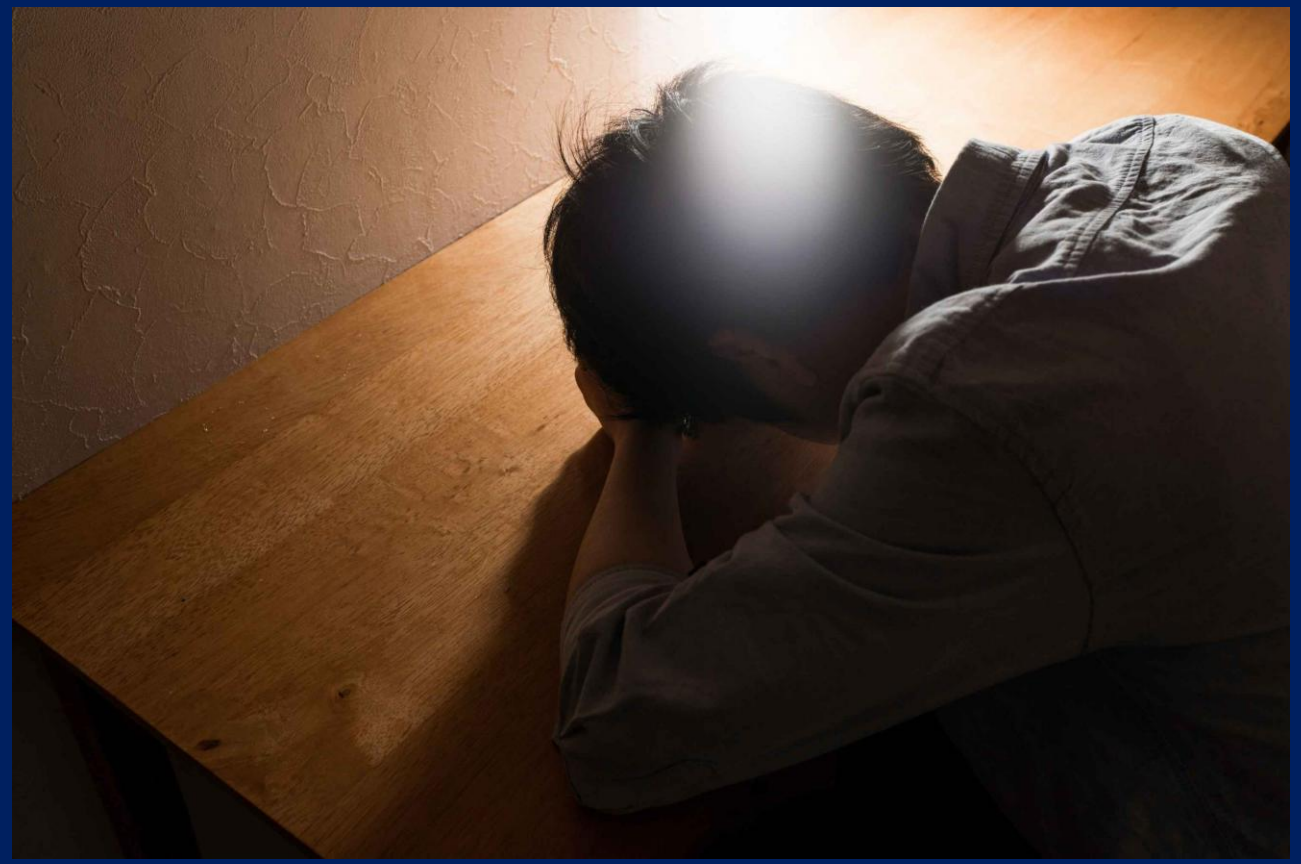
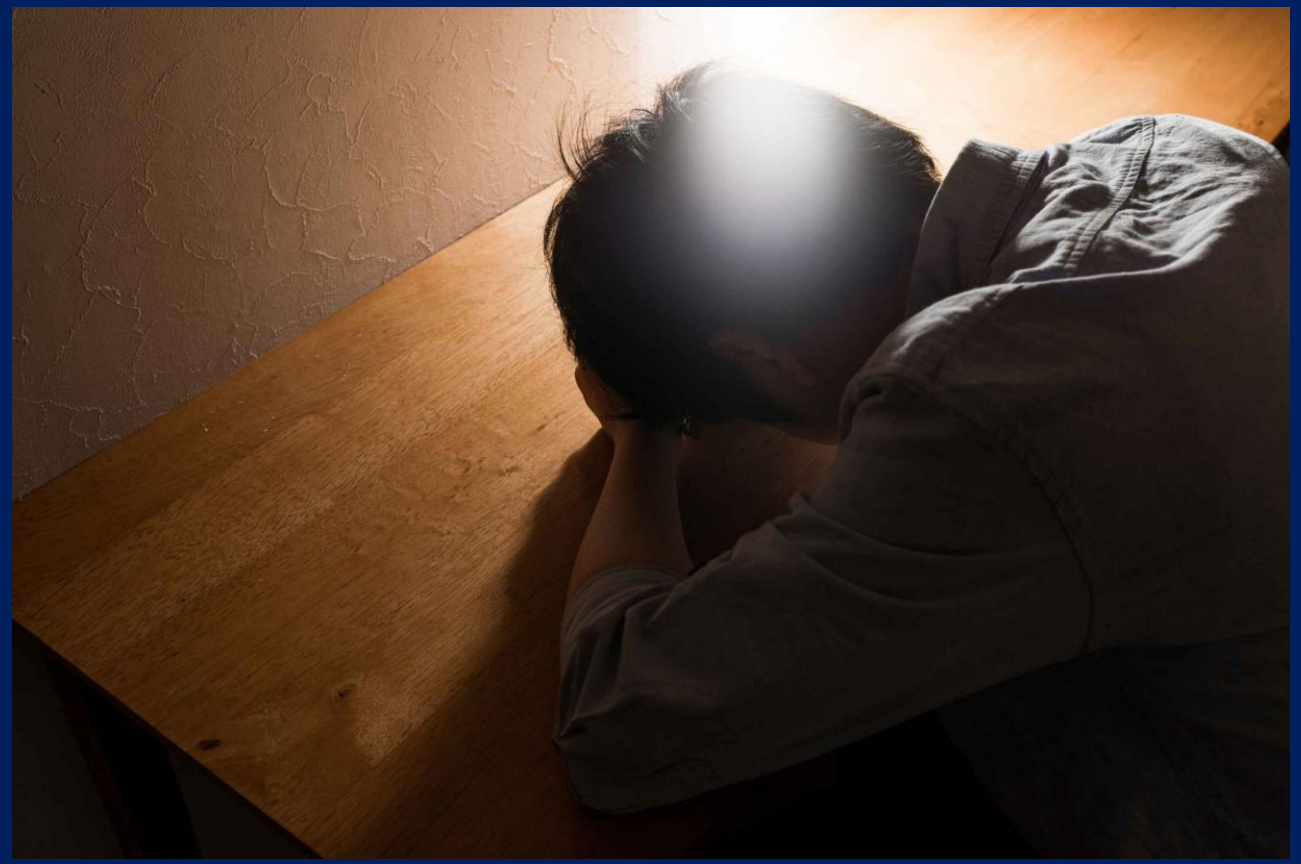


Decoding Antidepressant Pharmacodynamics

Toward Personalized Therapy

Andrea Fagiolini, M.D.
University of Siena, Italy



Decoding Antidepressant Pharmacodynamics

Toward Personalized Therapy

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University of Siena, Italy

Disclosures
Potential conflicts of interest

I have an interest in relation to one or more organisations that could be perceived as possible conflict of interest in the context of the subject of this presentation. The relationships are summarised below:

Interest	Name of organisation
Grants	Allergan, Angelini, Doc Generici, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer
Honoraria	Allergan, Angelini, Apsen, Boehringer Ingelheim, Doc Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sanofi Aventis, Sunovion, Vifor, Viatris
Shares	
Paid positions	
Advisory boards	Allergan, Angelini, Apsen, Boehringer Ingelheim, Doc Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sanofi Aventis, Sunovion, Vifor, Viatris
Other involvement	

Diagnosis of MDD

At least **5** 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** or **2**[1]

1. **Depressed mood**
2. **Diminished interest/pleasure**
3. Weight changes
4. Sleep disturbances
5. Psychomotor agitation / retardation
6. Fatigue / loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death / suicidal ideation

Each includes ≥2 sub-symptoms[1,2]

Two individuals who qualify for a diagnosis of MDD may not have a single symptom in common![2]

- DSM=Diagnostic and Statistical Manual; MDD=major depressive disorder
- 1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 2. Fried EI, Nesse RM. BMC Med. 2015;13(72);doi:10.1186/s12916-015-0325-4

Heterogeneity of Depression

Considering the extremes of sleep, appetite and psychomotor changes separately

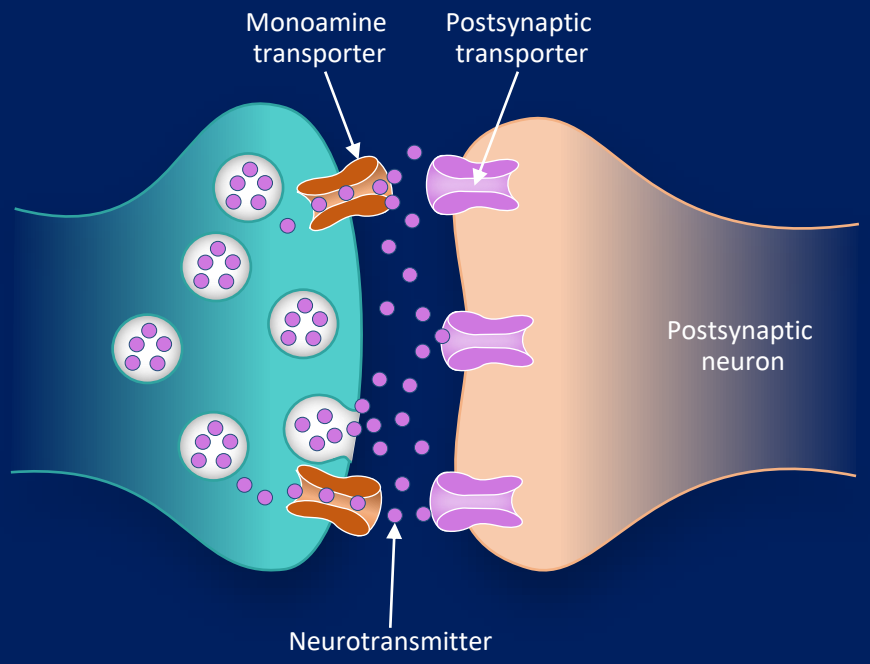
Number of symptom profiles that qualify for a diagnosis of MDD

945
unique profiles

- MDD=major depressive disorder; DSM=Diagnostic and Statistical Manual; STAR*D=Sequenced Treatment Alternatives to Relieve Depression
- Adapted from Fried EI, Nesse RM. J Affect Disord. 2015;172:96–102

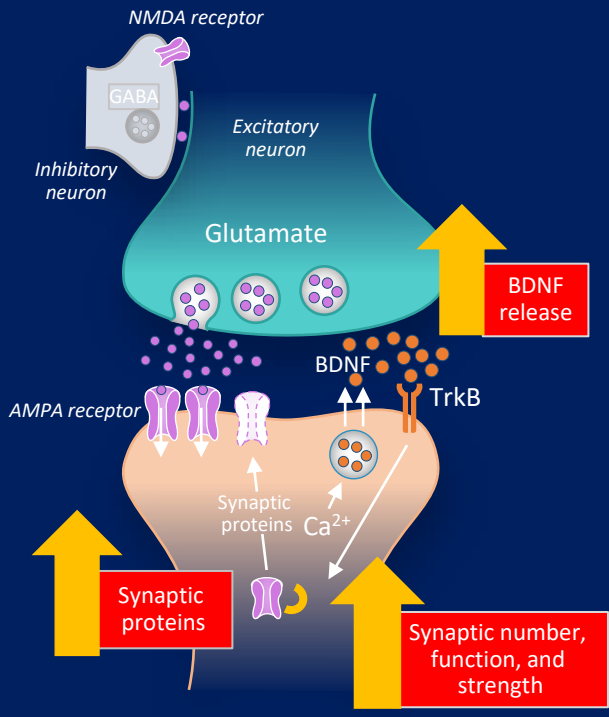
Psychopathology and Pharmacodynamics

Currently available treatments targeting monoamines (5-HT, NA, DA)[1]

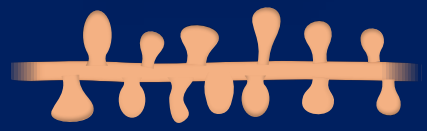


AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; DA, dopamine; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; TrkB, tropomyosin-related kinase B; 5-HT, 5-hydroxytryptamine; NA, noradrenaline.

Future treatments targeting glutamate[1]



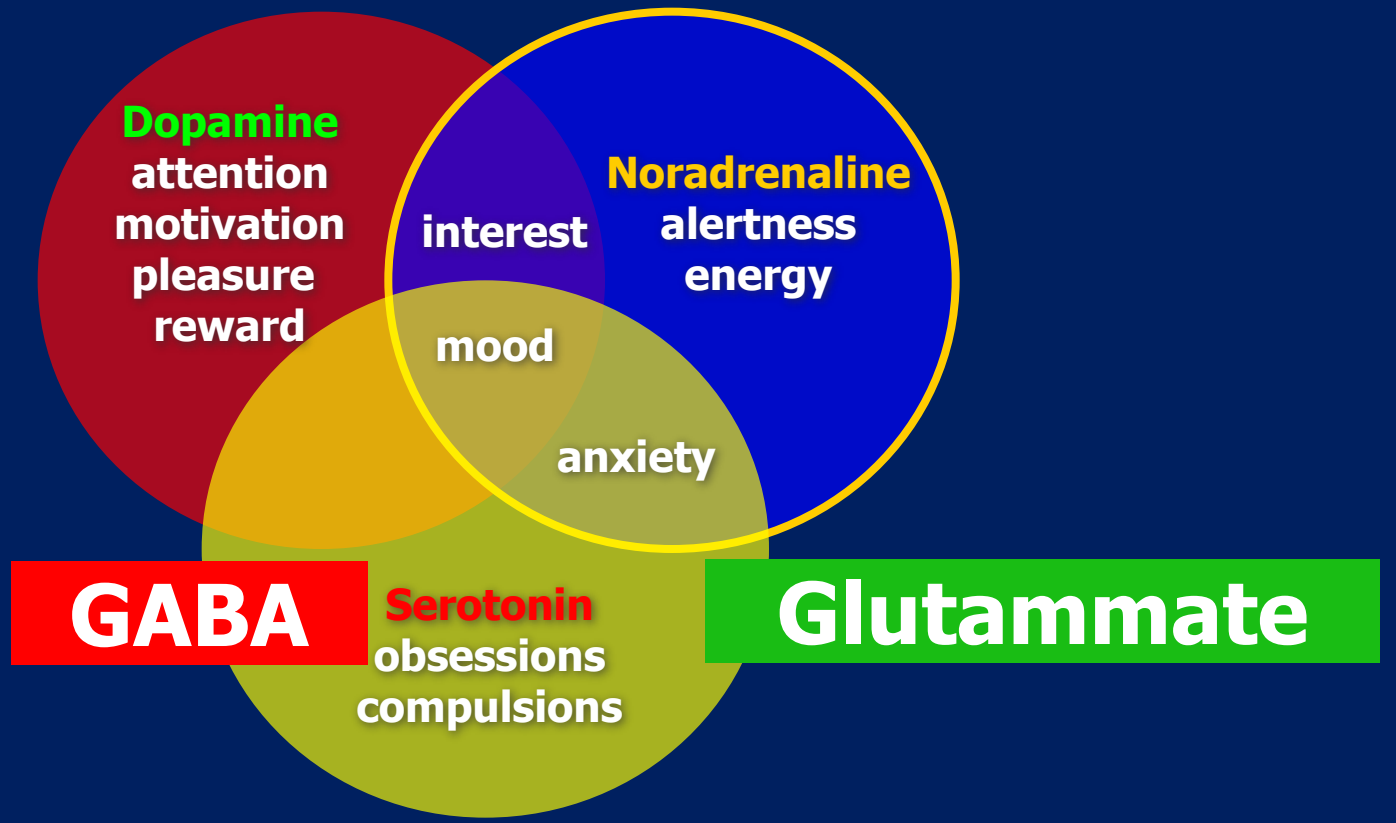
Increased synaptic density[2,5]



Figure[2–5] adapted from Duman RS, et al. Nat Med 2016;22:238–49

1. Hillhouse TM, Porter JH. Exp Clin Psychopharmacol 2015;23:1–21; 2. Duman RS, et al. Nat Med 2016;22:238–49; 3. Murrough JW, et al. Nat Rev Drug Discov 2017;16:472–86; 4. Sanacora G, et al. Neuropharmacology 2012;62:63–77; 5. Dale E. Biochem Pharmacol 2015;95:81–97.

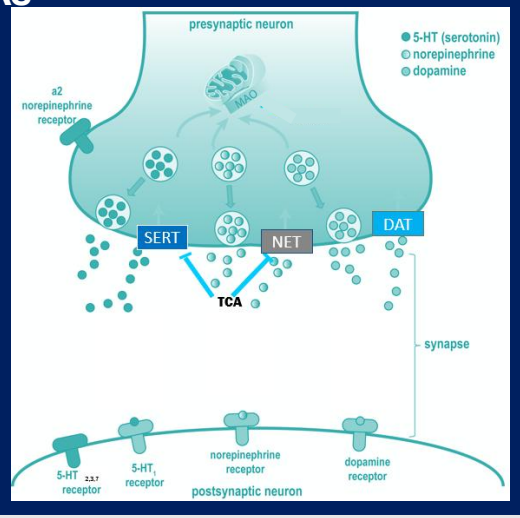
Monoamine neurotransmitter regulation of mood and behaviour



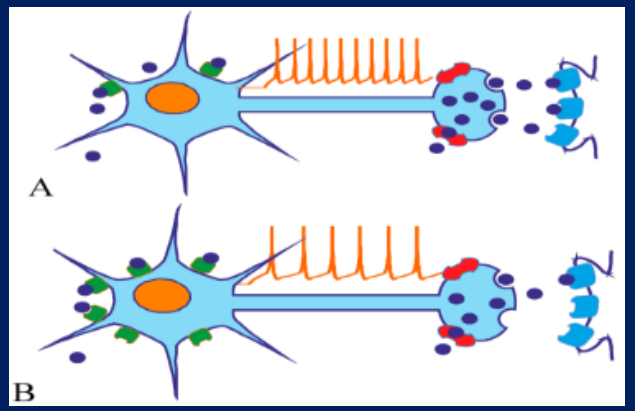
Fagiolini A et al. Expert Opin Pharmacother. 2023;24(15):1715-1723. ; Stahl SM. Essential Psychopharmacology. 2000; Foote SL, Aston-Jones GS. Psychopharmacology. 1995: 335-345; Nutt DJ et al., J Psychopharmacol 2007; Shelton AJ, Tomarken RC, Psychiatric Services 2000; 52 (11):1469–1478; Stahl SM J Clin Psychiatry 2003;64:1145-1146

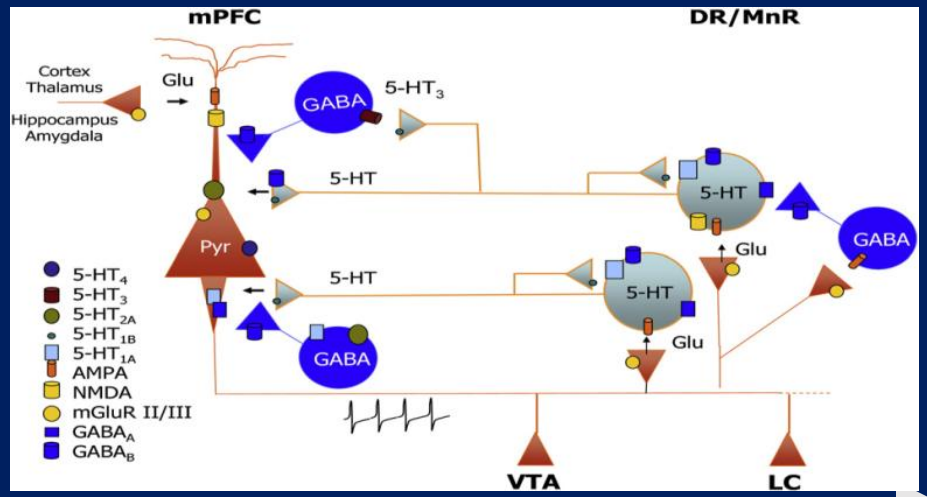
The Evolution of Antidepressants from Synapse to Networks

TCAs



SSRIs, SNRIs, NaSSAs, SARIs





1950 - Impact on synapse

Inhibit SERT and NET on pre-synaptic membrane and aim to increase monoamine levels in **synaptic cleft**.

1980 to 1990s - Impact on neuron but monomodal

SSRIs and SNRIs inhibit SERT and NET on pre-synaptic membrane.

NaSSAs (e.g. mirtazapine) inhibit α_2 NE receptor (pre-synaptic) and 5-$HT_{2,3}$ receptors (post-synaptic).

SARIs (e.g. trazodone) inhibit SERT (**pre-synaptic**) and 5-HT_2 receptors (**post-synaptic**).

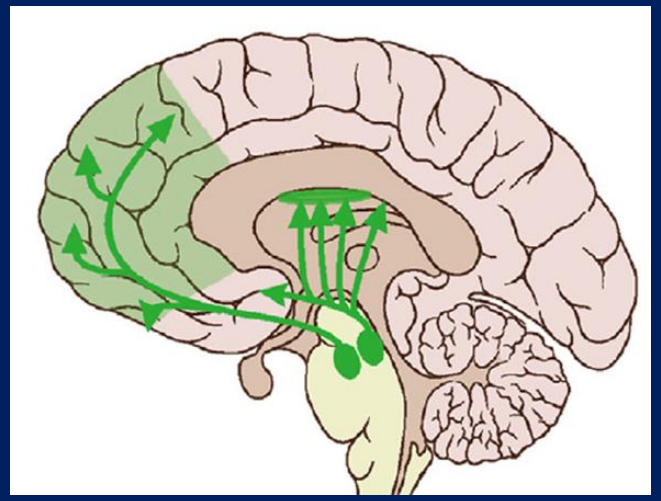
2000s to today - Impact on neuronal networks & multimodal

Newer modalities of antidepressants impacting many **neural networks,** with action on both **post- and pre-synaptic membranes**

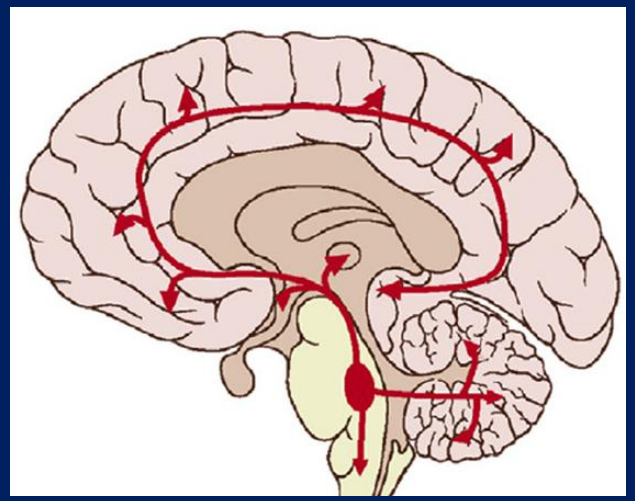
TCA, tricyclic antidepressants; SERT, serotonin reuptake transporter; NET, norephinerphrine transporter; NaSSA, noradrenergic and specific serotonergic antidepressant; SARI, serotonin receptor antagonist and reuptake inhibitors; 5-HT, serotonin; 1. Nutt DJ. J Psychopharmacol. 2009;23(4):343–345; 2. Ramachandraih CT et al. Ind J Psych. 2011;53(2): 180–182; 3. Faigus J et al. J Neurol Neurosurg Psychiatry. 1985;48(1): 65–69; 4. Sansone RA et al. Innov Clin Neurosci. 2014;11(3–4):37–42; 5. Fornaro M et al. Curr Neuropsychopharmacol. 2010;9;287–304; 6. Agomelatine EPAR (last accessed March 2021). 7. Cruz MP. Pharmacy and Therapeutics. 2012;37(1): 28–31; 8. Bang-Andersen B et al. J Med Chem. 2011;54(9)3206–3221; 9. Westrich L et al. Int J Psychiatry Clin Pract. 2012;16(1):47; 10. Vortioxetine Prescribing Information

Monoaminergic Pathways

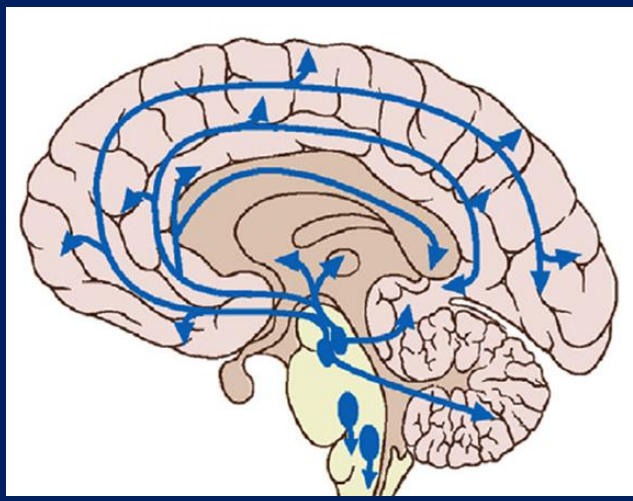
Dopamine



Norepinephrine



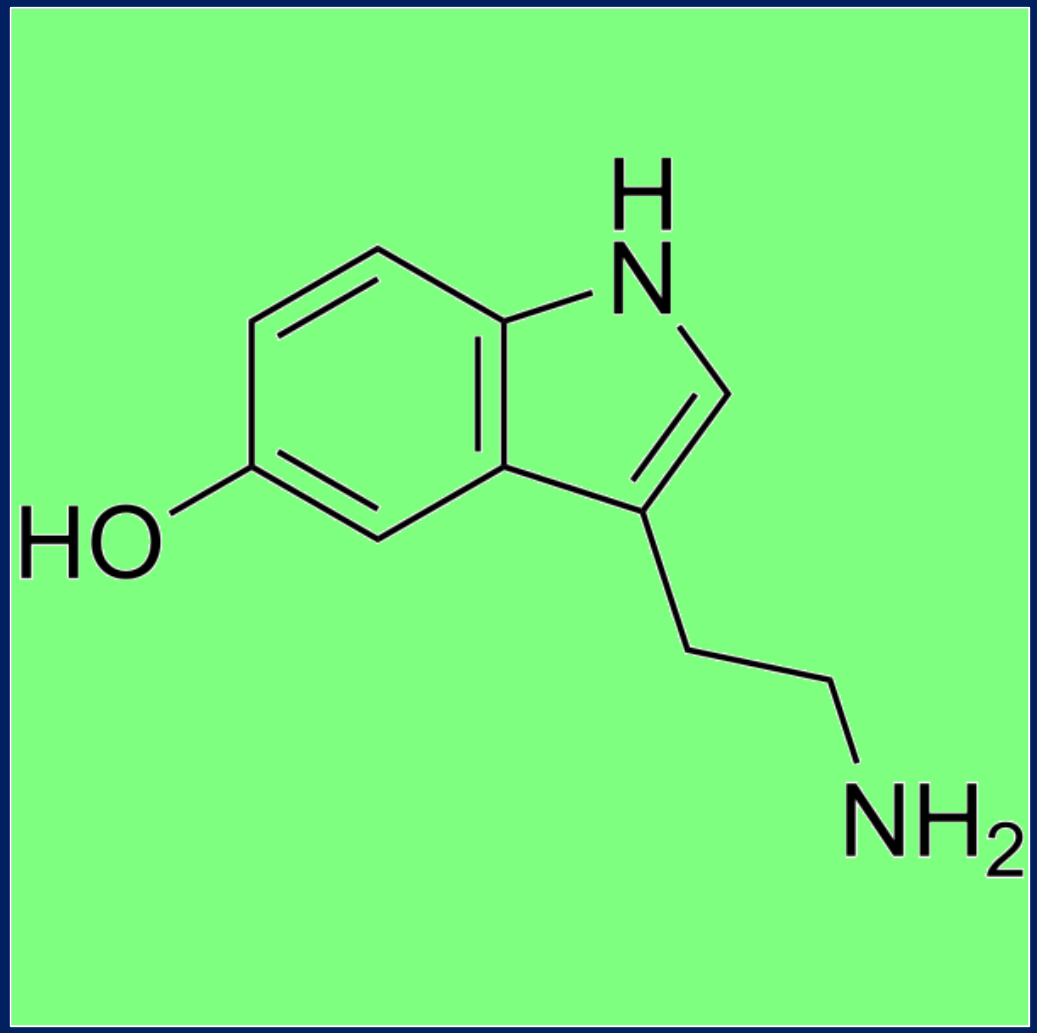
Serotonin



- Monoamine neurotransmitters are involved in the regulation of movement, basal muscle tone, activity levels, mood, attention, sleep, vascular tone, circulation, thermoregulation, and pain modulation[2]
- Monoamines are synthesized in pre-synaptic neurons and packaged into vesicles by a synaptic vesicular amine transporter (also known as vesicular monoamine transporter 2; VMAT2) for subsequent release into the synaptic cleft, where they bind to post-synaptic receptors[2]
- Neurotransmission is terminated by degradation or reuptake of the monoamine[2]

1. Frobose MI, Cools R. *Curr Opin Behav Sci*. 2018;22:121-127. doi:10.1016/j.cobeha.2018.01.027
2. Ng J et al. *Nat Rev Neurol*. 2015;11(10):567-584. doi:10.1038/nrneurol.2015.172

Serotonin



Pharmacodynamics: Serotonin

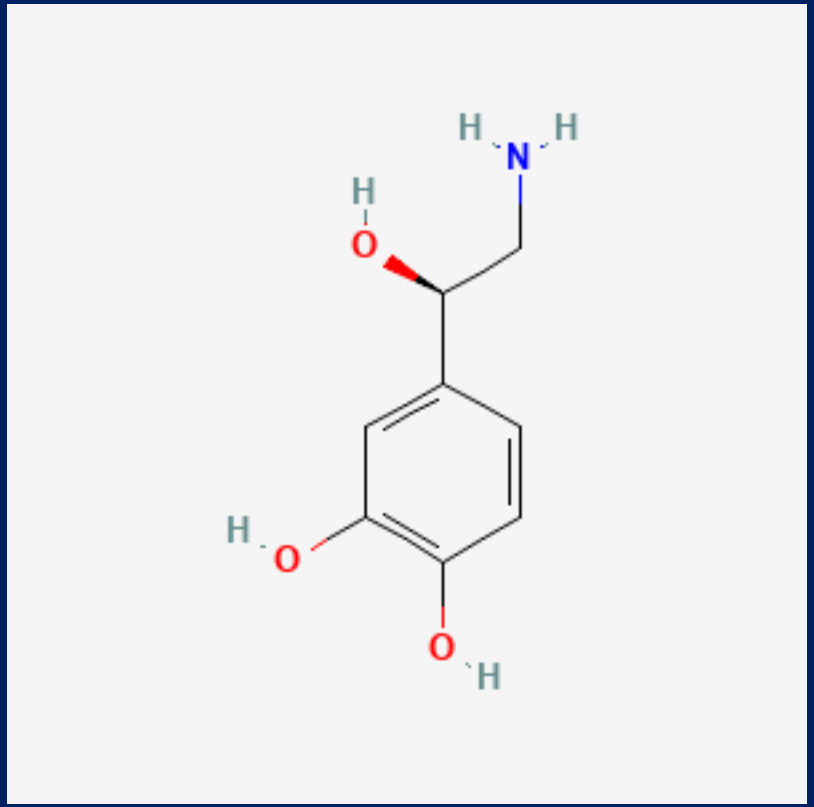
Serotonin receptor modulation

Target / action	Effect
5-HT_{1A} agonist	Potentiates SRI-induced increases of serotonin[1] Anxiolytic and antidepressant[2]
5-HT_{1D} antagonist	Potentiates SRI-induced increases of serotonin[1]
5-HT_{1B} partial agonist	Enhances antidepressant-like effects[3,4]
5-HT_3 antagonist	Augments SRI effects[1] Enhances noradrenaline and dopamine neurotransmission[1] Anxiolytic-like and antidepressant-like[5]
5-HT_7 antagonist	Improves cognitive function[1] Anxiolytic-like and antidepressant-like[6]
SERT inhibitor	Anxiolytic and antidepressant[1,5,6]

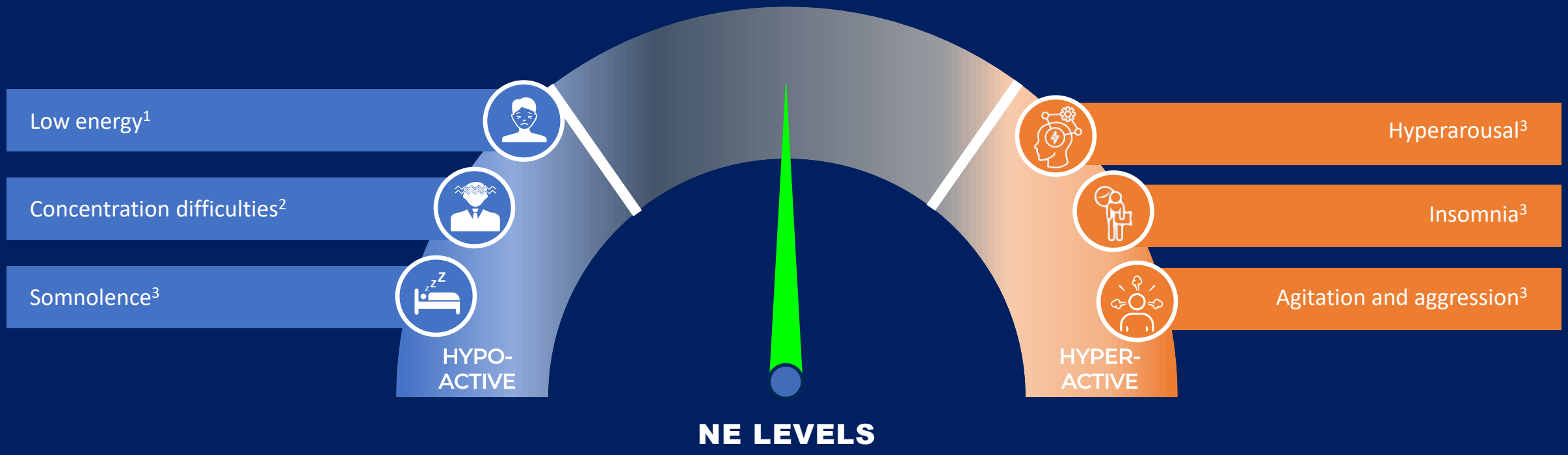
SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor

1. Sanchez C et al. Pharmacol Ther 2015;145:43-57;
2. Blier P, Ward NM. Biol Psychiatry 2003;53:193-203;
3. Chenu F et al. J Psychiatry Neurosci 2008;33:541-50;
4. Murrough JW, Neumeister A. Biol Psychiatry 2011;69:714-5;
5. Redrobe JP, Bourin M. Eur J Pharmacol 1997;325:129-35;
6. Mnie-Filali O et al. Neuropsychopharmacology 2011;36:1275-88

Norepinephrine



Dysregulation of the noradrenergic system

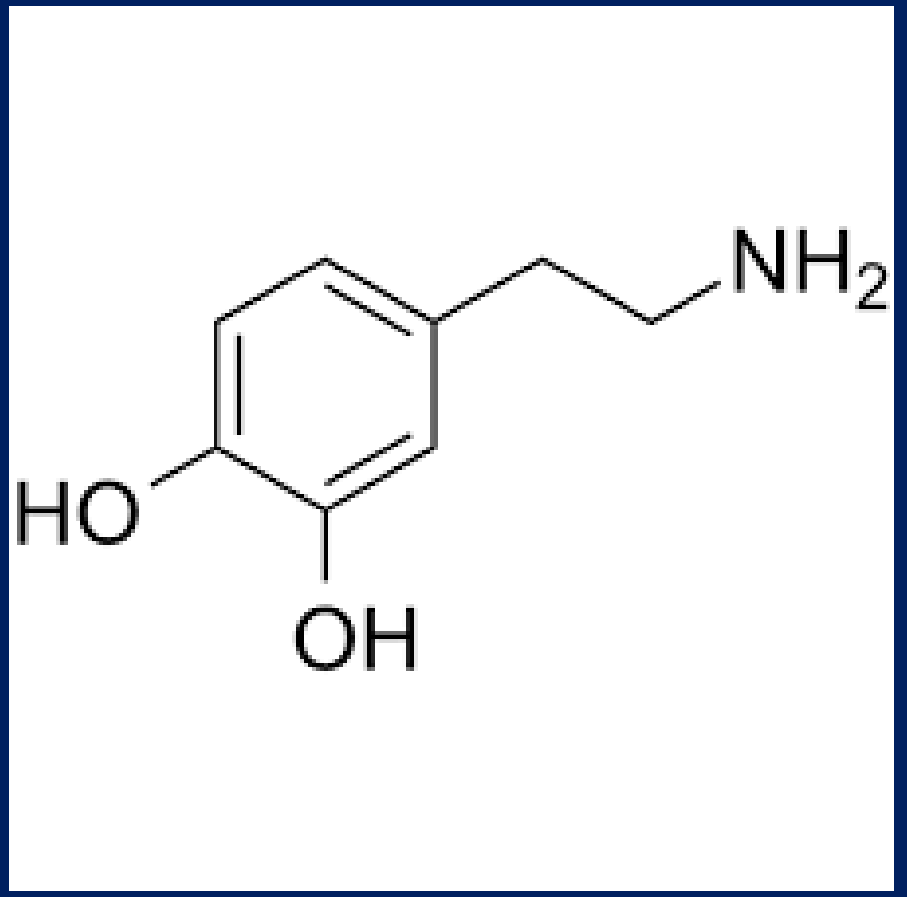


Adrenoceptors can modulate symptoms caused by the noradrenergic system dysregulation.*

MDD: Major depressive disorder; NE: Norepinephrine.

***Inference of speaker based on: 1.** Nutt DJ. Relationship of neurotransmitters to the symptoms of major depressive disorder. *J Clin Psychiatry*. 2008;69(Suppl E1):4–7. doi:10.2147/NDT.S19619; **2.** Moret C, Briley M. The importance of norepinephrine in depression. *Neuropsychiatr Dis Treat.* 2011;7(Suppl 1):9–13. doi:10.2147/NDT.S19619; **3.** Yamamoto K, Shinba T, Yoshii M. Psychiatric symptoms of noradrenergic dysfunction: A pathophysiological view. *Psychiatry Clin Neurosci*. 2014;68(1):1–20. doi: 10.1111/pcn.12126.


DESIRE


NH2
HO
OH

Choosing an Antidepressant

- Diagnosis
- Symptoms
- Risk/Benefits
- History - Alternative Treatments
- Comorbid Medical Diagnoses
- Previous Response/Tolerability
- Family History
- Comorbid Psychiatric Diagnoses / Symptoms
- Concurrent treatments

Symptoms of MDD and monoamine functions

EXPERT OPINION ON PHARMACOTHERAPY
2023, VOL. 24, NO. 15, 1715–1723
https://doi.org/10.1080/14656566.2023.2242264

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REVIEW

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Moving from serotonin to serotonin-norepinephrine enhancement with increasing venlafaxine dose: clinical implications and strategies for a successful outcome in major depressive disorder

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ABSTRACT

Introduction: Mental health disorders, especially depressive and anxiety disorders, are associated with substantial health-related burden. While the second-generation antidepressants are widely accepted as first-line pharmacological treatment for major depressive disorder (MDD), patient response to such treatment is variable, with more than half failing to achieve complete remission, and residual symptoms are frequently present.

Areas covered: Here, the pharmacodynamics of venlafaxine XR are reviewed in relation to its role as both a selective serotonin reuptake inhibitor (SSRI) and a serotonin-norepinephrine-reuptake inhibitor (SNRI), and we look at how these pharmacodynamic properties can be harnessed to guide clinical practice, asking the question 'is it possible to develop a symptom-cluster-based approach to the treatment of MDD with comorbid anxiety utilizing venlafaxine XR?.' Additionally, three illustrative clinical cases provide practical examples of the utility of venlafaxine-XR in real-world clinical practice. The place of venlafaxine XR in managing fatigue/low energy, a frequent residual symptom in MDD, is explored using pooled data from clinical trials of venlafaxine XR.

Expert opinion: Venlafaxine XR should be considered as a first-line treatment for MDD with or without comorbid anxiety, and there are clear pharmacodynamic signals supporting a symptom cluster-based treatment paradigm for venlafaxine XR.

ARTICLE HISTORY
Received 14 July 2023
Accepted 25 July 2023

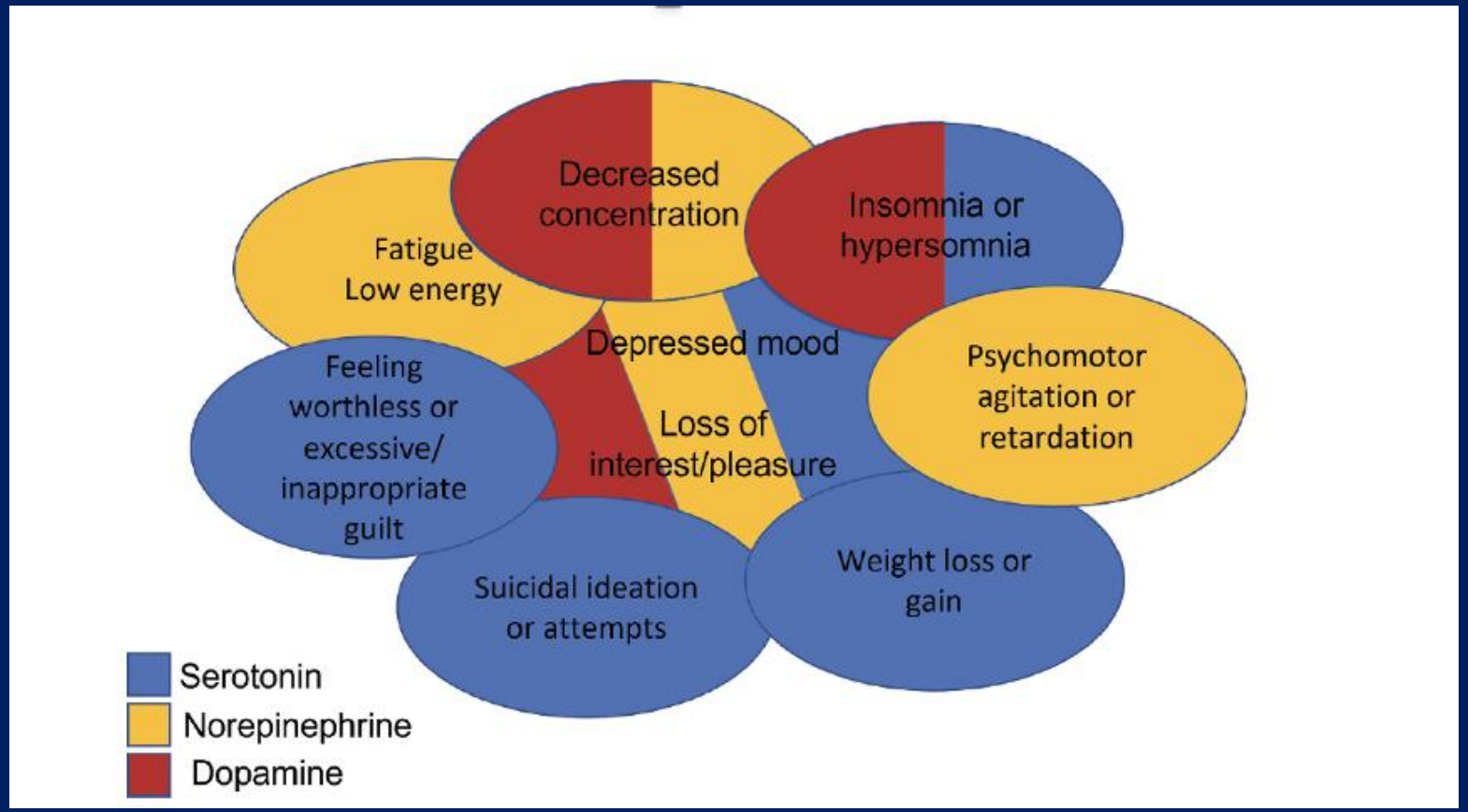
KEYWORDS
Venlafaxine; major depressive disorder; monoamines; symptom clusters; depression; anxiety

1. Introduction

Mental health disorders are associated with substantial health-related burden, with depressive and anxiety disorders the most disabling [1]. While global health has steadily improved over the past 30 years, there has been no reduction in the global prevalence of mental health disorders, despite evidence for interventions that reduce their impact [2,3]. Worldwide, the COVID-19 pandemic had significantly interrupted the continuity of care of chronic conditions, such as serious mental illness, as well as disrupting their detection and treatment [4,5]. The pandemic has created greater urgency and increased demand for improvements in the diagnosis and treatment of both anxiety and major depressive disorder (MDD) [6–10].

Complete remission of a depressive episode has long been considered the goal of treatment in MDD [11,12]. However, while complete remission is conceptualized as a return to normal functioning with minimal symptoms, it is defined in clinical trials by a cutoff or threshold on standardized scales Montgomery-Asberg Depression Rating Scale [MADRS] score of ≤ 10; Clinical Global Impressions Scale [CGI] score = 1), which do not require patients to be completely asymptomatic [13,14]. Importantly, many patients are left with residual symptoms, which frequently include loss of interest, fatigue and low energy, as well as anxiety, preventing complete functional recovery [13,15,16]. Relapse is more common in patients with residual symptoms following treatment of a MDD episode [13,17].

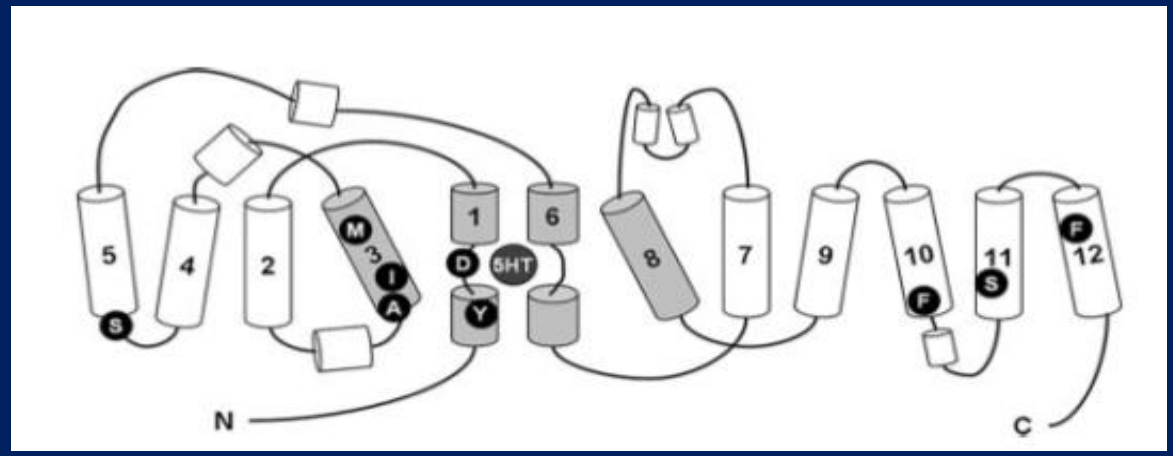
Tricyclic antidepressants (TCA) and mono-amine oxidase inhibitors (MAOI), termed first-generation antidepressants (FGA), were the mainstay of therapy prior to the 1980s. The second-generation antidepressants (SGA) were introduced from 1985 onwards and include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), like venlafaxine, and others including tetracyclics like mianserin and maprotiline [18]. The FGAs are plagued by multiple side effects which many



Fagiolini A et al. Expert Opin Pharmacother. 2023 Sep-Dec;24(15):1715-1723.

SSRIs Mechanism of Action

- Exact mechanism remains uncertain
- Ser-438 residue in the human serotonin transporter (hSERT) appears to be a determining factor in SSRI potency
- Antidepressants interact directly with hSERT



Selectivity on Serotonin Receptors

	Ki (nmol/l)		
	5HT	***NA***	***DA***
Escitalopram	1,1	7800	27000
Citalopram	1,6	6200	17000
R-Citalopram	36,0	12000	19000
Fluoxetine	1,1	600	3000
R-Fluoxetine	1,4	410	3800
Paroxetine	0,1	45	270
Sertraline	0,3	710	22
Fluvoxamine	2,3	1400	17000

Owens et al., Biological psychiatry, Vol.50(5), pp.345-350; 2001

Sertraline EU Approved Indications

- Major depressive disorder
- Panic disorder
- Obsessive Compulsive Disorder (Adults)
- Posttraumatic stress disorder
- Social anxiety disorder
- Obsessive compulsive disorder (6-17 yo)

Sertralina: Scheda Tecnica Italiana. Accessed March 2026 at https://www.torrinomedica.it/schede-farmaci/sertraline/

Sertraline: Indications (FDA)

- Major depressive disorder in adults
- Panic Disorder
- Obsessive Compulsive Disorder (Adults)
- Obsessive Compulsive Disorder (Children 6-17)
- Post Traumatic Stress Disorder
- Social Anxiety Disorder
- **Premenstrual Dysphoric Disorder (Continuous)**
- **Premenstrual Dysphoric Disorder (Intermittent)**

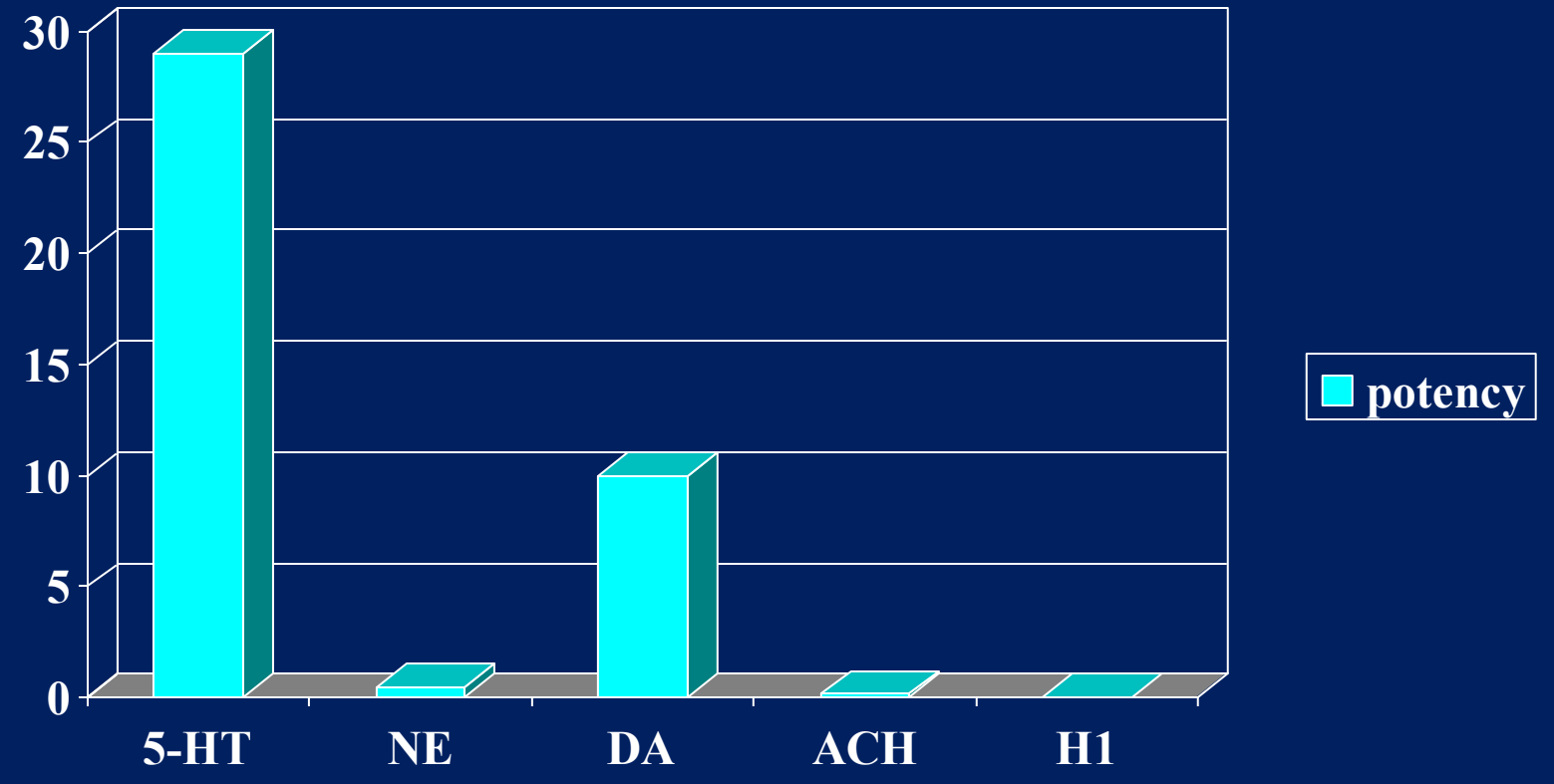
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019839s74s86s87_20990s35s44s45lbl.pdf

Sertraline FDA Approved Indications

Indication	Starting Dosage	Maximum Dosage
MDD (2.1)	50 mg per day	200 mg per day
OCD (2.1)	25 mg per day (ages 6-12) 50 mg per day (ages ≥ 13)	200 mg per day
PD, PTSD, SAD (2.1)	25 mg per day	200 mg per day
PMDD (2.2) continuous dosing	50 mg per day	150 mg per day
PMDD (2.2) intermittent dosing	50 mg per day during luteal phase only	100 mg per day during luteal phase only

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019839s74s86s87_20990s35s44s45lbl.pdf

Sertraline



Richelson E, Synaptic Effects of Antidepressants, Journal of Clinical Psychopharmacology, Vol. 16, No3, Suppl. 2, June, 1996

Dosage range

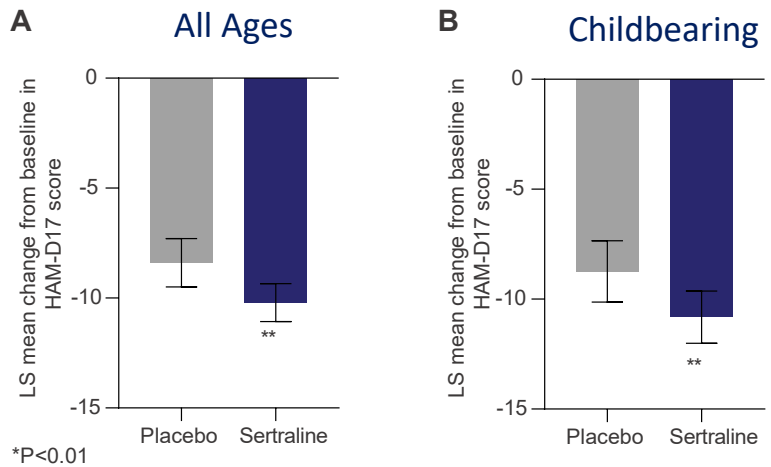
	Sertraline dose
Range	25-200mg/day

Prescribing Information. https://www.torrinomedica.it/schede-farmaci Last accessed January 2024

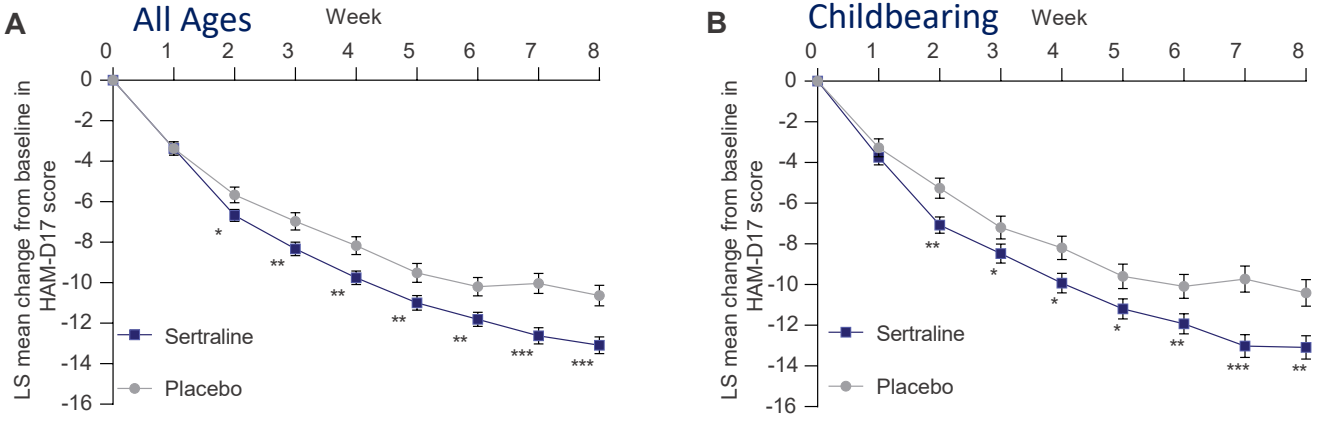
Clinical Utility of Sertraline Among Women of Reproductive Age

RESULT

- The change from baseline in HAMD17 total score was significantly higher for sertraline vs placebo at the end of 8 weeks.
- This change was statistically significant starting from week 2 across both the groups.



*P<0.01
HAM-D17 total score change from baseline in A. All age groups B. women of childbearing age (18-44 years)



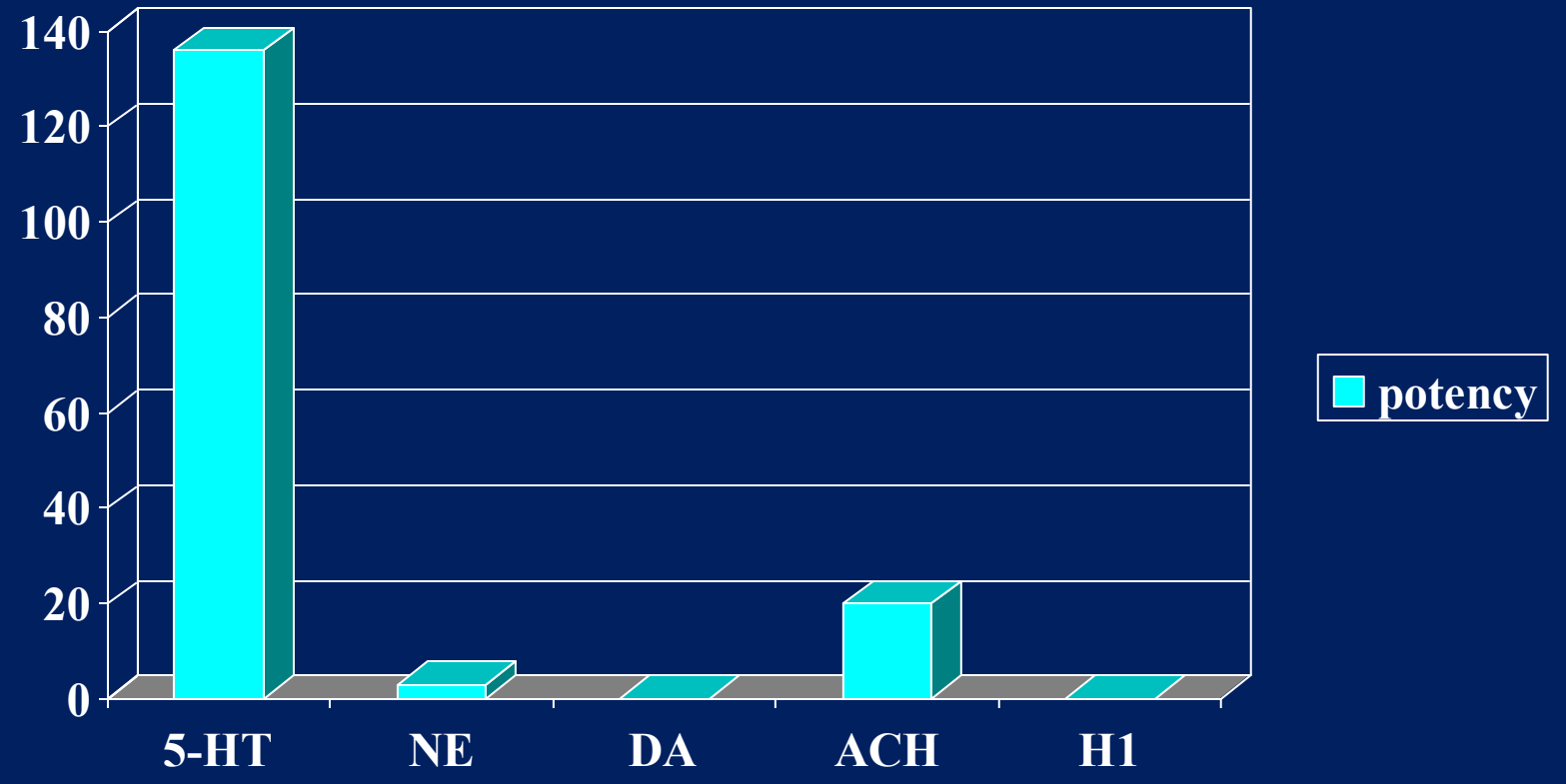
*P<0.05; **P<0.01; ***P0.0001
HAM-D17 total score change from baseline in A. All age groups B. women of childbearing age (18-44 years)

CONCLUSION

Significant improvement in HAM-D17 scores was observed in the analysis, suggesting that sertraline is efficacious in treating women with MDD, including those in the childbearing age.

Fagiolini A et al. , Annals of General Psychiatry Ann Gen Psychiatry. 2024 Nov 7;23(1):44

Paroxetine



Richelson E, Synaptic Effects of Antidepressants, Journal of Clinical Psychopharmacology, Vol. 16, No3, Suppl. 2, June, 1996

Paroxetine

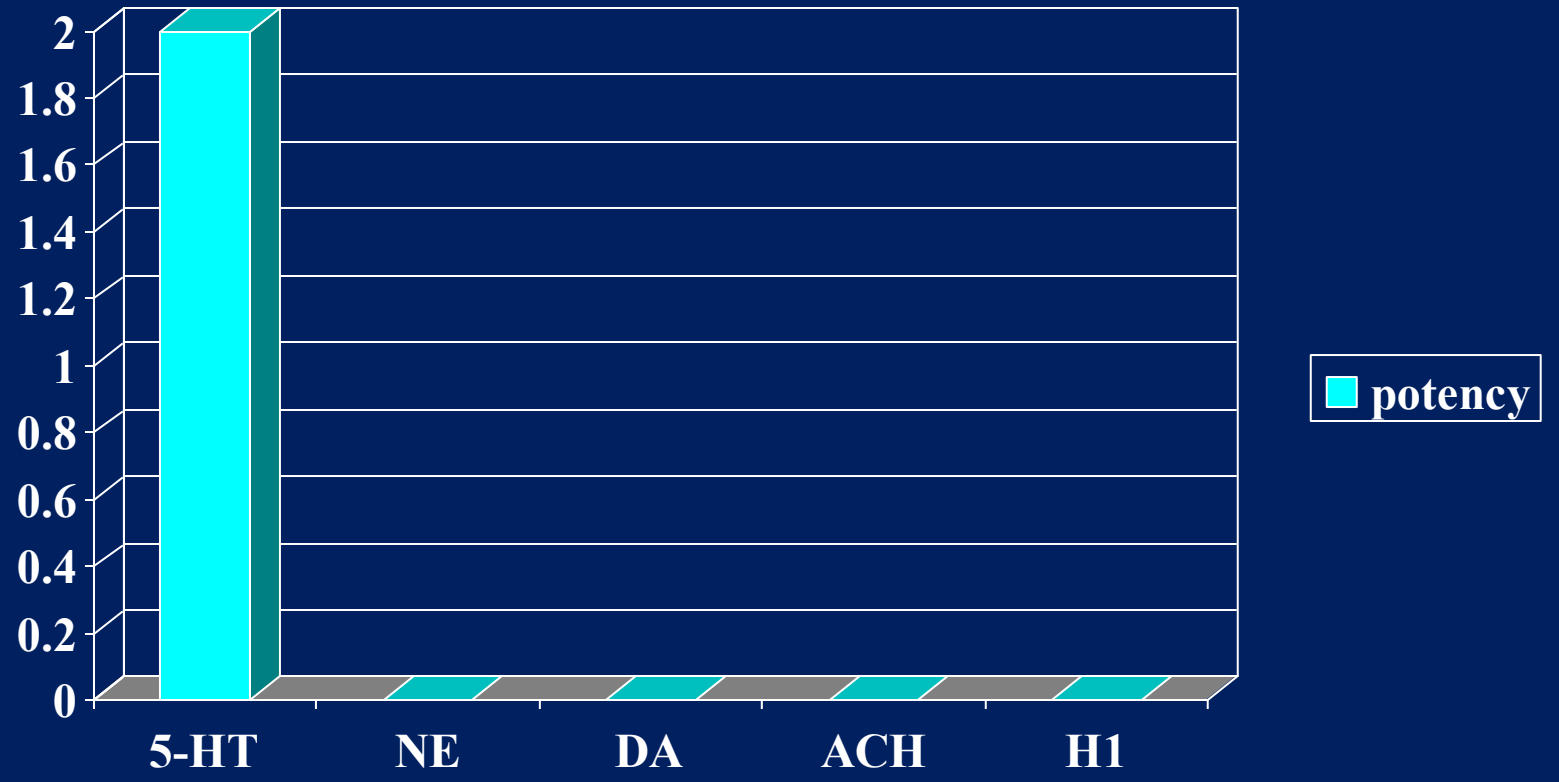
- Pros
  - Short half life with no active metabolite means no build-up (which is good if hypomania develops)
  - Sedating properties (dose at night) offers good initial relief from anxiety and insomnia
- Cons
  - Significant CYP2D6 inhibition
  - Sedating, wt gain, more anticholinergic effects
  - Likely to cause a discontinuation syndrome

Dosage range

	Paroxetine dose
Range	20-50mg/day

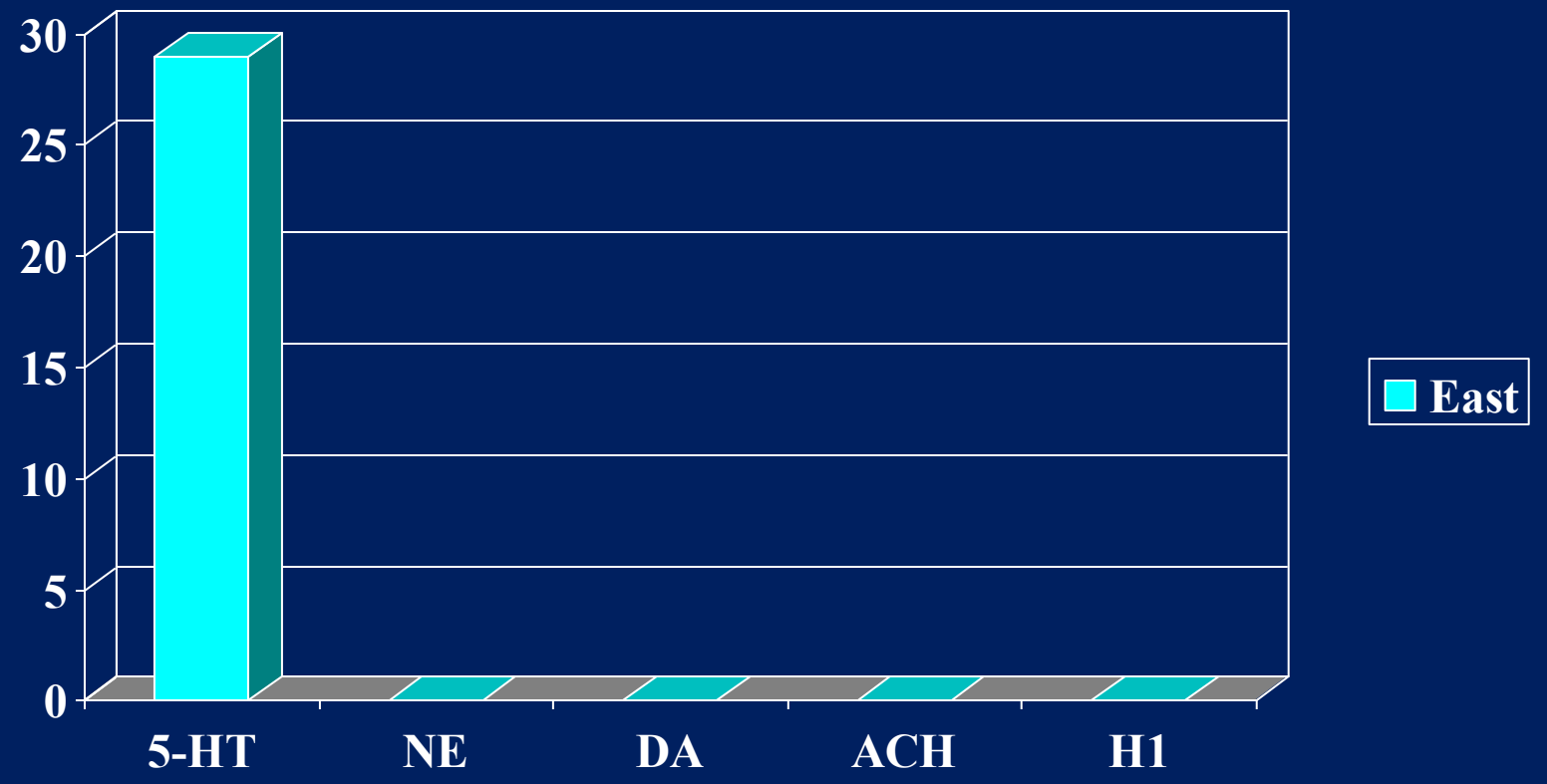
Prescribing Information. https://www.torrinomedica.it/schede-farmaci Last accessed March 2026

Citalopram



Richelson E, Synaptic Effects of Antidepressants, Journal of Clinical Psychopharmacology, Vol. 16, No3, Suppl. 2, June, 1996

s-citalopram



Citalopram

- Pros
  - Low inhibition of P450 enzymes so fewer drug-drug interactions
  - Intermediate ½ life
- Cons
  - Dose-dependent QT interval prolongation with doses of 10-40mg daily- due to this risk doses of >40mg/day not recommended
  - Can be sedating (has mild antagonism at H1 histamine receptor)
  - GI side effects

Prescribing Information. https://www.torrinomedica.it/schede-farmaci Last accessed May 2021

Approved Indications

- Major depressive disorder
- Panic disorder

Zoloft (Sertraline)[FDA Prescribing Information]. Accessed Oct 2020 at https://www.torrinomedica.it/schede-farmaci/efexor_75/

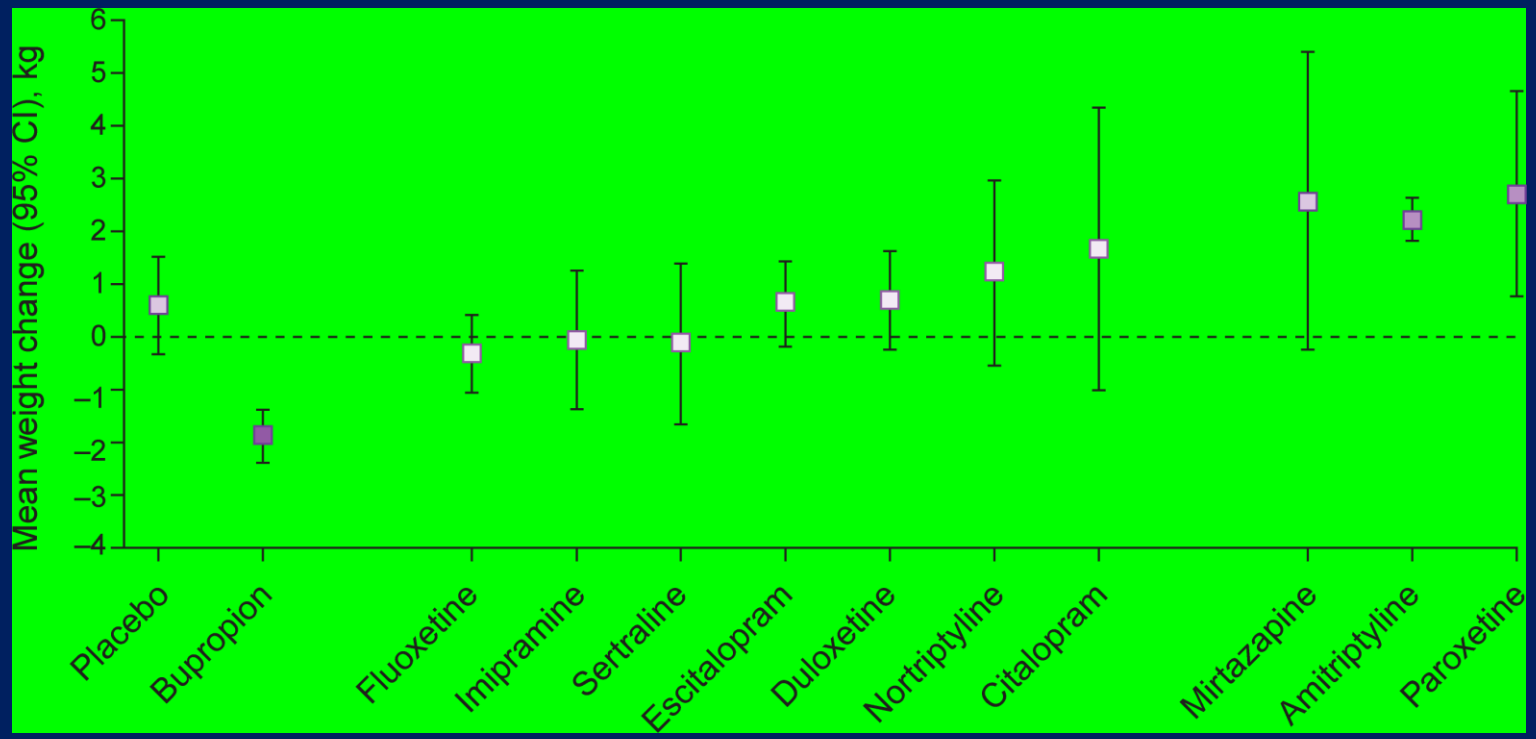
Dosage range

	dose
Range	20-40 mg/day 20 mg/day if 65+

Prescribing Information. https://www.torrinomedica.it/schede-farmaci Last accessed Oct 2020

Long-term weight change with antidepressants

Weight change during maintenance treatment with different antidepressants



Antidepressants differ in their potential to induce weight gain.

Sertraline showed no effect on body weight over the maintenance period, despite a slight weight loss observed during acute treatment.

Filled boxes indicate a significant effect.

A comprehensive review and meta-analysis was conducted to assess the effect on body weight potentially exerted by the most common antidepressant drugs employed for clinical purposes.

Serretti A, *et al*. *J Clin Psych.* 2010;71(10):1259–1272.

Norepinephrine Transporter affinity

Atypical antipsychotics

Drug	NET K_i (nM)
Norquetiapine	35
Quetiapine	>10,000
Haloperidol	2.122
Clozapine	3.168
Desmethyl-CLO	494
Olanzapine	>10.000
Asenapine	>10.000
Risperidone	>10.000
Aripiprazole	2.093
Ziprasidone	44

Antidepressants

Drug	NET K_i (nM)
Nortryptiline	2
Duloxetine	8
Amitryptiline	13-35
Nomifensine	16-29
Paroxetine	40-85
Mianserine	71
Venlafaxine	1.060-6.310
Desmethyl-VLX	2.753
Mirtazapine	4.600
Atomoxetine	5

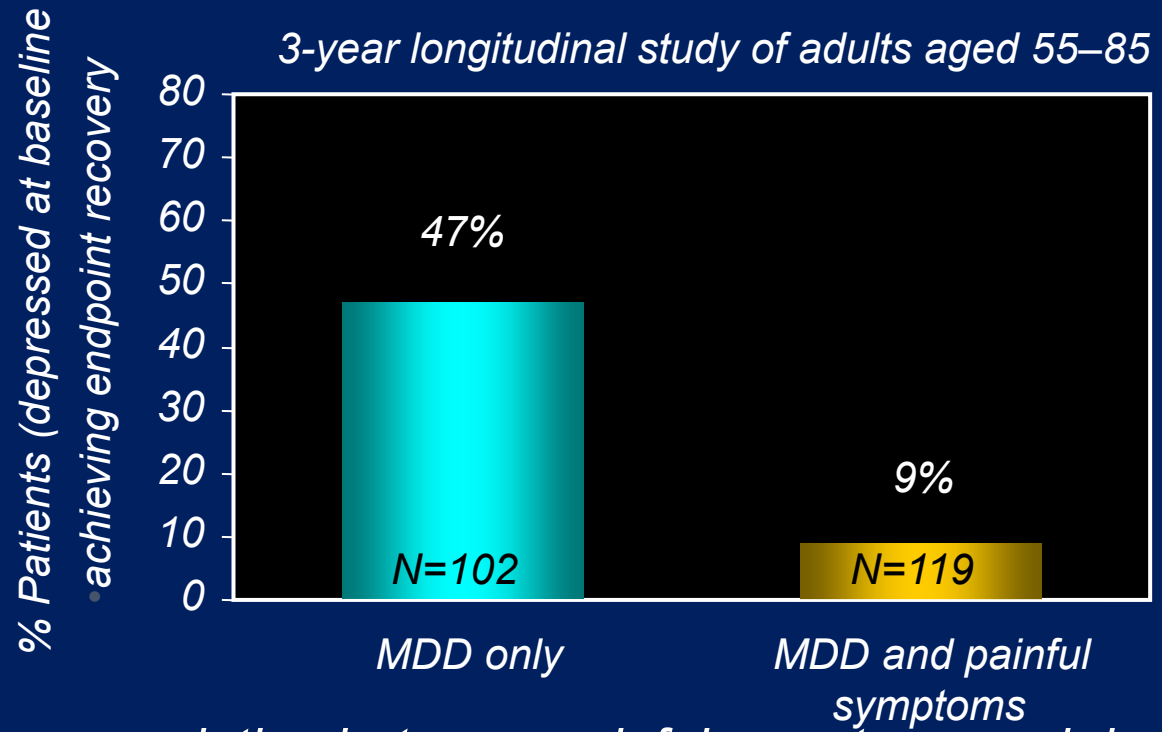
Jensen et al., 2008

Duloxetine Approved Indications (Italy)

- Major depressive disorder
- Diabetic neuropathic pain
- Generalized anxiety disorder

Prescribing Information. https://www.torrinomedica.it/schede-farmaci Last accessed March 2026

Painful Symptoms Decrease the Chance of Recovery in Depressed Patients

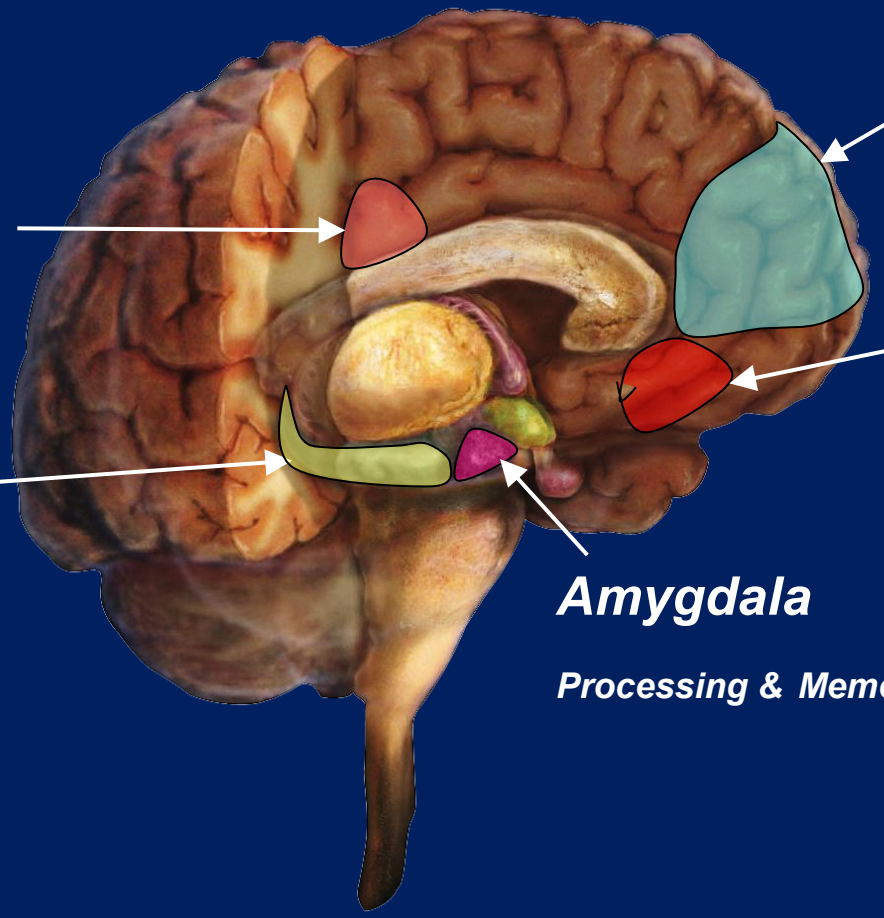


- *The close association between painful symptoms and depression emphasizes the need for progressive treatment strategies*

MDD=major depressive disorder.

*Geerlings SW, et al. Soc Psychiatry Psychiatr Epidemiol. 2002;**37**:23–30.*

Some Key Areas of the Brain that Play a Role in Both MDD and Pain



Insular cortex

Hippocampus

Prefrontal cortex

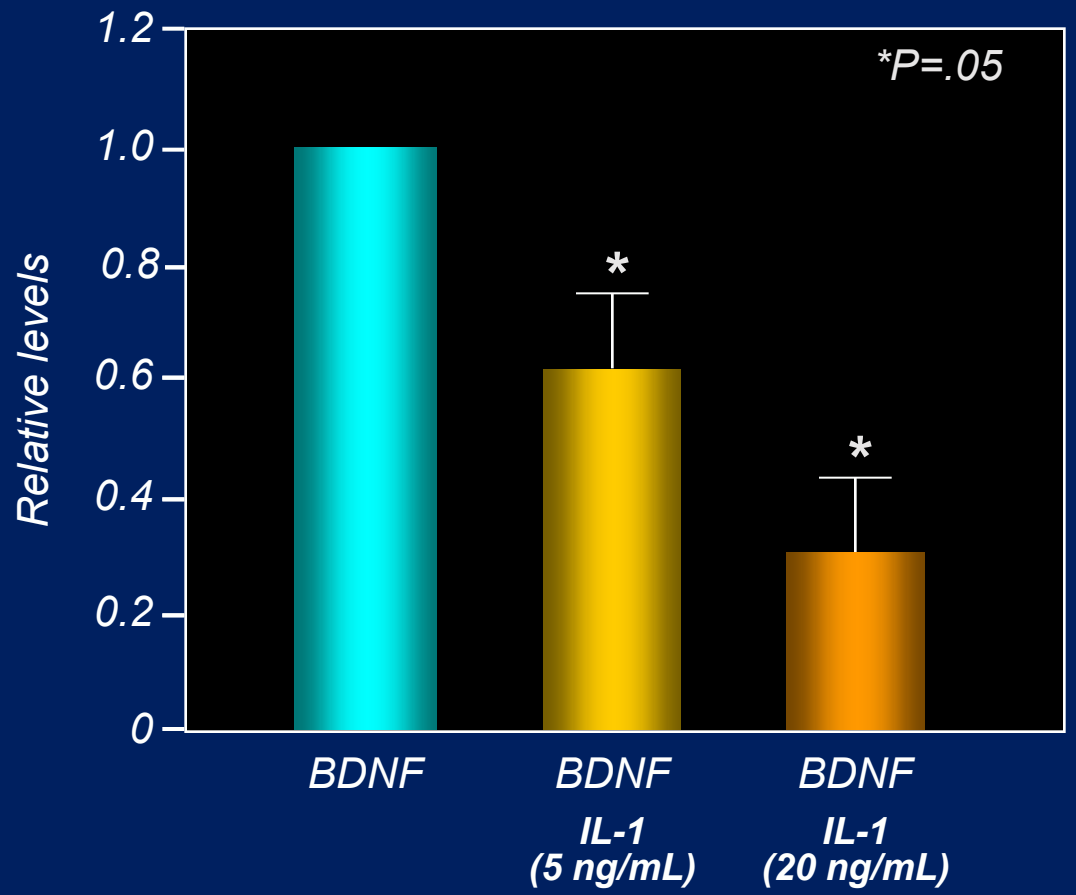
Anterior cingulate cortex

Affective Response, Anticipation, Motor Response to pain

Amygdala

Processing & Memory of pain

Inflammatory Cytokines Interfere With BDNF Signaling



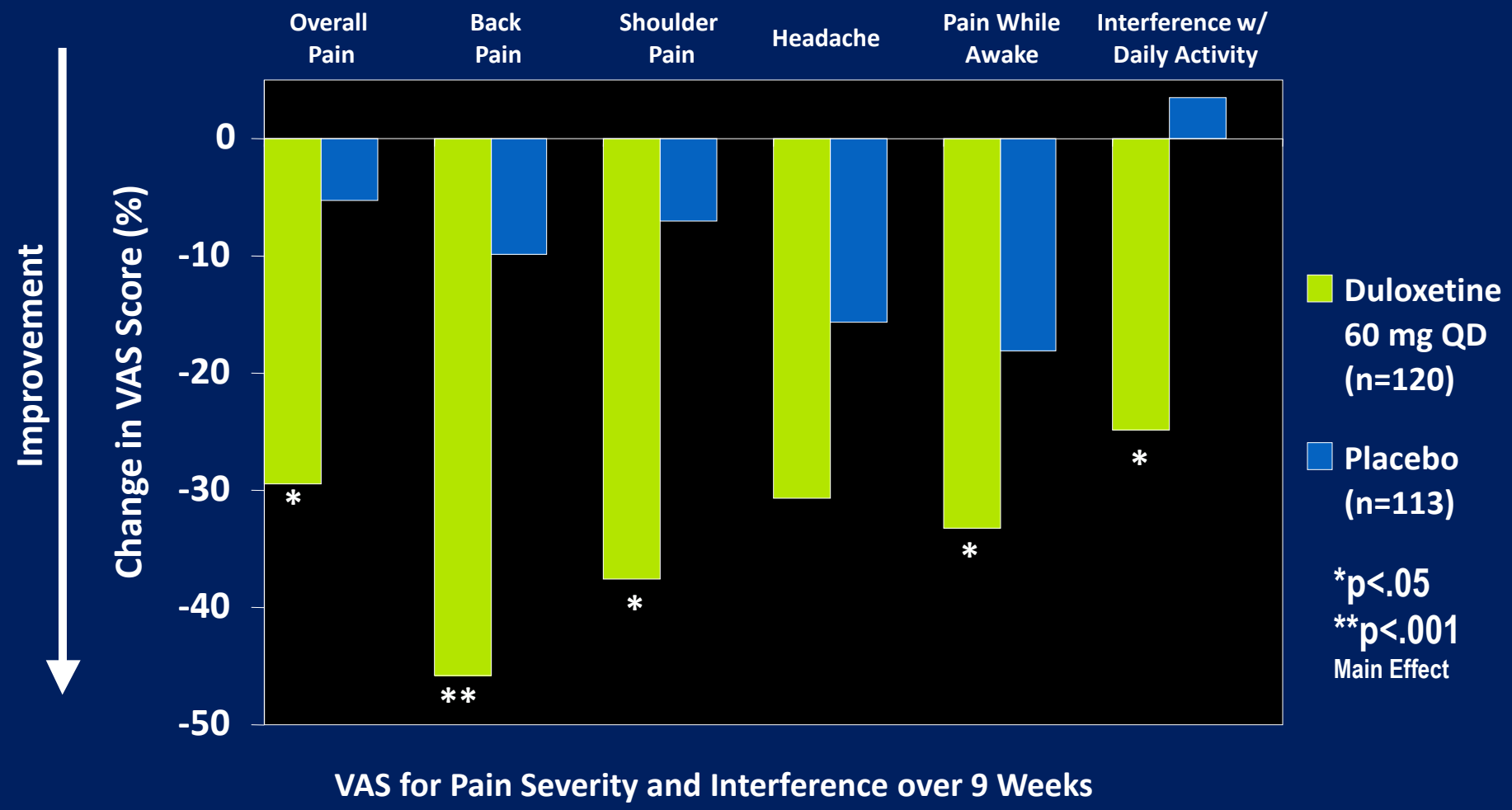
- *Primary culture of rat cerebral cortical neurons*

BDNF=brain-derived neurotrophic factor; IL=interleukin.

*Tong L. Neurobiol Aging. 2008;**29**:1380–1393.*

Duloxetine 60 mg Once-Daily vs. Placebo in MDD

Visual Analog Scale (VAS) Main Effect of Treatment (study 1)



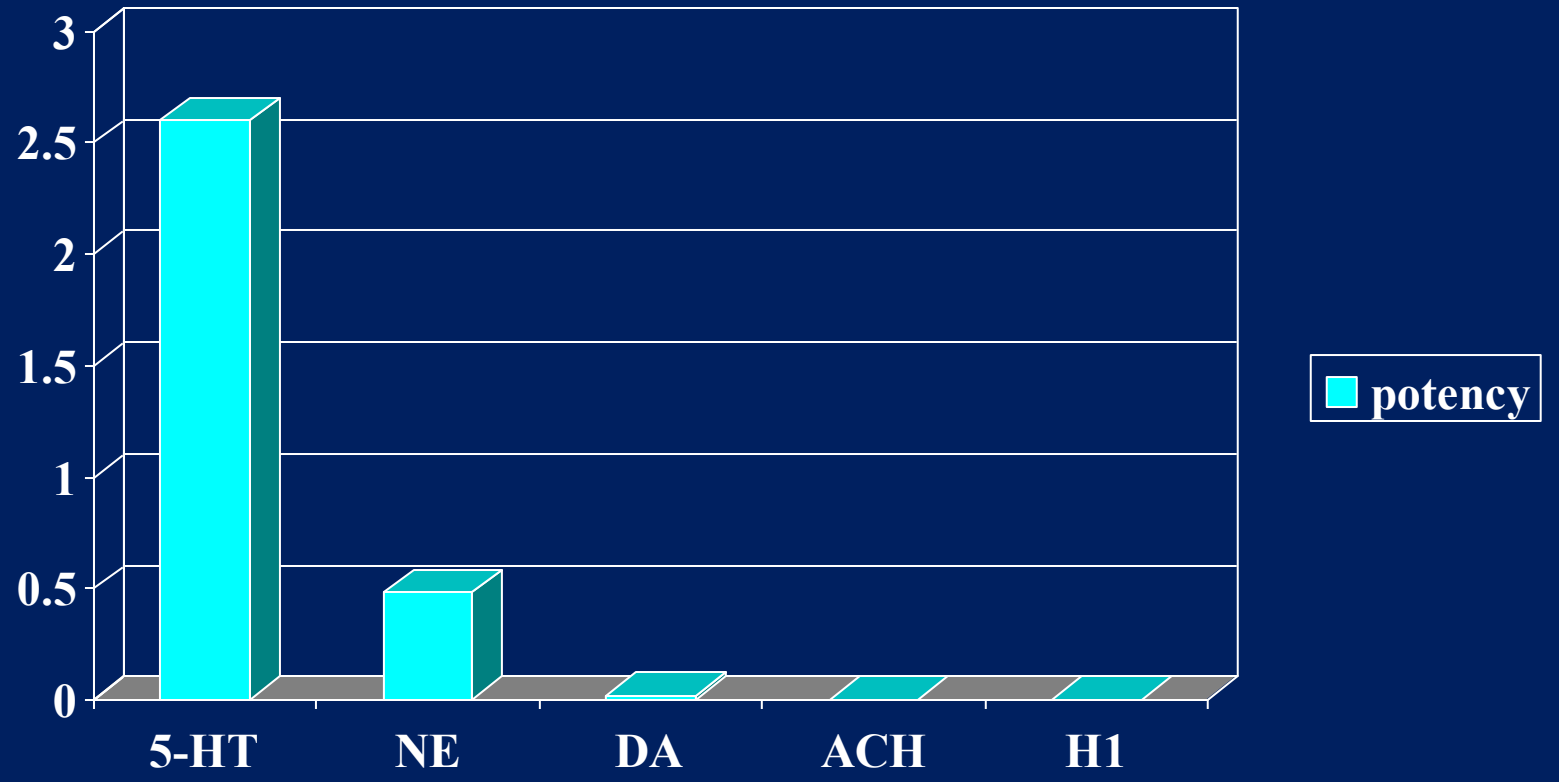
Nemeroff CB, et al. *Psychopharm Bull.* 2002;36:106-132.

Dosage range

	Dose
Range	30-120 mg/day

Prescribing Information. https://www.torrinomedica.it/schede-farmaci Last accessed Dec 2023

Venlafaxine



Richelson E, Synaptic Effects of Antidepressants, Journal of Clinical Psychopharmacology, Vol. 16, No3, Suppl. 2, June, 1996

Venlafaxine

- Pros
  - Minimal drug interactions and almost no P450 activity
  - Short half life and fast renal clearance avoids build-up (good for geriatric populations)
- Cons
  - Can cause a 10-15 mmHG dose dependent increase in diastolic BP.
  - Can cause discontinuation syndrome, and taper recommended after 2 weeks of administration

VENLAFAXINE

- Potent reuptake inhibitor of 5-HT, with less potent effect on NE and dopamine.
- Has minimal drug interaction risk. 30% protein-bound
- Short half-life and 87% renal excretion avoids build-up in geriatric patients.

Approved Indications

- Major depressive disorder
- Panic disorder
- Social anxiety disorder
- (Generalized anxiety disorder)

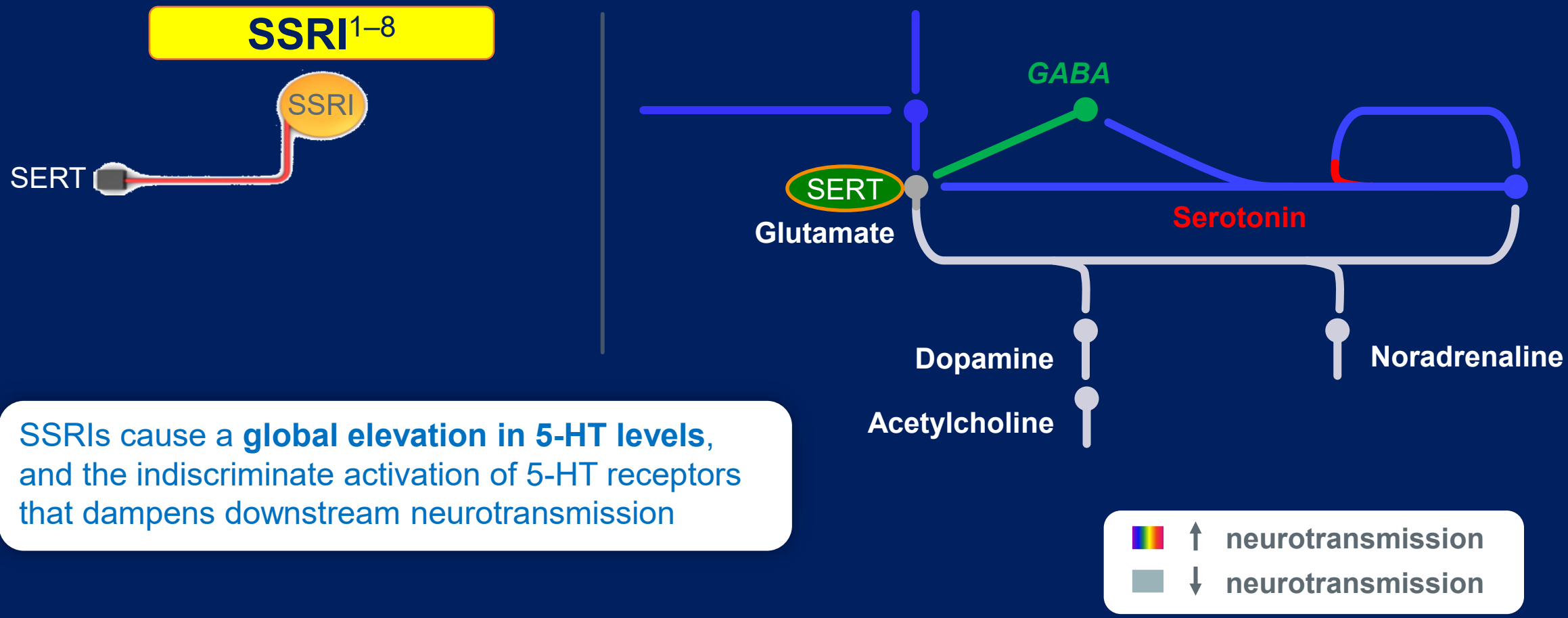
Prescribing Information. https://www.torrinomedica.it/schede-farmaci Last accessed May 2021

Dosage range

	Dose
Range	75-375 mg/day

Prescribing Information. https://www.torrinomedica.it/schede-farmaci Last accessed Oct 2020

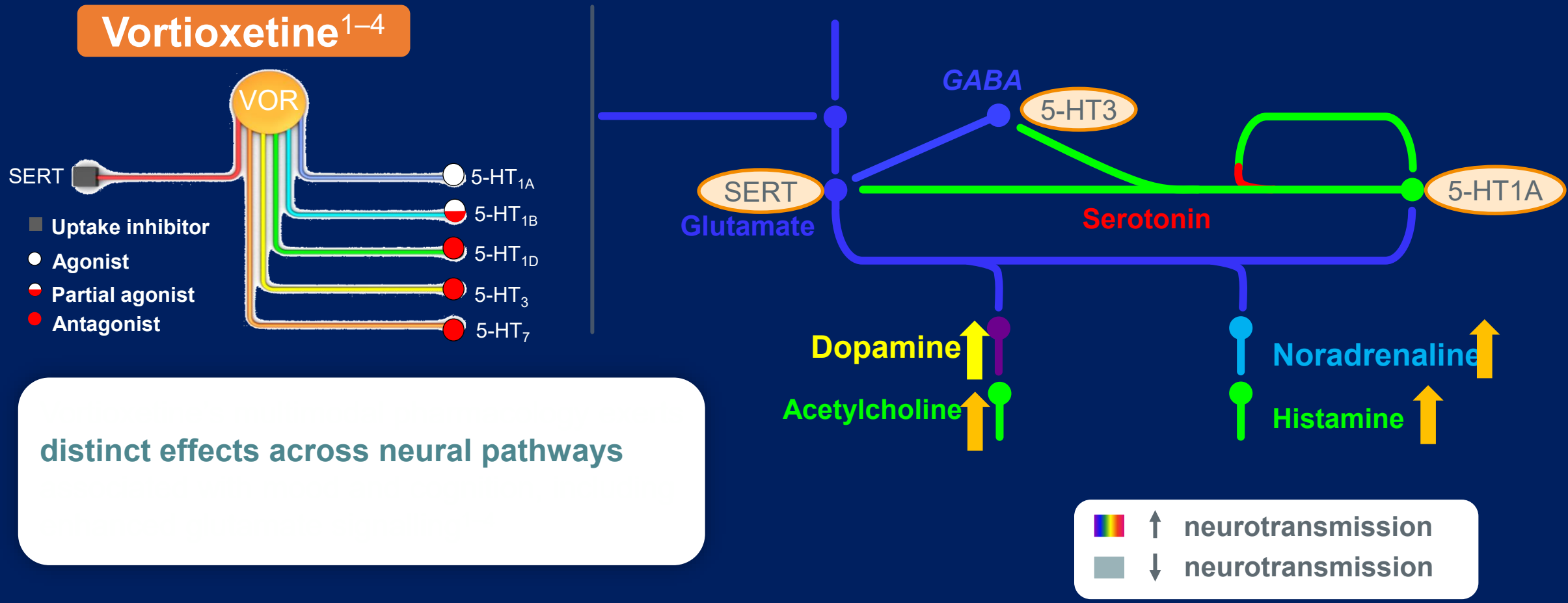
Consequences of SSRIs on neurotransmission in preclinical models



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

1. El Mansari M et al. CNS Neurosci Ther. 2010;16:e1–e17; 2. West CHK et al. Neuropsychopharmacol. 2009;12(5):627–641; 3. Szabo ST et al. Int J Neuropsychopharmacol. 2000;3(1):1–11; 4. Kawahara Y et al. Psychopharmacology (Berl). 2007;194(1):73–81; 5. Dremencov E et al. J Psychiatry Neurosci. 2009;34(3):223–229; 6. DeGroot A and Nomikos GG. Neuropsychopharmacol 2005;30(2):391–400; 7. Jackson D et al. Brain Res. 1988;457(2):259–266; 8. Komlósi G et al. J Neurosci 2012; 32(46):16,369–16,378.

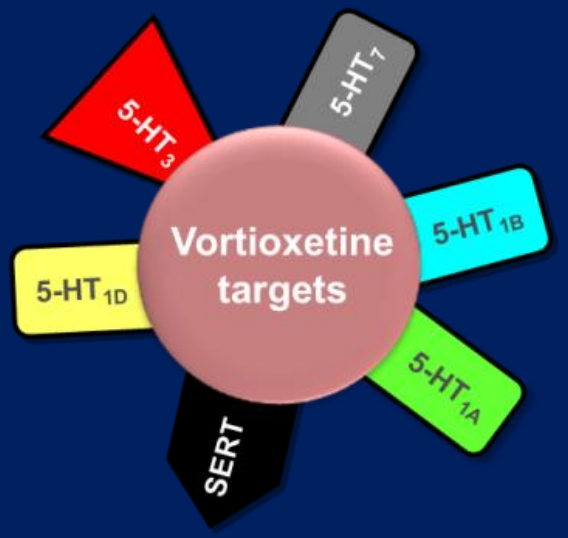
Consequences of vortioxetine on neurotransmission in preclinical models



distinct effects across neural pathways

1. Guilloux JP et al. Neuropharmacology. 2013;73:147–159; 2. Pehrson AL et al. Eur Neuropsychopharmacol. 2013;23(2):133–145; 3. Mørk A et al. Pharmacol Biochem Behav. 2013;105:41–50; 4. Pehrson AL and Sanchez C. CNS Spectr. 2014;19(2):121–133.

Pharmacology and clinical potential of vortioxetine in the treatment of major depressive disorder



Net Post-Synaptic prefrontal & hipocampal effect

↓

Enhance antidepresseant effect with additional cognitive and motivational improvements

Accelerates SSRI effect

SSRI

Post-synaptic receptor modulation

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

Enhances the antidepressant SSRI effect
+
Improves anxiety & Cognition

Additional antidepressant, pro-cognitive & anxiolytic effects

5-HT, serotonin; SSRI, selective serotonin reuptake inhibitor; SERT, serotonin reuptake transporter; Alvarez E et al. Neuropsychiatr Dis Treat. 2014 Jul 15;10:1297-307.

Personalized Treatment

Different Doses= Different Effects ?

How to determine the optimal dose of antidepressants?

What is the relationship between dose and efficacy of antidepressants?

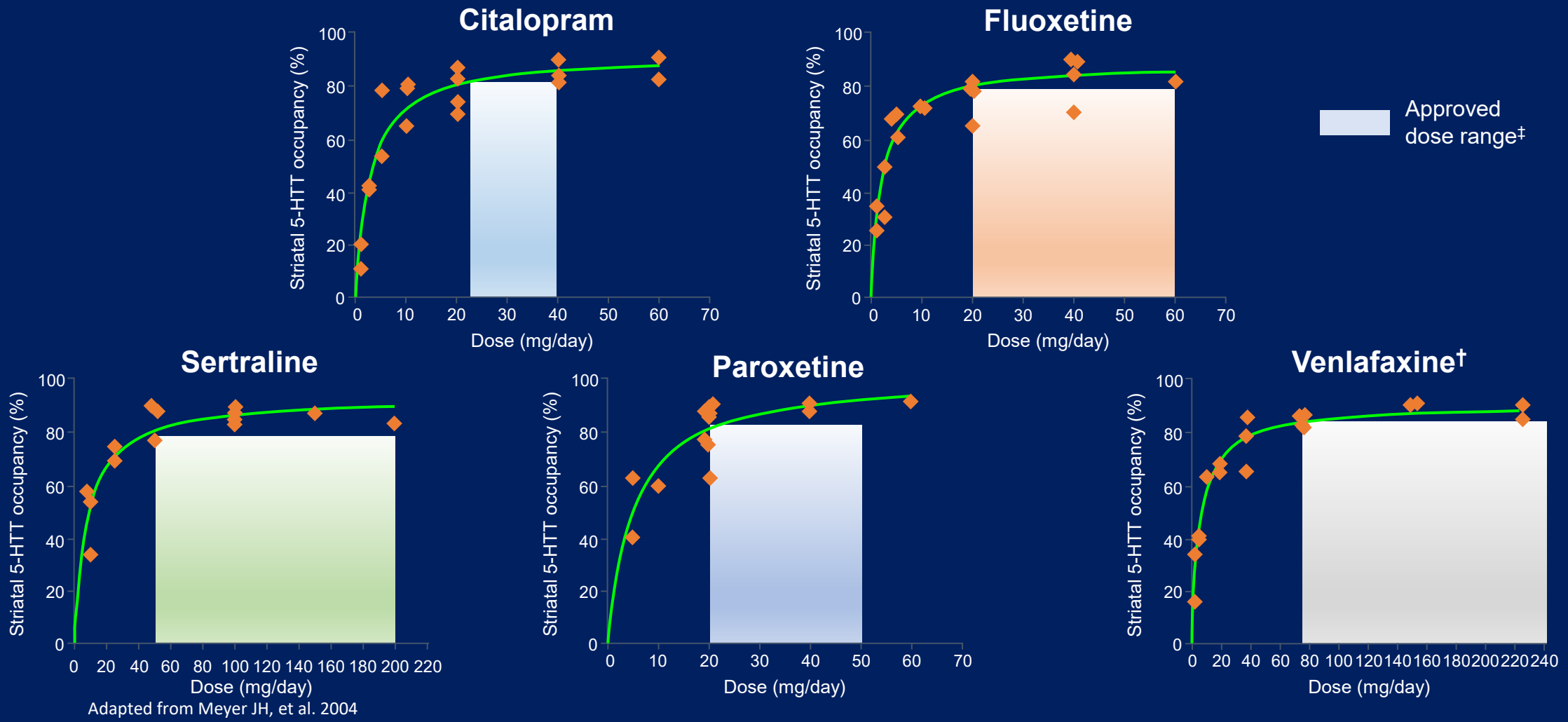
What is the relationship between dose and adverse events of antidepressants?

How to balance between efficacy and tolerability when selecting the most appropriate dose of antidepressants?

Furukawa TA, et al. Lancet Psychiatry 2019;6:601-609.

The dose–response relationship of antidepressants in patients with MDD

Many commonly used SSRIs and SNRIs have their approved dose range at a serotonin transporter occupancy of ~80%*



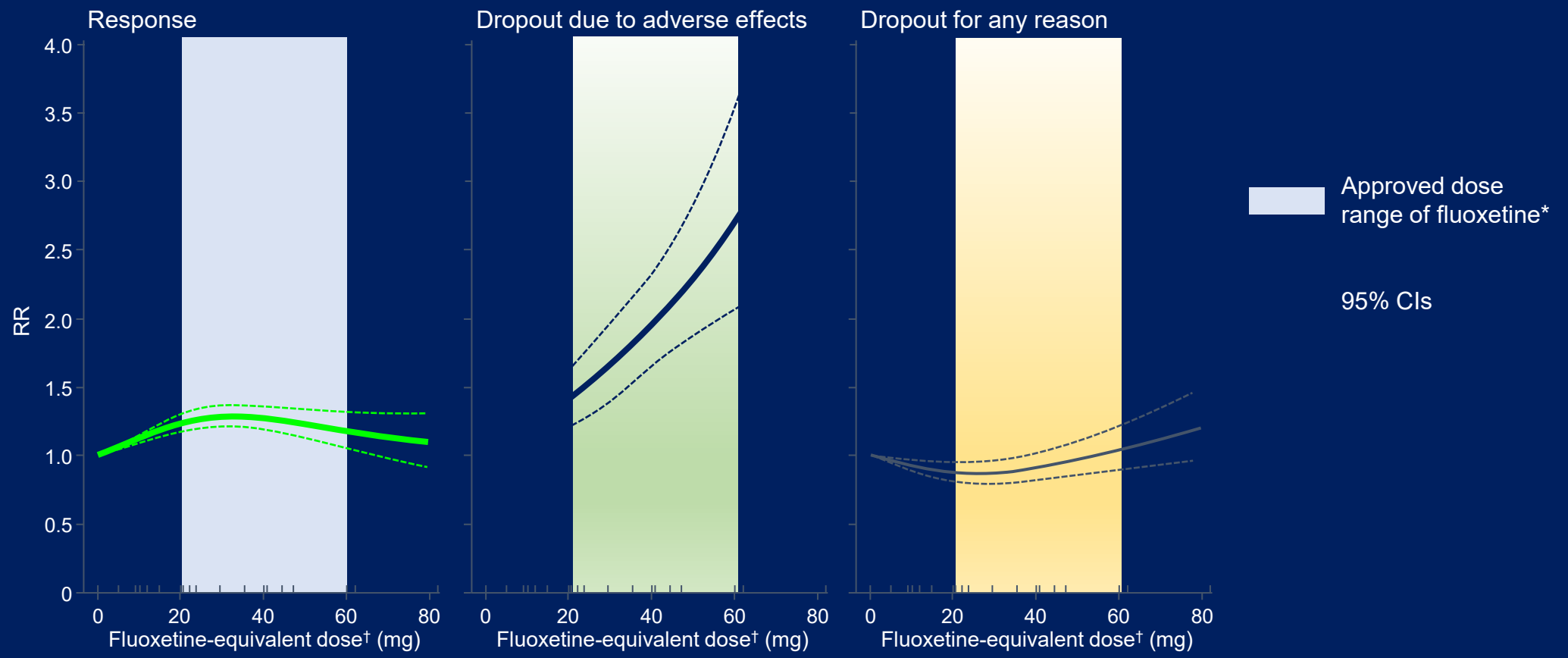
Adapted from Meyer JH, et al. 2004

*Data obtained from 18 healthy subjects. †The approved dose for venlafaxine is 75–375 mg/day (upper range not shown on the graph). ‡ Obtained from respective Summary of Product Characteristics of individual antidepressants. An abbreviated Prescribing Information for citalopram can be found at the end of this slide deck. For further information please consult your local Summary of Product Characteristics. 5-HTT = serotonin transporter; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin–noradrenaline reuptake inhibitor. Meyer JH, et al. Am J Psychiatry. 2004;161:826-835.

Increasing doses of SSRIs were associated with linear increase in AEs, whereas response rates were not

Meta-analysis: Dose–outcome relationships for SSRIs (99 treatment groups)

SSRIs studied included: citalopram, escitalopram, paroxetine and sertraline



Adapted from Furukawa TA, et al. 2019

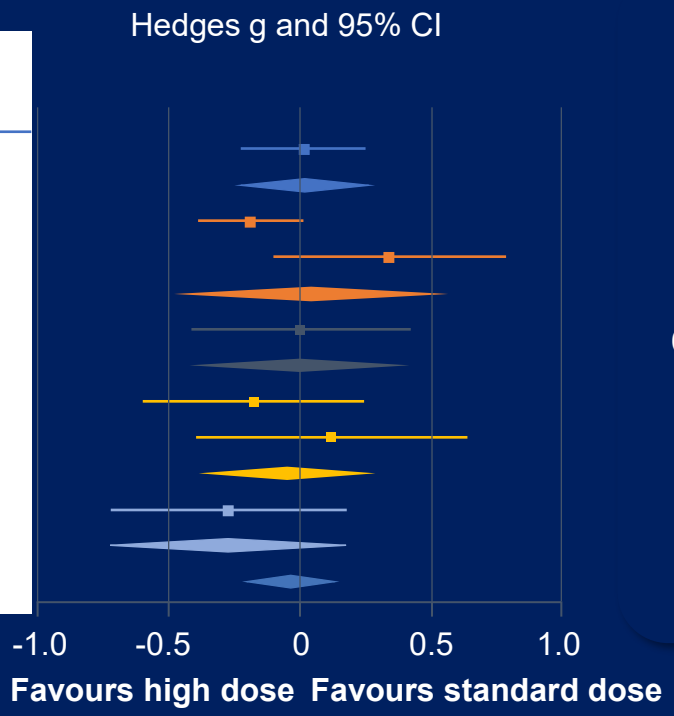
Each tick on the x-axis represents the dose examined in a treatment group. *Obtained from the Summary of Product Characteristics for fluoxetine. † Doses of citalopram, escitalopram, paroxetine and sertraline were converted to fluoxetine equivalents. Citalopram is indicated for the treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence. Citalopram is also indicated in the treatment of panic disorder with or without agoraphobia. Escitalopram is indicated for the acute and maintenance treatment of major depressive disorder in adults and in adolescents 12 to 17 years of age. An abbreviated Prescribing Information for citalopram and escitalopram can be found at the end of this slide deck. For further information please consult your local Summary of Product Characteristics. AE = adverse effect; CI = confidence interval; RR = risk ratio; SSRI = selective serotonin reuptake inhibitor. Furukawa TA, et al. Lancet Psychiatry. 2019;6:601-609.

When patients with MDD do not respond to an initial SSRI or SNRI, dose escalation may not be beneficial

Effect sizes for the mean change in HAM-D total score (N=1,208)*

Study	Antidepressant	Hedges g	Statistics for each study			n
			Lower limit	Upper limit	P value	
Kornstein et al., 2008		0.01	−0.24	0.26	0.92	248
Duloxetine pooled		0.01	−0.24	0.26	0.92	248
Dornseif et al., 1989	Fluoxetine	−0.19	−0.40	0.01	0.06	369
Schweizer et al., 1990	Fluoxetine	0.34	−0.11	0.78	0.14	77
Fluoxetine pooled		0.03	−0.48	0.55	0.90	446
Benkert et al., 1997	Maprotiline	0.00	−0.42	0.42	1.00	87
Maprotiline pooled		0.00	−0.42	0.42	1.00	87
Benkert et al., 1997	Paroxetine	−0.18	−0.60	0.25	0.42	86
Ruhe et al., 2009	Paroxetine	0.12	−0.39	0.63	0.65	57
Paroxetine pooled		−0.06	−0.38	0.27	0.74	143
Schweizer et al., 2001	Sertraline	−0.28	−0.73	0.17	0.23	75
Sertraline pooled		−0.28	−0.73	0.17	0.23	75
Overall pooled		−0.04	−0.20	0.12	0.63	999

Adapted from Dold M, et al. 2017.



No significant difference in mean HAM-D total score change was observed between the **pooled dose escalation group and the dose continuation group** (Hedges g=-0.004, p=0.63)

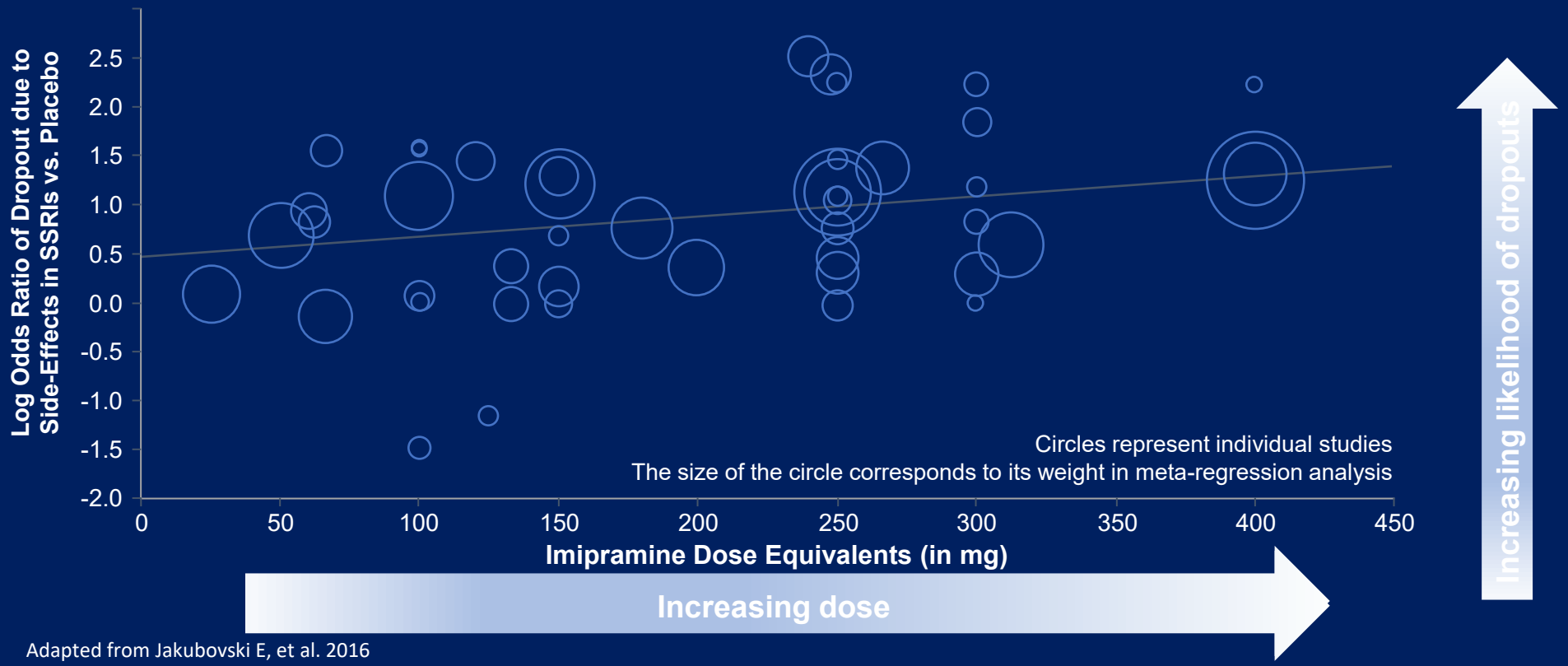
*Data based on a meta-analysis of 7 double-blind, parallel-group studies comparing a dose increase of SSRI/SNRIs directly to continuation of standard-dose treatment in patients with MDD who did not respond to SSRI/SNRI treatment.

CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; SNRI = serotonin–noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Dold M, et al. Psychother Psychosom. 2017;86:283-291.

Dropouts due to AEs increase with increasing dose in SSRIs

Meta-regression analysis: Association between SSRI dose and likelihood of dropouts due to AEs*



Adapted from Jakubovski E, et al. 2016

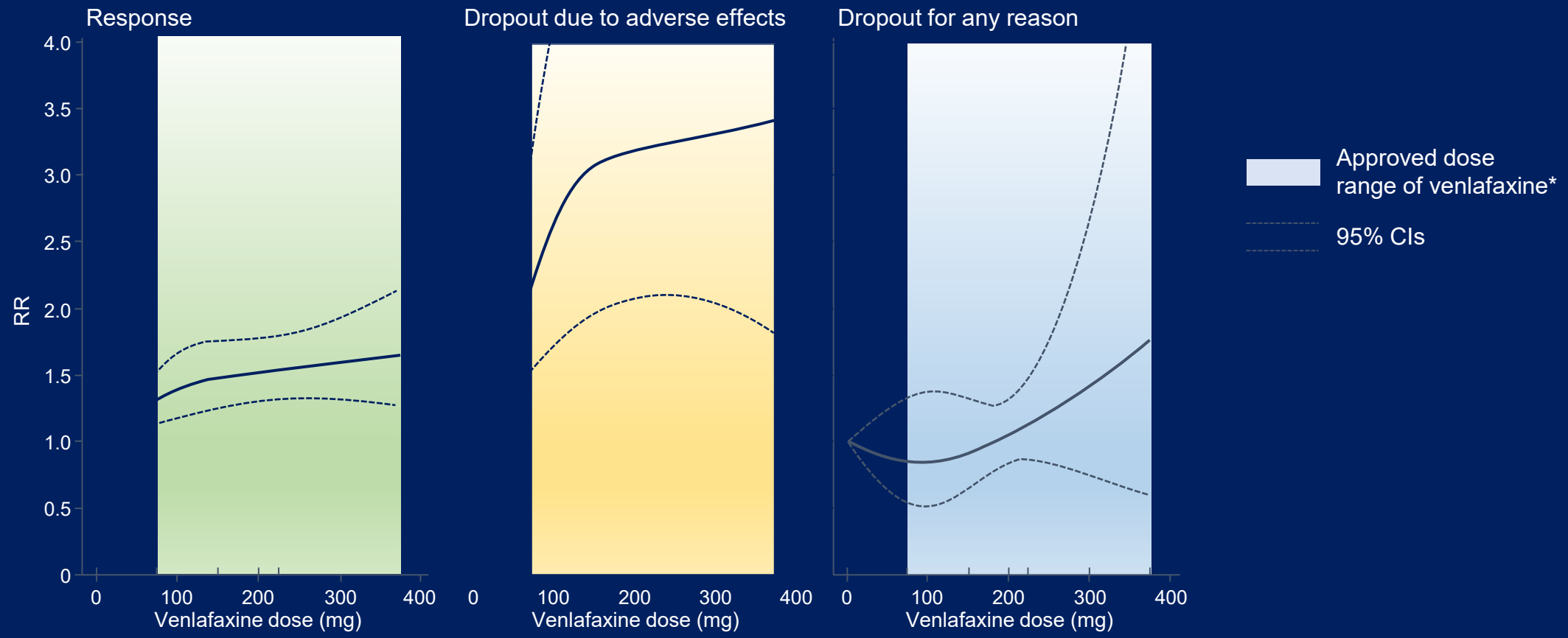
Higher doses of SSRIs were associated with a higher rate of dropouts due to adverse effects (β = 0.00207 95% CI 0.00071–0.00342, z = 2.98, p = 0.0028)

AE = adverse event; CI = confidence interval; MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitors.

Jakubovski E, et al. Am J Psychiatry. 2016;173:174-183.

Venlafaxine has an increasing dose–efficacy relationship only in the lower approved dose range (75–150 mg), but dropouts due to AEs increase steeply with increasing doses at this range

Meta-analysis: Dose–outcome relationships for venlafaxine (16 treatment groups)



Adapted from Furukawa TA, et al. 2019

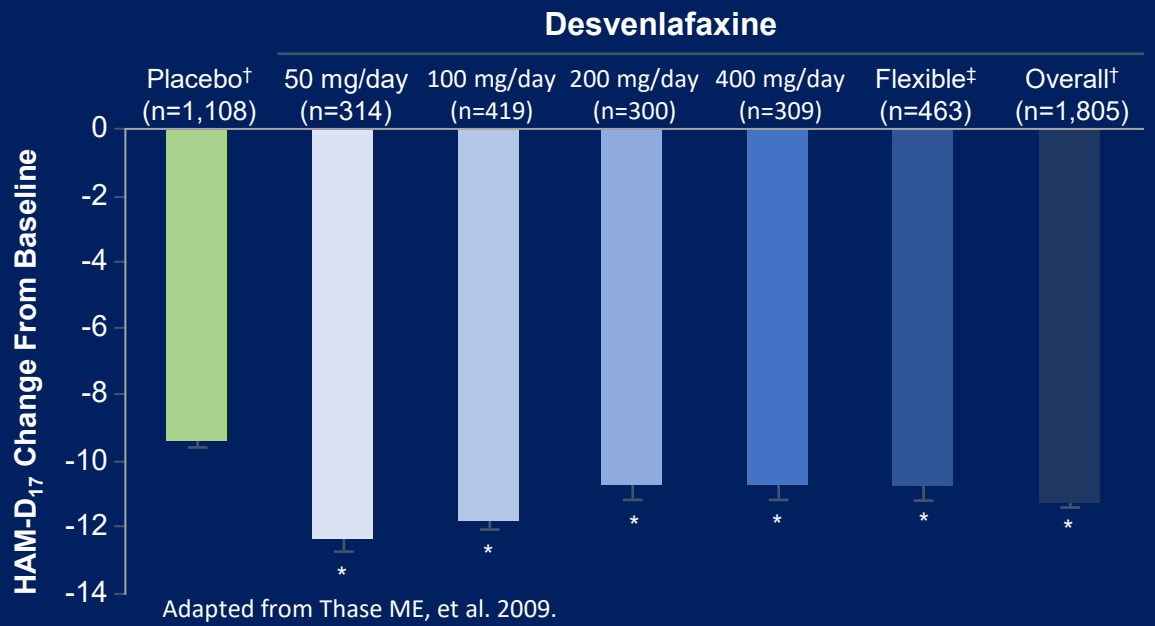
Each tick on the x-axis represents the dose examined in a treatment group. *Obtained from the Summary of Product Characteristics for venlafaxine.

AE = adverse effect; CI = confidence interval; RR = risk ratio.

Furukawa TA, et al. Lancet Psychiatry. 2019;6:601-609.

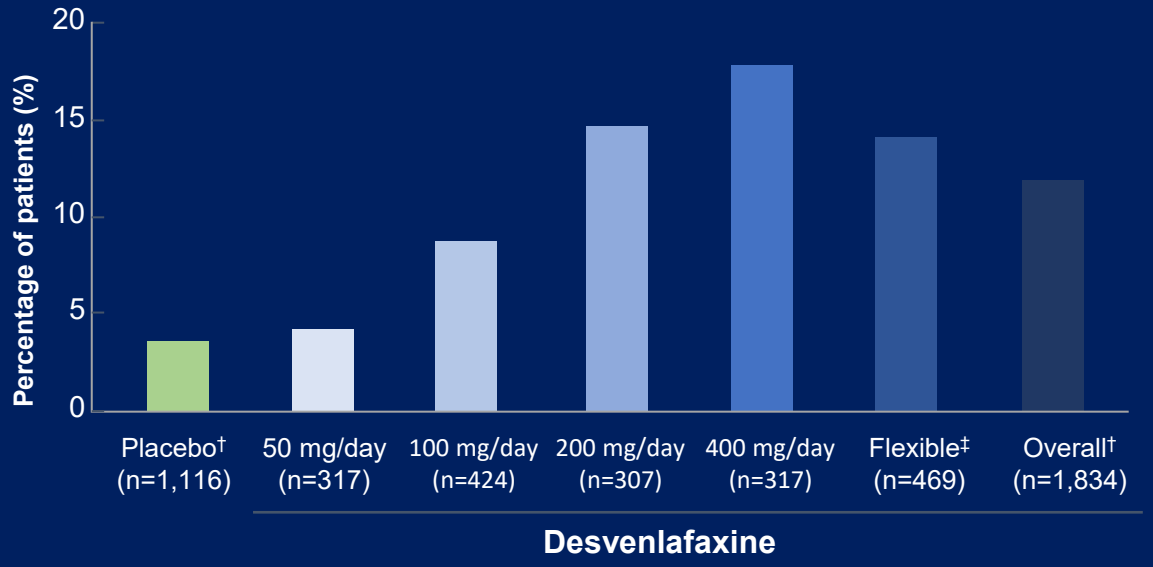
Desvenlafaxine shows no evidence of a dose–efficacy relationship but dropouts due to AEs increase steeply with increasing doses

Change in HAM-D total scores from baseline to final on-therapy evaluation



Adapted from Thase ME, et al. 2009.

Rates of dropouts due to AEs



- **In this meta-analysis, no evidence of greater efficacy was observed with doses >50 mg/day**
- **A strong dose–response effect on tolerability was observed, with substantially higher rates of dropouts due to AEs among patients treated with higher doses**

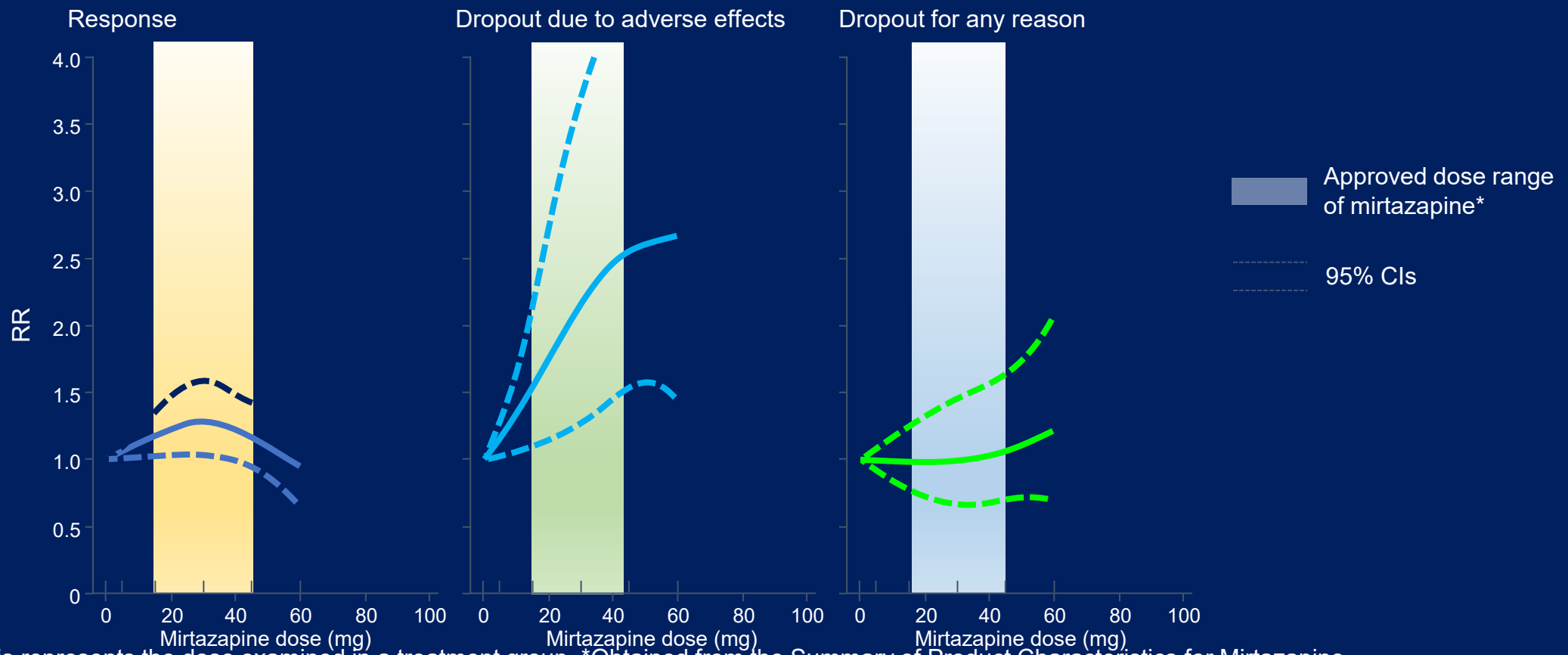
*p<0.001 vs placebo.

AE = adverse event; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; SNRI = serotonin–noradrenaline reuptake inhibitor.

Thase ME, et al. CNS Spectr. 2009;14:144-154.

Mirtazapine has a decreasing dose–efficacy relationship at doses higher than 30 mg/day and dropouts due to AEs increase steeply with increasing doses

Meta-analysis: Dose–outcome relationships for mirtazapine (11 treatment groups)



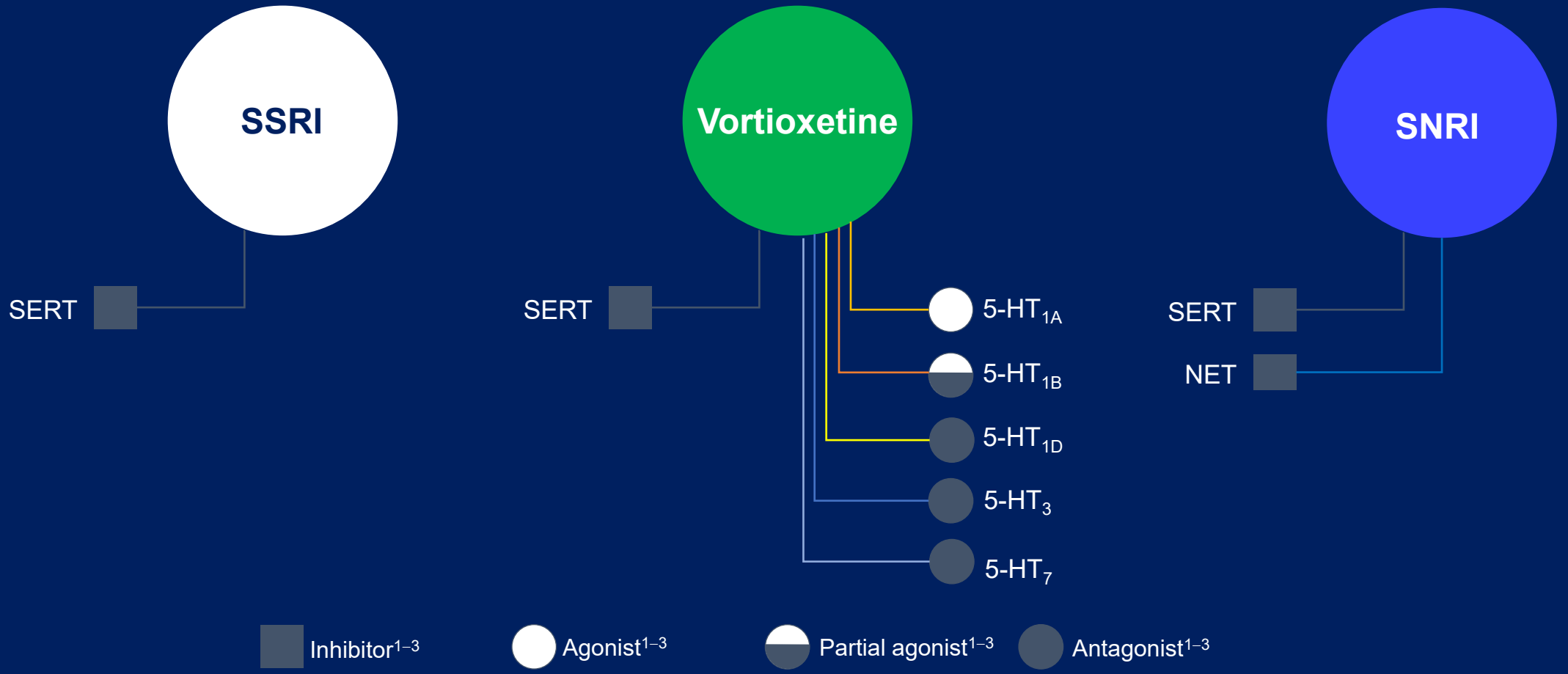
Each tick on the x-axis represents the dose examined in a treatment group. *Obtained from the Summary of Product Characteristics for Mirtazapine.

AE = adverse effect; CI = confidence interval; RR = risk ratio

Furukawa TA, et al. Lancet Psychiatry. 2019;6:601-609.

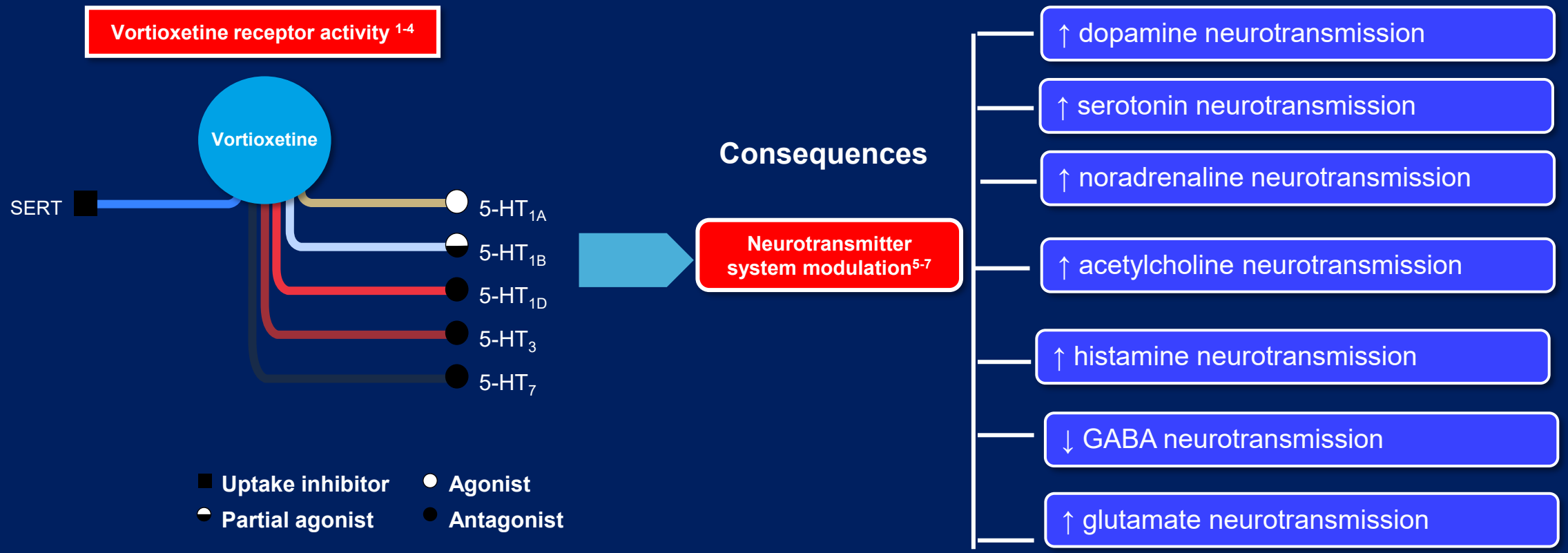
The dose–response relationship of vortioxetine in patients with MDD

Mechanism of action



. HT = hydroxytryptamine; NET = norepinephrine transporter; SERT = serotonin reuptake transporter; SNRI = serotonin–norepinephrine reuptake Inhibitor; SSRI = selective serotonin reuptake inhibitor.
Created from 1. Bang-Andersen B, et al. J Med Chem. 2011;54(9):3206-3221;
2. Sanchez C, et al. Pharmacol Ther. 2015;145:43-57; 3. vortioxetine)Summary of Product Characteristics 2020.

Vortioxetine Pharmacologic Profile



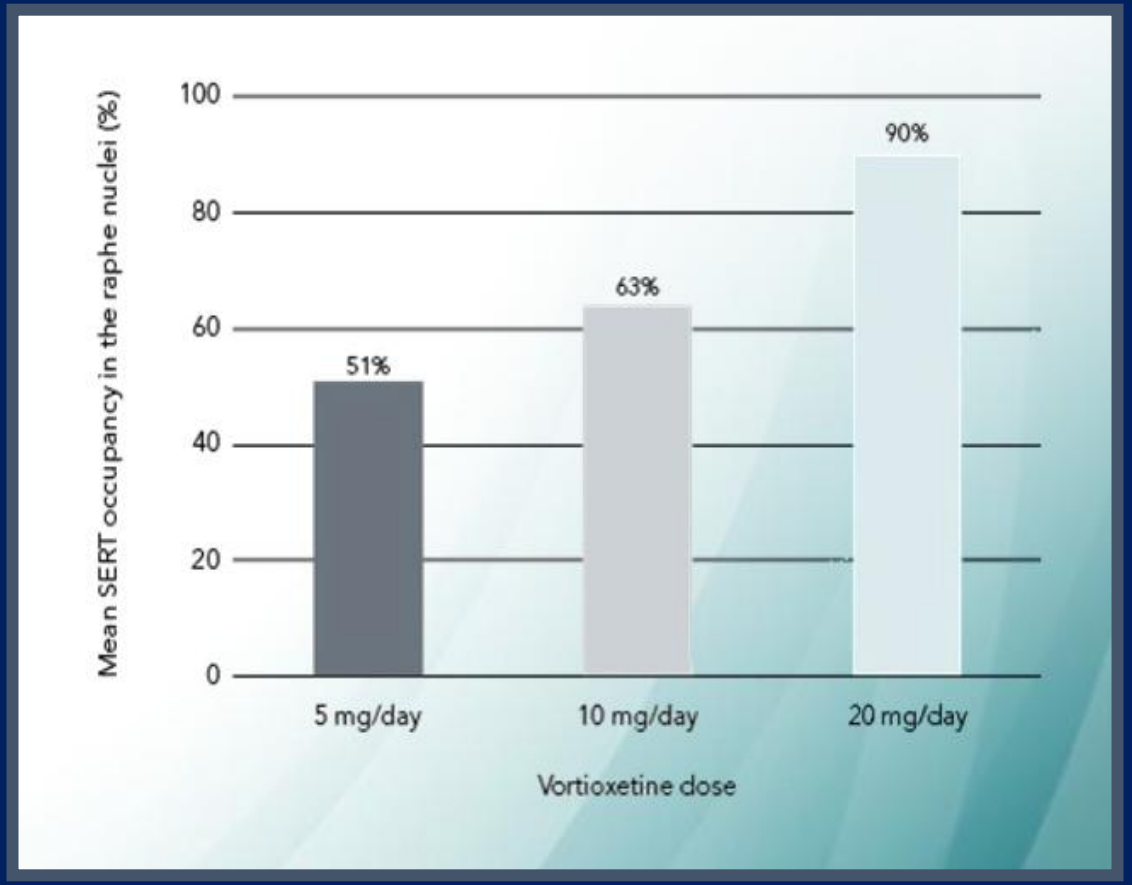
In the forebrain, the precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to man.

5-HT=serotonin; GABA=gamma-aminobutyric acid; SERT=serotonin transporter.

1. Bang-Anderson B, et al. *J Med Chem.* 2011;54:3206-3221; 2. Mørk A, et al. *J Pharmacol Exp Ther.* 2012;340:666-675; 3. Vortioxetine EPAR; 4. Westrich L, et al. Poster at IFMAD 2012; 5. Mørk A, et al. Poster at ECNP 2011; 6. Pehrson A, et al. Poster at ECNP 2013; 7. Mørk A, et al. Poster at APA 2013; 8. Alvarez E, et al. *Int J Neuropsychopharmacol.* 2012;15:589-600; 9. Katona C, et al. *Int Clin Psychopharmacol.* 2012;27:215-223; 10. Baldwin DS, et al. *Eur Neuropsychopharmacol.* 2012;22:482-491; 11. Henigsberg N, et al. *J Clin Psychiatry.* 2012;73:953-959; 12. Boulenger JP, et al. *Int Clin Psychopharmacol.* 2014;29:138-149; 13. Bidzan L, et al. *Eur Neuropsychopharmacol.* 2012;22:847-857.

Vortioxetine: Sert Occupancy

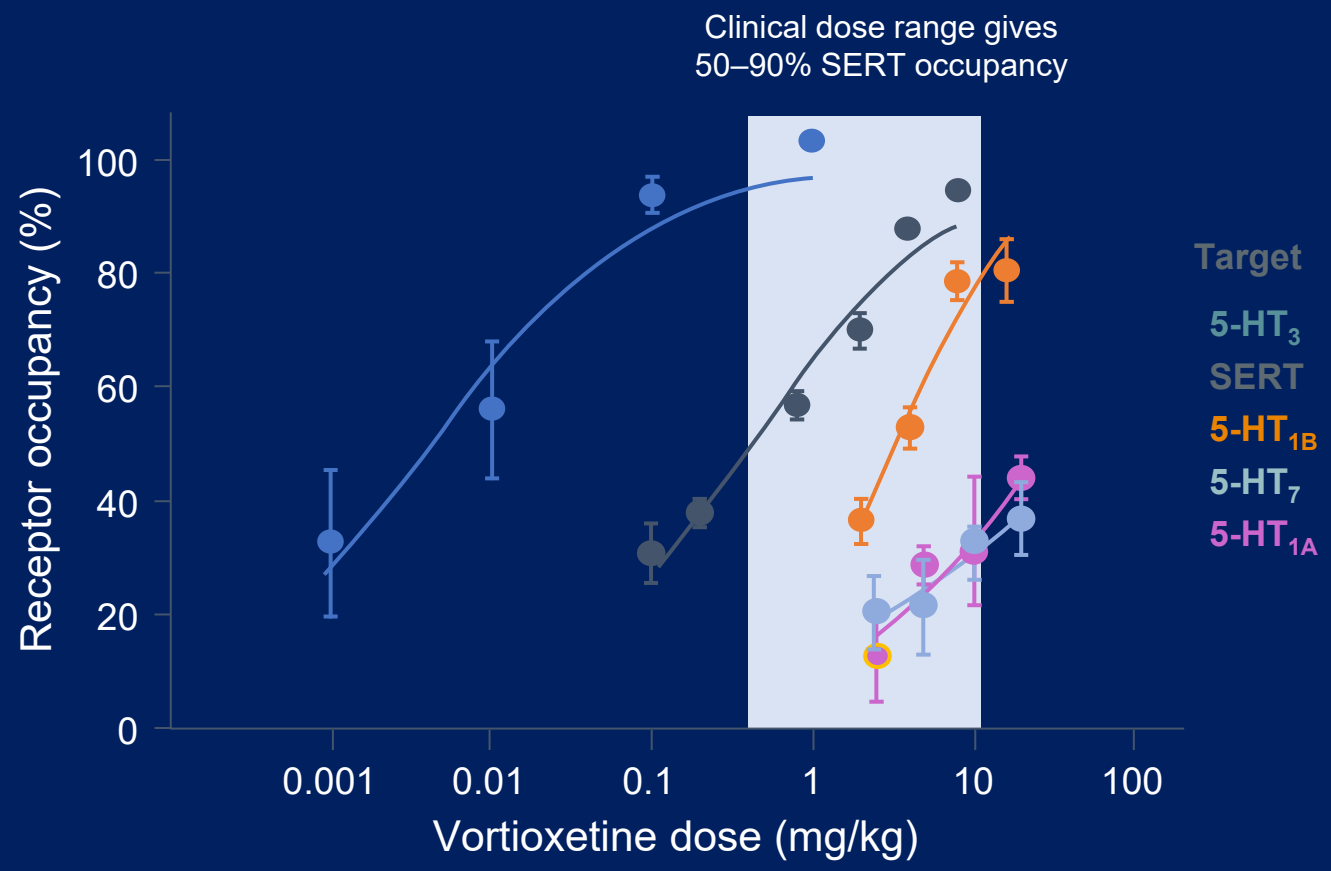
80% SERT blockage is key to therapeutic effect



Areberg J et al. Basic Clin Pharmacol Toxicol 2012; 110: 401-404
Meyer et al. Am J Psychiatry 2004;161[5]:826–835

Vortioxetine targets at clinically relevant doses

Target occupancies in rats dosed with vortioxetine[1,2]



Adapted from Sanchez C, et al. 2015[2]

A dose-related increase in SERT occupancy at steady-state conditions was also observed in healthy individuals:[2]

- **~50%** at vortioxetine **5 mg**
- **~65%** at vortioxetine **10 mg**
- **>80%** at vortioxetine **20 mg**

Due to the linear dose response of vortioxetine, there is a potential efficacy benefit of increasing the dose when there is a suboptimal initial response[1–3]

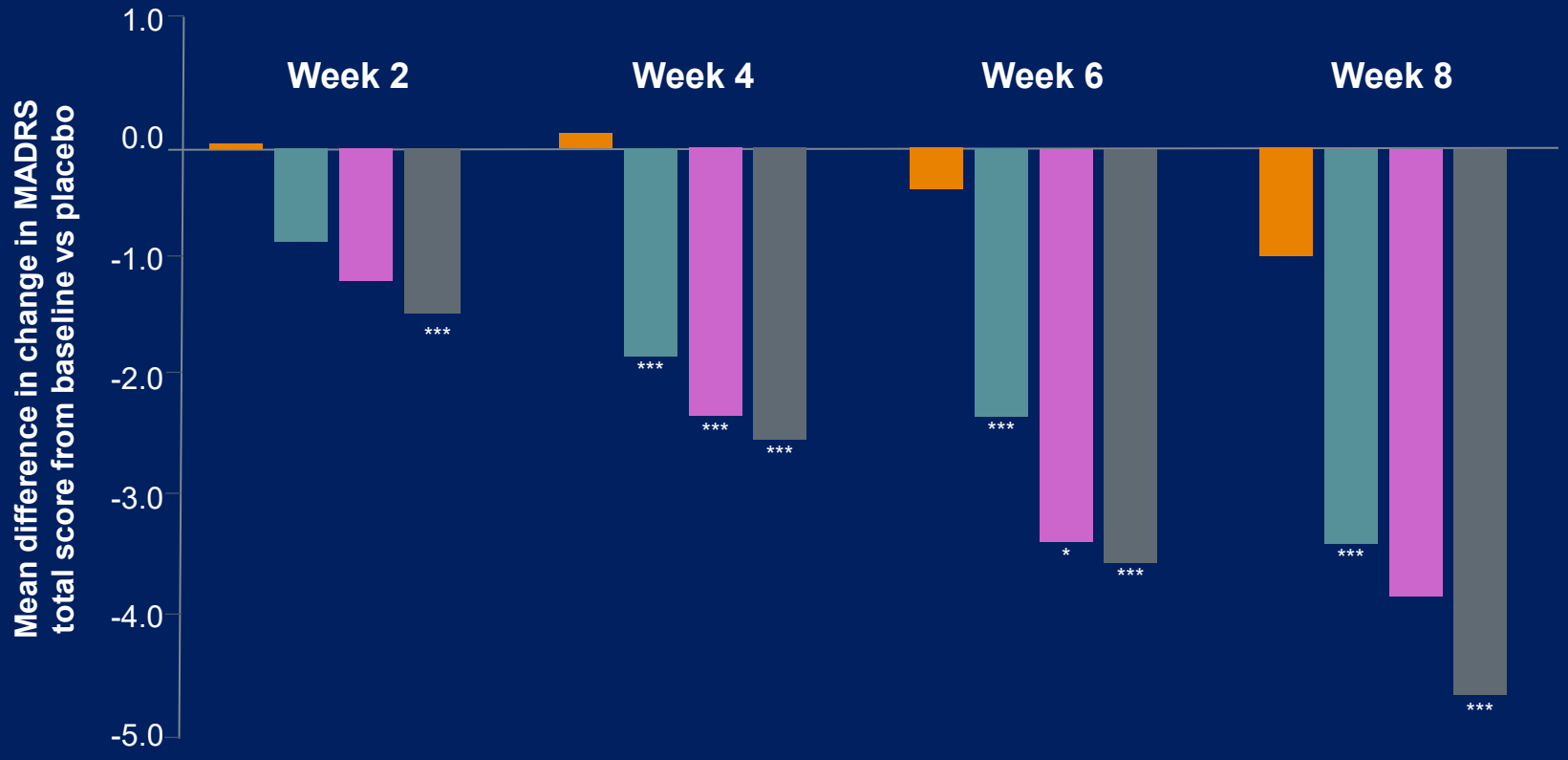
HT = hydroxytryptamine; SERT = serotonin reuptake transporter.

1. Pehrson AL, et al. Eur Neuropsychopharmacol. 2013;23:133-145; 2. Sanchez C, et al. Pharmacol Ther. 2015;145:43-57; 3. Areberg J, et al. Basic Clin Pharmacol Toxicol. 2012;110:401-404.

Vortioxetine 20 mg/day demonstrated statistically significant improvements in depressive symptoms† as early as Week 2[1]

Mean difference in change in MADRS total score from baseline[1‡]

Meta-analysis of 6 short-term, fixed-dose, placebo-controlled studies

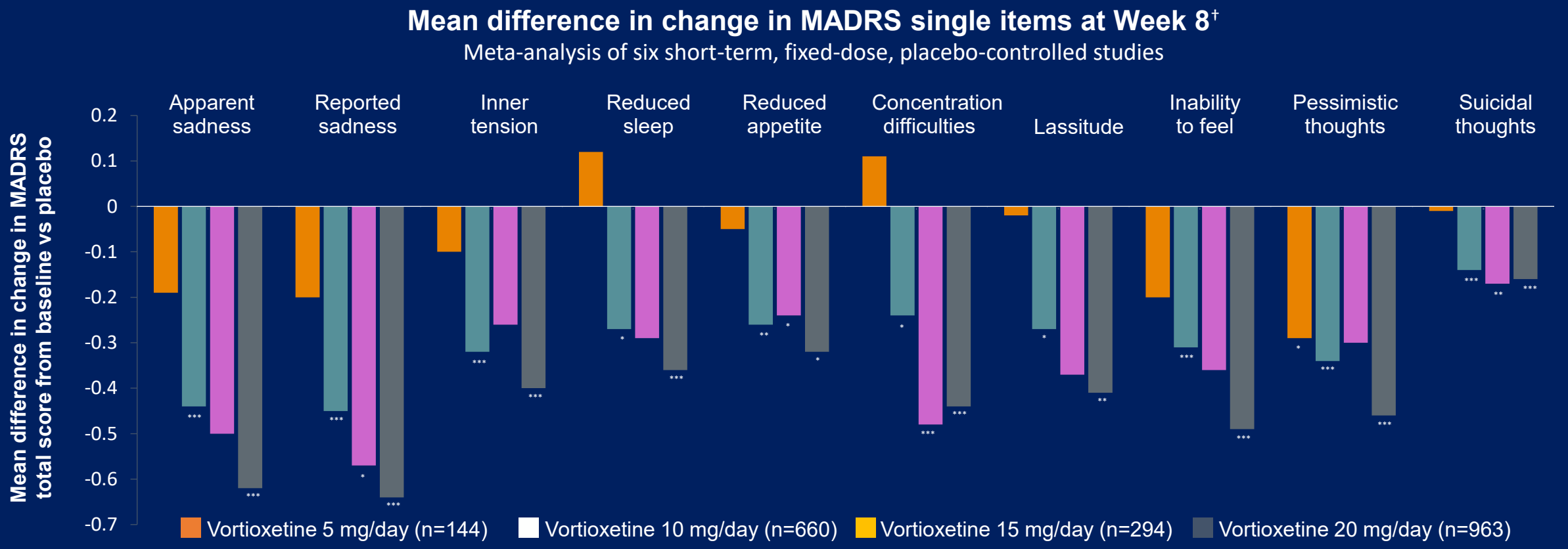


Adapted from Christensen MC, et al. 2021.[1]

- In this meta-analysis, for vortioxetine 20 mg, significant **differences in depressive symptoms† were observed vs placebo as early as Week 2 ($p<0.05$)[1]**
- At Week 8, vortioxetine 20 mg demonstrated statistically significant and clinically relevant **improvements in depressive symptoms† vs 10 mg** (treatment difference –1.03 and $p<0.05$, respectively)[1]

1. Christensen MC, et al. CNS Spectr. 2021;1-26; doi:10.1017/S1092852921000936; 2. Montgomery SA, Möller HJ. Int Clin Psychopharmacol. 2009;24(3):111-118; 3. Wang G, et al. Curr Med Res Opin. 2015;31(4):785-794.

Vortioxetine demonstrated a clear dose–response relationship across a broad range of MDD symptoms



Adapted from Christensen MC, et al. 2021.

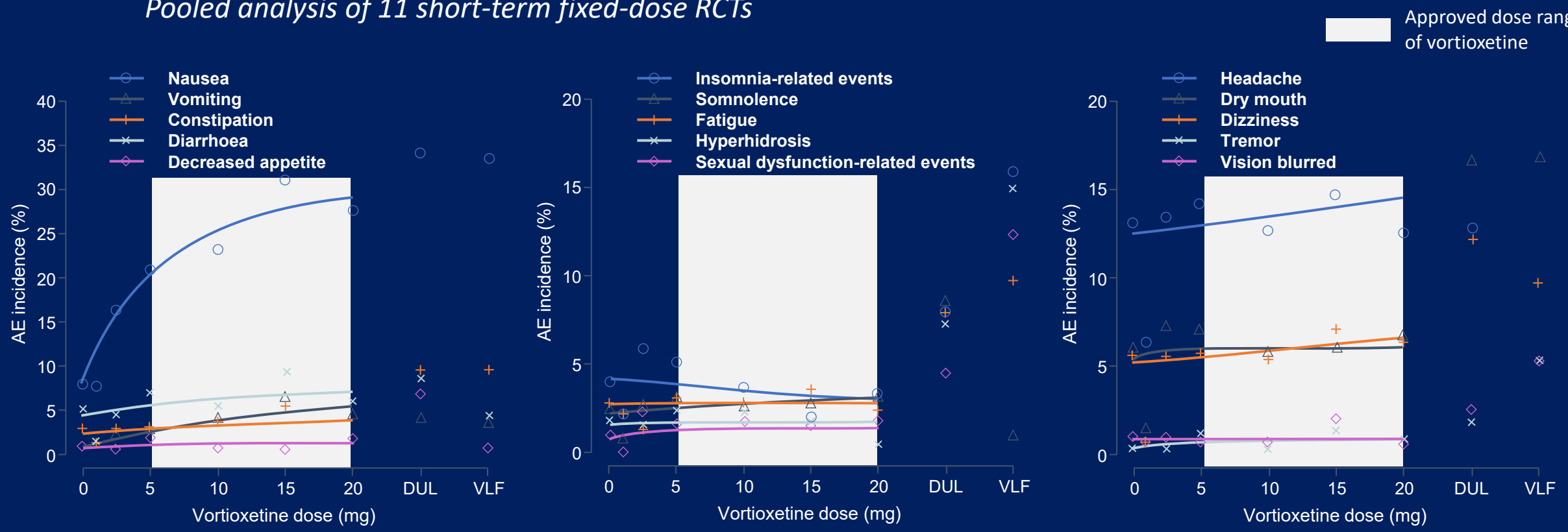
In this meta-analysis, the most pronounced therapeutic benefit across MDD symptoms was seen with 20 mg, with statistically significant improvements vs placebo on all MADRS single items

†Data based on a meta-analysis of six short-term, fixed-dose, placebo-controlled studies. In these fixed-dose studies, patients who were assigned to receive vortioxetine 20 mg received a 10 mg dose for the first week of the 8-week study. MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder.

Christensen MC, et al. CNS Spectr. 2021;1-26; doi:10.1017/S1092852921000936.

Increased doses of vortioxetine are not associated with increased AEs commonly observed with AD treatment

Pooled analysis of 11 short-term fixed-dose RCTs



- **The most common AEs (incidence ⩾5%) and occurring with at least twice the frequency that is seen with placebo during 6–8 weeks of treatment with vortioxetine were nausea and vomiting**
- **Dose effects for vortioxetine were seen primarily for nausea and vomiting, the incidence of which plateaued at 15 mg/day vortioxetine**

AD=antidepressant; AE=adverse event; DUL=duloxetine; RCT=randomised controlled trial; VLF= venlafaxine.

Adapted from Baldwin DS, et al. J Psychopharmacol. 2016;30(3):242–52.

Newer agents in MDD and TRD

Treatment	Esketamine nasal spray	IV ketamine	AXS-05	Zuranolone (SAGE-217)	Psilocybin
Mode of action	NMDA receptor antagonist[1]	NMDA receptor antagonist[3]	NMDA receptor antagonist[5]	Positive allosteric modulator of $GABA_A$ receptors[8]	Serotonin receptor agonist[10]
Current status	**Approved** • In combination with an SSRI or SNRI in adults with TRD[2] • In combination with OAD therapy, in adults with a moderate-to-severe episode of MDD*, for rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency[2]	**Not approved** For MDD/TRD: • Not approved in the EU/UK[4]	**Clinical development** **Phase III** • MDD/TRD[5,6] **Phase II** • MDD and suicidal ideation[7]	**Clinical development** **Phase III** • MDD[8,9]	**Clinical development** **Phase II** • MDD/TRD[11–13]

*As acute short-term treatment.
EU, European Union; GABA, gamma-aminobutyric acid; IV, intravenous; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; OAD, oral antidepressant; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TRD, treatment-resistant depression; UK, United Kingdom.

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11. ClinicalTrials.gov. NCT03775200: www.clinicaltrials.gov/ct2/show/NCT03775200 Accessed October 2021;
12. ClinicalTrials.gov. NCT03181529: www.clinicaltrials.gov/ct2/show/NCT03181529. Accessed October 2021;
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Key Summary Points

Transporter Affinity (SERT / NET / DAT)

High SERT Selectivity (Pure SSRIs):

- Escitalopram, Citalopram, Fluoxetine

SERT + NET (SNRIs):

- Duloxetine (balanced), Venlafaxine (dose-dependent), Desvenlafaxine (NET),

Dopaminergic Component:

- Bupropion (+++), Sertraline (++)

Owens et al., J Pharmacol Exp Ther, 1997, 283:1305–1322; Bymaster et al., Neuropsychopharmacology, 2001, 25:871–880; Sanchez et al., Psychopharmacology, 2004, 174:163–176; Mørk et al., J Pharmacol Exp Ther, 2012, 340:666–675; Hiemke et al., Pharmacopsychiatry, 2018, 51:9–62; Millan et al., Nat Rev Drug Discov, 2005, 4:41–54.

Receptor Binding Profile

- **Strong H1 Antagonism (Sedation):**
  Mirtazapine (+++), Trazodone (++), Paroxetine (+)

- **α1 Blockade:**
  Trazodone, Mirtazapine (mild), Duloxetine (mild)

- **M1 Anticholinergic:**
  Paroxetine (moderate)

Owens et al., J Pharmacol Exp Ther, 1997, 283:1305–1322; Bymaster et al., Neuropsychopharmacology, 2001, 25:871–880; Sanchez et al., Psychopharmacology, 2004, 174:163–176; Mørk et al., J Pharmacol Exp Ther, 2012, 340:666–675; Hiemke et al., Pharmacopsychiatry, 2018, 51:9–62; Millan et al., Nat Rev Drug Discov, 2005, 4:41–54.

Activating vs Sedating Antidepressants

- **Energy:**

  Bupropion, Sertraline (higher dose), Fluoxetine, High-dose Venlafaxine, Duloxetine

- **Neutral:**

  Escitalopram, Citalopram

- **Calming/ Sedating :**

  Mirtazapine, Trazodone, Paroxetine

Owens et al., J Pharmacol Exp Ther, 1997, 283:1305–1322; Bymaster et al., Neuropsychopharmacology, 2001, 25:871–880; Sanchez et al., Psychopharmacology, 2004, 174:163–176; Mørk et al., J Pharmacol Exp Ther, 2012, 340:666–675; Hiemke et al., Pharmacopsychiatry, 2018, 51:9–62; Millan et al., Nat Rev Drug Discov, 2005, 4:41–54.

Cognitive-Oriented Pharmacodynamic Clustering

- **Pro-Cognitive:**
  - Bupropion, Vortioxetine, Duloxetine, Sertraline (higher dose)
- **Neutral:**
  - Escitalopram, Sertraline (low dose)
- **Potential Cognitive Blunting:**
  - Paroxetine (anticholinergic), strongly sedating agents

Owens et al., J Pharmacol Exp Ther, 1997, 283:1305–1322; Bymaster et al., Neuropsychopharmacology, 2001, 25:871–880; Sanchez et al., Psychopharmacology, 2004, 174:163–176; Mørk et al., J Pharmacol Exp Ther, 2012, 340:666–675; Hiemke et al., Pharmacopsychiatry, 2018, 51:9–62; Millan et al., Nat Rev Drug Discov, 2005, 4:41–54.

Dopamine-Weighted Ranking (Apathy / Anhedonia)

- Bupropion (+++)
- Duloxetine
- Sertraline (++)
- High-dose Venlafaxine
- Vortioxetine (indirect modulation)

Owens et al., J Pharmacol Exp Ther, 1997, 283:1305–1322; Bymaster et al., Neuropsychopharmacology, 2001, 25:871–880; Sanchez et al., Psychopharmacology, 2004, 174:163–176; Mørk et al., J Pharmacol Exp Ther, 2012, 340:666–675; Hiemke et al., Pharmacopsychiatry, 2018, 51:9–62; Millan et al., Nat Rev Drug Discov, 2005, 4:41–54.

Conclusions

- Depression is prevalent and burdensome
- Acute treatment should target remission and maintenance treatment is often required to maintain the gains and work toward sustained recovery
- To optimise outcomes treatments should be tailored to the individual patients and specific situation/need
- Personalized treatment is key to treatment success

Thank you