Difficult to Treat Depression in Late Life: Getting to Remission

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Disclosures

Salary	University of Arizona
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Other	Preparation and presentation of (disease-state) educational activity for Otsuka. Compensation for editorial board service: American Journal of Geriatric Psychiatry and Journal of Clinical Psychiatry

Agenda

- Definitions and scope of the problem.
- What is unique about Difficult to Treat Depression in Late-Life?
- Moderators that matter
- When to refer
- Algorithms to get to remission
- Third, Fourth, and Fifth-Line Approaches to Care

Rationale for Treating Depression in 1° Care

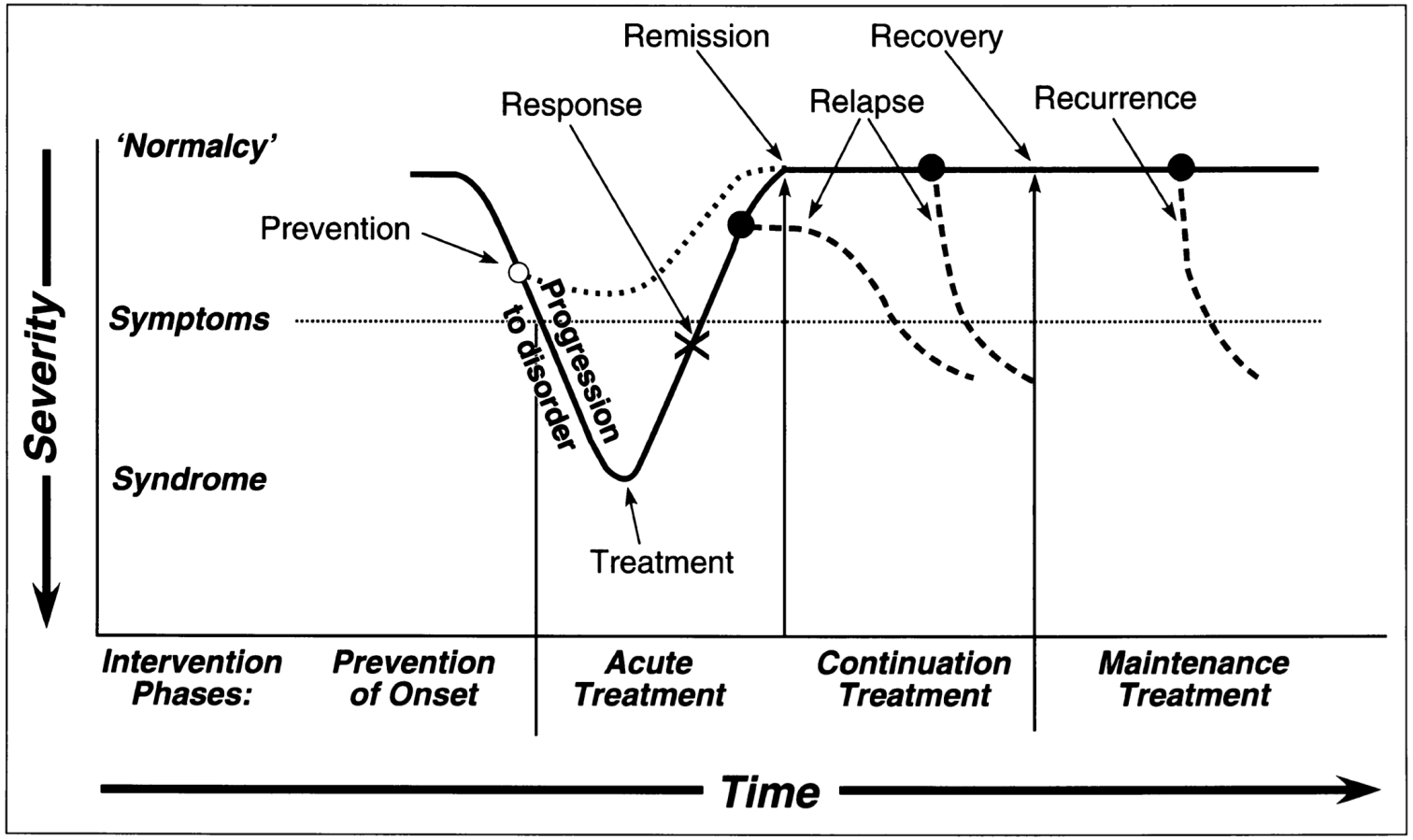
- Depression is a medical condition with psychological symptoms.
- Depression worsens medical conditions and is lethal.

  ↑Sticky platelets ↓Cardiac conduction variability ↓Immunity ↓Cognitive function ↓Vascular health

  3Ds: Depression, Diabetes, Dementia

- **What Matters Most** to patients (usually quality of life, vigor and energy, sleep, family and social, finances, independence, internal peace, joy, being pain-free) – are all impacted by depression.
- Disease silos in medicine are artificial. Like it or not, treating depression is a job responsibility of primary care providers.

Phases of Treatment and the 5 “Rs” of Depression



Kupfer DJ. Long-term treatment of depression. Journal of Clinical Psychiatry. 1991

Left untreated, mood disorders have profound consequences. Their impact on quality of life and economic productivity matches that of heart disease and surpasses the burdens associated with peptic ulcer, arthritis, hypertension, or diabetes (Wells et al., 1989). Suicide remains a leading cause of death across all age groups among people with mood disorders. Effective treatment of mood disorders decreases the utilization of health care resources and increases economic productivity (Sclar et al., 1994). In fact, the direct cost of treating mood disorders pales in comparison with the costs associated with decreased productivity, sick leaves, and premature death (P.E. Greenberg, Stiglin, Finkelstein, & Berndt, 1993).

Hollon et al. Tx and Prevention of Depression. Psych Science in the Public Interest. 2002.

U.S. Preventive Services TASK FORCE

Special Communication | USPSTF RECOMMENDATION STATEMENT

Screening for Depression in Adults
US Preventive Services Task Force Recommendation Statement

Albert L. Siu, MD, MSPH; and the US Preventive Services Task Force (USPSTF)

DESCRIPTION Update of the 2009 US Preventive Services Task Force (USPSTF) recommendation on screening for depression in adults.

METHODS The USPSTF reviewed the evidence on the benefits and harms of screening for depression in adult populations, including older adults and pregnant and postpartum women; the accuracy of depression screening instruments; and the benefits and harms of depression treatment in these populations.

POPULATION This recommendation applies to adults 18 years and older.

RECOMMENDATION The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up. (B recommendation)

JAMA. 2016;315(4):380-387. doi:10.1001/jama.2015.18392

Editorial pages 349 and 351

Author Audio and Video Interviews and **JAMA Report Video** at jama.com

Related article page 388 and **JAMA Patient Page** page 428

CME Quiz at jamanetworkcme.com and **CME Questions** page 411

Related articles at jamapsychiatry.com, jamainternalmedicine.com, and jamaneurology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Authors/Group Information: The USPSTF members are listed at the end of this article.

Corresponding Author: Albert L. Siu, MD, MSPH (albert.siu@mssm.edu).

Patients want to be screened for depression.

Qualitative study of patients with coronary heart disease.
Patients are in favor of standardized routine screening for depression in cardiac practice, **if the rationale was disclosed.**

Patients felt that standardized screening addresses holistic care demands, **promotes validation of individual symptom burden and legitimizes the display of psychological distress in cardiac practice.**

Ohanyan et al. Investigating patients´ views on screening for depression in cardiac practice: A qualitative interview study. J Psychosomatic Res. 2021.

How to Screen

- "Tell me about your mood."
- "Do you think you are depressed."
- *"In the past month, have you lost interest or pleasure in things you usually like to do?"*
- *"Have you felt sad, low, down, depressed or hopeless?"*

- For the PHQ-4, a score of $\geq$ 3 for either the anxiety or depression subset supports subsequent screening for depression or anxiety.

PHQ-4

Over the last 2 weeks, how often have you been bothered by the following problems? *(circle one per question)*		Not at all	Several Days	More than half the days	Nearly every day
1	Feeling nervous, anxious, or on edge	0	1	2	3
2	Not being able to stop or control worrying	0	1	2	3
3	Little interest or pleasure in doing things	0	1	2	3
4	Feeling down, depressed, or hopeless	0	1	2	3

Löwe B, et al. A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. J Affect Disord. 2010.

Risk Assessment and Screening Interval

Women, young and middle-aged adults, and minoritized persons have higher rates of depression, as do persons who are undereducated, previously married, or unemployed. Chronic illnesses, other mental health disorders, or a family history of psychiatric disorders also increases risk.

Risk factors in older adults include disability and poor health status related to medical illness, complicated grief, chronic sleep disturbance, loneliness, and history of depression.

Risk factors during pregnancy and postpartum include poor self-esteem, child-care stress, prenatal anxiety, life stress, decreased social support, single/unpartnered relationship status, history of depression, difficult infant temperament, previous postpartum depression, lower socioeconomic status, and unintended pregnancy.

The optimal timing and interval for screening for depression is not known.
A pragmatic approach might include screening all adults who have not been screened previously and using clinical judgment in consideration of risk factors, comorbid conditions, and life events to determine if additional screening of high-risk patients is warranted.

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Taking a Depression History

- Symptoms
  - Sleep
  - Interest
  - Guilt
  - Energy
  - Concentration
  - Appetite
  - Psychomotor
  - Suicide

(SIG E CAPS)

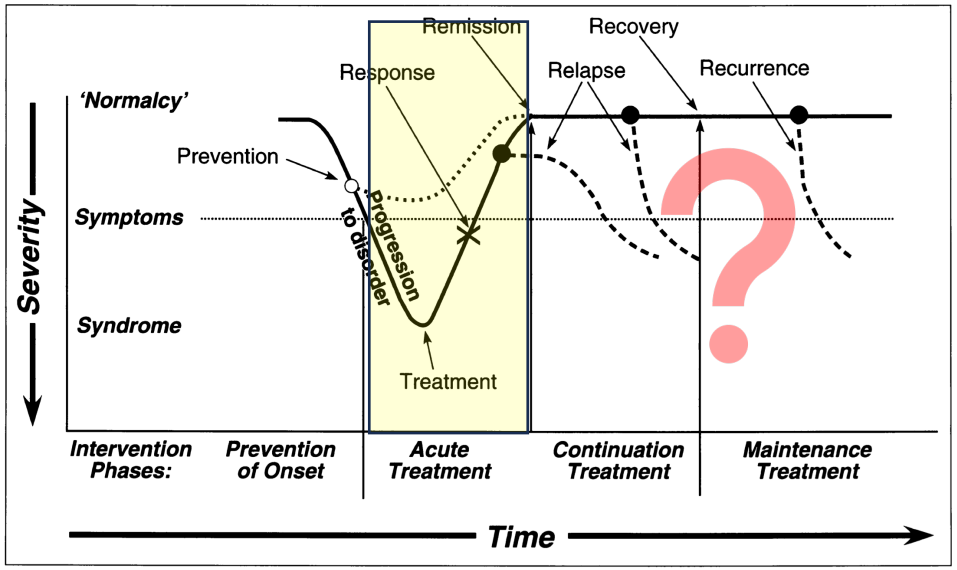
- Context
  - Duration
  - Triggers
  - Severity
  - Impairment
  - SDoH

- History
  - Previous episodes
  - Current treatment
  - Previous treatments
    - Dose and duration
  - Family hx
  - Hx suicide attempt(s)
  - Hospitalizations
  - “Is this the most depressed you’ve ever been?”
  - Have you ever been so depressed you couldn’t get out of bed?”

- Comorbidities
  - Anxiety
  - Substance use
  - Loneliness
  - Grief
  - Mania
  - SDoH & Trauma
  - Cognition
  - Somatic preoccupation
  - Psychosis
  - Sleep apnea
  - Pain
  - Multiple comorbidities

Defining ”Difficult to Treat Depression”*

- Let’s start with the generally accepted definition of Treatment Resistant Depression (TRD): Failure to respond to two different antidepressants of adequate dose and duration during the acute phase of treatment.



Personally, I think “DTD” is a kinder term than Treatment Resistant Depression (TRD). There is already enough stigma and patient-blaming in mental health care.

DTD: “Depression That Continues to Cause Significant Burden Despite Usual Treatment Efforts”

- Continuing burden may be due to difficulties in: achieving response or remission acutely, sustaining the acute phase response or remission, returning to premorbid levels of function and quality of life, lack of functional restoration despite good symptomatic control, or unacceptable tolerability or non-adherence or rejection of the tx option.

- “Usual treatment efforts” will depend on the health care setting and environment and relate to local treatment guidelines and practice.

- The key to the definition is that in the circumstances in which the patient's depression is being treated it is perceived as “difficult to treat.” It is patient defined.

- The treatment can be of any modality (e.g. psychotherapy, pharmacotherapy, neurostimulation) and the failure of this to reduce the burden of illness might be due to non-response, intolerance, lack of acceptance, or contraindication of the treatment.

- DTD differs from conventional descriptions of TRD that focus exclusively on acute treatment phase symptomatic response. It is acknowledged that the DTD ‘label’ will encompass a very heterogenous group.

McAllister-Williams et al. “The ID, assessment, and management of difficult-to-treat depression: An intern’l consensus statement. J Affective Disorders. 2020.

Patient and Illness-Related Characteristics Contributing to DTD

Characteristic	Odds Ratio	Characteristic	Odds Ratio
Older age		Recurrent episodes	1.5
Family hx of depression		Severity	1.7
Personality traits	3.4	# of hospitalizations	1.6
Any childhood mal-tx	2.5	Suicide risk	2.2
Multiple childhood mal-tx	4.1	Quality of remission	10.4
Illness duration	2.0	Anhedonia	
Onset < age 18	2.3	Comorbid anxiety d/o	2.6
Onset > age 60		Comorbid medical illness	
Substance use		Comorbid PTSD	

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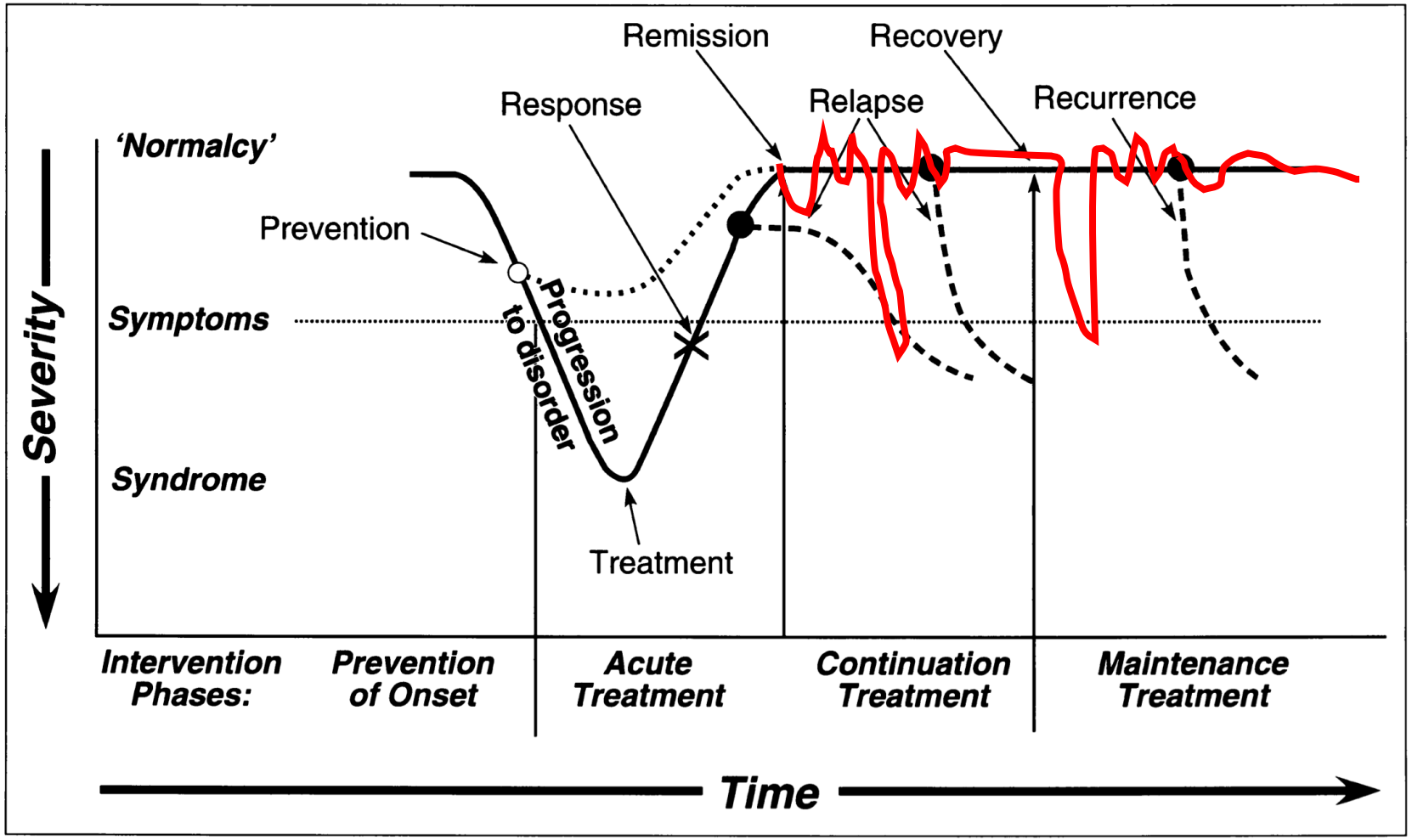
Quality of Remission in Late-Life is Often “Brittle”



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Patient and Illness-Related Characteristics Contributing to DTD – What About Older Adults

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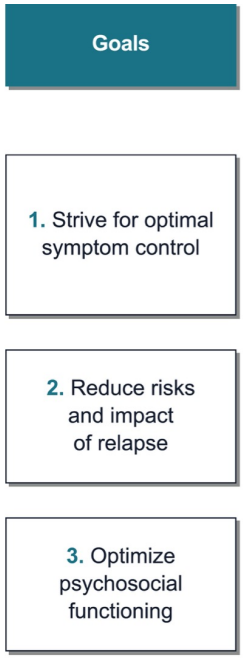
- Cognitive function
  - Mild cognitive impairment
  - Dementia
- Disability and frailty
- Neurological/Cardio-pulm/ metabolic/rheumatological diseases
- Grief
- Loneliness and social isolation
- Obstructive sleep apnea
- Fear of falling

Like so many consensus statements about mental health care, the unique features associated with aging are often excluded.

What is missing from this list?

Treatment Goals for DTD and How to Get There



McAllister-Williams et al. J Affective Disorders. 2020.

What if This Doesn't Work? When Should PCP Refer?

- Elevated risk of suicide
- Psychotic depression
- Treatment resistant depression or anxiety (i.e., not responded to 2 adequate dose and duration trials of an antidepressant).
- Bipolar condition that is not stable a/o is compromised by addiction (or in younger patients, reproductive concerns).
- Diagnostic uncertainty
- Personality traits interfering with medical management
- Neurodegenerative disease with emotional changes
- Excessive Case management needs

History: Case Example #1

- 76-year-old retired female teacher meets criteria for a fifth lifetime major depressive episode. She is compliant with notriptyline (Pamelor) 100 mg (plasma level 90 ng/ml) and olanzapine (Zyprexa) 10 mg. She has a family history of bipolar disorder, numerous motor vehicle accidents with 2 TBIs, she tried to die by suicide both by overdose, and has been treated with 4 different antidepressants in the past and 1 course of ECT (9 treatments). She has multiple comorbidities, smokes 1 ppd, and uses marijuana edibles nightly to help with insomnia. She lives in trailer, spending most of the day in bed. She will speak on the phone, but is resistant to video visits. She no longer drives, endorses frequent falls, and says she is increasingly misplacing objects.

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Treatment Resistant Depression in Late-Life: Clinical Pearls To Obtain a More Useful Clinical History

- Remember to screen for:
  - Obstructive sleep apnea
  - Alcohol and marijuana and opioid (and meth) misuse. (really any disorders that activate the reward system and can disrupt sleep including gaming and excessive social media use)
  - Benzodiazepine misuse
  - Adherence: Aim for $\geq$ 80%
  - Bipolar: “Have you even been the opposite of depressed, euphoric or incredibly irritable for many days…”
- Learn to take an actionable sleep and insomnia history.
- For all patients 70+ administer an annual cognitive screen.

Five (Minimal) Goals in the Primary Care Treatment of Late-Life Depression

1. Take a really good history.
2. Get really good at first- and second-line pharmacotherapy options.
3. Understand the impact cognitive changes and the changes in homeostasis occurring in the aging human has on depression outcomes and consistent engagement with treatment.
4. Implement what you will learn today from Dr. Anderson, Dr. Tariot, Dr. Stahl, and Dr. Fain about identifying and managing dementia, caregiver burden, and frailty.
5. Know when to refer and how to refer.

Considering Processes of Care to Improve DTD Outcomes

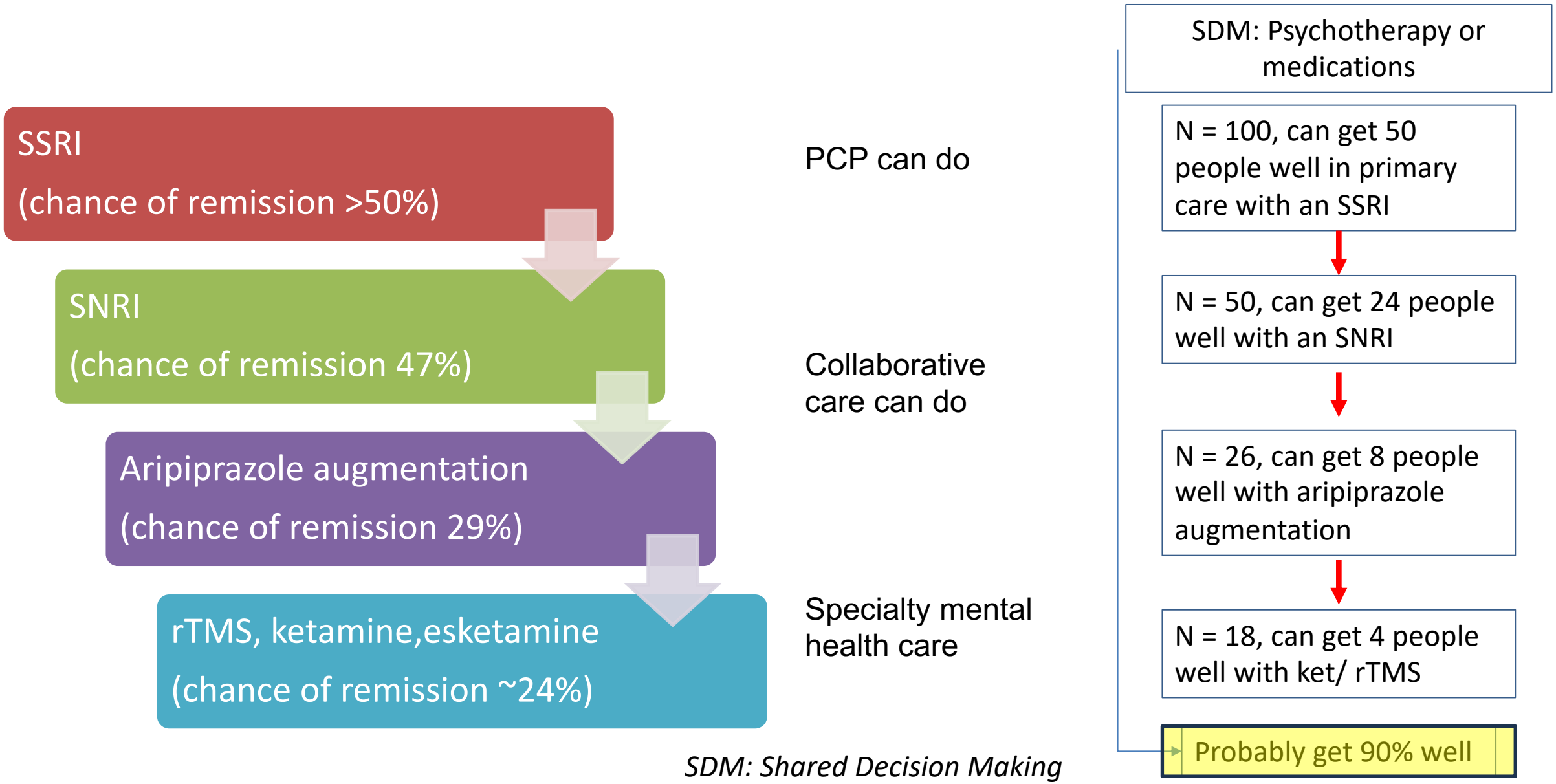
	Majority consensus and minority alternative
Step 1	Escitalopram Alternatives: sertraline, duloxetine
Step 2 for minimal or non-response)	Switch to duloxetine Alternatives: venlafaxine, desvenlafaxine
Step 3 for minimal or non-response	Switch to nortriptyline Alternative: bupropion
Step 2-3 for partial response	Augment antidepressant with lithium or an atypical antipsychotic Alternatives: combine SSRI or SNRI with mirtazapine or bupropion
Duration of each step	6 weeks Alternatives: 4 weeks; 8 weeks

Using Data From Studies of Late-Life Depression as an Example Depression Response Rates

Treatment as Usual	Collaborative Care	Receiving Placebo in a Randomized Controlled Trial
20%	40%	30-40%

Processes of Care When Using Antidepressants Under Usual Care vs Experimental Conditions	
	Usual Care (20% response)
Schedule of visits	Based on physician & patient availability; 2-3 visits/12 wks
Duration of visits	10-20 minutes
Treatment protocol	Individualized for each patient based on their characteristics and preferences
Selection of antidepressant	Large # of antidepressants, each used in a small number of patients; matching patient's clinical characteristics with perceived features of specific antidepressants
Dose titration and change in tx	Negotiated at each visit with each patients based on perceived adverse effects or lack of improvement. Changes often ill-advised or ill-times
Monitoring of sx and adverse effects	Monitoring based on spontaneous reports and ad-hoc clinical interviews
Main focus on clinical interactions	Negotiating whether and how antidepressants should be used, titrated up or down, switched, or augmented, selection of augmenting or alternative agents

An Algorithm for Late-Life Depression Treatment Adequacy and Access



SDM: Shared Decision Making

Karp's 5 Tips for Successful Treatment of Late-Life Depression in Primary Care

1. Clarify: Single Episode versus Recurrent depression.

2. Charter a course, instill confidence, and set expectations.
   - "Let's consider treatment as an experiment. If what I'm prescribing does not work, I have a plan for what to do next."
   - "I consider depression treatment in 6-month 'chunks' of time."

3. Leverage your medical assistants and nurses for between session check-ins.

4. Engage family supports. Consider a dyadic approach to treatment. If the family is not on-board with treatment planning, treatment may be sabotaged.

5. Assure obstructive sleep apnea and diabetes are well-controlled.

How do We Get This Other 10% of Late-Life DTD Well?

- Revisit and clarify the diagnosis.
- Re-evaluate cognitive status.
- Re-evaluate SDoH, adequacy of supports and residential situation, stability of comorbid medical problems, loneliness.
- Re-evaluate cognitive status.
- Refer to psychiatry with consultation question: ”Please evaluate for DTD and possible use of ECT.”

Things to Know About ECT

- The use of ECT should be considered in old-age patients who are treatment resistant to pharmacotherapy, unable to tolerate antidepressant medications, or urgently ill.

- ECT is safe, even in frail elderly patients with multiple medical comorbidities, including cardiac, pulmonary, and neurological disease.

- Moreover, ECT may be lifesaving in urgently ill geriatric patients with suicidal ideation or emergent medical conditions like catatonia.

Kerner & Prudic. Neuropsychiatry. 2014; Kellner et al. Am J Psychiatry 2012; Greenberg. Am J Geriatric Psychiatry. 2015

Right Unilateral Ultrabrief Pulse ECT in Geriatric Depression: Phase 1 of the PRIDE Study

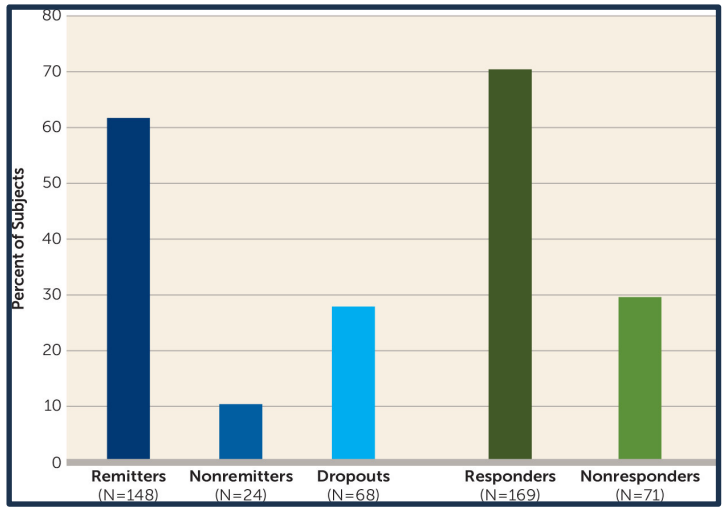


FIGURE 1. Remission, Response, and Dropout in a Study of ECT and Venlafaxine in Geriatric Depression

Remission was defined as having a score ≤10 on the 24-item Hamilton Depression Rating Scale (HAM-D) on two consecutive ratings; response was defined as having at least a 50% decrease in HAM-D score from baseline to last assessment.

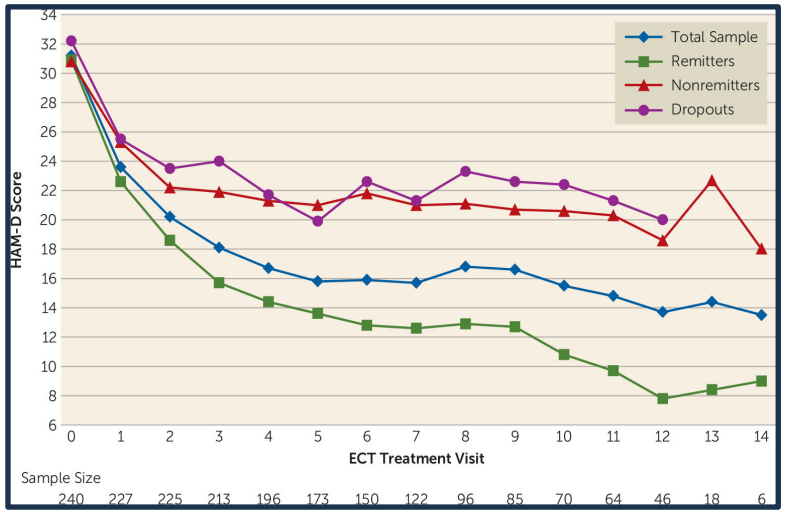


FIGURE 2. Trajectory of Observed Mean Scores on the 24-Item Hamilton Depression Rating Scale (HAM-D), by Outcome Group, in a Study of ECT and Venlafaxine in Geriatric Depression

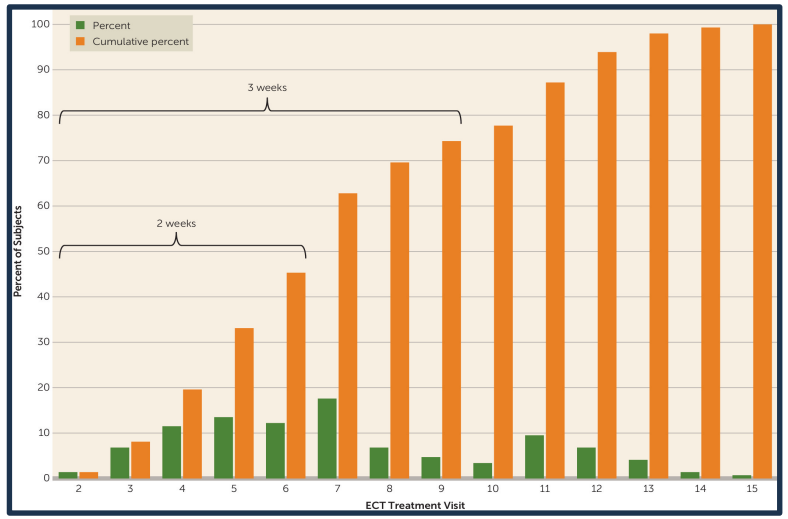


FIGURE 3. Speed of Remission Among Remitted Patients (N=148) in a Study of ECT and Venlafaxine in Geriatric Depression

Kellner et al. Am J Psychiatry 2016

Neurocognitive Effects of ECT in Late-Life Depression

- Despite its proven efficacy and safety, shortcomings of ECT include its adverse effect profile (mainly temporary cognitive impairment), and the fact that benefits are limited to the current episode of illness (unless continuation/maintenance ECT) is used (Manly et al. Am J Geriatric Psych. 2000).

- "Neurocognitive Effects of Combined Electroconvulsive Therapy (ECT) and Venlafaxine in Geriatric Depression: Phase 1 of the PRIDE Study (Lisanby et al. Am J Geriatric Psych. 2020).

- *"Of the cognitive domains assessed, only phonemic fluency, complex visual scanning, and cognitive flexibility qualitatively declined from low average to mildly impaired. While some acute changes in neurocognitive performance were statistically significant, the majority of the indices as based on the effect sizes remained relatively stable…The magnitude of change in neurocognitive function from baseline to end for most neurocognitive measures was modest."*

Arizona DTD Depression Resources to Help You Care for Your Patients

Banner University Medical Center South

Center for Interventional Psychiatry and Neurotherapeutics

Services for Difficult-to-Treat Depression

Depression and other psychiatric conditions impact every aspect of life. Depression often exacerbates other health problems including fatigue, insomnia, loneliness, and excessive worry. It can also worsen unhealthy behaviors, such as poor diet and reduced physical activity. Depression often affects the lives of those you love in addition to your own day-to-day experiences.

The Center for Interventional Psychiatry and Neurotherapeutics (CIPN) is for patients currently under psychiatric care for depression and other difficult-to-treat psychiatric conditions. Our team will provide an in-depth psychiatric consultation, including a review of your previous mental health records. You will also receive a detailed treatment recommendation shared with your referring mental health specialist.

The CIPN is one of only a handful of specialized centers in the world focused on difficult to treat depression and associated psychiatric conditions.

In addition to the consultation, our psychiatrists may recommend treatments including repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), IV ketamine, and esketamine (SPRAVATO®).

Psychiatry and Behavioral Medicine Clinics, Department of Banner - University Medical Center South
Behavioral Health Pavilion
2800 E. Ajo Way
Tucson, AZ 85713

More Information:
520.874.6657

Banner University Medical Center South

Center for Interventional Psychiatry and Neurotherapeutics

The Therapies We Offer & How They Work

What is rTMS?

rTMS uses a magnet to activate the brain. Unlike ECT, in which electrical stimulation is more generalized, rTMS can be targeted to a specific site in the brain. A typical rTMS session lasts 30 to 60 minutes and does not require anesthesia. A course of TMS takes four to six weeks, and patients receive the treatment five days a week.

What is ECT?

ECT treatments consist of a series of sessions, typically three times a week, for two to four weeks. Advances in ECT devices and methods have made modern ECT safe and effective for the vast majority of patients. Before ECT begins, a patient is put under brief anesthesia and given a muscle relaxant. Within one hour after the treatment session, which takes only a few minutes, the patient is awake and alert.

What is esketamine?

Esketamine or SPRAVATO® is a medication, delivered by nasal spray, that is FDA-approved for treating depression that has not resolved despite treatment with at least two antidepressant medications. Esketamine is self-administered, under supervision, in our clinic. There is an observation period of a few hours after each administration. SPRAVATO® is administered twice a week for the first month, then weekly per indicated.

What is IV ketamine?

Ketamine infusion therapy is a treatment that uses low doses of ketamine to treat severe major depressive disorder (MDD) in adults. Ketamine infusions are not a first-line treatment for MDD but may be used when antidepressant medications fail. Unlike most oral antidepressants, ketamine targets different receptors in the brain which may provide rapid relief from depressive symptoms. Ketamine is administered intravenously in a medically supervised setting. The usual schedule is twice each week for about three weeks.

People with a history of psychosis, schizophrenia, substance use disorder, or those currently pregnant or breastfeeding should not receive ketamine.

For information and to set up an appointment, please call 520.874.6657.

Website:
BannerHealth.com/Doctors
Psychiatry.arizona.edu/patient-care/cipn

Depression research wants to bring light back to your view.

Learn about the **VENTURA-1** research study for adults and elderly people with major depressive disorder (MDD) who experience a loss of interest or pleasure. This study is evaluating an investigational medication that is taken with your current antidepressant medication.

The purpose of this study is to evaluate the efficacy and safety of a once daily oral study medication in adults and elderly people with depression who continue to have depressive symptoms despite taking antidepressant medication.

To potentially be in this study, you must:

- Be 18 to 74 years of age
- Have been diagnosed with depression
- Be experiencing depressive symptoms despite currently taking antidepressant medication

If you are interested in learning more about the study, the study doctor will discuss additional eligibility requirements. All study visits and study-required medical care will be provided at no cost to you. The time commitment for study participation is up to 12 weeks.

For more information, you may visit clinicaltrials.gov and search "67953964MDD3001" or contact:

Brain & Mood Health Laboratory
520-626-1527
BaMHResearch@arizona.edu

Scan the QR Code to start the pre-screen process or go to: redcap.link/ventura1

Thank you for choosing to spend your Saturday with us at the Geri-Psych4PCPs conference.