Late-life depression, clinical picture, etiology, therapeutic options

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In our review we discuss various forms of aging and briefly touch upon its psychological aspects. We also explore the prevalence of and the clinical manifestations associated with late-life depression. We present the etiological factors of late-life depression, including psychological and psychosocial factors, as well as biological causes such as genetic and epigenetic factors, immune, inflammatory and neurodegenerative processes, changes in neurotransmitter and neurotrophic systems, alterations in the HPA axis, and the impact of physical illnesses, medications, and hormonal changes. The process of differential diagnosis is summarised, along with an exploration of the complex concept of quality of life. We provide an overview of the characteristics of suicide in older populations and offer insight into the key pharmacological and psychotherapeutic interventions.
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THE AGEING SOCIETY AND ITS PSYCHOLOGICAL ASPECTS

Characteristics and forms of ageing

Ageing is a process determined by biological, genetic, psychological, and social factors. It is also a dynamic state characterized by numerous challenges and the strategies to cope with them (Lampek, 2015; Csókási, 2015). The so-called active ageing encompasses the following phenomena: maintaining a low risk of diseases - which leads to functional independence- participating in social life, and ensuring the possibility of a safe and dignified life (WHO, 2002; Égerházi, 2023). According to Baltes and Smith, successful ageing is characterized by selective optimization (focusing on exercising retained functions while reducing tasks) and compensation (creatively counterbalancing deficiencies) (Baltes and Smith, 2002; Égerházi, 2023). According to another classification, successful ageing is characterized by balance, productivity, and activity, whereas ordinary ageing involves a gradual decline in function and the emergence of psychological issues. The term 'age-related deterioration' is used to describe the progression of both somatic and mental illnesses (Csókási, 2015).

Prevalence

In advanced regions of the world, the ageing of the population, characterized by an increase in the proportion of older age groups, is associated with improved life expectancy and declining fertility rates (Lampek, 2015; Monostori, 2015). In Hungary, the proportion of the population aged 65 and over increased from 13% to 18% between 1990 and 2014, and according to the calculations, this figure will reach 29% by 2060 (Monostori, 2015).

Worldwide, the proportion of females in the elderly population significantly exceeds that of males, and

this gender difference increases with age. For example, after the age of 80, there are only 61 men for every 100 women (Lampek and Rétsági, 2015).

The psychology of ageing

The psychological changes associated with ageing can be effectively understood through Erikson's theory of psychosocial development (Erikson, 1964; Erikson, 1982). Aligned with this concept, personality development is viewed as a lifelong process, characterized by crises that are typical for the given age group (Erikson, 1964; Erikson, 1982; Csókási, 2015). The crisis faced in late adulthood, according to Erikson's theory of psychosocial development, is characterized by a struggle between integrity and despair. In a favourable outcome, individuals achieve life satisfaction and face death with acceptance.

In a case of positive outcome, life events are integrated into a coherent whole, making self-integrity achievable. In an unfavorable outcome, dissatisfaction with life emerges, leading the elderly individual to feel that they have wasted their life. This leads to despair and an increased fear of death (Erikson, 1964; Erikson, 1982; Csókási, 2015).

THE CONCEPT, PREVALENCE, ETIOLOGY AND SYMPTOMS OF LATE-LIFE DEPRESSION (LLD)

Depression is not a normal part of ageing. However, studies show that depressive disorders are highly prevalent in people over the age of 65 and are associated with negative outcomes, including suicide, functional impairment, cognitive decline and an increased risk of mortality (Cheng, 2018; Zdanys és Steffens, 2022). LLD refers to a major depressive disorder (MDD) that manifests in individuals aged 65 and older (Taylor, 2014; Szymkowicz et al., 2023). According to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, 2013), a diagnosis of a major depressive episode (MDE) requires the presence of at least five out of nine listed symptoms for a minimum duration of two weeks. One of the nine symptoms must be a depressed mood or a loss of interest or pleasure in life (Szekeres et al., 2005; Rihmer et al., 2016,; Rihmer et al., 2017; American Psychiatric Association, 2013; Akiskal 2017). To be diagnosed with a MDE at least five of the following symptoms must be present: changes in appetite or body weight (either an increase or decrease), changes in sleep patterns, loss of energy or fatigue, reduced ability to concentrate or indecisiveness, psychomotor agitation or retardation, feelings of worthlessness or excessive, inappropriate guilt, and recurrent thoughts of death, suicidal ideation, or a specific plan to commit suicide (American Psychiatric Association, 2013). In addition, the DSM-5 states that an individual's current age does not directly influence the course of MDD and response to the treatment. Accordingly, although LLD is not classified as a separate diagnostic category in the DSM-5, it has distinct characteristics compared with depression in younger adults. These differences span demographic, etiological, and phenomenological aspects, as well as prognosis, comorbidity, suicidal risk, and treatment responses (Husain-Krautter and Ellison, 2021; Döme et al., 2022). Other researchers define LLD to include not only late-onset depression, which begins after age 65 and accounts for more than half of cases, but also MDD that begins before age 65 and continues into old age (Fiske et al., 2009; Cheng, 2018). LLD frequently goes underdiagnosed and undertreated, resulting in a diminished quality of life, along with social and physical dysfunction (Unützer, 2012; Cheng, 2018).

The point prevalence of LLD among elderly individuals aged between 65 and 100 years, who live in their own homes, ranges from 1% to 5% (Blazer, 2003; Husain-Krautter and Ellison, 2021; Szymkowicz et al., 2023). The one-year prevalence of LLD in the elderly population 3.0% - 4.3% (Commitee on the Mental Health Workforce for Geriatric Populations, 2012). The prevalence of what is commonly referred to as minor depression (dysthymia/persistent depressive disorder) is estimated to be 6% in this age group (Kok and Reynolds., 2017). Additionally, between 10 to 50% of older adults exhibit significant subthreshold depressive symptoms, which may not meet the full criteria for MDE as defined in the DSM-5 (Blazer, 2003; Szymkowicz et al., 2023). The prevalence of LLD in long-term care institutions and hospitalised patients is 11.5-14.4 % (Luppa et al., 2012; Cheng, 2018; Husain-Krautter and Ellison, 2021).

LLD is a heterogeneous condition that can be associated with different clinical manifestations (Döme et al., 2022; Zdanys és Steffens, 2022). In LLD certain symptoms are more common than in those with early-onset MDD. These symptoms include anhedonia, apathy, physical symptoms and pain, a wide range (6% to 45%) of somatic comorbidities, psychotic symptoms, sleep disturbances, feelings of uncertainty, and physical weakness. Furthermore, patients with LLD have a higher risk of suicide compared to patients with early-onset MDD (Cheng, 2018; Szymkowicz et al., 2023).

According to a new meta-analysis, changes in appetite, sleep disorders, psychomotor retardation, difficulty concentrating, an inability to make decisions, and fatigue are identified as the most common symptoms of depression in the elderly (Bergua et al., 2023). In particular, depression in LLD patients does not appear to be a prominent symptom compared to non-depressed cohorts (depressio sine depressione). Conversely, loss of interest and somatic symptoms (in 50-80% of cases) are more severe in older depressed patients than in younger patients with MDD (Norris et al., 2003; Bergua et al., 2023; Szekeres et al., 2023). Among depressed seniors, 37% report experiencing pain, while 12% suffer from fatigue or sleep disturbances (Torzsa et al., 2009; Gonda, 2017).

Cognitive impairment is common in LLD, with the following functions most commonly affected: executive functions, verbal fluency, response inhibition, switching, working memory, problem solving, episodic memory, visuospatial skills, processing speed, concentration (Szymkowicz et al., 2023). In LLD 38-58% are comorbid with one of the anxiety disorders meeting DSM-5 diagnostic criteria; this may manifest as tension, agitation or feelings of fear (Fountoulakis et al., 2003; Cheng, 2018).

Regarding the gender distribution, it has been established that LLD is more common in females. Examining the ratio of genders, it was found that the point prevalence of LLD in females is 4.4%, while in males it is 2.7% (Steffens et al., 2000). According to a recent study, 1 in 4 females and 1 in 5 males over the age of 65 suffer from clinically significant depressive symptoms (Cheung & Mui, 2023).

According to Hungarian data, 9% of females and 6% of males over the age of 65 show severe depressive symptoms, and this ratio increases to 24% among the population over 80 years old (Monostori & Gresits, 2018; Szekeres et al., 2023). In accordance with the Hungarostudy 2021 survey, clinical depression can be confirmed in 20.5% of pensioners of retirement age, while this rate was around 15.8% in the total sample (Tóth et al., 2021; Szekeres et al., 2023).

The difference between genders can be explained by factors that interact with each other. According to the stress-diathesis model, certain personality vulnerabilities increase stress sensitivity, which is more characteristic in females. The mediation theory is based on the notion that females are more prone to employing a depressogenic coping style. The transactional approach highlights that the continuation of symptom-maintaining behaviours is more common among females suffering from LLD (Girgus et al., 2017).

The gender differences in LLD are associated with the following biological factors:

a. Genetic factors (the expression of certain genes and their effects differ between females and males, influencing not only susceptibility to depression but also therapeutic responsiveness).
b. Hormonal effects (reduced estrogen levels during menopause are associated with a higher risk of depression, whereas in males, the decrease in testosterone levels is more gradual).
c. Structural and functional changes in the brain (changes in the function of the amygdala and prefrontal cortex, which are involved in emotion regulation, increase the propensity for mood disorders in females).
d. Biochemical factors (levels of neurotransmitters such as serotonin (5-OH-tryptamine-5-HT), dopamine (DA), and norepinephrine (NA), which are involved in mood regulation, are lower and receptor sensitivity is increased in women).
e. Inflammatory and immune responses (females have a more intense immune response, which has a depressogenic effect).
f. The prevalence of somatic diseases differs between genders (their direct biological and indirect psychological impacts vary) (Labaka et al., 2018).

ETIOLOGICAL FACTORS OF LLD

Psychological and psychosocial factors

Several authors emphasize the role of neuroticism (the propensity for perceiving negative affects) in LLD. This trait has been associated with poor response to treatment and cognitive impairment (Costa & McCrae, 1992; Zdanys & Steffens, 2022; Manning et al., 2017). In addition to neuroticism, LLD is also associated with eccentric, anxious/avoidant, and dependent personality traits/disorders, a history of childhood abuse, and maladaptive coping mechanisms (such as rumination and catastrophizing) (Kraaij & de Wilde 2001; Kraaij, 2002; Jang et al., 2002; Zdanys & Steffens, 2022; Sekhon et al., 2023). Significant risk factors for LLD include low self-efficacy, lack of social support, caregiving or loss of a spouse or child, the onset of life-threatening illness, relocation, loneliness, and low income (Rafnsson et al., 2020; Perissinotto et al., 2012; Heikkinen et al., 2004; Cacioppo et al., 2010; Husain-Krautter & Ellison, 2021; Bandura, 1994; Jang et al., 2002; Zdanys & Steffens, 2022).

Isolation and loneliness can lead to biological changes, such as increased sympathetic tone, systemic inflammation, and sleep disturbances, which in turn can lead to the development of depressive symptoms (Cacioppo et al., 2010). Active religious practice and social support are considered protective factors against LLD (Sekhon et al., 2023).

Biological factors

Genetic, epigenetic factors

It is likely that the genetic background of MDD developing at a younger age and LLD differs (Goldman et al., 2010; Husain-Krautter & Ellison, 2021). In cases of LLD, methylation of a serotonin transporter (SERT) gene (SLC6A4) has been identified. Genes that affect the plasticity and stress reactivity of the hippocampus are also significant, as is the role of apolipoprotein E4 (APOE4) and brain-derived neurotrophic factor (BDNF) variants in the development of LLD (Goldman et al., 2010; Lam et al.; Tsang et al., 2017; Husain-Krautter & Ellison, 2021). Recent research has indicated a C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) enzyme in cases of LLD (Sekhon et al., 2023).

Immune and inflammatory processes

Ageing causes a dysregulation of immune processes, which means an increase in the levels of pro-inflammatory cytokines, primarily interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) (Chung et al., 2019; Sochocka et al., 2017; Husain-Krautter and Ellison, 2021; Zhao et al., 2023). Inflammatory mediators play a role at multiple levels in the pathogenesis of LLD: they directly affect astrocytes and microglial cells, cause dysregulation in the glutamate system, promote excitotoxicity, reduce 5-HT synthesis, increase kynurenine production, thus leading to oxidative stress (OS), and as a consequence, to glial cell damage. By acting on the hypothalamic-pituitary-adrenal axis (HPA), cytokines eliminate the inhibitory effect of glucocorticoids on inflammatory mediators. The continuous activation of microglia due to inflammation has neurotoxic effects, leading to neuron loss and reduced neurogenesis (Alexopoulos, 2019; Sochocka et al., 2017; Husain-Krautter and Ellison, 2021; Zhao et al., 2023). Anhedonia, as a fundamental symptom of LLD, is positively correlated with C-reactive protein levels, strengthening the link between inflammatory processes and LLD (Straka et al, 2020; Zhao et al, 2023).

Neurotransmitter systems

According to the monoamine hypothesis, the cause of depression is an imbalance in monoamine neurotransmitters (5-HT; DA; NA) (Zhao et al., 2023). In LLD, low 5-HT transporter levels and 5-HT1A receptor dysfunction have been demonstrated (Edinoff et al., 2021; Meltzer et al., 2004). Anhedonia is associated with reduced DA neurotransmission in the reward system (Moriya et al., 2020). Disruption of the glutamine-glutamate cycle also plays a significant role in the pathophysiology of LLD (Hashimoto et al., 2016; Zhao et al., 2023). The safety and efficacy of ketamine confirm the role of N-methyl-D-aspartate (NMDA) receptors in the pathogenesis of LLD (Lijffijt et al., 2022; Zhao et al., 2023).

Neurotrophic factors

In patients with LLD, the levels of BDNF, which regulates synaptic plasticity and neurotransmission, are significantly lower, and BDNF DNA methylation is higher compared to healthy individuals (Dimitriadis et al., 2019; Kang et al., 2015; Zhao et al., 2023).

HPA-axis

Patients with LLD exhibited more significant dysregulation of the HPA axis compared to younger patients with Major Depressive Disorder (MDD), due to the absence of buffering mechanisms and the inherently higher activity of the stress axis (Humphreys et al., 2019; Rhebergen et al., 2015; Zhao et al., 2023). In LLD patients, significantly higher basal cortisol levels were measured in all phases of the diurnal rhythm, and their post-dexamethasone cortisol levels were also higher compared to healthy controls (Humphreys et al., 2019; Zhao et al., 2023).

Neurodegenerative processes

There is a bidirectional relationship between LLD and dementia (major neurocognitive disorder): 1. depression is a risk factor for dementia; 2. LLD can be a consequence of cognitive decline (due to neurodegenerative changes, psychological reactions); 3. depressive symptoms appear in the prodromal

phase of dementia; 4. in cases of pseudodementia (the dementia syndrome of depression), cognitive symptoms are part of the LLD spectrum; 5. LLD conceals latent, later irreversible cognitive decline (Hsiao and Teng, 2013; Brodaty and Connors, 2020; Husain-Krautter and Ellison, 2021). Research has confirmed that there is an overlap in the pathophysiological mechanisms of LLD and Alzheimer's disease (AD). The pathological accumulation of β-amyloid (Aβ), characteristic of AD, has also been described in patients with LLD (Zhao et al., 2023). The deposition of Aβ initiates a series of neurobiological processes that damage neural networks important in LLD (Mahgoub et al., 2016; Zhao et al., 2023).

Individuals with mild cognitive impairment and depression have been shown to have severe Aβ deposition in both frontal cortices (Chung et al., 2016; Zhao et al., 2023). LLD develops in 40-50% of people with Parkinson's disease, and the reason for this may be the disability caused by the disease, in addition to neurobiological changes (Rod et al., 2013; Zdanys and Steffens, 2022).

Somatic diseases, medicines, hormonal effects

Numerous somatic illnesses can cause or mimic LLD, including cardiopulmonary, cerebrovascular, endocrine, autoimmune, cancerous, and neurological diseases (Husain-Krautter and Ellison, 2021). An inverse relationship has also been described, LLD can manifest itself in somatic symptoms, or the physical illness can recur during a depressive episode (Husain-Krautter and Ellison, 2021). Several medications (antihypertensives, beta-blockers, corticosteroids, etc.) can cause or exacerbate depressive symptoms (Rogers and Pies, 2008). In older females, certain estrogen receptor polymorphisms increase the risk of LLD (Ryan et al., 2011). Testosterone is important in mood regulation in both females and males.

Some studies have shown that low-dose testosterone administration in females and hypogonadal males alleviates depressive symptoms (Daan and Fauser, 2015; Miller et al., 2009; Husain-Krautter and Ellison, 2021).

Cerebrovascular diseases

According to the vascular depression hypothesis, cerebrovascular (CV) disease affecting the small blood vessels can predispose to and sustain LLD (Alexopoulos et al., 1997; Husain-Krautter and Ellison, 2021). Vascular depression is characterised by executive dysfunction, psychomotor retardation, and imaging techniques can detect white matter hyperintensities (Taylor et al., 2013; Husain-Krautter and Ellison, 2021). Involvement of the large arteries, i.e., CV circulatory disturbances, and after a stroke, depressive symptoms develop in about one-third of cases (post-stroke depression - PSD) (Nickel and Thomalla, 2017; Husain-Krautter and Ellison, 2021). In PSD, it's common for brain areas important in decision-making, emotional regulation, and reward to be affected (Yang et al., 2015; Husain-Krautter and Ellison, 2021).

Damage localised to the left hemisphere or frontal pole increases the risk of PSD, while bilateral basal ganglia involvement results in PSD with apathy (Shi et al., 2014; Nickel and Thomalla, 2017; Husain-Krautter and Ellison, 2021).

Brain Networks, Depression-Executive Dysfunction Syndrome

According to studies, disturbances in the connectivity of different brain networks result in the behavioural manifestations of MDD. The so-called according to the triple network model, a change in the function of the default mode network (DMN) in terms of self-reference increases negative thinking (thus rumination) and reduces social functioning. The anterior salience network (ASN) is important in shifting and directing attention. In the case of LLD, the ASN shows increased processing for negative stimuli and reduced processing for positive stimuli. Disconnected cognitive control network (CCN) leads to executive dysfunction and reduced attentional function. Dysfunction of the positive valence system affects a wide range of reward functions, including evaluation, decision making, effort, and learning. At the behavioral level, this results in anhedonia, motivational disturbances and a decrease in willingness to exert effort (Szymkowicz et al., 2023).

Depression-executive dysfunction syndrome (DEDS) causes typical LLD symptoms. In the background of DEDS, it is assumed that there is primarily vascular damage to the fronto-striato-limbic pathways, which clinically manifests as apathy, anhedonia, loss of planning and initiative, suspicion, lack of insight, difficulty completing goal-directed activities, significant functional impairment, and non-responsiveness to pharmaco- and psychotherapies (Husain-Krautter and Ellison, 2021).

DIFFERENTIAL DIAGNOSIS OF LLD

The differential diagnosis of LLD is complex, as ageing is affiliated with several depressogenic processes, and existing somatic diseases are often associated with comorbid depression, and these two factors are reciprocally related (Alexopoulos, 2019).

In old age, the following depressogenic agents are known: biological changes associated with ageing (epigenetic modifications, telomere shortening, accelerated brain ageing), brain and peripheral pro-inflammatory changes, obesity, diabetes, vascular, neurodegenerative processes, pharmacological adversarial effects (Fountoulakis et al., 2003; Alexopoulos, 2019). Many somatic diseases are associated with depression, the most common of which are: CV, coronary diseases, basal ganglia diseases (Parkinson's disease, progressive supranuclear palsy, Huntington's disease), dementias (vascular dementia, AD), cancer diseases (pancreatic carcinoma, lymphoma), psychoactive substance abuse/dependence, sleep apnea syndrome, inflammatory, autoimmune, endocrine disorders (hypo, hyperthyroidism, hyperparathyroidism) (Fountoulakis et al., 2003; Alexopoulos, 2019). For the reasons detailed above, in the case of depression in the elderly, careful, detailed internal medicine, neurological, laboratory and imaging tests (computed tomography, magnetic resonance imaging) and a multidisciplinary approach are necessary (Van Damme et al., 2018; Döme et al., 2022).

Few validated test results are available in LLD with regard to validated self-completed and investigator-administered questionnaires for depression screening (Szekeres et al., 2023). The most commonly used examination tools adopted for older people:

1. Self-assessment questionnaires:
   Short Geriatric Depression Scale; the Geriatric Depression Scale which represents the severity of depression; the SELFCARE-D: Self-rating Depression Scale which can be used in general medical practice; CES-D: Center for Epidemiological Studies Depression Scale; in patients with cognitive impairment NIHM-DMAS: Dementia Mood Assessment Scale (Shah et al., 1997; Sheikh and Yesavage, 1986; Bird et al., 1987; Irwin et al., 1999; Sunderland et al., 1988; Szekeres et al., 2023).
2. Tests/questionnaires that can be completed by the patient and the examiner, as well as by the relative/caregiver:
   Brief Assessment Schedule Depression used to examine geriatric inpatients; Depressive Sign Scale suitable for estimating depressive symptoms in patients with dementia; in research, the Nuremberg Gerontopsychological Inventory used to describe behavior (Adshead et al., 1992; Katona and Aldridge., 1985; Pék et al., 1989; Szekeres et al., 2023).
3. Examination tools used by an external, trained observer/examiner:
   Geriatric Mental State Schedule; Canberra Interview for the Elderly; Cambridge Mental Disorders of the Elderly Examination; Cornell Scale for Depression in Dementia; Addenbrooke's Cognitive Test taken by examiners with neuropsychological knowledge (Copeland et al., 1976; Mackinnon et al., 1993; Roth et al., 1986; Alexopoulos et al., 1988; Mathuranath et al., 2000; Szekeres et al., 2023).

OLD AGE AND QUALITY OF LIFE

The quality of life (QoL) does not have a uniform definition and therefore no standard measurement tool (Füzesi and Boros, 2015; Leewuen et al., 2019). According to some views, QoL is the same as happiness and life satisfaction (Füzesi and Boros, 2015).

In terms of taxonomy, it is a dynamic, multi-level, complex concept that includes subjective, macro-social and micro-individual factors that interact with each other (van Leewuen et al., 2019).

QoL consists of the following factors in the case of elderly persons: 1. health status/perception: the older person does not suffer from physical, mental or cognitive symptoms, does not feel limited 2. autonomy: independence, decision-making ability, dignity 3. roles and activity: 'keep busy', sense of value, assistance, performance, positive self-worth 4. relationships: support, attachment, care, reciprocity 5. attitude and adaptation: positive attitude, acceptance, ability to change 6. emotional comfort, feeling of peace 7. spirituality 8. safe home and neighbourhood 9. financial security (van Leewuen et al., 2019).

According to Hungarian data, good quality of life for the elderly is related to intrinsic goals, such as personality development, relationships, and the importance of society (Szili et al., 2021). Males were more hopeless than females in the aforementioned sample of retirees. This is important because hopelessness is a cognitive factor in suicide, and a negative outlook on the future is a predictor of suicide (Perczel-Forintos et al., 2001; Rihmer 2001; Szili et al., 2021).

ELDERLY SUICIDE

Across the life course, suicide rates are highest in old age and are increasing worldwide (Bickford et al., 2020; Baraczka 2020; Fernandez-Rodrigues et al., 2022). Globally, the suicide rate in the 50-69 age group is 16.17/100,000; while in the group older than 70 years it is 27.45/100,000 (GBD, 2017; De Leo and Gionatti, 2021). Regarding the gender distribution, a male predominance was confirmed, which increases with age. Depressed men aged 75 or older are six times more likely to die by suicide than depressed older women. The reasons for the difference are not yet sufficiently clear (WHO, 2017; IHME, 2017; Choi and Marti, 2022). According to the Hungarostudy 2021 survey, 35.8% of pensioners had suicidal thoughts in the previous year (Tóth et al., 2021; Szekeres et al., 2023).

In accordance with a study by Conwell et al., more than 87% of elderly people who died by suicide met the criteria for MDE (Conwell et al., 2008). The following risk factors have been highlighted in relation to current MDE: severe symptoms, recurrent episodes, therapy resistance (Fernandez-Rodrigues et al., 2022). Other factors are also important in the increased risk of suicide in old age: comorbid anxiety and addictive disorders, increased pain tolerance, pain symptoms, as well as previous suicide attempts, anxious, compulsive personality traits, impulsivity, cognitive decline or its anticipation, chronic somatic or tumor diseases, disability (Yoshimani et al. , 2008; Reynolds III and Kupfer, 1999; Waern et al., Wand et al., 2018; Seyfried et al., 2011; De Leo and Gionatti, 2021; Fernadez-Rodrigues et al., 2022).

According to estimates, ¾ of suicides in the elderly could be prevented if LLD were recognized and treated in time. This is important because impulsive suicide is rarer in the elderly, the act of suicide often takes place after a long preparation, and more than half of the elderly who have committed suicide visited their family doctor in the 3 months before their death (Beautrais et al., 2002; Baraczka, 2020; Szekeres et al., 2023).

Research into sociodemographic risk factors yielded several contradictory results, of which only two risk factors were considered valid, one being a low level of education (with consequent emotional dysregulation and poor coping) and the other being widowhood, especially in the first six months after the loss of a spouse (Aslan et al. , 2019; Innamorati et al., 2014; Baraczka, 2020; Fernandez-Rodrigues et al., 2022). Other studies have emphasised the role of loneliness and social isolation (Fernandez-Rodrigues et al., 2022).

PHARMACOTHERAPY OF LATE-LIFE DEPRESSION

There have been several meta-analyses comparing the efficacy of different classes of antidepressants (ADs) in LLD. Studies have shown that all ADs are more effective than placebo, but none of the drug groups outperformed the others in LLD (Zdanys and Steffens, 2022).

Accordingly, the choice of AD for LLD depends on the predominant symptoms, comorbidities, response to previous treatments, side effects of the given drug and potential drug interactions (Zdanys and Steffens, 2022). The first AD used in LLD patients was approx. it is effective at 33-40%, AD switching is required for the remaining 2/3. In treatment-resistant cases, a lower dose of augmentation is required than in young people, especially with atypical antipsychotics (aripiprazole) and lithium, which should be used only after careful consideration due to the higher risk of interactions and side effects (Husain-Krautter and Ellison, 2021; Döme et al, 2022; Zdanys and Steffens, 2022).

In the case of LLD, the following therapeutic principles must be taken into account 1. AD treatment must be started at a lower dose than in young people and the dose must be increased gradually and slowly 2. polypharmacy (use of 5 or more drugs) escalates the risk of side effects and interactions, therefore it is better to change the medication in case of ineffectiveness of AD therapy 3. the effectiveness of AD can be assessed 6 weeks after adjusting the medication, the maximum therapeutic effect appears after 8-16 weeks in the elderly (Döme et al., 2022; Zdanys and Steffens, 2022). In mild/moderate cases, selective serotonin reuptake inhibitors (SSRIs) are recommended, which have a lower cardiac, anticholinergic and orthostatic hypotension effect and are less sedating than, for example, tricyclic antidepressants (TCD) (Kok and Reynolds, 2017). Although SSRs appear to be a beneficial choice in LLD, gastrointestinal side effects, weight loss, hyponatremia, osteoporosis, tremors, and sexual dysfunction may occur (Döme et al., 2022; Zdanys and Steffens, 2022). Rarely, serious side effects - gastrointestinal bleeding, arrhythmia - can develop during SSRI treatment. Paroxetine is less recommended in LLD because of anticholinergic side effects, the long half-life of fluoxetine, and the

QTc-prolonging effect of higher doses of citalopram (Husain-Krautter and Ellison, 2021; Döme et al, 2022; Zdanys and Steffens, 2022). Selective serotonin norepinephrine reuptake inhibitors (SNRIs) are widely used in the treatment of LLD. Duloxetine can also be effective in musculoskeletal and chronic pain. SNRIs can cause nausea, dizziness, hyperhidrosis and hypertension (Zdanys and Steffens, 2022). Mirtazapine can be given to LLD patients who experience loss of appetite, weight loss, and insomnia (Zdanys and Steffens, 2022). There are few data on the use of bupropion in older people, despite its favourable side-effect profile (Zdanys and Steffens, 2022).

TCADs are drugs used rarely, primarily for the treatment of severe depression, in cases where other ADs are not effective, or when patients tolerate the emerging adverse effects.

TCADs cause many serious side effects in the elderly (anticholinergic side effects-delirium, confusion, blurred vision, constipation, urinary retention and sedation, high risk of falls due to postural hypotension, QTc prolongation, ventricular arrhythmia) (Husain-Krautter and Ellison., 2021 ; Zdynes and Steffens, 2022). Irreversible monoamine oxidase inhibitors (monoamine oxidase inhibitors) are of little use in elderly depressed patients due to their side-effect profile and drug-drug interactions (Zydness and Steffens, 2022).

According to CANMAT (Canadian Network for Mood and Anxiety Treatments) guidelines, duloxetine is the drug of first choice because it is well tolerated and causes few interactions (although there is little evidence to support its effectiveness). Also the first choice AD is escitalopram, which causes less QTc prolongation than citalopram.

If these drugs are not effective, the following active substances are recommended: sertraline, venlafaxine, vortioxetine, citalopram. If these are ineffective, fluoxetine or moclobemide can be given, and eventually tianeptine or bupropion can be introduced (Kennedy et al, 2016; Döme et al, 2022).

NEUROSTIMULATION

Electroconvulsive therapy (ECT) is the cornerstone of the treatment of LLD, and according to some data, it may be more effective than at a younger age (Döme et al., 2022). The use of ECT is specifically recommended in the case of psychotic, catatonic symptoms, suicidal urges, nutritional negativism, and AD-related non-responsiveness and intolerable side effects (Meyer et al., 2020; Zdanys and Steffens, 2022). In the elderly, temporary hypertension, arrhythmias, tarnsitory confusion and, rarely, compression fractures may occur as side effects of ECT (Geduldig and Kellner, 2016; Zdanys and Steffens, 2022). There is limited data on the use of repetitive transcranial magnetic stimulation (rTMS) in older people (Döme et al, 2022; Zdanys and Steffens, 2022). Advantages of rTMS include no sedation and no cognitive side effects. Side effects may include muscle twitching, headache, local pain depending on the stimulation, and rarely epileptic seizures (Gálvez et al., 2015; Zdanys and Steffens, 2022).

PSYCHOTHERAPIES IN THE TREATMENT OF LLD

Evidence-based psychotherapies are used alone or in combination with pharmacotherapy for mild/moderate LLD (Nasreddine et al., 2005; Husain-Krautter and Ellison, 2021). Psychotherapy is only recommended in cases where there is an inadequate response or side effects to therapeutic doses of antidepressants, or when interactions occur when administered together with other drugs (Husain-Krautter and Ellison, 2021). Psychotherapeutic interventions may be significantly hampered by cognitive and sensory impairment and immobility in old age (Husain-Krautter and Ellison, 2021).

Several randomized, controlled studies have confirmed the effectiveness of cognitive-behavioral therapy and problem-solving, interpersonal and engage psychotherapy in LLD (Ellison et al., 2012; Husain-Krautter and Ellison, 2021). In older age, modifications to standard therapies are recommended, such as the use of shorter sessions and problem-focusing (Husain-Krautter and Ellison, 2021).

Cognitive-behavioral therapy (CBT) is an active, directive, time-limited, structured therapy whose primary goal is to reduce depressive symptoms and modify maladaptive cognitions, i.e. negative automatic thoughts and dysfunctional attitudes (Beck, 1972; Tölgyes, 2000). In the case of LLD, CBT primarily targets symptoms such as hopelessness, pessimism, helplessness, and health (DiNapoli et al., 2015).

Problem solving therapy (PST) conceptualizes depression as a lack of skills. The therapist helps LLD patients learn and apply new skills. PST is effective in reducing suicide risk, even in the presence of severe depressive symptoms and executive dysfunction (Alexopoulos et al., 2020).

Interpersonal therapy (IPT) is also a time-limited form of treatment, which considers depression as a consequence of social stress and lack of support and biological/psychological vulnerability. In IPT, treatment focuses on a better understanding of the interpersonal disorder, addressing four main problem areas (role transitions, role disputes, complicated grief, and interpersonal deficits) (Raune & Arean, 2015). During IPT, life events and circumstances that cause depressive symptoms are identified and processed (Raune & Arean, 2015).

Engage therapy is a psychotherapy method based on the Research Domain Criteria, which accordingly integrates a neurobiological, epigenetic, neurodevelopmental and social approach (Alexipoulos et al., 2020; Osváth, 2017). According to the engage theory, the cause of LLD is the dysfunction of the reward system (Alexopoulos and Arean, 2014). Engage therapy includes step-by-step interventions aimed at behavioral disorders. During therapy, repeated, important, positive social or physical activity normalizes the functioning of the reward network (Alexopoulos et al., 2017). According to the engage theory, there are several behavioral manifestations that interfere with reward exposure, such as negative bias, apathy and emotional dysregulation. These phenomena result from the dysfunction of the negative valence system, the arousal and the cognitive control network. (Alexopoulos et al., 2021).

Cognitive remediation seems to be a promising method, which reduces cognitive dysfunction by increasing neuroplasticity, which is essential in maintaining depressive symptoms, loss of function and recurrence (Legemaat et al., 2021).

COMPLEMENTARY TREATMENTS

Physical activity

Physical activity has a preventive and therapeutic effect in case of LLD, due to the anti-inflammatory and oxidative stress-reducing effect of movement. If exercise is combined with pharmacotherapy, the development of the effect of medication is faster and the remission rate is higher than in cases without exercise (Belvederi et al., 2015; Husain-Krautter and Ellison, 2021; Szekeres et al., 2023).

Restful sleep

Over the age of 50, sleep quality deteriorates (Mander et al., 2017; Husain-Kreutter and Ellison, 2021; Szekeres et al., 2023). Sleep disturbance is a characteristic symptom of MDE, which may predict the appearance of affective symptoms.

In the case of association of mood symptoms and sleep disorder, relapse is more frequent, the clinical picture of MDE is more severe, and the episode lasts longer (Franzen et al., 2008; Husain-Krautter and Ellison, 2021). Ensuring proper sleep hygiene, e.g. with brief behavioral therapy for insomnia, is therefore of fundamental importance in the case of LLD (Gebara et al., 2019; Husein-Krautter and Ellison, 2021).

Nutrition, microbiome

Several studies have confirmed the role of gut-brain axis and gut microbiome dysfunction in depressive disorders. In the case of MDE, inflammatory processes damage the structure and function of the intestinal barrier, and changes in the intestinal microbiome affect the 5-HT level in the central and peripheral nervous system.

The importance of the above factors is also supported by the fact that probiotics alleviate depressive symptoms, reduce the level of inflammatory markers and increase the availability of 5-HT (Cheung et al., 2019; Wallace et al., 2017; Husain-Krautter and Ellison, 2021).

Smoking, alcohol consumption

Smoking is more common in depressed elderly compared to cohorts who do not smoke. Risky and problematic alcohol consumption is a significant risk factor for the development of LLD and impairs responsiveness (Husain-Krautter and Ellison, 2021).

DISCUSSION

Due to the expanding proportion of the elderly population, the prevalence of LLD shows an increasing trend. LLD can lead to pronounced health damage, quality of life deterioration, increased mortality and, within that, a significant suicide risk (Szymkowicz et al., 2023). The recognition of LLD is difficult mainly due to the predominance of somatic complaints/symptoms that are non-specific to MDD, and accordingly it is typically an "underdiagnosed" and "undertreated" condition (Husain-Krautter and Ellison, 2021). Treatment of LLD is complex. The setting of pharmacotherapy requires great caution due to comorbid somatic diseases, their drug treatment

and possible interactions. Modification of evidence-based psychotherapy methods (abbreviation of sessions, problem-centeredness) is justified in the vast majority of cases due to age characteristics.

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Időskori depresszió, klinikai kép, etiológia, terápiás lehetőségek

Áttekintő cikkünkben az öregedés különböző formáit tárgyaljuk, és röviden érintjük annak pszichológiai aspektusait is. Ezen kívül foglalkozunk a késői életkorban jelentkező depresszió prevalenciájával, klinikai megnyilvánulásaival. Bemutatjuk az időskori depresszió etiológiai faktorait, így a pszichológiai, pszichoszociális tényezőket, a biológiai okok között a genetikai, epigenetikai faktorokat, az immun, gyulladásos és neurodegeneratív folyamatokat, a neurotranszmitter és neurotrofikus rendszerek, valamint HPA-tengely változásait, illetve a testi betegségek, gyógyszerek és hormonális változások hatását. Összegezzük a differenciáldiagnózis folyamatát, valamint az életminőség komplex fogalmát. Áttekintést adunk az idősebb korosztályok öngyilkosságára vonatkozó jellemzőkről és betekintést nyújtunk a legfontosabb farmakológiai és pszichoterápiás beavatkozásokról.

Kulcsszavak: öregedés, időskori depresszió, etiológia, farmakoterápia, pszichoterápia