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Addressing Unresolved Symptoms of Major Depressive Disorder

A Focus on Norepinephrine

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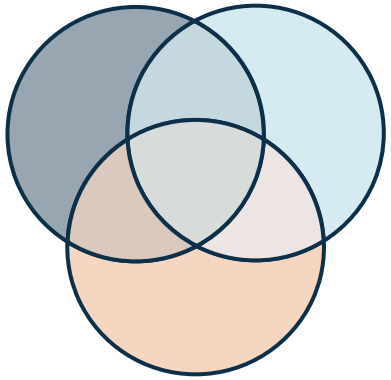
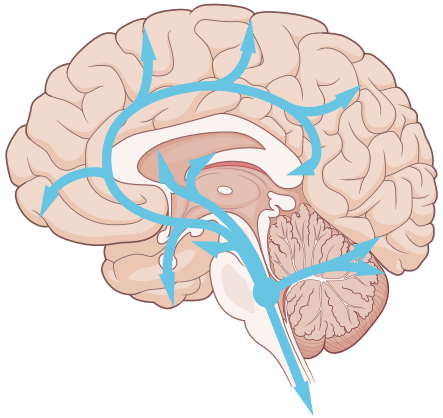
Objectives

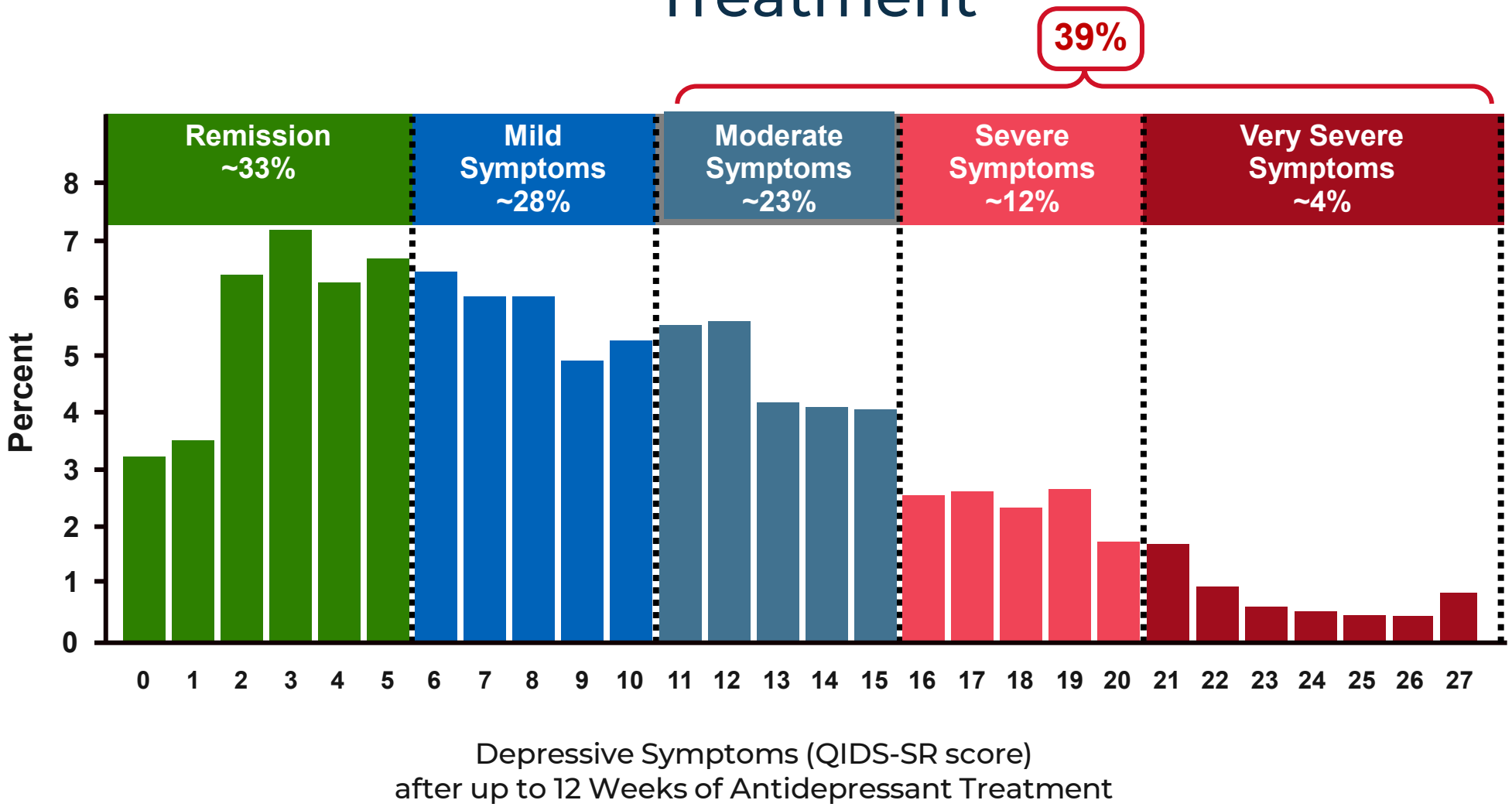


Review common unresolved symptoms of depression after antidepressant treatment, and how several monoamines may be involved



Understand how the noradrenergic system contributes to MDD and how it is an important target for some patients with MDD

STAR*D: Unresolved Symptoms following Antidepressant Treatment



N=2876.
STAR*D = Sequenced Treatment Alternatives to Relieve Depression; QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.

1. Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

Commonly Reported Unresolved Symptoms

Why Do They Matter?

- Some unresolved symptoms are identified as especially disruptive to global functioning[1-4]

Low energy

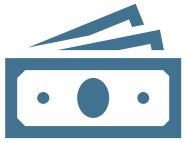
Insomnia

Concentration/ memory problems

- Patients with unresolved symptoms[5]:

More likely to experience a chronic course of illness

Less likely to recover over time



Experience increased psychosocial and socioeconomic impairment[2]

- Some unresolved symptoms are identified as independent predictors of MDD recurrence[2]

Insomnia

Sleep disturbances

Anxiety

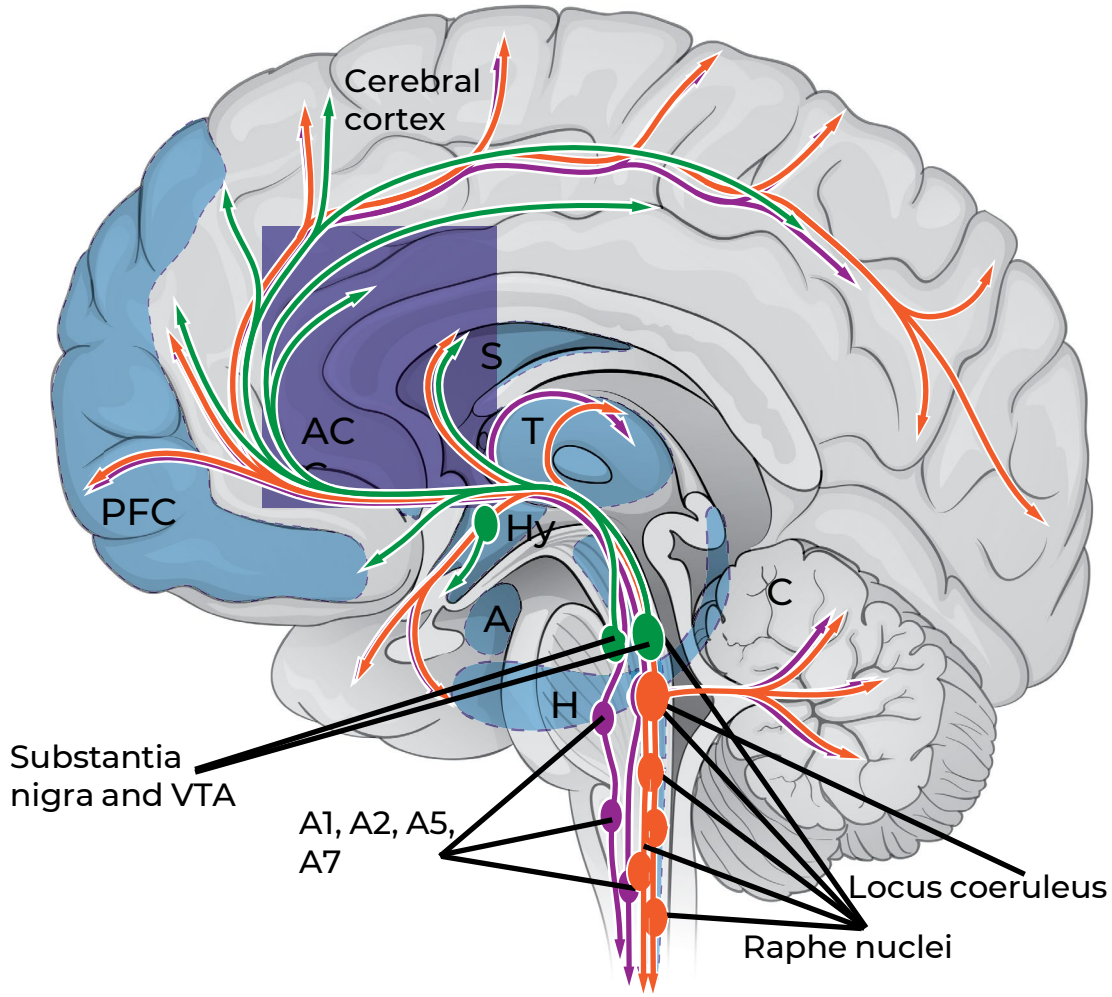
Some Commonly Reported Unresolved Symptoms in patients achieving remission with an SSRI

Symptom	% reporting (n=943)
Anxiety[3,*]	78.2
Sleep disturbances[4]	71.7
Appetite/weight disturbances[4]	35.9
Sad mood[4]	27.1
Hypersomnia[4]	24.0
Energy[4]	22.5
Concentration/decision-making[4]	20.9

*Anxiety data originates from a different study (n=624).

1. Saltiel PF, et al. *Neuropsychiatr Dis Treat.* 2015;11:875-888. 2. Israel JA. *Pharmaceuticals (Basel).* 2010;3(8):2426-2440. 3. Romera I, et al. *BMC Psychiatry.* 2013;13:51. 4. Nierenberg AA, et al. *Psychol Med.* 2010;40(1):41-50.
5. Jackson WC, et al. *J Clin Psychiatry.* 2020;81(3):OT19037BR2.

Monoamine Pathways Overlap In Several Areas Of The Brain[1-8]



Serotonin

Dopamine

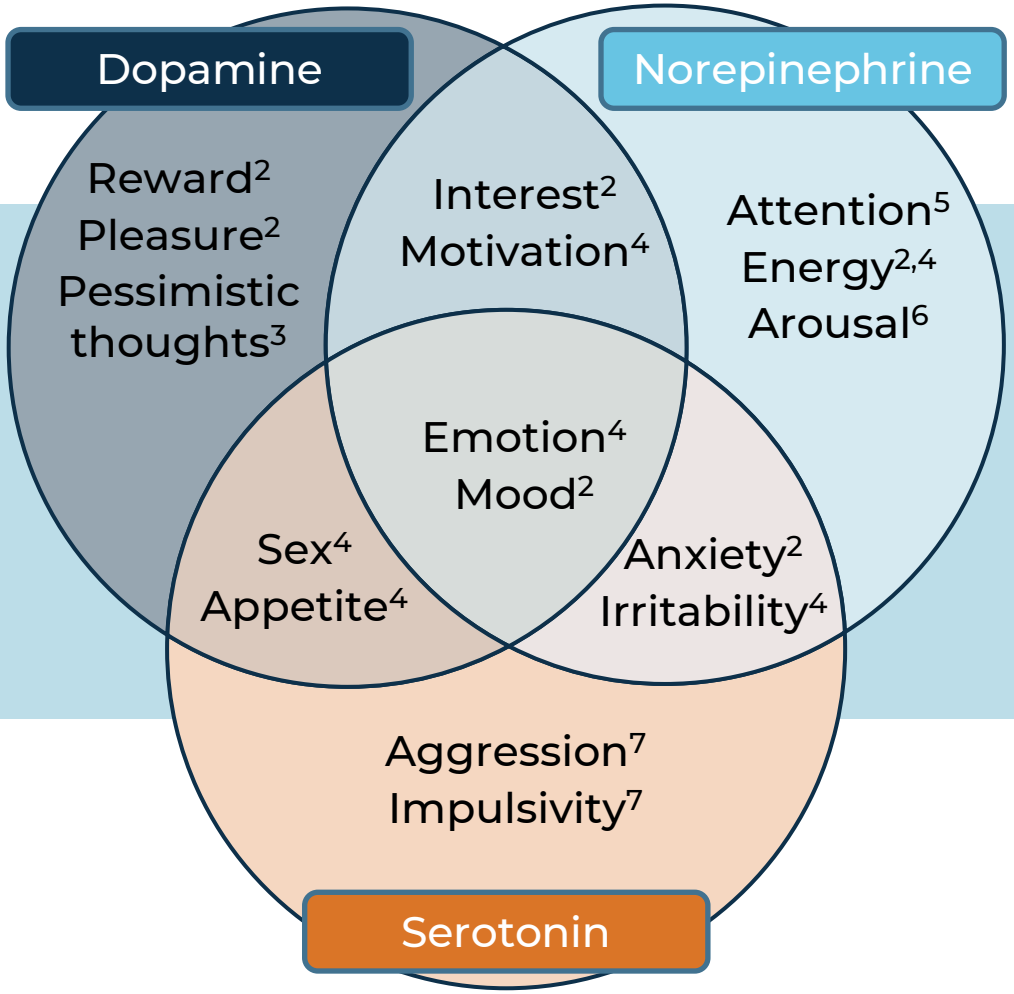
Norepinephrine

A = Amygdala; ACC = Anterior Cingulate Cortex; C = Cerebellum;
H = Hippocampus;
Hy = Hypothalamus; NA = Nucleus Accumbens; PFC = Prefrontal Cortex;
S = Striatum; T = Thalamus;
VTA = Ventral Tegmental Area

1. Fuchs and Flugge *Dialogues Clin Neurosci.* 2004;6(2):171-183.
2. Stahl Chapter 7. In: Stahl SM, ed. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application.* 4th ed; 2013:284-369
3. Jacobs and Azmitia. *Physiol Rev.* 1992;72(1):165-229.
4. Abercrombie et al. *J Neurochem.* 1989;52(5):1655-1658.
5. Stanford *Pharmacol Ther.* 1995;68(2):297-242.
6. Meana et al. *Biol Psychiatry.* 1992;31:471-490.
7. Garcia-Sevilla et al. *J Neurochem.* 1999;72(1):282-291.
8. Roiser and Sahakian *CNS Spectr.* 2013;18(3):139-149.

Pathophysiology of MDD:

The Monoamine Model (Dopamine, Serotonin, and Norepinephrine)

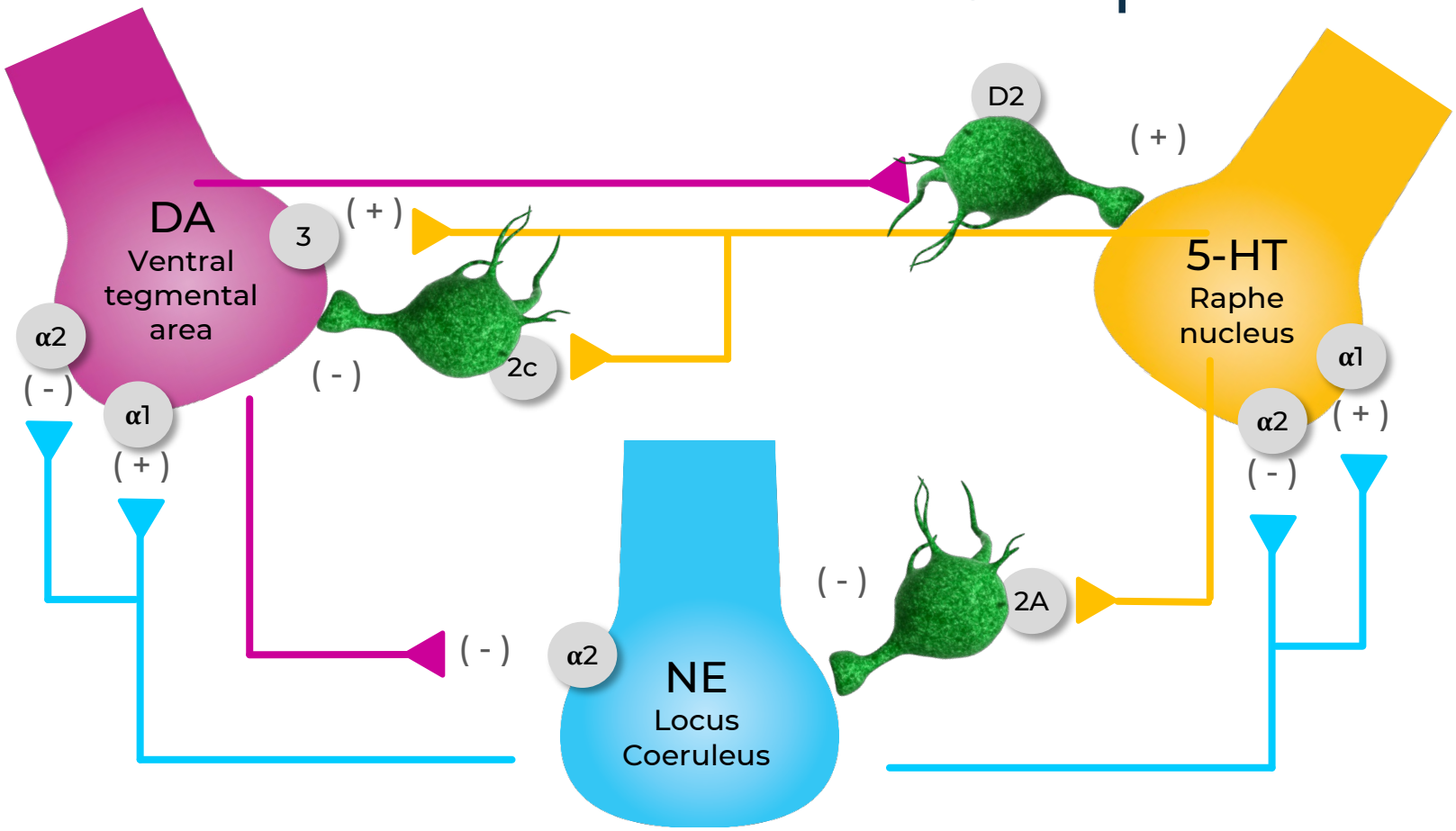


These monoamines are intrinsically linked to each other through a wide variety of mechanisms[1]

Dysfunction of one monoamine system can cause dysregulation of the others[1,7,8]

1. Azizi SA. *Neuroscientist*. 2022;28(2):121-143. 2. Nutt DJ. *J Clin Psychiatry*. 2008; 69(Suppl E1):4-7. 3. Sharot T, et al. *Curr Biol*. 2012;22(16):1477-1481. 4. Zajecka J, et al. *J Clin Psychiatry*. 2013;74(4):407-414.
5. Kuo HI, et al. *Int J Neuropsychopharmacol*. 2021;24(6):490-498. 6. España RA, et al. *Brain Res*. 2016;1641(Pt B):207-216. 7. Seo D, et al. *Aggress Violent Behav*. 2008;13(5):383-395. 8. Blier P. *J Psychiatry Neurosci*. 2001;26(Suppl):S3-S10.

Functional Interactions Among Neurotransmitters Are Complex



Impact on neuronal firing:	DA	NE	5-HT
DA		-	+
NE	+ or -		+ or -
5-HT	+ or -	-	

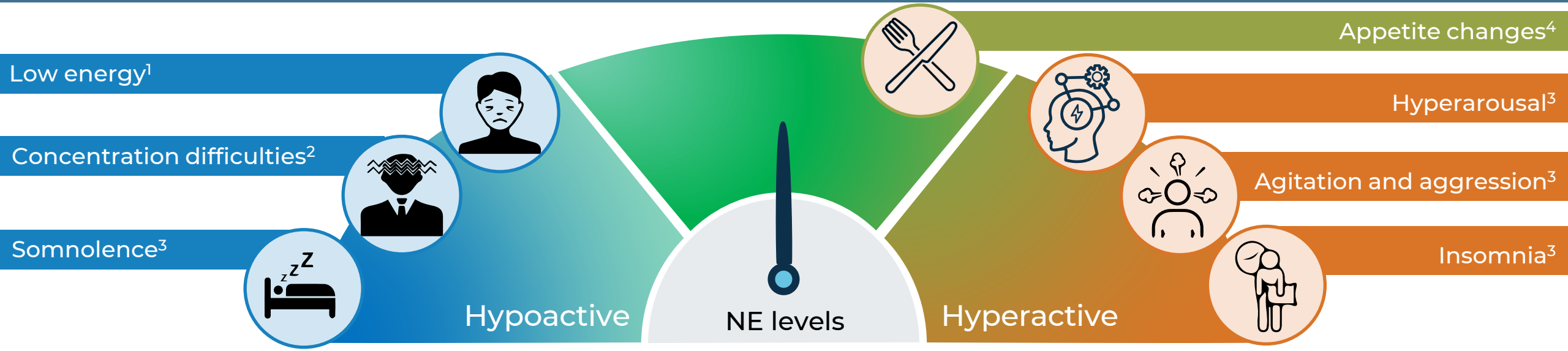
Alterations in the signaling of 1 neurotransmitter can affect the activity of the other neurotransmitter systems[5]

5-HT=serotonin; DA=dopamine; LC=locus coeruleus; NE=norepinephrine; RN=raphe nuclei; VTA=ventral tegmental area.

Adapted from:
1. Guiard BP et al. *Int J Neuropsychopharmacol.* 2008;11(5):625-639. 2. Boureau YL, Dayan P. *Neuropsychopharmacology.* 2011;36(1):74-97. 3. Mongeau R et al. *Brain Res Brain Res Rev.* 1997;23(3):145-195. 4. Inyushin MU et al. *Neuroscience.* 2010;167(2):287-297. 5. El Mansari M et al. *CNS Neurosci Ther.* 2010; 16:e1-e17. 6 Kennedy SH et al. *J Affect Disord.* 2011;132(Suppl 1):S21-S23. 7. Trivedi MH et al. *J Clin Psychiatry.* 2008;69(2):246-258.

Norepinephrine (NE):
A Component of the Monoamine Profile

Dysregulation of the noradrenergic system is associated with MDD[1-3]



Some MDD symptoms are thought to be related to hypoactivity of the NE system[1,2]

Some MDD symptoms are thought to be related to hyperactivity and overactivation of the NE system[3,4]

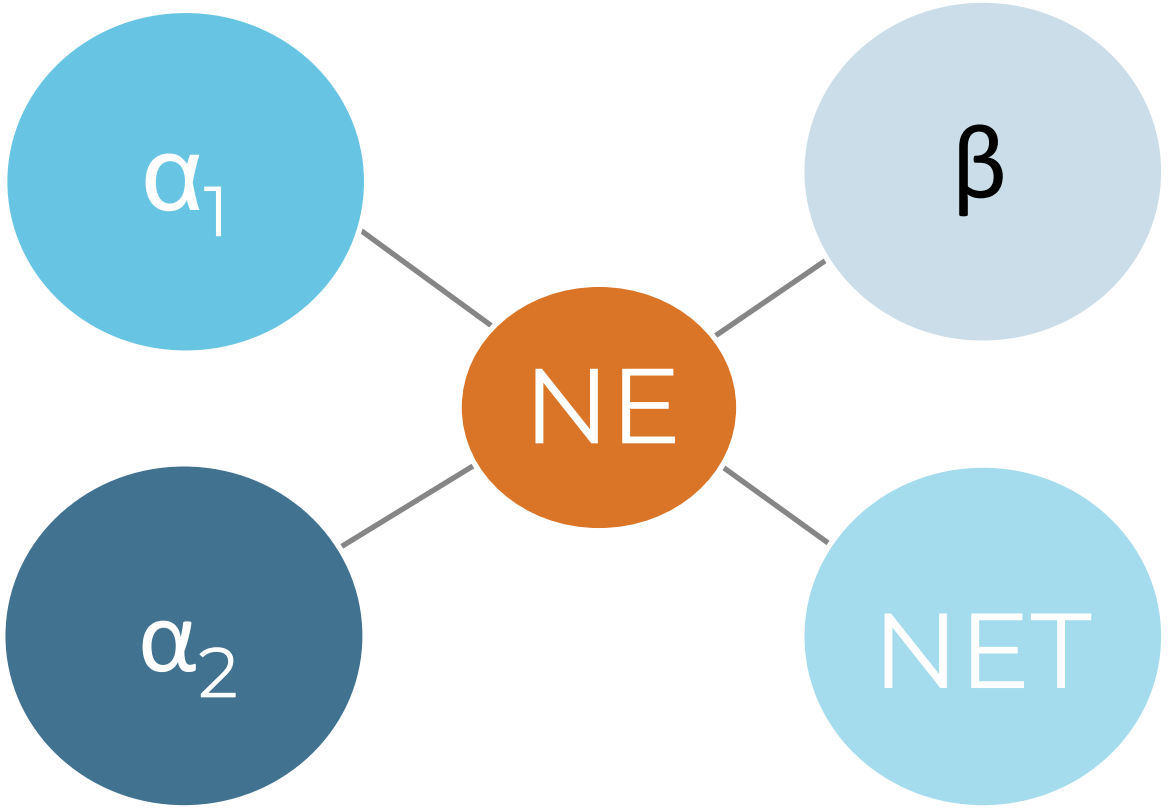
Modulation of NE systems may provide relief from these depressive symptoms

There are individual differences in the expression of different symptoms in MDD; in this pictorial depiction of the monoamine model, the position on the scale here does not signify severity of symptoms

1. Nutt DJ. *J Clin Psychiatry*. 2008;69 Suppl E1:4-7.
2. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(Suppl 1):9-13.
3. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.
4. Zajecka J, et al. *J Clin Psychiatry*. 2013;74(4):407-414.

Localization of Norepinephrine Receptors in the Brain

$\alpha_{1A/D}$- Cortex[1]
α_{1B}- Ubiquitous[1]
α_{1C}- Cortex & Cerebellum[1]



β_1- Ubiquitous[2]
β_2- hippocampus, thalamus, & cerebellum[2]

α_{2A}- Ubiquitous & high in LC[3]
α_{2B}- thalamus[3]
α_{2C}- Cortex, basal ganglia, olfactory tubercle, & hippocampus[3]

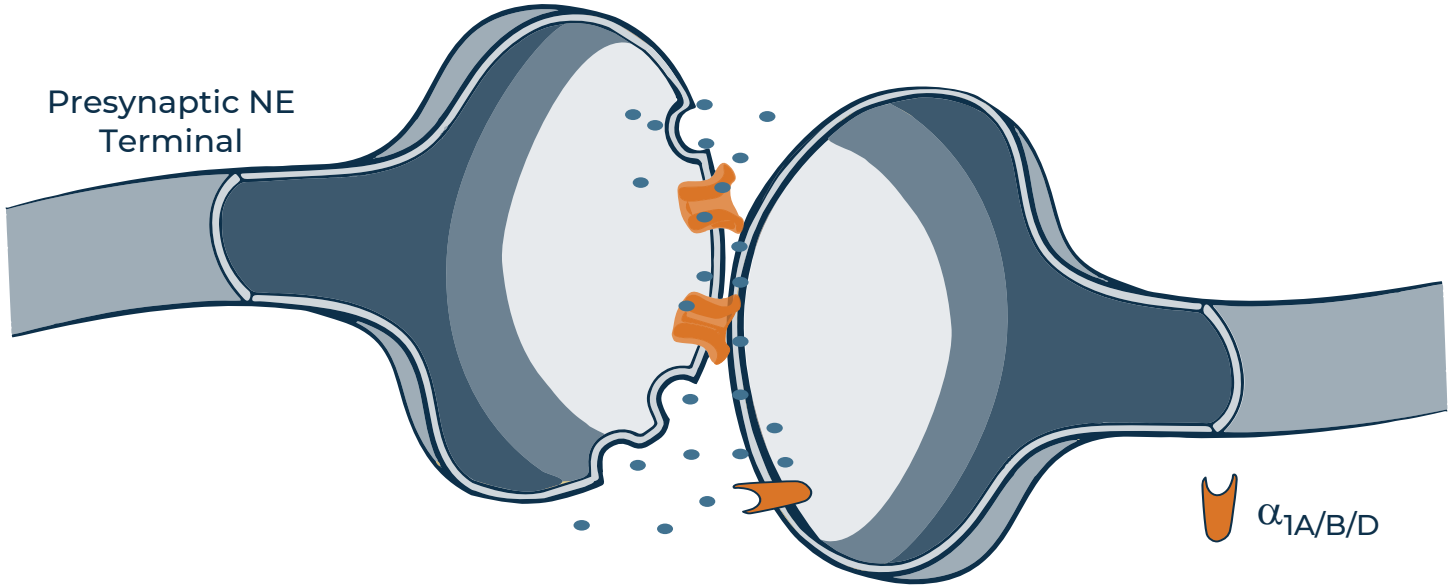
LC, cortex, cerebellum, thalamus, caudate & putamen[4]

1. Price et al. *Mol Pharmacol.* 1994;45(2):171-175.
2. Nicholas et al. *Neuroscience.* 1993;56(4):1023-1039.
3. Saunders et al. *Pharmacol Ther.* 1999;84(2):193-205.
4. Schou et al. *Eur Neuropsychopharmacol.* 2005;15(5):517-520.

NE = norepinephrine; NET = norepinephrine transporter

NE Receptors in MDD:
α_1-Receptors (α_{1A}, α_{1B}, and α_{1D})

- Activated at high NE concentrations
- α_1 receptors are located mainly postsynaptically



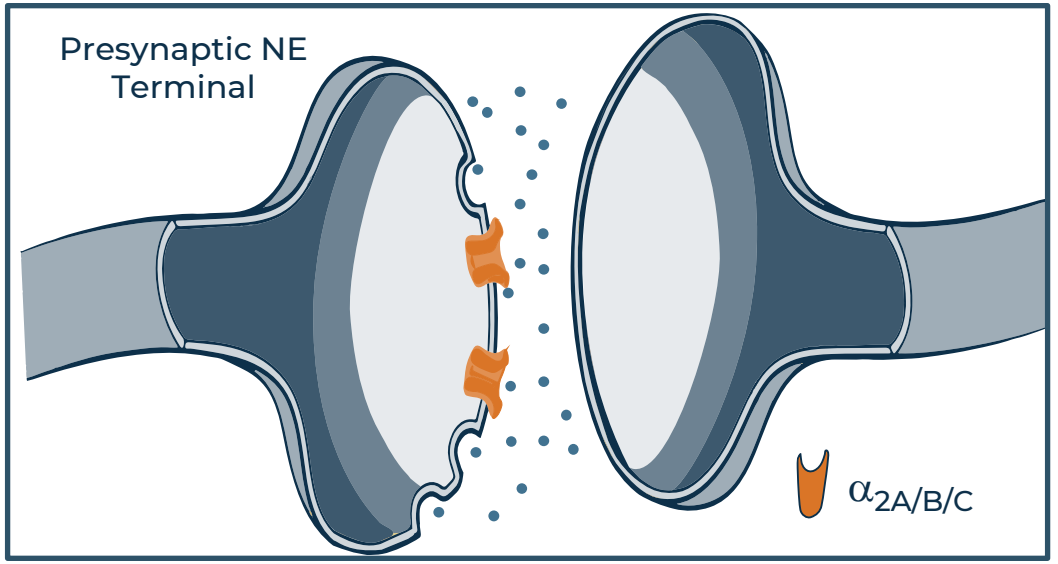
Receptor Type			Clinical Significance
α	α_1	α_{1A}	Antagonists increase and agonists decrease depressive behavior[2,5]
		α_{1B}	Antagonism is associated with improvement in irritability; transgenic mice with overactive α_{1B}receptors exhibit depressive behavior[2]
		α_{1D}	Low expression in the brain[1]

PLC: phospholipase C; DAG: diacylglycerol; IP_3: inositol triphosphate; Ca^{2+}: calcium; PKC: protein kinase C; GPCR: g-protein coupled receptor

1. Hussain LS, et al. StatPearls Publishing; 2022. Accessed December 7, 2022. https://www.ncbi.nlm.nih.gov/books/NBK540977.
2. Maletic V, et al. Front Psychiatry. 2017;8:42.
3. Asnis GM, et al. *Psychiatry Res*. 1992;44(3):237-250.
4. Doze VA, et al. *Brain Res*. 2009;1285:148-157.
5. Handley, SL, et al. Naunyn Schmiedebergs Arch Pharmacol. 1984;327(1):1-5.

NE Receptors in MDD:
α_2-Receptors (α_{2A}, α_{2B}, and α_{2C})

- Highest NE binding affinity of NE receptors[1]
  - Activated at low NE concentrations[1]
  - Located both presynaptically and postsynaptically[1,2]



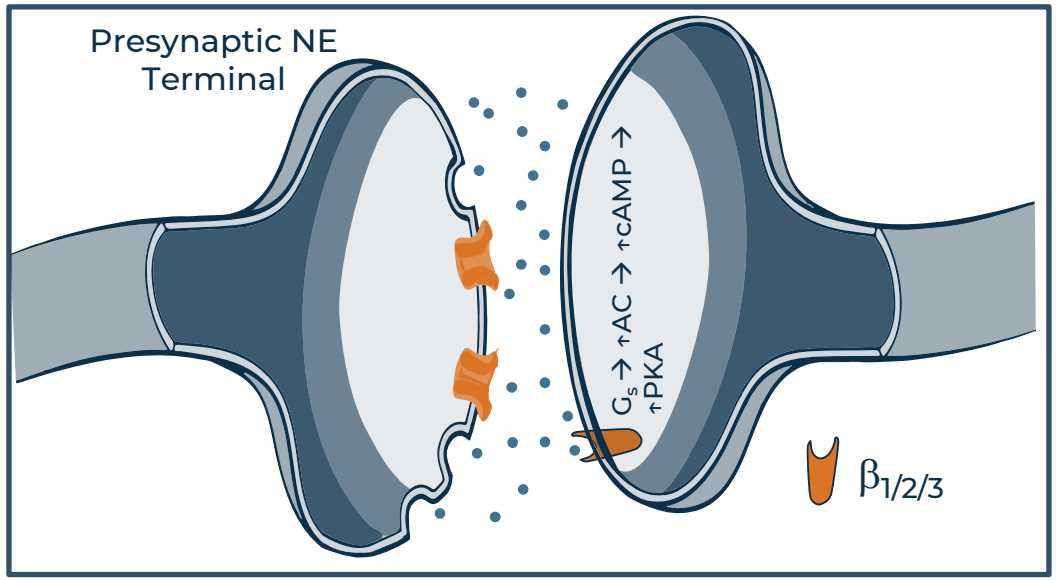
Receptor Type			Clinical Significance
α	α_2	α_{2A}	Can be expressed in pre- or postsynaptic compartments[4] and plays a protective role in depression[6]; antagonists have an antidepressant role[8]
		α_{2B}	Low expression in the brain[9]
		α_{2C}	Mediated stress susceptibility[6]; antagonists or partial agonists have antidepressant actions[10] and improve cognitive problems, insomnia, or low energy in MDD[11]

AC: adenylyl cyclase: cAMP: cyclic adenosine monophosphate; PKA: protein kinase A

1. Hussain LS, et al. StatPearls Publishing; 2022. Accessed December 7, 2022. https://www.ncbi.nlm.nih.gov/books/NBK540977 2. Maletic V, et al. *Front Psychiatry*. 2017;8:42. 3. Correll CU. *Eur Psychiatry*. 2010;25 Suppl 2:S12-S21. 4. Ordway GA, et al. *Biol Psychiatry*. 2003;53(4):315-323. 5. Cottingham C, et al. *Neurosci Biobehav Rev*. 2012;36(10):2214-2225. 6.Schramm NL, et al. *J Neurosci*. 2001;21(13):4875-4882. 7. Weiss JM, et al. Neuropharmacology. 1986;25(4):367-384. 8. Dwyer JM, et al. *Int J Neuropsychopharmacol*. 2010;13(9):1193-1205. 9. Uys MM, et al. *Front Psychiatry*. 2017;8:144. 10. Goddard AW, et al. *Depress Anxiety*. 2010;27(4):339-350. 11. Stone EA, et al. *Biol Psychiatry*. 1999;46(9):1287-1300.

NE Receptors in MDD:
β-Receptors (β_1, β_2, and β_3)

- Lowest binding affinity to NE[1]
  - Activated by high concentrations of NE[3]
- Predominantly produces postsynaptic excitatory effects[3]
  - Coupled to G_s[3]

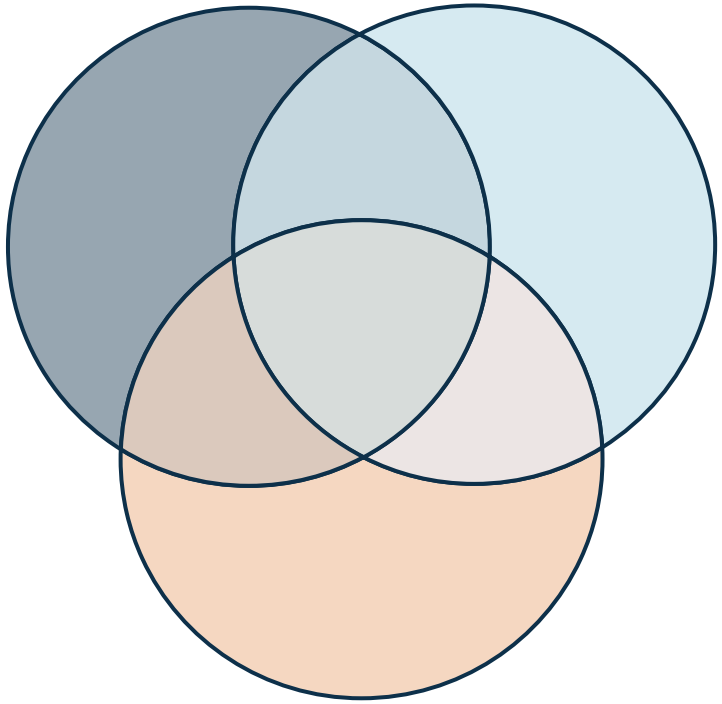


Receptor Type		Clinical Significance
β	β_1	May play a role in regulating symptoms of depression and anxiety[5-7]
	β_2	Expression in adipose tissue may be involved in depression[5,8]
	β_3	Involved in mediating stress resilience,[1] agonists produce anxiolytic and antidepressant effects[2]

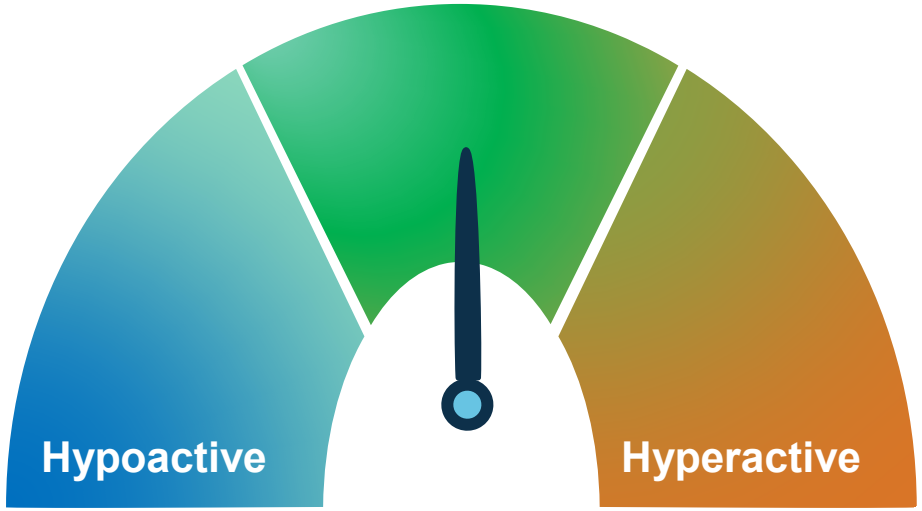
1. Hussain LS, et al. *StatPearls Publishing*; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK540977/. 2
2. Maletic V, et al. *Front Psychiatry*. 2017;8:42.
3. Fu A, et al. *Brain Res*. 2008;1211:85-92.
4. Silberman, Y.; et al. J. Pharmacol. Exp. Ther. 2012, 343, 451–459.
5. Liu S, et al. *Nat Commun*. 2021;12(1):6937.
6. Zhang H, et al. *Biomedicines*. 2022;10(10):2378.
7. Sun X, et al. *Behav Brain Res*. 2021;412:113417.

Effective Therapies Should Theoretically
Increase Monoamine Activity While Avoiding Overactivation

Target MDD-related monoamines



Modulate monoamine levels

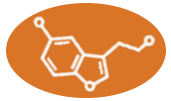


Increasing monoamine levels through pharmacology may alleviate symptoms of hypoactivity in some patients with MDD

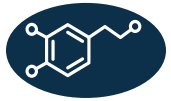
The potential overactivation of monoamine systems with pharmacological interventions should be considered

*This slide is intended as a summary of the previous section with the concept of the monoamine gauge included for illustrative purposes only.

Summary



5-HT



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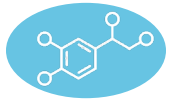
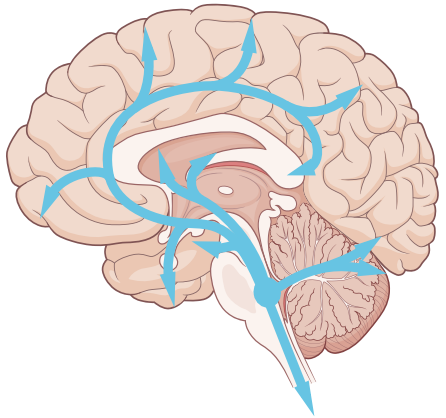


NE

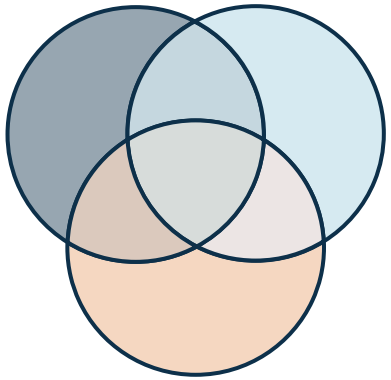
Different symptoms of MDD are associated with dysfunction of specific monoamines

Treatments could benefit by targeting 3 of the MDD-related monoamines



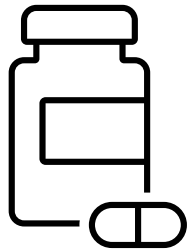
Symptoms of MDD may be related to hypo- or hyperactive NE systems

Modulation of α_2 receptors may help regulate NE levels in appropriate ranges



First-line treatments only target 1 or 2 of the monoamines involved in MDD

First-line treatments are ineffective in many people, leaving unresolved symptoms



Tune in for future discussions on treatment options to address unresolved symptoms of depression

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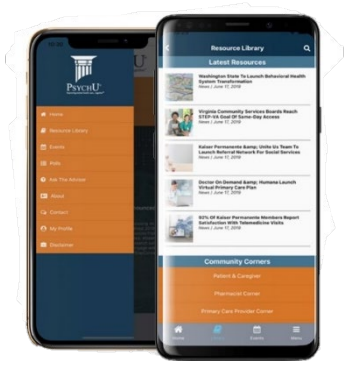

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