Iran University of Medical Sciecies

• Elderly Depressive disorder

Molavi P MD
Professor of Psychiatry

Iran University of Medical Sciecies

EPIDEMIOLOGY

malakouti SK., Rasool Hosp.,
psychiatric ward

Iran University of Medical Sciecies

Minor depressive disorder

- Sub-clinical
  - GDS-15>8, not fulfilled the DSM criteria
  - GDS-11>6
  - CES-10,8 >5
- Minor depression, defined as two to 4 depressive symptoms lasting for 2 consecutive weeks
- 10% to 25% develop major depression within the next year

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Depressive Disorders prevalence (Community studies)

- Major Depression
  - point prevalence : 1% (NIMH) - 9%
    - Male: 0.4%
    - Female: 1.4%
  - Life time prevalence: 16% (Steffens)
- Minor depression: 2.5% - 9.8%
- Depressive symptoms (sub-clinical): 13.5% - 25%

Diagnosis key of depression in elderly

- Look carefully for symptoms of depression
- rather than relying on the patient to report mood changes

Barriers to proper diagnosis and treatment of depression in elderly

- Attributing depressive symptoms to "normal" aging, physical illness
- Masking the effects of coexisting medical problems,
- Self-medication (e.g. alcohol use)
- Stigma
- Poverty, low socioeconomic status
- Bereavement
- Social isolation
- Lack of family support
- Misdiagnosis of depression as dementia, hypochondriasis, somatization
- Cost issues
- Time constraints

Risk factors for MDD

- Pain
- Functional limitations
- Visual impairment
- Stroke
- Loneliness (OR=3.3)
- Lack of social support
- Negative life events
- Perceived inadequacy of care
- Urban residence>rural area (OR=3.8)
- Assistance in IADLs (OR=1.2).

Demoralization vs comorbidity!

- Hypothyroidism (50%)
- Myocardial infarction (45%)
- Macular degeneration (33%)
- Diabetes (8% to 28%)
- Cancer (24%)
- Coronary artery disease (20%)

Depression effect on heath

- Aging biology, short telomere length
- Pro-inflammatory change
- Obesity, frailty,
- Diabetes
- CVD
- Cancer
- Cognitive impairment
- Alzheimer's

Complicated by depression

- Cerebrovascular disease
- Coronary artery disease
- BG disease
- Dementia disorder
- Cancer
- Autoimmune disease
- Endocrine disease

1. Depressed people may have poorer health behaviors, sedentary life style, which in turn lead to heart problems.

2. The other possibility is physiological: a problem with the autonomic nervous system (ANS) imbalance.

Infarction and depression

In the first 10 days after infarction

- minor depression 27%
- major depression 18%,

- By the third month 33%,
- The risk is highest within the first 2 years after a stroke,
  - major depression 20%
  - minor depression 20%

Depression & dementia

- 11 – 25% of demented patients have depression
- More common with mild to moderate dementia
- Manifestation with agitation, anger, sleep problem

DEPRESSION AND COGNITIVE IMPAIRMENT

- late-life depression showed cognitive declines, 6.4 times higher
- Patients with LOD showed to have a higher incidence of subsequent dementia (Odds Ratio: 2.8)

4 clinical relation between congtive disorders and MDD

Alan Thomas, O'brian, 2008

1. prodromal phase of dementia (LOD)
    1. In secondary care the conversion rate was reported as 4-5 fold
    2. in a primary care 1-2 fold
2. superimposed on dementia
    1. 29% with VaD, DLB (33%) , 13% in AD
3. risk factor for dementia (EOD)
    1. a nine-year follow-up risk of VaD by three fold
    2. 40% and 54% of those with late-life depression meet criteria for (MCI).
4. Pseudo-dementia

Late onset vs Early onse

LOD vs EOD

LOD features

- Apathy (ACA)
- Limited depressive ideation
- Less guilt
- Psychomotor retardation(ACA)
- Poor insight
- Absence of family history
- Excessive cognitive impairment
- Greater impairment in motivation, attention, and decision making (OFC)
- High levels of WMHIs
- Poorer response to ADs

2 types of depression in the elderly

- Early-onset (EOD)
- first episodes during adulthood
- recurrence in old age associated with bereavement
- with personality disorders, neuroticism, greater medical morbidity

- Late-onset (LOD)
- Associated with cognitive impairment
- Increased ventricular-to-brain ratio
- WMHIs in neuroimaging,
- Poorer outcome
- Evolution towards dementia
- Resistance to drug treatment

Why LOD accompany cognitive impairment?

1. HPA axis and associated hypercortisolemia, Hippocampal damage
2. Possession of the short allele of the serotonin transporter linked to cognitive deficits
3. Cerebral atrophy
4. White matter hyperintensities (Alexopoulos-2001)
    1. disruption of fronto-striatal pathways
    2. executive dysfunction

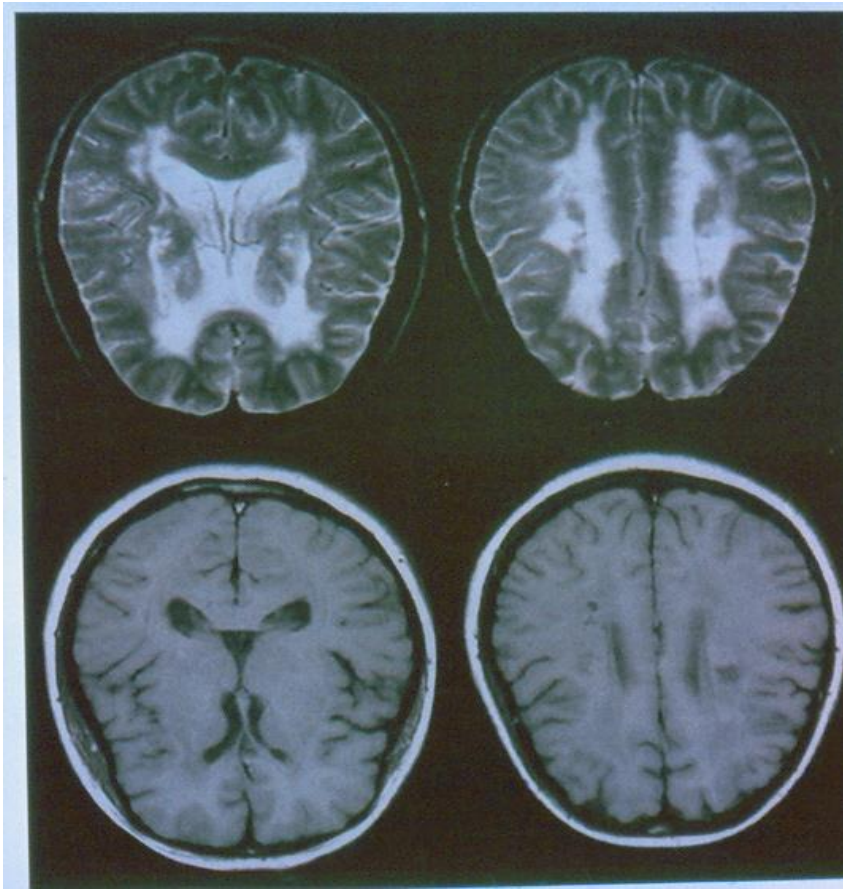
Elevated serum cortisol (OR=1.6) levels were associated with the risk of cognitive decline

LOD vs EOD

- OR=4 WMHIs for LOD
- LOD had scores of d=0.7–0.8 standard deviations above EOD

- L L Herrmann, 2012

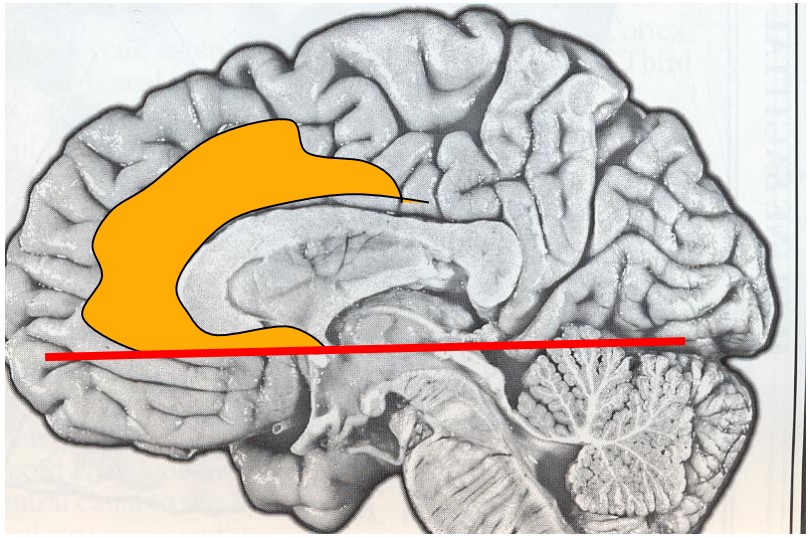
- More prevalent in DLPFC
- Poor outcome and treatment resistance
- Predict future depression of VaD



WMHIs in depression

longitudinal study-Taylor WD, 2003

- WMHIs 10-15 mm, above the AC-PC line is associated with a lower rate of remission
- every 1% increase in WMH volume carried with it a 7% increased risk of poor outcome



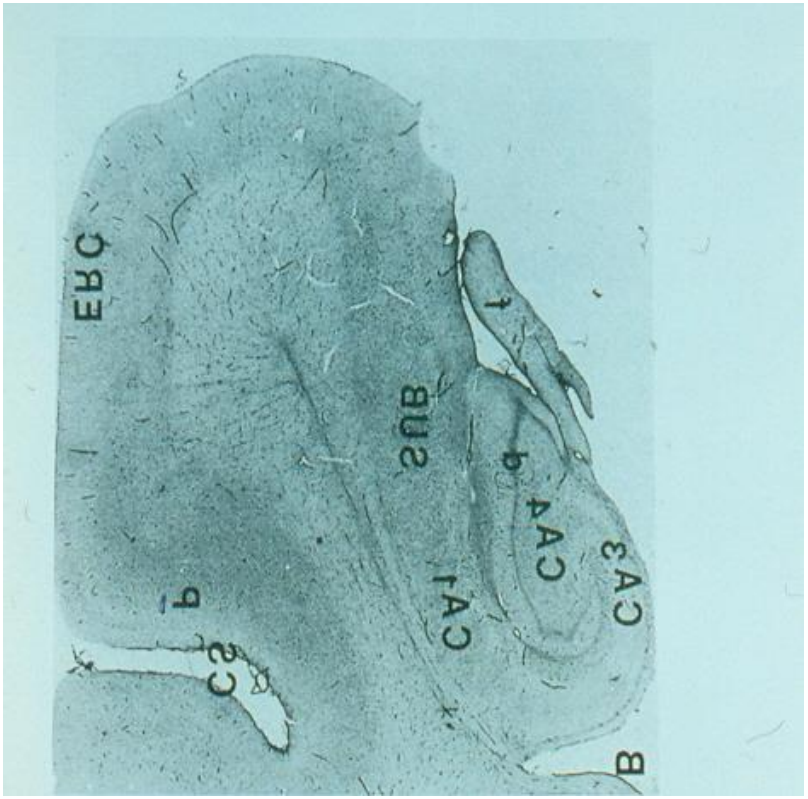
- Bidirectional relationship with vascular and depression
- Increased cell adhesion molecule expression in the DLPFC, showing vascular changes in frontal grey
- late-life major depression where vascular disease indicate in about 50%

FRONTAL

- Frontal WMHIs (fronto-striatal pathways) specifically medial orbital prefrontal cortex lesions
  - younger patients have prominent amygdala and sub-genual cingulate dysfunction associated with their more prominent affective symptoms
  - older patients have prominent dorsolateral prefrontal, dorsal anterior cingulate and hippocampal

LOD and Hippocamp

- Inverse relationship between number of years with depressive episode and total hippocampal-entorhinal cortex volume
- Hippocampal volume correlate negatively with age, depression, cognitive impairment



THEORITIES ON LATE LIFE DEPRESSION

malakouti SK., Rasool Hosp.,
psychiatric ward

LLD, Alexopoulos, 2019

- Depression executive dysfunction
- Vascular depression
- Inflammatory hypothesis
- Tau and amyloid beta accumulation

1. Depression executive dysfunction

30% of LLD

- Presentation: DLPFC dysfunction
  - Anhedonia, retardation, lack of insight, less depressive idea, mild vegetative sign, lack of insight, low depressive idea, apathy, low motivation
  - Low verbal fluency, response inhibition, low problem solving, low cognitive flexibility, low working memory and planning
- Neuroimaging
  - WMHIs in frontal region
  - hypoactivity of DLPFC
  - Low connection of DLPFC and dACC
- Treatment response
  - Poor, early relapse,
  - Develop in PD, VaD, HD, PSP, BG calcification, stroke of CAUDATE

2. Vascular depression

- Presentation
  - Late onset, worsening of course of EOD, CVD, carotid p. executive dys, retardation, anhedonia, lack of insight,
- Neuroimaging
  - WMHIs, low CBF, LACUNA
  - Low CBF in cuneus, pecuneus, fronto-cingulate
  - 50% delineated by WMHIs
- Treatment
  - low response to treatment

3. Mechanisms of an association between immune system and geriatric depression

- Increase pro-inflammatory cytokines,
- High activity of microglia, low neurogenesis
- Long depression increase microglias
- Increase Cytokines and reduce 5HT
- Increase excitotoxicity, low neuroplasticity
- Peripheral inflammatory factors increase
- The TNF-α antagonist infliximab reduced symptoms of major depression
- Nonsteroidal anti-inflammatory drugs (NSAIDs), omega-3 fatty acids, and cytokine antagonists may have antidepressant

4. Amyloid and Tau accumulation one of the mechanisms of LLD

- In cognitively normal, increased amyloid in the precuneus/posterior cingulate cortex associated with depression
- In community-dwelling, cognitively normal, Aβ was associated with increasing anxious-depressive symptoms during a 1–5 year follow-up

- Patients with a lifetime history of depression had amyloid accumulation in brain regions related to mood regulation
- Patients with aMCI and history of major depression had higher Aβ deposition, mainly in the frontal cortex

- Alzheimer’s patients with history of depression had more amyloid plaques in the hippocampus
- Individuals with LLD had higher plasma Aβ42/Aβ40 ratio

- A citalopram decreased Aβ in the brain's interstitial fluid in a dose-dependent manner in aged, transgenic (APP/PSI), plaque bearing, AD mice
- Chronic administration of citalopram arrested the growth of preexisting plaques and the development of new plaques by 78%

- In healthy individuals, acute administration of citalopram 60 mg slowed the production of Aβ in the CSF by 37% compared to placebo
- Community volunteers treated with antidepressants over a period of 5 years (mean: 34.5 months) had significantly lower amyloid load in brain PET scans than those who had never received antidepressants

FDG-PET, LOD

- The rate of Aß positivity was higher among DEPRESSED+MCI than HC (39.4% versus 27.3%) NON SIGNIFICANT
- The average onset age of LOD was signifycantly higher in GD+ Aß than in GD- Aß (73.6 ± 7.1 versus 58.7 ± 17.8
- prevalence of GD+ Aß (39.4%) was comparable to the reported 45–50% in MCI patients without GD of the conversion of MCI to AD
- GD+ Aß is a risk factor for AD

nationwide longitudinal study

- Resistant MDD, LOD patients consistently showed higher risks development of dementia (HR 6.64) and AD (HR 4.97) than did responsive patients

- Yee-Lam E.Chan, 2020

- depression increases the risk of conversion of MCI to Alzheimer's dementia and long-term treatment with antidepressants delays the conversion of mild cognitive impairment to Alzheimer's dementia

Emery and Oxman proposed:

late-life mood disorders

and

cognitive abnormalities

may exist on a continuum

TREAMENT

PHARMACHOTHERAPY

A Systematic Review of Comparative Studies

- remission rates of depression in patients in late life are little different from those in midlife, but relapse rates appear higher

- **Alex J. Mitchell, 2005**

Does depression in elderly responds to treatment?

- Response rate of 67% (vs placebo 38%)in elderly depressed patients with serious life-threatening disease (e.g. CVA)
- 75% remission rate in primary care is quite comparable with the 78% rate in a mental health setting
- Cumulative probability of remaining well without recurrence is 70%.

CONTRAVERSIES

- no difference between antidepressant and placebo groups in depressive symptoms over 6 to 13 weeks (standardized mean difference [SMD] −0.10, 8 studies) with low heterogeneity (I2 = 7%).
- moderate quality evidence suggested that the remission rate was likely higher in patients treated with antidepressants compared to placebo (antidepressant: 40%, placebo: 21.7%; OR 2.57

- aMCI with donepezil, vitamin E, or placebo, patients with self-reported depressive symptoms lower conversion rate to AD over a 1.7-year period
- MCI without depression, cholinesterase inhibitor treatment has not affected the rate of conversion to Alzheimer's disease
- DEP-CI. combined antidepressant and AChEIs has been associated with cognitive improvement in pilot studies (Pelton et al., 2008),

- The combination of an antidepressant and memantine in older patients with combined depression and cognitive impairment may delay conversion to dementia.
- is well tolerated without major side effects
- Improve verbal cognition

- Gregory H. Pelton, 2016, geritatic psychiatry

- 2.6–28.5% annual conversion rate reported in naturalistic studies of patients with DEP-CI
- 6.0–8.3 % annual conversion rate in cognitively impaired, non-depressed patients receiving AChEI treatment

- Fluoxetine
- Sertraline
- Paroxetine
- Duloxetine
- Citalopram
- Escitalopram

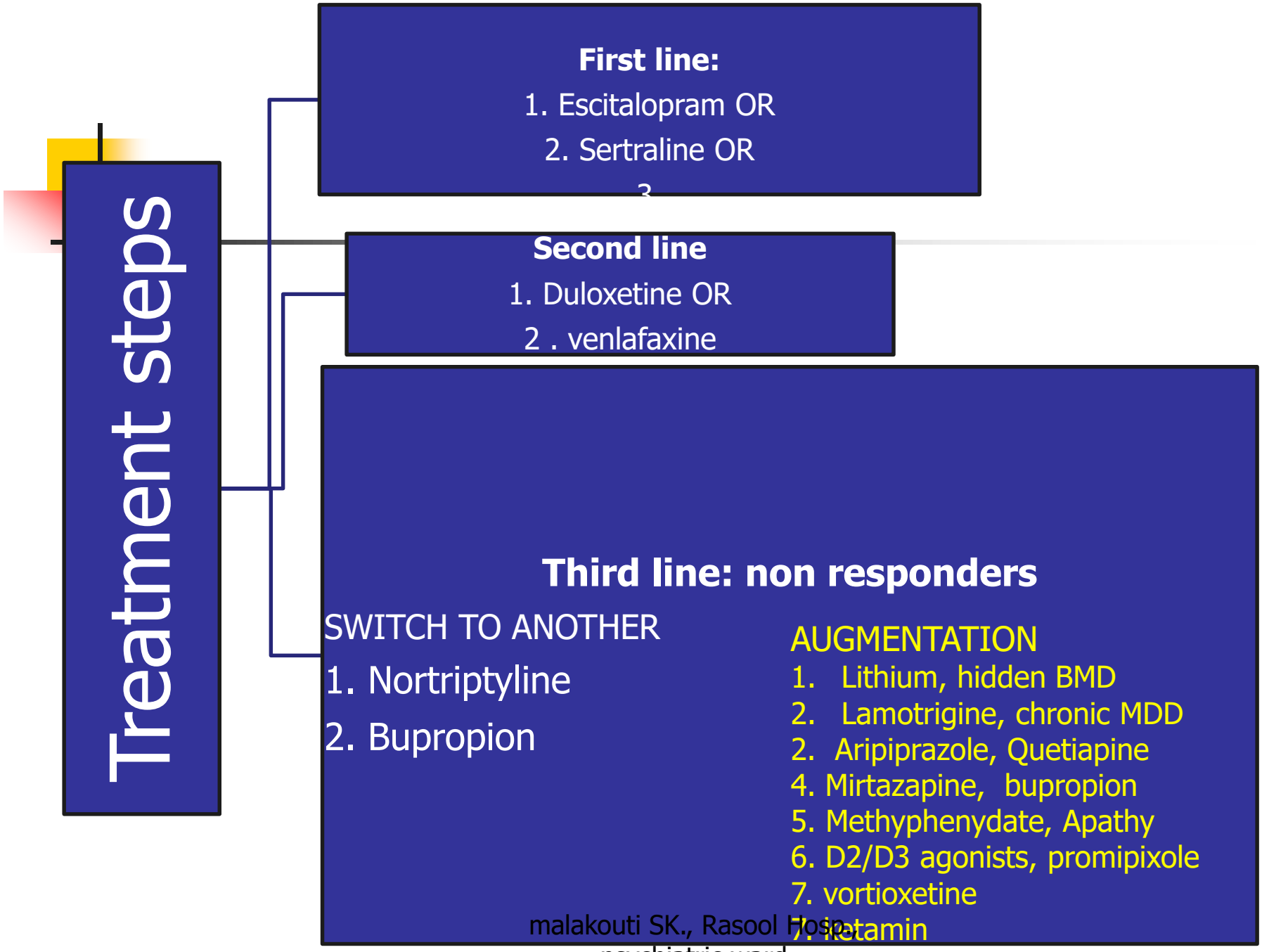
- Mirtazapine
- Bupropion

- Venlafaxine

- Lithium
- Aripiprazole
- quetiapine

Some principle

- LLD responds less well to antidepressants/ higher relapse rate
- Lithium, aripiprazole, and methylphenidate are efficacious augmentations
- Antidepressants may improve depression of most medical illnesses but it is unclear if they improve the outcomes of medical illnesses
- Antidepressants may reduce amyloid load and may delay the conversion of MCI to Alzheimer's dementia
- Dopamine receptor D2/D3 agonists definitive studies in DED are lacking
- Brief pulse right unilateral ECT may be slightly more efficacious than ultra-brief pulse unilateral ECT
- Addition of ECT to continuation pharmacotherapy may reduce relapse rate in antidepressant resistant depression


Treatment steps
First line:
1. Escitalopram OR
2. Sertraline OR
3
Second line
1. Duloxetine OR
2 . venlafaxine
Third line: non responders
SWITCH TO ANOTHER
1. Nortriptyline
2. Bupropion
AUGMENTATION
1. Lithium, hidden BMD
2. Lamotrigine, chronic MDD
2. Aripiprazole, Quetiapine
4. Mirtazapine, bupropion
5. Methyphenydate, Apathy
6. D2/D3 agonists, promipixole
7. vortioxetine
7. ketamin

Augmentation in VaDep

- Angiotensin receptor blockers
  - Losartan
  - Valsartan
- Angiotensin converting enzyme
  - Captopril
  - Enalapril
  - Calcium channel blockers:
    - nimodipine

- A meta-analysis of nonsteroidal anti-inflammatory drugs and cytokine inhibitors suggests that anti-inflammatory treatment, in particular celecoxib, decreases depressive symptoms in individuals with major depression or with clinically significant depressive symptoms
- The TNF-α antagonist infliximab reduced symptoms of major depression in individuals with baseline high-sensitivity CRP (hs-CRP) greater than 5 mg/L

Antidepressant + anti-inflammatory

- Vortioxetine + celecoxib
  - CRP more than 3 mg/L
  - Positive effect on cognition
- Vilazodone, 20-40 mg

- **Levomilnacipran, 40-120 mg**
  - noradrenergic
  - Induce motivation/energy
  - Lower relapse, 50%
  - More effective on cognition
  - Age range of 18-78 y.o

Anti NMDA

- Ketamine, esketamine
  - Esketamine nasal spray in conjunction with an oral antidepressant (56, 84 mg)
- MDD patients who have failed to respond to most treatment options, including ECT.
- Considerable evidence demonstrates that ketamine, a glutamatergic modulator, has rapid antidepressant, anti-suicidal, anxiolytic, and anti-anhedonic effects in nonelderly individuals
- Carlos A. Zarate ,2017

ASPIRIN , cohort population based study

- A total of 6028 (13.4%) and 40,411 (86.6%) patients were defined as, with and without diagnosis of LOD, 2,424 (41.9%) were aspirin users.
- Patients with LOD had more comorbidities such as cardiovascular diseases, diabetes, and hypertension comparing to those without LOD.
- Among patients with LOD, aspirin users had lower incidence of subsequent incident dementia than non-users (Hazard Ratio = 0.734)

- Ya-Hsu Yang, 2020

- of 25(OH)D were 14% lower in persons with minor and major depressive disorder
- levels of PTH were 5% and 33% higher in those with minor and major depressive disorder

- Advances in TMS may reach the deep structures implicated in DED over the dorsolateral and ventrolateral prefrontal cortex showed that deep TMS is safe in LLD and
- led to higher remission rate than sham rTMS (40.0 vs. 14.8%)
- However, rTMS has been found efficacious in vascular depression accompanied by executive dysfunction

- A series of meta-regression found no evidence of greater rTMS effects on executive functions as age advances.
- no significant rTMS effects on executive functions in older depressed individuals
- the size of the executive function benefits from rTMS in depression are positively related to the effect size of mood symptom reduction.
- improvement in executive function may play a critical role in depression recovery

- Irena P.Ilieva, George S.Alexopoulos, 2018

LONG TERM TREATMENT

- Continue the treatment at least one year preferable 2 years
- Reduce the load of Amyloid beta and reduce the chance of conversion of MCI to AD

Maintenance treatment

- meta-analysis of eight double blind trials reported the number needed to treat to prevent one additional relapse or recurrence to be only three
- A review of nonpharmacological approaches to depression prevention suggested modest effectiveness with a NNT of 20

Box 39.4 Poor outcome predictors

- Physical ill health
- Depression severity
- Chronicity of depression
- Presence of white matter hyperintensities
- Cognitive impairment (especially executive dysfunction)

TREAMENT

NON-PHARMACOTHERAPY

Kathleen S. Bingham, Current Psychiatry Reports (2019)

- did not identify any RCTs published in the last 4 years that examined neurostimulation, i.e., electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or transcranial direct current stimulation (tDCS), for depression in neurocognitive disorders.

Kathleen S. Bingham, Current Psychiatry Reports (2019)

- light control or bright light therapy, delivered as 10,000 lx of light for 30 min twice a day, five times a week.
- There was a statistically significant interaction between bright light condition and time, with participants in the bright light condition

- SAMe , adenosyle methionine,
- Omega-3 approved by FDA, 1.3 gr/d
- FOLATE. Not adequate data for monotherapy, combination with SSRIs
- Light therapy, not adequate data
- Acupuncture, not recommended

- Neuroplasticity-based computerized cognitive remediation (nCCR-GD) targeting executive dysfunction
- 30 hours of cognitive remediation over 4 weeks on computer stations in private treatment rooms at the Weill Cornell Institute of Geriatric Psychiatry

- Sarah Shizuko Morimoto , 2017

TREAMENT

PSYCHOTHERAPY

APA, 2019

- Initial treatment of MDD
  - Group CBT
  - Life –review therapy
  - Interpersonal psychotherapy
  - Psychotherapy + Combine medication
- Initial treatment for minor depression
  - CBT
  - Life review
  - Problem solving
- Depression + dementia
    - Problem solving therapy
- Prevention
  - IPT + Medication
  - Supportive therapy + medication
  - Group CBT + Medication

Depression with MCI/Dementia

- Problem solving therapy is more effecious than supportive therapy
- Treatments evaluated included exercise [19], cognitive training in MCI [6], music therapy in dementia [10], and reminiscence therapy in dementia [11].
- Only music therapy showed some evidence (of moderate quality) in reducing depressive symptoms
- Kathleen S. Bingham, Current Psychiatry Reports (2019)