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Beyond Memory Loss: Optimizing the Role of Primary Care in Assessing & Treating Agitation in Alzheimer's Dementia

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Our Featured Speakers

C. Brendan Montano, MD, PC

Director and Principal Investigator for Connecticut Clinical Research in Cromwell, Connecticut

Beth DiNapoli, PhD

Senior Clinical & Scientific Liaison

Otsuka Neuroscience Medical Affairs

Elika Hefazi, PharmD, BCPP

Clinical & Scientific Liaison

Otsuka Neuroscience Medical Affairs

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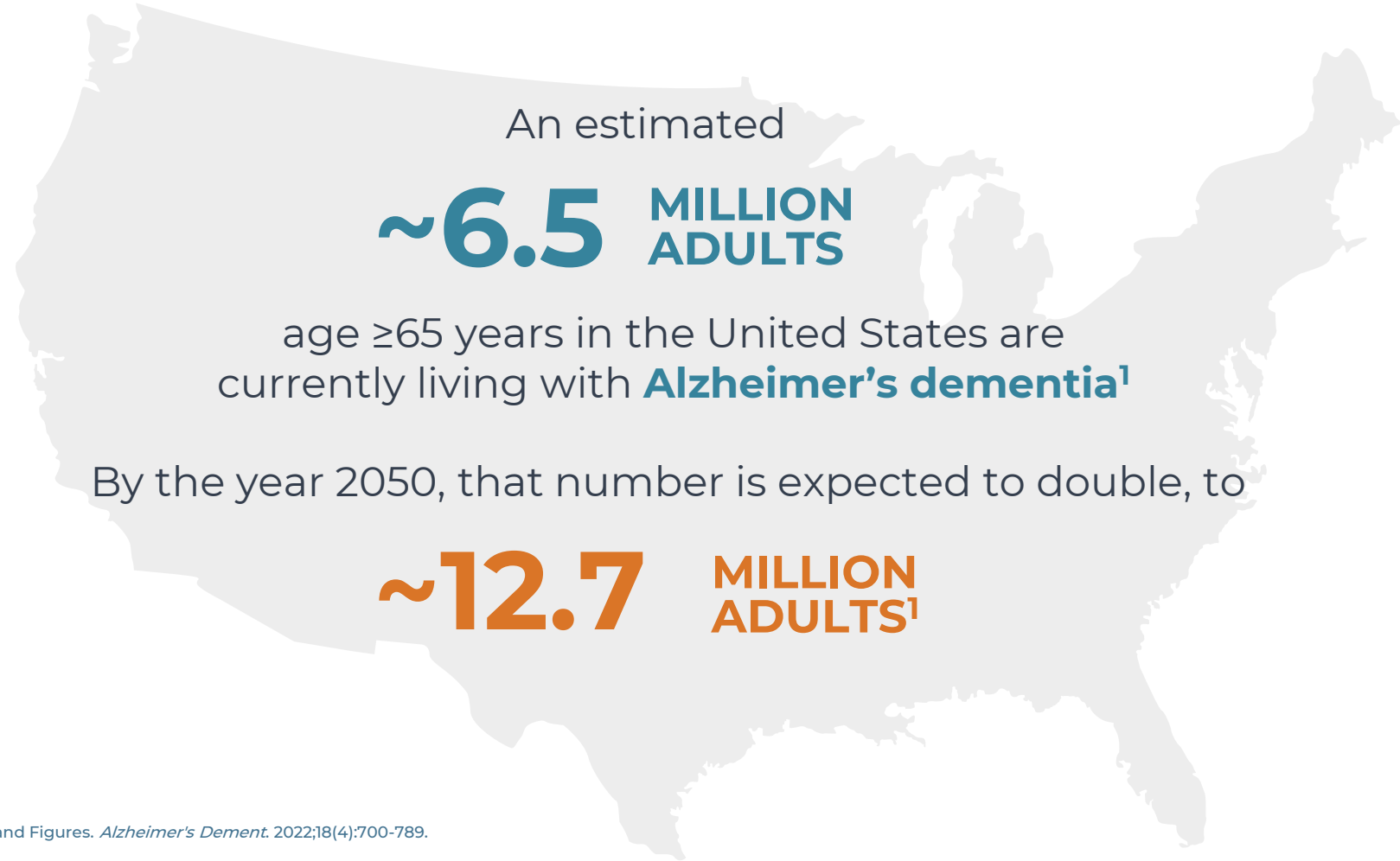
Objectives

- Review the prevalence and diagnostic challenges of agitation in Alzheimer's dementia (AAD)
- Explore the potential pathobiological correlates in AAD
- Discuss the clinical and humanistic burden of AAD
- Highlight current guidelines for nonpharmacological and off-label pharmacological treatments of AAD

Alzheimer's Dementia (AD) Is Highly Prevalent and Predicted to Increase Significantly[1]



An estimated

~6.5 MILLION ADULTS

age ≥65 years in the United States are currently living with **Alzheimer's dementia**[1]

By the year 2050, that number is expected to double, to

~12.7 MILLION ADULTS[1]

1. 2022 Alzheimer's Disease Facts and Figures. *Alzheimer's Dement*. 2022;18(4):700-789.

Neuropsychiatric Symptoms (NPS) Like Agitation Are Core Features of AD[1]

In addition to cognitive decline, manifestations of AD include a range of NPS, such as depression, anxiety, irritability, and **agitation**[1,2]

Agitation is one of the most **complex, prominent, stressful, and costly** aspects of AD care[2,3]

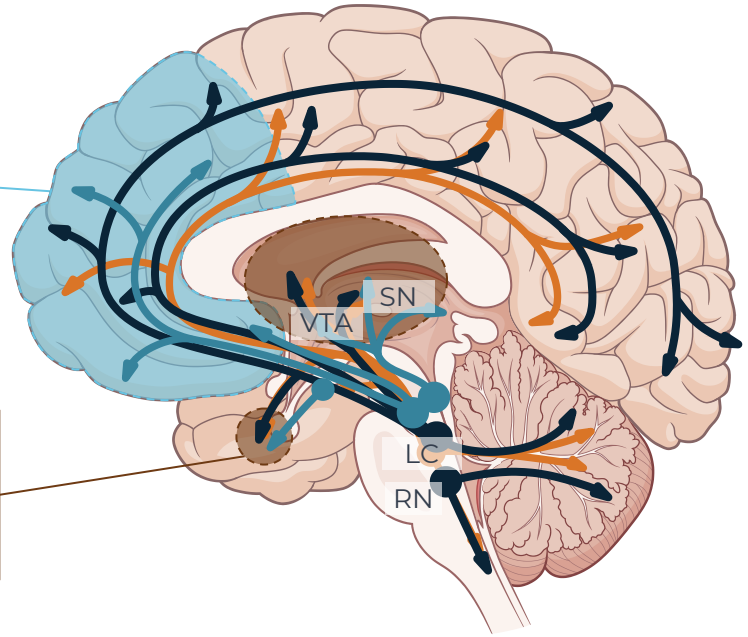
1. Anatchkova M, et al. *Int Psychogeriatr.* 2019;31(9):1305-1318.
2. Kales HC, et al. *BMJ.* 2015;350:h369.
3. Antonsdottir IM, et al. *Expert Opin Pharmacother.* 2015;16(11):1649-1656.

Summary of NSD Monoamine Dysfunction in AAD

Tau pathology and neurodegeneration in key prefrontal and subcortical brain regions may increase the risk of developing AAD[1]

AAD may reflect an imbalance between top-down **executive control** and bottom-up **emotional drive**[1]

PFC function[2] **(executive control)**



Amygdala function[3] **(emotional drive)**

Dysfunction of NSD neurotransmitter system may contribute to imbalance between **executive control** and **emotional overdrive**[2-10]

Norepinephrine system

Overactivity[4]

Serotonin system

Deficits[6]

Dopamine system

Dysregulation[9]

LC=locus coeruleus. NSD=norepinephrine, serotonin, dopamine. PFC=prefrontal cortex. RN=raphe nuclei. SN=substantia nigra. VTA=ventral tegmental area.

1. Rosenberg PB, et al. *Mol Aspects Med*. 2015;43-44:25-37.
2. Banno K, et al. *Neuropsychiatr Dis Treat*. 2014;10:339-348.
3. Wright CI, et al. *Biol Psychiatry*. 2007;62(12):1388-1395.
4. Jacobs HI, et al. *Mol Psychiatry*. 2021;26(3):897-906.
5. Arnsten AF, et al. *Neurobiol Stress*. 2015;1:89-99.
6. Lanctôt KL, et al. *J Neuropsychiatry Clin Neurosci*. 2001;13(1):5-21.
7. Evers EA, et al. *Curr Pharm Des*. 2010;16(18):1998-2011.
8. Duke AA, et al. *Psychol Bull*. 2013;139(5):1148.
9. Cox SM, et al. *Br J Psychiatry*. 2011;199(5):391-397.
10. Lindenmayer JP. *J Clin Psychiatry*. 2000;61(14):5-10.

The International Psychogeriatric Association (IPA) Definition of Agitation in Patients With Cognitive Disorders[1]

The consensus definition for agitation in cognitive disorders includes four criteria:

1. The patient meets the criteria for cognitive impairment or dementia syndrome
2. The patient must exhibit ≥1 agitation behavior(s), and the behavior(s) must be persistent or frequently recurrent for ≥2 weeks or the behavior represents a dramatic change from the patient's usual behavior*
3. The agitation must be severe enough to produce excess disability beyond that due to cognitive impairment
4. The agitation cannot be attributed to another psychiatric disorder, suboptimal care conditions, a medical condition, or the physiological effects of substance use.

Agitation behaviors include:

Excessive motor activity behaviors:

- Pacing
- Rocking
- Gesturing
- Pointing fingers
- Restlessness
- Performing repetitious mannerisms

Verbal aggression behaviors:

- Yelling
- Speaking in an excessively loud voice
- Using profanity
- Screaming
- Shouting

Physical aggression behaviors:

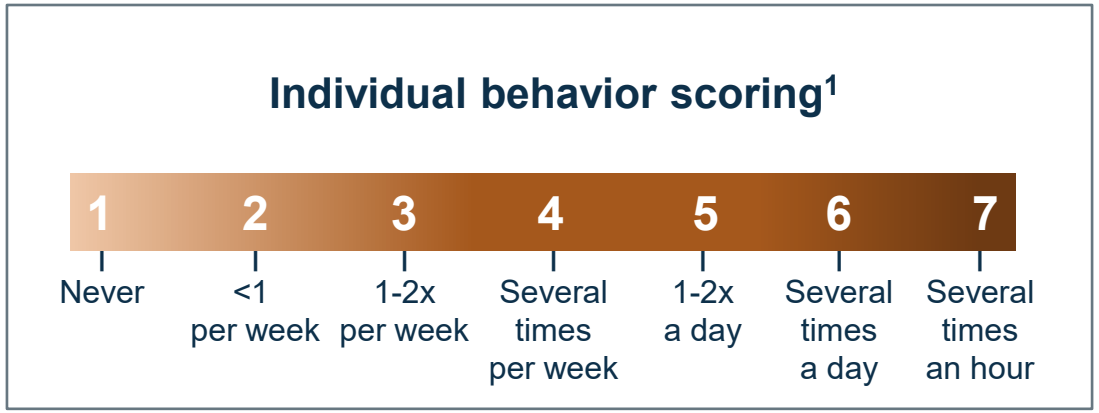
- Grabbing
- Shoving
- Pushing
- Resisting
- Hitting others
- Kicking objects or people
- Scratching
- Biting
- Throwing objects
- Hitting self
- Slamming doors
- Tearing things
- Destroying property

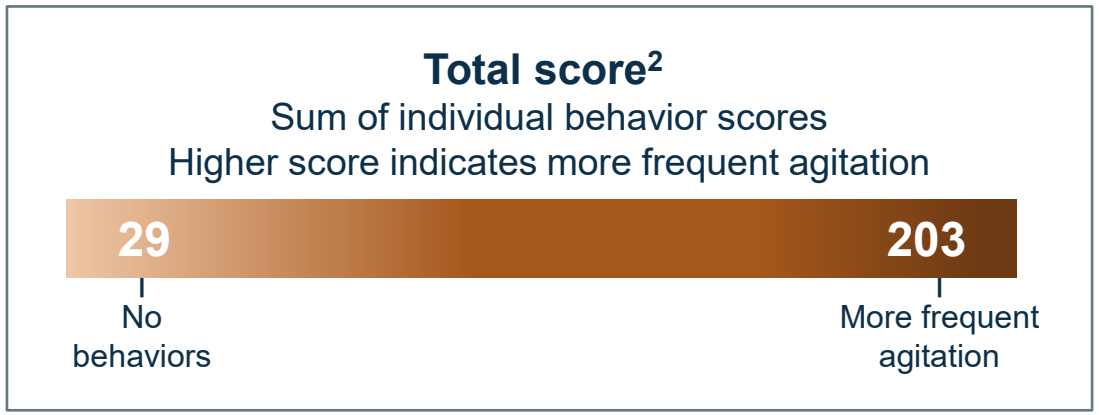
*In special circumstances the ability to document the behaviors over two weeks may not be possible and other terms of persistence and severity may be needed to capture the syndrome beyond a single episode.

1. Sano, M. et al., *International Psychogeriatrics*, 2023; 1-13. doi: 10.1017/S1041610222001041.

The Cohen-Mansfield Agitation Inventory (CMAI) Measures the Frequency of a Broad Range of Agitated Behaviors

1. The CMAI questionnaire quantifies the frequency of 29 agitated behaviors within the previous two weeks, rated on a 7-point scale[1]
2. The questionnaire can be completed by caregivers or healthcare practitioners[1,2]
3. Point changes within the CMAI scale should be compared and interpreted with care[1]





1. Cohen-Mansfield J. *Instruction Manual for the Cohen-Mansfield Agitation Inventory (CMAI)*. The Research Institute of the Hebrew Home of Greater Washington; 1991.
2. Sano M, et al. *J Prev Alzheimers Dis*. 2018;5(2):98-102.

The CMAI Measures a Broad Range of Behaviors of Agitation Consistent With the IPA Consensus Definition of Agitation

- Many behaviors in the CMAI are relevant to the three domains of the IPA definition of agitation, including[1,2]:

Excessive motor activity

Verbal aggression

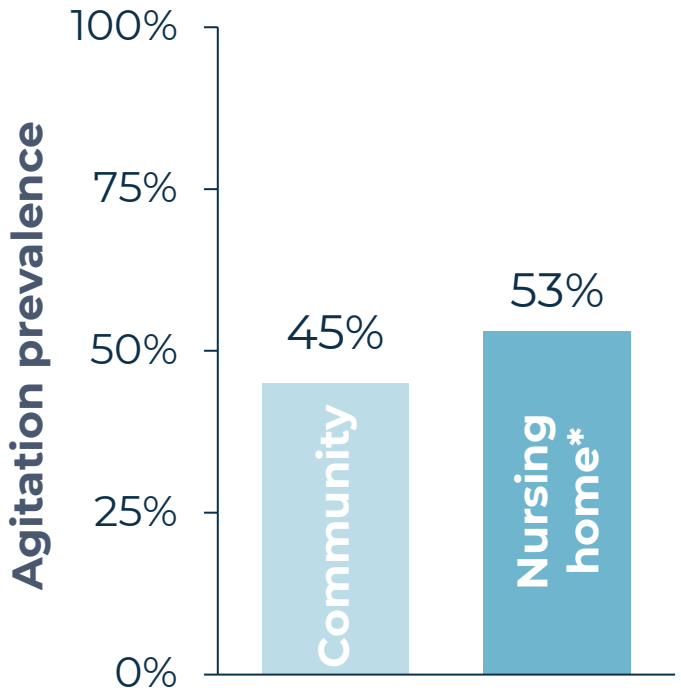
Physical aggression

29 CMAI behaviors[2,3]				
Pacing and aimless wandering	Hiding things	Throwing things	Spitting	Making physical sexual advances or exposing genitals
Inappropriate dressing or disrobing	Hoarding things	Screaming	Cursing or verbal aggression	Eating or drinking inappropriate substances
Trying to get to a different place	Constant unwarranted request for attention and/or help	Biting	Hitting self or others	Making strange noises
Handling things inappropriately	Repetitive sentences and questions	Scratching	Kicking	Intentional falling
Performing repetitious mannerisms	Complaining	Hurting self or others	Grabbing people or things inappropriately	Making verbal sexual advances
General restlessness	Negativism	Tearing things or destroying property	Pushing	

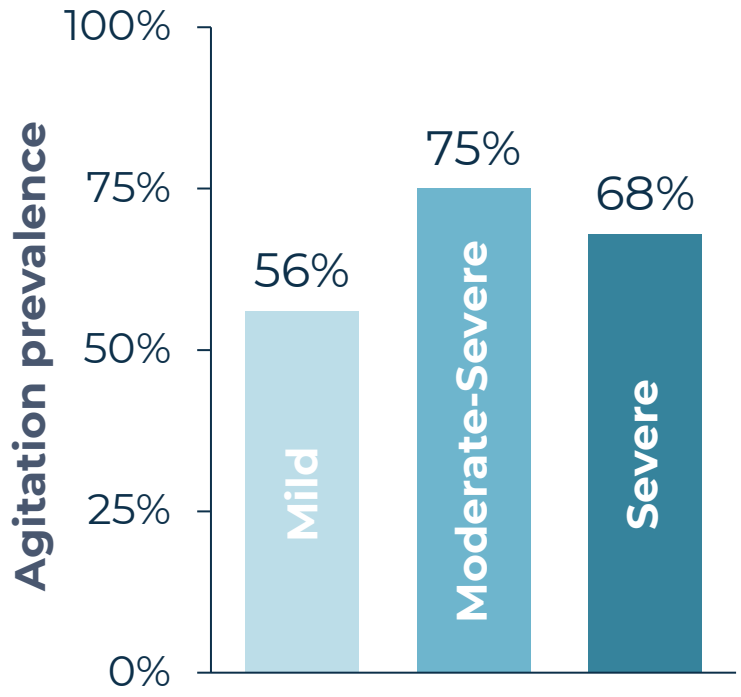
1. Cummings J, et al. *Int Psychogeriatr.* 2015;27(1): 7-17.
2. Cohen-Mansfield J. *Instruction Manual for the Cohen-Mansfield Agitation Inventory (CMAI)* 1991.
3. Rabinowitz J, et al. *Am J Geriatr Psychiatry.* 2005;13(11):991-998.

Agitation Associated with AD Is Highly Prevalent Across Patient Settings and Disease Severity[1,2]

Patient Care Setting[2,3]



AD Severity[2]



*Nursing home percentage reported includes those with AD and other dementias.

1. Kales H, et al. BMJ. 2015;350:h369.
2. Halpern R, et al. Int J Geriatr Psychiatry. 2019;34(3):420–431.
3. Fillit H, et al. Int J Geriatr Psychiatry. 2021;36(12):1959-1969.

AAD Worsens the Impact of an Already Devastating Disease for the Patient

AAD is associated with[1-5]:

Accelerated disease progression

Functional decline

Decreased quality of life

Increased risk of institutionalization

Earlier death

1. Banerjee S, et al. *J Neurol Neurosurg Psychiatry*. 2006;77(2):146-148.
2. Halpern R, et al. *Int J Geriatr Psychiatry*. 2019;34(3):420–431.
3. Koenig AM, et al. *Curr Psychiatry Rep*. 2016;18(1):3.
4. Peters ME, et al. *Am J Psychiatry*. 2015;172(5):460-465.
5. Scarmeas N, et al. *Arch Neurol*. 2007;64(12):1755-1761.

Caregivers Are Needed to Identify Symptoms of AAD Despite Carrying a Substantial Burden Themselves[1-6]

- Detection of agitation is often based on **caregiver report**[5]
  - **Underdiagnosis of AAD** may result from inadequate reporting by caregivers due to the burden involved in providing care[5,6]
- Burden of care **increases with severity** of agitation[1-4]
- Caregiver distress can lead to **increased institutionalization** of patients with dementia[4]
- Informal caregivers spend more than **20 additional hours per week** actively helping patients with agitation[4]

1. Allegri RF, et al. Neuropsychiatr Dis Treat. 2006;(1):105–110.
2. Grossberg GT, et al. Am J Geriatr Psychiatry. 2020;28(4):383-400.
3. Mohamed S, et al. Am J Geriatr Psychiatry. 2010;18(10):917-927.
4. Okura T, et al. Alzheimer Dis Assoc Disord. 2011;25(2):116-121.
5. Stella F, et al. Int J Geriatr Psychiatry. 2015;30(12):1230-1237.
6. Amjad H, et al. J Gen Intern Med. 2018;33(7):1131-11387.

Treatment Guidelines for Agitation Associated with Alzheimer's Disease[1,2]

Differential diagnosis

Careful evaluation and treatment for general medical, psychiatric, environmental, or psychosocial problems that may underlie the disturbance

Nonpharmacological intervention

If agitation does not cause significant danger or marked distress to the patient or others, symptoms are best treated with environmental or behavioral measures

Pharmacological intervention

If nonpharmacological measures are unsuccessful or behaviors are dangerous or markedly distressing, then judicious pharmacological intervention is recommended

1. Rabins PV, et al. *Am J Psychiatry.* 2007;164(12):5-56.
2. Reus VI, et al. *Am J Psychiatry.* 2016;173(5):543-546.

Treatment Considerations

Currently, clinicians may prescribe the following[1-3]:

- Antidepressants
- Anxiolytics or sedative-hypnotics
- Antipsychotics (typical and atypical)
- Other Medications

Pharmacological treatments for AAD can be associated with adverse events:[2,5-7]

- Sedation*
- Extrapyramidal symptoms
- Orthostatic hypotension
- Cognitive worsening
- Fractures and falls
- Cerebrovascular and cardiovascular complications

*Some family caregivers of patients with Alzheimer's disease and other forms of dementia find sedative effects distressing and unhelpful[7].

1. Aigbogun MS, et al. *J Alzheimers Dis.* 2020;77(3):1181-1194.
2. Schneider LS, et al. *Am J Geriatr Psychiatry.* 2006;14(3):191-210.
3. Rabins PV, et al. *Am J Psychiatry.* 2007;164(12):5-56.
4. Porsteinsson AP, et al. *JAMA.* 2014;311(7):682-691.
5. Caraci F, et al. *F1000Res.* 2020;9:F1000 Faculty Rev-686.
6. Marcinkowska M, et al. *CNS drugs.* 2020;34(3):243-268.
7. Harding R, et al. *Med Law Rev.* 2012;21(2):243-277.

There Is an Unmet Need for FDA-approved Treatments for AAD

There is a need for approved pharmaceutical treatments that demonstrate efficacy, in addition to safety, in the treatment of AAD

FDA=US Food and Drug Administration.

1. Caraci F, et al. *F1000Res.* 2020;9:F1000 Faculty Rev-686.

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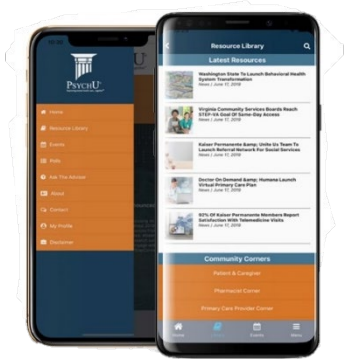

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