DIAGNOSIS AND TREATMENT OF DEPRESSION IN ELDERLIES

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DEPRESSION IN OLD AGE PEOPLE

- geriatric depression continues to be underdiagnosed.
- The failure to recognize geriatric depression stems from the
  1. clinical complexity of the syndrome,
  2. symptom overlap with medical comorbidities,
  3. social bias,
  4. barriers of the settings in which most depressed elderly patients are treated.

EPIDEMIOLOGY OF DEPRESSION IN OLD AGE PEOPLE

- The National Comorbidity Survey Replication discovered that:
- the overall prevalence of major depression among persons aged 65 years or older was estimated to be ***1.5 percent in women*** and ***0.2 percent in men***, with an overall prevalence of ***1 percent***, approximately one-fourth of that in younger adults.

EPIDEMIOLOGY OF DEPRESSION IN OLD AGE PEOPLE

- Combining symptoms of major or minor depression with reported treatment for depression:

  the cumulative depression prevalence in later life is noted to be as high as 11.19 percent

  with similar rates for men (10.19 percent) and women (11.44 percent).

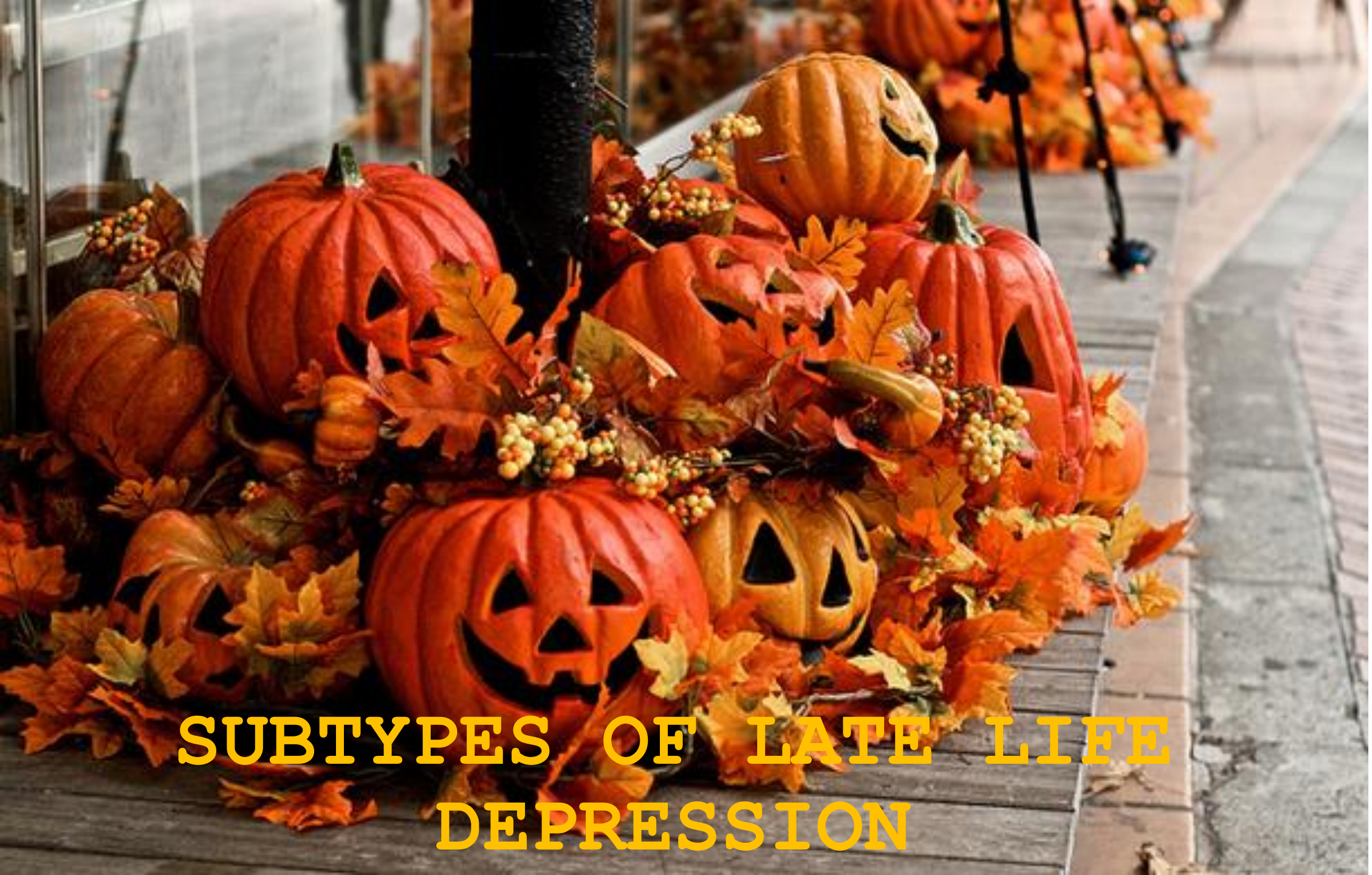
- Subthreshold depression has a median community point prevalence of ***9.8 percent***, approximately two to three times more prevalent than major depression.

EPIDEMIOLOGY OF DEPRESSION IN OLD AGE PEOPLE

- Approximately ***8 to 10 percent*** of older persons with subthreshold depression developed major depression per year.
- For patients treated in primary care settings, depression was identified in ***17 to 37 percent*** of patients. Approximately ***30 percent*** of these patients had major depression

EPIDEMIOLOGY OF DEPRESSION IN OLD AGE PEOPLE

- Major depression occurs in roughly
  1. 25 percent of older home care patients
  2. 11 percent of medically hospitalized patients
  3. up to 48 percent for individuals in long-term care settings



SUBTYPES OF LATE LIFE DEPRESSION

DEPRESSION IN MEDICALLY ILL PATIENTS

- subclinical hypothyroidism increases the risk for depression more than fourfold
- a third of patients develop depression within a year after a myocardial infarction
- Older adults with chronic disease have a 50 percent greater risk for depression than older, medically healthy adults.
- Depression increases the risk of coronary disease by over 60 percent
- malnutrition, metabolic syndrome, and post hip fracture surgery

DEPRESSION IN MEDICALLY ILL PATIENTS

- Depression impairs social function more than heart and lung disease, arthritis, hypertension, and diabetes and leads to greater impairment in physical function than arthritis, hypertension, and diabetes.
- This effect seems to be mediated through:
  1. decreasing adherence to treatment
  2. biological mechanisms such as changes in sympathetic-parasympathetic balance
  3. changes in serotonin-mediated thrombogenesis
  4. changes in the immune system

DEPRESSION IN PATIENTS WITH DEMENTIA

- Depressive occur in approximately ***50 percent*** of patients with dementia
- Depression is both a risk factor for AD and a prodrome
- a history of depression ***doubles the risk*** for developing dementia in late life.
- Depression occurs in
  - ***25 percent*** of patients with cerebrovascular disease
  - ***up to 50 percent*** of those with Parkinson disease
- Sad mood and psychic rather than vegetative features

DEPRESSION WITH REVERSIBLE DEMENTIA

- pseudodementia, dementia syndrome of depression, or depression with reversible dementia
- Depressed elderly patients who remain with some cognitive impairment(***executive function, processing speed, and working memory***)even after improvement of depression usually have an early-stage dementia
- Even those individuals with nearly complete cognitive recovery develop high rates of irreversible dementia (about ***20 percent per year***) on follow-up.
- Many of these patients may remain nondemented for ***1 to 2 years*** before the development of irreversible dementia.

PSYCHOTIC DEPRESSION

- Occurs in ***20 to 45 percent*** of hospitalized elderly depressives and in ***3.6 percent*** of elderly depressives living in the community
- Patients with psychotic depression have ***delusions***, whereas hallucinations are less frequent.
- The usual themes of depressive delusions are:
  1. guilt
  2. hypochondriasis
  3. nihilism
  4. persecution
  5. jealousy

BEREAVEMENT

- Older persons appear to be at ***lower risk*** for developing depressive symptoms or syndromes than younger adults ***during the first months after loss of a spouse***.
- In fact, the prevalence of major depression continues to increase during the ***second year of bereavement***.
- At the end of the second year after loss, ***14 percent*** of bereaved elderly individuals have major depression.


SUICIDE

SUICIDE RISK FACTORS

1. Caucasian men older than 80 years
2. Severity of depression & psychotic depression
3. Alcoholism & abuse of sedatives
4. recent bereavement
5. recent development of disability & chronic medical conditions
6. cognitive difficulties
7. previous serious suicide attempts
8. Poor social support & Isolation
9. perceived health status & perceived burdensomeness
10. hopelessness
11. Insomnia

SUICIDE RISK FACTORS

- ***Depression*** is the most common psychiatric diagnosis in elderly suicide victims.
- Major depression is identified in ***80 percent*** of suicide victims older than 74 years of age.

BIOLOGICAL DYSFUNCTION

THE LATE-ONSET HYPOTHESIS

Neurological brain abnormalities

Major depression with the onset of first episode in late life

THE LATE-ONSET HYPOTHESIS

- ***First episode in late life = neurological brain abnormalities***
- Individuals with late-onset major depression have
  1. less frequent family history of mood disorders
  2. higher prevalence of dementing disorders
  3. higher rate of dementia development on follow-up
- Most elderly patients with major depression and an initially reversible dementia have late-onset depression.
- Despite improvement of cognitive functions with remission of the depressive syndrome, many of these patients develop irreversible dementia during long-term follow-up.

THE DEPRESSION-EXECUTIVE DYSFUNCTION HYPOTHESIS

- This hypothesis postulates that a ***"depression-executive dysfunction (DED)" syndrome*** exists with a clinical presentation resembling medial-frontal lobe syndrome.
- DED syndrome is characterized by:
  1. psychomotor retardation
  2. reduced interest in activities
  3. Apathy
  4. impaired insight
  5. severe behavioral disability
  6. less pronounced depressive ideation and vegetative signs

THE DEPRESSION-EXECUTIVE DYSFUNCTION HYPOTHESIS

- Similarly, depressed older adults who reported executive functioning complaints at baseline had a ***slower response to escitalopram treatment*** than those without executive functioning complaints.
- The DED hypothesis assumes that executive dysfunction is the clinical expression of ***frontolimbic dysfunctions*** predisposing to late-life depression.
- The limbic system evaluates reward-related stimuli and organizes stress responses, and higher neocortical structures exert control over these processes

THE DEPRESSION-EXECUTIVE DYSFUNCTION HYPOTHESIS

- *Insula metabolism : a treatment-specific biomarker in major depression.*

Insula hypometabolism

- response to cognitive-behavioral therapy

Insula hypermetabolism

- remission to escitalopram

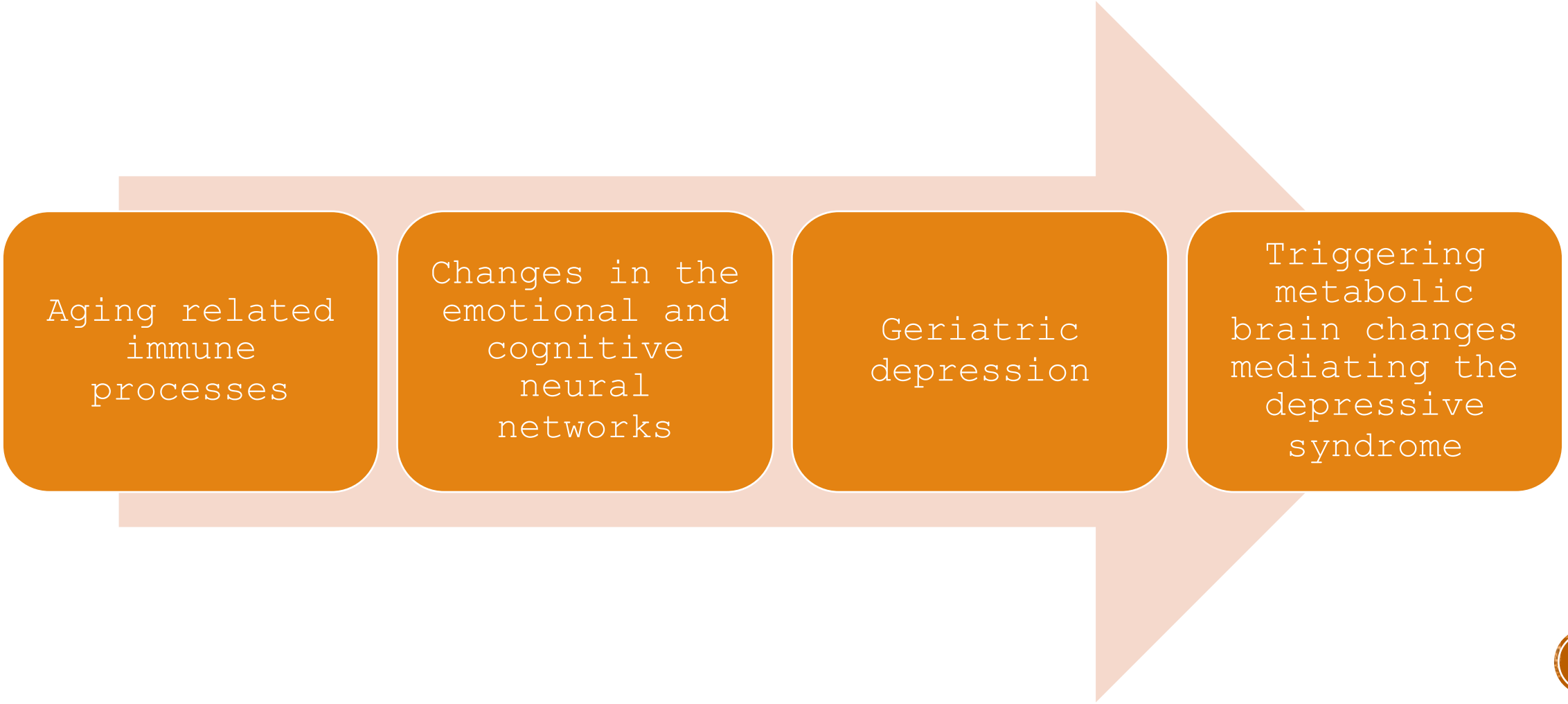
THE DEPRESSION-EXECUTIVE DYSFUNCTION HYPOTHESIS

- White matter abnormalities compromising connections between limbic and dorsal cortical structures may interfere with limbic–dorsal cortical balance and lead to chronic depressive syndromes.
- Subcortical white matter hyperintensities (WMHs) have been associated with both executive dysfunction and nonremission of late-life depression.

THE DEPRESSION-EXECUTIVE DYSFUNCTION HYPOTHESIS

- Diffusion tensor imaging studies documented that reduced white matter integrity in distributed cerebral networks is associated with poor response of late-life major depression to a serotonin reuptake inhibitor:
  1. dorsal and rostral anterior cingulate cortex [ACC]
  2. dorsolateral-prefrontal cortex [DLPFC]
  3. hippocampus
  4. posterior cingulate
  5. insula
  6. neostriatum
  7. midbrain
  8. selected temporal and parietal regions

THE INFLAMMATION HYPOTHESIS



THE INFLAMMATION HYPOTHESIS

1. Aging leads to a proinflammatory state
2. Immune responses of the CNS can influence the function of some of the emotional and cognitive networks pertinent to geriatric depression
3. Elevation of peripheral cytokines is associated with depressive symptoms in older adults
4. Some antidepressants reduce the expression of several inflammation markers in the periphery
5. pretreatment cytokine plasma levels may influence the response to antidepressantsa

THE INFLAMMATION HYPOTHESIS

- Aging promotes a chronic state of neuroinflammation, and animal and human studies suggest that this proinflammatory state may compromise neural systems related to depression.
- Elevation of IL-1Ra was a risk factor for developing depressive symptoms during a 6-year follow-up in older adults.
- Clinical studies of depressed patients, documented a plasma elevation of several inflammatory markers (TNF-α, IL-6 and IL-1b) and a correlation with the severity of depressed mood and cognitive symptoms of depression.

THE INFLAMMATION HYPOTHESIS

- Some tricyclic antidepressants (TCAs) may reduce some proinflammatory cytokines, increase anti-inflammatory cytokines, and reduce polysaccharide-induced "sickness behavior" in animals.
- Pretreatment cytokine plasma levels may influence the response to antidepressants in humans. Selective serotonin reuptake inhibitor (SSRI)-resistant patients had higher TNF-α plasma levels while euthymic patients with a history of depression had TNF-α levels similar to those of normal controls.

THE VASCULAR DEPRESSION HYPOTHESIS

- The hypothesis was based on the
  1. high comorbidity of depression and vascular risk factors
  2. the high incidence of depression in stroke
  3. the high prevalence of WMHs in late-onset depression
  4. the high frequency of cognitive impairment in depressed patients with vascular risk factors
  5. the similarity of cognitive abnormalities of depression to those associated with WMH

THE VASCULAR DEPRESSION HYPOTHESIS

- Recent studies show greater WMH severity in specific white matter fiber tracts in late-life depression, including
  1. the cingulum bundle,
  2. uncinate fasciculus, and
  3. superior longitudinal fasciculus. Fiber tract structural connectivity is positively correlated with resting state functional connectivity of connected regions.

THE VASCULAR DEPRESSION HYPOTHESIS

- A syndrome of "subcortical ischemic depression" has been proposed based on WMH literature.
- This syndrome is defined by the combination of depression and MRI evidence of subcortical ischemic changes.
- Age, lassitude, and a history of hypertension were positively associated with the diagnosis of subcortical ischemic vascular depression, whereas a family history of mental illness and loss of libido were negatively associated with this diagnosis.

THE VASCULAR DEPRESSION HYPOTHESIS

- WMH and microstructural brain abnormalities predict poor response of late-life depression to antidepressants.
- Increases in WMH volume over 2- and 4-year intervals are associated with nonremission or relapse.
- Microstructural white matter abnormalities in multiple frontolimbic brain areas, including the rostral- and dorsal-anterior cingulate, DLPFC, genu, hippocampus, posterior cingulate, left superior corona radiata, and right inferior longitudinal fasciculum are associated with nonremission.

THE VASCULAR DEPRESSION HYPOTHESIS

- At least three interconnected processes may lead to "vascular depression," that is:
  1. disconnection of networks responsible for regulation of mood and cognition
  2. reduced regional CBF
  3. inflammatory responses related to vascular disease

BRAIN STRUCTURE STUDIES

- Neuroradiological studies suggest frontostriatal and limbic impairment in depression.
- WMHs prevalent in geriatric depression are mainly located in subcortical structures and the medial-orbitofrontal cortex.
- Increase in volume of WMHs over a 2-year period predicted lower rates of sustained late-life MDD remission during the same period.
- Worsening of white matter grade in the elderly over a 5-year period has been associated with cognitive decline.

BRAIN STRUCTURE STUDIES

- Low volumes of some brain regions have been noted in mixed-age depressed patients.
  1. the subgenual anterior cingulate
  2. the head of the caudate nucleus
  3. the putamen
  4. the hippocampus
  5. orbitofrontal cortex volume

BRAIN FUNCTION STUDIES

- Increased metabolism has been noted in limbic regions, including the amygdala, the rostral-anterior cingulate, and the posterior orbital cortex
- In contrast, dorsal neocortical areas, such as the lateral and DLPFC, and the dorsal-anterior cingulate, as well as the caudate have reduced blood flow during depression.
- Reduced bilateral activation of the dorsal-anterior cingulate and the hippocampus was demonstrated in severely depressed, nondemented elderly patients performing a word-activation task.

BRAIN FUNCTION STUDIES

- A recent positron emission-based study provided evidence for insula metabolism as a treatment-specific biomarker in MDD.
- Insula hypometabolism (relative to whole-brain levels) was associated with remission in response to cognitive-behavioral therapy and poor response to escitalopram,
- Insula hypermetabolism was associated with remission to escitalopram and poor response to cognitive-behavioral therapy in a mixed-age sample

COURSE AND OUTCOME

- Despite advances in antidepressant therapies, longitudinal studies of 1 to 6 years duration suggest that 7 to 30 percent of geriatric patients have a chronic major depression.
- If partially remitted subjects are considered chronic, the rat
- Chronicity of depression may be predicted by history of a long current episode or long previous episodes, coexisting medical illness, high severity of depression, nonmelancholic presentation, and delusions. e of chronicity reaches 40 percent.

EVALUATION AND TREATMENT

- The objectives of geriatric depression treatment include the following:
  1. remission of depression
  2. reduction in the risk of relapse and recurrence
  3. improvement of cognitive and functional status
  4. development of skills or provision of supports needed for coping with handicaps and psychosocial adversity

EVALUATION AND TREATMENT

- Long-term outcomes of elderly depressed patients can be improved by:
  1. identifying and treating comorbid psychiatric and medical conditions
  2. minimizing medication side effects
  3. striving for full remission of acute symptoms, and
  4. providing psychoeducation for patients, families, and health care professionals

EVALUATION AND TREATMENT

- The evaluation of geriatric depression should include
  1. Assessment of psychopathology
  2. Medical and Neurological status
  3. Functional impairment
  4. Psychosocial factors as well as suicide risk.

- Conditions that often contribute to late-life depression and worsen its course:
  1. dementing disorders
  2. use of drugs that may cause depression (e.g., steroids)
  3. benzodiazepine and alcohol abuse

EVALUATION AND TREATMENT

- A further complexity of assessment includes the risk of ***missing a bipolar depression diagnosis***, as such a diagnosis would alter clinical management and contraindicate the use of antidepressant monotherapy
- Rating scales that can be useful in assessment:
  1. Hamilton Depression Rating Scale
  2. the Cornell Scale for Depression in Dementia
  3. the Geriatric Depression Scale
  4. Mini-Mental State Examination
  5. Montreal Cognitive Assessment (MOCA)

EVALUATION AND TREATMENT

- a number of other medical conditions are often associated with depression:

1. viral infections
2. endocrinopathies (e.g., thyroid and parathyroid abnormalities)
3. vitamin B12 deficiency
4. malignancies (e.g., lymphoma and pancreatic cancer)

EVALUATION AND TREATMENT

- For example, depression in a hypothyroid elderly patient rarely responds to thyroid supplementation alone. Similarly, an antidepressant trial often is ineffective before hypothyroidism is corrected
- If the depression occurs in a patient receiving methyldopa (Aldomet), cimetidine (Tagamet), clonidine (Catapres), hydralazine, propranolol (Inderal), or reserpine, switching to another medication is recommended.

EVALUATION AND TREATMENT

- If the depression occurs in a patient treated with digitalis, estrogens, tamoxifen (Soltamox), vinblastine, or vincristine, the medication should be continued and depression should be treated with antidepressants.
- There is no agreement on the best strategy for depression that occurs in patients treated with benzodiazepines, corticosteroids, progesterone, propoxyphene (Darvon), or psychostimulants.

EVALUATION AND TREATMENT

- As interferon-α treatment frequently is associated with depression, increased frequency of psychiatric follow-up and starting or increasing antidepressant treatment prophylactically should be considered before initiating such treatment in patients with a history of depression.

PSYCHOTHERAPY

- For the treatment of major depression in later life, current practice guidelines recommend a combination of pharmacotherapy and psychotherapy, with psychotherapy alone often sufficing as a first-line treatment for minor depression in later life.
- A number of psychotherapeutic modalities including interpersonal therapy, cognitive-behavioral therapy, and problem-solving therapy have been found effective in depressed elderly patients without significant cognitive impairment or medical burden.

- For patients with executive dysfunction, a number of psychotherapies have been found effective including a modification of problem-solving therapy (PST) where the therapist is more directive, the focus is on less complex problems to facilitate learning, and the program is more structured.
- problem-adaptation therapy (PATH) was developed for older individuals with major depression and intermediate cognitive impairment and disability; this modality combines problem-solving therapy, environmental adaptation tools, and caregiver involvement to target the behavioral limitations inherent in depression and disability.

PHARMACOTHERAPY

- Benzodiazepines should generally be avoided.
- Residual insomnia in depressed elderly patients should be treated with trazodone (Desyrel) and, if it fails, with zolpidem (Ambien), or zaleplon (Sonata).
- Residual anxiety should be treated with an increase of the dosage of the antidepressant to maximum levels rather than prescribing a benzodiazepine.

PHARMACOTHERAPY

- Clinical practice guidelines recommend that SSRIs and other second-generation antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors [SNRIs], bupropion, mirtazapine) are the first-line treatment for late-life depression.
- Executive dysfunction, slow cognitive processing speed, WMH, microstructural white matter abnormalities, and small hippocampal volumes each predict a slower and less complete response to antidepressant treatment.

PHARMACOTHERAPY

- Elderly patients who respond to antidepressant treatment usually require 8 to 12 weeks to achieve full remission.
- The minimal length of an antidepressant trial should be 3 to 4 weeks before a switch to another antidepressant or an augmentation agent is used.
- Patients who show no signs of improvement by the 4th week, however, will not likely respond to further treatment with the same agent.

SSRIS

- The dosages of SSRIs should be increased gradually. The starting daily dosages are 10 to 20 mg for fluoxetine, paroxetine, and citalopram, 5 to 10 mg for escitalopram, and 25 to 50 mg for sertraline.
- For some patients, daily dosages of 20 mg of fluoxetine, paroxetine, and citalopram, 10 mg of escitalopram, and 100 mg of sertraline are sufficient, although higher dosages may be required.

SSRIS

- The most frequent side effects of SSRIs are insomnia, akathisia, nausea, anorexia, and pseudoparkinsonism.
- Inappropriate secretion of antidiuretic hormone (SIADH) leading to hyponatremia is much more common in the elderly than in younger adults.
- Further, SSRIs may lead to an increased risk of bleeding, fragility fractures, poor mobility, and stroke.

SNRIS

- Venlafaxine XR (extended release) leads to high remission rates (asymptomatic states) and has been found effective in hospitalized depressed patients as well as in drug-resistant depression and in depressed patients with chronic pain.
- For this reason, venlafaxine should be considered in severe depression and in depression unresponsive to other agents. Elderly patients appear to require dosages comparable to those of younger adults. Daily dosages of 112.5 to 225.0 mg are adequate for the majority of elderly patients.

SNRIS

- Nausea, a rather frequent side effect of venlafaxine, can be minimized by a slow increase of the daily dosage. Blood pressure should be monitored, especially in patients receiving dosages above 225 mg daily, since venlafaxine can increase blood pressure.

SNRIS

- Duloxetine, an SNRI with relatively balanced serotonergic and noradrenergic action, has demonstrated efficacy in late-life depression as well as treatment of comorbid pain.
- Following a week of 30 mg/day, the dose can usually be increased to 60 mg/day after a week of treatment, if tolerated.
- For patients who remit on a dose of 60 mg, remission will typically occur by week 12 of treatment with additional time on that dose not associated with an increased chance of remission.

TCAS

- The secondary amines, nortriptyline and desipramine, are the most frequently used TCAs in geriatric depression. They have lower anticholinergic and sedative effects than the tertiary amines amitriptyline, doxepin, and imipramine.
- The plasma levels of antidepressants required for the treatment of depressed elderly patients are similar to those needed by young adults (nortriptyline plasma levels of 60 to 150 ng/mL and desipramine above 115 ng/mL).

- Elderly patients often develop therapeutic blood levels of nortriptyline or desipramine while on low daily dosages (nortriptyline 1.0 to 1.2 mg/kg of body weight and desipramine 1.5 to 2.0 mg/kg).
- Older patients are more likely than younger patients to develop delirium, constipation, urinary retention, dry mouth, and orthostatic hypotension. For this reason, the dosages of antidepressants should be increased at slower pace than in younger adults.

- Pretreatment systolic orthostatic hypotension has been found to correlate with antidepressant response to nortriptyline in some elderly patients. Therefore, nortriptyline, rather than desipramine, should be considered in such patients and orthostatic blood pressure and subjective symptoms of orthostasis should be monitored carefully.

- Nortriptyline and desipramine have properties similar to those of type 1A antiarrhythmic drugs (quinidine-like drugs). When administered to patients with right or left bundle branch block, tricyclics may cause second-degree block in approximately 10 percent of cases. For this reason, an ECG should always precede the use of tricyclics in the elderly.

- Low dosages of MAO inhibitors (e.g., phenelzine [Nardil] 30 to 45 mg daily or tranylcypromine 20 to 30 mg daily) should be used in the elderly.
- Orthostatic hypotension is the most frequent important side effect of MAO inhibitors. This side effect is of concern in the elderly because it may lead to falls and fractures especially of the hip or the humerus.
- Other side effects include weight gain, insomnia, lack of energy, and daytime somnolence in phenelzine-treated patients and nervousness, insomnia, and excessive perspiration in tranylcypromine-treated patients.

- Bupropion, a noradrenaline and dopamine reuptake inhibitor, has proven efficacy in younger adults as well as older adults with major depression based on a number of limited trials of the IR, SR, and XL formulations.
- Bupropion does not cause cognitive impairment or sedation, is safe in overdose, and lacks significant cardiotoxicity; it should be considered in elderly cardiac patients
- Bupropion may exacerbate pre-existing hypertension and regular monitoring of blood pressure is required.
- Seizures have been reported in 0.4 percent of patients treated with bupropion, but the risk of seizures can be minimized by the use of sustained release preparations, slow introduction of bupropion (100 mg daily), and restriction of the total daily dosage to 450 mg. Most elderly patients require a total daily dose of 300 mg.

- Mirtazapine has been increasingly used in frail depressed nursing home patients with anorexia. Mirtazapine antagonizes the α-2 presynaptic inhibitory receptor as well as the 5-HT2 and the 5-HT3 serotonin receptors. Mirtazapine is an antagonist of histaminergic receptors and has a mild antagonist effect on the α-1 adrenergic and muscarinic receptors. These effects account for the sedative, hypotensive, and anticholinergic side effects of mirtazapine. Mirtazapine is not an inhibitor of the P450 cytochrome. Side effects include somnolence, dizziness, increased appetite, weight gain, and hyponatremia. Mild increase of cholesterol and triglycerides has been observed in 15 and 6 percent of patients, respectively. The starting dosage of mirtazapine is 15 mg and should be administered at bedtime to reduce sedation. Daily dosages from 30 to 45 mg are sufficient as a rule for the treatment of late-life depression.

- ECT should be considered in both geriatric depression and mania because of its efficacy, rapid onset of action, and safety. ECT may be chosen in patients with severe mood syndromes unable to tolerate the long waiting imposed by the gradual introduction of antidepressants or mood stabilizers and the slow onset of drug action in the elderly. In addition, ECT can be effective in treating neuropsychiatric comorbidities such as catatonia and parkinsonism often present in the depressed elderly.