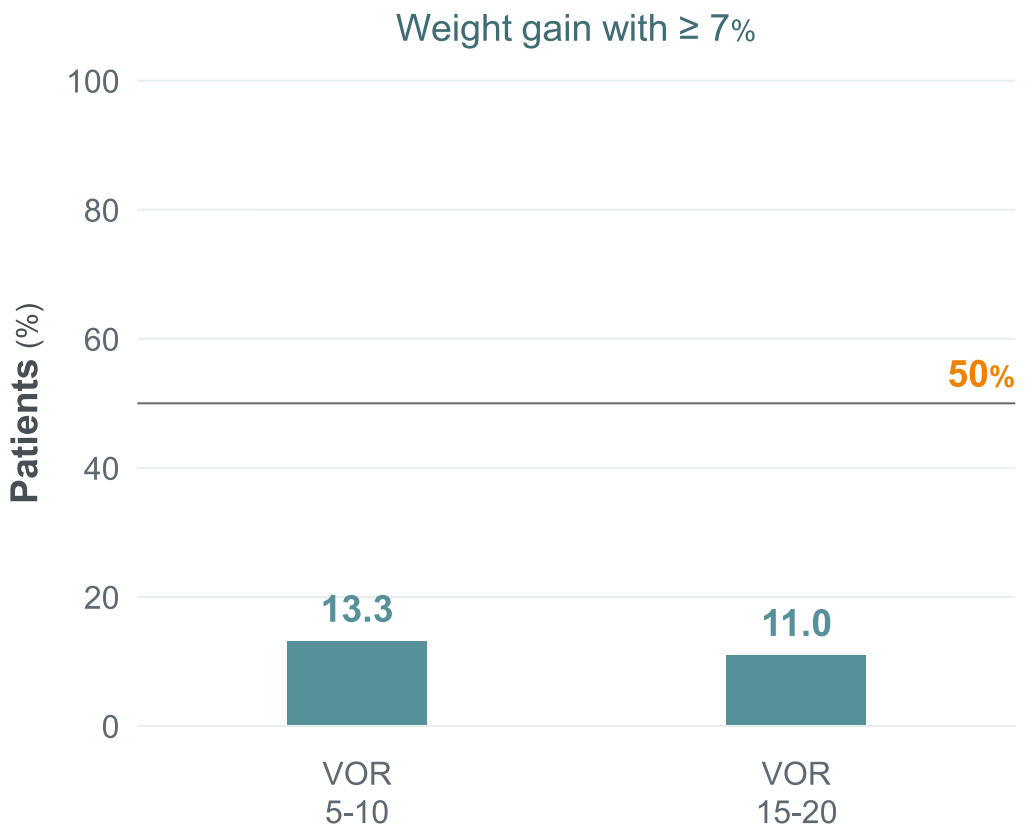


Uguz *et al. Gen Hosp Psychiatry*. 2015 Jan-Feb;37(1):46-8

Weight gain effects of vortioxetine (12 months)

Vortioxetine seems to be neutral to body weight in long term studies





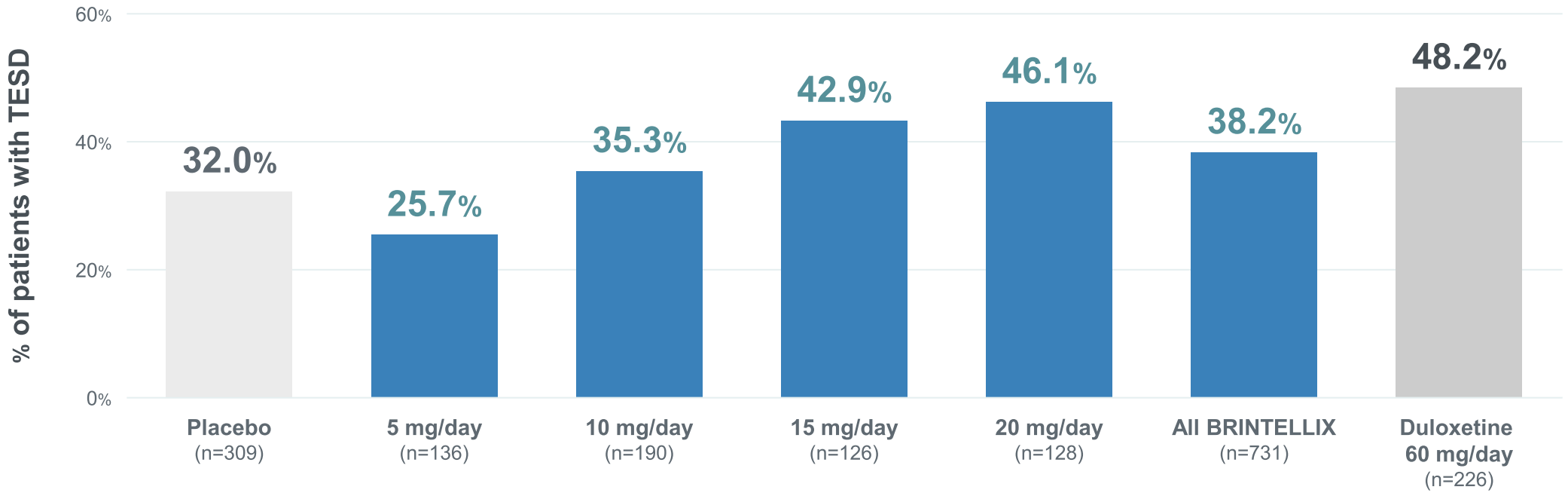
Baldwin *et al. J Psychopharmacol*. 2016 Mar;30(3):242-52.

Tolerability of Brintellix®

Sexual dysfunction : TESD based on ASEX

TESD* at Any Visit in Patients Without Sexual Dysfunction at Baseline (n=1,266)

Across all studies in which ASEX was collected, approximately 30% of subjects in each treatment group were **without** sexual dysfunction at baseline



*TESD: treatment-emergent sexual dysfunction
Sexual dysfunction defined as ASEX total score ≥19, score ≥4 on 3 or more items, or score ≥5 on any single item

Jacopsen *et al. CNS Spectr*. 2016 Oct;21(5):367-378.

Tolerability of Brintellix®

Classification of antidepressants according to risk of sexual dysfunction

Summary of antidepressants and augmentation agents

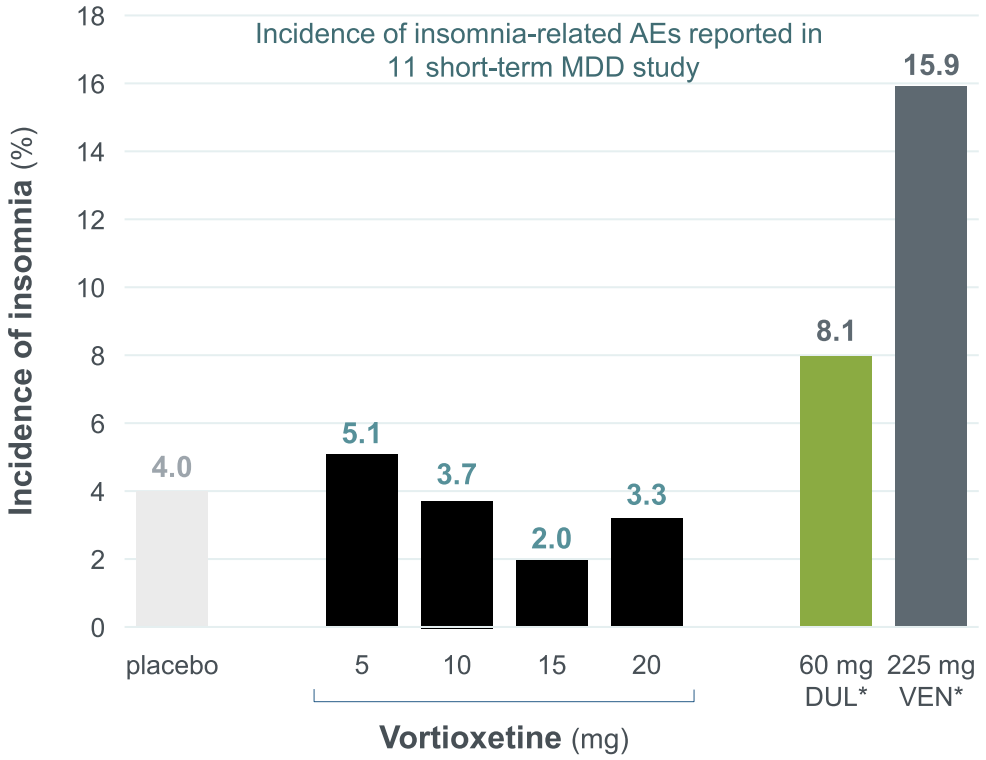
Category A (improves sexual functioning)	• Sildenafil	• Tadalafil	• Vardenafil	• Flibanserin	• **Bupropion**
Category B (No significant effect on sexual functioning)	• Agomelatine • **Vortioxetine**	• **Desvenlafaxine**	• Moclobemide	• Trazodone	• Vilazodone
Category C (Significant negative effect on sexual functioning)	• **Citalopram** • **Paroxetine**	• Clomipramine • Phenelzine	• **Escitalopram** • **Sertraline**	• **Fluoxetine** • **Venlafaxine**	• Imipramine
Category D (Inconclusive)	• **Duloxetine**	• Levomilnacipram	• Mirtazapine		

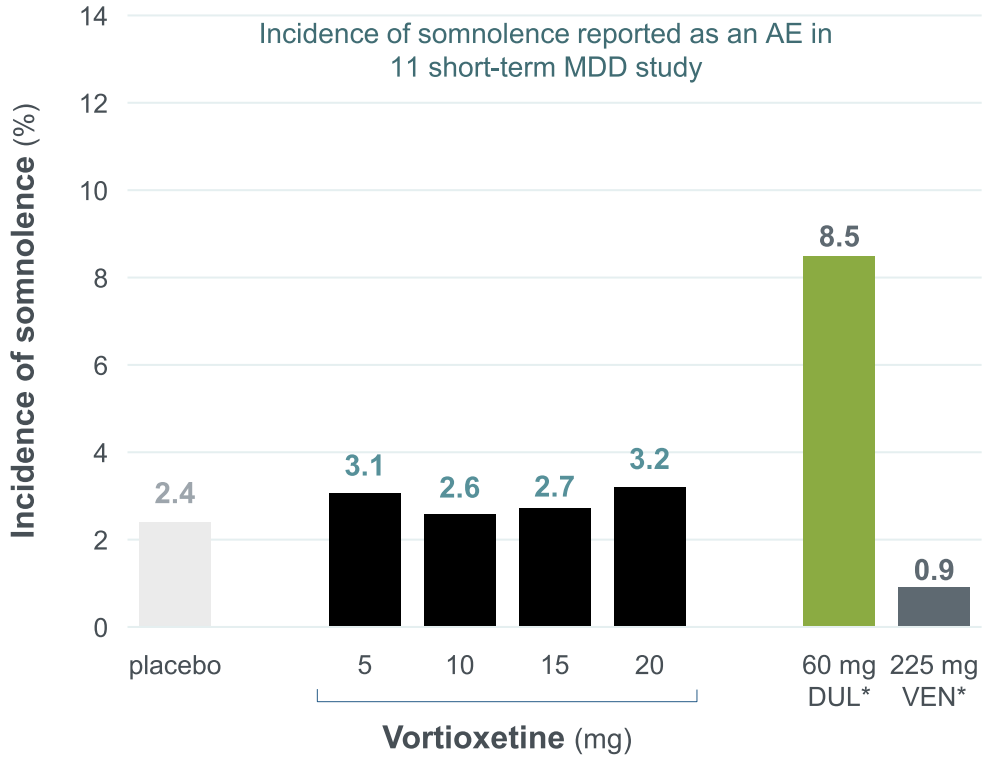
Chokka *et al. Ther Adv Psychopharmacol*. 2018

Tolerability of Brintellix®

Sleep disturbance (insomnia & somnolence)

Vortioxetine does not increase the incidence of insomnia or somnolence relative to placebo





According to the **FDA** clinical trial register, the rate of treatment-emergent **insomnia complaints or somnolence** during the therapy with **vortioxetine is lower when compared to SSRI and SNRI drugs** (Wichniach et al. *Curr Psychiatry Rep*. 2017)

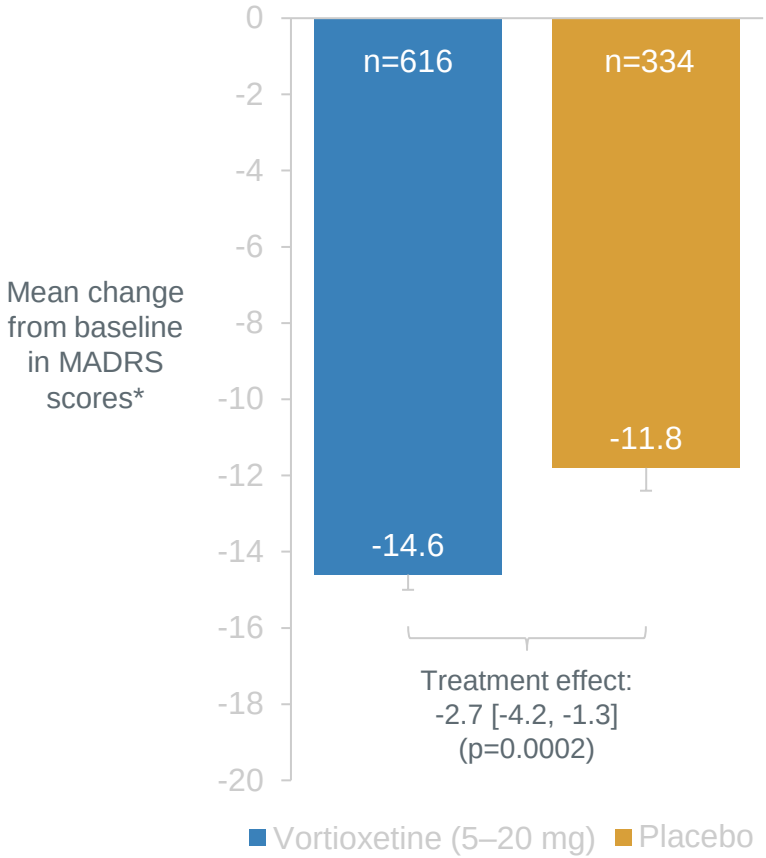
Baldwin *et al. J Psychopharmacol*. 2016 Mar; 30(3): 242–252.; *referred from SmPC of Cymbalta (duloxetine) & Effexor (venlafaxine)

Vortioxetine (5–20 mg/day) significantly reduced depression severity in patients with MDD and CVD

Vortioxetine **significantly reduced MADRS total score by Week 8** compared with placebo in patients with MDD and CVD (mean difference: −2.7; p=0.0002)[1*]

Treatment with vortioxetine was **generally well tolerated**[1*]

- 63.8–68.8% of patients experienced ≥1 TEAE; the most commonly reported AE was nausea (18.5–25.0%)



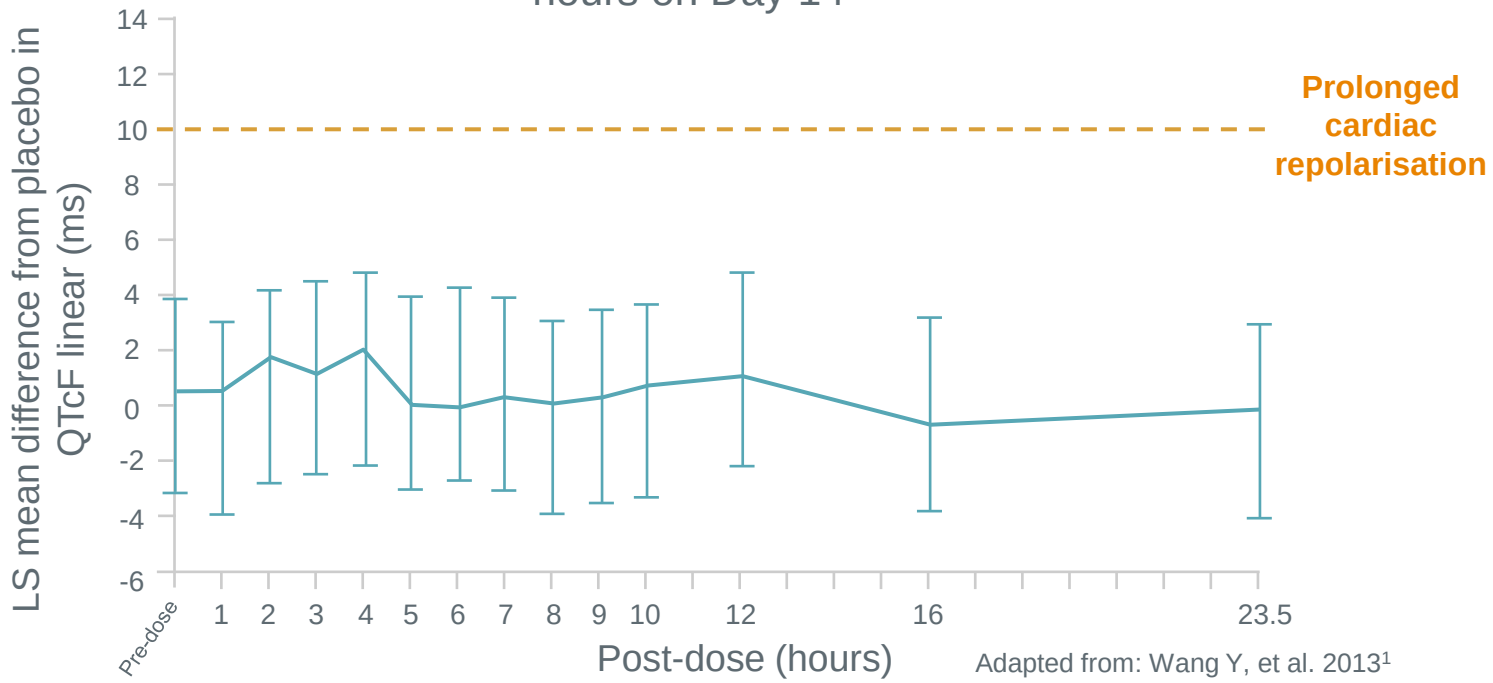
Adapted from: Baldwin DS, et al. 2022[1]

*Data based on a pooled analysis of 13 randomised placebo-controlled trials which evaluated the efficacy (MADRS) and safety of vortioxetine (5–20 mg/day) in adult patients with MDD and a diagnosis of CVD (n=963).
AE = adverse event; CVD = cardiovascular disease; MADRS = Montgomery-Åsberg Depression Rating Scale; TEAE = treatment-emergent adverse event.
1. Baldwin DS, et al. J Affect Disord. 2022;311:588–594.

Vortioxetine has a low risk of QTC prolongation and an effect on bleeding risk similar to placebo

Low risk of QTC prolongation (mean difference from placebo: <10 ms; p = 0.1353) [1]*

Vortioxetine (10 mg) LS mean difference (90% CI) from placebo in QTcF over 24 hours on Day 14[1]



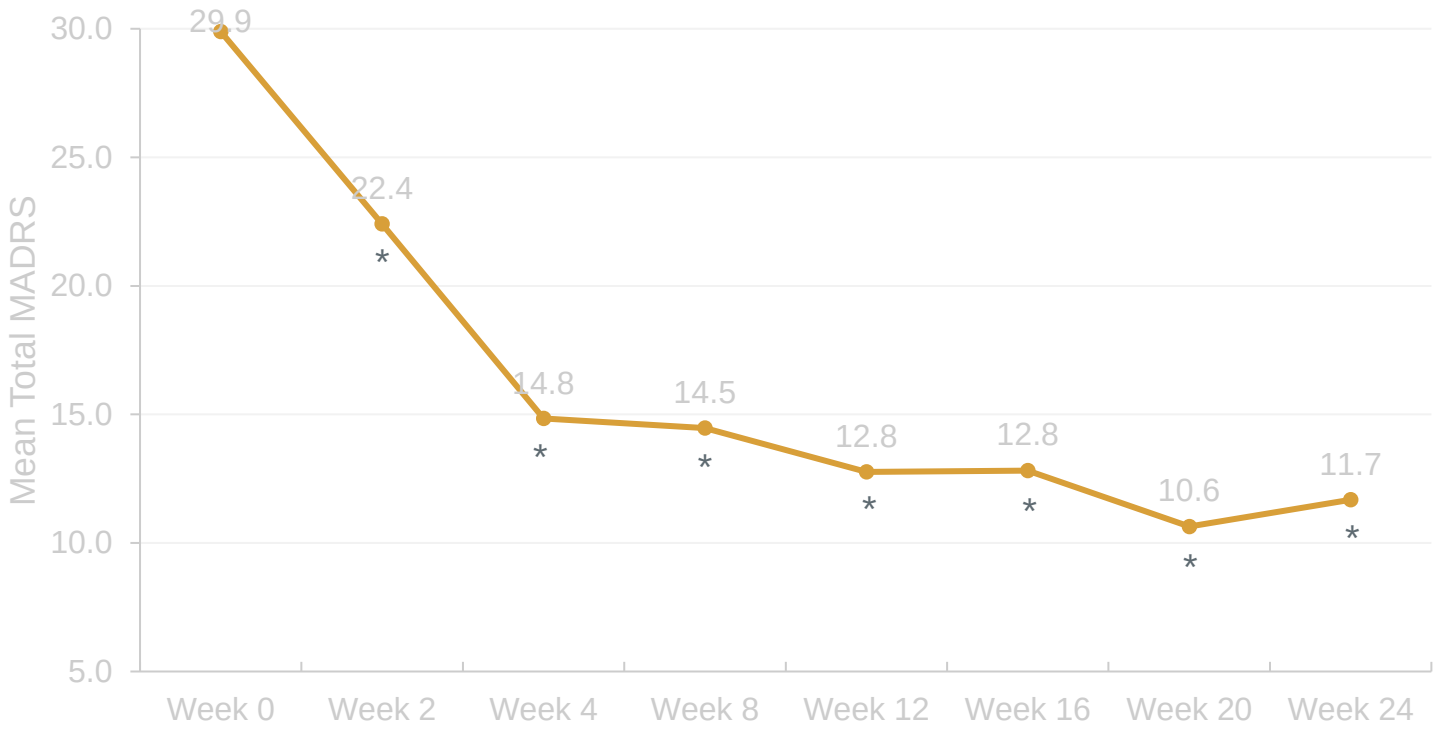
Adapted from: Wang Y, et al. 2013[1]

- **Effect on aspirin or warfarin** pharmacokinetics or pharmacodynamics is **similar to placebo**[2†]
- **Low bleeding risk:** Low incidence of haemorrhage compared with placebo (1.7% and 1.2%, respectively) [2‡]

*Data based on a randomised placebo-controlled trial of healthy men aged 18–45 years (n=85). †Aspirin study: healthy males and females aged 18–45 years; Warfarin study: Healthy males and females aged 18–55 years. ‡Data based on pooled safety analysis (N=4681) of short-term clinical studies of vortioxetine (1–20 mg/day). For more information on warnings, precautions, and interactions, prescribing information for vortioxetine can be found at the end of this slide deck. CI = 90% confidence interval; LS = least squares; QTC, corrected QT interval; QTcF = the duration of ventricular electrical systole corrected for heart rate (Fredericia). 1. Wang Y, et al. Clin Pharmacol Drug Dev. 2013;2(4):298–309; 2. Chen G, et al. J Clin Pharmacol. 2015;55(6):671–679.

Vortioxetine significantly improved depressive symptoms in patients with MDD and comorbid cancer[1]

Mean Total **MADRS** score from baseline to Week 24[1]



A statistically significant difference in total MADRS from baseline starting from Week 2.

This improvement in scores was **maintained throughout the 24 weeks** of the study. (*p<0.05)

* P-value <0.05, Data based on A 6-Month Open-Label Study of Vortioxetine among Cancer Patients with Major Depressive Disorder (MDD); A range of cancers: breast cancer 46.7%, colon cancer 13.3%, endocrine cancer 2.2%, leukaemia 2.2%, liver cancer 4.4%, lymphoma 4.4%, ovarian cancer 2.2%, prostate cancer 6.7% and uterine cancer 4.4%.

1. Ng, Chong Guan et al. Asian Pac J Cancer Prev. 2023 Aug 1;24(8):2583-2591.

Treatment of patients with MDD and common comorbidities:

Some of the latest data with vortioxetine

Some of the latest data in the treatment of patients with MDD and common comorbidities with vortioxetine

Neurological comorbidities

MEMORY study: Vortioxetine (10–20 mg/day*) significantly improved depressive symptoms in patients with **MDD and comorbid early dementia**[1]

VOPARK study: Vortioxetine (5–20 mg/day) improved depressive symptoms and HRQoL in patients with **MDD and Parkinson's disease**[2]

Psychiatric comorbidities

Vortioxetine (5–20 mg/day) significantly improved depressive symptoms and functional impairment in patients with **MDD and comorbid SUD**[3]

Vortioxetine (10–20 mg) significantly reduced depressive and anxiety symptoms in patients with **severe MDD and severe comorbid GAD**[4]

Somatic comorbidities

Vortioxetine (5–20 mg/day) significantly reduced depression severity in patients with **MDD and CVD**[5]

Vortioxetine (5–20 mg/day) significantly reduced depression severity in patients with **MDD and type 2 diabetes**[5]

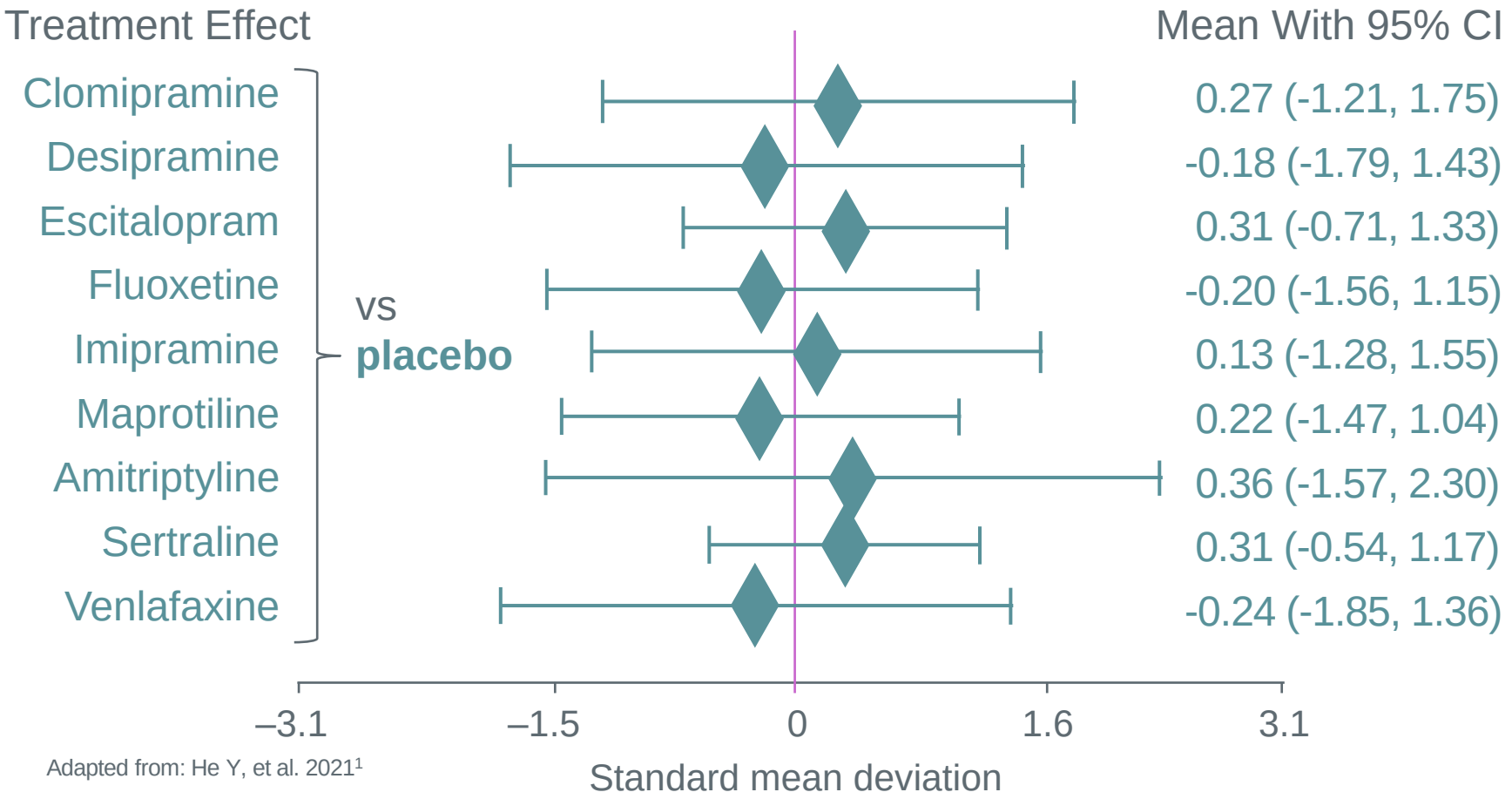
*Starting dose 5 mg first week.

CVD = cardiovascular disease, GAD = generalised anxiety disorder, HRQoL = health-related quality of life; SUD = substance use disorder.

1. Christensen MC, et al. J Affect Disord. 2023;338:432–431; 2. Santos Garcia D, et al. Brain Sci. 2022;12(11):1466; 3. Basurte-Villamor I, et al. Neuropsychiatr Dis Treat. 2022;18:965–976; 4. Christensen MC, et al. J Psychopharmacol. 2022;36(5)566–577; 5. Baldwin DS, et al. J Affect Disord. 2022;311:588–594.

In a network analysis, antidepressants and placebo showed no statistically significant difference in cognitive function in patients with MDD and Alzheimer's disease

MMSE scores from 10 studies in this network meta-analysis **showed no statistically significant difference** between antidepressants and placebo **in cognitive performance**[1]

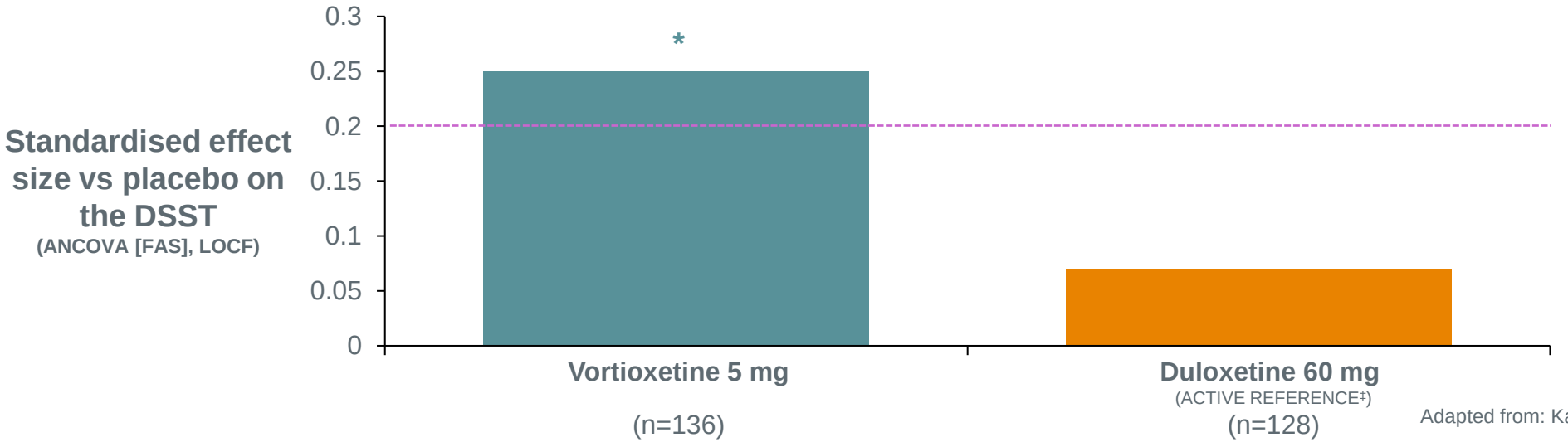


Adapted from: He Y, et al. 2021[1]

The diamond in each line represents the estimated summary standard mean deviation of each comparison.
The black lines represent the confidence intervals (CIs) for summary standard mean deviation for each comparison.
The pink line is the line of no effect (mean change equal to 0). **Registration status may differ from country to country**.
MMSE = Mini-Mental State Examination. 1. He Y, et al. J Psychopharmacol. 2021;35(8):901–909.

Vortioxetine (5 mg) mediated an improvement in cognitive performance in older patients with recurrent MDD

Randomised, double-blind, placebo-controlled, active-referenced study in elderly patients with recurrent MDD† (primary efficacy analysis)[1]



Clinical relevance of standardised effect sizes is assessed by Cohen's *d* values[4§]

Adapted from: Katona C et al. 2012[1]

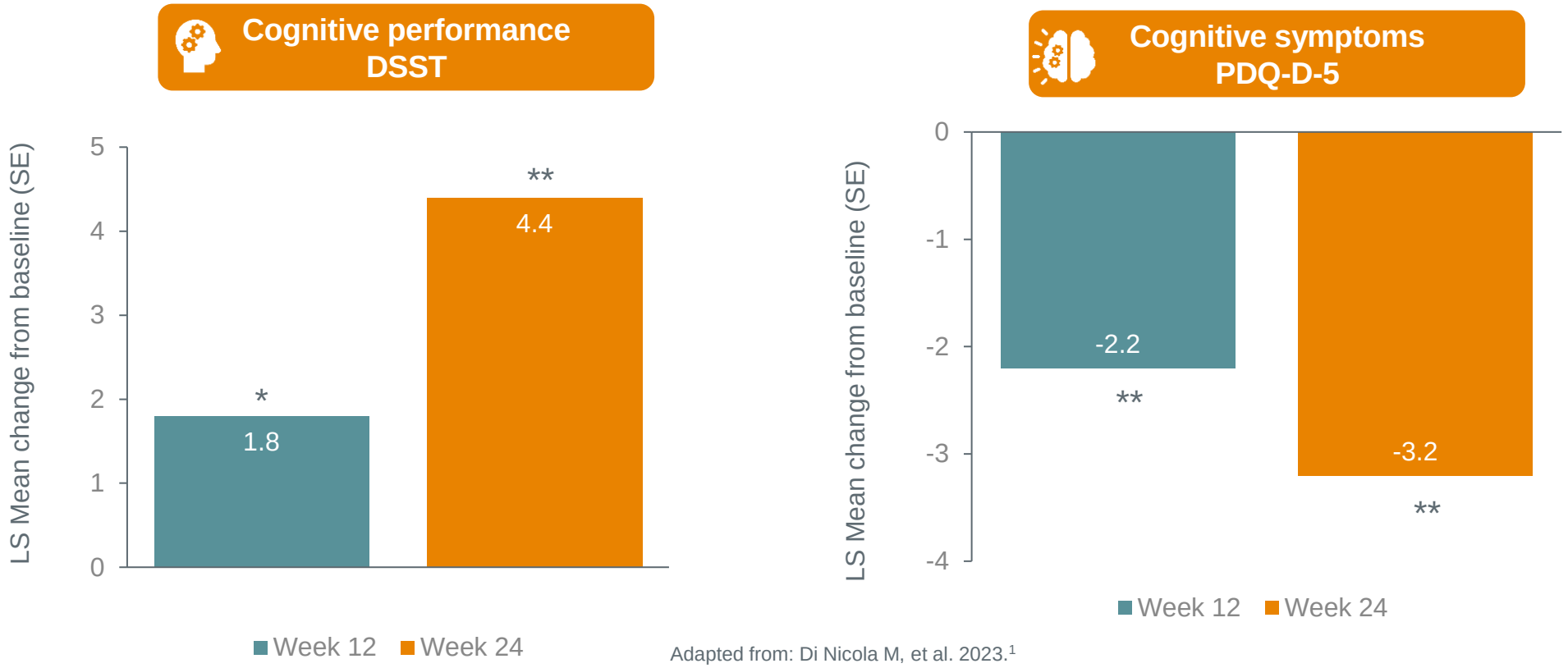
DSST – Replication: Number of correct symbols, change from baseline at Week 8

DSST measures executive functioning, working memory, attention and speed of processing[1,3]

The effect of vortioxetine on DSST performance is not mediated solely through an improvement in general depressive symptoms (measured by MADRS / HAM-D_{24})[1]

*p<0.05. †Study population: age ≥65 years, primary diagnosis of MDD, ≥1 previous MDE before the age of 60 years, female (vortioxetine 68.6%, duloxetine 66.2%), Caucasian (vortioxetine 92.9%, duloxetine 95.4%). HLu 12541A study locations: Europe, Canada and USA. ‡Duloxetine was included as active reference for study validation, not for comparison of effect sizes; §Cohen's d>0.2. ANCOVA = analysis of covariance; DSST = digit symbol substitution test; FAS = full analysis set; HAM-D_{24} = 24-item Hamilton Depression Rating Scale; LOCF = last observation carried forward; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = major depressive episode. 1. Katona C, et al. Int Clin Psychopharmacol. 2012;27:215–223; 2. McIntyre RS, et al. Int J Neuropsychopharmacol. 2014;17:1557–1567; 3. Jaeger J, et al. Eur Neuropsychopharmacol. 2016;26:S341; 4 McIntyre RS, et al. Int J Neuropsychopharmacol. 2016;19(10):1-9.

In clinical practice, vortioxetine (5–20 mg/day) was associated with significant improvements in cognitive performance and cognitive symptoms in elderly patients with MDD



Adapted from: Di Nicola M, et al. 2023.[1]

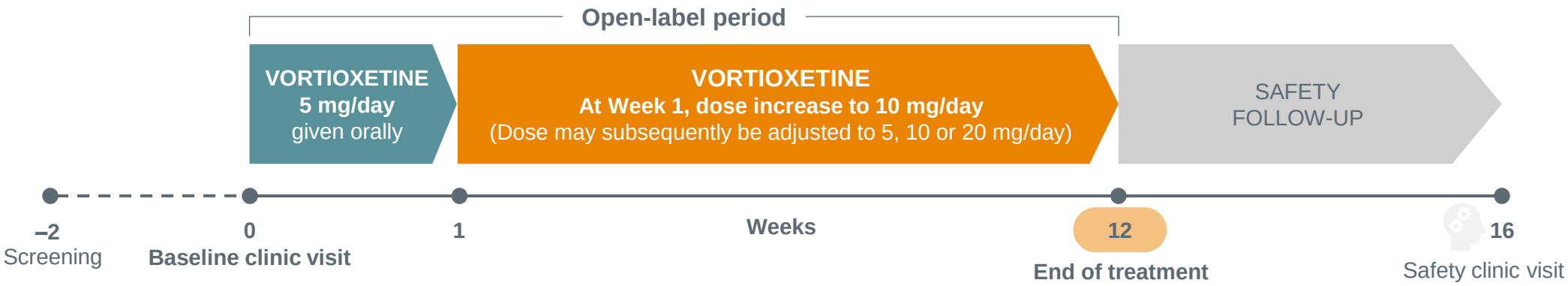
* $p < 0.05$ versus baseline. * $p < 0.01$ versus baseline.

RELIEVE was a 24-week, observational, multinational prospective cohort study in outpatients with MDD initiating treatment with vortioxetine in routine clinical practice. This post-hoc subgroup analysis included elderly patients (≥65 years). Of the 737 patients in the RELIEVE study, 130 (17.6%) were aged ≥65 years, with a mean (SD) age of 71.4 (5.3) years. DSST = Digit Symbol Substitution Test; LS = least squares; PDQ-D-5 = 5-item Perceived Deficits Questionnaire–Depression.

1. di Nicola, M et al. Poster presented at Psych Congress. Poster 68. 2023

MEMORY study: The effect of vortioxetine in patients with MDD and comorbid early dementia

Interventional, open-label study investigated the **effectiveness of 12-week acute treatment with flexible doses of vortioxetine (5–20 mg/day)** on depressive symptoms, cognitive performance, verbal learning and memory, daily functioning, adverse events and HRQoL in patients with MDD and comorbid early dementia[1]



Patient population (n=82)[1]

- Age: 55–85 years
- Primary diagnosis of recurrent MDD with onset before age of 55
- MADRS score ≥26
- Current MDE for <6 months
- Diagnosis of dementia onset occurring ≥6 months prior to screening and after MDD diagnosis
- MMSE-2 total score 20–24, inclusive

Primary endpoint[1]

- Change in MADRS total score from baseline to Week 12

Secondary endpoints[1]

- Change from baseline to Week 12 in DSST score, RAVLT score, IADL score, CGI-S score, CGI-I score and BASQID score
- Response at Week 12 (≥50% decrease from baseline in MADRS total score)
- Remission at Week 12 (MADRS ≤10)

BASQID = Bath Assessment of Subjective Quality of Life in Dementia; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; DSST = Digital-Symbol Substitution Test; HRQoL = health-related quality of life; IADL= Instrumental Activities on Daily Living; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = major depressive episode; MMSE-2 = Mini-Mental State Examination; 2nd Edition, Standard Version; RAVLT = Rey Auditory Verbal Learning Test.

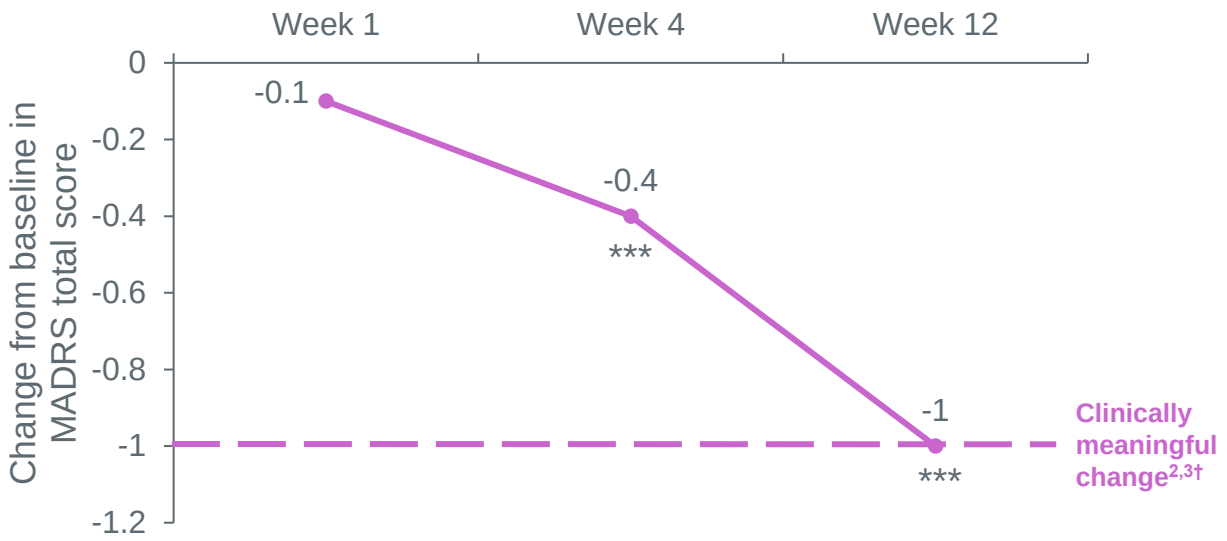
1. Christensen MC, et al. J Affect Disord. 2023;338:432-431.

Vortioxetine significantly improved depressive symptoms in patients with MDD and comorbid early dementia

Mean change in **MADRS** total score from baseline[1]

Adapted from: Christensen MC, et al. 2023[1]

Mean change in **CGI-S** score from baseline[1]



Adapted from: Christensen MC, et al. 2023[1]

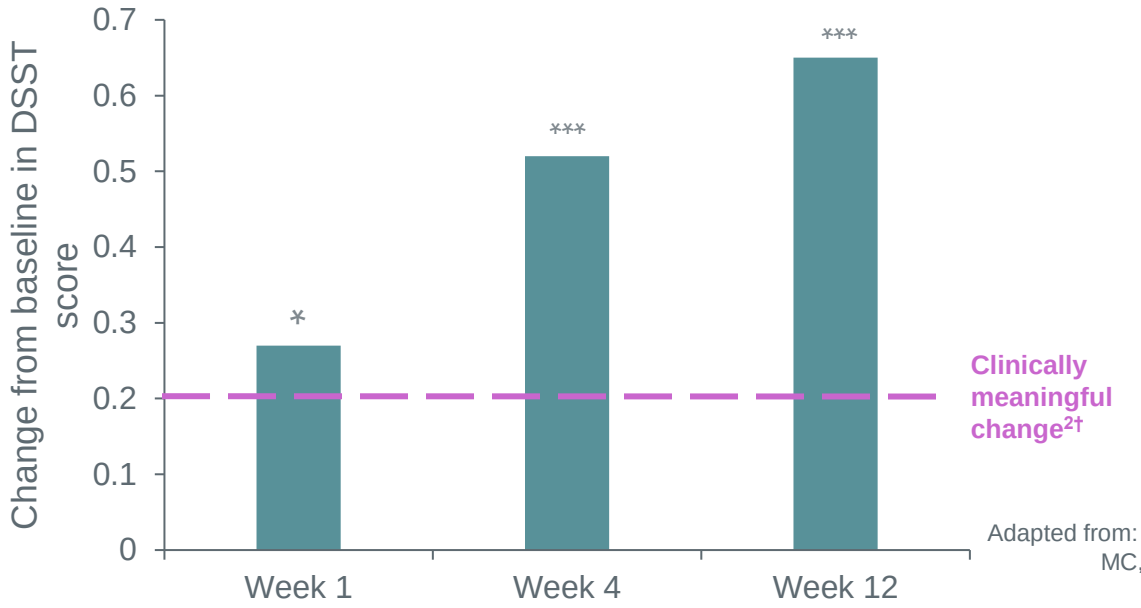
36% of patients showed a **response** with at least a 50% reduction in MADRS score **at Week 12[1]**

***p<0.001. MEMORY is an open-label study of flexible doses of vortioxetine (10-20 mg/day), with a starting dose of 5 mg/day during Week 1. At baseline, patients had moderate to severe MDD (mean MADRS total score = 30.4 points) and early-onset comorbid dementia (mean MMSE score = 21.9 points). Patients included in the MEMORY study had the following dementia types: Alzheimer's disease (42.7%), mixed-type dementia (26.8%), vascular dementia (14.6%), frontotemporal dementia (2.4%) and other types of dementia (13.4%).[2] †Standardised effect sizes (SES) vs baseline of > -1 (as assessed by Cohen's d-values) are considered to be clinically relevant.[2] CGI-S = Clinical Global Impression-Severity; MADRS = Montgomery–Åsberg Depression Rating Scale; MMSE = Mini-Mental State Examination.

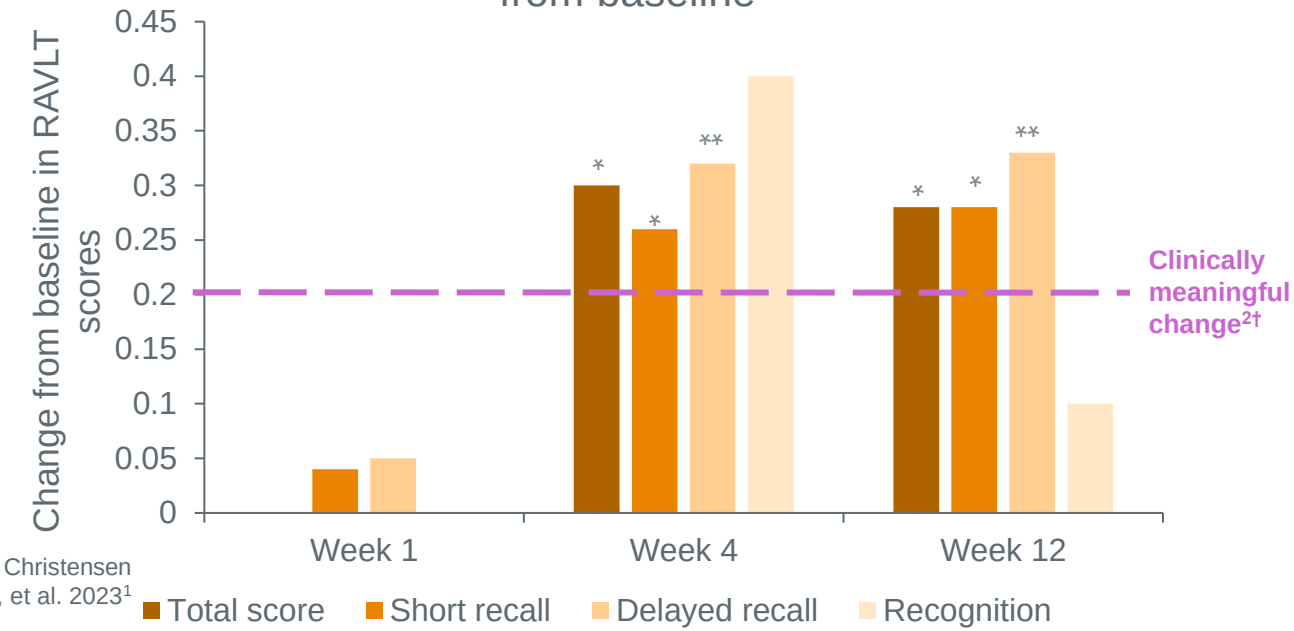
1. Christensen MC, et al. J Affect Disord. 2023;338:432–431; 2. Turkoz I, et al. J Affect Disord. 2013;150(1):17–22; 3. Guy W. ECDEU Assessment Manual for Psychopharmacology. U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health. 1976.

Vortioxetine significantly improved cognitive performance and verbal learning and memory in patients with MDD and comorbid early dementia

Mean change in cognitive performance (DSST) total score from baseline[1]



Mean change in verbal learning and memory (RAVLT) from baseline[1]



Adapted from: Christensen MC, et al. 2023[1]

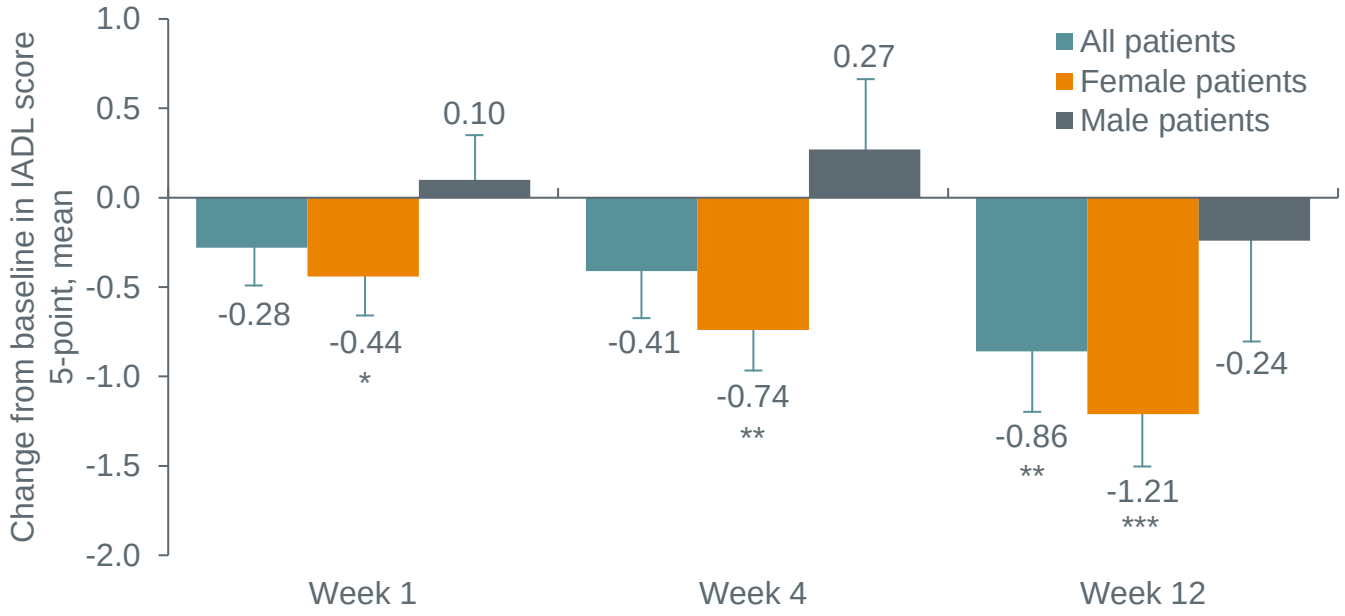
- **Significant improvement** in cognitive performance (as assessed by **DSST total score**) seen over the 12 weeks of vortioxetine treatment
- **Significant** and **clinically relevant improvement** in verbal learning and memory (as assessed by **RAVLT**) was observed from week 4 onwards

*p<0.05, **p<0.01, ***p<0.001. At baseline, patients had moderate to severe MDD (mean MADRS total score = 30.4 points) and early-onset comorbid dementia (mean MMSE score = 21.9 points). DSST at baseline = 23.3. RAVLT at baseline = 28.7[1]. †Standardised effect sizes (SES) vs baseline of >0.2 (as assessed by Cohen's d-values) are considered to be clinically relevant.[2] DSST = Digital-Symbol Substitution Test; MADRS = Montgomery–Åsberg Depression Rating Scale; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test.

1. Christensen MC et al. J Affect Disord. 2023;338:432-431; 2. Cohen, J. Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Routledge. 1988.

Vortioxetine significantly improved daily functioning in patients with MDD and comorbid early dementia

Mean change in IADL 5-point (polytomous) score[1] from baseline[2†]



Adapted from: Christensen MC, et al. 2023.[2]

Daily functioning (IADL) significantly improved, with more patients being able to perform daily tasks on their own after 12 weeks of vortioxetine treatment[2]

Improvements were observed across all IADL domains[2]

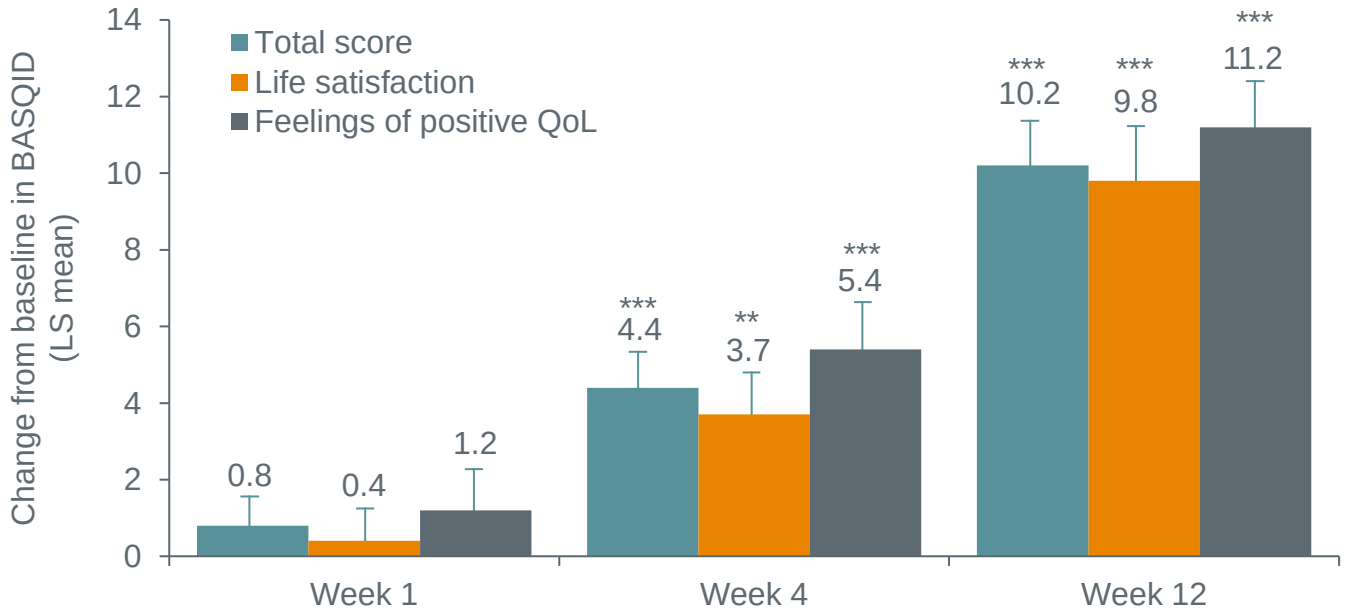
*p<0.05, **p<0.01, ***p<0.001. At baseline, patients had moderate to severe MDD (mean MADRS total score = 30.4 points) and early-onset comorbid dementia (mean MMSE score = 21.9 points). IADL 5-point at baseline = 15.6.[1] †IADL 5-point (polytomous) score is used to measure daily functioning, including ability to handle finances, to use telephone, shopping for groceries, housekeeping and responsibility for own medications.[2] Scores 1–5: Lower score indicates greater ability.[1] The IADL scale is gender sensitive, men are more likely not to do the IADL activities for reasons unrelated to health limitations, which may reflect gendered expectations regarding household activities.[3]

IADL = Instrumental Activities of Daily Living; LS = least squares; MADRS = Montgomery–Åsberg Depression Rating Scale; MMSE = Mini-Mental State Examination.

1. Pashmdarfard M, Azad A. Med J Islam Repub Iran. 2020;34:33; 2. Christensen MC, et al. J Affect Disord. 2023;338:432-431; 3. Sheehan C, Tucker-Drob E. J Gerontol B Psychol Sci Soc Sci. 2017;74(4):715–723.

Vortioxetine significantly improved HRQoL in patients with MDD and comorbid early dementia

Mean change in BASQID for total score from baseline[1]



Significant improvement in HRQoL as assessed using the **BASQID**

Patients' subjective ratings of overall QoL also improved over time

Improvements in MADRS total score were **significantly correlated** with improvements in HRQoL (BASQID total score, -0.57; p<0.0001)[1]

Adapted from: Christensen MC, et al. 2023[1]

**p<0.01, ***p<0.001. At baseline, patients had moderate to severe MDD (mean MADRS total score = 30.4 points) and early-onset comorbid dementia (mean MMSE score = 21.9 points). BASQID total score at baseline = 31.3.[1] Scores 1–5: Lower score indicates greater ability.[1]

BASQID = Bath Assessment of Subjective Quality of Life in Dementia; HRQoL = health-related quality of life; IADL = Instrumental Activities of Daily Living; LS = least squares; MADRS = Montgomery–Åsberg Depression Rating Scale; MMSE = Mini-Mental State Examination; QoL, quality of life.

1. Christensen MC, et al. J Affect Disord. 2023;338:432–431.

Safety outcomes

- No new safety signals were observed during the MEMORY study; vortioxetine was generally well tolerated
- During the study, 38 (46%) patients reported TEAEs, with few patients (n=6, 7.3%) withdrawing due to AEs
  - The most commonly reported AEs were abdominal pain (n=9, 11%) and nausea (n=9, 11%)

Total TEAEs, n	56
Number of patients with TEAEs, n (%)	38 (46.3)
Serious TEAE, n (%)	1 (1.2)
TEAEs leading to withdrawal, n (%)	6 (7.3)

51.4% (n=37/72)
of patients remained on vortioxetine
20 mg/day
until study end **at Week 12**

AE = adverse event; SAE = serious adverse event; TEAEs = treatment emergent adverse events

1. Christensen MC, et al. J Affect Disord. 2023;338:432-431.

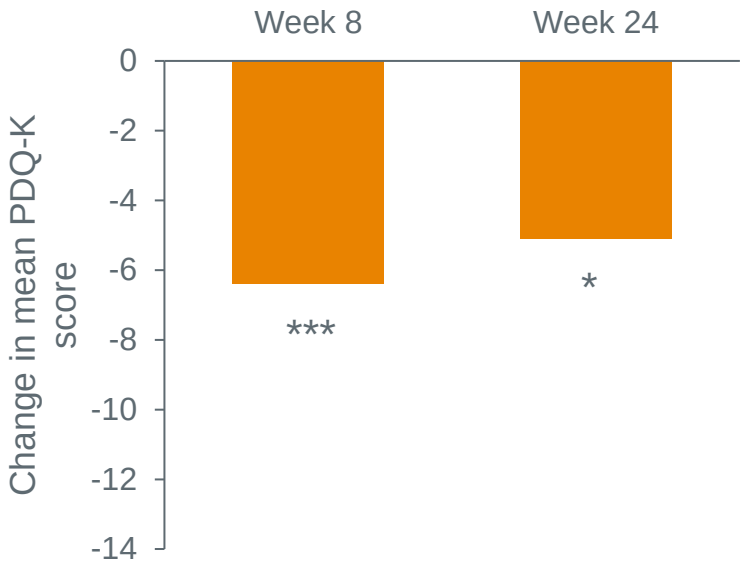
In Korean clinical practice, patients with MDD and comorbid Alzheimer's disease had significant long-term improvements in depressive and cognitive symptoms with vortioxetine (5–20 mg/day)

Depressive symptoms

Change in mean **MADRS score** from baseline

Cognitive symptoms

Change in mean **PDQ-K score** from baseline



Adapted from: Cumbo E, et al. Front Aging Neurosci. 2023.[1]

Tolerability

	Patients, n (%)	Events, n
Any AE	27 (13)	37
Serious AE	9 (4.3)	12
AE occurring in ≥2 patients		
Decreased appetite	4 (1.9)	4
Nausea	2 (1)	2
Dizziness	2 (1)	2
Lower limb fracture	2 (1)	2

Adapted from: Cumbo E, et al. Front Aging Neurosci. 2023.[1]

- Vortioxetine was generally well tolerated with no unexpected AEs
- 27 (13%) patients reported AEs, which were mostly mild in intensity (89.2%)

*p=0.03, ***p<0.0001.
Data based on a subgroup analysis of a mandatory 6-month, prospective, multicentre, noninterventional postmarketing surveillance study of patients with MDD and comorbid Alzheimer's disease (N=207); most patients with available dose data (91.6%) were receiving 5 mg/day vortioxetine.
AE, adverse event; MADRS = Montgomery–Åsberg Depression Rating Scale; PDQ-K = Perceived Deficits Questionnaire–Depression.
1. Cumbo E, et al. Front Aging Neurosci. 2023;14:1037816.

CANMAT 2023 Guidelines recommend Vortioxetine as first-line therapy for cognitive symptom in MDD patients

Summary Medication Recommendations for DSM–5-TR Episode Specifiers and Symptom Dimensions

Line of treatment	DSM-5-TR episode specifiers				Symptom dimensions		
	• Anxious distress • Atypical features • Melancholic features	• Mixed Features	• Psychotic features	• Catatonic features	• **Cognitive Dysfunction**	• Sleep disturbance	• Somatic symptoms
First line	Any first-line antidepressant from Table 3.3 ●	Any first-line antidepressant* from Table 3.3 ●	Any first-line antidepressant from Table 3.3 + atypical antipsychotic ●	Benzodiazepine and any first-line antidepressant from Table 3.3 ◔	**Vortioxetine** ●	Agomelatine† ●	Duloxetine (pain) Bupropion (fatigue)
Second line	Any second-line antidepressant from Table 3.3 ●	Lurasidone** ◔			Bupropion ◔ Duloxetine ◔ SSRIs** ◔	Mirtazapine ◔ Quetiapine-XR ◔ Trazodone ◔	Duloxetine** (fatigue) ◔ Other SNRIs (pain) ◔ SSRIs** (fatigue) ◔

● Level 1; ◔ Level 2; ◐ Level 3; ◴ Level 4;

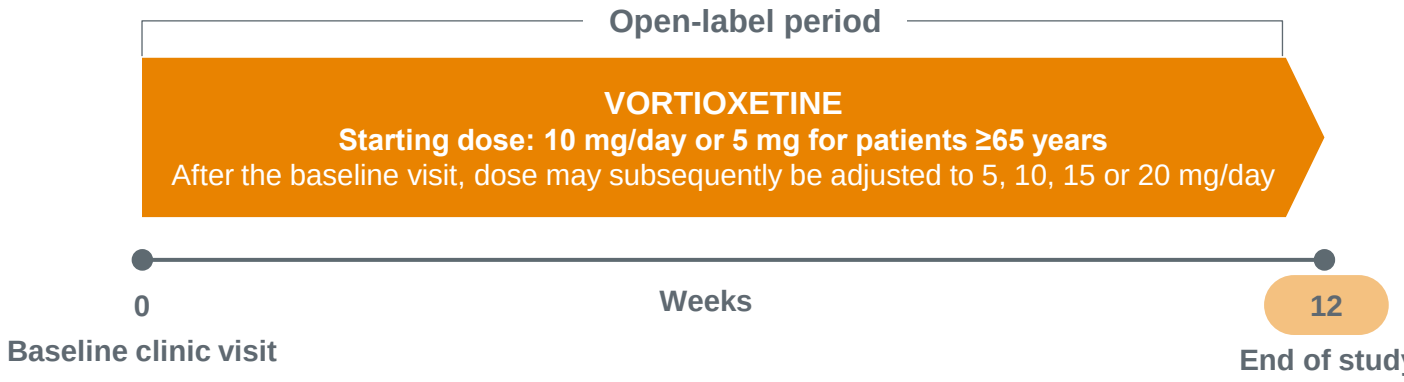
* When initiating medications, monitor for activating side effects (e.g., agitation, increase in suicidal ideation) and potential switch to (hypo)mania.
** Comparisons only with placebo.
†Not available in Canada

SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor, MDD=Major Depressive Disorder

1, Lam RW, *et al*. Can J Psychiatry. 2024 Sep;69(9):641-687.

VOPARK study: The effect of vortioxetine in patients with MDD and Parkinson's disease

Observational, prospective, open-label, single-arm study investigated the **effectiveness of 12-week treatment with flexible doses of vortioxetine (5–20 mg/day)** on depressive symptoms, cognition, apathy, fatigue and HRQoL in patients with MDD and Parkinson's disease[1]



Patient population (n=30)[1]

- ≥40 years old
- Diagnosis of MDD according to DSM-5 and HAM-D_{17} score ≥16
- Diagnosis of Parkinson's disease according to the United Kingdom Parkinson's Disease Society Brain Bank criteria
- Undergoing stable dopaminergic treatment and no expectations of dose or drug changes in the next 3 months
- No dementia criteria

Primary endpoint[1]

- Change in HAM-D_{17} total score from baseline to Week 12

Secondary endpoints[1]

- Change from baseline to Week 12 in apathy (AS), cognition (PD-CRS) and fatigue (FSS) scores
- Analysis of vortioxetine on QoL (health-related [PDQ-39] and global [EUROHIS-QOL8 item index]) and functional capacity for ADL (ADLS)

ADL = activities of daily living; ADLS = Schwab and England Activities of Daily Living Scale; AS = Apathy Scale; DSM-5 = Diagnostic and Statistical Manual of Mental Health Disorders, Fifth Edition; FSS = Fatigue Severity Scale; HAM-D_{17} = 17-item Hamilton Depression Rating Scale; HRQoL = health-related quality of life; PD-CRS = Parkinson's Disease Cognitive Rating Scale; PDQ-39 = 39-item Parkinson's Disease Quality of Life Questionnaire; QoL = quality of life.

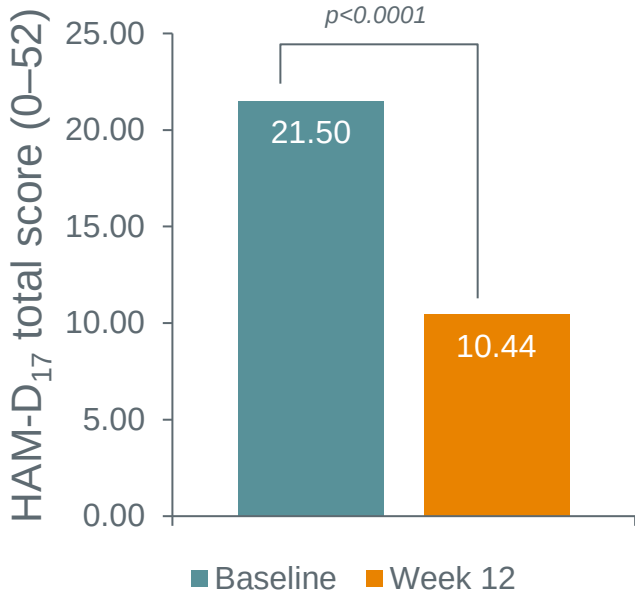
1. Santos Garcia D, et al. Brain Sci. 2022;12(11):1466.

VOPARK study: Vortioxetine (5–20 mg/day) improved depressive symptoms and HRQoL in patients with MDD and Parkinson's disease

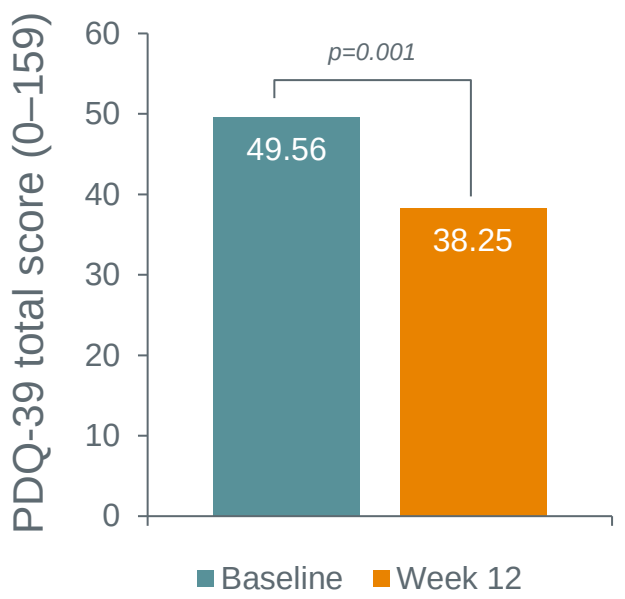
Depressive symptoms were reduced by 52.7%[1]

HRQoL was improved by 23.8%[1]

Mean change in HAM-D_{17} total score from baseline to Week 12



Mean change in PDQ-39 total score from baseline to Week 12



VOPARK is a multicentre, phase IV, prospective, open-label, follow-up study of patients with Parkinson's disease diagnosed with major depression (N=30) receiving vortioxetine (5–20 mg/day).

HAM-D_{17} = 17-item Hamilton Depression Rating Scale; HRQoL = health-related quality of life; PDQ-39 = 39-item Parkinson's Disease Quality of Life Questionnaire.

1. Santos Garcia D, et al. Brain Sci. 2022;12(11):1466.

VOPARK study: Patients with MDD and Parkinson's disease treated with vortioxetine (5–20 mg/day) had improved non-motor symptoms* at Week 12

	Baseline (N=30)	Week 12 (N=27)	Cohen's d	Change in score from BL to W12	p
MOTOR ASSESSMENT					
H&Y-ON	2 (1.75–2)	N.A.	N. A	N.A.	N.A.
UPDRS-III-ON	23.1 ± 9.85 (9–51)	21.63 ± 8.28 (7–39)	-0.21	-6.90%	0.483
UPDRS-IV	2.53 ± 2.04	N.A.	N. A.	N.A.	N.A.
NON MOTOR ASSESSMENT					
HAM-D17	21.5 ± 4.75 (16–33)	10.44 ± 7.54 (1–30)	-2.5	-52.70%	<0.0001
AS (Apathy Scale)	17.6 ± 6.54 (1–31)	11.29 ± 7.18 (1–26)	-1.3	-35.10%	<0.0001
PD-CRS(Cognitive Rating Scale)	80.66 ± 19.14 (29–116)	86.81 ± 20.45 (38–127)	0.8	7.94%	0.007
PD-CRS FS sub-score	54.17 ± 18.19	59 ± 18.96	0.39	8.90%	0.104
Immediate verbal memory	7.3 ± 2.03 (4–12)	7.85 ± 2.14 (4–12)	0.46	7.50%	0.091
Sustained attention	7.37 ± 3.21 (0–10)	8.33 ± 2.07 (2–10)	0.49	13%	0.094
Working memory	5.9 ± 2.67 (0–9)	6.19 ± 2.2 (0–19)	0.08	4.90%	0.946
Clock drawing	8.57 ± 2.3 (1–10)	9 ± 1.54 (5–10)	0.16	5%	0.711
Delayed verbal memory	4.4 ± 2.67 (0–11)	4.96 ± 2.54 (0–10)	0.54	12.70%	0.047
Alternating verbal fluency	9.67 ± 4.22 (2–17)	10.7 ± 4.71 (2–20)	0.48	10.60%	0.114
Action verbal fluency	12.53 ± 4.68 (5–24)	13.07 ± 5.61 (6–27)	0.25	4.30%	0.654
PD-CRS PC sub-score	26.5 ± 8.94	27.81 ± 7.06	0.44	4.90%	0.098
Confrontation naming	15.57 ± 4.98 (7–24)	17.48 ± 3.78 (8–26)	0.46	12.30%	0.067
Clock copy	9.2 ± 2.14 (1–10)	9.37 ± 1.36 (4–10)	0.22	1.80%	0.566
FSS	38.7 ± 18.49 (9–76)	29.04 ± 16.3 (9–60)	-0.77	-27.90%	0.014

	Baseline (N=30)	Week 12 (N=27)	Cohen's d	Change in score from BL to W12	p
QOL AND AUTONOMY					
PDQ-39	49.56 ± 19.39 (15–95)	38.25 ± 22.6 (7–83)	-0.78	-23.80%	0.001
Mobility	33.83 ± 22 (0–35)	30.37 ± 24.27 (0–35)	-0.26	-10.20%	0.109
Activities of daily living	22.64 ± 18.94 (0–18)	20.22 ± 18.37 (0–16)	-0.23	-10.70%	0.273
Emotional well-being	59.72 ± 24.05 (1–24)	33.95 ± 24.23 (0–21)	-1.28	-43.20%	<0.0001
Stigmatization	13.96 ± 18.18 (0–10)	8.8 ± 13 (0–6)	-0.46	-36.90%	0.092
Social support	11.39 ± 18.88 (0–8)	7.41 ± 13.73 (0–6)	-0.38	-35.20%	0.143
Cognition	34.17 ± 26.19 (0–15)	27.31 ± 22.14 (0–13)	-0.6	-20.10%	0.033
Communication	14.72 ± 16.47 (0–6)	10.49 ± 15.77 (0–6)	-0.48	-28.70%	0.069
Pain and discomfort	40.56 ± 21.52 (0–10)	43.21 ± 26.85 (0–12)	0.2	6.50%	0.583
EUROHIS-QOL8	25.1 ± 4.99 (12–38)	28.19 ± 4.38 (20–36)	1.35	12.30%	<0.0001
Quality of life	2.93 ± 0.94 (1–4)	3.48 ± 0.7 (2–4)	0.9	18.70%	0.004
Health status	2.3 ± 0.87 (1–4)	2.78 ± 0.93 (1–4)	0.71	20.80%	0.02
Energy	2.73 ± 0.98 (1–5)	3.33 ± 0.92 (1–5)	0.96	21.90%	0.002
Autonomy for ADL	2.8 ± 1.03 (1–5)	3.3 ± 0.95 (2–5)	1.01	17.80%	0.002
Self-esteem	2.87 ± 1.04 (1–5)	3.37 ± 1 (1–5)	0.86	17.40%	0.004
Social relationships	3.7 ± 0.75 (1–5)	4.04 ± 0.51 (3–5)	0.61	9.10%	0.025
Economic capacity	3.57 ± 0.72 (2–5)	3.59 ± 0.84 (1–5)	0.24	0.50%	0.356
Habitat	4.2 ± 0.61 (3–5)	4.3 ± 0.61 (3–5)	0.51	2.30%	0.059
ADLS	82.66 ± 11.72 (50–100)	84.81 ± 11.22 (50–100)	0.32	2.60%	0.227
Functional dependency (%)	23.3	14.8	N.A.	N.A.	0.687

Data based on a multicentre, phase IV, prospective, open-label, follow-up study of patients with Parkinson's disease diagnosed with major depression (N=30) receiving vortioxetine (5–20 mg/day) *Including cognition, apathy and fatigue. N.A. = not applicable; ADLS = Schwab & England Activities of Daily Living Scale; AS = Apathy Scale; FSS = Fatigue Severity Scale; HAM-D17 = 17-item Hamilton Depression Rating Scale score; H&Y = Hoenh & Yahr; PD-CRS = Parkinson's Disease Cognitive Rating Scale; PDQ-39 = 39-item Parkinson's Disease Quality of Life Questionnaire; QoL = quality of life; UPDRS = Unified Parkinson's Disease Rating Scale. 1. Santos Garcia D, et al. Brain Sci. 2022;12(11):1466.

VOPARK study: Patients with MDD and Parkinson's disease treated with vortioxetine (5–20 mg/day) had improved non-motor symptoms* at Week 12

Mean change in AS score from baseline to Week 12

17.60 at baseline

11.29 at Week 12

Apathy reduced by 35.1% (p<0.0001)[1]

Mean change in PD-CRS score from baseline to Week 12

80.66 at baseline

86.81 at Week 12

Cognition improved by 7.94% (p=0.007)[1]

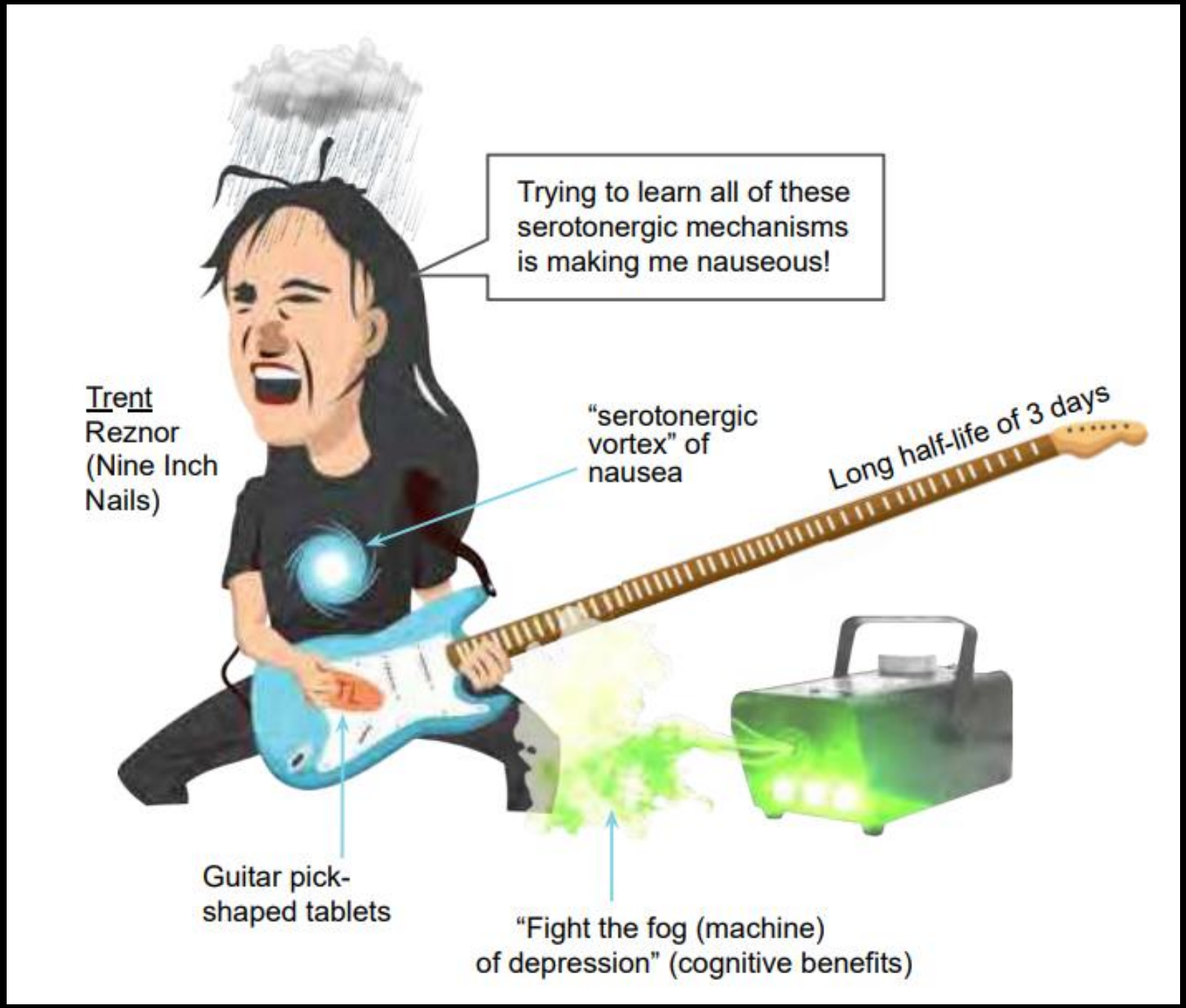
Mean change in FSS score from baseline to Week 12

38.70 at baseline

29.04 at Week 12

Fatigue reduced by 27.9% (p=0.014)[1]

Data based on a multicentre, phase IV, prospective, open-label, follow-up study of patients with Parkinson's disease diagnosed with major depression (N=30) receiving vortioxetine (5–20 mg/day)
*Including cognition, apathy and fatigue.
AS = Apathy Scale; FSS = Fatigue Severity Scale; PD-CRS = Parkinson's Disease Cognitive Rating Scale.
1. Santos Garcia D, et al. Brain Sci. 2022;12(11):1466.


Trying to learn all of these serotonergic mechanisms is making me nauseous!
Trent Reznor (Nine Inch Nails)
"serotonergic vortex" of nausea
Long half-life of 3 days
Guitar pick-shaped tablets
"Fight the fog (machine) of depression" (cognitive benefits)

경청해 주셔서 감사합니다

Vortioxetine is primarily metabolized by CYP2D6, and demonstrated a low potential for drug–drug interactions

Potential consequences for vortioxetine when co-administered with inhibitors or inducers of CYP enzymes

CYP450 enzyme	Inhibitors	Inducers	Drug class	Potential consequences for vortioxetine plasma levels
CYP2D6	Bupropion		Antidepressant (NDRI)	↑ plasma vortioxetine levels
	Quinidine		Anti-arrhythmic agent	
	Fluoxetine		Antidepressant (SSRI)	
	Paroxetine		Antidepressant (SSRI)	
CYP3A4	Ketoconazole		Antifungal agent	No clinically relevant change
	Itraconazole		Antifungal agent	
	Voriconazole		Antifungal agent	
	Clarithromycin		Antibiotic	
	Telithromycin		Antibiotic	
	Nefazodone		Antidepressant	
	Conivaptan		Vasopressin receptor antagonist	
	HIV protease inhibitors			
CYP2C9	Fluconazole		Antifungal agent	No clinically relevant change
	Amiodarone		Anti-arrhythmic agent	
CYP450		Rifampicin	Antibiotic	↓ plasma vortioxetine levels
		Carbamazepine	Anticonvulsant	
		Phenytoin	Anticonvulsant	

NDRI, noradrenaline–dopamine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

1. Vortioxetine. EU Summary of Product Characteristics. 2018. www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/002717/WC500159449.pdf.; Accessed Nov 2020; 2. Baldwin DS et al. J Psychopharmacol 2016;30:242-52

Impact of intrinsic factors on vortioxetine PK

Population description Test / Reference	PK	Fold change and 90% CI	Recommendation
Age: 65-85/18-45	AUC C_{max}		No dose adjustment
Sex: Females/Males	AUC C_{max}		
Race: Black/White	AUC C_{max}		

Population description Test / Reference	PK	Fold change and 90% CI	Recommendation
Renal impairment:			
Mild / Normal	AUC C_{max}		No dose adjustment needed for mild/moderate renal impairment
Moderate / Normal	AUC C_{max}		
Severe / Normal	AUC C_{max}		
ESRD / Normal	AUC C_{max}		
Hepatic impairment:			
Mild / Normal	AUC C_{max}		No dose adjustment
Moderate / Normal	AUC C_{max}		
Severe / Normal	AUC C_{max}		

. Chen *et al*. *Clin Pharmacokinet.* 2018 Jun;57(6):673-686; Trintellix SmPC. *FDA.* 2018.

Brintellix® vortioxetine

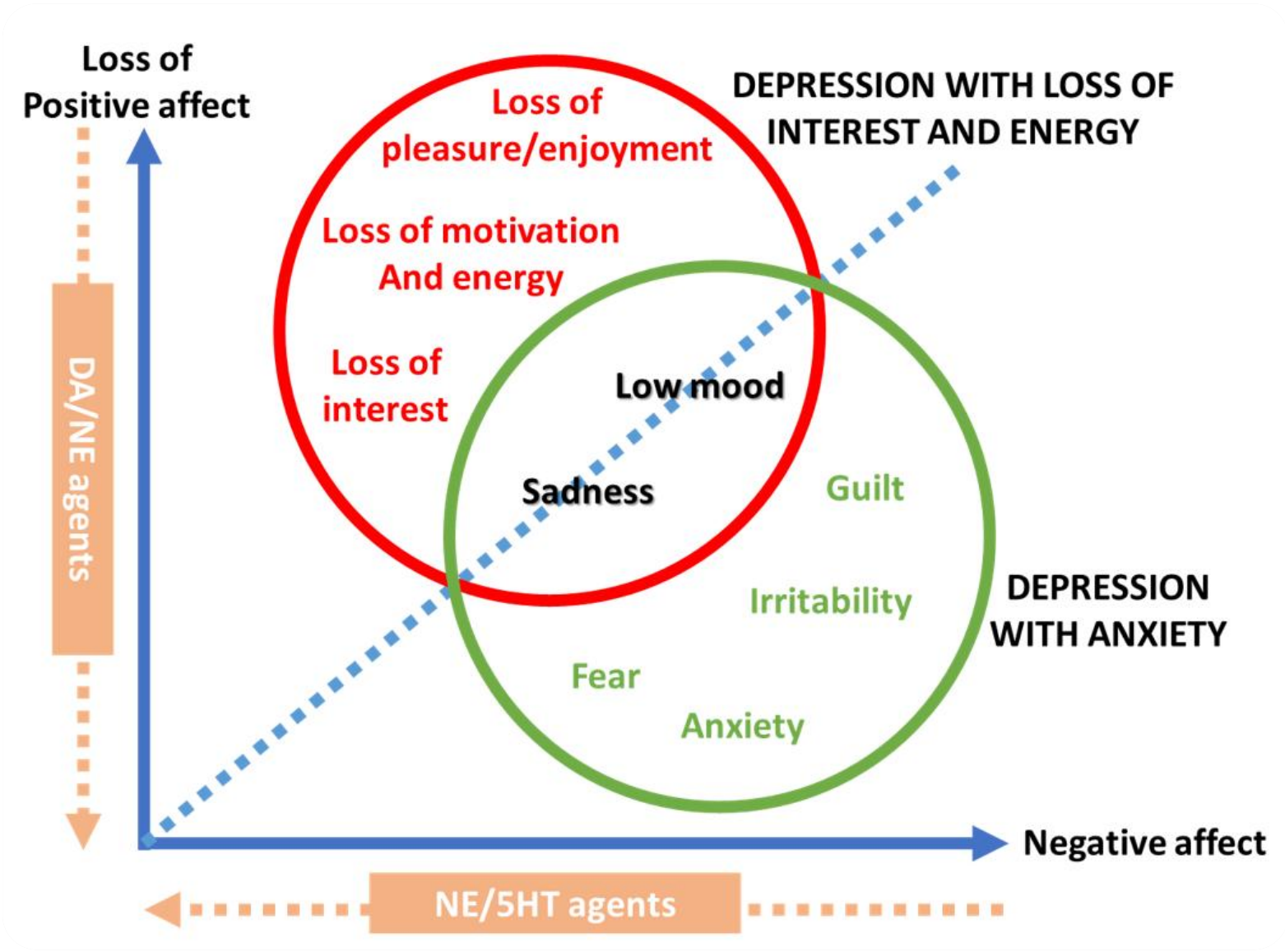
Cardiovascular side effect profile of common antidepressants

Antidepressant	Orthostatic hypotension	Hypertension	Proarrhythmic effects	Heart palpitations
SSRIs				
Citalopram	–	–	+	++
Escitalopram	–	*	+/0	*
Fluoxetine	+	*	0	++
Fluvoxamine	+	*	++	++
Paroxetine	+	*	+/0	*
Sertraline	*	+	+/0	++
SNRIs				
Desvenlafaxine	+	++	++	++
Duloxetine	0	++	+/0	+

* = cannot be estimated from available data; – = Not known; 0 = Rare; + = Uncommon; ++ = Common

Data obtained from individual SmPCs based on placebo-controlled clinical trials and postmarketing experience. Common (≥1/100 to <1/10); Uncommon (≥1/1000 to ≤1/100); Rare (≥1/10000 to ≤1/1000). **Registration status may differ from country to country**.
SNRI = serotonin–noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Negative & Positive affects of Depression



David Nutt, et al. The other face of depression, reduced positive affect, *J Psychopharmacol. 2007 Jul;21(5):461-71.*