DEPRESSION IN LATER LIFE:
What's The Difference

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DISCLOSURE

Dr. Krautter has nothing to disclose relevant to this presentation.

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LEARNING OBJECTIVES

At the conclusion of this presentation, the learner will be able to describe and explain:

- How depression presents differently in later life.
- How evaluation of depression in later life is modified to take the effects of age into account.
- How treatment options for depression are affected by older age.

3

PRE-TEST QUESTIONS

Please answer the questions as they appear on your screen.

4

Late-Life Depression

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Key Points

- Depressive symptoms/syndromes in later life: significant and treatable!
- Depressive disorders are not a "normal part of aging"
- Age influences demographics, cause, symptoms, assessment, acute and maintenance treatment, outcome
- Treatment options: Recent advances in both psychotherapies and somatic therapies

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Prevalence of Depressive Syndromes in Later Life

	Clinically Significant Depressive Symptoms[1]	Major Depressive Disorder[1]
Community	8-15% 9.7-26.1% for 75+[3] 6.1% for men, 9.6% for women in age 60+ (2013-6)[3]	1-4%[1] 4.4-10.6% for 75+[2]
Primary Care		6-9%[3]
Long Term Care	30-50%	6-25%
Bipolar Disorder		0.1-0.4%[4]

1. Blazer DG. Depression in late life: review and commentary. The journals of gerontology Series A, Biological sciences and medical sciences. 2003
2. 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; 3. Luppa et al. J Aff Dis 2012; 4. National Health and Nutrition Survey 2013-2016; 5. Unutzer et al. Milbank Q 1999

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Some Risk Factors for LLD

Demographics
- Older age
- Female
- 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

Vink et al. Journal of Affective Disorders 2008.

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Adverse Outcomes of Untreated LLD[1-6]

- Increased use of non-mental health services
  - Twice as many doctor appointments
  - Twice as likely to receive 5 or more medications
- Reduced adherence to medical treatment
- Functional Decline / Increased disability
- Increased medical morbidity/mortality:
  - CVA/MI/Dementia
- Increased risk for suicide
- And yet – more than ½ of depressed elders go untreated.

1. Beekman et al. Psychol Med 1997; 2. Bruce and Leaf. Am J Public Health. 1989; 3. Romanelli et al. J Am Geriatr Soc 2002; 4. Alexopoulos GS. Lancet 2005; 5. Katon et al. Arch Gen Psychiatry 2003; 6. Hall and Reynolds. Maturitas 2014;79:147-52; 7. Barry et al. J Affect Dis 2012

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Diagnosis: The Definitions

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DSM 5 MDD

- **Depressed mood OR loss of interest/pleasure, plus**
- At least 4 other SIGECAPS
- Present at least during the same 2-week period
- Distress or functional impairment
- Medical/Substance/Psychiatric exclusions
- There has not been a manic/ hypomanic episode
- NO BEREAVEMENT EXCLUSION (differs from DSMIVTR: Depression resembles but differs from "responses to a significant loss")

SIG E CAPS

Sleep
Interest
Guilt/worthlessness
Energy
Concentration
Appetite/weight
Psychomotor
Suicidal

MDD = "Major Depressive Disorder"
American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.

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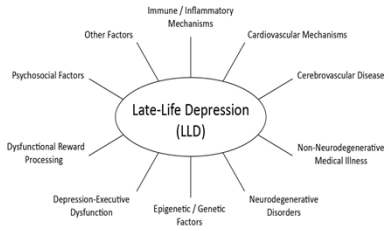
Contributing Factors



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Special Symptomatic Presentations of LLD

- Beneath the "Major Depression" threshold
- "Depression without sadness"[1]
- Somatic (sometimes cognitive) focus
- Depression with psychotic features
- Depression with cognitive impairment [2-3]

1. Gallo and Rabins. Am Fam Physician 1999.
2. Butters et al. Am J Psychiatry 2000.
3. Sáez-Fonseca et al. J Affect Disord 2007.

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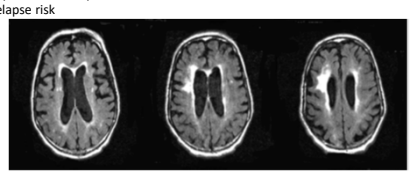
Vascular Depression

- Presence of moderate to severe white matter hyperintensities in depressed patients has been linked with decreased agitation/guilt, increased psychomotor retardation and disability, and Neuropsychological Correlations[1];
  - Poorer Executive Functioning
  - Slower response to citalopram treatment[2]
  - Greater relapse risk



Courtesy of Martin Goldstein MD

1. Kelly Jr and Alexopoulos. In Ellison et al (eds). Mood Disorders in Later Life. Informa Healthcare 2008
2. Manning et al. Am J Geriatr Psychiatry. 2015 May.

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Post-Stroke Depression

- More than 795,000 CVAs per year in U.S.[1]
- About 1/3 of CVA patients have Post-Stroke Depression[2]
  - Compared to Vascular Depression, PSD is disorder of larger blood vessels

Treatment

- Risk of PSD after CVA is reduced with use of prophylactic escitalopram or active rehabilitation program.[3]
- SSRIs and TCAs have been shown more effective than placebo.[4]
- Side effects can be significant.[4]
- Change treatment if no response after 6 weeks.[4]
- Treat at least 4 months beyond initial recovery.[4]

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

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Depression with Psychotic Features

- Psychotic symptoms (delusions or hallucinations) with major depression
- More prevalent among older vs younger depressives
- Associated with:
  - Later onset
  - Hypochondriacal and nihilistic delusions
  - Poorer response to monotherapy/maintenance
  - Higher recurrence rate
  - Higher suicide risk

Gournellis et al. Int J Geriatr Psychiatry 2001;16:1085-91;
Flint and Rifat Am J Psychiatr 1998;155:178-83.

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Depression with Cognitive Impairment

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

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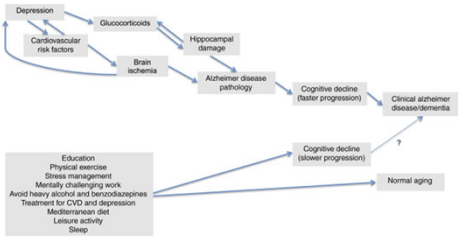
Relationship Between Depression and Cognitive Decline



Chen et al. Am J Ger Psychiatry 2019;27(3):213-36.

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Assessment

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1. Detection: 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
2. Phelan et al. BMC Fam Pract. 2010.
Source: Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Sep. CADTH Rapid Response Reports.

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Psychometrics of GDS

- Appears to be most widely used screen
- In public domain, multiple translations
- 4 versions range from 4 to 30 questions
- GDS15 with cut-off of 5/6:
  - Sensitivity overall 86%
  - Specificity 79%
  - Figures are lower in in outpatient and nursing home settings

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

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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)

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2. Assessing Effect of Medical Burden

- Medications, Alcohol, Drugs
- Endocrinopathy
- Malignancy
- Infection
- Metabolic disorders
- Nutritional deficiencies
- Sleep disorders
- Vascular disease
- Neurological disorders

- Depressive episode should be treated while managing the comorbid medical condition

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3. Assessing Laboratory Results

- **Hematology**
  - CBC with indices/differential
  - ESR
- **Chemistry**
  - Lytes, BUN, Creatinine
  - Liver function tests
  - Thyroid function tests
  - Fasting glucose level
  - Folate, B121
- **Urine**
  - Urinalysis
  - Culture and sensitivity
- **Additional tests, e.g.**
  - Electrocardiogram
  - Chest X-Ray
  - Neuroimaging (?)

1. Petridou et al. Aging Ment Health 2015 Jun 8:1-9 epub.

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Treatment Approach
Non-Pharmacological Treatments

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1. Psychotherapy: Several are Evidence-based Treatments for Late-Life Depression

- RCTs support[1]
- Cognitive Behavioral Therapy (CBT)
- Interpersonal Therapy (IPT)
- Problem Solving Therapy (PST)
- ENGAGE

1.Antognini and Liptzin in Ellison et al. Mood Disorders in Later Life. Informa 2008.

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2. Physical Activity

- Greater midlife physical activity is associated with lower depressive symptomatology in later life.[1]
- Physical inactivity in older adults is associated with both depression and cognitive deficits.[2]
- Meta-analysis supports benefit of Physical Exercise, less evidence supporting use over 80 years old or with MMSE < 23/303.
- Higher and faster remission in LLD linked with exercise augmentation of sertraline (24 wk of PAE).[4]

1. Chang et al. J Gerontol A Biol Sci Med Sci 2015 Nov
2. Paulo et al. J Aging Phys Act 2015
3. Klil-Drori et al. J Clin Psychiatry 2020 Jan 21
4. Belvederi Murri et al. Br J Psychiatry 2015

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Pharmacologic Treatment Antidepressant Efficacy

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Pharmacologic Treatment Antidepressant Efficacy

- All FDA-indicated antidepressants treat LLD[1]
- Response rate (50% symptom decrease)[2]
  - 50 - 65% in trials with ITT analyses
  - 25 - 30% respond to placebo
  - Number Needed to Treat (NNT): 2.5 - 5
- Remission (≥90% symptom decrease)[2]
  - Typically 30 - 40% with medication vs 15% for placebo
  - NNT: 4 - 7

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

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Antidepressant Side Effects: SSRIs

- Discontinuation is less common with SSRI treatment (17%) than with TCA treatment (24%).
- Significant side effects with SRIs:
  - Sedation
  - Weight gain
  - GI symptoms
  - Hyponatremia
  - Risk for bruising
  - Risk for GI bleeding
  - Sexual dysfunction
  - Falls?

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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_1 receptor antagonism	CNS depressant potentiation, sedation, weight gain, hypotension
Muscarinic receptor antagonism	Blurred vision, dry mouth, constipation, urinary retention, cognitive dysfunction
NE α_1 receptor antagonism	Potentiation of some antihypertensives, postural hypotension, dizziness, reflex tachycardia

Adapted/modified from http://www.cpgnews.org/DEP/tools.cfm

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SSRIs and Cardiac Safety

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

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.

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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 5 prescribed medications
- Many interactions are possible
  - Pharmacodynamic
  - Pharmacokinetic

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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)
  - Viibryd (vilazodone)
  - Emsam (transdermal selegiline)

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SSRIs – Still 1st Choice in LLD

- Several well-tested, generic, well-tolerated, with limited drug interactions, appropriate elimination half-lives:
  - Sertraline
  - Citalopram (Note FDA dosage warning)
  - Escitalopram

Ellison et al., in Ellison et al (eds). Mood Disorders in Later Life. Informa HealthCare 2008.

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SNRIs

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

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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[1]
  - Associated with small/significant risk for neutropenia, agranulocytosis; minimal interaction with warfarin

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.

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The Newer Antidepressants

- **Vilazodone (Viibryd)**
  - SSRI and partial agonist at 5HT1a
- **Vortioxetine (Trintellix)**
  - SSRI, agonist 5HT1a, partial agonist at 5HT1b antagonist 5HT3a/5HT7
- **Levomilnacipran (Fetzima)**
  - Balanced SNRI

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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.

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ECT Efficacy

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

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 non-comparable RCTs

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Additional Neurotherapies[1]

- Repetitive Transcranial Magnetic Stimulation[2]
  - 20-50% response rate open label, older adults
  - Poorer response associated with cortical atrophy
  - Better response with higher intensity stimulation?
- VNS– limited data in elderly
- *Transcranial Direct Current Stimulation
- *Magnetic Seizure Therapy
- *Deep Brain Stimulation

*these neurotherapies are used investigationally or off label in treatment of depression

1. Alexopoulos GS, Kelly Jr RE. Research advances in geriatric depression. World Psychiatry. 2009; 8(3): 140–149
2. Galvez et al. Curr Psychiatry Rep 2015;17:59-74

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Treatment of Depression in Dementia

- Multiple antidepressants studied, including
  - Citalopram[1]
  - Sertraline[2,5]
  - Clomipramine[3]
  - Moclobemide[4]
  - Mirtazapine[5]
- 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.

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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

Spotlight on Bereavement/Grief

- Definition: Bereavement is the fact of the loss, grief the associated feelings and behaviors linked with awareness of loss.[1]
- Can include sadness, insomnia, poor appetite, sense of the deceased one's presence, hearing the voice of the deceased
- MDD can co-occur, but reaction to loss is not necessarily "depression"

1. Zisook and Shear. World Psychiatry 2009;8:67-74

Spotlight on Substance Use

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

1. Wu and Blazer 2010 (in press) J Aging and Health; 2. Culberson 2006;Geriatrics 61:23-27.

Spotlight on Pain

- Pain often accompanies MDD[1]
  - 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.[1]
  - 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[2]

1. Brannan et al. J Psychiatr Research 2005;39:43-53;
2. Bonnewyn et al. J Aff Dis 2009;117:193-6.

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The Next Step in Treatment Resistant Depression

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

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Suicide in Later Life

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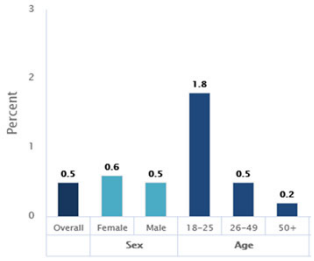
Past Year Prevalence of Suicide Attempts Among U.S. Adults 2016 Data Courtesy of SAMHSA



https://www.nimh.nih.gov/health/statistics/suicide.shtml accessed 12/31/18

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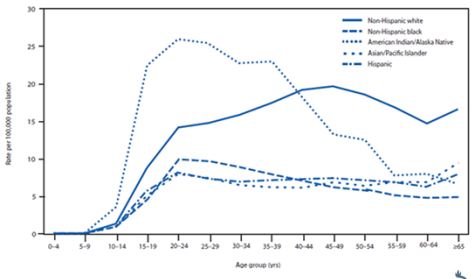
Suicides in U.S. 1999-2007 by Age/Ethnicity



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

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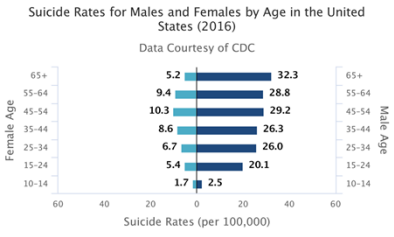
Age and Demographics of Suicide

- 2016 data:



https://www.nimh.nih.gov/health/statistics/suicide.shtml accessed 12/31/18

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Epidemiology of Suicide in Later Life

- In older adults, one of 4 suicide attempts is fatal.
- Increased risk with:
  - 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
2. Also see Conwell et al. Completed suicide at age 50 and over. J Am Geriatr Soc 1990;38: 640-644
3. Conwell et al. Completed suicide among older patients in primary care practices: a controlled study. J Am Geriatr Soc 2000;48: 23-29.2000

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Treatment of Depression in Primary Care Settings

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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.

See Harnett and Pies, in Ellison et al (eds). Mood Disorders in Later Life..Informa Health Care 2008.

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"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

Unutzer et al. JAMA 2002;288:2836-2845

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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)[1]
- 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[2]
  - Better depression outcomes in cognitively impaired[3]

1. Unutzer et al. JAMA 2002;288:2836-2845;
2. Katon et al. Arch Gen Psych 2005;62: 1313-20;
3. Steffens et al. Am J Geriatr Psychiatry 2006;14:401-9.

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Comments on Primary Care Treatment of LLD

- **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

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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!**

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POST-TEST QUESTIONS

Please answer the questions as they appear on your screen.

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THANK YOU

QUESTIONS & DISCUSSION

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