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Exploring Unresolved Symptoms in Major Depressive Disorder (MDD)

Potential role of norepinephrine

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Our Featured Speakers

Roger S. McIntyre, MD, FRCPC

Professor of Psychiatry and Pharmacology, University of Toronto,
Chairman and Executive Director, Brain and Cognition Discovery Foundation (BCDF), Toronto, Canada
www.bcdfoundation.ca
Board Chair, Depression and Bipolar Support Alliance (DBSA) Board of Directors, Chicago, Illinois, USA

John Awad, MD

Moderator
Senior Clinical and Science Liaison
Field Medical Affairs, OPDC, Inc.

Objectives

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

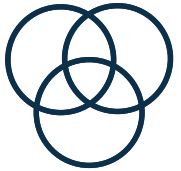
1

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 how first-line treatments target one or two of the monoamines involved in MDD

3

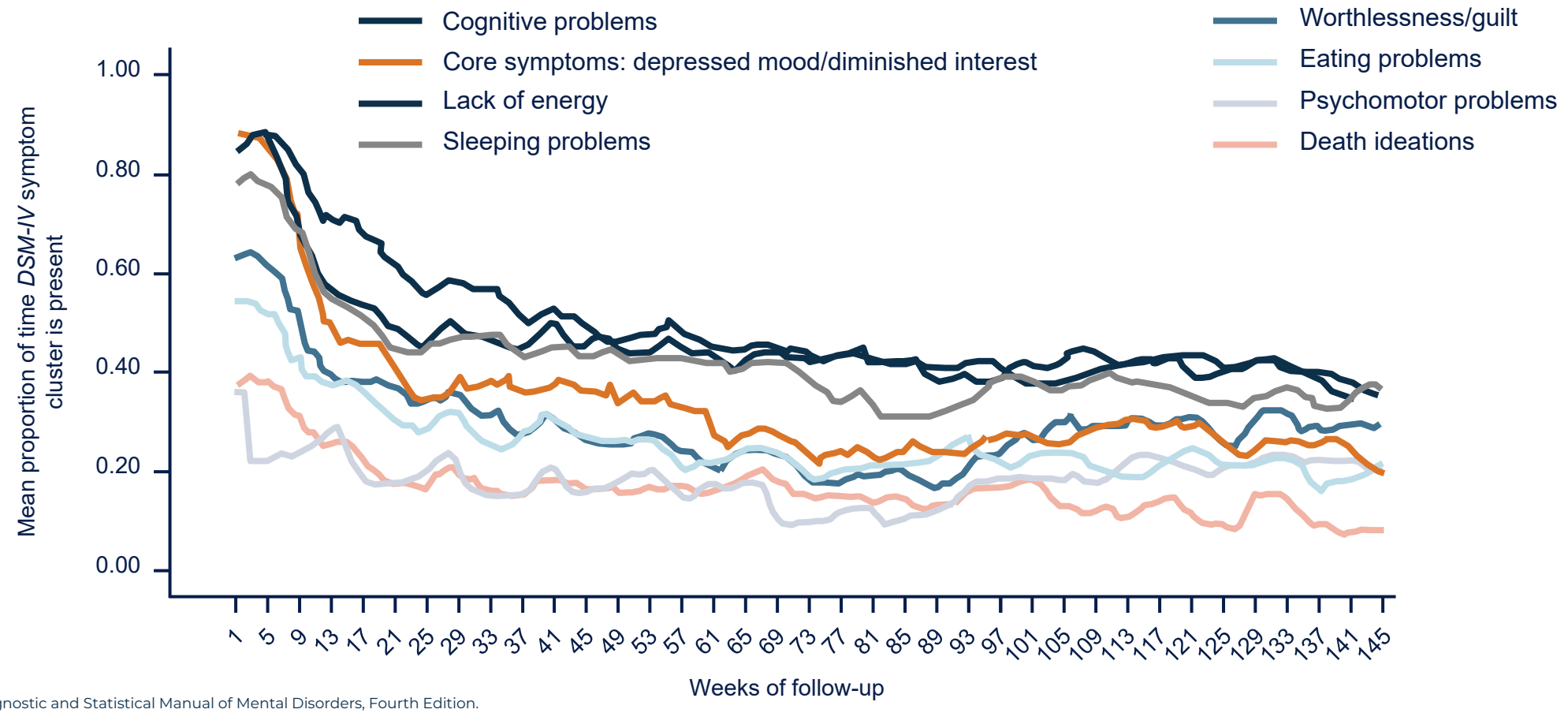


Learn how adjunctive atypical antipsychotics (AAPs) may improve MDD symptoms by addressing dysregulation of the NE system, in addition to DA and 5-HT

4

Unresolved Symptoms Following Antidepressant Treatment (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.

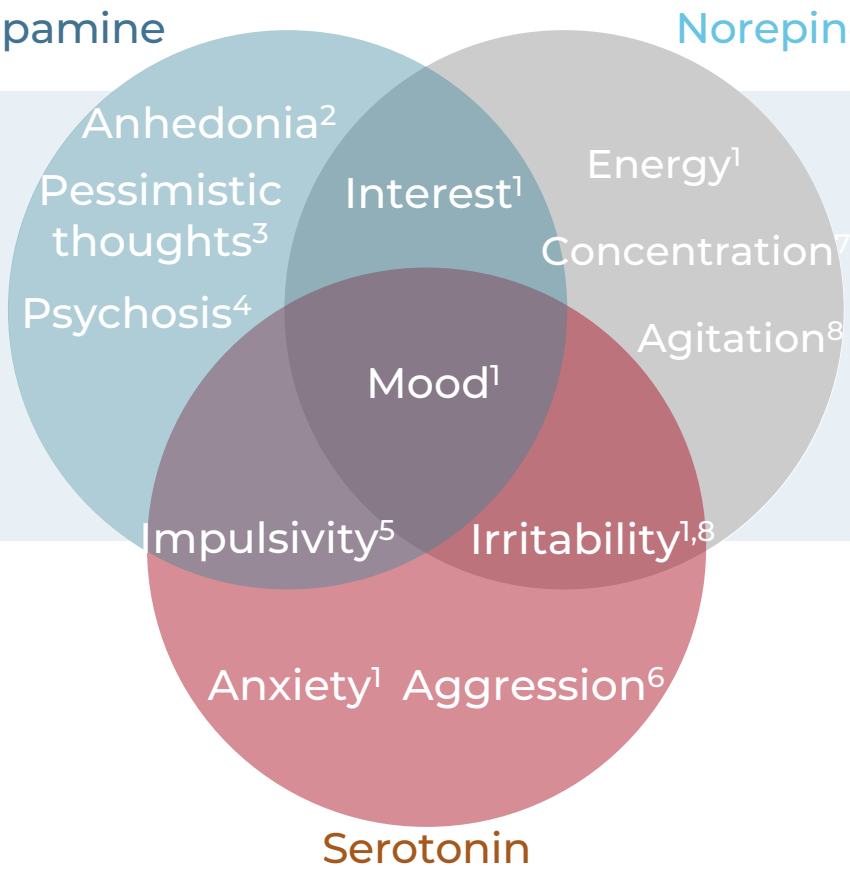
1. Conradi HJ, et al. Psychol Med. 2011;41(6):1165-1174.

Monoaminergic Dysregulation in MDD

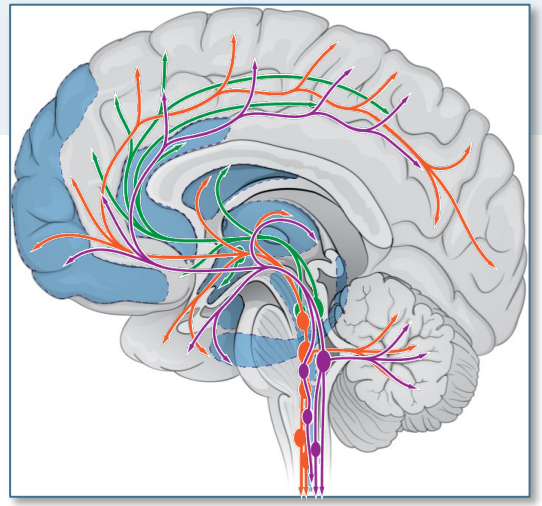
A Closer Look at Norepinephrine

Monoamine Neurotransmitter System Dysfunction[1-8]

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



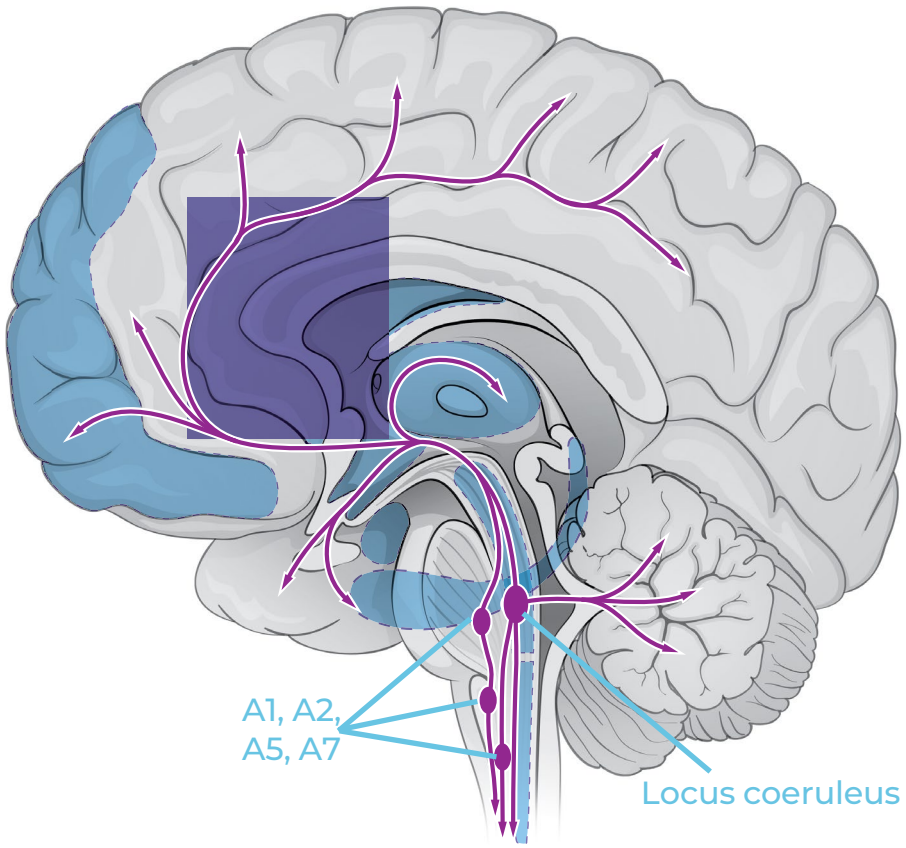
Noradrenergic system dysfunction may contribute to unresolved symptoms of MDD[7,8]



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.
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.
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[1-4]

Circuitry[1]

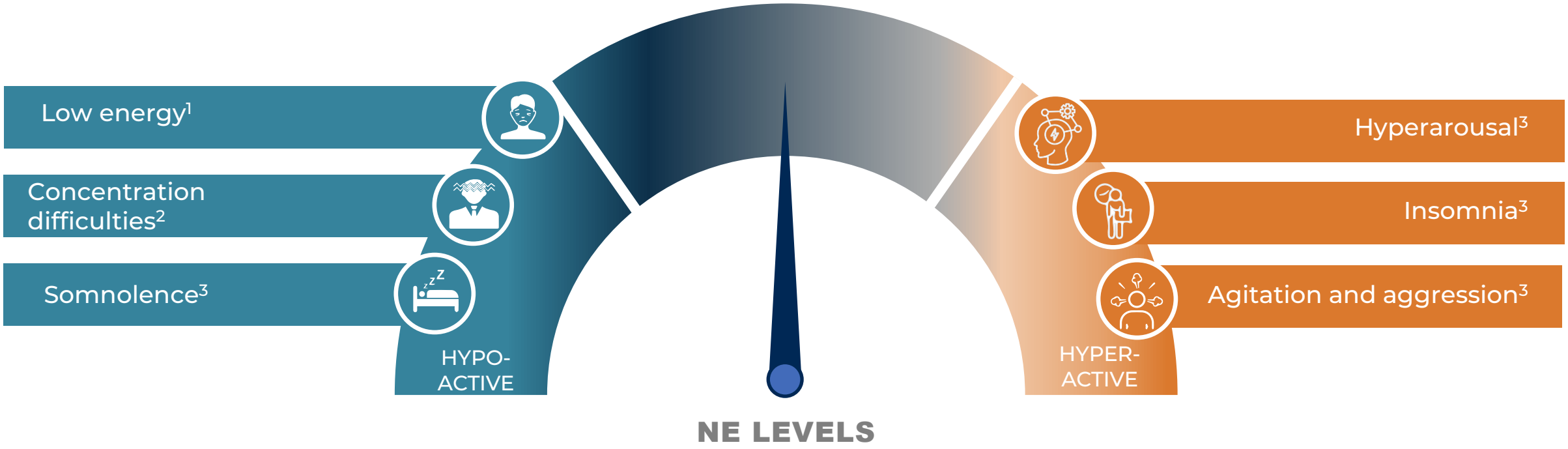


Adrenergic Receptors[5]

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.

Dysregulation of the Noradrenergic System[1-3]

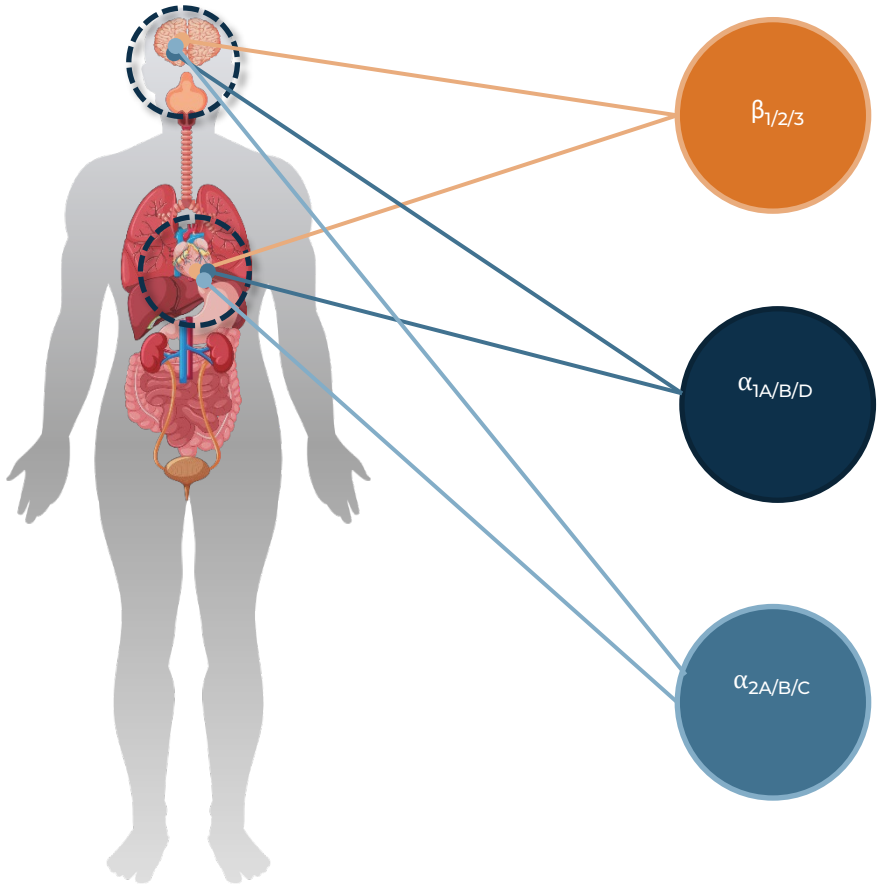


Adrenoceptors can modulate symptoms caused by noradrenergic system dysregulation

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.

Adrenoceptor Localization and Function

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



$\beta_{1/2/3}$

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

$\alpha_{1A/B/D}$

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

$\alpha_{2A/B/C}$

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

CNS=central nervous system.

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.

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

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

α_1 **Not engaged** (low affinity)

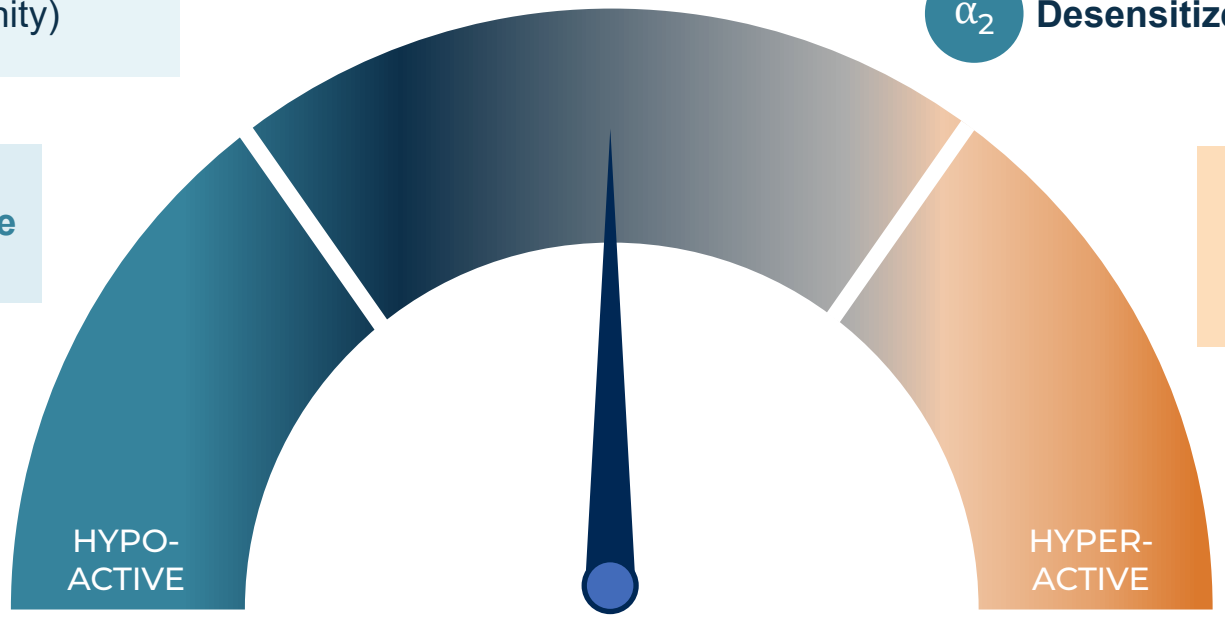
α_2 **Engaged** (high affinity)

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

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]



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.

Treatment Considerations

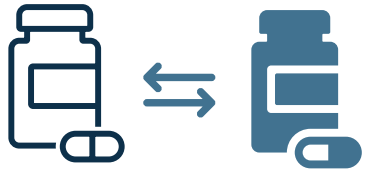
Meta-analyses: Efficacy of Second-line Treatments for MDD

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[7,8]†‡

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.[6]
†Combining a reuptake inhibitor with an α_2 antagonist was more effective than other combinations.[7]
‡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.

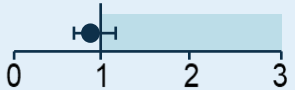
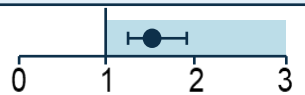
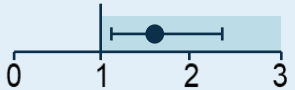
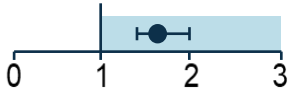
1. American Psychiatric Association. 3rd ed. 2010.
2. Nutt DJ, et al. J Clin Psychiatry. 2010;71(suppl E1):e08.
3. Dold M, et al. Psychother Psychosom. 2017;86(5):283-291.
4. Ruhé HG, et al. Br J Psychiatry. 2006;189:309-316.
5. Bschor T, et al. J Clin Psychiatry. 2018;79(1):16r10749.
6. Rush AJ, et 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.

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). RCT=randomized controlled trial.

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

α-Adrenoceptors Can Modulate Noradrenergic Tone

The impacts of α-adrenoceptor antagonism can depend on levels of norepinephrine 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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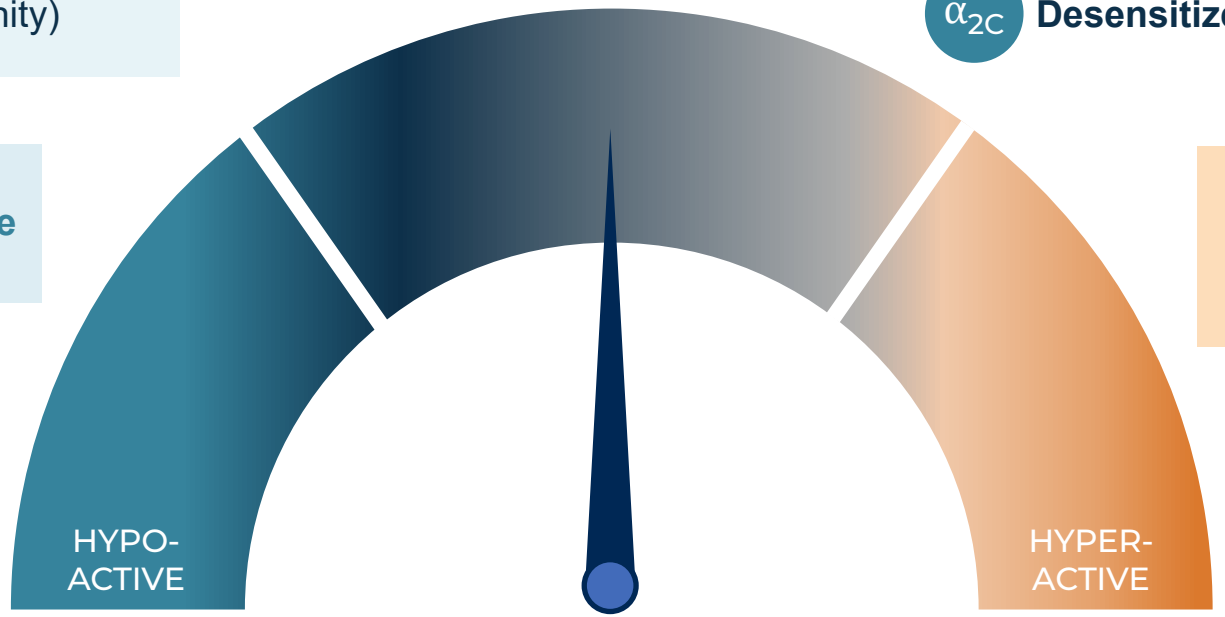
α_{2C} **Desensitized** (prolonged exposure)

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



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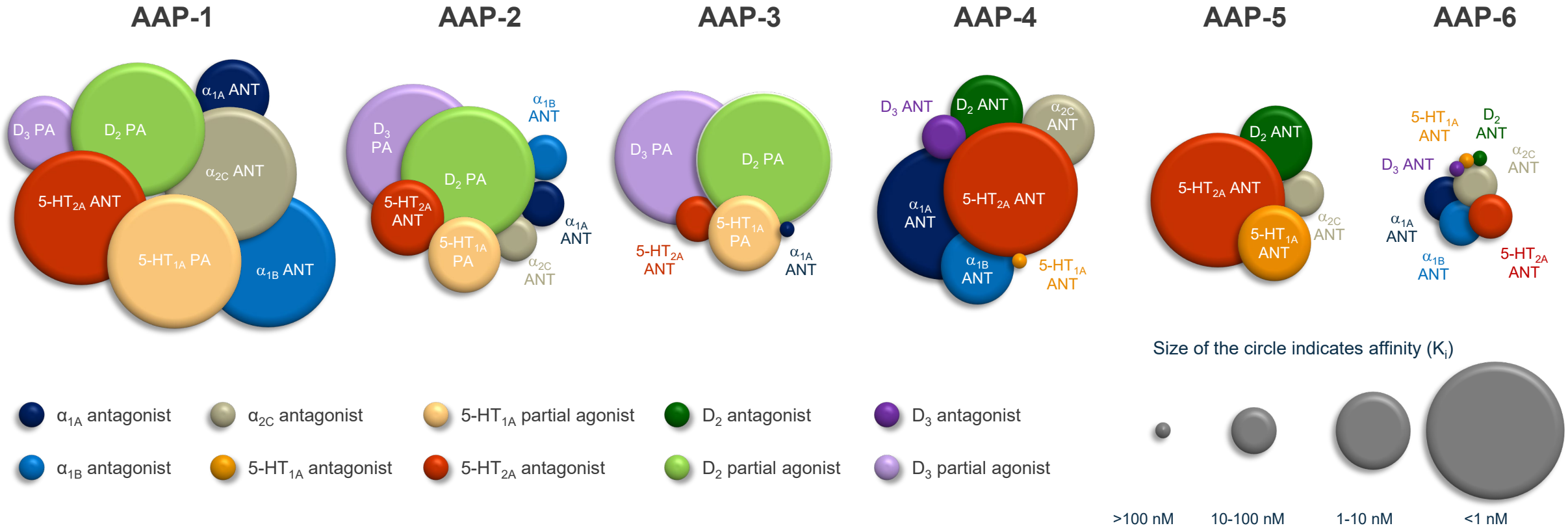
1. Yamamoto K, et al. Psychiatry Clin Neurosci. 2014;68(1):1-20.
2. Bücheler MM, et al. Neuroscience. 2002;109(4):819-826.
3. Arnsten AF, et al. Neurobiol Stress. 2015;1:89-99.
4. Uys MM, et al. Front Psychiatry. 2017;8:144.

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



ANT=antagonist. Ki=inhibitory constant. nM=nanomolar. PA=partial agonist.

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

Considerations for Augmentation With AAPs

Potential Advantages[1-6]

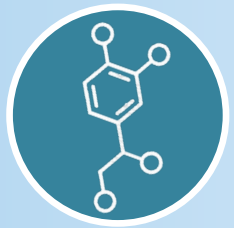
Maintain any therapeutic benefit of the first-line agent[1,2]

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.

Summary

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

1

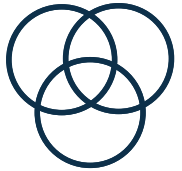
Symptoms of MDD may be related to hypo- or hyperactive NE systems[3-6]

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

2

First-line treatments target one or two of the monoamines involved in MDD

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.

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Potential role of norepinephrine

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