Apathy, anhedonia and cognitive dysfunction: common symptoms of depression and neurological disorders

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Depression is one of the most common mental disorders in neurological practice. Among other symptoms of depression, a symptom complex represented by apathy, anhedonia, and cognitive impairment plays an important role. This review presents the clinical characteristics of the symptoms described above and discusses modern neurochemical and neuroimaging concepts of their pathogenesis. The problem of pathogenetically substantiated therapy of depression with a predominance of apathy, anhedonia and cognitive impairment is discussed. Fundamental and clinical arguments are presented in favor of the high efficacy of vortioxetine in depression with a predominance of apathy, anhedonia, and cognitive impairment.

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Depression – is one of the most common mental disorders accompanying various neurological diseases [1, 2]. The incidence of depression is higher in Alzheimer's disease, Parkinson's disease, cerebral stroke, epilepsy, multiple sclerosis, traumatic brain injury and other health conditions [3]. Timely diagnosis and correct treatment of depressive conditions in neurological practice are important because of the significant adverse impact of depression on the course and prognosis of neurological pathology [4][1]. However, in real clinical practice, depression is hardly ever diagnosed, because it is frequently masked by somatic symptoms, neurologists have limited knowledge about depression, and patients are rarely referred to a psychiatrist. Cognitive dysfunction, apathy and anhedonia are among the most important common symptoms for diagnosing depression and understanding its clinical structure.

Advances in modern neuroscience over the past decade allow to regard depression as a clinically heterogeneous condition [5]. In particular, a study by E. Vares et al. [6] identified six major groups of symptoms characterizing depressive pathological states. One of the most widespread and clinically significant group is a cluster of symptoms comprising apathy, anhedonia and cognitive impairments (CIs). In addition to the results of this analysis, there is also evidence of the unity of these symptoms – both clinical, and based on neurochemical and neuroimaging data [7, 8]. At the same time, assessment of the contribution of depressive pathology and neurological disease, respectively, to the dominance of the above-described symptoms seems to be a difficult task [9].

This review deals with clinical manifestations of anhedonia, apathy, and CIs in depressive patients and issues of differential diagnosis of the described symptoms with neurological pathology.

Apathy and anhedonia

According to the existing consensus definitions, apathy can be characterized as a general lack of motivation based on reduced goal-directed behaviour and targeted learning [10].

The high prevalence and pronounced adverse effects on the level of functioning make apathy one of the most important manifestations both of depression and of some neurological diseases. According to large-scale epidemiological studies, 40% to 70% of patients suffering from stroke, post-traumatic brain injury, Alzheimer's disease, Parkinson's disease, and frontotemporal dementia [9] are clinically apathetic. In turn, up to one third of adults and seniors with depression present with the dominant complaints of the "apathic circle" [11].

It has been proven repeatedly that the presence of pronounced apathetic symptoms is one of the leading factors in the maladaptation of patients, as well as a significant burden on relatives and caregivers [10]. In addition, apathy greatly hinders patients' adaptation, being a major obstacle to rehabilitation programs, returning to work, etc. [12].

It should be borne in mind that apathy is not a holistic symptom complex; researchers such as Levy and Dubois have identified three components, or vectors, of apathy: emotional, behavioral, and cognitive, which correspond well to the neurobiological model of purposeful ('goal-oriented') behavior [8, 13].

In clinical practice, emotional apathy manifests itself primarily through smoothed affect and reduced response to events in the environment. Patients with emotional apathy respond less intensively to various emotionally significant events,

[1]According to modern thinking, the negative impact of depression on the course of somatic and neurological diseases is related to both behavior (reduced adherence to treatment, less healthy lifestyle) and general biological mechanisms. Further consideration of this topic is beyond the scope of this review.

regardless of whether they are positive or negative. At the same time, patients with the predominance of emotional apathy can be quite easily involved in various activities at the initiative of others, while reporting a complete lack of interest in the activities performed.

Behavioral apathy is characterized primarily by a direct decline in the willingness to act. In clinical trials, patients complain of inability to begin an action. Even if there is a formally expressed desire to do something, patients are inactive, postpone even the minimum necessary actions (in severe cases they may neglect personal hygiene).

Finally, cognitive apathy is characterized by inability to plan or perform an action.

According to modern ideas, apathy can equally be regarded as a manifestation of depression or neurological pathology of various kinds, which is connected with the common mechanisms of manifestation of this symptom complex (see below), though apathy as a manifestation of an organic brain lesion is difficult to cure, while for apathy as a manifestation of depression there is effective treatment [9].

In this regard, it is important to find reliable and clinically justified approaches to the detection of depressive pathology in patients with predominant complaints of apathy.

It is believed that the most reliable distinction can be made on the basis of the presence of the pathognomonic symptom of depression – anhedonia complex [14].

According to the existing definitions, anhedonia in the broad sense of the word is understood as alteration of the spectrum of psychic functions related to positive reinforcement: inability to expect pleasant events, to enjoy them, to memorize the stimuli associated with positive reinforcement, and form the behavior based on positive reinforcement. The key to the diagnosis of anhedonia is inability to derive pleasure in the things that used to be associated with strong positive emotions [15].

Modern clinical and neurobiological research allows to divide anhedonia into two principal types – anticipatory (anhedonia of wanting) and consummatory (anhedonia of liking) [16]. In the first case, it is the inability to enjoy the incentives that are associated with the process of receiving and anticipating positive reinforcement ('wanting'). Patients report that they enjoy eating, receiving money (e.g. bonuses), simple hobbies, etc. However, the formation of any more or less complex behavior aimed at getting pleasure, such as shopping, doing some work for a fee, planning a trip with the loved ones, does not give any pleasure. When interviewing a patient, it may appear that the patient is complaining of apathy, but in the case of anticipatory anhedonia the principal sign is a painful lack of pleasure that prevents planning of any action even in the case when the activity level is sufficient.

In turn, consummatory anhedonia is associated with the inability to directly enjoy the already available sources of positive reinforcement – food, money, delivered new purchase, sexual activity, etc.

In addition, in the structure of anhedonia several types can be distinguished, depending on what interests are primarily lost: social, physical and intellectual-aesthetic anhedonia [17]. In the first case, we speak about the impaired ability to enjoy communicating with other people, getting their attention, approval, admiration. In the second case, the leading factor is lack of pleasure from immediate physical sensations – taste, touch, smell. Finally, intellectual and aesthetic anhedonia is characterized by loss of pleasure from listening to music, hobbies, disappearance of sense of humor.

The key role of anhedonia in the structure of depressive syndrome is generally recognized and reflected in recent diagnostic recommendations (ICD-11, DSM-V), which consider anhedonia along with a pathologically reduced mood to be two main symptoms of depression. Anhedonia also plays a key role in many screening questionnaires aimed at diagnosing depression.

Despite formal differences (including diagnostic differences), the modern literature accumulates evidence that apathy and anhedonia may share biological mechanisms. This evidence includes both neuroimaging and neurochemical aspects.

Thus, studies using functional magnetic resonance imaging (functional MRI) have revealed several neuronal circuits and groups of brain structures, the decline of which may be related to the formation of both apathy and anhedonia. The following structures are most clearly associated with the development of apathy and anhedonia [10, 13]:

- the medial prefrontal cortex (with the largest contribution of the anterior cingulate cortex) and the orbitofrontal cortex;
- subcortical structures (the ventral striatum, the medial dorsal core of the thalamus, the ventral tegmental area, the nucleus accumbens, the amygdala).

In terms of neuronal circuits, the dysfunction of the anterior cingulate cortex and ventral striatum complex [10] can be considered to relate most closely to the development of the symptoms of apathy and anhedonia.

In general, it has been shown that the formation of apathy and anhedonia can be related to both functional impairment of the brain structures described above, and direct morphological changes due to organic brain damage [8]. In particular, the manifestation of symptoms of apathy has been shown to be negatively correlated with the volume of gray matter of the ventromedial prefrontal cortex, as well as with dorsal anterior cingulate and dorsolateral prefrontal cortex activity at rest [16].

Based on the data on the neurotransmitters which play a key role in signal transmission between the structures discussed above, as well as on experimental pharmacological studies, it is possible to draw conclusions about the neurotransmitters underlying the development of apathy and anhedonia.

The most important neurotransmitter involved in the formation of motivated behavior and pleasure is dopamine [8, 15, 18]. Thus, apathy and anhedonia can be described in a simplified form as a state of relative hypodopaminergy in neuronal circuits responsible for motivated behavior and positive reinforcement. In addition, apathy is characterized by a functional decrease in noradrenergic neuron activity [19]. In turn, insufficiency of endogenous opioid peptides [20] is involved in the formation of anhedonia.

Cognitive dysfunction

As mentioned above, in depression, cognitive dysfunction forms a single cluster of symptoms with apathy and anhedonia. In addition, current research shows a close relationship between apatho-anhedonic symptoms on the one hand, and cognitive functioning on the other [21, 22]. Thus, the second of the cited papers showed that the level of apathy largely determined

patients' performance in attention tests, information processing speed, speech fluency, visual and verbal memory, operational memory, and executive functions.

Over the past decades, there has been an accumulation of evidence that CIs are an integral component not only of neurological diseases (primarily neurodegenerative), but also of depression [23]. In particular, it has been proven that not only emotional CI (ideas of guilt, incorrect pessimistic perception of the surrounding reality) but emotionally independent cognitive dysfunction is present in depressive patients.

In depression, dysfunction is established in the following domains: executive skills, attention, memory, visual-spatial function, verbal skills, speed of information processing. It should be emphasized that both individual symptoms of depression and a general decrease in the level of functioning may in some cases be due to specific cognitive dysfunctions. For example, attention deficit partly affects mood regulation as well as formation and intensity of ruminations (repetitive thoughts of a negative nature). Deficiency in the domain of executive functions leads to reduced ability to discard unnecessary information, resulting in retention of negative thoughts, low mood, and a decrease in other cognitive functions [24]. According to recent studies, it is executive deficiency that is the main barrier to the functional recovery of patients with depression [25].

It is possible to distinguish two main hypotheses aimed at explaining the genesis of CI in patients with depression. The historical priority belongs to the resource allocation hypothesis [23]. According to this hypothesis, the total amount of cognitive resources in humans is limited, and in the case of depression, there is marked «overload» of the brain circuits responsible for processing information by numerous repetitive thoughts of a negative nature.

However, despite the logic of the hypothesis presented, it does not agree well with more recent data on CI persistence during remission of a depressive disorder. Prospective studies have shown not only the persistence of CI from one episode of depression to another, but also its gradual build-up, allowing recurrent depressive disorder to be regarded as a progressive disease [26]. Moreover, cognitive dysfunction has been shown to be a significant predictor of a suboptimal response to therapy (both with antidepressants and through transcranial magnetic stimulation and cognitive behavioral therapy) [27].

The logical consequence of the data obtained was the inclusion of CI among the diagnostically significant symptoms of a depressive episode in the leading international classifications and guides for diagnosis (ICD-11, DSM-V). Therefore, cognitive function assessment (based on clinical interviews supported by diagnostic scales if necessary) should be part of the examination of any patient with depressive circle pathology.

In neurological practice, the most interesting example of cognitive dysfunction as a common symptom is called depressive pseudo-dementia. This condition is characterized by a pronounced decline in cognitive functions (mainly in domains of executive function, memory, and speech) during a depressive episode, requiring differential diagnosis with true dementia [28]. The classic description refers to mature patients who seek help with complaints of clear impairment of memory, misdirection, inability to cope with their professional duties and domestic affairs. Antidepressant therapy usually results in a rapid and complete regression of the symptoms [29].

However, the reversible nature of depressive pseudo-dementia does not reject its presumable contribution to neurological mechanisms. Prospective studies with a correct design proved that a few years after the manifestation of depressive pseudo-dementia, the risk of developing true dementia increased significantly. In particular, J. Saez–Fonseca et al. [30] showed that after 5–7 years, true dementia develops in 71% of patients with depressive pseudo-dementia, which is significantly higher than 18% in the control group comparable by sex, age and comorbid states. The study found that depressive pseudo-dementia was a significant predictor of true dementia, with a relative risk of 3.292 (95% confidence interval 1,985–7,775).

In this regard, modern researchers believe that in depressive pseudo-dementia the depressive symptom unmasks the already existing cognitive deficit, which is still in a compensated state [31].

Approaches to CI drug therapy, apathy, and anhedonia in patients with depression and neurological pathology

Current clinical guidelines consider antidepressants from the selective serotonin reuptake inhibitor class (SSRIs) as the drugs of the first choice for treating depression due to their high efficiency and good safety/tolerance profile, which makes them more acceptable in neurological practice than tricyclic antidepressants [32–34]. However, a number of considerations cast doubt on the optimal class of drugs for neurological patients with CI, apathy and anhedonia.

First, SSRIs can worsen the existing apathetic symptoms or contribute to their manifestation in patients without initial apathy. This side effect is traditionally described in the scientific literature as serotonin-associated apathy or indifference [35, 36]. Increased apathy in the context of SSRI therapy is associated with the reciprocal interaction of serotonergic and dopaminergic neurotransmission in some parts of the brain. So, according to W. Barnhart et al. [37], apathy is formed either by suppressing dopamine release in the frontal lobes due to serotonin inhibition or by directly suppressing dopaminergic neurons in the midbrain. Given the role of dopamine in the formation of motivated behavior, the pathogenesis of serotonin-conditioned apathy in general is obvious.

The main risk factor for this condition is believed to be long-term exposure to SSRIs at high doses [38]. Thus, according to M. Fava et al. [39], one third of patients have been diagnosed with apathy at doses above the average therapeutic level for more than a year. However, clinical evidence is accumulating that patients with accompanying neurological pathology of the neurodegenerative circle may be significantly more vulnerable to serotonin-induced apathy and may develop it more rapidly [40].

Modern approaches to the correction of serotonin-conditioned apathy suggest three main strategies: reduction of the dose of SSRIs, combination with another drug (atypical antipsychotic, atomoxetine, mirtazapine, etc.) or replacement with an alternative antidepressant [38]. In patients with apathy prior to initiation of the therapy, the latter strategy is preferred [40].

Secondly, there is experimental evidence that SSRIs may exacerbate symptoms of anhedonia. So, C. McCabe et al. [41], using fMRI, showed that a seven-day SSRI treatment leads to lower activation of the brain in response to both neg-

ative and positive stimuli, which at the clinical level can be correlated with a slight increase in anhedonia. In most patients, this effect is not noticeable given the general improvement of well-being and reduction of depressive affect, but it may be critical in patients with the predominance of anhedonia.

Finally, there is evidence in the scientific literature of minor, but negative effects of SSRIs on cognitive function [42]. This effect is certainly much smaller than for older antidepressants such as tricyclic, but it is worth detailed attention when treating patients with pre-existing CI. Also, based on the data of Montoya–Murillo et al. presented above [22], it can be assumed that increased apathy against the background of SSRIs may be one of the causes of cognitive impairment proven in this meta-analysis.

According to the above-presented arguments, patients with the prevalence of CI, apathy and anhedonia need effective and safe alternatives to SSRIs. The most promising drug in this regard is the new antidepressant vortioxetine. This drug has a multimodal mechanism of action that combines serotonin reuptake inhibition, agonism to 5-HT1A receptor, partial agonism to 5-HT1B receptor, and antagonism to 5-HT1D-, 5-HT3- and 5-HT7-receptors [43]. Such a pharmacodynamic profile, on the one hand, allows to maintain antidepressant and anti-anxiety activity inherent in SSRIs, and on the other hand – contributes to procognitive and activating effects of the drug.

Of particular interest in the context of this review is vortioxetine binding to 5-HT1B-, 5-HT3- and 5-HT7-receptors. Thus, in patients with neurodegenerative diseases, an association has been shown between cognitive functions, mood and 5-HT1B receptor activity [44]. Serotonin receptors of the third and seventh subtype, in turn, binding with serotonin, exert inhibiting effect and, thus, contribute to impaired cognitive function and increased apathy, which can be regarded as a mechanism of SSRI side effects [45, 46]. Vortioxetine, due to its potent antagonism to these receptors, not only prevents the negative effects of SSRIs, but also exerts a procognitive and activating action.

The potential anti-apathetic effect of vortioxetine, evident in the study of its receptor profile, is fully confirmed in clinical trials. A. Fagiolini et al. [47] evaluated the effectiveness of switching to vortioxetine in patients with severe apathy who did not respond to a single course of SSRI therapy or a serotonin-norepinephrine reuptake inhibitors (SNRIs). After eight days of therapy, 50% of patients reported a complete disappearance of complaints of apathy, impotence, and emotional devastation.

Anhedonia is also one of the symptoms for which vortioxetine has pronounced selective action. Thus, in the meta-analysis of 2021, R. McIntyre et al. [48] analyzed eleven randomized clinical trials, in which vortioxetine was compared with placebo in patients with depression who did not respond to SSRIs/SSNIs. Pronounced effects of vortioxetine in anhedonia as well as improvements in function have been demonstrated, with anhedonia reduction acting as a mediator for improving patient functioning, according to multiple regression analysis. Thus, within the paradigm of evidence-based medicine, vortioxetine may be considered a drug of choice for treating depression with the predominance of anhedonia.

Finally, procognitive properties of vortioxetine have been shown in randomized clinical trials. Meta-analysis by B. Baune et al. [49], based on 12 randomized clinical studies, has shown that vortioxetine is the only antidepressant demonstrating positive effects in the symbol coding test. It is also worth mentioning that vortioxetine in this meta-analysis has surpassed not only placebo and SSRIs, but also SNRIs duloxetine, whose profile suggests a positive influence on cognitive functions.

Conclusion

Apathy, anhedonia and CI are common symptoms of depression and neurological pathology, acting as a distinct symptom complex. Patients with the predominant symptoms described above require clinical attention, taking into account the sub-optimal response to standard therapeutic tactics. The multimodal antidepressant vortioxetine is a promising drug for the treatment of CI, apathy and anhedonia as part of depression in neurological patients.

REFERENCES

1. Головачева ВА, Парфенов ВА. Депрессия в неврологической практике: распространенность, диагностика, стандарты лечения и новые возможности фармакотерапии. *Медицинский Совет*. 2015;(5):55-61. doi: 10.21518/2079-701X-2015-5-55-61 [Golovacheva VA, Parfyonov VA. Depression in neurological practice: prevalence, diagnosis, treatment standards and new options for pharmacotherapy. *Meditsinskiy sovet = Medical Council*. 2015;(5):55-61. doi: 10.21518/2079-701X-2015-5-55-61 (In Russ.)].

2. Романов ДВ, Волель БА, Петелин ДС. Подходы к терапии депрессии в неврологии (перспективы применения агомелатина). *Неврология, нейропсихиатрия, психосоматика*. 2018;10(4):101-10. doi: 10.14412/2074-2711-2018-4-101-110 [Romanov DV, Volel BA, Petelin DS. Approaches to therapy for depressions in neurology: prospects for the use of agomelatine. *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics*. 2018;10(4):101-10. doi: 10.14412/2074-2711-2018-4-101-110 (In Russ.)].

3. Романов ДВ, Петелин ДС, Волель БА. Депрессии в неврологической практике. *Медицинский Совет*. 2018;(1):38-45. doi: 10.21518/2079-701X-2018-1-38-45 [Romanov DV, Petelin DS, Volel BA. Depression in neurological practice. *Meditsinskiy sovet = Medical Council*. 2018;(1):38-45. doi: 10.21518/2079-701X-2018-1-38-45 (In Russ.)].

4. Rickards H. Depression in neurological disorders: Parkinson's disease, multiple sclerosis, and stroke. *J Neurol Neurosurg Psychiatry*. 2005 Mar;76 Suppl 1:i48-52. doi: 10.1136/jnnp.2004.060426

5. Vrieze E, Demyttenaere K, Bruffaerts R, et al. Dimensions in major depressive disorder and their relevance for treatment outcome. *J Affect Disord*. 2014 Feb;155:35-41. doi: 10.1016/j.jad.2013.10.020

6. Vares EA, Salum GA, Spanemberg L, et al. Depression Dimensions: Integrating Clinical Signs and Symptoms from the Perspectives of Clinicians and Patients. *PLoS One*. 2015 Aug 27;10(8):e0136037. doi: 10.1371/journal.pone.0136037

7. Сорокин СА. Эндогенные апатические депрессии (вопросы психопатологии, клиники и терапии): Дис. ... канд. мед. наук. Москва; 2015. 196 p. [Sorokin SA. *Endogennyye apaticheskiye depressii (voprosy psikhopatologii, kliniki i terapii): Dis. ... kand. med. nauk* [Endogenous apathetic depressions (issues of psychopathology, clinic

and therapy): Dis. ... cand. med. sci]. Moscow; 2015. 196 p. (In Russ.)].

8. Lanctot KL, Agüera-Ortiz L, Brodaty H, et al. Apathy associated with neurocognitive disorders: Recent progress and future directions. *Alzheimers Dement.* 2017 Jan;13(1):84-100. doi: 10.1016/j.jalz.2016.05.008

9. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nat Rev Neurosci.* 2018 Aug;19(8):470-84. doi: 10.1038/s41583-018-0029-9

10. Fahed M, Steffens DC. Apathy: Neurobiology, Assessment and Treatment. *Clin Psychopharmacol Neurosci.* 2021 May 31;19(2):181-9. doi: 10.9758/cpn.2021.19.2.181

11. Yuen GS, Bhutani S, Lucas BJ, et al. Apathy in late-life depression: common, persistent, and disabling. *Am J Geriatr Psychiatry.* 2015 May;23(5):488-94. doi: 10.1016/j.jagp.2014.06.005

12. Lenze EJ, Skidmore ER, Dew MA, et al. Does depression, apathy or cognitive impairment reduce the benefit of inpatient rehabilitation facilities for elderly hip fracture patients? *Gen Hosp Psychiatry.* 2007 Mar-Apr;29(2):141-6. doi: 10.1016/j.genhosppsych.2007.01.001

13. Le Heron C, Holroyd CB, Salamone J, Husain M. Brain mechanisms underlying apathy. *J Neurol Neurosurg Psychiatry.* 2019 Mar;90(3):302-12. doi: 10.1136/jnnp-2018-318265

14. Cooper JA, Arulpragasam AR, Treadway MT. Anhedonia in depression: biological mechanisms and computational models. *Curr Opin Behav Sci.* 2018 Aug;22:128-35. doi: 10.1016/j.cobeha.2018.01.024

15. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev.* 2011 Jan;35(3):537-55. doi: 10.1016/j.neubiorev.2010.06.006. Epub 2010 Jul 11.

16. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. *Trends Neurosci.* 2012 Jan;35(1):68-77. doi: 10.1016/j.tins.2011.11.005

17. Касимова ЛН, Святогор МВ. Ангедония в структуре аффективных расстройств: возможности терапии. *Журнал неврологии и психиатрии им. С.С. Корсакова.* 2019;119(11):116-22. doi: 10.17116/jnevro2019119111116 [Kasimova LN, Svyatogor MV. Angedonia in the structure of affective disorders: therapeutic opportunities. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova.* 2019;119(11):116-22. doi: 10.17116/jnevro2019119111116 (In Russ.)].

18. Chong TT, Husain M. The role of dopamine in the pathophysiology and treatment of apathy. *Prog Brain Res.* 2016;229:389-426. doi: 10.1016/bs.pbr.2016.05.007. Epub 2016 Jul 29.

19. Hezemans FH, Wolpe N, O'Callaghan C, et al. Noradrenergic deficits contribute to apathy in Parkinson's disease through the precision of expected outcomes. *PLoS Comput Biol.* 2022 May 9;18(5):e1010079. doi: 10.1371/journal.pcbi.1010079

20. Pecina M, Karp JF, Mathew S, et al. Endogenous opioid system dysregulation in depression: implications for new therapeutic approaches. *Mol Psychiatry.* 2019 Apr;24(4):576-87. doi: 10.1038/s41380-018-0117-2

21. McIntyre RS, Woldeyohannes HO, Soczynska JK, et al. Anhedonia and cognitive function in adults with MDD: results from the International Mood Disorders Collaborative Project. *CNS Spectr.* 2016 Oct;21(5):362-6. doi: 10.1017/S1092852915000747

22. Montoya-Murillo G, Ibarretxe-Bilbao N, Pena J, Ojeda N. The impact of apathy on cognitive performance in the elderly. *Int J Geriatr Psychiatry.* 2019 May;34(5):657-65. doi: 10.1002/gps.5062

23. Ахапкин РВ, Маслова МА. Когнитивные нарушения при непсихотических депрессивных расстройствах. *Российский психиатрический журнал.* 2015;(1):43-50. [Akhapkin RV, Maslova MA. Cognitive impairments in non-psychotic depressive disorders. *Rossiyskiy psikhiatricheskiy zhurnal = Russian Journal of Psychiatry.* 2015;(1):43-50 (In Russ.)].

24. Knight MJ, Mills NT, Baune BT. Contemporary methods of improving cognitive dysfunction in clinical depression. *Expert Rev Neurother.* 2019 May;19(5):431-43. doi: 10.1080/14737175.2019.1610395. Epub 2019 Apr 25.

25. Knight MJ, Baune BT. Cognitive dysfunction in major depressive disorder. *Curr Opin Psychiatry.* 2018 Jan;31(1):26-31. doi: 10.1097/YCO.0000000000000378

26. Lam RW, Kennedy SH, Mclntyre RS, Khullar A. Cognitive dysfunction in major depressive disorder: effects on psychosocial functioning and implications for treatment. *Can J Psychiatry.* 2014 Dec;59(12):649-54. doi: 10.1177/070674371405901206

27. Park C, Pan Z, Brietzke E, et al. Predicting antidepressant response using early changes in cognition: A systematic review. *Behav Brain Res.* 2018 Nov 1;353:154-60. doi: 10.1016/j.bbr.2018.07.011

28. Jones RD, Tranel D, Benton A, Paulsen J. Differentiating dementia from "pseudodementia" early in the clinical course: utility of neuropsychological tests. *Neuropsychology.* 1992;6(1):13-21. doi: 10.1037/0894-4105.6.1.13

29. Berrios GE. "Depressive pseudodementia" or "Melancholic dementia": a 19th century view. *J Neurol Neurosurg Psychiatry.* 1985 May;48(5):393-400. doi: 10.1136/jnnp.48.5.393

30. Saez-Fonseca JA, Lee L, Walker Z. Long-term outcome of depressive pseudodementia in the elderly. *J Affect Disord.* 2007 Aug;101(1-3):123-9. doi: 10.1016/j.jad.2006.11.004

31. Sekhon S, Marwaha R. Depressive Cognitive Disorders. [Updated 2022 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559256/

32. Kendrick T, Peveler R. Guidelines for the management of depression: NICE work? *Br J Psychiatry.* 2010 Nov;197(5):345-7. doi: 10.1192/bjp.bp.109.074575

33. Bauer M, Pfennig A, Severus E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. *World J Biol Psychiatry.* 2013 Jul;14(5):334-85. doi: 10.3109/15622975.2013.804195. Epub 2013 Jul 3.

34. Российское общество психиатров. Клинические рекомендации. Рекуррентное депрессивное расстройство, диагностика и лечение. Москва; 2014. [*Rossiyskoye obshchestvo psikhiatrov. Klinicheskiye rekomendatsii. Rekurrentnoye depressivnoye rasstroystvo, diagnostika i lecheniye* [Russian Society of Psychiatrists. Clinical guidelines. Recurrent depressive disorder, diagnosis and treatment]. Moscow; 2014 (In Russ.)].

35. Price J, Cole V, Goodwin GM. Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study. *Br J Psychiatry.* 2009 Sep;195(3):211-7. doi: 10.1192/bjp.bp.108.051110

36. Padala PR, Padala KP, Majagi AS, et al. Selective serotonin reuptake inhibitors-associated apathy syndrome: A cross sectional study. *Medicine (Baltimore).* 2020 Aug 14;99(33):e21497. doi: 10.1097/MD.0000000000021497

37. Barnhart WJ, Makela EH, Latocha MJ. SSRI-induced apathy syndrome: a clinical review. *J Psychiatr Pract.* 2004 May;10(3):196-9. doi: 10.1097/00131746-200405000-00010

38. Петрова НН, Маркин АВ. Синдром апатии у депрессивных пациентов, получавших лечение селективными ингибиторами обратного захвата серотонина. *Журнал неврологии и психиатрии им. С.С. Корсакова.* 2020;120(1):111-7. doi: 10.17116/jnevro2020120011111 [Petrova NN, Markin AV. Apathy syndrome in depressed patients previously treated with selective serotonin reuptake inhibitors. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova.* 2020;120(1):111-7. doi: 10.17116/jnevro2020120011111 (In Russ.)].

39. Fava M, Graves LM, Benazzi F, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. *J Clin Psychiatry.* 2006 Nov;67(11):1754-9. doi: 10.4088/jcp.v67n1113

40. Петелин ДС, Гамирова АН, Воскресенская ОН, Волель БА. СИОЗС-ассоциированная апатия при болезни Альцгеймера: серия клинических наблюдений. *Неврология, нейропсихиатрия, психосоматика.* 2022;14(4):51-3. doi: 10.14412/2074-2711-2022-4-51-53 [Petelin DS, Gamirova AN,

Voskresenskaya ON, Volel BA. SSRI-associated apathy in Alzheimer's disease: a case series. *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics.* 2022;14(4):51-3. doi: 10.14412/2074-2711-2022-4-51-53 (In Russ.)].

41. McCabe C, Mishor Z, Cowen PJ, Harmer CJ. Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biol Psychiatry.* 2010 Mar 1;67(5):439-45. doi: 10.1016/j.biopsych.2009.11.001

42. Hindmarch I. Cognitive toxicity of pharmacotherapeutic agents used in social anxiety disorder. *Int J Clin Pract.* 2009 Jul;63(7):1085-94. doi: 10.1111/j.1742-1241.2009.02085.x

43. Sowa-Kucma M, Panczyszyn-Trzewik P, Misztak P, et al. Vortioxetine: A review of the pharmacology and clinical profile of the novel antidepressant. *Pharmacol Rep.* 2017 Aug;69(4):595-601. doi: 10.1016/j.pharep.2017.01.030

44. Varrone A, Svenningsson P, Marklund P, et al. 5-HT1B receptor imaging and cognition: a positron emission tomography study in control subjects and Parkinson's disease patients. *Synapse*. 2015 Jul;69(7):365-74. doi: 10.1002/syn.21823

45. Arnsten AF, Lin CH, Van Dyck CH, Stanhope KJ. The effects of 5-HT3 receptor antagonists on cognitive performance in aged monkeys. *Neurobiol Aging.* 1997 Jan-Feb;18(1):21-8. doi: 10.1016/s0197-4580(96)00162-5

46. Meneses A. 5-HT7 receptor stimulation and blockade: a therapeutic paradox about memory formation and amnesia. *Front BehavNeurosci*. 2014 Jun 12;8:207. doi: 10.3389/fnbeh.2014.00207

47. Fagiolini A, Florea I, Loft H, Christensen MC. Effectiveness of Vortioxetine on Emotional Blunting in Patients with Major Depressive Disorder with inadequate response to SSRI/SNRI treatment. *J Affect Disord*. 2021 Mar 15;283:472-9. doi: 10.1016/j.jad.2020.11.106

48. McIntyre RS, Loft H, Christensen MC. Efficacy of Vortioxetine on Anhedonia: Results from a Pooled Analysis of Short-Term Studies in Patients with Major Depressive Disorder. *Neuropsychiatr Dis Treat.* 2021 Feb 22;17:575-85. doi: 10.2147/NDT.S296451

49. Baune BT, Brignone M, Larsen KG. A Network Meta-Analysis Comparing Effects of Various Antidepressant Classes on the Digit Symbol Substitution Test (DSST) as a Measure of Cognitive Dysfunction in Patients with Major Depressive Disorder. *Int J Neuropsychopharmacol.* 2018 Feb 1;21(2):97-107. doi: 10.1093/ijnp/pyx070

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