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Addressing Unresolved Symptoms of Major Depressive Disorder (MDD)

January 2024 US.PSY.D.24.00003

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 why many patients with MDD continue to experience unresolved symptoms following first-line treatment

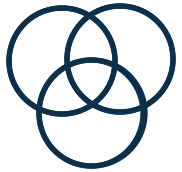
1

Understand why, although serotonin (5-HT) and dopamine (DA) are important monoamines, norepinephrine (NE) dysregulation may also contribute to unresolved symptoms in MDD

2

Discuss the role of three classes of noradrenergic receptors on neuronal activity

3

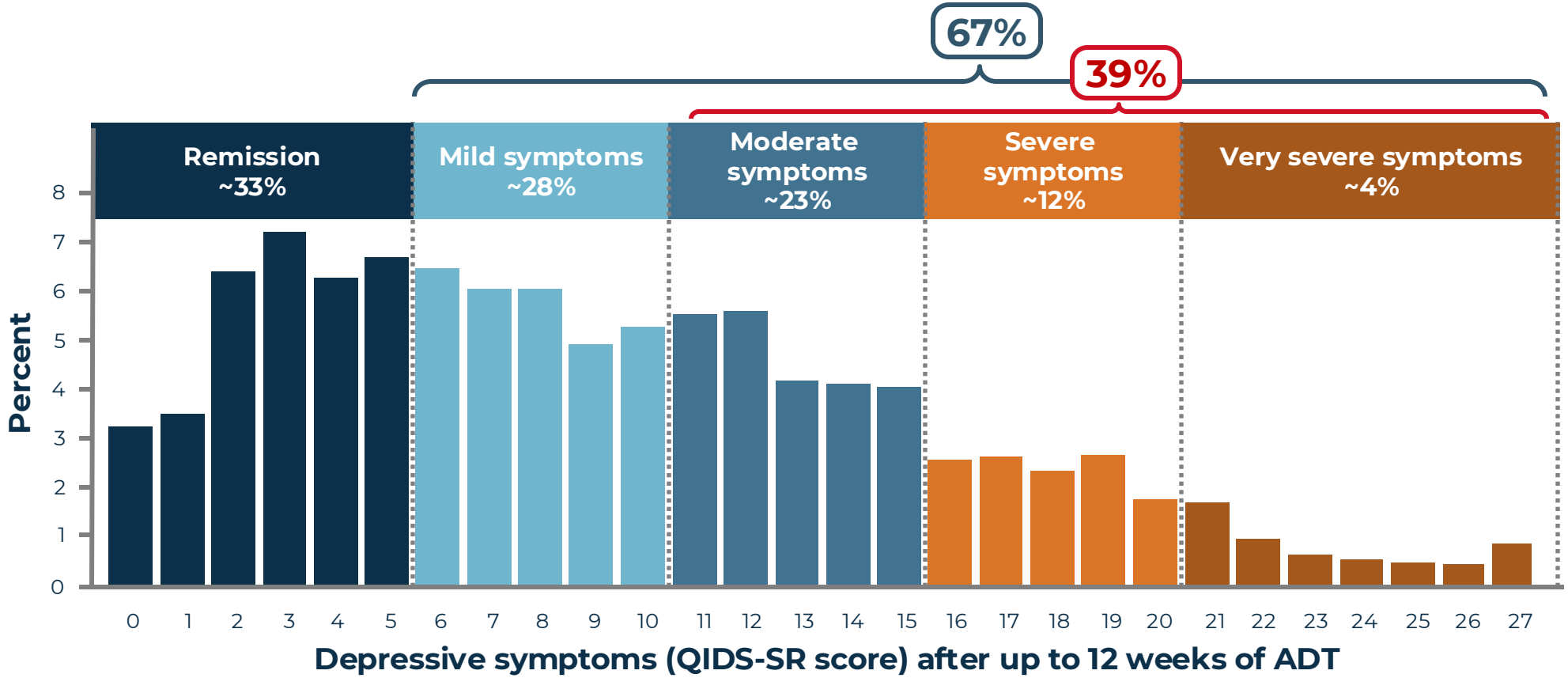


Learn how adjunctive atypical antipsychotics (AAPs) may address MDD symptoms by modulating dysregulation of the NE system, in addition to DA and 5-HT

4

Unresolved Symptoms of MDD Following Monotherapy Antidepressant Treatment (ADT)[1]

Approximately ***two out of three*** patients with MDD have unresolved symptoms following treatment with first-line antidepressants (N=2876)



QIDS-SR=Quick Inventory of Depressive Symptomatology–Self-Report.

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

Polling Question

In your clinical experience, which of the following unmet needs have you recognized with ADT pharmacotherapy?

A Limited specific efficacy with first-line therapies

B Intolerable side effects

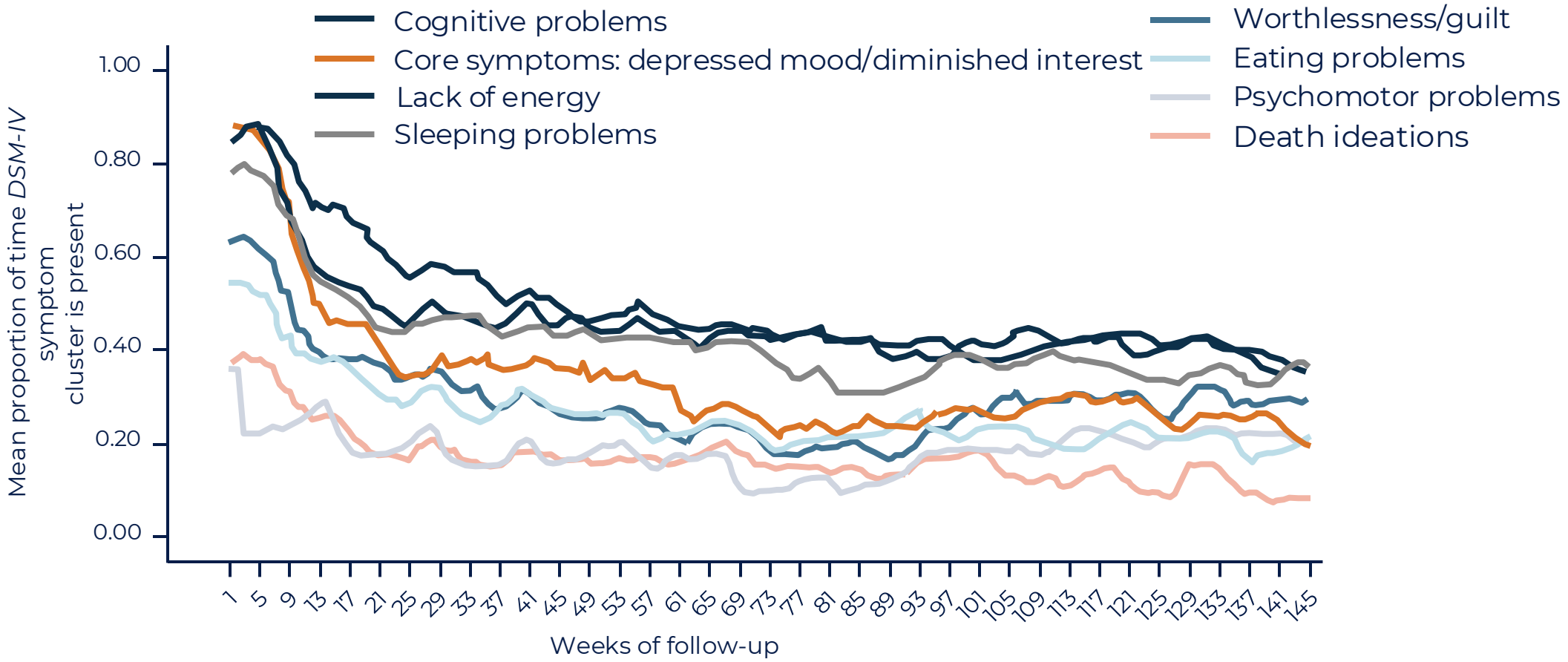
C Inconsistent treatment response

D Relatively slow onset of action

E Need for second-line treatment modalities

Unresolved Symptoms Following ADT[1]

Mean Proportion of the *DSM-IV* Symptoms Present During 3-Year Follow-up Period (N=267)



DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

1. Conradi HJ, et al. Psychol Med. 2011;41(6):1165-1174.

Unresolved Symptoms Following ADT[1-4] (cont'd)

Unresolved symptoms are associated with:

Poorer functional outcomes[1,2]

More chronic depressive episodes[3]

Impairment in work and relationships[3]

Increased economic burden[4]

1. Nierenberg AA, et al. *Psychol Med*. 2010;40(1):41-50.
2. American Psychiatric Association. 3rd ed. 2010.
3. Papakostas GI. *J Clin Psychiatry*. 2009;70(suppl 6):16-25.
4. Arnaud A, et al. *Pharmacoeconomics*. 2021;39(6):691-706.

Monoaminergic Dysregulation in MDD

A Closer Look at Norepinephrine

Polling Question

How familiar are you with monoaminergic dysregulation in MDD?

A. Not at all familiar

B. Somewhat familiar

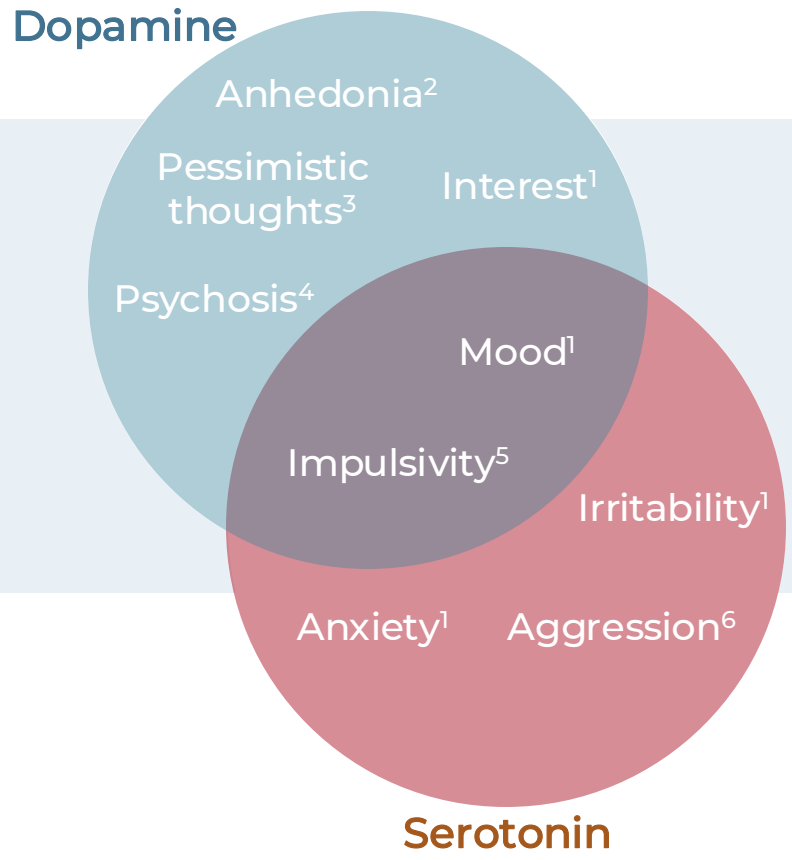
C. Familiar

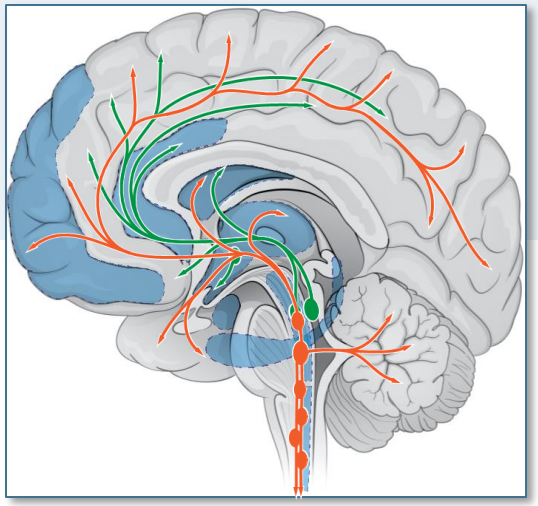
D. Very familiar

E. Extremely familiar

Monoamine Neurotransmitter System Dysfunction[1-6]

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

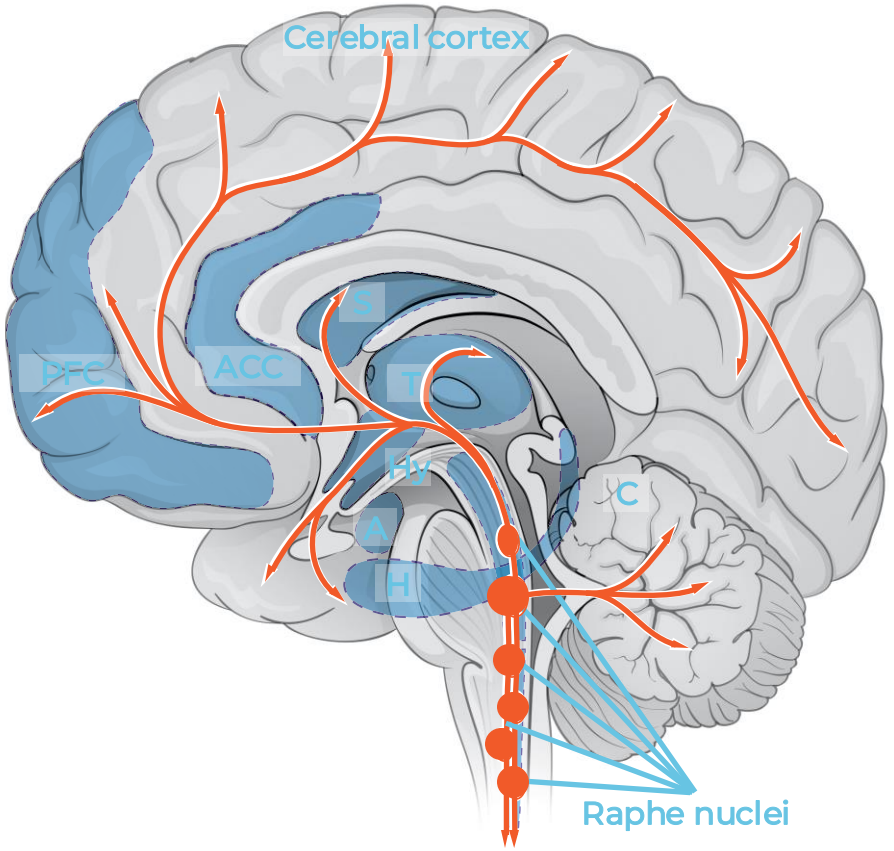




1. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
2. Belujon P, et al. *Int J Neuropsychopharmacol*. 2017;20(12):1036-1046.
3. Sharot T, et al. *Curr Biol*. 2012;22(16):1477-1481.
4. Kesby JP, et al. *Transl Psychiatry*. 2018;8(1):30.
5. Dalley JW, et al. *Neuroscience*. 2012;215:42-58.
6. Seo D, et al. *Aggress Violent Behav*. 2008;13(5):383-395.

Serotonergic System Dysfunction[1-6]

Circuitry[1,6]




Anxiety[2]


Mood[3]


Aggression[4]

Serotonergic Receptors[5]

G protein-coupled

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

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

Ligand-gated ion channel

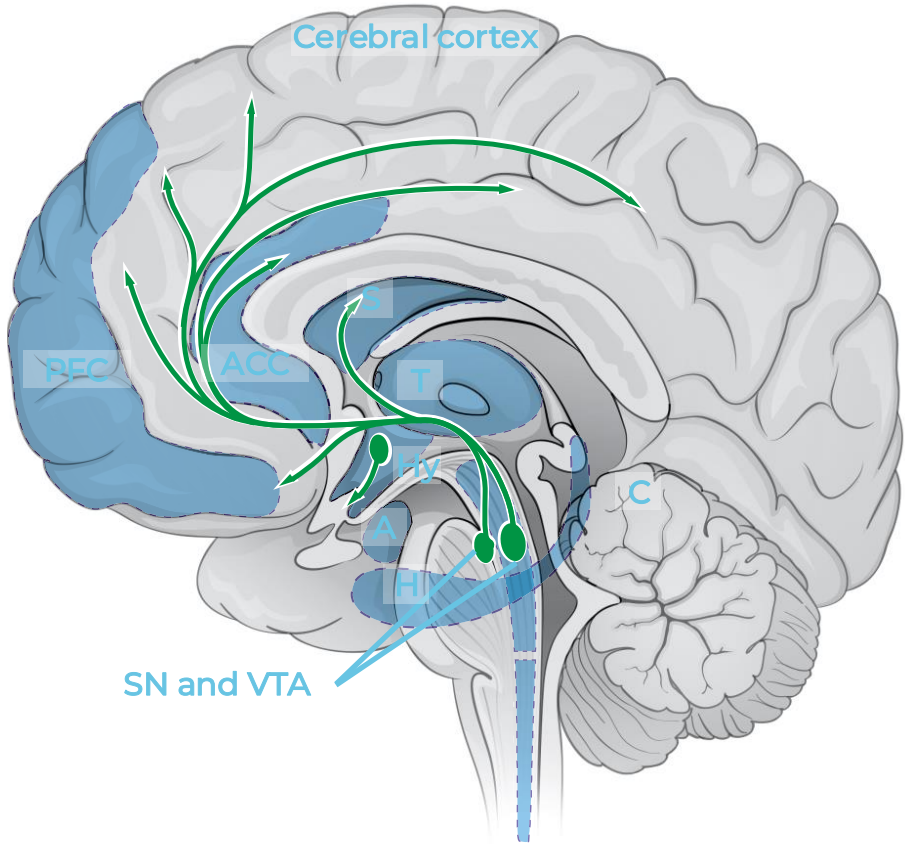
5-HT$_3$

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. Albert PR, et al. Front Behav Neurosci. 2014;8:199.
3. Nutt DJ. J Clin Psychiatry. 2008;69(suppl E1):4-7.
4. Seo D, et al. Aggress Violent Behav. 2008;13(5):383-395.
5. Barnes NM, et al. Pharmacol Rev. 2021;73(1):310-520.
6. Levinson S, et al. Front Neuroimaging. 2023;1:1009399.

Dopaminergic System Dysfunction[1-7]

Circuitry[1,7]



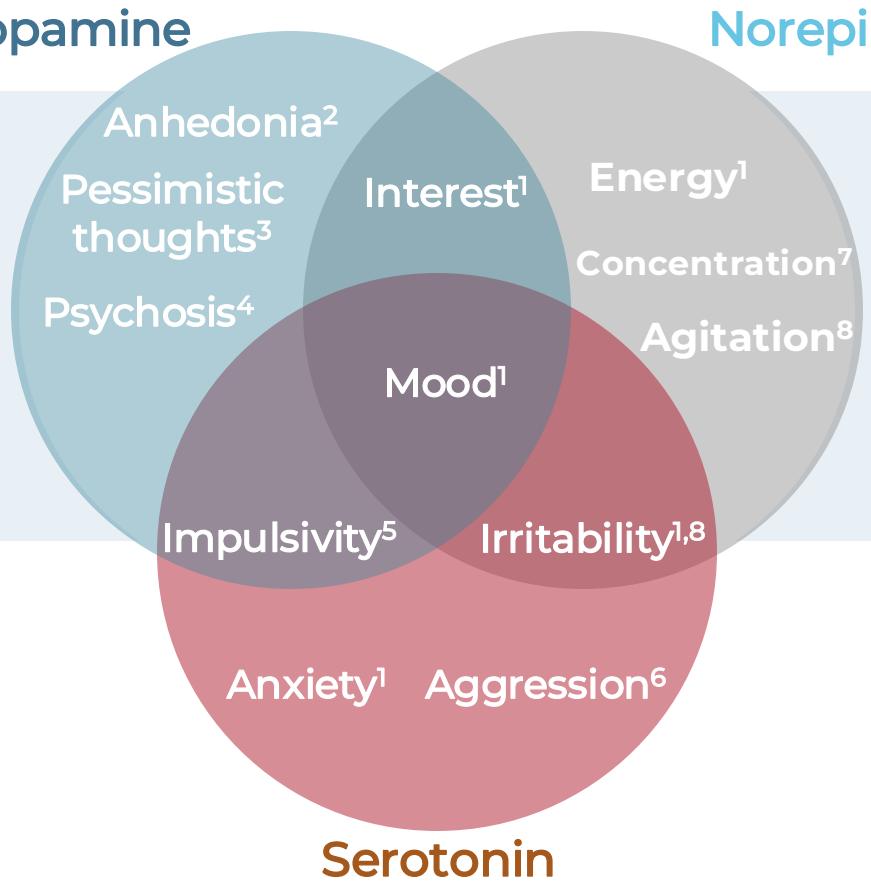
Dopaminergic Receptors[6]

D_1-like[7]		D_2-like		
D_1	D_5	**D_2**	**D_3**	D_4

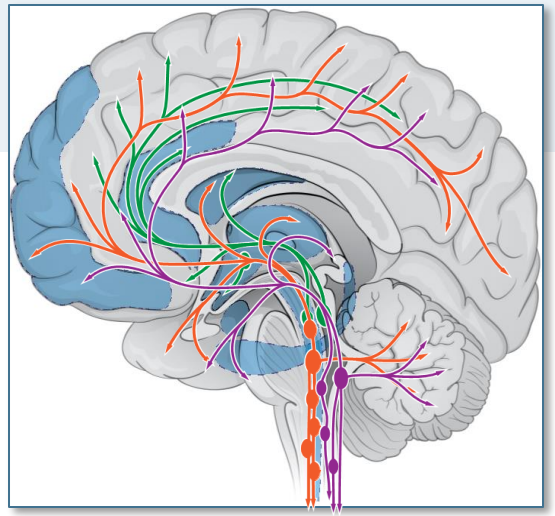
1. SN=substantia nigra. VTA=ventral tegmental area.
2. Fuchs E, et al. Dialogues Clin Neurosci. 2004;6(2):171-183.
3. Sharot T, et al. Curr Biol. 2012;22(16):1477-1481.
4. Nutt DJ. J Clin Psychiatry. 2008;69(suppl E1):4-7.
5. Belujon P, et al. Int J Neuropsychopharmacol. 2017;20(12):1036-1046.
6. Dalley JW, et al. Neuroscience. 2012;215:42-58.
7. Zhao F, et al. Front Pharmacol. 2022;13:947785.
8. Levinson S, et al. Front Neuroimaging. 2023;1:1009399.

Monoamine Neurotransmitter System Dysfunction[1-8]

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



Noradrenergic system dysfunction may contribute to unresolved symptoms of MDD[7,8]



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.
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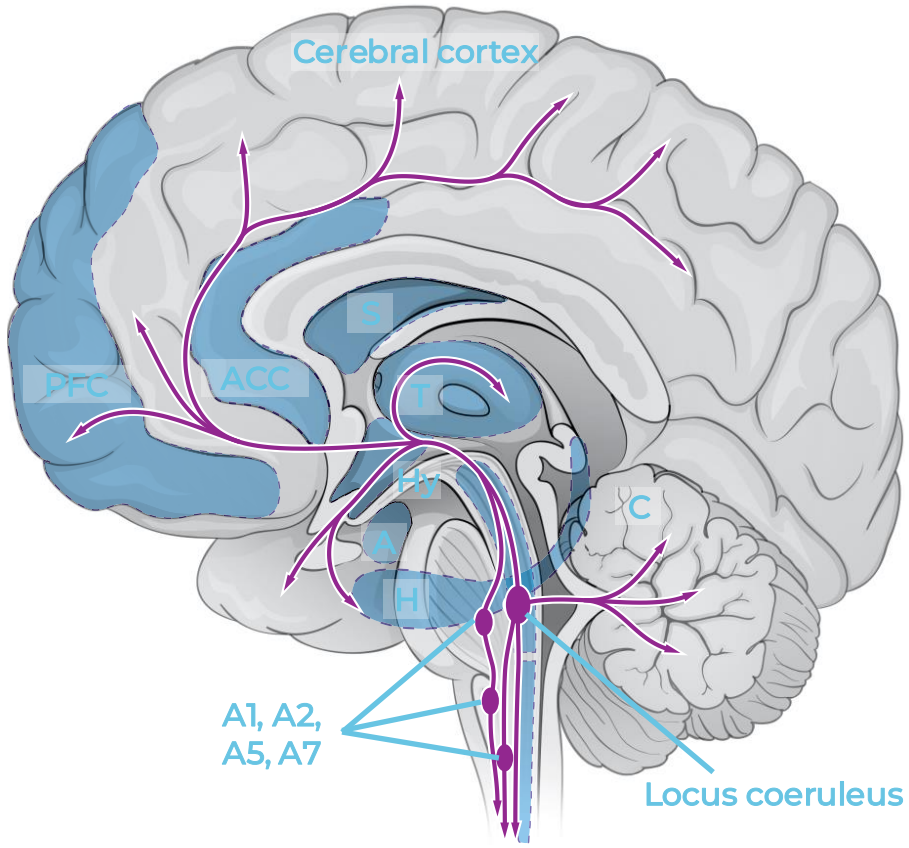
5. Dalley JW, et al. Neuroscience. 2012;215:42-58.
6. Seo D, et al. Aggress Violent Behav. 2008;13(5):383-395.
7. Moret C, et al. Neuropsychiatr Dis Treat. 2011;7(suppl 1):9-13.
8. Yamamoto K, et al. Psychiatry Clin Neurosci. 2014;68(1):1-20.

Noradrenergic System Dysfunction[1-6]

Circuitry[1,6]

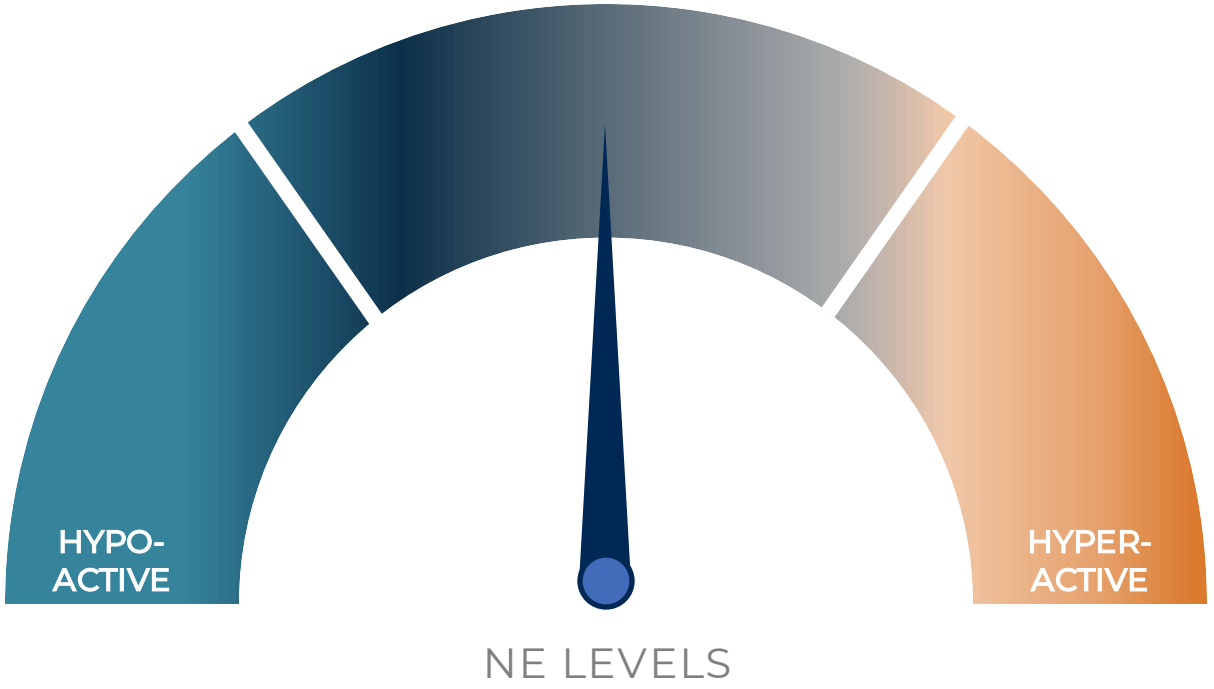


Adrenergic Receptors[5]

α_1			α_2			β		
α_{1A}	**α_{1B}**	α_{1D}	α_{2A}	α_{2B}	**α_{2C}**	β_1	β_2	β_3

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. Moret C, et al. Neuropsychiatr Dis Treat. 2011;7(suppl 1):9-13.
4. Yamamoto K, et al. Psychiatry Clin Neurosci. 2014;68(1):1-20.
5. Maletic V, et al. Front Psychiatry. 2017;8:42.
6. Levinson S, et al. Front Neuroimaging. 2023;1:1009399.

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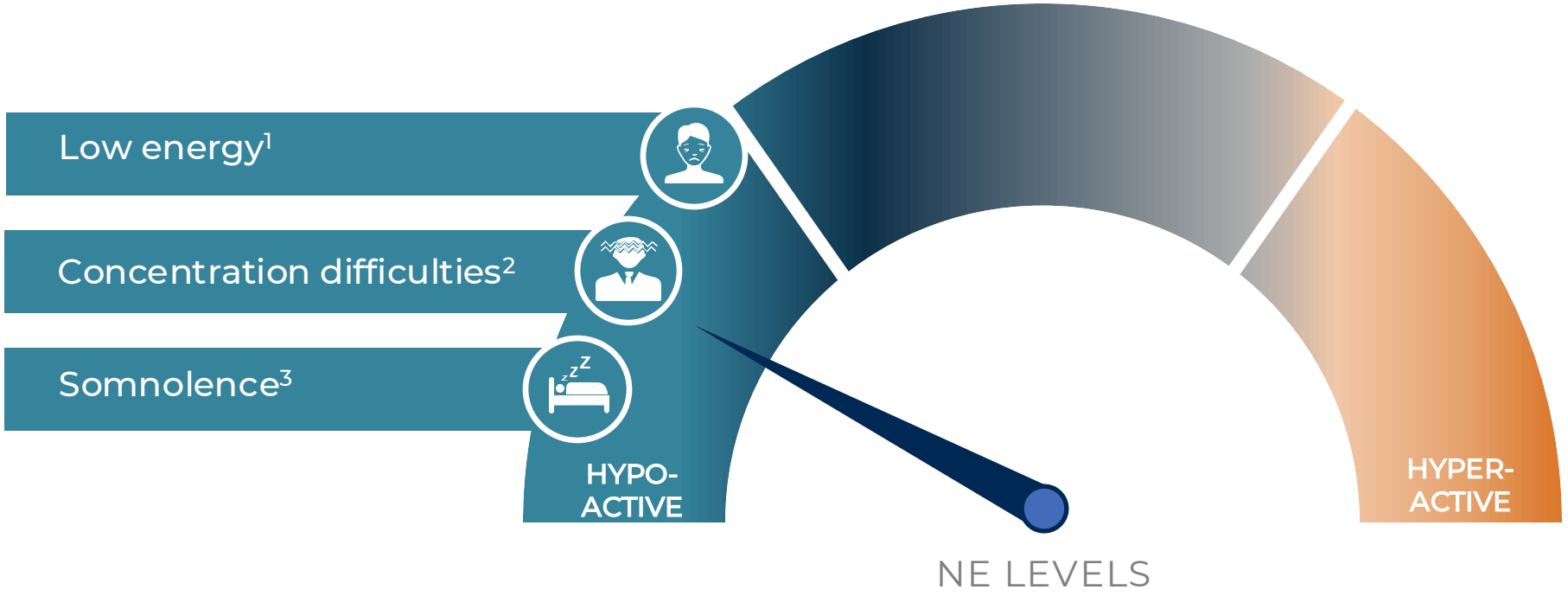

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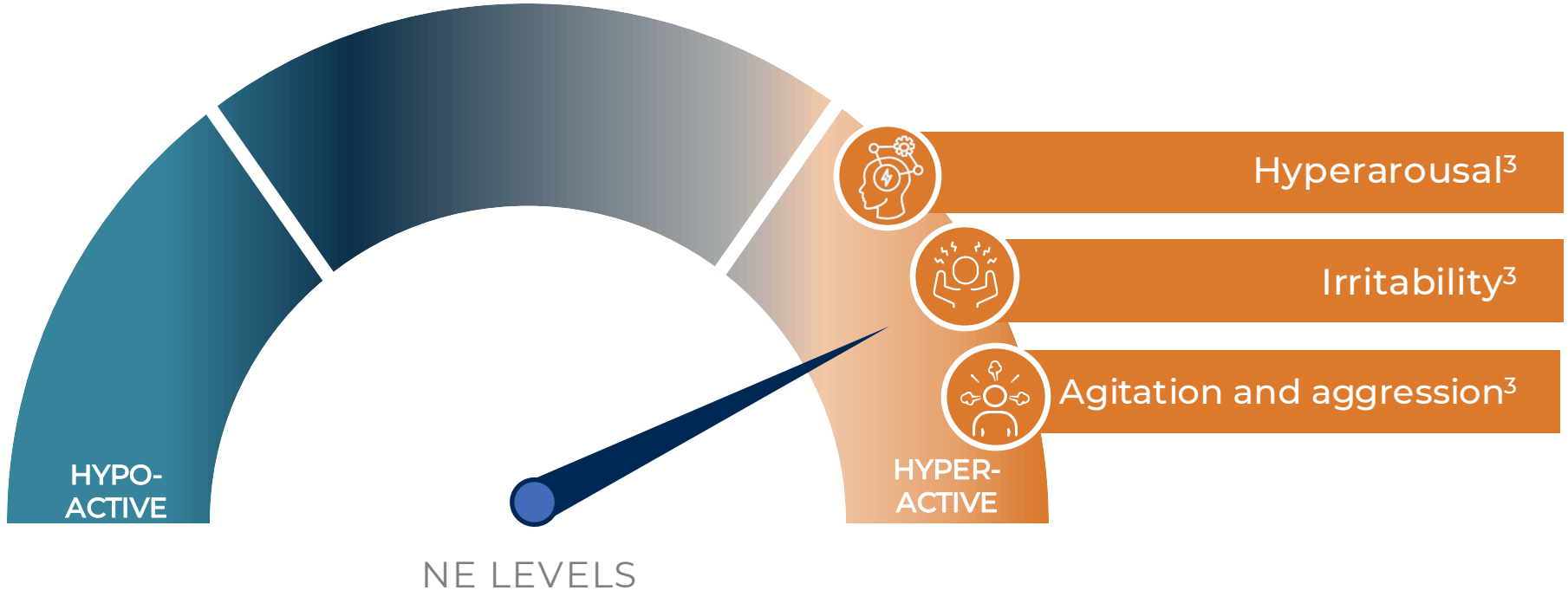

1. Nutt DJ. J Clin Psychiatry. 2008;69(suppl E1):4-7.
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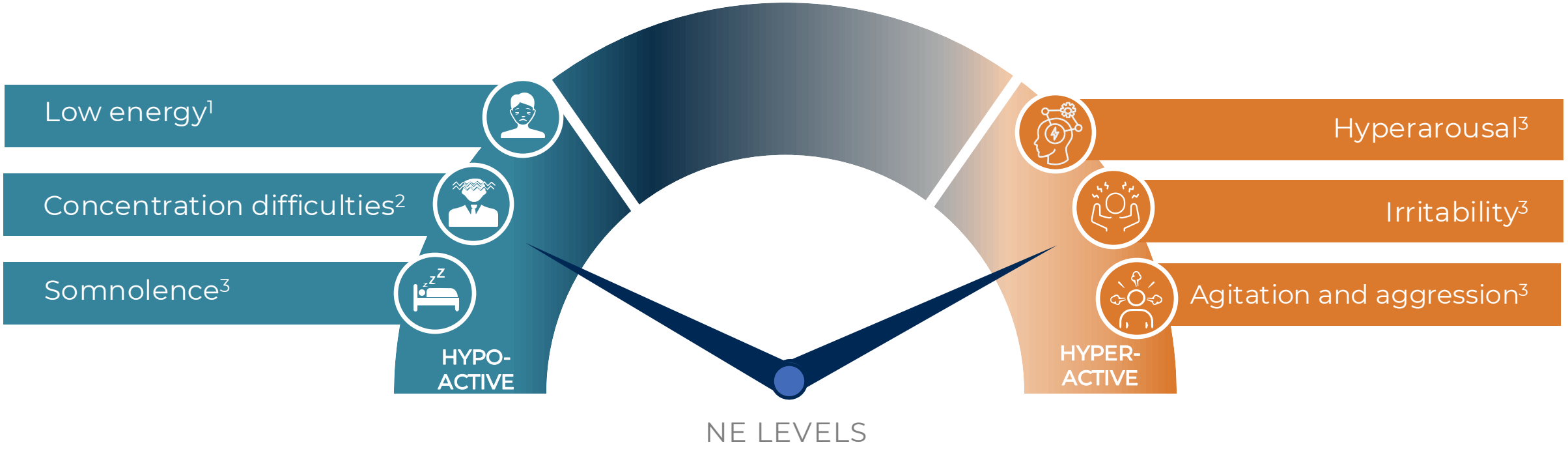


Adrenoceptors (ARs) can modulate symptoms caused by noradrenergic system dysregulation

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.

Polling Question

How likely are you to consider modulation of norepinephrine when prescribing treatment to patients with unresolved symptoms?

A Never

B Rarely

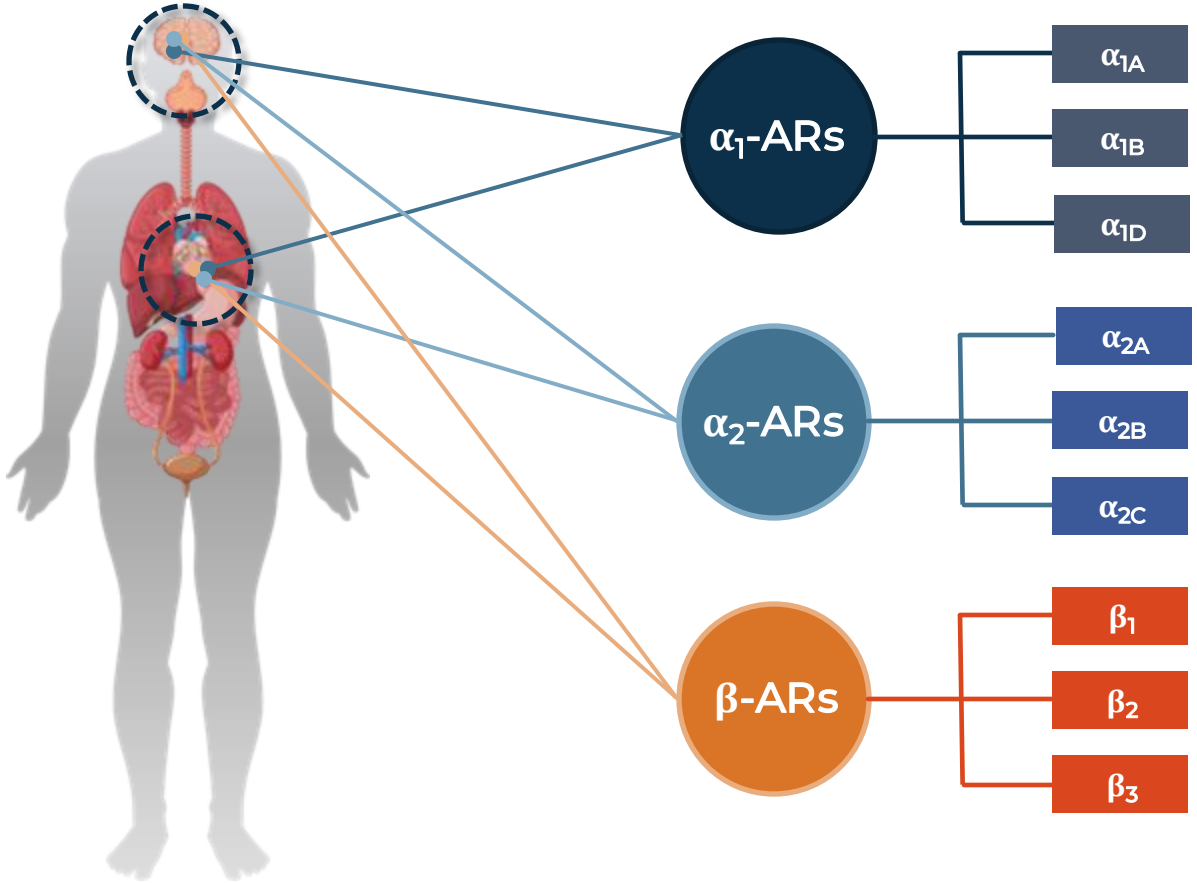
C Sometimes

D Often

E Always

Adrenoceptor Localization and Function

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



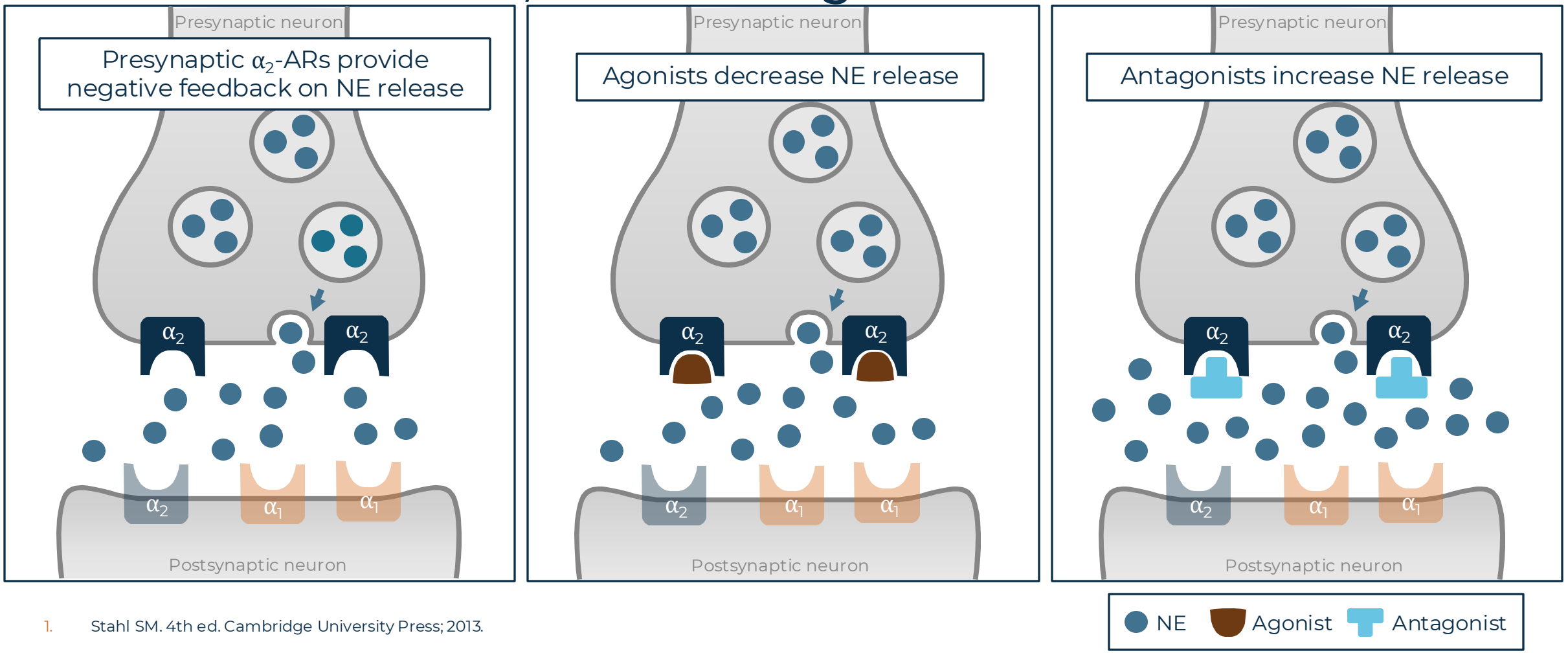
- Mainly ***postsynaptic***[1]
- Typically ***excitatory***[1]

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

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

1. CNS=central nervous system.
2. Maletic V, et al. Front Psychiatry. 2017;8:42.
3. Triposkiadis F, et al. J Am Coll Cardiol. 2009;54(19):1747-1762.
4. Uys MM, et al. Front Psychiatry. 2017;8:144.

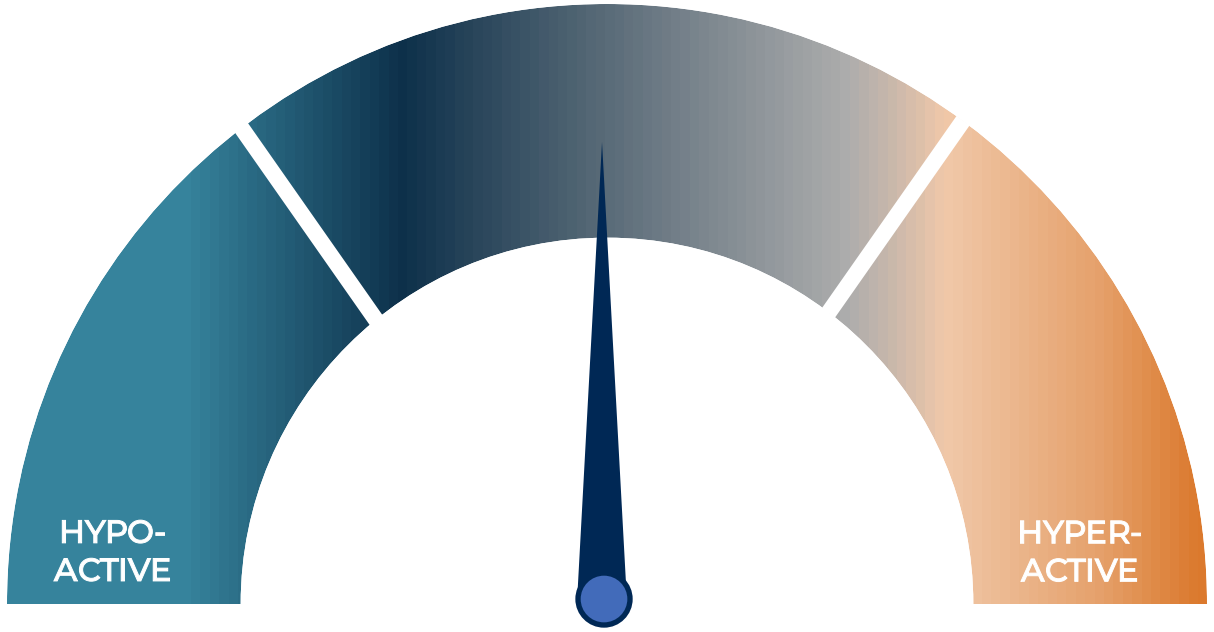
Presynaptic α_2-Noradrenergic Receptors: Agonists Decrease NE Levels, While Antagonists Increase NE Levels



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

α-Adrenoceptors Can Modulate Noradrenergic Tone[1-4]

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



Levels of CNS norepinephrine activity[1]

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.
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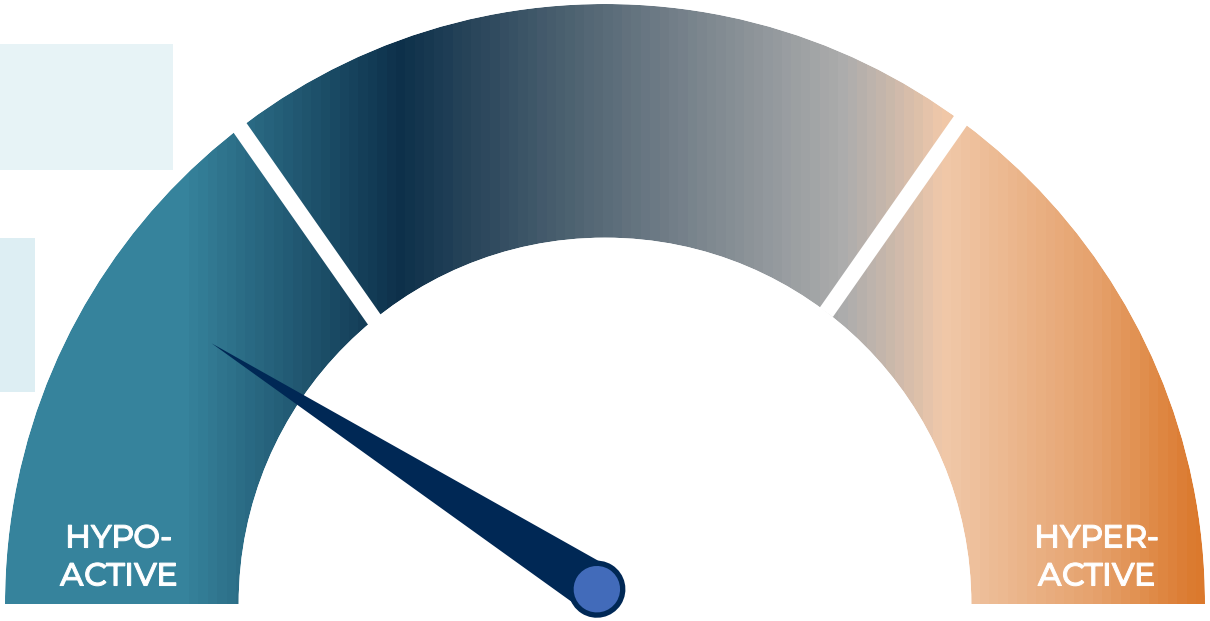
α-Adrenoceptors Can Modulate Noradrenergic Tone[1-4]

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

α_1 **Not engaged** (low affinity)

α_2 **Engaged** (high affinity)

Selective α_2-adrenoceptor antagonism works to **increase NE levels**[2,4]



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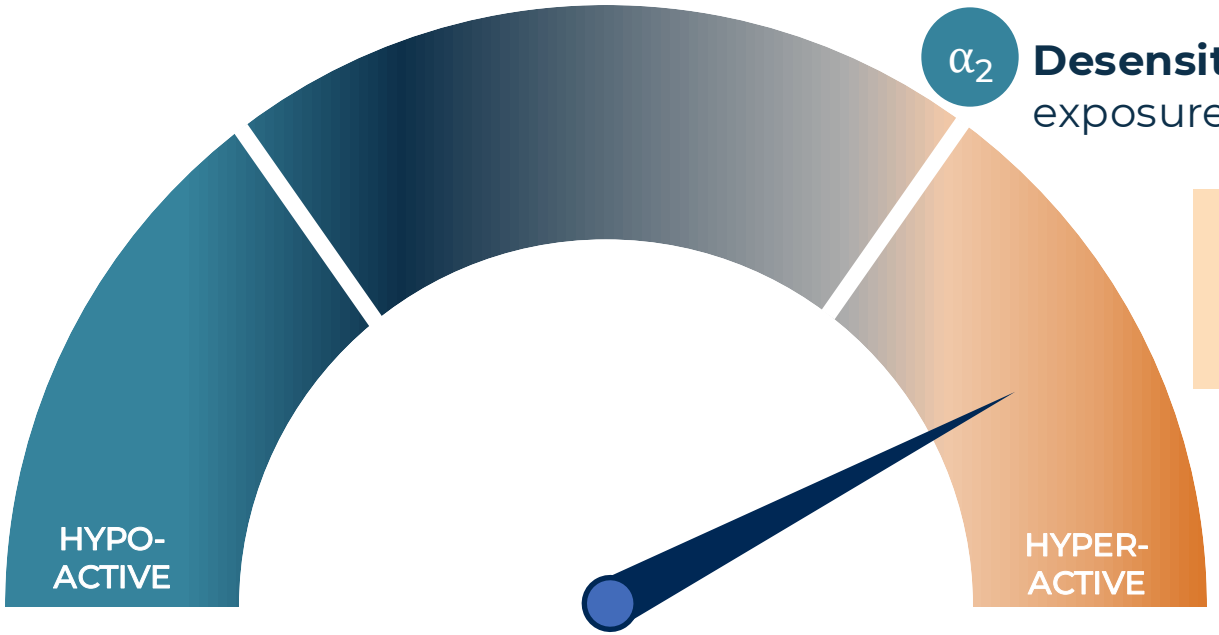
The impacts of α-adrenoceptor antagonism can depend on levels of NE activity[1-4]

α_1 **Engaged** (low affinity)

α_2 **Desensitized** (prolonged exposure)

Selective α_1-adrenoceptor antagonism may work to **block the action of excessive NE levels[3]**



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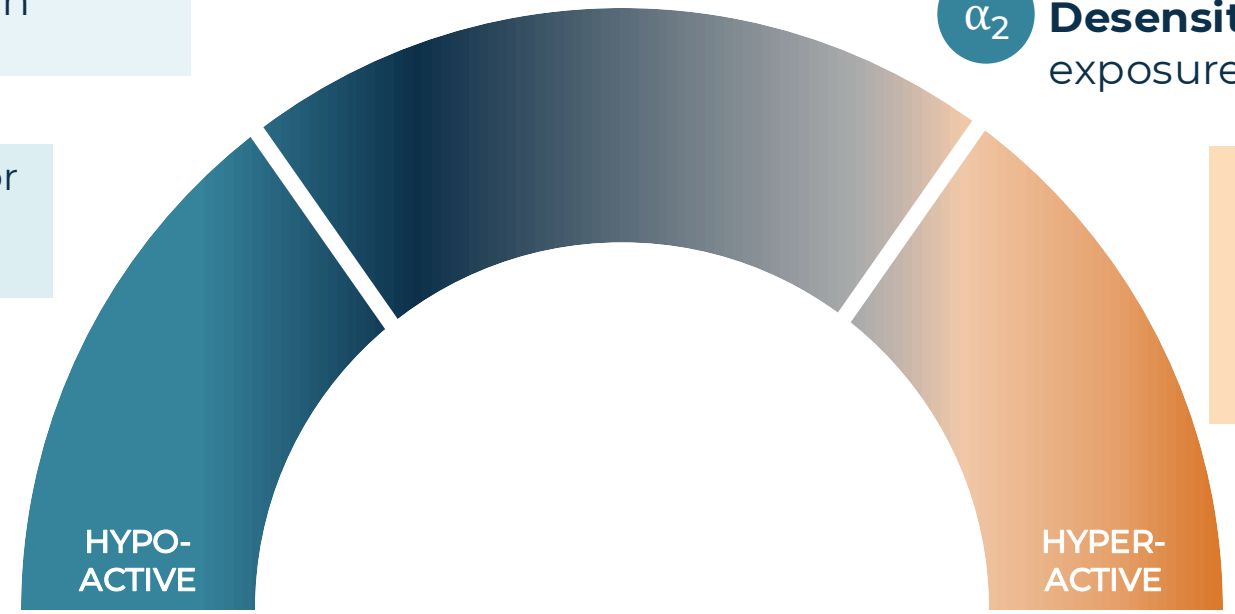

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3. Arnsten AF, et al. Neurobiol Stress. 2015;1:89-99.
4. Uys MM, et al. Front Psychiatry. 2017;8:144.

Polling Question

In a hypoactive state, when norepinephrine levels are low, which of the following receptors would you want to target?

A α_1

B α_2

C β_1

D None of the above

Management Considerations for MDD

Polling Question

In your clinical practice, what is your preferred second-line treatment strategy when your first-choice ADT is ineffective?

A. Increase dose and optimize current ADT

B. Switch to a different ADT (SSRI or SNRI)

C. Switch to a DNRI

D. Stay on same ADT and combine with another ADT (SSRI or SNRI)

E. Stay on same ADT and augment with a DNRI

F. Stay on same ADT and augment with a non-ADT (AAP)

DNRI=dopamine/norepinephrine reuptake inhibitor. SNRI=serotonin/norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.

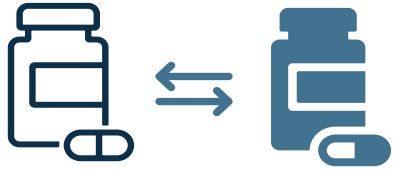
Meta-analyses: Efficacy of Second-line Treatments for MDD

Meta-analyses examining the efficacy of second-line treatments have informed some guideline recommendations[1,2]:

DOSE ESCALATION

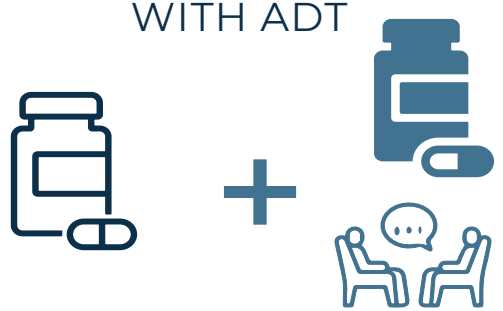
Studies suggest that dose escalation after initial nonresponse may not be particularly effective[3,4]

SWITCHING ADT



Studies have shown similar efficacy between switching ADTs and continuing with the current ADT[5]*

COMBINING/AUGMENTING WITH ADT



Evidence supports improvement over monotherapy[6,7]†‡

Data suggest that switching antidepressant therapies is frequently ineffective, whereas combining antidepressant therapies with different monoamine profiles may be more effective[5-8]

*In the STAR*D trial, nearly 75% of patients with MDD who were switched to a second ADT failed to achieve remission.[7]
†Combining a reuptake inhibitor with an α_2 antagonist was more effective than other combinations.[8]
‡Guidelines also suggest that psychotherapy should be added or increased when appropriate and that the diagnosis should be re-evaluated if clinically warranted.[1]

STAR*D=Sequenced Treatment Alternatives to Relieve Depression.

1. American Psychiatric Association. 3rd ed. 2010.
2. Nutt DJ, et al. J Clin Psychiatry. 2010;71(suppl E1):e08.
3. Dold M, et al. Psychother Psychosom. 2017;86(5):283-291.
4. Ruhé HG, et al. Br J Psychiatry. 2006;189:309-316.
5. Bschor T, et al. J Clin Psychiatry. 2018;79(1):16r10749.
6. Rush AJ, et al. Am J Psychiatry. 2006;163(11):1905-1917.
7. Henssler J, et al. Can J Psychiatry. 2016;61(1):29-43.
8. Henssler J, et al. JAMA Psychiatry. 2022;79(4):300-312.

Practice Guidelines and Recommendations For Augmentation of ADTs[1-6]

Some Clinical Evidence Supports Augmenting Reuptake Inhibitors With Different Drug Classes and Psychotherapy

Adjunctive Treatment	APA[1]	NICE[2]	BAP[3]	WFSBP[4]	CANMAT[5]
Antipsychotics	●	●	●	●	●
Mood stabilizers	●	●	●	●	●
Benzodiazepines	●	●		●	
Psychotherapy	●		●	●	●

Clinical confidence

● Substantial ● Moderate ● Low ● None

APA=American Psychiatric Association. BAP=British Association for Psychopharmacology. CANMAT=Canadian Network for Mood and Anxiety Treatments. NICE=National Institute for Health and Care Excellence. WFSBP=World Federation of Societies of Biological Psychiatry.

1. American Psychiatric Association. 3rd ed. 2010.
2. National Collaborating Centre for Mental Health (UK). British Psychological Society; 2010.
3. Cleare A, et al. J Psychopharmacol. 2015;29(5):459-525.
4. Bauer M, et al. World J Biol Psychiatry. 2013;14(5):334-385.
5. Kennedy SH, et al. Can J Psychiatry. 2016;61(9):540-560.
6. Parikh SV, et al. Can J Psychiatry. 2016;61(9):524-539.

Response and Remission Rates of Augmentation With AAPs, ADT Monotherapy, and Augmentation With a DNRI[1]

In a 12-week follow-up of an RCT of 1522 patients with MDD:

Patients with unresolved symptoms were separated into three treatment groups:

- Switch to a DNRI
- Augment ADT with a DNRI
- Augment ADT with an AAP

Augmentation with an AAP was superior in response and remission rates compared to:

- Switching ADTs to a DNRI
- Augmenting current ADT with a DNRI

	Response %	Remission %
Switch to a DNRI	62.4%	22.3%
Augment current ADT with a DNRI	65.6%	26.9%
Augment current ADT with an AAP	74.3%	28.9%

RCT=randomized controlled trial.

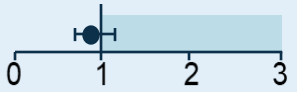
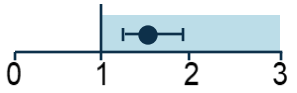
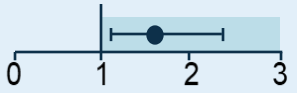
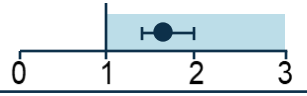
1. Mohamed S, et al. JAMA. 2017;318(2):132-145.

Remission Rates of Augmentation With AAPs and Monotherapy[1]

In a meta-analysis of 11 RCTs consisting of 3341 patients with MDD:

- AAP augmentation showed superior efficacy compared to monotherapy
- Effect size positively correlated with severity of treatment-resistant depression

Remission Rates

	AAP n/N	Monotherapy n/N	Odds Ratio* (95% CI)	
Non-TRD	32/49	39/53		0.89 (0.69-1.14)
TRD 1	248/753	85/434		1.55 (1.25-1.92)
TRD 2	54/198	34/203		1.63 (1.11-2.38)
TRD 2-4	281/931	127/720		1.68 (1.40-2.03)

*Odds ratio >1=superior to placebo.
CI=confidence interval. n/N=number of patients achieving remission/total number of patients.
TRD=treatment-resistant depression (number after acronym indicates number of ADT failures within the current depressive episode).

1. Wang HR, et al. Int J Neuropsychopharmacol. 2015;18(8):pyv023.

Polling Question

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

A. Atypical antipsychotics

B. Mood stabilizers

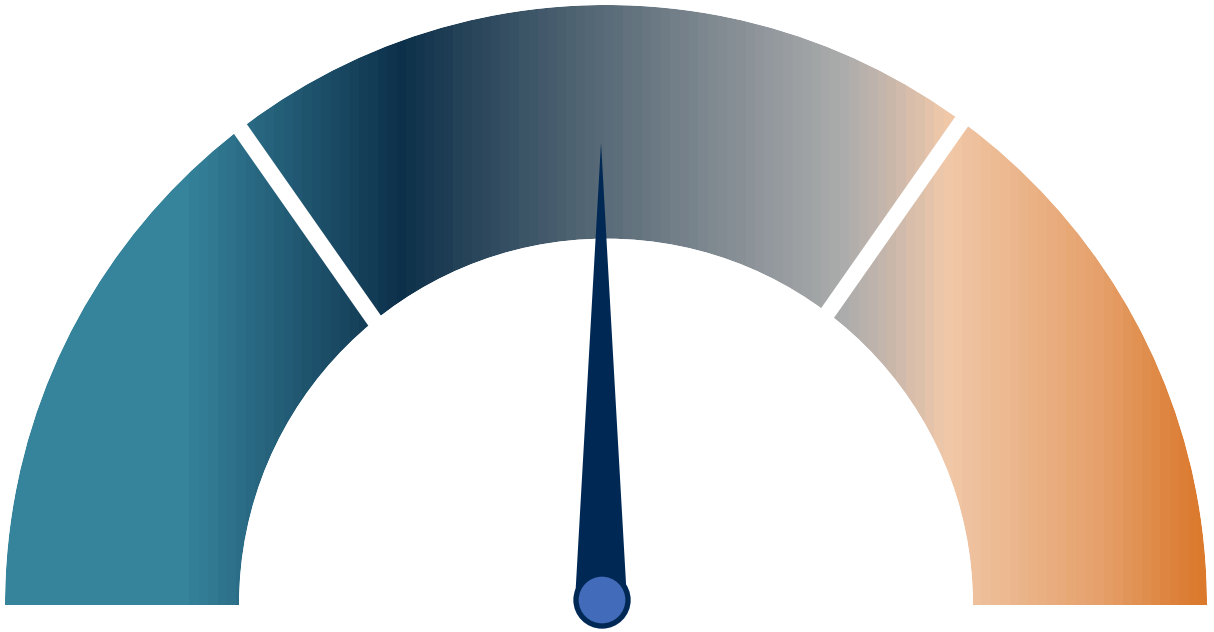
C. Benzodiazepines

D. Psychotherapy

E. Augment by adding an antidepressant

α-Adrenoceptors Can Modulate Noradrenergic Tone

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



Levels of CNS norepinephrine activity[1]

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.

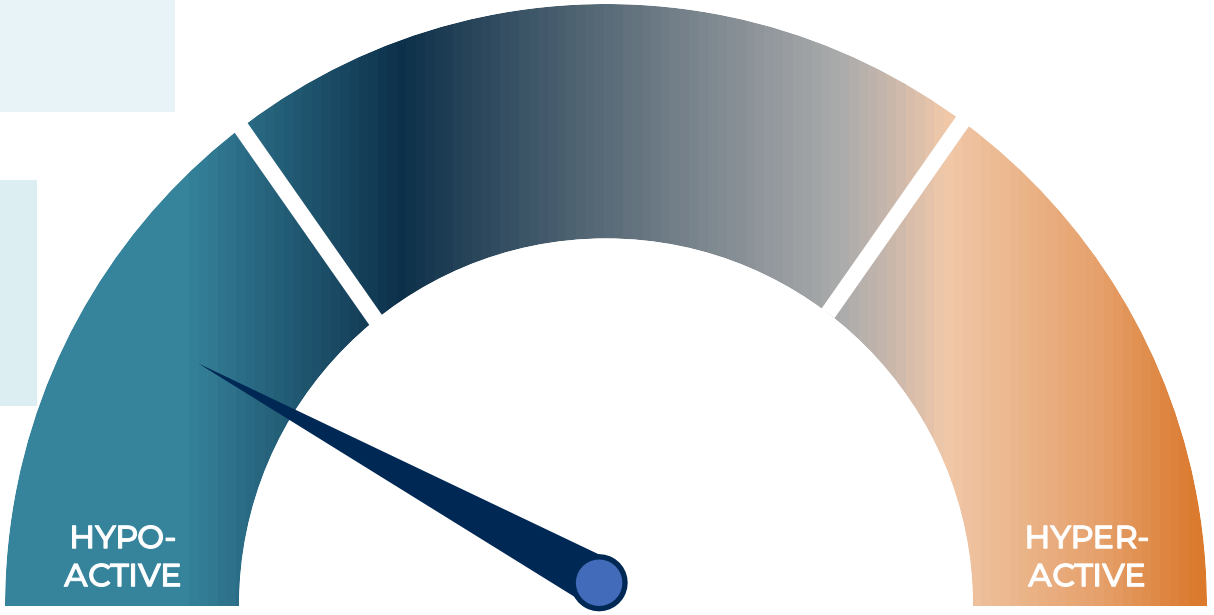
α-Adrenoceptors Can Modulate Noradrenergic Tone

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

α_{1B} **Not engaged** (low affinity)

α_{2C} **Engaged** (high affinity)

Selective α_{2C}-adrenoceptor antagonism works to **increase NE levels**[2,4]



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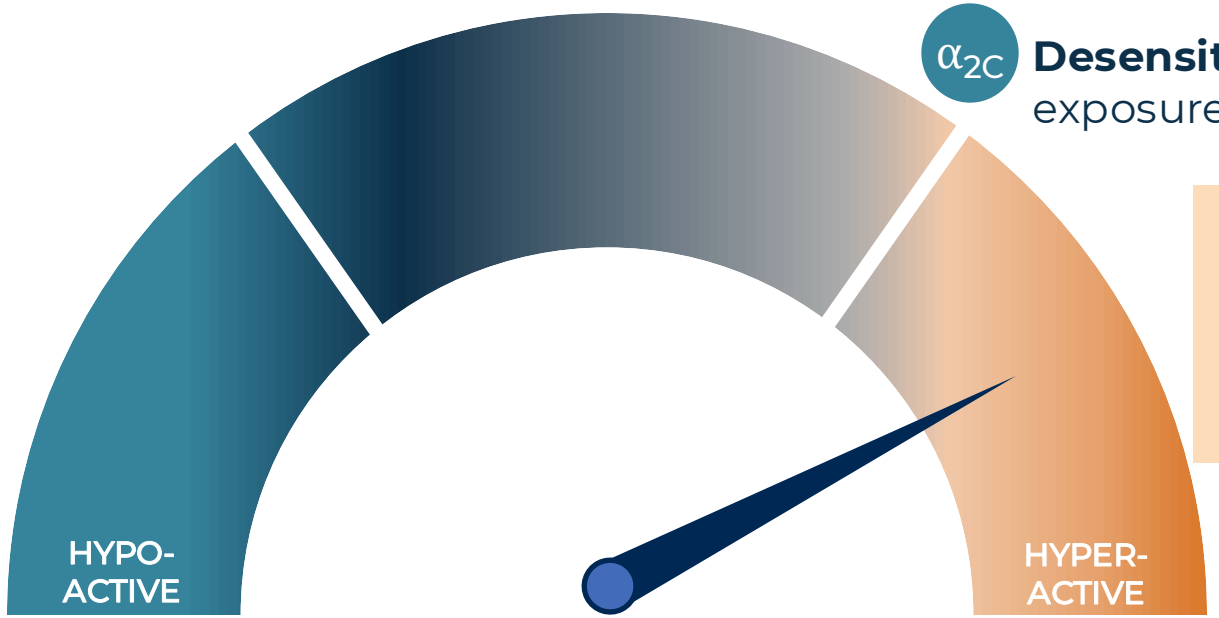

Levels of CNS norepinephrine activity[1]

Selective α_{1B}-adrenoceptor antagonism may work to **block the action of excessive NE levels[3]**

1. Yamamoto K, et al. *Psychiatry Clin Neurosci*. 2014;68(1):1-20.
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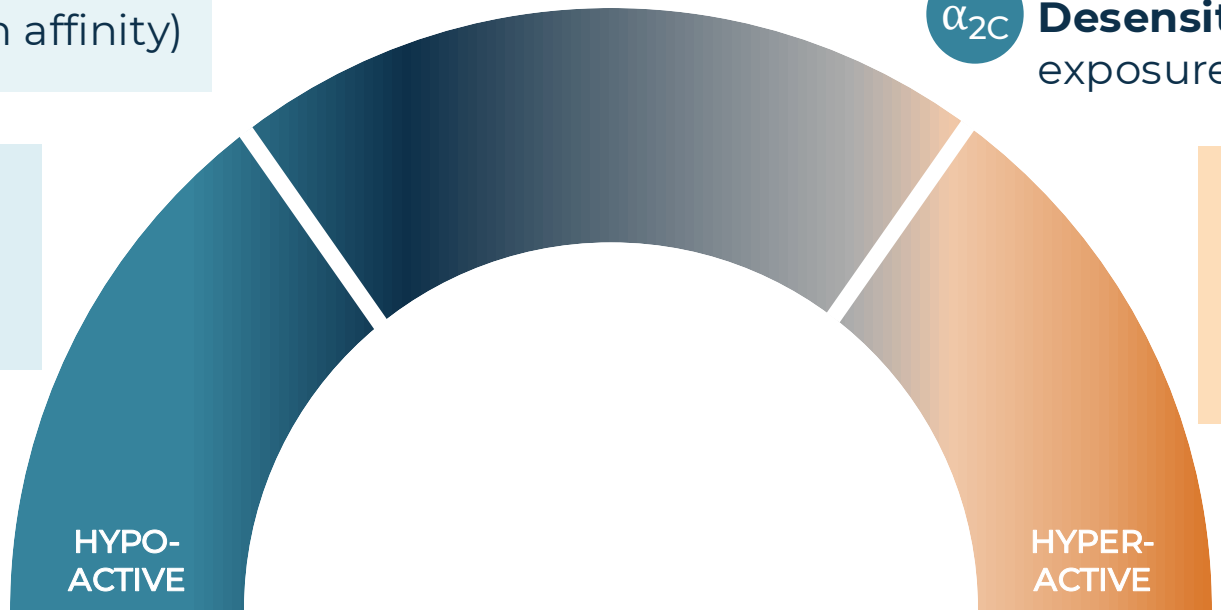

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4. Uys MM, et al. *Front Psychiatry*. 2017;8:144.

Polling Question

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

A α_{1A}

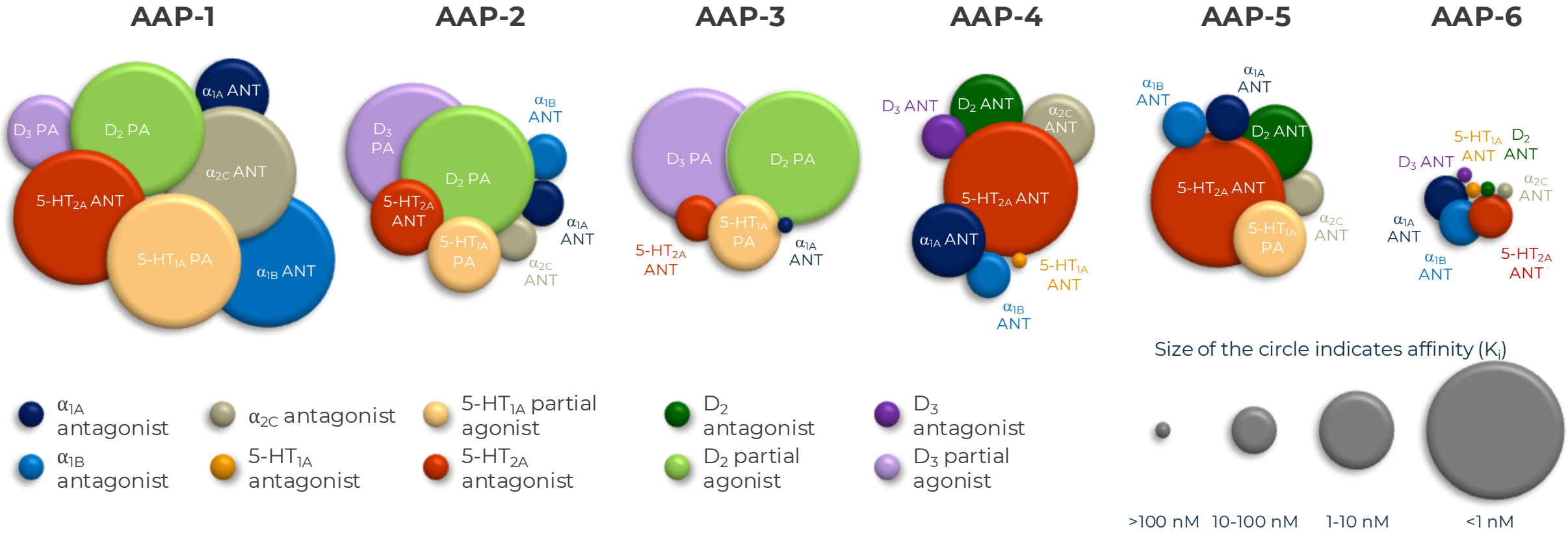
B α_{1B}

C α_{2B}

D α_{2C}

E β_2

Illustrative Representation: Affinity Profiles of Atypical Antipsychotics (AAPs)[1]



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]

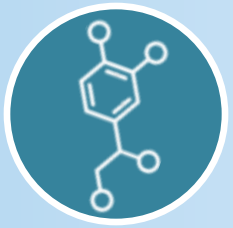
Maintain any therapeutic benefit of the first-line agent[1,2]

Enhance the antidepressant effect[1,3]

Increase remission rates[1,3]

Avoid withdrawal symptoms due to switching[2]

Counteracts 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]

1. American Psychiatric Association. 3rd ed. 2010.
2. Papakostas G. *J Clin Psychiatry*. 2009;70(suppl 6):16-25.
3. National Collaborating Centre for Mental Health (UK). British Psychological Society; 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.

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 NE 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]

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.

Summary

Following first-line treatment, many patients with MDD continue to experience unresolved symptoms[1,2]

1

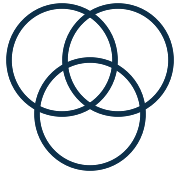
Symptoms of MDD may be related to hypo- or hyperactive NE systems[3-6]

Antagonism at α-adrenoceptors may help regulate NE levels in appropriate ranges[7]

2

NE 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

1. Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.
2. Conradi HJ, et al. *Psychol Med*. 2011;41(6):1165-1174.
3. Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.
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.