



# Late-Life Depression: Essential Features, Assessment and Treatment

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# DISCLOSURES

## Depression in Later Life

- James M. Ellison MD MPH
  - No affiliation or financial interest to disclose
  - Will discuss off-label medication use and identify as such

# Key Points

1. MDD not a “normal part of aging”.
2. Age influences demographics, etiology, presentation, assessment, acute and maintenance treatment, and outcome .
3. Depressive syndromes in later life are significant and very treatable and recent advances in psychotherapies and somatic therapies improve treatment effectiveness.

# Prevalence of Depressive Syndromes in Later Life

	Clinically Significant Depressive Symptoms <sup>1</sup>	Major Depressive Disorder <sup>1</sup>
<b>Community</b>	<u>8-15%</u> 9.7-26.1% for 75+ <sup>3</sup>	<u>1-3%</u> 4.4-10.6% for 75+ <sup>2</sup>
<b>Primary Care</b>		6-9% <sup>3</sup>
<b>Long Term Care</b>	30-50%	6-25%
<b>Bipolar Disorder</b>		0.1-0.4% <sup>4</sup>

1. Ellison JM, Gottlieb G: Recognition and management of late life mood disorders. In: Sirven JI, Malamut BL (eds): Clinical Neurology of the Older Adult, 2nd Edition. Philadelphia, Lippincott Williams & Wilkins, 2008; 2. Luppá et al. J Aff Dis 2012;136:212-221; 3. National Health and Nutrition Survey 2013-2016; 4. Unutzer et al. Milbank Q 1999;77:225-6

# Adverse Outcomes of Untreated LLD<sup>1-7</sup>

- Increased use of non-mental health services
  - 2x medical appointments, 2x polypharmacy
- Reduced medical treatment adherence
- Functional Decline / Increased disability
- Increased morbidity/mortality:
  - CVA/MI/Hypertension/Diabetes/Dementia/SUD/Suicide
- Increased health care costs<sup>7</sup>
- And yet – more than ½ of depressed elders go untreated.<sup>8</sup>

# Some Risk Factors for LLD

- Demographic Risk Factors

- Older age
- Female sex
- Lower income

- Health

- New/chronic medical illness
- Vascular disease
- Psychiatric illness history
- Cognitive impairment
- Sleep disturbance
- Pain
- Functional limitations

- Coping/Social Support

- Recent negative life events
- Lack of social support
- Small social network
- Unmarried
- Bereaved
- Loneliness

- Habits

- Alcohol problem
- Smoking
- Low exercise level

# Race/Ethnicity and Late Life Depression Risk

- A cross-sectional study of 25,503 participants of mean age = 67.1 controlled for confounding factors and found that compared to non-Hispanic white subjects:
  - **Hispanic** participants' PHQ-8 scores were 23% higher.
  - **Black** participants' PHQ-8 scores were 10% higher.
  - Anhedonia, sadness, psychomotor symptoms were more prevalent in minority groups than in white participants.
  - Underrecognized/undertreated? Among the depressed, Black participants were 61% less likely to report any treatment (meds, counseling) vs Non-Hispanic white participants.

# Diagnosis: The Definitions



# DSM-5-TR MDD = DSM-4-TR Minus Bereavement Exclusion and Depressed

- 5 required sx (present at least 2 wk), depressed mood OR loss of interest/pleasure must be present. At least 4 additional symptoms present most or all days:
  - weight loss or appetite decrease/weight gain (A)
  - insomnia/hypersomnia (S)
  - psychomotor agitation/retardation (P)
  - fatigue/loss of energy (E)
  - worthlessness/guilt (G)
  - diminished concentration/decision-making (C)
  - thoughts of death/suicide/attempt (S)
- Distress or functional impairment
- Medical/Substance/Psychiatric exclusions
- There has not been a manic/hypomanic episode

**SIG**  
**E CAPS**

**S**leep  
**I**nterest  
**G**uilt/worthlessness  
**E**nergy  
**C**oncentration  
**A**ppetite/weight  
**P** psychomotor  
**S**uicidal

**MDD = “Major Depressive Disorder”**

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Text Revision. Washington DC, American Psychiatric Association, 2022.

# New for DSM 5/5-TR: Persistent Depressive Disorder

- Incorporates 2 DSM IV disorders: **Chronic Major Depressive Disorder** and **Dysthymic Disorder**
  - Depressed mood more days than not, for at least 2 years
  - Two or more of these sx: appetite, sleep, energy, self-esteem, concentration, hopelessness
  - No remission more than 2 mo at a time in 2 yr period
  - Major Depressive Disorder criteria may also be met.
  - Symptoms not explained by manic, hypomanic, cyclothymic, other psychiatric, substance, medical
  - Significant distress (social, occupational, other)

# What Is Exceptional About LLD?

- 1. Etiologies can differ
  - Recurrence of early onset mood disorder
  - Psychosocial stressors of late life (including loneliness)
  - Affective consequences of medical burden:
    - Medical sx can mimic depressive sx
    - Vascular depression hypothesis<sup>1</sup>
    - Inflammation hypothesis<sup>2</sup>
- 2. Locus of Care: Help sought in Primary Care
  - Comfort/relationship with Primary Care setting
  - Higher medical burden (illnesses, symptoms)
  - Untreated/undertreated patients are common<sup>3</sup>

1. Alexopoulos et al. Dialogues Clin Neurosci 1999;1:68-80 ;2. Maes et al. Metab Brain Dis 2009;24:27-53;  
3. Mitchell et al. Psychother Psychosom 2010;79:285-94.

# 3. Presentations Can Obscure Dx

- Subthreshold: Beneath the “Major Depression”
- Different symptoms:
  - “Depression without sadness”<sup>1</sup>
  - Somatic (sometimes cognitive) focus
  - Depression with psychotic features
- Medical etiology of symptoms:
  - Depression with cerebrovascular disease
  - Depression with cognitive impairment<sup>2,3</sup>

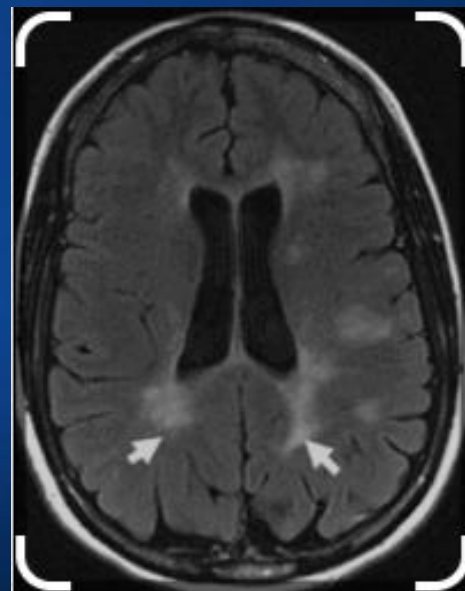
# Depression with Psychotic Features

- Delusions (mood-congruent)/hallucinations (auditory) with MDD symptoms.
- Higher prevalence in older depressives.<sup>1</sup>
  - 20-45% of hospitalized older depressed adults
  - 15% of community older depressed adults
- Associated with:<sup>2,3</sup>
  - Later onset
  - Poorer response to monotherapy/maintenance
  - Higher recurrence rate/suicide risk
- ECT or combination ADD/APD are best treatments.<sup>4</sup>

1. Reinhardt and Cohen. *Curr Psychiatry Rep* 2015;17:1; 2. Gournellis et al. *Int J Geriatr Psychiatry* 2001;16:1085-91; 3. Flint and Rifat *Am J Psychiatr* 1998;155:178-83; 4. Meyers et al. *Arch Gen Psychiatry*. 2009;66:838-47.

# Vascular Depression: Neuropsychological Correlations<sup>1</sup>

- Presence of moderate to severe white matter hyperintensities in depressed patients has been linked with increased psychomotor retardation and disability, and Neuropsychological Correlations<sup>1</sup>:
  - Poorer Executive Functioning
  - Slower response to citalopram<sup>2</sup>
  - Greater relapse risk



# Post-Stroke depression

- More than 795,000 CVAs per year in US<sup>1</sup>
- About 1/3 of CVA patients have Post-Stroke Depression<sup>2</sup>
  - Compared to Va Depression, PSD is disorder of larger blood vessels
  - Correlation of PSD with lesion location is controversial, and current research approaches focus on effect on larger brain networks.
- Treatment
  - Risk of PSD after CVA is reduced with use of prophylactic escitalopram or active rehabilitation program.<sup>3,5</sup>
  - SSRIs and TCAs have been shown more effective than placebo.<sup>4</sup>
  - Side effects can be significant.<sup>4</sup>
  - Change treatment if no response after 6 weeks.<sup>4</sup>
  - Treat at least 4 months beyond initial recovery.<sup>4</sup>
  - Treatment of PSD is associated with significant increase in survival.<sup>5</sup>

1. Benjamin EJ et al. *Circulation* 2017;135:e229-e445; 2. Nickel A and Gotz T. *Front Neurol* 2017;Vol 8:Article 498. doi: 10.339/fneur2017.00498;3.Xiao-Min X et al. *Medicine* 2016;95(45):e5349. doi: 10.1097/MD.0000000000005349;4. Alexopoulos GS, Kelley Jr., RE: *World Psychiatry* 2009;8:140-9; 5. Robinson RG and Jorge RE. *Am J Psychiatry* 2016;173:221-231.

# Depression With Cognitive Impairment

- Risk factor?
- Prodrome?
- Consequence?
- Manifestation of shared etiology?



# Depression in Persons with Dementia Can Present with Misleading Symptoms

- Likelihood that depression is present is increased in the presence of:
  - Delusions<sup>1</sup>
  - Verbal/physical aggressive behaviors<sup>2</sup>
  - Suicidal or self-destructive behaviors<sup>2</sup>
  - Disruptive vocalizations<sup>3</sup>
  - Weight loss<sup>4</sup>

# Assessment: Best Practices

# 1. Screening: Tools for LLD

- SELFCARE-D (Self-administered)
- Center for Epidemiological Studies – Depression Scale (CES-D)
- **\*Geriatric Depression Scale (GDS)**
- **\*PHQ-2, PHQ-9**
- **\*Cornell Scale for Depression in Dementia (CSDD)**

1. Diagnosing, Screening, and Monitoring Depression in the Elderly: A Review of Guidelines. Canadian Agency for Drugs and Technologies in Health. Accessed 12/27/15; [https://www.cadth.ca/sites/default/files/pdf/htis/sep-2015/RC0691\\_Diagnosing%20depression%20in%20elderly\\_Final.pdf](https://www.cadth.ca/sites/default/files/pdf/htis/sep-2015/RC0691_Diagnosing%20depression%20in%20elderly_Final.pdf)
2. Phelan et al. BMC Fam Pract. 2010;11:63.

# Assessment: GDS 15

1. Are you basically satisfied with your life ?
2. Have you dropped many of your activities and interests ?
3. Do you feel that your life is empty ?
4. Do you often get bored ?
5. Are you in good spirits most of the time ?
6. Are you afraid that something bad is going to happen to you ?
7. Do you feel happy most of the time ?
8. Do you often feel helpless ?
9. Do you prefer to stay at home, rather than going out and doing new things ?
10. Do you feel you have more problems with memory than most?
11. Do you think it is wonderful to be alive now ?
12. Do you feel pretty worthless the way you are now?
13. Do you feel full of energy ?
14. Do you feel that your situation is hopeless ?
15. Do you think that most people are better off than you are ?

GDS is in the Public Domain, can be freely reproduced and used. Score 1 pt for each “Yes” on 2,3,4,6,8,9,10,12,14,15 or “No” on 1,5,7,11,13. A score of 6 or higher suggests need for definitive diagnostic evaluation. (<http://www.stanford.edu/~yesavage/GDS.html>)

# Psychometrics of GDS

- Appears to be most widely used screen
- In public domain, with multiple translations
- 4 versions: range from 4 to 30 questions
- GDS15 with cut-off score of  $\geq 6$ :<sup>1</sup>
  - Sensitivity overall 84.3% (risk for FN)
  - Specificity 73.8% (risk for FP)

1. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Sep 8. Diagnosing, Screening, and Monitoring Depression in the Elderly: A Review of Guidelines [Internet]. <https://www.ncbi.nlm.nih.gov/books/NBK321381/> accessed 12/31/18; 2. Krishnamoorthy et al. Arch Gerontol Geriatr 2019 Dec 19;87:104002. doi: 10.1016/j.archger.2019.104002

# PHQ-2 for MDD or “Dysthymia”

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3

Score Cut-Off	Sensitivity (mixed age)	Specificity (mixed age) FP high
≥1	99%	28%
≥2	97%	48%
≥3	64%	85%
≥4	44%	93%
≥5	23%	98%

Geriatric Sensitivity = 100%  
 Geri. Specificity = 77%  
**With cutoff score of ≥ 1**

Performance is better in younger elderly, men vs women, non-Hispanic black individuals.

Staples et al. Gen Hosp Psychiatry 2019;56:13-18 (mixed age)

Li et al. JAGS 2007;55:596-602 (geriatric)

## PHQ-9 (Each point multiplied by 0,1,2,3 for not, several days, more than ½ of days, nearly all days in past 2 wk):

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or of hurting yourself in some way

**If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?**

# PHQ-9 Psychometric Properties

- In a study of **older adults** in primary care, a cut off point of  $\geq 9$  for major depressive disorder yielded:
  - Sensitivity = 88%
  - Specificity = 80%
- For PHQ9 score  $\geq 10$  in older primary care adults,
  - **Sensitivity = 63%**
  - Specificity = 82%
  - Small specificity gain balanced by sensitivity loss



# Cornell Scale for Depression in Dementia

## Scoring System

A = unable to evaluate 0 = absent 1 = mild or intermittent 2 = severe

Ratings should be based on symptoms and signs occurring during the week prior to interview.

No score should be given in symptoms result from physical disability or illness.

## A. Mood-Related Signs

- |   |   |   |   |
|---|---|---|---|
| 1. Anxiety: anxious expression, ruminations, worrying | 0 | 1 | 2 |
| 2. Sadness: sad expression, sad voice, tearfulness    | 0 | 1 | 2 |
| 3. Lack of reactivity to pleasant events              | 0 | 1 | 2 |
| 4. Irritability: easily annoyed, short-tempered       | 0 | 1 | 2 |

## B. Behavioral Disturbance

- |   |   |   |   |
|---|---|---|---|
| 5. Agitation: restlessness, handwringing, hairpulling         | 0 | 1 | 2 |
| 6. Retardation: slow movement, slow speech, slow reactions    | 0 | 1 | 2 |
| 7. Multiple physical complaints (score 0 if GI symptoms only) | 0 | 1 | 2 |
| 8. Loss of interest: less involved in usual activities        | 0 | 1 | 2 |

(score only if change occurred acutely, i.e. in less than 1 month)

### **C. Physical Signs**

- |  |       |
|--|-------|
| 9. Appetite loss: eating less than usual   | 0 1 2 |
| 10. Weight loss (score 2 if greater than 5 lb. in 1 month)   | 0 1 2 |
| 11. Lack of energy: fatigues easily, unable to sustain activities<br>(score only if change occurred acutely, i.e., in less than 1 month) | 0 1 2 |

### **D. Cyclic Functions**

- |   |       |
|---|-------|
| 12. Diurnal variation of mood: symptoms worse in the morning        | 0 1 2 |
| 13. Difficulty falling asleep: later than usual for this individual | 0 1 2 |
| 14. Multiple awakenings during sleep                                | 0 1 2 |
| 15. Early morning awakening: earlier than usual for this individual | 0 1 2 |

### **E. Ideational Disturbance**

- |   |       |
|---|-------|
| 16. Suicide: feels life is not worth living, has suicidal wishes,<br>or makes suicide attempt | 0 1 2 |
| 17. Poor self esteem: self-blame, self-depreciation, feelings of failure                      | 0 1 2 |
| 18. Pessimism: anticipation of the worst  | 0 1 2 |
| 19. Mood congruent delusions: delusions of poverty, illness, or loss                          | 0 1 2 |

# Psychometrics of CSDD

	Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)
DSM-IV-TR (n=231)	6/7	84	61	67
	7/8	77	69	71
	<b>&gt;8</b>	<b>74</b>	<b>74</b>	<b>74</b>
	9/10	69	82	78
	10/11	63	86	79
Nursing Home (DSM-IV-TR)	6/7	85	64	68
	7/8	80	70	72
	8/9	75	77	76
	9/10	70	82	79
Hospital Patients (DSM-IV-TR)	6/7	83	58	67
	7/8	75	68	70
	8/9	73	72	72
	9/10	69	81	77
	10/11	65	88	80

Data from Barca et al. Dement Geriatr Cogn Disord 2010;29:438-447

## 2. Medical Burden: Assess Contribution

- Medications, Alcohol, Drugs
  - Endocrinopathy
  - Malignancy
  - Infection
  - Metabolic disorders
  - Nutritional deficiencies
  - Sleep disorders
  - Vascular disease
  - Neurological disorders
- Depressive episode should be treated while independently managing medical condition

# 3. Laboratory Results: Identify and Manage Remediable Medical Contributors

## ● Hematology

- CBC with indices/differential
- ESR

## ● Chemistry

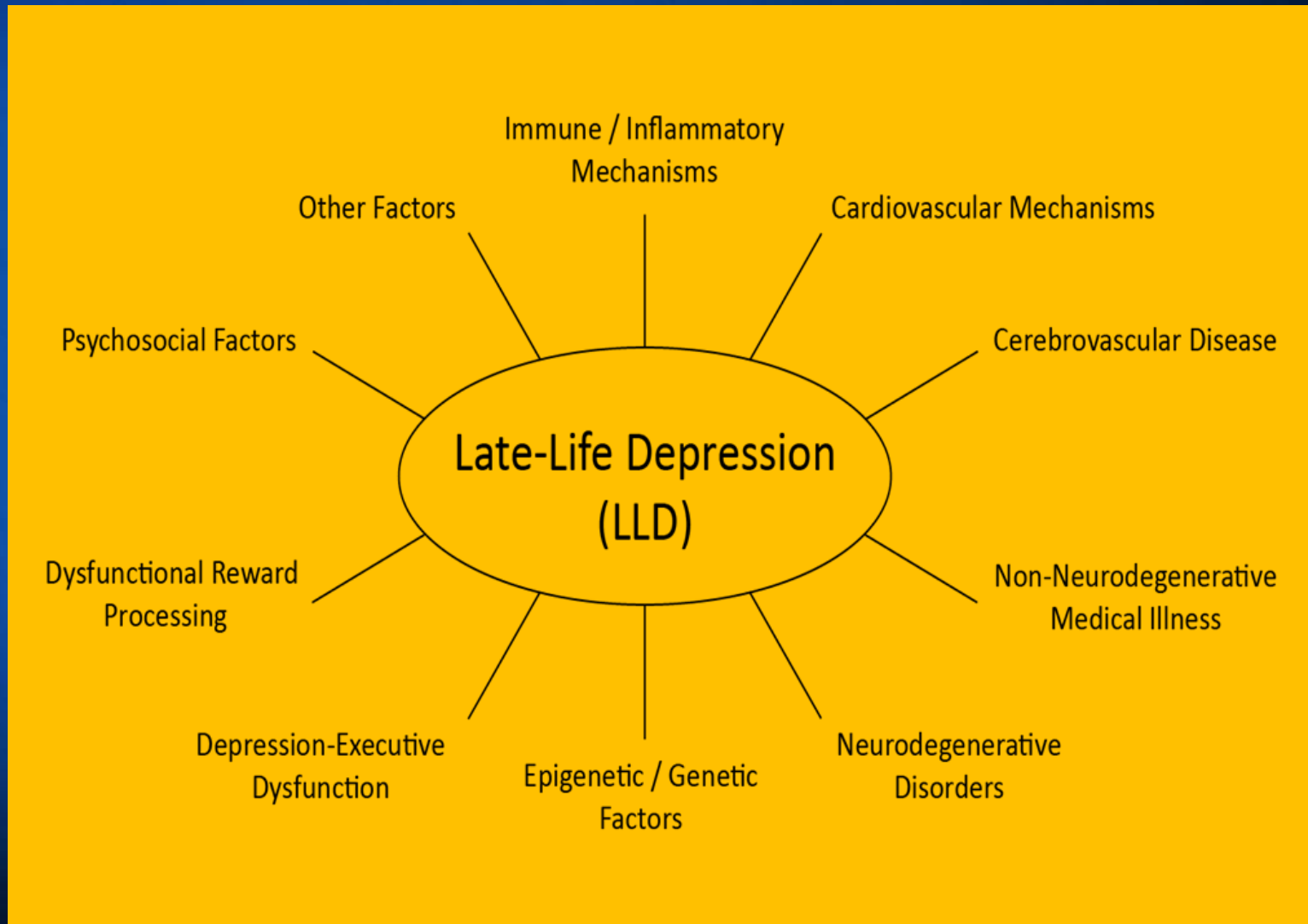
- Lytes, BUN, Creatinine
- Liver function tests
- Thyroid function tests
- Fasting glucose level
- Folate, B12<sup>1</sup>

## ● Urine

- Urinalysis
- Culture and sensitivity
- **Additional tests, e.g.**
  - Electrocardiogram
  - Chest X-Ray
  - Neuroimaging (?)

# Treatment Approach

# 1. Assess Contributing Factors



## 2. Address Substance Use

- Benzodiazepines:
  - Chronic use (daily>3 months): 12% of elderly <sup>1</sup>
  - 9.5% of users are dependent<sup>1</sup>
- Alcohol (>7 drinks/wk is considered excessive)
  - 25% of elderly are daily drinkers
  - 10% of elderly alcohol users “binge drink”<sup>2</sup>
- Other drugs of concern: analgesics, hypnotics
- Illicit and nonmedical prescription drug use much greater among 50-64 year olds.<sup>1</sup>



# 3. Address Pain

- Pain often accompanies MDD<sup>1</sup>
  - Chronic painful physical conditions are increased fourfold in MDD patients.
  - Headache, neck and back, abdominal, and musculoskeletal pain are common.
- Chronic painful physical conditions are an independent risk factor for MDD and poor treatment response.<sup>1</sup>
  - Pain affects other depressive symptoms adversely (exacerbates sleep, energy, anxiety symptoms).
  - MDD+pain is associated with worse outcome to SSRI treatment proportional to pain severity.
- The presence of pain is associated with increased help-seeking<sup>2</sup>

# 4. Consider Non-pharmacological treatments

- Non-pharmacological strategies, alone or with antidepressants, are effective in treating Late Life Depression and should be strongly considered when planning treatment.



Reynolds CF 3rd, Dew MA, Martire LM, *et al.* Treating depression to remission in older adults: a controlled evaluation of combined escitalopram with interpersonal psychotherapy versus escitalopram with depression care management. *Int J Geriatr Psychiatry* 2010; 25:1134–1141.

# A. Psychosocial: Several Are Evidence-Based Treatments for Late Life Depression

- Spirituality<sup>1</sup>:
  - Spirituality attenuates the link between depressive symptom severity and feelings of meaningless in life.
- Psychotherapy RCTs support:<sup>2</sup>
  - Cognitive Behavioral Therapy (CBT)
  - Interpersonal Therapy (IPT)
  - Problem Solving Therapy (PST)
  - ENGAGE

1. Bamonti et al. Aging Ment Health 2016;20:494-9; 2. See Antognini and Liptzin in Ellison et al. Mood Disorders in Later Life. Informa 2008.

# CBT Premises

- People, environment, social situations trigger cognitive reactions
- Cognitive reactions trigger emotional and behavioral responses
- Response depends on past experience and the skills we have to cope and react.
- These thoughts and plans can change with new cognitive and behavioral experiences.

# CBT Strategies

- Collaborative framework
- Educational principles
- Skill building
- Questioning and inductive reasoning
- Behavioral activation

# Interpersonal Therapy

- Based on Sullivanian interpersonal psychoanalysis
- Depression results from interactional style associated with attachment issues.
- Focuses on four areas of conflict
  - Grief
  - Role transition
  - Interpersonal deficits
  - Interpersonal conflict

# Problem Solving Therapy

- Problem solving is a component of all psychotherapies.
- PST formulates depression as a function of:
  - Insufficient problem solving skill
  - Abandonment of skill
  - Perceived complexity of problems

# PST techniques

- Problem Orientation
- Definition
- Brain storming
- Decision making
- Planning
- Implementation
- Evaluation
- Use of “forms”



# ENGAGE: A New Evidence-Based Psychosocial Treatment for LLD

- An RDOC-domain based approach
  - Easily learned behavioral approach
  - Addresses dysfunction of positive valence system
    - Reward exposure: repeated activation of networks
    - Stepped
    - Personalized
- Preliminary positive results: Behavioral activation predicted depression improvement

## B. Physical Activity

- Greater midlife physical activity is associated with lower depressive sx in later life<sup>1</sup>
- Physical inactivity in older adults is associated with both depression and cognitive deficits<sup>2</sup>
- Meta-analysis supports LLD benefit for Physical Exercise, more evidence needed to support use over 80 years old or with MMSE < 23/30.<sup>3</sup>
- Higher and faster remission in LLD linked with exercise augmentation of sertraline (24 wk of PAE).<sup>4</sup>

1. Chang et al. J Gerontol A Biol Sci Med Sci 2015 Nov 2.pii: glv 196 (epub);
2. Paulo et al. J Aging Phys Act 2015 (epub); 3. Klil-Drori et al. J Clin Psychiatry 2020 Jan 21;81(1). Pii: 19r12877. doi: 10.40888/JCP. 19r12877.
4. Belvederi Murri et al. Br J Psychiatry 2015;207:235-42.

# 5. Pharmacologic Treatment

## Antidepressant Efficacy

- All FDA-indicated antidepressants treat LLD<sup>1</sup>
- Response rate (50% symptom decrease)<sup>2</sup>
  - 50 – 65% in ITT\* trials, 25 – 30% respond to placebo
  - Number Needed to Treat (NNT\*): 2.5 to 5
- Remission ( $\geq 90\%$  symptom decrease)<sup>2</sup>
  - Typically 30 – 40% with medication vs 15% for placebo, NNT: 4 to 7
- Most important barrier = undertreatment!<sup>3,4</sup>

**\*ITT: Intention to Treat, NNT: Number Needed to Treat**

1. See Ellison et al. Mood Disorders in Later Life. Informa Health Care 2008; 2. Shanmugham et al. Psychiatr Clin North Am. 2005;28:821-35;3.Wang et al. J Clin Psychopharmacol 2005;25:118-26;
4. Barry et al. J Affect Disord 2012;136:789-96.

# Pharmacodynamic Basis of Adverse Effects

Medication Property	Possible Clinical Consequences
NE reuptake blockade	Tremors, tachycardia, erectile/ejaculatory dysfunction, elevated blood pressure
Serotonin reuptake blockade	GI symptoms, sexual dysfunction, EPS, bruising/bleeding, bone mass density loss
Dopamine reuptake blockade	Activation, aggravation of psychosis
Histamine H <sub>1</sub> receptor antagonism	CNS depressant potentiation, sedation, weight gain, hypotension
Muscarinic receptor antagonism	Blurred vision, dry mouth, constipation, urinary retention, cognitive dysfunction, sexual dysfunction
NE $\alpha_1$ receptor antagonism	Potentiation of some antihypertensives, postural hypotension, dizziness, reflex tachycardia

# Geriatric Side Effects:

## SRIs

- Discontinuation is less common with SSRI treatment than with TCA treatment.
- But significant side effects with SRIs include:
  - Sedation
  - Weight gain
  - GI symptoms
  - Hyponatremia
  - Risk for bruising
  - Risk for GI bleeding
  - Sexual dysfunction
  - Falls?

# SRIs and Cardiac Safety

- SADHART<sup>1</sup> reported no adverse effects on LV EF, HR, BP, ECG with sertraline; ENRICH<sup>2</sup> found decreased cardiac life threatening events among SSRI treated cardiac patients.
- Newer findings show risk of QTc prolongation with citalopram, escitalopram (less), amitriptyline<sup>3,4</sup>
- Demonstrated low risk for QTc prolongation in older adults:
  - Vilazodone<sup>5</sup>
  - Vortioxetine<sup>6</sup>

1. Shapiro et al. Am Heart J. 1999;137:1100-6;; 2. Taylor et al. Arch Gen Psychiatry. 2005;62:792-8; 3. Castro et al. BMJ 2013;346:f299. doi: 10.1136/bmj.f288; 4. Maljuric et al. Br J Clin Pharmacol 2015;80:698-705;5. Edwards et al. Int J Clin Pharmacol Ther 2013;51:456-65; 6. Katona et al. Int Clin Psychopharmacol 2012;27:215-23.

# Antidepressant Drug/Drug Interactions

- Age exacerbates potential for adverse effects and interactions
  - Hepatic inactivation of drugs ↓
  - Renal elimination of drugs ↓
  - Anticholinergic vulnerability ↑
- Average adult > 65 years old is on 4 or more prescribed medications daily, 39% on 5 or more/d<sup>1</sup>
- Many interactions are possible
  - Pharmacodynamic
  - Pharmacokinetic

# Antidepressant Cost

- Adherence can depend upon affordability
- Limitations of Medicare Part D
- Range of generically available antidepressants
- Avoid first line use of brand name drugs:
  - Trintellix (vortioxetine)
  - Fetzima (levomilnacipran)
  - Spravato (intranasal ketamine isomer)
  - Auvelity (dextromethorphan/bupropion)
  - Exxua (gepirone)



# Predictors of Antidepressant Response<sup>1</sup>

- Age or Sex – not predictive
- Episode recurrent vs single – not predictive
- Executive Function is a predictor
  - Cognitive Control system – important for response inhibition, planning, problem solving, working memory - tested by Stroop test or (in office) trail-making test.
  - Intact CC predicted better response to escitalopram in LLD.<sup>2</sup>

# SSRIs – Still 1<sup>st</sup> Choice in LLD

- Several well-tested, generic, well-tolerated, with limited drug interactions, appropriate elimination half-lives:
  - **Sertraline = best overall safety&efficacy<sup>1</sup>**
  - Citalopram is not more effective than other SRIs (Note FDA dosage warning to not use with QTc above 500 or with dose > 20 mg/d).
  - **Escitalopram** may be less likely to prolong QTc.
  - Paroxetine – considered effective/problematic

# SNRIs

- SNRIs share potential adverse effects of:
  - Hypertension
  - Anxiety
  - Insomnia
  - Share with SSRIs the potential for discontinuation symptoms
- Duloxetine – analgesic effects are a bonus

# Other Antidepressants to Consider

## ● Bupropion

- Less sedation and sexual side effects
- Less help with anxiety/psychosis
- Special contraindications

## ● Mirtazapine

- More anxiolytic, less sexual side effects, less nausea
- More weight gain and sedation
- Could exacerbate REM sleep behavior in PD<sup>1</sup>
- Associated with small/significant risk for neutropenia, agranulocytosis; minimal interaction with warfarin

Don't forget TCAs, MAOIs!

1. Onofrj M, Luciano AL, Thomas A, Iacono D, D'Andreamatteo G. Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism. *Neurology* 2003;60:113–5.

# And now for something completely different... Quetiapine monotherapy

- Quetiapine XR monotherapy tested in a 9 week double-blind placebo controlled study, n=338, ages 66 and older with MDD
- Flexible dosing of 50-300 mg/d (mean dose 159 mg/d) vs placebo showed improvement on MADRS
- Sleep improved on PSQI. Excessive sleepiness was predominant adverse effect.

# The Newer Antidepressants

- Viibryd (Vilazodone)
  - SSRI and partial agonist at 5HT1a
- Trintellix (Vortioxetine)
  - SSRI, agonist 5HT1a, partial agonist at 5HT1b  
antagonist 5HT3a/5HT7
- Fetzima (Levomilnacipran)
  - Balanced SNRI
- Spravato (esketamine)
  - Different mechanism and effects
- Auvelity (bupropion/dextromethorphan)
- Exxua (gepirone)
- [Brexanolone and zuranolone – only for PPD]

# Stimulants\*

- Limited data on use in LLD
- Small RTC showed MPH well-tolerated, effective in treating apathetic depression in medically burdened elders<sup>1</sup>
- MPH (mean 16 mg) + citalopram (mean 32 mg) associated with faster and greater improvement in RTC of LLD with anxiety.<sup>2</sup>
- Stimulants alone or with TRD not promising<sup>3</sup>

\*stimulants are used off label in treatment of depression

1. Padala et al. Methylphenidate may treat apathy independent of depression, *Ann Pharmacother* 39:1947–1949.
2. Lavretsky et al. *Am J Psychiatry* 2015;172:561-9;
3. Nelson JC. *Am J Psychiatry* 2015;172:505-7.

# Ketamine\*?

## • Limited data in elderly

- Early open trial (n=4) and more recent case series (n=6): limited benefit, significant relapse, dissociative adverse effects.<sup>1,3</sup>
- SubQ ketamine up to 0.5 mg/kg in 16 older TRD adults superior to midazolam in RCT. At 6 months, response+remission = 68.8% with repeated tx.<sup>2</sup>
- Recent IV ketamine pilot study (n=25, no comparator) in TRD older adults showed response in 48%.<sup>4</sup>

\*Parenteral (IV or Subq) ketamine is still investigational or off label in the treatment of depression but intranasal esketamine has been given an FDA indication for use WITH an oral antidepressant in adults with treatment-resistant depression.



# Esketamine (intranasal)?

- Esketamine plus antidepressant was studied in older adults with TRDOA (TRANSFORM-3), flexible dosing up to 84 mg q 2/wk for 4 wk.<sup>1</sup>
- Although the study failed to meet endpoint of significant decline in MADRS, secondary analyses suggested benefit in subjects with earlier onset ( $\leq 55$ ) or younger age (65-74 vs  $\geq 75$ ).<sup>1</sup>
- Delivery of this treatment is challenging because of requirement for post-use observation and enrollment in “Spravato REMS”.
- National Institute for Health and Care Excellence has chosen not to recommend this for TRD.<sup>2</sup>

1. Ochs-Ross et al. Am J Geriatric Psychiatry 2020;28:121-141; 2. Mahase. BMJ 2020;368:m329 doi: 10.1136/bmj.m329 (published 28 January 2020)

# 6. Electroconvulsive Therapy

- Underused modality, especially suitable with:
  - Antidepressant intolerance or non-response
  - Prior positive response to ECT
  - Delusions
  - Catatonia
  - Mania
  - Emergency

Flint and Rifat. *Int J Geriatr Psychiatry* 1998;13:23-8; Manly et al.

Electroconvulsive therapy in old-old patients *Am J Geriatr Psychiatry*. 2000 Summer;8(3):232-6.

# ECT Efficacy

- Greater in older adults<sup>1</sup>
  - RUL: for  $\geq 60$  yr old, 70.4% remission vs 46% in  $< 60$
  - BT: for  $\geq 60$  yr old, 75% remission vs 58.3% in  $< 60$
- Better than meds in recent comparison:<sup>\*</sup>
  - 3.1 +/- 1.1 wk to ECT remission vs 4.0 +/- 1 wk with meds<sup>2</sup>
  - Remission rate: 63.8% at 6 wk vs 33.3% at 12 wk in med group<sup>2</sup>
- Cognitive effects: stable or improved in recent study<sup>3</sup>, mixed findings in earlier studies attributed to technique and/or underlying disease.<sup>4</sup>

1. Sanghani et al. Am J Geriatr Psychiatry 2014;22:S114. 2. Spanns et al. Br J Psychiatry 2015;206:67-71; 3. Verwijk et al. Int Psychogeriatr 2014;26:315-24. 4. Galvez et al. Curr Psychiatry Rep 2015;17:59-74

\*This study contrasted results from two possibly noncomparable RCTs

# 7. Transcranial Magnetic Stimulation

- TMS (rTMS) is considered safe and well-tolerated in LLD.<sup>2</sup>
  - 20-50% response rate open label, older adults
  - Poorer response associated with cortical atrophy
  - Better response with higher intensity stimulation?
- May be suitable for individuals unable to accept ECT.
- Modifications:
  - Adjusted treatment schedule
  - Deep rTMS achieved efficacy in LLD of 40% vs 14.8% in control group.
  - There is interest in assessing for TR LLD

# 9. Treatment of Depression in Dementia

- Multiple antidepressants studied, including
  - Citalopram<sup>1</sup>
  - Sertraline<sup>2,5</sup>
  - Clomipramine<sup>3</sup>
  - Moclobemide<sup>4</sup>
  - Mirtazapine<sup>5</sup>
- Large controlled trial (DIADS) failed to show superiority of sertraline over placebo
- Side effect assessment - more difficult in dementia
- Clinical approach – try, but discontinue if ineffective

1. Nyth et al. Acta Psychiatr Scand 1992;86:138-45; 2. Lyketsos et al. Am J Psychiatry. 2000;157:1686-9;  
3. Petracca et al. J Neuropsychiatry Clin Neurosci.1996;8:270-5;4. Roth et al. Br J Psychiatry 1996;168:149-57;  
5. Banerjee et al. Health Technology Assessment 2013;17(7):1-166.

# Antidepressant Treatment in Depressed, Demented Patients: What's A Clinician To Do?

- Assess symptoms severity, “masked” depression, and differential diagnosis including: pain, neuropsychiatric symptoms, cognitive decline, social isolation, quality of life<sup>1</sup>
- Choose target symptoms and medication and monitor improvement and adverse effects
- Based on outcome, modify approach and/or discontinue antidepressant.

# 10. Treatment Resistant Depression and the “ABCD” Review

- **A**dequacy of prior treatment
  - Duration of treatment
  - Dosage of medication
- **B**ehavioral/Environmental factors
  - Personality disorder
  - Psychosocial stressors
- **C**ompliance/Adherence
  - Patient education
  - Treatment intolerance
- **D**iagnosis
  - Missed medical diagnosis or adverse medication effect
  - Missed psychiatric diagnosis

# The Next Step in Treatment Resistant Depression

- Optimize
- Switch
- Augment/Co-prescribe
- ECT



# To Switch or To Augment?

## Switch

- Slower
- Simpler, less costly
- Fewer drug interactions
- Can reduce side effects
- Introduces “new mechanism”
- Outpatient setting

## Augmentation

- Quicker
- More complex, costly
- More drug interactions
- Can increase side effects
- Avoids loss of earlier partial response
- Inpatient setting

# SWITCH after SSRI-Nonresponse: What Is the Next Medication to Try?

- Some popular strategies:
  - Change drug “mechanism”?
  - Target different depressive symptoms?
  - Address depressive subtype?
    - Atypical
    - Melancholic
    - Bipolar

# Rational Polypharmacy<sup>1</sup>

## ● Augmenters:

- Lithium carbonate+\*
- Triiodothyronine+\*
- Atypical antipsychotic+
  - Aripiprazole augmented venlafaxine in TR LLD<sup>2</sup>
  - Brexiprazole (open label in older adults)<sup>3</sup>
  - Cariprazine
- Testosterone+\*

## ● Co-Prescribed Antidepressants:

- Mechanisms/interactions+\*

+ signifies presence of credible evidence base for use/ \*signifies “off label” in this use

1. See Ellison et al, in Ellison et al (eds): Mood Disorders in Later Life. New York, Informa 2008;
2. Lenze et al. Lancet 2015;Sep 24. pii: S0141-6736(15)00308-6. doi: 10.1016/S0140-6736(15)00308-6;
3. Lenze EJ et al. Lancet. 2015 Dec 12;386(10011):2404-12.

# 11. The Importance of Maintenance

- Even with maintenance, there is a high recurrence rate
- Maintenance pharmacotherapy reduces recurrence risk
  - Nortriptyline + IPT<sup>1</sup>
  - Citalopram<sup>2</sup>
  - Paroxetine<sup>3</sup>
- Slower initial responders may do better with combined therapy in maintenance<sup>4</sup>

Bereavement: Similar to but  
Different from Depression

# Definitions

- 11% of men, 34% of women 65 and older are “widowed”.<sup>1</sup>
- Bereavement = loss, grief = associated feelings and behaviors. Mourning is behavioral manifestation of grief. Integrated or abiding grief develops with acceptance.<sup>2</sup>
- Grief can include sadness, insomnia, poor appetite, sense of the deceased’s presence or voice - proceeds in waves, mixed with positive feelings, NOT typically associated with feelings of worthlessness, persistent social/occupational dysfunction, suicidality.

# Healing of Normal Grief<sup>1</sup>

- 4 stages: Predeath, Acute, Adaptation, Integration<sup>1</sup>
- 4 major tasks for integration: Accepting reality of the loss; Processing the emotional pain; Adjusting to life without the deceased; Establishing an enduring connection with deceased while moving forward.
- Peer support groups: efficacy not shown except in participants with “low interpersonal and emotional competencies”.
- Symptom and self-care improvement has been shown with **structured groups, specialist leaders, mindfulness techniques/spirituality.**

# Grief with Depression

- Grief can complicate depression.
- CGT (Complicated Grief Therapy) vs IPT (Interpersonal Therapy) :
  - Both effective treatment for grief-related depression in one study, CGT>IPT<sup>1</sup>
  - In another nortriptyline was superior to IPT=placebo, however combined IPT/nortriptyline participants had highest rate of treatment completion.<sup>2</sup>
- Citalopram, as adjunct to CGT, helped depressive, not grief symptoms.<sup>3</sup>

1. Glickman et al. Clin Psychol Psychother 2017;23:118-24;

2. Reynolds et al. Am J Psychiatry 1999;156:202-8; 3. Miller et al. J Psychother Pract Res 1994;3:149-62;



# Prolonged Grief Disorder in DSM-5-TR

## (Under Trauma- and Stressor- Related Disorders)

Diagnosis (summarized)

- A. Death of close relationship at least 12 months ago.
- B. For more days than not, nearly every day in past month, clinically significant, intense yearning for deceased and/or preoccupation with thoughts/memories
- C. At least 3 of these symptoms most days, nearly every day for last month:
  - Identity disruption, disbelief, avoidance of reminders, emotional pain, difficulty reintegrating, emotional numbness, feeling life is meaningless, intense loneliness
- D. Significant functional impairment/distress
- E. Duration of grief too long for cultural/religious/age-appropriate norms
- F. Not substance, medical condition, or other mental disorder

# Complicated Grief's Complications

- Complicated Grief develops in about 7% of bereaved people.<sup>1</sup>
- Negative Health Consequences of complicated grief include increased risk for <sup>2</sup>
  - Impaired self-care
  - Disturbed sleep
  - Substance use
  - Increased suicidality
  - Worse executive function
  - Increased brain atrophy
  - Increased cognitive decline

# Complicated Grief: Risk Factors

- Pre-loss factors:
  - Dysfunctional attachment
  - History of anxiety or depression
  - Female sex, older age, lower educational level, lower socioeconomic status, lower social support
- Loss-related factors:
  - Type of loss (e.g. spouse/child, stigma)
  - Suddenness
  - Immediate response
- Post-loss factors:
  - Negative coping strategies (e.g. avoidance, alcohol)
  - Lack of social support, Negative consequences

# Interventions for Complicated Grief

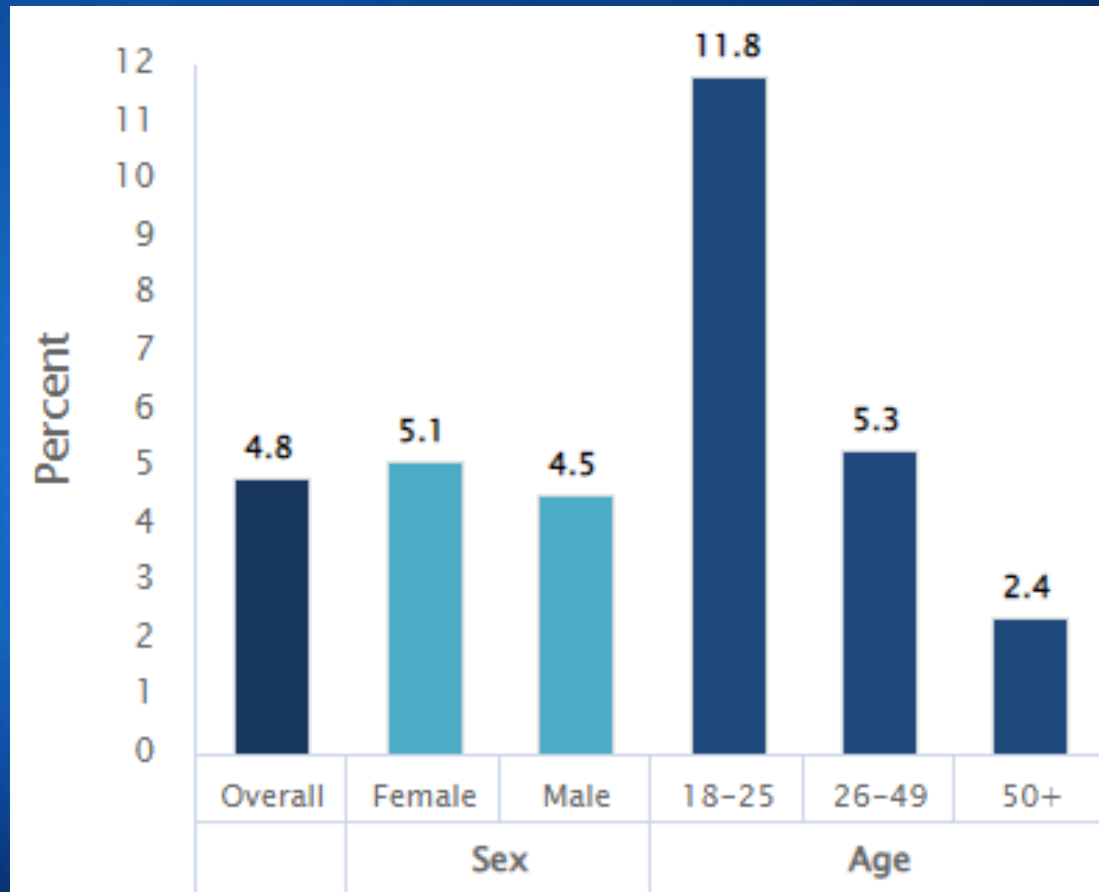
- Prolonged grief disorder symptoms can be “prevented” or diminished in high-risk individuals by internet-based, therapist-assisted CBT intervention addressing education, stress management, behavioral activation, accommodation of loss, relapse prevention.<sup>1</sup>
- In established Complicated Grief, Complex Grief Therapy (CGT) does better than CBT, focusing on **history, grief experience, situation revisiting, and personal goals** e.g. coping strategies and social connections. Exposure, IPT and motivational interviewing are included in CGT.<sup>2</sup>

1. Litz et al. Behav Res Ther 2014;61:23-34;

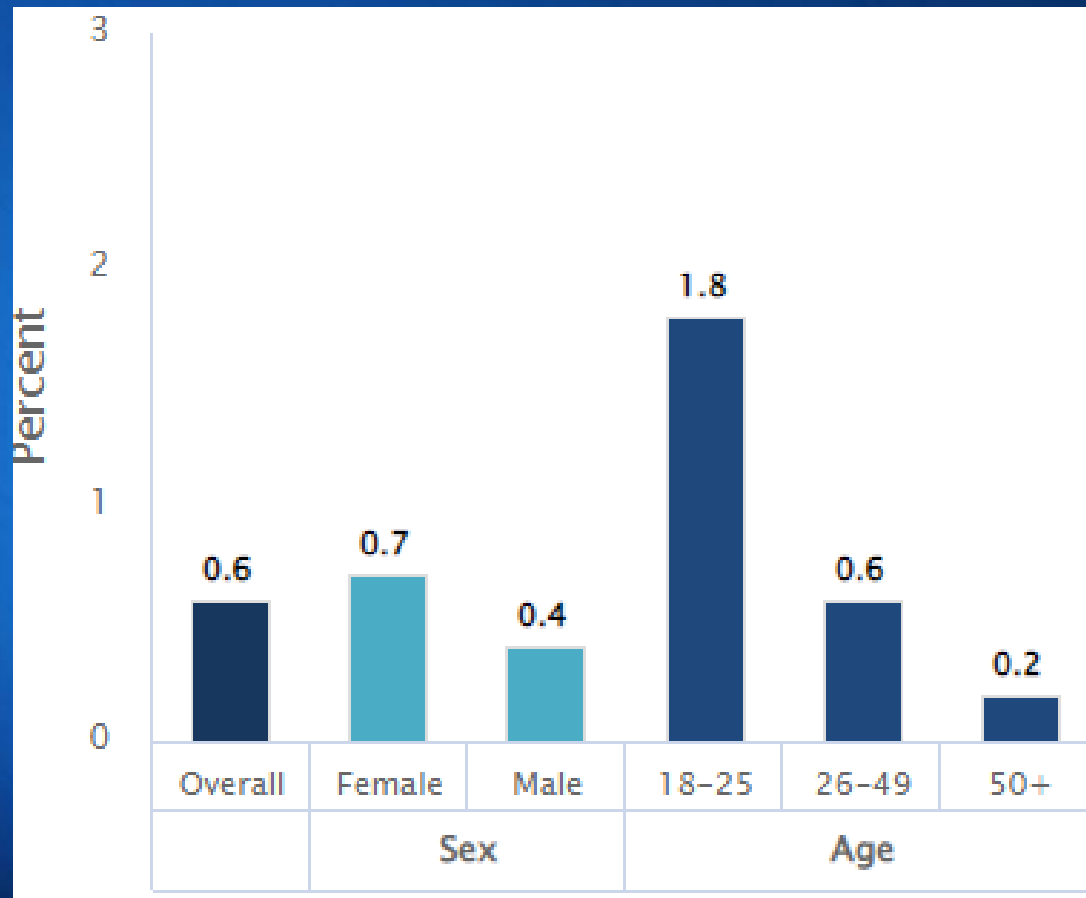
2. Shear et al. JAMA Psychiatry 2014;71:1287-95.

# Suicide in Later Life

# Past Year Prevalence of Suicidal Thoughts Among U.S. Adults 2019 Data Courtesy of SAMHSA

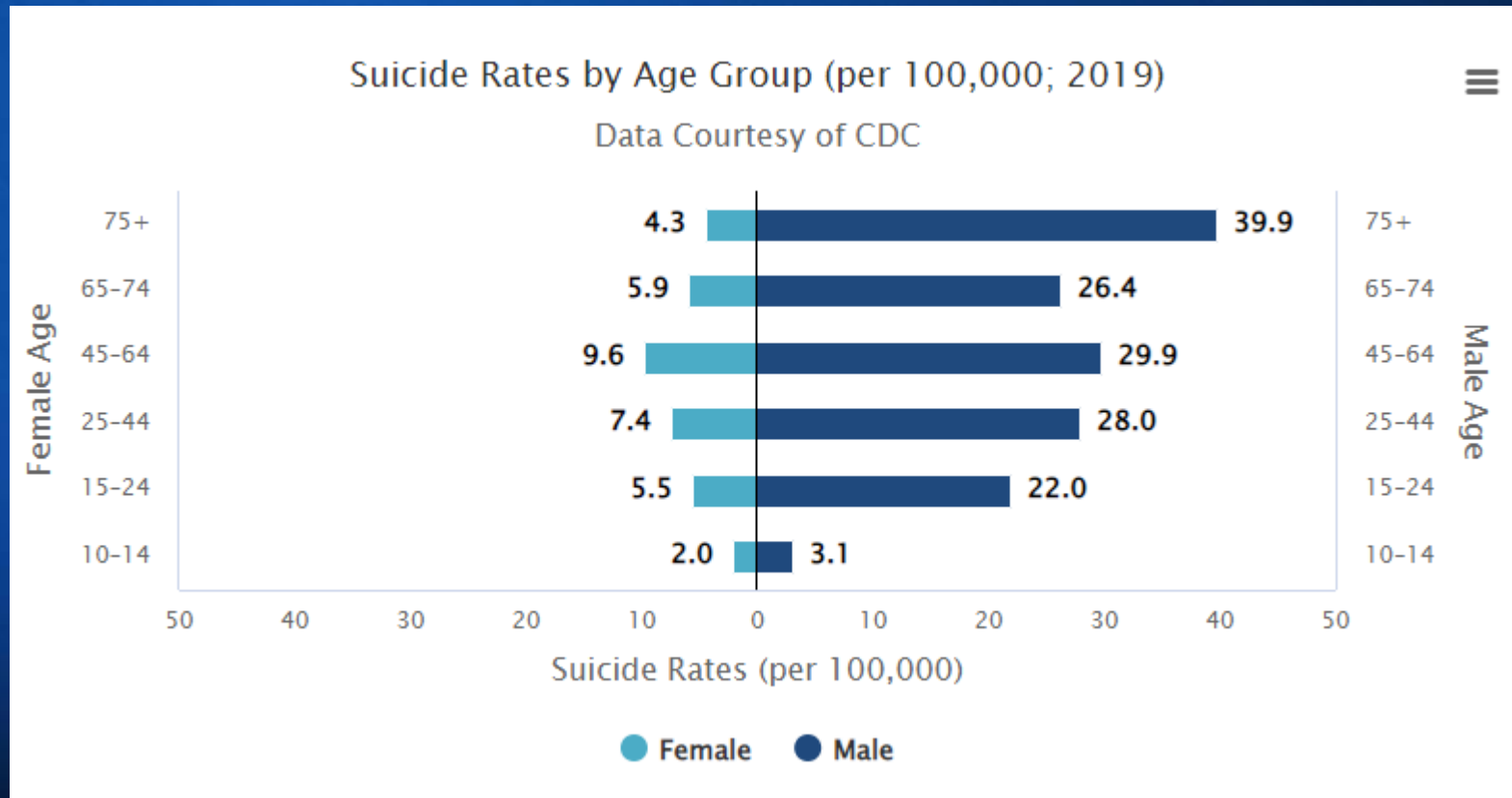


# Past Year Prevalence of Suicide Attempts Among U.S. Adults 2019 Data Courtesy of SAMHSA



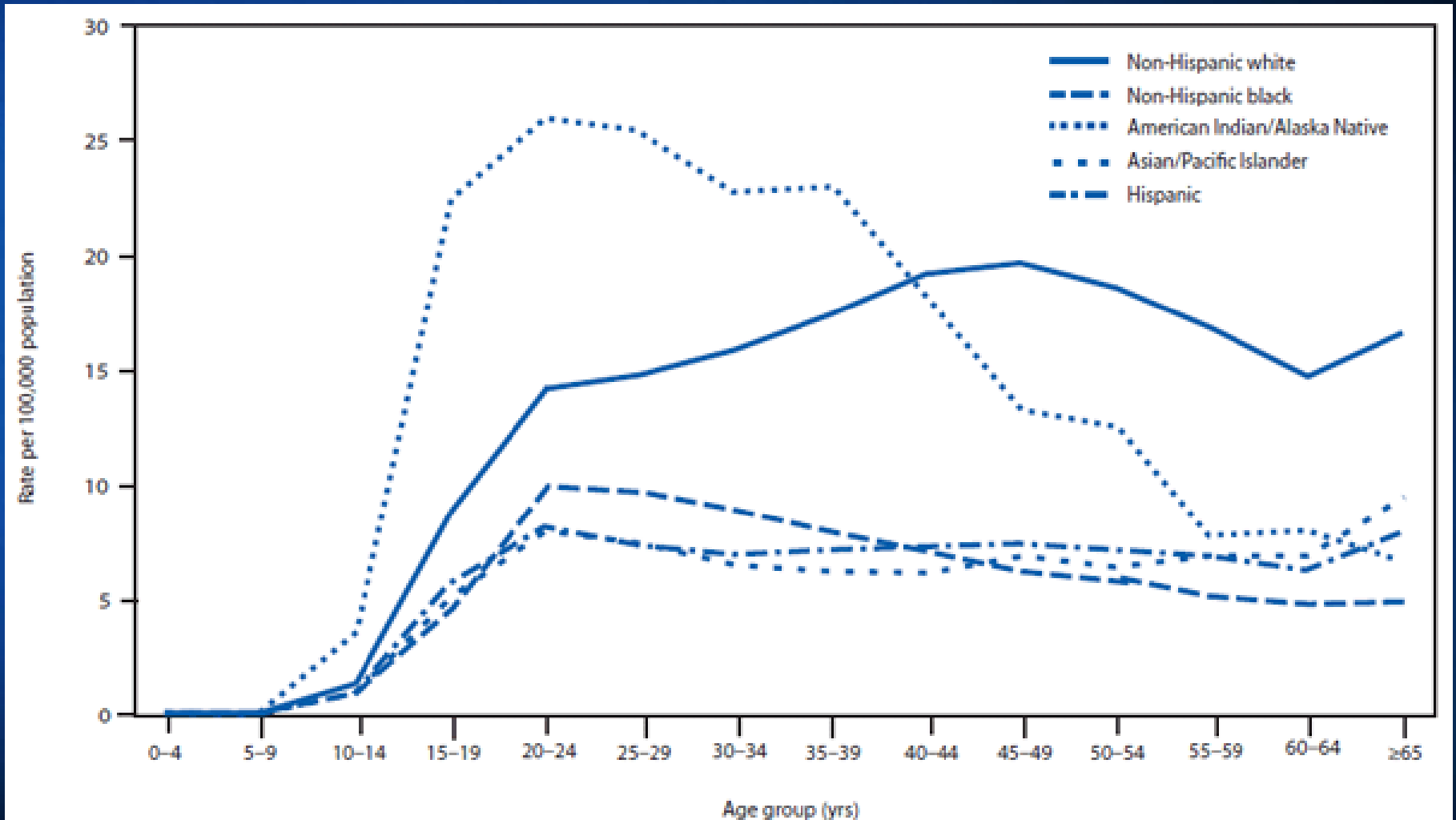
# Age and Demographics of Suicide

- 2019 data:





# Suicides in US 1999-2007 by Age/Ethnicity



Crosby et al. Suicides — United States, 1999–2007. CDC. Morbidity and Mortality Weekly Report (MMWR), January 14, 2011 / 60(01);56-59

# Epidemiology of Suicide in Later Life

- In older adults, one of 4 suicide attempts is fatal.<sup>1</sup>
- Increased risk with<sup>2</sup>:
  - Older, white, male
  - Widower, living alone, isolated, loss of social support, financial stress
  - Pain, Perceived poor health
  - Greater functional impairment
  - Acute stressful event, bereavement
  - Access to lethal means
  - DEPRESSION!

1. Crosby et al. Suicide Life Threat Behav 1999;29: 131-140; 2. Blazer and Friedman. Am Fam Physician 1979;20:91-6; also see Conwell et al. Completed suicide at age 50 and over. J Am Geriatr Soc 1990;38: 640-644; Conwell et al. Completed suicide among older patients in primary care practices: a controlled study. J Am Geriatr Soc 2000;48: 23-29.2000

# Illness Risk Factors

- Major depression<sup>1</sup>:
  - Among depressed elderly seen in primary care during 12 months preceding suicide attempt, fewer than 1/10 received appropriate depression dx.
- Medical illnesses<sup>2</sup>:
  - Cancer, neurological diseases and cardiovascular diseases are the most frequently reported disorders associated with suicide. Associated Relative Risk = 1.5 to 4.
  - Recent data suggest increase in older adult suicide associated with COVID19 pandemic.<sup>3</sup>

# Assessment/Intervention: The 5 D's

Characteristic	Description	Potential Intervention
Deadly means	Firearm in home (used in 7% of late life suicides)	Firearm safety legislation, weapons removal, disposal of expired medications
Depression	Depression in 87% of older adults who die by suicide	Depression care managers in primary care, adequate treatment of late life depression
Disease/ Disability	Physical illness as well as functional disability is important	Improved health care maintenance, education, access
Disconnected	Lack of structural, functional, emotional supports	Identification and intervention for those at risk
Developmental	Vulnerability is increased by lack of safe upbringing, supports, lack of early safe, trusted relationships	Bolstering social support to modify attachment anxiety

Modified from Conwell and Lutz. *Int Psychogeriatr* 2021;33(2):117–119.

# Treatment of Depression in Primary Care Settings

# Depression and Medical Illness

- Medical burden in the elderly is great, and illnesses complicate the diagnosis of depression because of overlapping symptoms.
- Many illnesses are linked with increased depression risk: e.g. Coronary Artery Disease (15-23%), Diabetes Mellitus (17-25%), ESRD with dialysis (25%), Cancer (25%)
- Disease mechanisms can be synergistic; treatment requires attention to adverse effects / interactions.
- In general, the medical disorder and depression are both treated.

# How Can Late Life Depression Be Detected and Treated More Effectively in Primary Care Settings?

- Primary Care settings are optimal site for detecting and initiating treatment of late life depression.
- Several model programs have demonstrated efficacy:
  - IMPACT
  - PROSPECT
  - PRISM-E
  - TIDES

# “Improving Mood-Promoting Access to Collaborative Treatment”: IMPACT

- 1801 patients, 25 sites, 60 or older, with major depression and/or dysthymic disorder excluding substance abuse, psychosis, high suicide risk, cognitive impairment
- “Depression Care Manager” (CM) supervised by primary care expert and psychiatrist
- Step 1: PST or AD; Step 2: alternate; Step 3: combo; Step 4: Specialty care or ECT



# IMPACT Results

- At 12 months, 45% of intervention patients vs 19% of “usual care” had at least 50% reduction of depressive symptoms (OR=3.45, NNT=4-5)<sup>1</sup>
- Intervention was associated with:
  - Greater rates of depression treatment
  - Higher treatment satisfaction, Greater quality of life
  - Reduced functional impairment
  - Low increment in health care costs<sup>2</sup>
  - Better depression outcomes in cognitively impaired<sup>3</sup>

# Comments On Collaborative Treatment of LLD in Primary Care Settings

- Evolving model of late life depression increases the emphasis on medical factors.
- Evolving care models demonstrate value of integration of medical with mental health care.
  - Outcome in PC setting similar to MH/SA clinic
  - Superior engagement, coordination of care
  - Possible advantage for high-risk subpopulations
  - Opportunity to integrate preventive, medical and mental health care effectively

# Conclusions

- Depression: Not a normal part of aging
- Age affects LLD:
  - Risk
  - Etiology
  - Presentation
  - Assessment
  - Treatment
  - Prognosis
- Remember to look for LLD and to treat actively!

Questions/Discussion?