MEDICAL SCIENCE MONITOR

REVIEW ARTICLES

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 3643-3651
DOI: 10.12659/MSM.895156

Received: 2015.06.28
Accepted: 2015.08.14
Published: 2015.11.24

Influence of Pharmacotherapy on Cognitive Functions in Depression: A Review of the Literature

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Statistical Analysis C
Data Interpretation D
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Source of support: This study was supported by the funds of the Medical University of Łódź – grant No. 503/5-062-02/503-51-004 and 503/5-062-02/503-51-006

In addition to irregularities relating to the emotional sphere, the cognitive impairment in depression is a part of the clinical picture of this affective disorder. Some of the cognitive deficits may be associated with the severity of psychopathological symptoms of depression, while others are more established and can also occur during periods of remission. The participation in cognitive functioning of people with depression have a number of factors: the severity of symptoms, concurrent anxiety disorders, gender, age, education, duration of the disease, and number of previous episodes, as well as general somatic health or medication used. The pharmacological treatment may have varying impact on the different areas of cognition. Research on pharmacotherapy for depression and its impact on cognitive functioning continue and are very popular among clinicians and researchers. The relationship between antidepressants and cognitive abilities is always modulated by the type of depressive disorder, neurobiological factors, and demographic variables. This article presents a review of the studies relating to assessment of the effects of various antidepressants on cognitive abilities among patients with depression.

MeSH Keywords: Cognition • Depression • Drug Therapy

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/895156

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Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Affective disorders are a major cause of psychiatric hospitalization. It is estimated that approximately 5–15% of the general population suffers from depression and requires psychiatric or psychological intervention. Depression is now the fourth most serious public health problem in the world, affecting about 350 million people and is expected to be the most common mental disorder in 2020 [1]. In 2010, depression was the second leading cause of health problems resulting in inability to work [2]. According to the World Health Organization (WHO) [1], depression will become the worldwide leading cause of disability resulting from the state of health (after heart failure).

The most visible symptoms of depression relate to the emotional sphere, but they also have a strong impact on patients' cognitive abilities, which play a crucial role in their functioning. Cognitive functions are those mental activities that a person needs to gain a better understanding of the environment, to collect information about oneself and one's body, to analyze situations, draw conclusions, make appropriate decisions, and instigate action. The following processes constitute the cognitive abilities: perceptual processes (verdict, observations), attention, memory, and thought processes, as well as learning and language (speech and language) [3].

Cognitive impairment in depression is a part of the clinical picture of bipolar affective disorder. Some disorders may be associated with the severity of psychopathological symptoms of depression, while others are more established and can also occur during periods of remission [4–6]. Psychomotor speed decrease, attention impairment (vigilance and selectivity in particular), and spatial functions disorder, as well as learning and memorizing dysfunction, are all disorders that occur during the intensification of depression symptoms. Recently, more attention has been drawn to the phenomenon of hypofrontal depression, which is reflected in worse performance in most of the tests investigating various aspects of memory, and significantly worse functioning of patients with depression [7,8].

The effects on cognitive functioning of people with depression have a number of factors: the severity of symptoms, concurrent anxiety disorders, gender, age, education, duration of the disease, and a number of previous episodes, as well as general somatic health or medication used. Many authors emphasize that the apparent cognitive decline in depressed patients significantly improves in remission [9]. An improved mood, however, is not always accompanied by a consistent improvement in all cognitive functions [10], and that may cause deterioration in social functioning associated with the subjective feeling of incapability and difficulties in decision making [2]. The occurrence of cognitive deficits in affective disorders has increased research interest in whether the intensity of the changes in the pharmacotherapy of depression may be an early indicator of how fast the antidepressants work and their effectiveness [11].

In this publication we review some of the existing scientific reports on the impact of medication on the cognitive functioning of patients with depressive disorders. We used the literature primarily of the past 10 years, also using some older reports in which the key point was to evaluate the role of pharmacological treatment of depression in improvement of cognitive abilities.

Cognitive Impairment in Depression – Causes

The weakening of cognitive function among depressed patients may have a different character and intensity (from selective, specific, and benign changes to generalized and significantly intensified) depending on the severity of the symptoms of depression. A slight decrease in the efficiency of intellectual functioning, and thus cognitive functioning, is observed among patients with mild symptoms of depression. However, among patients diagnosed with severe depressive episodes, significant impairment of cognitive functioning is reported, although the patients still preserve a generally good intellectual level [3,12–14]. Furthermore, cognitive impairment, especially of episodic memory, is regarded as a potential risk factor for depressive disorders during a 3-year prognostic period [14].

Symptoms of bipolar disorder may also be a consequence of gradually increasing cognitive impairment, which entails difficulties in the organization of work and everyday life. This mostly applies to the concurrent depression and organic processes in the form of dementia. Depression can also be the beginning of a pathological dementia process, and its presence in neurological diseases exacerbates cognitive disorders. The presence of these 2 independent syndromes is of special importance due to the multiple problems with distinguishing dementia symptoms and depression symptoms [15]. Symptoms of depression are often incorrectly diagnosed as dementia, while depressive symptoms are often indicative of dementia. In a single patient these 2 syndromes can also occur independently [14].

In clinical practice, apart from the group of elderly patients with depression and depression in patients with dementia, there are also patients with depression who were diagnosed with mild cognitive impairment (MCI) [13,16]. This impairment relates to the clinical condition in which patients have worse memory disorders than expected in the course of a normal aging, but they do not reach the severity that would fit the diagnosis of dementia, and their functioning is not significantly impaired [17].

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Studies estimate the occurrence of depression in patients with MCI at 12 to 20% [18–20]. Little is known about the course of depression in patients with MCI. There are conflicting reports relating to the occurrence of depression with a severe cognitive impairment. Most studies show that the occurrence of depression is higher in patients with MCI than in healthy elderly, and less than in those with dementia [18]. Further studies are needed to assess the course of depression in patients with MCI to clarify the relationship between affective and cognitive symptoms, and to establish whether the depression in patients with MCI is a risk factor for developing dementia [13].

In recent years, cognitive impairment has been of special interest to clinicians, primarily due to the better understanding of its etiopathogenesis and the importance it has in the course of mental illness, its clinical picture, and prognosis. Recent research has shown that not only the etiopathogenesis of diseases such as schizophrenia, but also the affective disorders, play an important role in the development of abnormalities in the brain and its functional organization. It was also found that neural connections linking individual brain centers do not work properly in people with mental disorders, which is the main reason for different functional organization of the brain, and thus the changes in cognitive functions such as information processing, memory, attention processes, and executive functions. Many factors that lead to abnormalities in the brain development were distinguished. The most important among these are genetic abnormalities during pregnancy and childbirth (especially hypoxia, maternal disease, and perinatal trauma), as well as mental stress in the early stages of child development [21].

While cognitive impairment in depression, together with the symptoms of depression due to the medical treatment, may improve, it had been observed that some of the cognitive deficits persist despite periods of remission [2]. During several years-long studies in patients with recurrent major depressive episodes, it had been observed that the number of complaints concerning worsened cognitive performance reached 94% during acute episodes of depression, and remained at 44% despite a full or partial remission of symptoms as a result of pharmacotherapy [22]. In comparison with the healthy patients, the depressed patients who meet the criteria for remission of symptoms continue to report problems with immediate memory, attention [23], and speed of information processing [24], as well as with the executive functions [25,26]. Some researchers explain these persistent deficits in cognitive abilities as psychosocial problems in the psychosocial functioning, which are present despite the receded symptoms of depression.

Cognitive deficits are also observed in patients with diagnosed bipolar disorder (BD). Most studies of cognitive function in bipolar disorder refer to the period of depression. In studies conducted in the 1990s, patients diagnosed with unipolar affective disorder (UD) were compared with patients diagnosed with bipolar disorder and both groups were examined during the episode of depression. It has been found that both groups displayed similar psychomotor disorders [27], attention (especially vigilance) disorders, and decreased reaction time and visuospatial function disorder [28]. A Polish study [7] has shown that, compared with patients diagnosed with unipolar affective disorder, patients with bipolar disorder have much larger deficits in working memory and executive functions during period of severe depressive symptoms (assessed using the Wisconsin Card Sorting Test, Trail Making Test, and Stroop Test). Compared with patients with unipolar affective disorder, who were also tested, the patients with bipolar disorder achieved far worse results, especially in the WCST, which showed increased perseverative errors and a smaller number of correctly arranged categories. This reflects the reduced cognitive flexibility and poor thinking efficiency when compared with patients with unipolar affective disorder. More severe frontal dysfunctions in depression are associated with hypofrontality phenomenon occurring during this period, which relates to the reduction in prefrontal cortex activity as established in neuroimaging [29,30].

Antidepressants and Cognitive Functions in Depression

The history of the pharmacological treatment of depression dates back to the early 1950s. A number of chemical compounds with antidepressant effects were registered as useful in health care in the last 50 years [31]. Use of tricyclic antidepressants (TCAs) began in 1955 when clinical trials on the efficacy of imipramine in the treatment of schizophrenia were conducted. Careful analysis of clinical trial documentation protocols indicated that imipramine can improve low mood. Studies on the pharmacological mechanism of tricyclic antidepressant activity have shown that these drugs inhibit the reuptake of norepinephrine and serotonin, which can lead to increased amounts of these neurotransmitters in the synapses of the central nervous system. This corresponded with contemporary pathogenetic biological concepts of depression, according to which this disease is a deficiency of these neurotransmitters, and the action of antidepressants may also include changes in the amount and activity of neurotransmitter receptors. The postulated therapeutic action of almost all antidepressants introduced to psychiatric treatment by the end of the 1990s was based upon modifications to the serotonergic neurotransmitter, noradrenaline, or both. Present-day clinicians aim to make optimal use of registered, available antidepressants through the establishment of more precise rules for their selection for individual patients and elucidate the prognostic value of the effectiveness of pharmacological treatment in depression [32].

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In psychiatry, cognitive impairment is considered to be an important goal of pharmacological treatment. This approach stems from a change in perception of mental illness primarily through the prism of acute symptoms, such as positive or affective symptoms. It turned out that the cognitive status depends largely on the patient's psychosocial functioning, as well as their active participation in the treatment process. Pharmacological treatment may have varying effects on different areas of cognition, although new-generation antipsychotics and antidepressants can improve cognitive function. In the assessment of cognitive dysfunction, neuropsychological tests are often used, including modern computer programs containing neurocognitive batteries of tests that allow for an objective assessment of the efficiency of different areas of cognition, such as memory, attention, executive, spatial, or verbal functions. On this basis, the neuropsychological profile of the patient can be determined, which is an important tool for planning treatment and rehabilitation, as well as monitoring the effectiveness of therapy [21].

The effect of antidepressants on cognitive processes in patients with depressive disorders is multifaceted. As evidenced by the results of numerous studies [33], drugs with anticholinergic effect (e.g., tricyclic antidepressants) may adversely affect cognitive functions. Drugs without the anticholinergic effect do not affect cognitive functions, including selective serotonin reuptake inhibitors (SSRIs) [34], moclobemide [35], tianeptine [36], and venlafaxine [37]. It has been shown that tricyclic antidepressants can impair cognitive function in healthy individuals [38] and in patients with depression [35,39]. As mentioned above, this is mainly due to their anticholinergic effect [40]. There was, however, no negative effect on cognitive function in healthy individuals given a single dose of citalopram, a selective serotonin reuptake inhibitor (SSRIs) [41] and moclobemide, a selective and reversible inhibitor of monoamine oxidase (MAO) [42], or mirtazapine, a noradrenergic and specific serotonergic antidepressant (NASSAs, nonadrenergic, and specific serotoninergic antidepressant), increasing serotonergic and noradrenergic neurotransmission and blocking serotonergic receptors 5-HT2 and 5-HT3 [43].

The sample studies included 1780 subjects aged 70 and older, and are examples of this theory. Data on socio-demographic characteristics, medical history and drug use were collected using a standardized questionnaire. Cognitive performance was assessed using the following neuropsychological tests: the Mini-Mental State Examination (MMSE) which evaluates global cognitive functioning, the Benton Visual Retention Test (BVRT) which assesses immediate visual memory, and the Isaacs' Set Test (IST) which assesses verbal fluency. About 13.7% of the subjects used at least one drug with anticholinergic properties. In multivariate analyses, the use of these drugs was significantly associated with low performance in the BVRT and in the IST. The association found with low performance in the MMSE was barely statistically significant. These findings suggest that the use of drugs with anticholinergic properties is associated with low cognitive performance among community-dwelling elderly people [33].

Some antidepressants (e.g., escitalopram) may improve the efficiency of cognitive processes [44]. In the present 4-week, single-center, randomized, open-label trial we investigated the antidepressive effects of escitalopram, an SSRI, in 18 elderly depressed patients (mean age 76.2±1.8 years) compared to 22 healthy age-matched controls (mean age 76.9±1.8 years). Affective and cognitive symptoms were assessed using the Geriatric Depression Scale (GDS), Mini-Mental State Examination (MMSE), and a face portrait recognition test to assess memory of happy and angry faces. Depressed patients prior to treatment had markedly reduced memory performance. Treatment with escitalopram significantly improved affective and cognitive symptoms. Furthermore, escitalopram treatment improved memory of negative facial stimuli. Control subjects confirmed the well- established memory bias favoring recognition of identities acquired with happy expressions. Importantly, this bias was absent in depressed patients prior to, but also after, treatment. In conclusion, escitalopram, even after a relatively short treatment period, was effective in treating depression in the elderly and may help improve cognitive performance for social stimuli [44].

It should be noted that there is a small number of studies that attempted to assess the impact of long-term treatment with antidepressants on cognitive function. A study conducted by Gorenstein et al. [45], which assessed cognitive performance in patients with depressive disorders who were treated for at least 6 months with different antidepressants (imipramine, clomipramine, fluoxetine and sertraline), showed that the degree of severity of a range of cognitive functions studied was small and their impact on the clinical condition remains questionable. Psychomotor performance of patients taking imipramine was worse than that of controls in inserting pins and in a visual reaction time task on the performance of tapping various controls according to dose/weight for patients taking clomipramine and fluoxetine. For memory tests, differences between patients taking sertraline and controls were observed in the number of digits and words recalled. The difference between patients and controls varied according to dose/weight on the number of familiar words correctly completed for patients taking clomipramine and on backward digit span for those taking sertraline. Metamemory was worse in all patient groups irrespective of patient clinical state [45].

Some clinicians [11,46,47] believe that antidepressant drugs do not have a direct beneficial effect on cognitive processes and may even make them worse. The observed improvement

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is probably mainly due to decreased symptoms of depression, such as psychomotor retardation, increased motivation for solving tests, and the effect of cholinergic mechanisms of these drugs [46,47].

A study by Pużyński et al. [11] in a group of 43 patients with a diagnosed depressive syndrome in bipolar disorder and during the course of treatment with an antidepressant showed no difference in the effect on cognitive processes of classic antidepressants (first-generation) and new-generation drugs (second-generation). The study involved 22 patients treated with tricyclic antidepressants, 9 with selective inhibitors of serotonin uptake, and the remainder with venlafaxine, mianserin, and tianeptine. All patients underwent psychological testing using the Vienna Test System (a simple reaction test, multiple choice test, vigilance test, and PERSEV test) and clinical status was measured on the MADRS scale (Montgomery-Asberg Depression Rating Scale). Out of the total group, 8 responded positively to the treatment on day 28, as well as the subgroup treated with second-generation antidepressants. The authors found no significant improvement in cognitive processes during the pharmacotherapy of depression in subsequent studies between days 1 and 28 of pharmacotherapy. It has not been shown that the improvement of clinical condition (significant reduction in symptoms of depression measured by questionnaires MADRS) is followed by a significant improvement in terms of cognitive processes. According to Pużyński et al. [11], changes in a range of cognitive functions are not an early predictor of effectiveness of the medication. Lack of improvement in the first 3 weeks of treatment (measured with the results of MADRS) does not mean there was no improvement on day 28 of the treatment. Psychological tests used to assess cognitive regression during the pharmacotherapy of depression in the first four weeks of treatment proved to be insensitive [11].

Tsourtos [47] et al. compared 20 unmedicated unipolar depressed inpatients with 19 medicated depressed inpatients and 20 age-, sex-, and verbal IQ-matched controls on inspection time (IT), a measure of speed of information processing that does not require rapid motor response. They also examined the relationship between IT and current mood and length of depressive illness. Unmedicated depressed patients showed slowing of information processing speed when compared to medicated depressed patients and controls. The latter 2 groups were not significantly different from each other. Slowing of IT was not associated with current mood, but was negatively correlated with length of illness since first episode. No differences in IT were found between patients receiving medication with anticholinergic effects and patients receiving medication with no anticholinergic effects [47].

A number of pathologies have been suggested as the basis of neuropsychological impairments in depression, including medial temporal and frontostriatal dysfunction. Hypothalamic-pituitary-adrenal (HPA) axis abnormalities have also been reported to play a role. There is some suggestion that the mood-alleviating effects of antidepressants are in part mediated by effects on corticosteroidal systems. While the neurobiological basis of speed of information processing appears to involve cholinergic systems, other neuromodulatory systems such as those involving glucocorticoids may play some role. In conclusion, this study showed that information processing speed is slowed in young, unmedicated, depressed patients. Cognitive slowing should thus be considered in future studies of the neuropsychological profile of depression, and IT is a quick, simple, and easily administered measure. Medication status should also be considered when examining cognitive function in depression [47].

Furthermore, some authors suggests that cognitive impairment in depression may be related to the weakening of neurogenesis, mainly in the area of the hippocampus, which may be a reflection of cognitive function, particularly memory and learning. This problem in patients with brain damage of various etiologies can thus be particularly important. As shown, improvement of cognitive function following treatment with antidepressants may reflect favorable changes in neuroplasticity [48,49]. These findings open the possibility that antidepressants might improve hippocampal function under conditions of impaired stress hormone regulation, and that these drugs might in part act through this mechanism to attenuate cognitive deficiency in disorders such as depression [48]. Benefit and side effects are reported for Parkinson's disease, Alzheimer's dementia, depression syndrome, and panic disorders. The preclinical and clinical effects of selegiline with regard to neuroprotection are highlighted and the conclusion is drawn that there is good evidence for a clinical neuroprotective capacity based on the assumption that the 50% recovery of MAO-B is obtained after a 10-day withdrawal of selegiline. There is also a focus on selegilines metabolism to amphetamine and methamphetamine. Developments in MAO-I research are discussed in detail, including moclobemide, lazabemide, rasagiline. Interactions of MAO-Is with tricyclics and serotonin selective reuptake inhibitors (SSRIs) are described, as there is mention of interactions of MAO-Is with other compounds in general [49].

Cognitive deficits in depressive disorders are confirmed in many studies [29,50]. Still, the relationship between the severity and type of mood disorders and the degree of cognitive impairment of the function remains unresolved. Factors that may affect it are among the most common to the neurobiological, demographic, and clinical course of the disease [51]. Pharmacotherapy has a significant impact on cognitive functioning in this group of patients. Constant et al. [52] and Schrijvers et al. [53] found that sertraline treatment had a positive effect on psychomotor retardation as well as attention and executive

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functions in patients with depression. The assessment of attention and memory functions during a depressive episode and during remission [54] revealed that partial recovery of cognitive function can be achieved in patients treated with fluoxetine and reboxetine. Another study of duloxetine and escitalopram noted that they effectively improved cognitive deficits in terms of concentration and executive functions [55], as well as memory and speed of thought processes [56]. Also, 3-month tianeptine treatment was reported to lead to improved short-term memory and attention in patients with mild to moderate depression [57].

Slightly older scientific reports indicate that in the 1990s the only antidepressant using selective norepinephrine reuptake inhibitors, called reboxetine, had been introduced. Clinical efficacy and somatic tolerance of reboxetine were comparable with SSRIs. In addition to activity stimulation and motivation, not causing sexual dysfunction and having mild adverse effects, the main advantage arising from the selectivity of action of reboxetine is the beneficial effect on cognitive function [58,59]. However, among patients with attention deficit hyperactivity, atomoxetine, a drug using norepinephrine reuptake inhibitors, demonstrated high efficacy [31].

Another antidepressant worth noting is registered in Poland as moclobemide, and is highly popular. Its beneficial procognitive effect has been observed in patients with recurrent major depressive episodes among patients with depression in the elderly and patients with dementia. Moclobemide, a new-generation antidepressant, is a selective and reversible inhibitor of monoamine oxidase type A (MAO-A). Moclobemide's pharmacological mechanism of action involves increasing the level of serotonin, norepinephrine, and dopamine in the central nervous system. Due to a different profile of pharmacological action compared with tricyclic antidepressants (no anticholinergic effects or sedation), moclobemide may have beneficial effects on cognitive functions [60].

A study conducted among the 23 patients with depression, based on changes in the brain vessels, used cerebrovascular clinical and neuropsychological memory examinations before and after 3 months of treatment with moclobemide. Moclobemide treatment resulted in improvement in the symptoms of depression and cognitive functions. In the cited work, after 3 months of treatment with moclobemide, a significant improvement in performance in neuropsychological tests except of the TMT B test assessing visuospatial functions of memory, was observed in patients with vascular depression. This may indicate that the visuospatial functions disorder, including the aspect of visual working memory, is a deficit that is well-established and to a lesser extent improved after treatment in these patients. Of significance here may be advantageous, but specific, activity of moclobemide on cognitive functions [60].

Recent research into the effects of antidepressants containing the active substance vortioxetine on cognitive ability showed an improvement of attention, memory, and flexibility of the thinking process [61,62]. The effect of these drugs is based on the modulation and stimulating serotonergic transduction of many neurotransmitters in a complex mechanism of action: they inhibit the reuptake of serotonin and are a partial agonist of the serotonin 5HT1A and 5HT1B, as well as the antagonist of receptors 5HT1D and 5HT7. The authors of these studies link the improvement of cognitive function following treatment with the vortioxetine agents with the multimodality of its effects on 5-HT receptors, particularly in the areas of the prefrontal cortex [63]. The clinical trials, which compared patients treated over a period of 8 weeks with Vortioxetine and placebo-treated patients, showed significant improvement in cognitive functions relating to attention, memory, executive function, and speed of information processing in the group of patients taking antidepressant medication. This improvement was parallel with the improvement in the symptoms of depression [64].

Some clinicians believe that pharmacotherapy combined with improves cognitive functioning in depression. Klasik et al. [65] compared the effect of therapy type on cognitive functioning improvement among 60 patients treated for 8 weeks for depressive disorders and a diagnosed moderate depressive episode. The patients were divided into 3 groups of 20, depending on the type of therapy, to which they were subjected during hospitalization. The first group participated only in psychodynamic psychotherapy. The second group participated in psychotherapy and also received an antidepressant called sertraline. The third group of patients only received sertraline. The authors assessed the change in the field of cognitive abilities relating to short-term memory and concentration with the neuropsychological performance test. After 8 weeks of therapy, the group that was subjected to a combination of therapies, which was a pharmacotherapy and psychotherapy, received best results.

According to Harmer et al. [66–68] and Arnone et al. [69] the effect of antidepressants on cognitive functions in the individuals treated is present from the start of administration. Repeated experience interpreted in a positive context (or at least no negative interference of interpretation characteristic to depression) provides patients with new information about themselves and evoke positive emotional associations. A process different from the previous interpretation follows, and the stage of redirecting person with symptoms of depression to a new way of experiencing and interpreting emotional events starts. Neuroplasticity processes which are enhanced by the administration of antidepressants may be of an importance in this context. The impact of this group of drugs on neuroplasticity, and thus on the improvement of the memory processes

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may further enhance processes of learning occurring during treatment [67]. According to this author [67], qualitative changes in information processing may explain the improvement in such a complex phenomenon as depression, because the controllers of remarks, which are the executive functions, decide how they perceive emotional stimuli. Antidepressant pharmacotherapy reduces the focus on the negative stimuli and the brain opens up again to a positive emotional tone and positive interpretations of experiences (positive cognitive patterns). Change in receiving the stimulus, resulting in the reduction of negative impacts and strengthening of positive emotions, may consequently lead to changes in the severity of depression or even for the depression to cease.

These authors believe delay in noticeable improvement in mood is considered equivalent to the delayed effects of antidepressants. The studies of Harmer [70,71] and Harmer et al. [67], devoted to the cognitive neuropsychological business model of the effect of antidepressants, undermine the belief in the delayed onset of the drug's effects in this class, but do not deny the fact that improvement in mood occurs in patients taking the medicine regularly for a significant amount of time. According to Harmer [67,68], onset of antidepressants effects occurs rapidly, within a few hours following their administration. However, they initially have an impact on the processing of emotional information, and only at a later stage, and as such may indirectly influence the improvement of mood [72].

Conclusions

Scientific reports in which different groups of antidepressants are compared to placebo dominate in the area of research on the effects of pharmacotherapy of depression on cognitive functioning. There is less research on the comparison of therapies using different group of drugs, as well as studies evaluating the effects of long-term treatment on cognitive function for depression [2,73,74]. A large part of the clinical evaluation of studies is also associated with the impact of pharmacotherapy on improvement of cognitive functions in elderly patients with depression, where cognitive deficits are more noticeable in the study of neuropsychological [75,76]. Studies in which the contribution of antidepressant treatment in improving various aspects of cognitive processes in patients with depression is estimated may also be flawed due to methodological errors resulting from, inter alia, ignoring the effect of learning, while assessing the ability of patients twice by psychological tests.

Clinical trial researchers do not always accurately define cognitive functions, which are assessed during the description of the impact of pharmacotherapy on this sphere of mental functioning in patients with depression. Most frequently, in trials cited in this study, cognitive functions were analyzed in relation to psychometric tests by which depressive patients are diagnosed. Therefore, the conclusions reached are presented in relation to various mental capacities, most frequently concentration of attention, executive function, and memory processes, because such "features" of cognitive functions are tangible and amenable to psychological testing.

Thus, another aspect of formulating proposals for the assessment of cognitive functioning of patients with depression under the influence of medication is revealed. The effectiveness of treatment is dependent upon patient age. Natural cognitive impairments associated with the aging process in the elderly who are also treated for depression will present a different clinical picture as a result of medication compared with that of younger patients. This also applies to patients with diseases of the CNS. Therefore, these results are not comparable or equable.

The study area dedicated to the pharmacotherapy of depression and its impact on cognitive functioning is active and popular among clinicians. Great interest can be observed in studies of neurobiological substrates of cognitive functioning of patients with depression and thus shaping of these functions under the influence of drugs. However, it must be realized that the link between antidepressants and cognitive abilities is always modulated by the type of depressive disorder, neurobiological factors, and demographic variables.

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