Cognitive dysfunctions in depression – underestimated symptom or a new dimension?

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Summary

Cognitive deficits constitute an integral part of clinical picture of depression, but often not enough attention has been paid to these deficits, mainly because of the presumption that they are secondary to typical depressive symptoms. It is considered that cognitive impairment is one of the main causes of depressive patients’ poor functioning. Cognitive deficits are observed already in the first depressive episode. They may correlate with the severity of depression, with the patient’s age and level of education. They may persist regardless of the improvement of depression during treatment. Cognitive deficits in depression are divided into “cold” which are not related to emotions, and “hot” – related to emotions. The “cold” deficits are supposed not to respond to antidepressants and seem to persist even in clinical remission. Vortioxetine is a novel antidepressant with a unique mechanism of action: it acts through the serotonin reuptake inhibition, but works also as 5HT₁A agonist, as well as partial agonist of the 5HT₁B receptor and antagonist of the 5HT₁D, 5HT₃, and 5HT₇ receptors. In preclinical studies vortioxetine showed the normalization of serotoninergic, noradrenergic, and dopaminergic transmission, additionally through GABA-ergic and glutaminergic effects. It has antidepressive property, it proved to be efficacious in various types of depression (severe, depression with anxiety, and depression in elderly); it also proved to be efficacious in those patients who did not respond sufficiently to SSRIs and SNRIs treatment. Vortioxetine is also beneficial for cognitive functions in depressed patients.

Key words: depression, cognitive deficits, vortioxetine

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Introduction

The clinical picture of depression is commonly known and the symptoms are relatively easy to recognise. We are currently witnessing a significant rise in numbers of reported cases of depression as well as an increased demand for its assessment and treatment. This is partly due to the considerably improved public awareness of both causes of depression and the available treatment methods. Nonetheless, parallel to the widening access to treatment, there is also an increased risk of inadequate therapeutic response. This term comprises the insufficient abatement of objectively assessed depressive symptoms as well as the subjective lack of improvement during and after treatment. It can be explained by both inherent limitations of psychiatric pharmacotherapy, and treatment not being properly tailored to patient’s needs.

Both objectively and subjectively unsatisfactory therapeutic response can, among others, stem from clinicians remaining excessively focused on the typical manifestations of depression, concurrently overlooking symptoms less distinctive, but equally crucial for patient’s functioning.

Impaired cognitive functioning is a common, although, frequently underestimated phenomenon in patients with depression. The typical symptoms, including slowing, impairment of executive functions and working memory [1] significantly contribute to the patients’ deteriorated functioning, and may prolong their malaise even after the resolution of typical depressive symptoms [2, 3]. They also play an important role in diminishing the capacity to perform the activities of daily living, thus hindering psychosocial activity and negatively affecting patients’ everyday functioning [4]. The cognitive deficits often tend to be dismissed as secondary to the typical symptoms of depression, like sadness, gloom, psychomotor slowing, anhedonia, etc. Apart from being merely cross-linked with other clinical signs, they can, however, directly result from depression pathogenetic factors (for example genetic) [5], therefore representing a primary rather than utterly secondary quality. On the other hand, the cognitive dysfunctions can be alleviated with antidepressant treatment, with some antidepressant drugs being apparently more effective in this regard than others [6].

Types and areas of cognitive dysfunction in depression

Two major types of cognitive dysfunction can be identified in depressive disorders: cognitive biases, understood as distorted information processing leading to depressive thinking errors, and cognitive deficits encompassing areas such as attention, memory and learning, executive functions and drive [7].

Distorted depressive cognitive patterns are the result of neurophysiologically determined cognitive processes and their deficits as well as personal life experiences and environmental influences [8]. They are usually rigid, unrealistic, hardly susceptible to the influence of everyday experiences, hence dysfunctional. Depressive thinking is
dominated by involuntarily emerging negative content about oneself, the surrounding world and the future, while defective information processing allows this “depressive philosophy” to retain a semblance of credibility to the patient [9]. Such distorted processing of information is interrelated with other clinical symptoms of depression: emotional, motivational, behavioural, somatic [10].

Cognitive impairment is estimated to occur in 94% of patients in the acute phase of depression, but persist in as many as 44% of patients in remission [11]. Moreover, with subsequent depressive episodes the cognitive deficits are expected to accrue [12].

Depressive cognitive distortions are closely associated with some cognitive functions, such as attention, memory, executive functions. For example, attention in depression is focused particularly on negative stimuli [13], and individuals suffering from depression more efficiently memorise negative information [14-16]. The cognitive deficits observed in depression can be assumed to further impair reality testing and sustain distorted thinking patterns. The areas of cognitive deficits typical for depression are presented in table 1.

<table>
<thead>
<tr>
<th>Area of cognitive deficit</th>
<th>Description</th>
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<tbody>
<tr>
<td>Attention</td>
<td>The ability to focus and sustain attention</td>
</tr>
<tr>
<td>Memory/learning</td>
<td>Episodic memory (memory of events, autobiography) Verbal memory, visuospatial memory, learning</td>
</tr>
<tr>
<td>Executive functions</td>
<td>The ability to monitor and regulate cognitive processes with the use of attention and planning; working memory and mental flexibility; initiating and monitoring task performance; multitasking; decision making</td>
</tr>
<tr>
<td>Drive</td>
<td>The speed with which the brain controls the execution of tasks by the body</td>
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**Cognitive dysfunction in recurrent depression – underestimated dimension?**

The diagnostic criteria for depression, both in ICD-10 and DSM-5, take into consideration the symptoms associated with cognitive impairment. DSM-5 lists diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or observed by others), and psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) [17], while the ICD-10 – reduced concentration and attention, and a definite psychomotor retardation or agitation [18]. Nevertheless, cognitive dysfunctions in depression are too rarely recognised and subject to therapeutic interventions. In part, this is due to being rather sought out in the elderly, therefore often overlooked in younger adults. Furthermore, cognitive impairments are often not considered one of the essential dimensions of depression which leads to other symptoms being prioritised in clinical practice (for example, depressed mood, anhedonia,
suicidal ideations). Another source of concerns is the limited access to psychological and neuropsychological diagnostics, hence the difficulty in objective assessment of various dimensions of cognitive deficits. The available psychometric instruments are mainly employed for research purposes (Table 2)

Table 2. Methods of assessing various areas of cognition [19]

<table>
<thead>
<tr>
<th>Area of cognitive functioning</th>
<th>Tests</th>
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<tbody>
<tr>
<td>Psychomotor drive</td>
<td>Trail Making Test A - TMT A, Digit Symbol Coding Modalities Test</td>
</tr>
<tr>
<td>Attention</td>
<td>Spatial Span (SSP), Continuous Performance Test</td>
</tr>
<tr>
<td>Working memory</td>
<td>Wechsler Adult Intelligence Scale (WAIS) – backward digit-span,</td>
</tr>
<tr>
<td></td>
<td>Spatial Span (SSP), Sternberg Test</td>
</tr>
<tr>
<td>Visual learning and visual memory</td>
<td>Wechsler Memory Scale (WMS) – Visual Reproduction subscales 1 &amp; 2, Rey Complex Figure Test</td>
</tr>
<tr>
<td>Alternating attention (set-shifting)</td>
<td>Trail Making Test B - TMT B</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Tests of semantic and category fluency</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>Wisconsin Card Sorting Test (WCST)</td>
</tr>
<tr>
<td>Planning</td>
<td>Tower of London (TOL), Stockings of Cambridge (SOC)</td>
</tr>
</tbody>
</table>

It seems thought-provoking that the issue of cognitive functioning in depression has only recently gained the due interest of researchers. The bulk of the available literature comprises small cross-sectional studies comparing patients to healthy volunteers. The patient groups have been heterogeneous in terms of depression subtype, symptom severity, number of episodes, and applied treatment, the results are, therefore inconsistent and ambiguous [20]. Despite those limitations, the studies suggest that specific cognitive deficits are already present in first episode of depression. Greater deficits were associated with the severity of depressive symptoms, inpatient treatment, age and level of education of the study participants [19].

Cognitive impairment appears not to be exclusively related to the ongoing depression. In some patients, it persists regardless of a significant improvement in other depressive symptoms during treatment. This applies in particular to the domains of attention, learning, verbal memory, and executive functions [21]. Such enduring deficits significantly impoverish the psychosocial functioning of the patients. Moreover, they are inferred to increase the risk of relapse and disease recurrence [22, 23].

In patients with recurrent depression, cognitive dysfunctions accrue with the number of subsequent illness episodes and the cumulative time of remaining depressed, possibly indicating that depression is “toxic” to the brain [24-26]. Such hypothesis
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is corroborated by amassing evidence that recurrent depression is a risk factor for Alzheimer’s dementia in older age [25]. This, in principle (but not exclusively) relates to late-onset depression [27, 28]. In this context, it should be borne in mind that depression is often comorbid with somatic disorders, such as cardiovascular diseases, stroke, diabetes, cancer, which have a negative impact on cognitive functions as well [29].

In light of the aforementioned data, it seems justifiable to conclude that improving the cognitive dimension of depression should constitute an important therapeutic target – even more so given the patient’s subjective experience of depression-related cognitive deficits can be very tedious. The subjective experience of cognitive deficits in depression is illustrated in a book by William Styron “Darkness Visible”.

“...And zombie like halfway through the dinner, I lost the Del Duca prize check for $25,000. Having tucked the check in the inside breast pocket of my jacket, I let my hand stray idly to that place and realized that it was gone. Did I “intend” to lose the money? Recently I had been deeply bothered that I was not deserving of the prize.” [30]

One of the major questions regarding cognitive impairment in depression is not only its impact on shaping the clinical picture, but also the temporal relationship of cognitive dysfunctions and depression. Do these abnormalities precede the occurrence of a full clinical picture of depression as is often suggested? Can the incomplete, unsatisfactory response to antidepressant treatment be explained by, among others, resistance of cognitive deficits to treatment [1]? Another issue is that, apart from depression, cognitive deficits are present in other mental disorders, for example schizophrenia. An intriguing question therefore arises of whether they reflect an underlying malfunction of particular neural circuits, not specific for individual clinical entities [3], rather than show a merely clinical association with certain psychopathological symptoms.

Antidepressant medication and cognitive function – current state of the art and future directions

At present, cognitive deficits in depression are typically broken down into those associated with “cold” cognition (not related to emotions) and “hot” cognition (associated with emotions). The “cold” deficits are considered not to subside during remission, and, when persistent, are associated with poorer response to antidepressant therapy. They seem unrelated to a motivational factor and are evaluated in tests utilizing emotionally neutral stimuli, such as the Wisconsin Card Sorting Test or California Verbal Test. The emotionally conditioned “hot” cognition is derived from negative prejudices and a faster response to negative stimuli. The “hot” and “cold” cognitions are not independent of one another – negative attitudes may adversely affect “cold” cognition [31].
Contemporary neuroimaging research links “cold” cognition to structural changes in dorsolateral prefrontal cortex (DLPFC), while “hot” cognition is typically associated with structural abnormalities in orbitofrontal cortex (OFC) and the hippocampus [31]. The presence of cognitive impairment in depressed patients compared to the control group has been demonstrated in numerous studies, including meta-analyses [32]. In a recent meta-analysis, deficits have been observed in all cognitive domains, particularly in verbal fluency (Effect Size – ES = 0.59), cognitive flexibility (ES = 0.53), visual memory (ES = 0.53), the psychomotor speed (ES = 0.48), and attention (ES = 0.36) [33]. In another up-to-date study, depressed patients performed significantly worse than healthy volunteers in the areas of executive functions (for example, spatial working memory), memory and attention [34]. Research on “hot” cognition in untreated patients with depression indicated significantly longer reaction times to positive stimuli and significantly shorter to negative stimuli compared with controls [35]. The clinical significance of cognitive dysfunctions severity during depressive episode [36], as well as their fairly minor reduction in response to antidepressant therapy [37] have also been confirmed in depressed elderly.

The information presented above should modify the cognitive theory of depression originally postulated by Aaron Beck. Combined data on neurostructural changes in depression and subsequent neurotransmitter abnormalities allows us to assume that there is an entirely biological substrate determining the preference for negative stimuli and the development of “depressive thinking styles” which are in turn classified as depressive symptoms, such as the “diminished ability to think or concentrate.” (DSM-5) [17]

Studies on the prevalence of depression in patients with left-sided stroke provide another source of insight into the significance of structural damage and associated cognitive impairment for depression. Compared to right-sided stroke, depressive symptoms turned out to be more frequent and cognitive dysfunction more severe, moreover, the language deficits were predictive of post-stroke depression [38]. In another study, however, no effect of age, gender, and depression severity on cognitive deficits in depression was observed, possibly indicating that cognitive symptoms can be considered the basis for depression development rather than its epiphenomenon [39]. Genetic and neuroimaging studies also highlight the importance of genetic polymorphisms in the BDNF (Brain-Derived Neurotrophic Factor) gene for the manifestation of cognitive deficits in depression [40].

The evaluation of cognitive impairment in depression, apart from typical psychometric tests for the assessment of “cold” cognition, and ICD-10 [18] and DSM-5 [17] diagnostic criteria for depression, should also include interpretation of responses to questions such as: Do you struggle making everyday decisions?; Do you have problems with understanding what you read, what you see on TV, or what you talk about?; Do you lose things or forget about them?; Do you have problems with initiating, planning and completing tasks?; Does all of this trouble you in your daily life? This principle underlies the highly accurate 6-item tool for the early diagnosis of cognitive impair-
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As mentioned above, the influence of antidepressant treatment on “cold” cognitive deficits is rather limited. Other therapeutic methods potentially targeting those symptoms include transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) and deep brain stimulation (DBS) of the anterior cingulate cortex (ACC) [31].

Vortioxetine – new antidepressant drug in clinical trials

Vortioxetine is a novel medication with a unique combination of both antidepressant and “procognitive” properties. It acts not only through the serotonin reuptake inhibition, but also as 5HT1A agonist, 5HT1B partial agonist, and antagonist of the 5HT1D, 5HT2 and 5HT7 receptors [42]. In preclinical studies on animal models vortioxetine significantly normalised the serotonergic, noradrenergic, and dopaminergic transmissions. Furthermore, through additional GABA-ergic and glutamatergic effects not only did it exert an antidepressant effect, but also bolstered cognitive functions, particularly attention [42].

As yet, SNRI and SSRI antidepressants have not been proven to exert a clinically significant procognitive effect. For example, duloxetine – a potent SNRI medication (thus acting on both serotonergic and noradrenergic systems) significantly improved mood in elderly patients with major depression (compared with placebo), its influence on “cold” cognitive functions, however, was notably lower [43]. A study comparing the antidepressant efficacy of vortioxetine and duloxetine demonstrated that in the subgroup of elderly patients (aged 65 and older) both drugs had a positive effect on cognitive functions; notwithstanding, after further statistical analyses it can be argued that in vortioxetine group it was the consequence of its direct influence on cognition rather than purely a spin-off of its antidepressant action [44]. The antidepressant effectiveness of both drugs (5 mg vortioxetine and 60 mg duloxetine daily) in this study was comparable [44]. In another trial comparing the effects of 10 mg vortioxetine, 30 mg mirtazapine, and placebo on cognitive functions in healthy volunteers, no negative influence of vortioxetine was observed, as opposed to the initial stage of using mirtazapine [45]. In a recent study on cognitive functions (assessed with DSST and RVLT tests) in depressed adults (18-65 years of age) during the 8-week treatment with 10 mg or 20 mg of vortioxetine versus placebo (group size ratio 1:1:1), a statistically significant improvement in both cognitive functions and depressive symptoms was observed in both vortioxetine groups compared to placebo [46].

In a meta-analysis of 11 short-term studies a statistically significant reduction in depressive symptoms was confirmed for each of the administered doses of vortio-
etine (from 5 mg to 20 mg per day) [42]. In a medium-term trial comparing the risk of depressive relapse for vortioxetine versus placebo, after 12 weeks of active treatment a positive response was observed in 76% of patients, while remission in 69% of patients. After 36 weeks, the risk of relapse was twice lower in the vortioxetine group compared to placebo (13% vs 26%, p < 0.0013) [47]. In a study comparing the antidepressant efficacy of vortioxetine (5 mg daily and 10 mg per day), venlafaxine (225 mg daily) and placebo, quicker onset of antidepressant effect of vortioxetine (compared to venlafaxine) and comparable efficacy of vortioxetine and venlafaxine (compared to placebo) was reported [48].

In another trial comparing vortioxetine (15 mg and 20 mg daily), duloxetine (60 mg daily) and placebo in an 8-week study in patients with depression and prominent anxiety, the efficacy of all active therapies turned out to be comparable and significantly better than placebo [49]. In terms of tolerability profile, the risk of discontinuation of vortioxetine due to side effects was observed to be significantly lower compared to SNRI medication (duloxetine and venlafaxine) [50]. The most common adverse effect was nausea, the frequency of others, typical for SNRI therapy (for example, insomnia), was similar to placebo; no cases of treatment discontinuation were reported for vortioxetine [50]. In one of the most recent studies (REVIVE), vortioxetine (10-20 mg daily) was compared to agomelatine (25-50 mg daily), a significant reduction in depressive symptoms (assessed with MADRS scale) was observed in vortioxetine group from the 8th week of study [51].

In the most recent trial (FOCUS) a significant improvement in cognitive functions was reported for vortioxetine (daily doses of 10 mg and 20 mg) compared with placebo. These objective results were confirmed by patients themselves owing to the use of a special cognitive abilities self-assessment questionnaire (Perceived Deficit Questionnaire – PDQ). It was also proven that the reduction of cognitive difficulties was a consequence of vortioxetine’s direct procognitive effect rather than secondary to its antidepressant efficacy [52].

To summarise, the available data from clinical trials on vortioxetine in depression, it seems justified to conclude that:

• it is an effective antidepressant; its potency is comparable to SNRI medication (for example, venlafaxine or duloxetine) or agomelatine
• it is effective in various subtypes of depression: severe depression, depression with anxiety, geriatric depression
• it is effective in patients who do not respond adequately to treatment with SSRIs or SNRIs
• it exerts a positive effect on cognitive functions
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