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Depression and cognitive functions in perimenopause

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Summary. Major depression is the most common mental disorder. Women are affected by depression about twice as much as men, from adolescence to adulthood, with earlier onset, greater clinical severity and longer duration of episodes. Perimenopause is a particularly vulnerable time for depressive recurrences. In addition to the physical and emotional symptoms, attention should be paid to cognitive symptoms such as learning memory, executive functions and psychomotor speed. Cognitive symptoms are often found as residual symptoms, and are closely related to the failure to recover the psychosocial functioning. During perimenopause, only 20% of women are asymptomatic. Of the remaining proportion, 70% complain of vasomotor symptoms associated with at least one among sleep disturbances, affective disorders and impaired cognitive functions. Perimenopause is a window of vulnerability for depression, but also for the onset of cognitive deficits. One of the most accepted hypotheses emphasizes the role of estrogens and their fluctuating state in this phase of life. Depression is also a risk factor for neurodegenerative diseases related to brain aging and estrogen deficiency. Finally, for the pharmacological approach to perimenopause-related affective and cognitive disorders, as well as for anxiety issues and vasomotor symptoms, a growing evidence supports the use of serotonergic antidepressants.

Key words. Depression, perimenopause, gender.

Depressione e funzioni cognitive nella perimenopausa

Riassunto. La depressione maggiore è il disturbo mentale più comune. Le donne risultano affette da depressione circa due volte più degli uomini dall'adolescenza all'età adulta, con esordio più precoce, maggior gravità clinica e durata degli episodi. La perimenopausa si configura come un periodo di particolare vulnerabilità per le ricorrenze depressive. Oltre alla sintomatologia fisica e affettiva va posta attenzione ai sintomi cognitivi quali memoria di apprendimento, funzioni esecutive e velocità psicomotoria. I sintomi cognitivi spesso si ritrovano come sintomi residui e sono strettamente correlati al mancato recupero del funzionamento psicosociale. Durante la perimenopausa solo il 20% delle donne risulta asintomatico. Della restante percentuale, il 70% lamenta sintomi vasomotori associati al almeno uno tra disturbi del sonno, disturbi affettivi e alterazione delle funzioni cognitive. La perimenopausa rappresenta una finestra di vulnerabilità per depressione ma anche per l'insorgenza di deficit cognitivi. Una delle ipotesi più accreditate pone l'accento sul ruolo degli estrogeni e del loro andamento fluttuante in questa fase di vita. La depressione è anche fattore di rischio per malattie neurodegenerative legate all'invecchiamento cerebrale e alla carenza estrogenica. Infine, per l'approccio farmacologico ai disturbi affettivi e cognitivi legati alla perimenopausa, come anche per le problematiche d'ansia e i sintomi vasomotori, evidenze crescenti supportano l'uso di antidepressivi serotoninergici.

Parole chiave. Depressione, perimenopausa, genere.

Major depression is the most common mental disorder, affecting 350 million people worldwide, with a globally increasing incidence. It is characterized by an impairment of personal and social functioning and by cognitive, behavioral, somatic and affective symptoms.

Thirthy percent of all female conditions concern the area of mental health (psychiatric and neurological diseases). The protagonist in this scenario is major depression which, as is known, affects women more frequently than men, and often accompanies other typically female mental disorders, such as anxiety, sleep disturbances and eating behavior.

The data provided by the international literature agree that women are affected by depression two to three times more than men, from adolescence to adulthood.[1-3] In particular, women tend to develop the disease earlier, and manifest a more severe symptomatology than men.

In addition to having an increased chance of getting depressed over the course of life and to reporting more symptoms than men, women have a longer duration of episodes. On the other hand, no significant differences were found in the literature in terms of a tendency to more frequent recurrences.

During the perimenopause period, women are at higher risk of incurring the onset or a recurrence of a major depressive episode. Depression during this phase of life can have a substantial impact on the woman and her life (couple, family, profession).

Perimenopause (which includes the early and late menopausal transition and the early postmenopause) is considered by the clinician as a "vulnerability window" to depression, therefore worthy of being identified

and carefully evaluated in order to activate a treatment intervention should the psychopathological symptoms interfere with the woman's quality of life.[4,5]

The studies on mood disorders in menopause are characterized by the difficulty of establishing a methodological rigor, due to the heterogeneity of the clinical pictures and the hormonal status. More rigorous studies, which use standardized assessments of depression under defined perimenopause conditions, support an association between major depressive disorder and menopause.

Cohen et al[6] examined the impact of the transition to menopause on depressive symptoms in 460 women aged 36-45 with a negative history of major depression. During the three years of follow-up, the menopause arm, especially women with hot flashes, showed a two-time greater chance of experiencing significant depressive symptoms in comparison with the pre-menopause arm. Mood disorders occurred in 9.5% of pre-menopausal women and 16.6% of perimenopausal women. These studies have all used rigorous, standardized criteria to reach psychiatric diagnoses, and their results strongly support the hypothesis of an increasing vulnerability for a major depressive episode occurring at the time of the passage of menopause.

In addition to the physical and affective symptoms, also cognitive symptoms are now a diagnostic criterion of depression (reduced ability to think and concentrate, indecision, psychomotor slowdown). All cognitive domains are affected, from learning memory to executive functions (controlling and regulating cognitive processes, use of attention, planning, working memory, mental flexibility, multitasking and decision-making processes) and psychomotor speed (speed with which the brain controls the body's execution of physical activities).

The importance of cognitive symptoms during depression is recognized by most psychiatrists, especially as regards the negative significance of impaired functioning, persistence as a residual symptomatology, and its driving force for recurrences.[7]

Cognitive symptoms – consisting of alterations of executive functions, memory, attention and reaction time (measured through specific neuropsychological tests) – are present both in the acute phase of the disease and in the remission, as evidenced by a recent meta-analysis (effect sizes between -0.4 and -0.6 for all the individual cognitive functions measured).[8,9]

A 3-year follow-up study after resolution of the episode showed that cognitive symptoms are those to be found most frequently as residual symptoms, and are reported for about 40% of the follow-up time.[10] The persistence of cognitive symptoms is closely related to alterations and/or the failure to recover the psycho-social functioning.[11]

During perimenopause, only 20% of women are asymptomatic. Of the remaining proportion, 70% complain of vasomotor symptoms associated with at least one among sleep disturbances, affective disorders and impaired cognitive functions.[12,13] The close relation between the cognitive and affective sphere and the hormonal alterations typical of the period consisting of the years preceding menopause and the year following it ("periclimaterio") is evident.

Both in DSM-5 and in ICD-10, the diagnostic criteria for depression include a "reduced ability to think or concentrate", "agitation or psychomotor slowdown", therefore – when addressing the clinical dimension of depression or the affective disorders in the broad sense – it is not possible to ignore the evaluation of the cognitive domain.

Cognitive processes consist of a series of different interrelated domains, which include episodic memory, visuospatial function, language, praxia, working memory, executive functions, attention and processing speed. Commonly used tests are never totally specific to a single domain, so they are generally evaluated in combination. One of the most used tests is the DSST (*Digit Symbol Substitution Test*), since it is simple, fast and easy to understand[8]. As reported by Conradi HJ et al,[10] in a sample of depressed patients the proportion of time spent in the presence of cognitive symptoms was 94%; however, impairment was present in 44% of the time also in the interepisodic remission phase.

It is important to keep in mind that there are other causes of cognitive dysfunction in patients with depression, including cognitive decline associated with senescence or other forms of dementia, sleep disturbances, head injuries, side effects of psychotropic drugs or substance abuse. In addition to a purely clinical aspect, the impairment of the cognitive functions leads to a deterioration of the overall quality of life, as well as productivity at work. In a study by Lam RW et al,[14] 52% of the depressed patients surveyed reported that cognitive difficulties seriously interfered with their occupational functioning. An interesting fact is the direct proportionality between the number of depressive episodes and the reduced memory recovery in the intercritical phases, to demonstrate that the prevention of depressive recurrences is critical in reducing progressive cognitive impairment.[15]

When we talk about depressive disorders and cognitive sphere, the so-called HOT and COLD cognitive processes are often mentioned. COLD processes include non-emotional domains, such as planning capacity and memory, measurable through specific tests, while HOT processes are influenced by emotions. An excessive response (increased attention, perception and memory) towards negative feedback, with a mutual influence between the HOT and COLD domains has been observed in depressed patients.[16,17] A meta-analysis of McDermott LM indicates that the cognitive deficits within the different domains of COLD processes are related to the sever-

ity of the depressive episode.[18] On the other hand, as far as HOT processes are concerned, studies indicate a bias towards negative stimuli, to the detriment of positive ones. Compared to healthy subjects, depressed patients tend to pay more attention to tasks with negative emotional content, to perceive it as more negative and to remember it later on[19]. Functional imaging studies identified the neural basis of this phenomenon: the emotional responses generated by the limbic system pass through the regulatory circuits of the prefrontal regions: in depressed patients there is an imbalance in the relationship between these two systems, with an anomalous predominance of the role of the amygdala in the perception of negative emotions, at the expense of positive ones.[20,21] A very interesting data also reports that healthy young subjects with familiarity for depression also present a decrease in the response of the DLPFC (*dorsolateral prefrontal cortex*) during emotional processing.[22] Specifically, Barent-Spillson et al[23] studied how the metabolic and hormonal structure can influence the emotional processing in women in the various menopausal stages. It was found that, during perimenopause, the sample tended to attribute a negative value to images with neutral content, implementing the so-called *Negative Interpretation Bias*. Perimenopausal women present objective and subjective deficits of immediate and delayed verbal fluency and memory, working memory and attention even in the absence of a major depressive episode.[24] Therefore, perimenopause is a window of vulnerability not only for depression, but also for the onset of cognitive deficits. One of the most accepted hypotheses emphasizes the role of estrogens and their fluctuating status in this phase of life. We know of their powerful neurotrophic effect: they improve the repair mechanisms of neuronal membranes, increase the ability of dendritic sprouting – i.e. the capacity to create connections between different nerve cells –, the synthesis and the turnover of neurotransmitters. Conversely, chronic estrogen deficiency reduces neuronal repair capacity, the number of dendritic spines, the synthesis and the deposit and release of critical neurotransmitters, with an ubiquitous effect on the whole CNS.[25,26] They also act on the cholinergic system, critical for the memory and the higher cognitive functions, as well as on the hippocampus and the pre-frontal cortex (PFC).[27,28] Depression is also a predictor of neurodegenerative diseases related to brain aging and estrogen deficiency, such as Alzheimer's disease, and Parkinsonism. Early iatrogenic menopausal women have a significantly higher risk of developing Alzheimer's and Parkinson's.[29,30,31] Another interesting data concerns women who underwent mono- or bilateral ovariectomy in their fertile age and who present a significant increase in the risk of cognitive impairment [OR] = 1.46 (95% CI 1.13-1.90), with an increase as much greater as younger was their age at the time of ovariectomy ($p < 0.0001$).

As regards the pharmacological approach to the treatment of affective and cognitive disorders related to perimenopause, as well as for the anxiety issues and the vasomotor symptoms, growing evidence supports the use of serotonergic antidepressants. Paroxetine is currently the only FDA-approved drug for the treatment of vasomotor symptoms. In a 2017 preliminary study by Freeman,[24] the efficacy of vortioxetine in the major depressive disorder (MDD) during the menopausal transition was studied, as well as the effects on vasomotor symptoms, anxious symptoms and cognitive disorders. Vortioxetine has a multimodal activity which consists in the inhibition of the serotonin reuptake (5HT), as well as 5HT1A agonist and 5HT3 antagonist activity. In addition to this, it has effects on the dopaminergic, noradrenergic and glutamatergic system. There was a significant reduction in MADRS scores ($p = .0001$), as well as DSST ($p = 0.0133$) and the frequency and intensity of vasomotor symptoms ($p = .0291$ and $p = .0299$, respectively), therefore not only a reduction of depressive symptoms, but also an improvement in cognitive and vasomotor symptoms.

Key messages

- Women are affected by depression about twice as much as men, with earlier onset, greater clinical severity and longer duration of episodes.
- During perimenopause, only 20% of women are asymptomatic. Of the remaining proportion, 70% complain of vasomotor symptoms associated with at least one among sleep disturbances, affective disorders and impaired cognitive functions.
- Perimenopause is considered by the clinician as a "vulnerability window" to depression and to the onset of cognitive deficits.
- For the pharmacological approach to perimenopause-related affective and cognitive disorders, as well as for anxiety issues and vasomotor symptoms, growing evidence supports the use of serotonergic antidepressants.

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