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Monoaminergic Dysregulation in MDD: A Closer Look at Noradrenaline

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This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) and Lundbeck, LLC.

Speakers are paid consultants for Otsuka Pharmaceutical Development & Commercialization, Inc.

Objectives

Understand how the dysregulation of the noradrenergic system contributes to the heterogeneous presentation of MDD symptoms

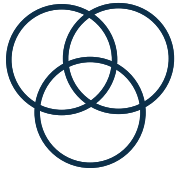
1

Understand why, in addition to serotonin (5-HT) and dopamine (DA), noradrenaline (NA) dysregulation may also contribute to unresolved symptoms in MDD

2

Discuss the role of adrenoreceptors (ARs) on neuronal activity and how ARs can help modulate symptoms caused by noradrenergic system dysfunction

3



Learn how adjunctive atypical antipsychotics (AAPs) may address MDD symptoms by modulating dysregulation of the NA system, in addition to DA and 5-HT

4

Polling Question

How familiar are you with monoaminergic dysregulation in MDD?

A. Not at all familiar

B. Somewhat familiar

C. Familiar

D. Very familiar

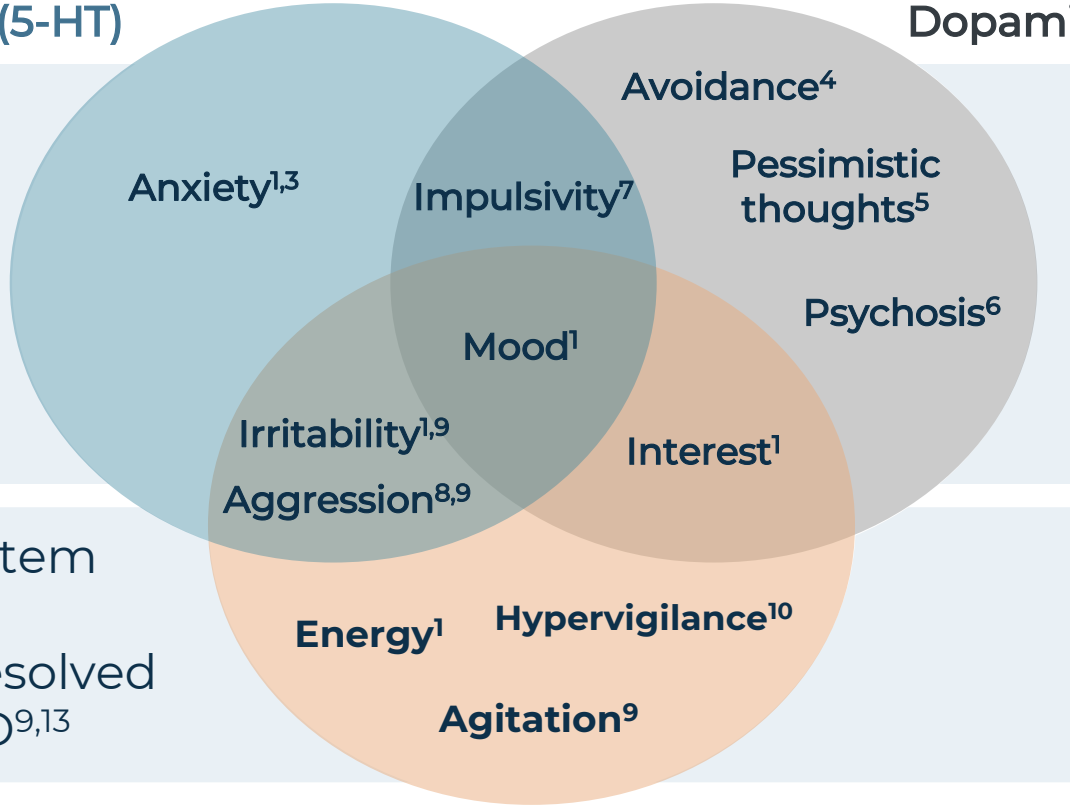
E. Extremely familiar

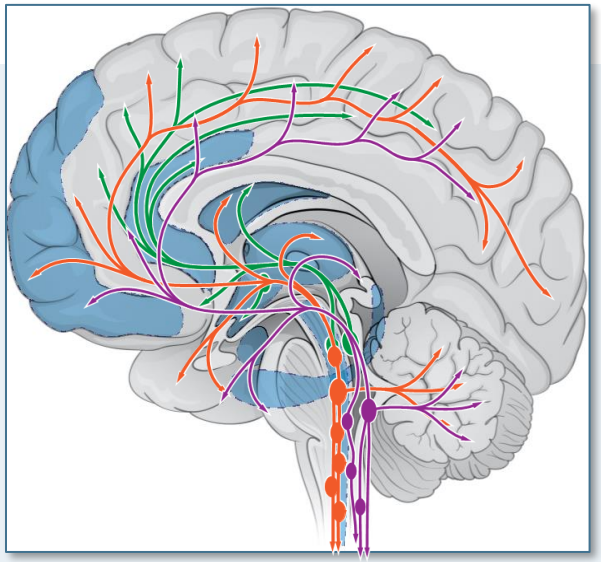
MDD=major depressive disorder.

Psychiatric Symptoms Associated With Monoamine Neurotransmitter System Dysfunction

The serotonergic & dopaminergic systems have established roles in psychiatric conditions[1,2]

Noradrenergic system dysfunction may contribute to unresolved symptoms of MDD[9,13]



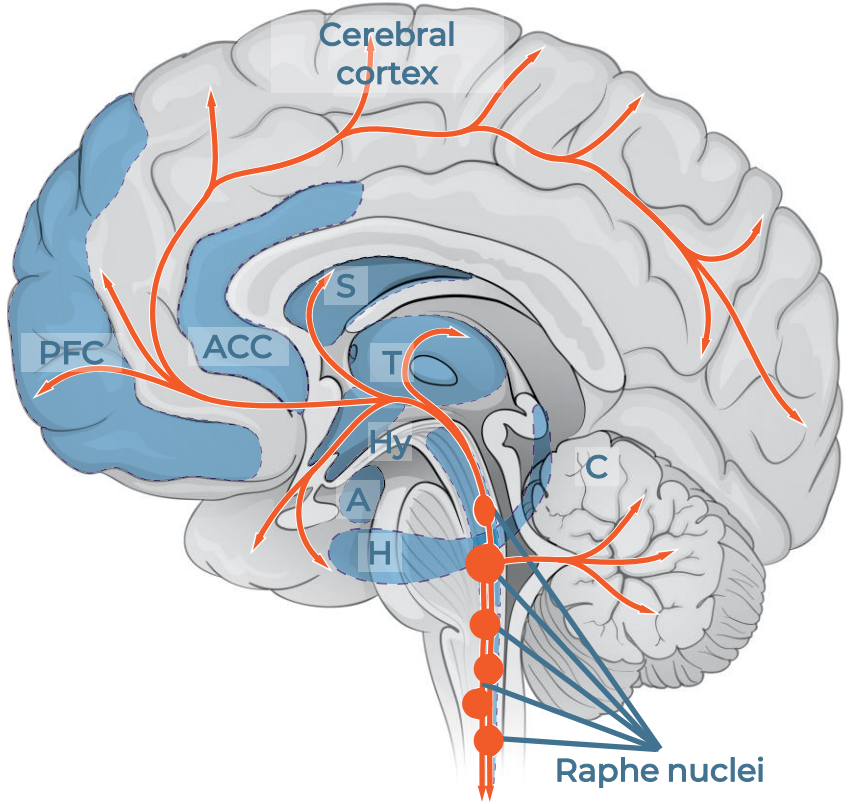


Monoamine neurotransmitter systems have overlapping projections throughout the brain, and individual behaviors can be modulated by multiple systems.[1,11] Preclinical studies indicate that NA, 5-HT, and DA can modulate one another's activity.[12] This diagram depicts areas of mental health in which these systems have been identified as playing key roles.

1. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
2. Belujon P, et al. *Int J Neuropsychopharmacol*. 2017;20(12):1036-1046.
3. Albert PR, et al. *Front Behav Neurosci*. 2014;8:199.
4. Torrisi SA, et al. *Front Pharmacol*. 2019;10:404.
5. Sharot T, et al. *Curr Biol*. 2012;22(16):1477-1481.
6. Stahl SM. 5th ed. Cambridge University Press; 2021.
7. Dalley JW, et al. *Neuroscience*. 2012;215:42-58.
8. Seo D, et al. *Aggress Violent Behav*. 2008;13(5):383-395.
9. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20
10. Arnsten AF, et al. *Neurobiol Stress*. 2015;1:89-99.
11. Fuchs E, et al. *Dialogues Clin Neurosci*. 2004;6(2):171-183.
12. El Mansari M, et al. *CNS Neurosci Ther*. 2010;16(3):e1-e17
13. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9-13.

Serotonergic System Dysfunction

Circuitry[1,2]



Anxiety[4,6]

Mood[4]

Impulsivity[7]

Irritability[4]

Aggression[8]

Serotonergic Receptors[5,a]

5-HT$_{1A}$/1B/1D/1E/1F **5-HT$_{2A}$**/2C

5-HT$_3$ 5-HT$_4$ 5-HT$_5$ 5-HT$_6$ **5-HT$_7$**

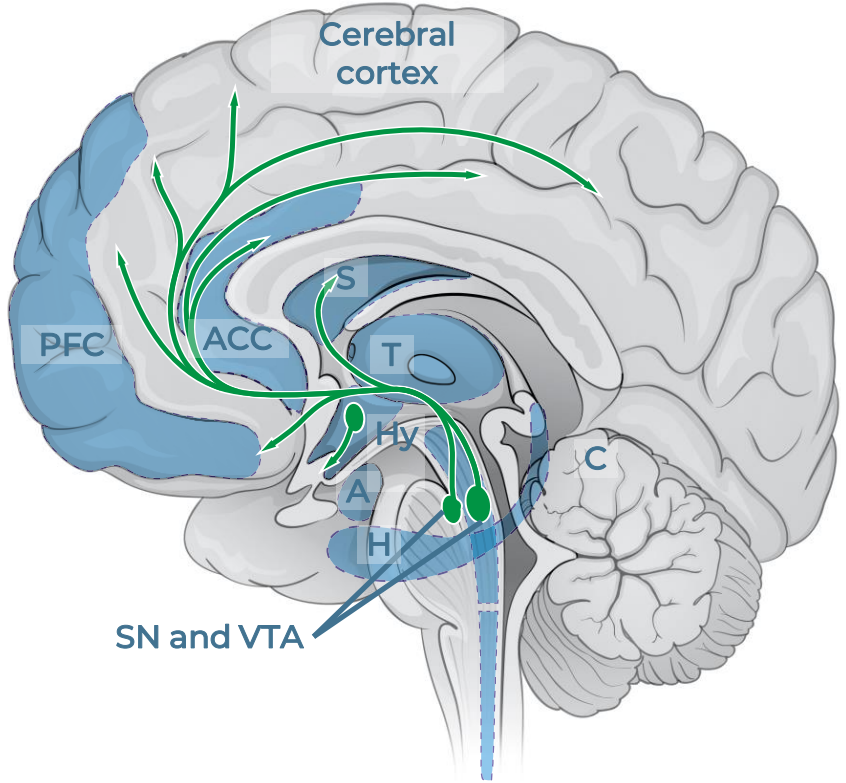
[a]The highlighted receptors have been identified as potentially playing key roles in psychiatric symptoms.[5,9]

A=amygdala. ACC=anterior cingulate cortex. C=cerebellum. H=hippocampus. Hy=hypothalamus. PFC=prefrontal cortex. S=striatum. T=thalamus.

1. Fuchs E, et al. *Dialogues Clin Neurosci*. 2004;6(2):171-183.
2. Levinson S, et al. *Front Neuroimaging*. 2023;1:1009399.
3. Maejima T, et al. *Front Integr Neurosci*. 2013;7:40.
4. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
5. Barnes NM, et al. *Pharmacol Rev*. 2021;73(1):310-520.
6. Albert PR, et al. *Front Behav Neurosci*. 2014;8:199.
7. Dalley JW, et al. *Neuroscience*. 2012;215:42-58.
8. Seo D, et al. *Aggress Violent Behav*. 2008;13(5):383-395.
9. Okubo R, et al. *Front Psychiatry*. 2021;12:623684.

Dopaminergic System Dysfunction

Circuitry[1,2]



Dopaminergic Receptors[4,a]

D_1 D_5 **D_2** **D_3** D_4

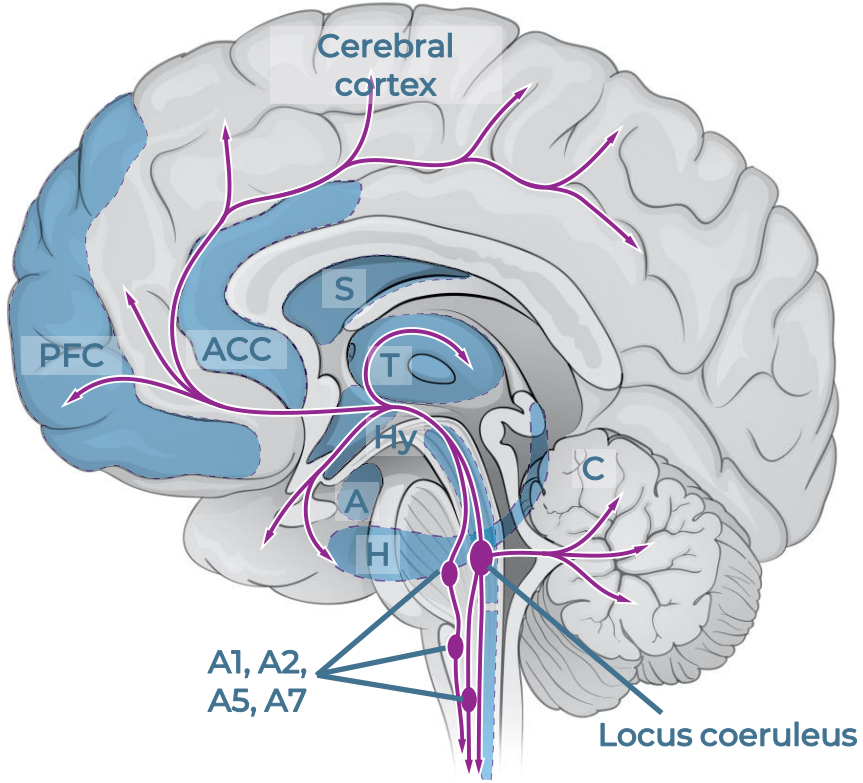
[a]The highlighted receptors have been identified as potentially playing key roles in psychiatric symptoms.[4,7,9]

A=amygdala. ACC=anterior cingulate cortex. C=cerebellum. H=hippocampus. Hy=hypothalamus. PFC=prefrontal cortex. S=striatum. SN=substantia nigra. T=thalamus. VTA=ventral tegmental area.

1. Fuchs E, et al. *Dialogues Clin Neurosci*. 2004;6(2):171-183.
2. Levinson S, et al. *Front Neuroimaging*. 2023;1:1009399.
3. Torrisi SA, et al. *Front Pharmacol*. 2019;10:404.
4. Zhao F, et al. *Front Pharmacol*. 2022;13:947785.
5. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
6. Sharot T, et al. *Curr Biol*. 2012;22(16):1477-1481.
7. Stahl SM. 5th ed. Cambridge University Press; 2021.
8. Dalley JW, et al. *Neuroscience*. 2012;215:42-58.
9. Frankel JS, et al. *Ther Adv Psychopharmacol*. 2017;7(1):29-41.

Noradrenergic System Dysfunction

Circuitry[1,2]




Low energy[3]


Depressed mood[3]


Interest[3]


Hypervigilance[3]


Irritability[3]


Agitation and aggression[3]

Adrenergic Receptors[4,a]

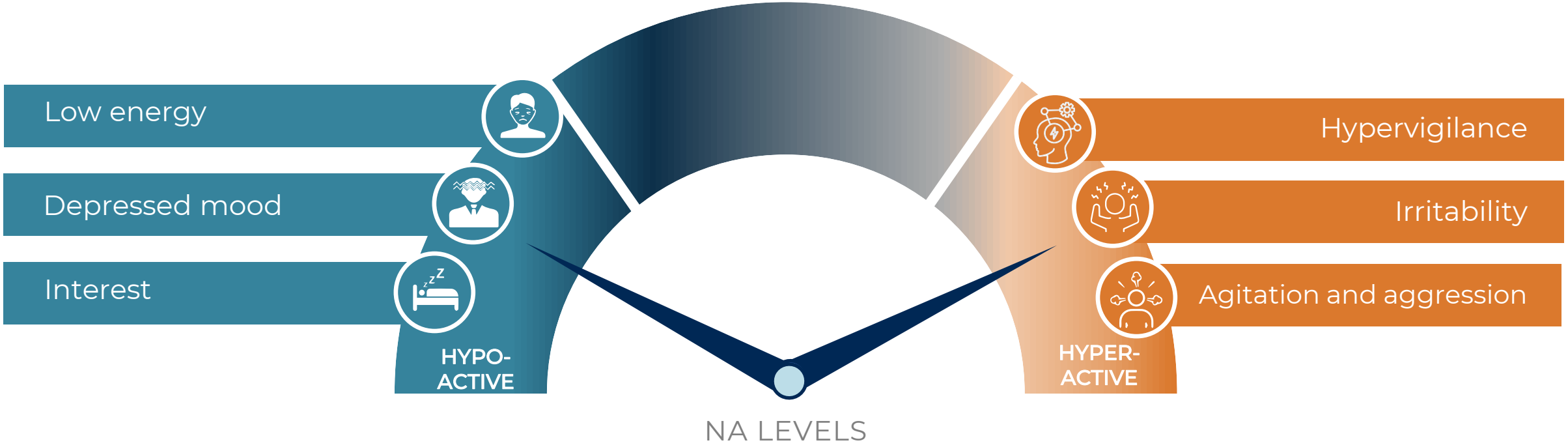
α_{1A} **α_{1B}** α_{1D} α_{2A} α_{2B} **α_{2C}** β_1 β_2 β_3

[a]The highlighted receptors have been identified as potentially playing key roles in psychiatric symptoms.[4]

A=amygdala. ACC=anterior cingulate cortex. C=cerebellum. H=hippocampus. Hy=hypothalamus. PFC=prefrontal cortex. S=striatum. SN=substantia nigra. T=thalamus. VTA=ventral tegmental area.

1. Fuchs E, et al. *Dialogues Clin Neurosci*. 2004;6(2):171-183.
2. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
3. Jain R, et al. *J Clin Psychiatry*. 2024;85(4):plunaro2471ah.
4. Maletic V, et al. *Front Psychiatry*. 2017;8:42.

Dysregulation of the Noradrenergic System Is Associated With a Wide Array of Psychiatric Symptoms



Adrenoceptors (ARs) can modulate symptoms caused by noradrenergic system dysregulation

NA=noradrenaline.

1. Jain R, et al. *J Clin Psychiatry*. 2024;85(4):plunaro2417ah.

Polling Question

How likely are you to consider prescribing treatment options that modulate norepinephrine to patients with unresolved symptoms?

A Never

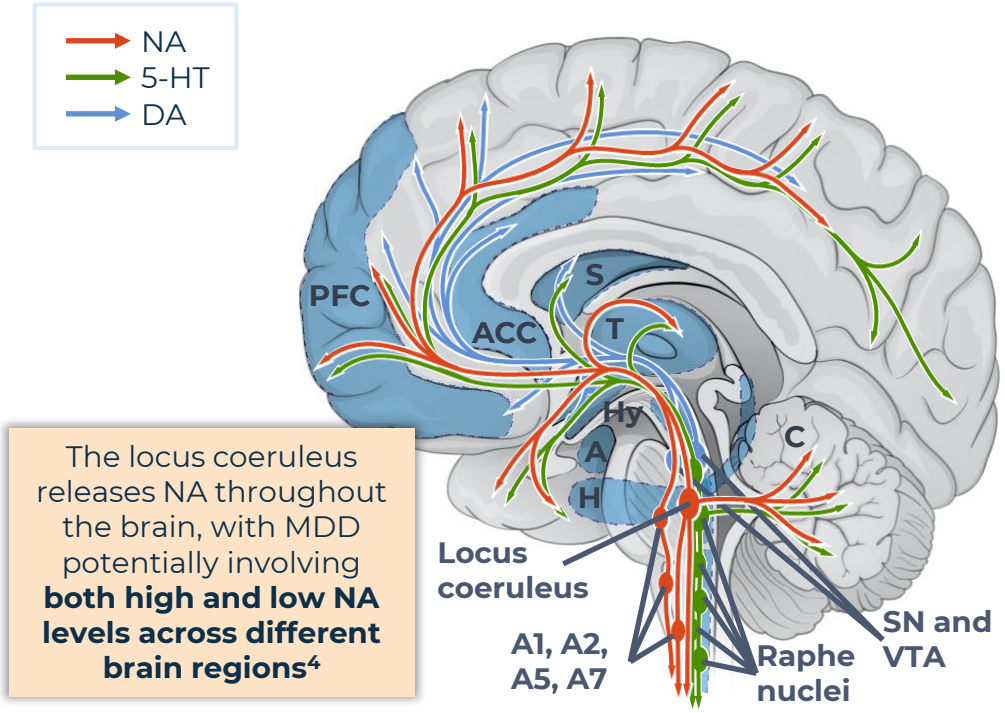
B Rarely

C Sometimes

D Often

E Always

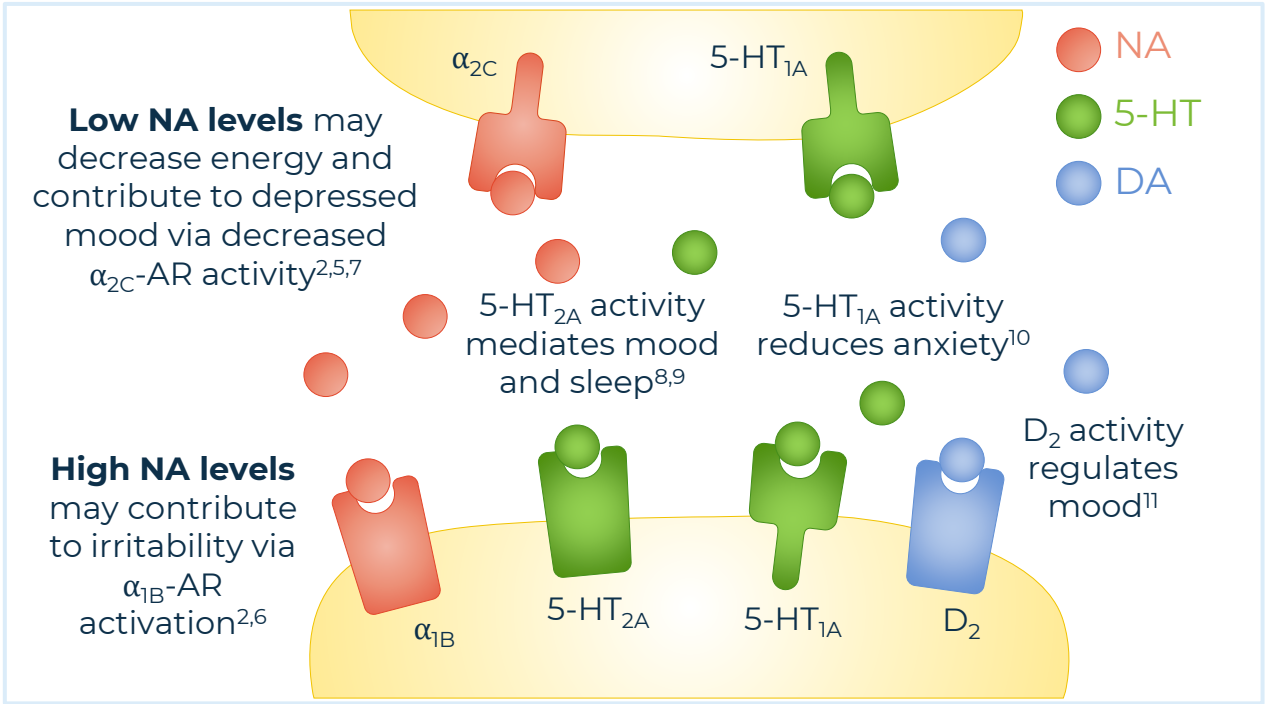
MDD Is Thought to Involve Dysregulated NA Activity As Well As 5-HT and DA System Deficits[1,2]



The locus coeruleus releases NA throughout the brain, with MDD potentially involving **both high and low NA levels across different brain regions[4]**

Several current treatments for MDD target overall NA levels or α-ARs[3,4]

Symptoms of MDD may be influenced by NA activity through α-ARs, as well as by 5-HT and DA receptors[4,5]



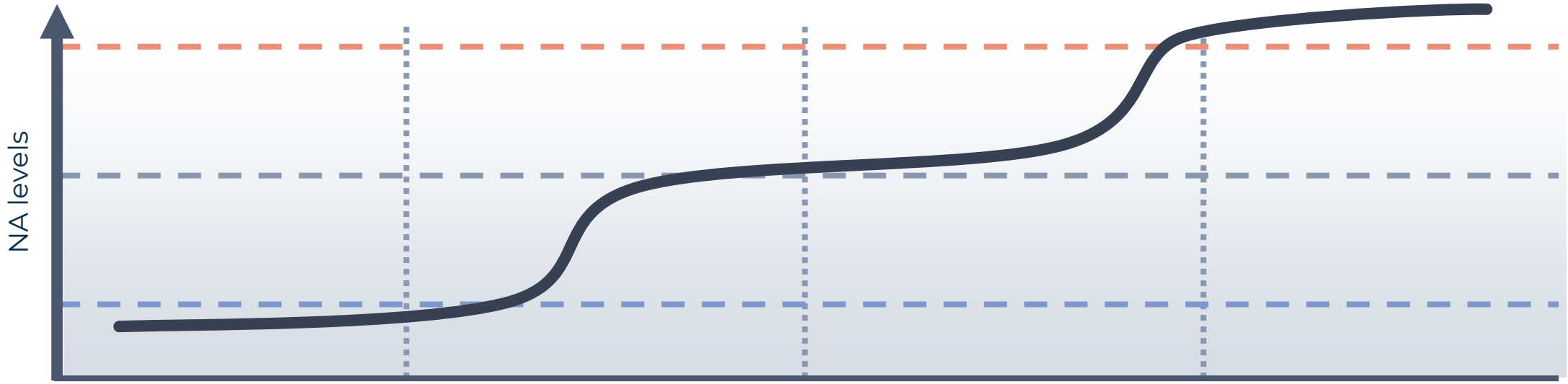
A=amygdala. ACC, anterior cingulate cortex. C=cerebellum. H=hippocampus. Hy=hypothalamus. MDD=major depressive disorder. PFC=prefrontal cortex. S=striatum. SN=substantia nigra. T=thalamus. VTA=ventral tegmental area.

1. Delgado PL. *J Clin Psychiatry*. 2006;67 Suppl 4:22-26.
2. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.
3. Montoya A, et al. *Neuropsychiatr Dis Treat*. 2016;12:541-557.
4. Maletic V, et al. *Front Psychiatry*. 2017;8:42.
5. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
6. Miller CWT, et al. *West J Emerg Med*. 2020;21(4):841-848.
7. Uys MM, et al. *Front Psychiatry*. 2017;8:144.
8. 8. Barnes NM, et al. *Pharmacol Rev*. 2021;73(1):310-520.
9. Vanover KE, et al. *Nat Sci Sleep*. 2010;2:139-150.
10. Akimova E, et al. *Biol Psychiatry*. 2009;66(7):627-635.
11. Zhao F, et al. *Front Pharmacol*. 2022;13:947785

Noradrenaline Levels Play a Major Role in Regulating Behavior States

Noradrenaline (NA) is one of the major monoamines and regulates wakefulness, energy levels, attention, and behaviors related to agitation, irritability, aggression, and fear[1-3]

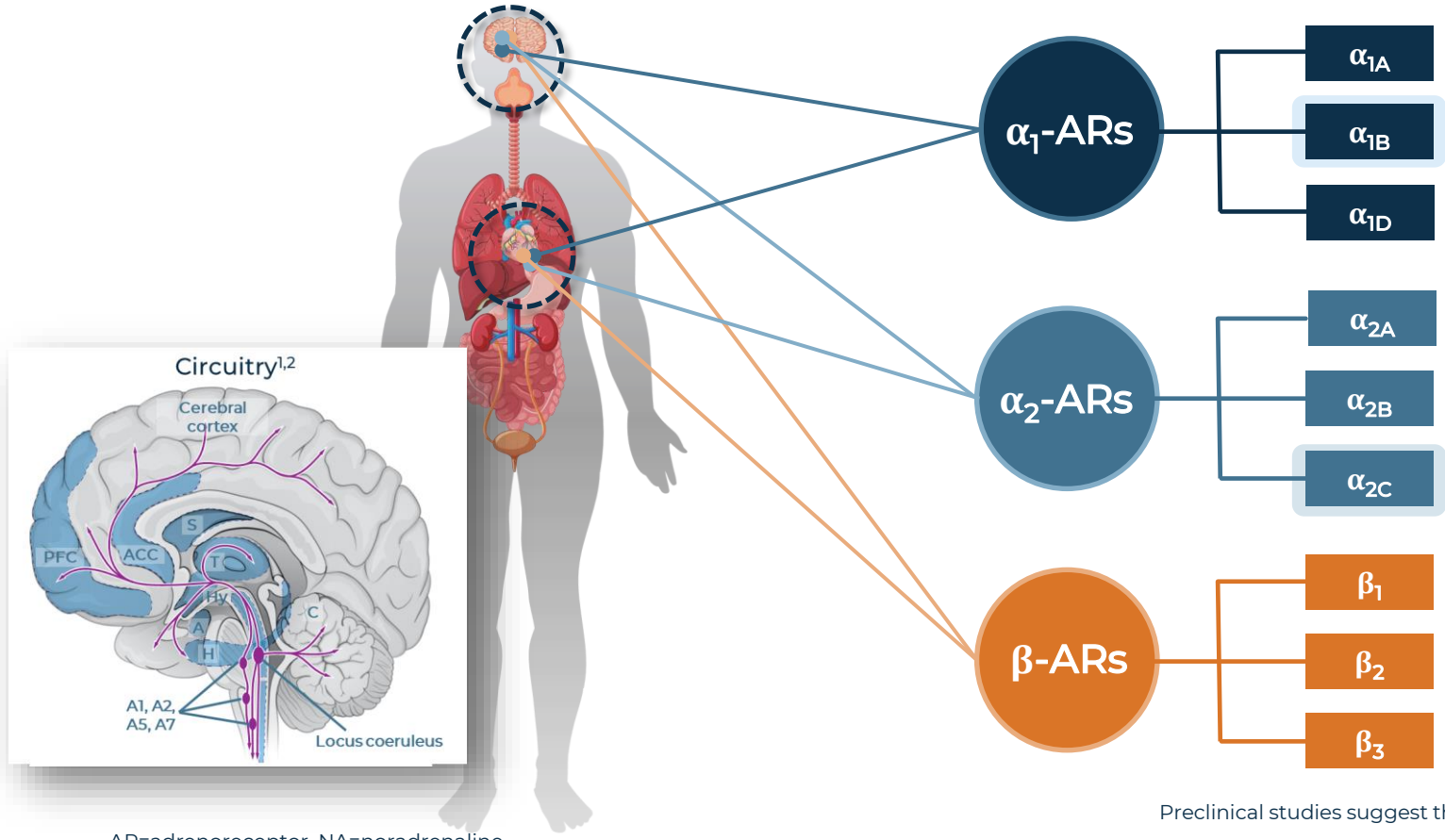
Relationship Between NA Levels and Behavioral States[3,4]



1. Nutt DJ. *J Clin Psychiatry*. 2008;69(Suppl E1):4-7.
2. Sara SJ, et al. *Neuron*. 2012;76(1):130-141.
3. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.
4. Arnsten AF. *Nat Rev Neurosci*. 2009;10(6):410-422

Adrenoceptor Localization and Function

The effects of NA are mediated by three classes of ARs expressed in the CNS and periphery[1,2]



- Mainly ***postsynaptic***[1]
- Typically ***excitatory***[1]

- Both ***presynaptic and postsynaptic***[1]
- Typically ***inhibitory***[1]
- Can function as ***autoreceptors*** to inhibit NA release[3]

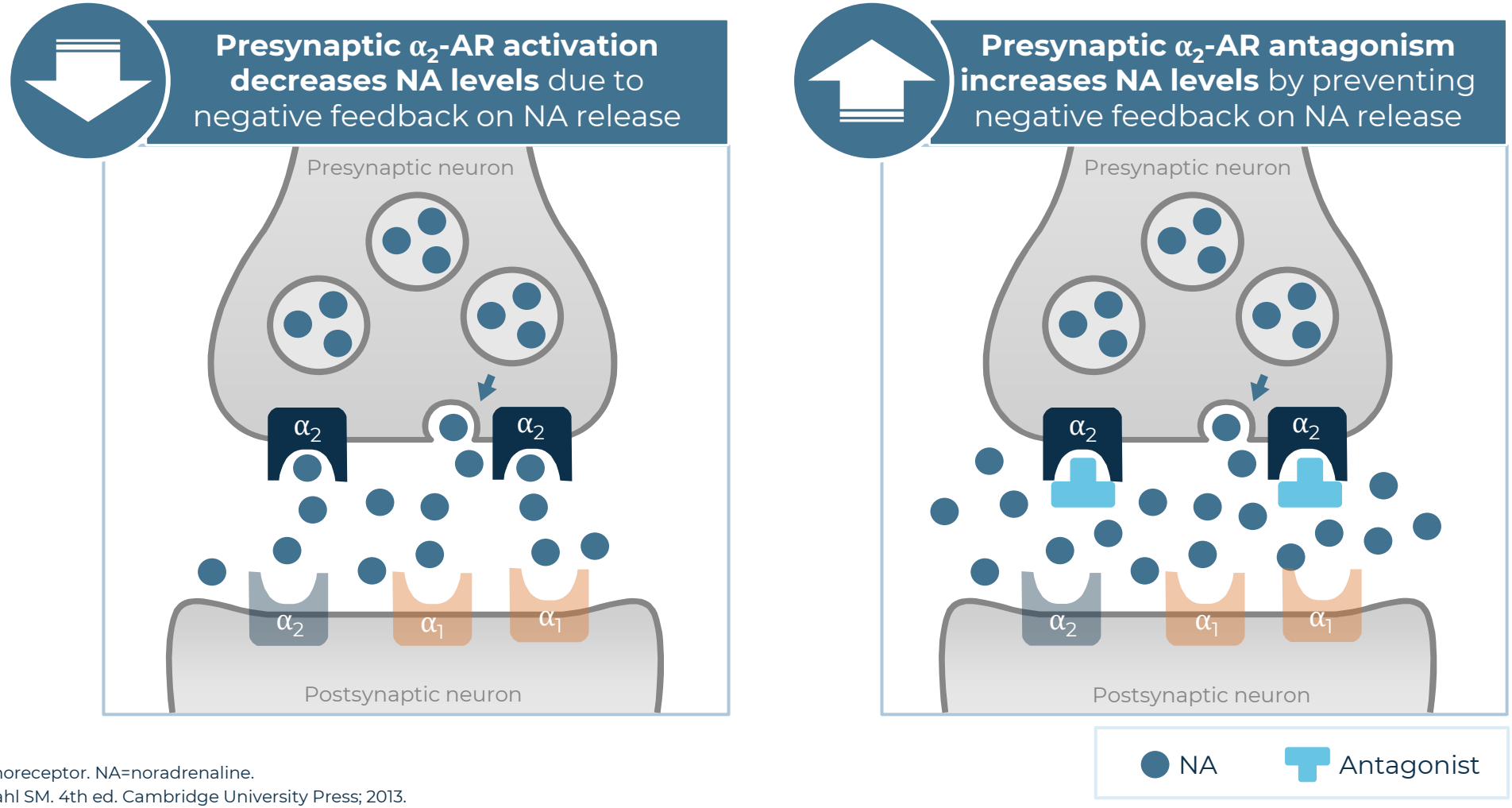
- Predominantly ***postsynaptic***[1]
- Typically ***excitatory***[1]

Preclinical studies suggest that the highlighted receptors may play key roles in psychiatric conditions.[3,4]

AR=adrenoreceptor. NA=noradrenaline.

1. Maletic V, et al. *Front Psychiatry*. 2017;8:42.
2. Triposkiadis F, et al. *J Am Coll Cardiol*. 2009;54(19):1747-1762.
3. Uys MM, et al. *Front Psychiatry*. 2017;8:144.
4. Drouin C, et al. *J Neurosci*. 2002;22(7):2873-2884.

Antagonism of Presynaptic α_2-Adrenoreceptors Increases NA Levels

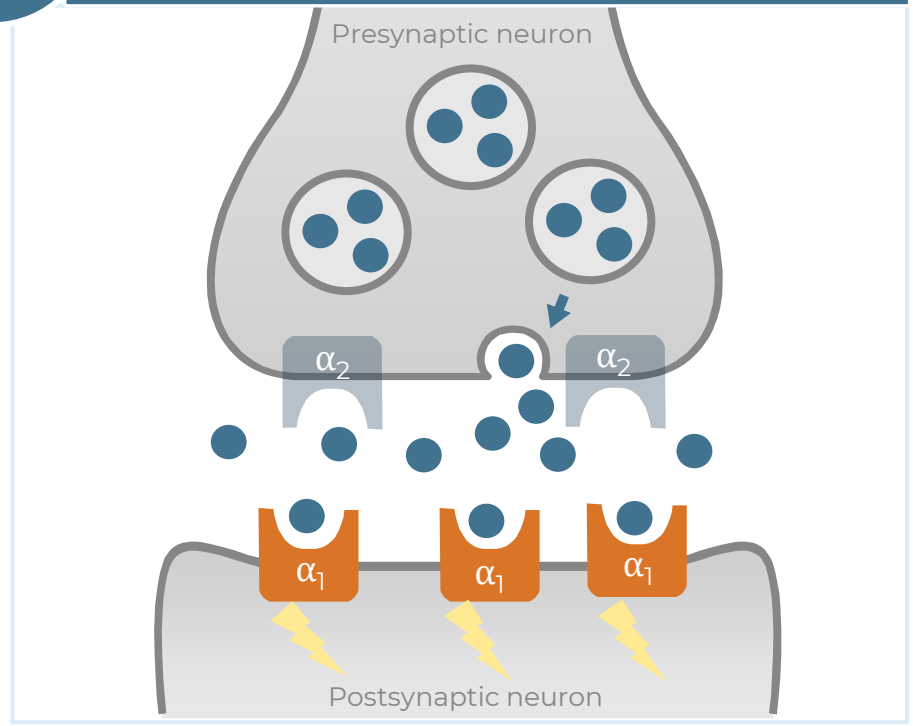


AR=adrenoreceptor. NA=noradrenaline.

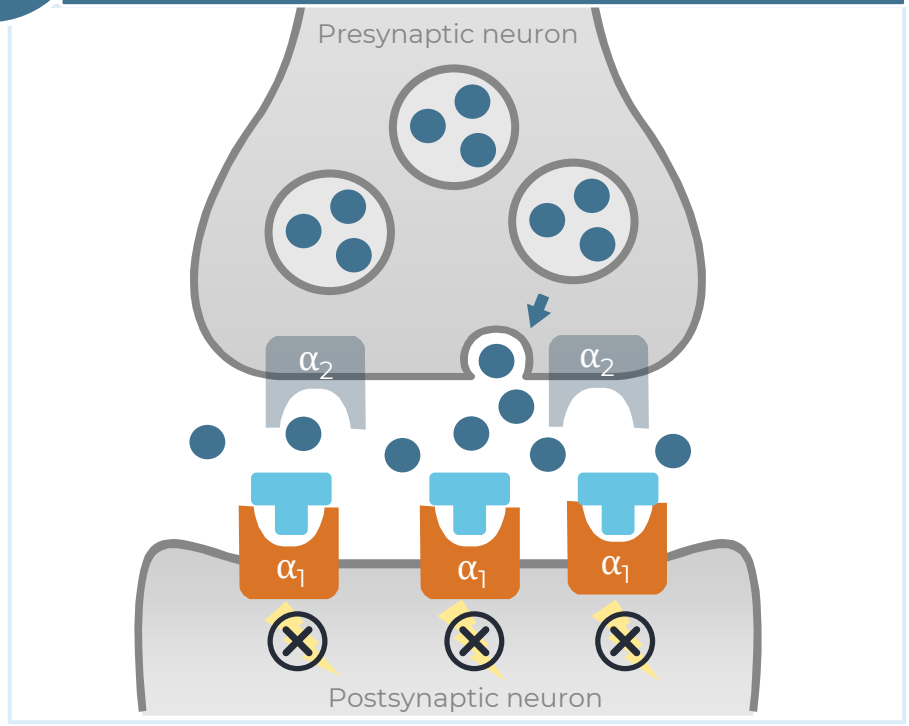
1. Stahl SM. 4th ed. Cambridge University Press; 2013.

Antagonism of Postsynaptic α_2-Adrenoreceptors Decreases NA Signaling

Postsynaptic α_1-AR activation increases NA signaling through activation of downstream signaling pathways



Postsynaptic α_1-AR antagonism decreases NA signaling through blockade of postsynaptic α_1-ARs



AR=adrenoreceptor. NA=noradrenaline.

1. Stahl SM. 4th ed. Cambridge University Press; 2013.

Polling Question

Which of the following receptors can be engaged to improve low NA states?

A α_{1A}

B α_{1B}

C α_{2B}

D α_{2C}

E β_2

NA=noradrenaline.

α-Adrenoceptors Can Modulate Noradrenergic Tone

The impacts of α-adrenoceptor antagonism can depend on levels of NA activity[1-4]

α_{1B} Not engaged (low affinity)

α_{2C} Engaged (high affinity)

Conditions including MDD are associated with **low NA levels[1,5]**

Selective α_2-AR antagonism can **increase NA levels[2,4]**

α_{1B} Engaged (low affinity)

α_{2C} Desensitized (prolonged exposure)

Conditions including AAD, PTSD, and MDD are associated with **high NA levels[1,3]**

Selective α_1-AR antagonism can **block the action of excessive NA levels[3]**

AAD=agitation in Alzheimer's dementia. MDD=major depressive disorder. NA=noradrenaline. PTSD=posttraumatic stress disorder.

1. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.
2. Bücheler MM, et al. *Neuroscience*. 2002;109(4):819-826.
3. Arnsten AF, et al. *Neurobiol Stress*. 2015;1:89-99.
4. Uys MM, et al. *Front Psychiatry*. 2017;8:144.
5. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9-13

Management Considerations for MDD

Proposed Mechanisms for Antidepressant Activity[1-6]

Antidepressants

- Reuptake inhibitors: SSRIs, SNRIs, NDRIs, TCAs
- MAOIs

Mood stabilizers

- Evidence suggests some may enhance serotonergic neurotransmission

Antipsychotics

- All alter D_2 neurotransmission
- Some atypicals also target 5-HT receptors, NA receptors, and a variety of other receptor types

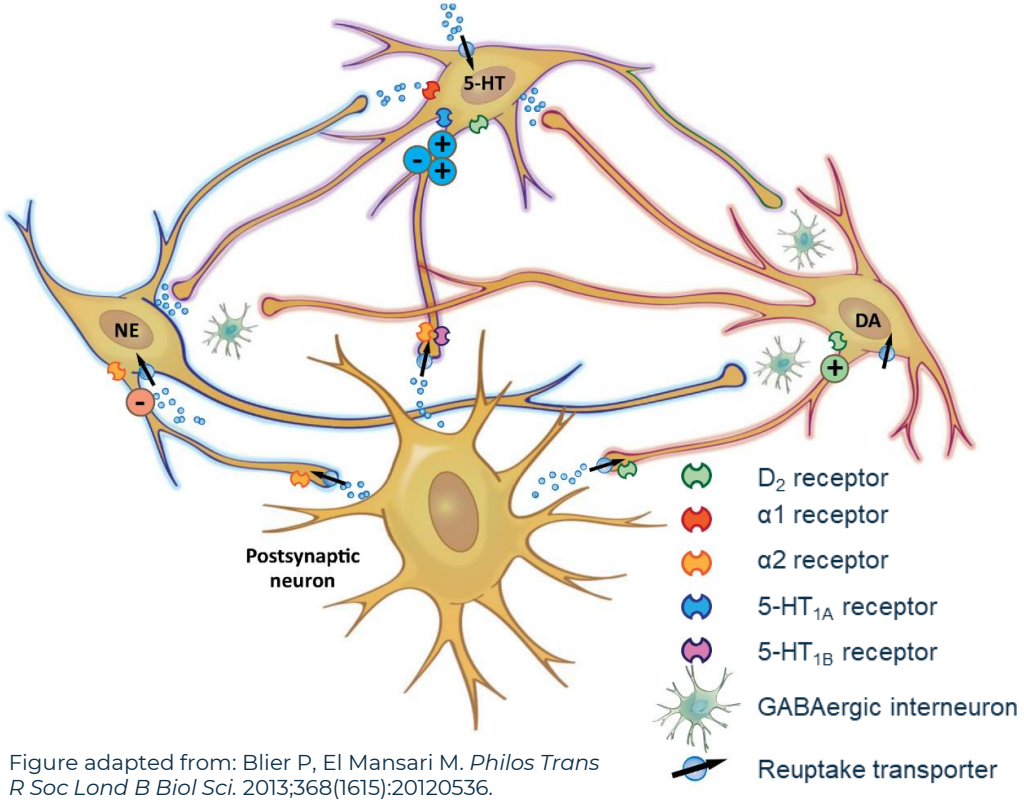


Figure adapted from: Blier P, El Mansari M. *Philos Trans R Soc Lond B Biol Sci.* 2013;368(1615):20120536.

5-HT=serotonin. GABA=gamma aminobutyric acid. MAOI=monoamine oxidase inhibitor. NDRI=norepinephrine-dopamine reuptake inhibitor. NA=noradrenaline. SSRI=selective serotonin reuptake inhibitor. SNRI=serotonin-norepinephrine reuptake inhibitor. TCA=tricyclic antidepressant.

1. Stahl SM. 4th ed. Cambridge University Press; 2013.
2. Blier P, El Mansari M. *Philos Trans R Soc Lond B Biol Sci*. 2013;368(1615):20120536.
3. Rang HP, Dale MM. 7th ed. Churchill Livingstone; 2012.
4. Nugent AC, et al. *J Psychopharmacol*. 2013;27(10):894-902.
5. Andrews PW, et al. *Front Psychol*. 2011;2(159).
6. Artigas F. *Pharmacol Ther*. 2013;137(1):119-131.

Commonly Prescribed First-line MDD Treatments Target One or Two Monoamine Systems

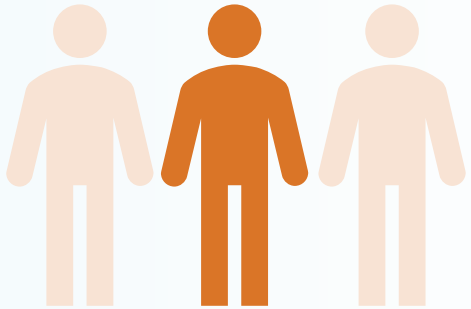
Common first-line MDD treatments target monoamine systems

COMMONLY PRESCRIBED FIRST-LINE ANTIDEPRESSANT MEDICATIONS[1,2]

Drug Class	NA	DA	5-HT
Selective serotonin reuptake inhibitors (SSRIs)			X
Serotonin/noradrenaline reuptake inhibitors (SNRIs)	X		X
Dopamine/norepinephrine reuptake inhibitors (DNRIs)	X	X	

None of these treatments target all three major monoamines together

In the STAR*D trial, **~1 out of 3** adult patients with MDD **achieved remission** following first-line antidepressant treatment[3]



Rate of response diminished with each subsequent oral antidepressant treatment change[3]

MDD=major depressive disorder. NA=noradrenaline; STAR*D=Sequenced Treatment Alternatives to Relieve Depression

1. American Psychiatric Association. *Am J Psychiatry*. 2010;167(Suppl):1-152.
2. National Collaborating Centre for Mental Health (UK). British Psychological Society; 2010.
3. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917.

Methods Currently Used to Modulate the Monoamine System Without Overactivation in MDD

Therapeutic goals in the treatment of MDD may include increasing monoamine activity without overactivating the systems

INCREASE DRIVE

Unresolved Symptom	Potential Treatment Strategy	Potential Receptor Mechanisms[a]
Anxiety[1]	↑ 5-HT	5-HT_{1A} partial agonism
Low energy[2]	↑ NA	α_{2C} antagonism
Difficulty concentrating[3]	↑ NA	α_{2C} antagonism
Pessimistic thoughts[4]	↑ DA	D_2 partial agonism

MITIGATE OVERDRIVE

Treatment Concern	Potential Receptor Mechanisms[a]
Worsening or introduction of anxiety symptoms[5]	5-HT_{1A} partial agonism
Irritability[5]	α_{1B} antagonism

[a]These are not the only potential receptor mechanisms available therapeutically.

5-HT=serotonin. DA=dopamine. MDD=major depressive disorder. NA=noradrenaline.

1. Albert PR, et al. *Front Behav Neurosci*. 2014;8:199.
2. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
3. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9-13.
4. Sharot T, et al. *Curr Biol*. 2012;22(16):1477-1481.
5. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.

Polling Question

In your clinical practice, what is your preferred adjunctive strategy for patients with MDD who have a partial response to ADT monotherapy?

A. Atypical antipsychotics

B. Mood stabilizers

C. Benzodiazepines

D. Psychotherapy

E. Augment by adding an antidepressant

ADT=antidepressant treatment.

The Importance of the Monoamine Neurotransmitter Systems in Unresolved Symptoms of MDD

5-HT and DA have established roles in MDD symptomology[1,2]

Several commonly unresolved symptoms in MDD are associated with NA dysfunction[3,4]

Some studies reported that augmentation with an AAP was more effective than monotherapy, switching ADTs, or combining ADTs[5,6]

Some AAPs target multiple monoamine receptors[7]

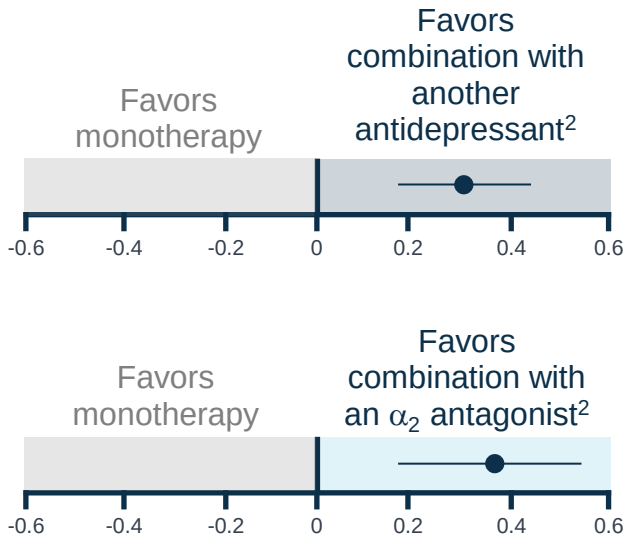
5-HT=serotonin. AAP=atypical antipsychotic. ADT=antidepressant therapy. DA=dopamine. MDD=major depressive disorder. NA=noradrenaline.

1. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
2. Belujon P, et al. *Int J Neuropsychopharmacol*. 2017;20(12):1036-1046.
3. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.
4. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9-13.
5. Mohamed S, et al. *JAMA*. 2017;318(2):132-145.
6. Wang HR, et al. *Int J Neuropsychopharmacol*. 2015;18(8):pyv023.
7. Grinchii D, et al. *Int J Mol Sci*. 2020;21(24):9532.

Combining/Augmenting ADTs That Target Different Monoamines May Allow for Increased Clinical Efficacy[1]

In two separate meta-analyses comparing the efficacy of combination therapies with monotherapies in the treatment of depression, combination of reuptake inhibitors with α_2 antagonists was the most effective treatment option[1,2]:

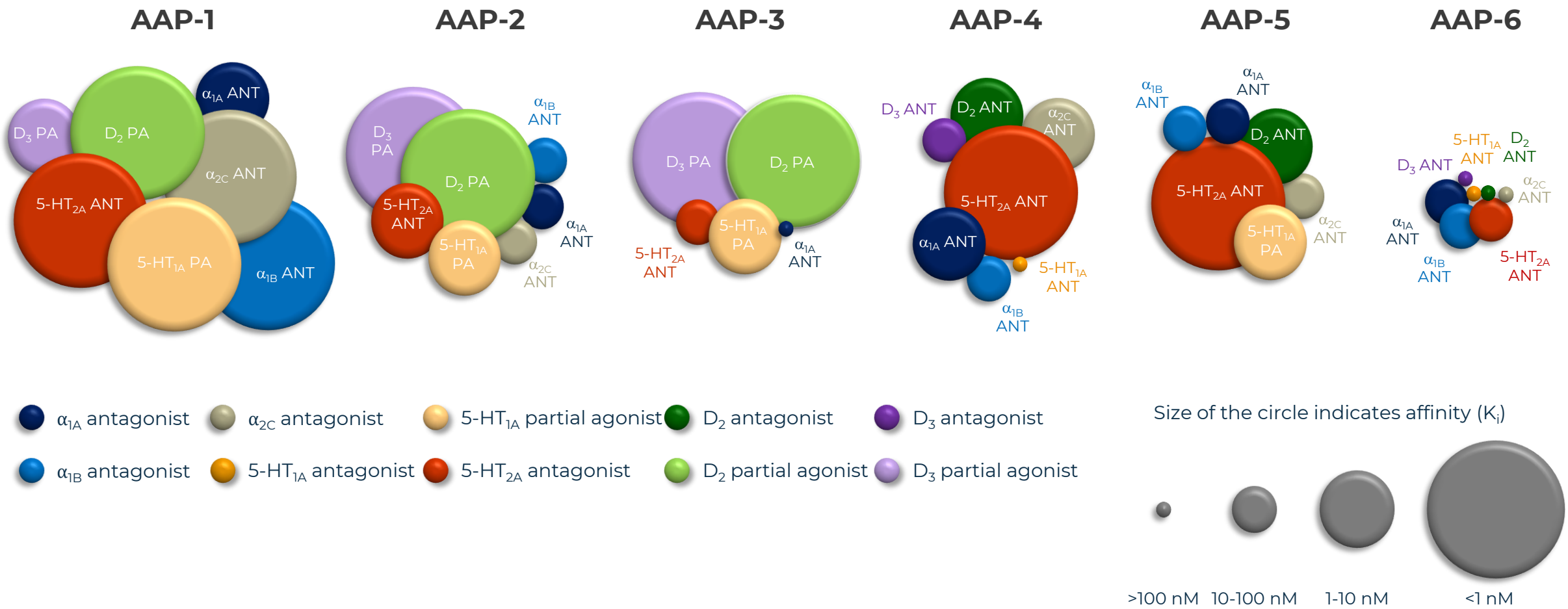
FIRST-LINE ANTIDEPRESSANT MONOTHERAPY < **COMBINATION OF TWO ANTIDEPRESSANTS** < **COMBINATION OF REUPTAKE INHIBITOR WITH α_2 ANTAGONIST**



ADT=antidepressant therapy.

1. Henssler J, et al. *Can J Psychiatry*. 2016;61(1):29-43.
2. Henssler J, et al. *JAMA Psychiatry*. 2022;79(4):300-312.

Illustrative Representation: Affinity Profiles of AAPs[1]



AAP=atypical antipsychotic. ANT=antagonist. K_i=inhibitory constant. nM=nanomolar. PA=partial agonist.

1. Siafis S, et al. *Curr Neuropharmacol*. 2018;16(8):1210-1223.

Considerations for Augmentation With Atypical Antipsychotics (AAPs)

POTENTIAL ADVANTAGES[1-6]

Maintain any therapeutic benefit of the first-line agent[1,2] → Enhance antidepressant effect[1,3] → Increase remission rates[1,3]

Avoid withdrawal symptoms due to switching[2] & Counteract ADT side effects[2]

Certain AAPs target three MDD-related monoamines[4] → AAPs can act synergistically with reuptake inhibitors[6]

POTENTIAL DISADVANTAGES[2,5,7]

Additional daily medications[5]

Additional side effects[2]

Stigma associated with antipsychotics[7]

AAP=atypical antipsychotic. ADT=antidepressant therapy. MDD=major depressive disorder.

1. American Psychiatric Association. 3rd ed. 2010.
2. Papakostas GI. *J Clin Psychiatry*. 2009;70(suppl 6):16-25.
3. National Collaborating Centre for Mental Health (UK). 2010.
4. Grinchii D, et al. *Int J Mol Sci*. 2020;21(24):9532.
5. Ghaed-Sharaf M, et al. *BMC Psychol*. 2022;10(1):12.
6. Stahl SM. 4th ed. Cambridge University Press; 2013.
7. Townsend M, et al. *Patient Prefer Adherence*. 2022;16:373-401.

Summary

The heterogenous presentation of MDD symptoms is theoretically related to dysregulation of one or more of the major monoamines[1,2]

1

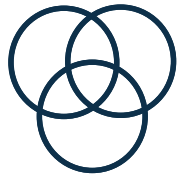
Symptoms of MDD may be related to hypo- or hyperactive NA systems,[1,3-6]

and antagonism at α-adrenoceptors may help regulate NA levels in appropriate ranges[7]

2

NA signaling is mediated by three classes of noradrenergic receptors that differentially modulate neuronal activity[7]

3



Augmentation with AAPs may target several monoamine neurotransmitter systems and improve symptoms related to monoamine dysregulation

4

AAP=atypical antipsychotic. MDD=major depressive disorder. NA=noradrenaline.

1. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7
2. Fuchs E, et al. *Dialogues Clin Neurosci*. 2004;6(2):171-183.
3. Conradi HJ, et al. *Psychol Med*. 2011;41(6):1165-1174.
4. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(suppl 1):9-13.
5. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.
6. Zajecka J, et al. *J Clin Psychiatry*. 2013;74(4):407-414.
7. Maletic V, et al. *Front Psychiatry*. 2017;8:42.