

# Psychopharmacological treatment of cognitive deficits in Schizophrenia and mood disorders

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## Summary

### Objectives

Cognitive dysfunction is a core feature and a transdiagnostic domain of psychiatric disorders, such as Schizophrenia, Bipolar Disorder and Depression. The study of these disorders may contribute to the development of novel drugs and to the repurposing of existing agents for the treatment of cognitive impairment. This manuscript will review the literature regarding the effects of pharmacological treatment of cognitive deficits in psychiatric disorders.

### Methods

PubMed was used for the search including the following terms: Schizophrenia, Major Depressive Disorder, Bipolar Disorder, pharmacological treatment, antipsychotics, antidepressants, lithium and anticonvulsant medications.

### Results

The treatment of Schizophrenia with First Generation Antipsychotics (FGAs) has relatively little influence on cognitive symptoms. It has been indicated that Second Generation Antipsychotics (SGAs) may partially improve cognitive dysfunction, due to their relatively high affinity for serotonin 5HT<sub>2A</sub> receptors. Dysfunction of  $\gamma$ -aminobutyric acid (GABA) led to the "GABA hypofunction" theory and to the development of novel compounds to treat cognitive deficits. The effects of glutamatergic agents indicated benefits on cognition of a group of amino acids that act as glutamate agonists by binding to the glycine site on NMDA receptors. It was discovered that the administration of muscarinic antagonists potentiated the cognitive impairments, and the  $\alpha_7$  nicotinic acetylcholine receptors have been shown to play an important role in cognition with potential therapeutic applications in Schizophrenia. A number of studies regarding drugs targeting neuroinflammation and oxidative stress to improve cognitive deficits emerged.

Regarding Major Depressive Disorder (MDD), conventional antidepressants are generally associated with beneficial effects on cognitive impairment in individuals with MDD, which may be mediated at least in part by the improvement obtained in affective symptoms, suggesting a partially indirect effect. Furthermore, it has been hypothesized that vortioxetine may improve the cognitive symptoms of MDD through its effects on serotonergic receptors which may modulate glutamatergic neurotransmission, exerting its antidepressant and beneficial effect on cognitive function via a distinct mechanism.

The literature findings regarding the effects of lithium on cognition in Bipolar Disorder are inconclusive, while anticonvulsant medications, such as valproic acid, lamotrigine and carbamazepine, showed well-established mood stabilizing and cognitive enhancing properties.

### Conclusions

Cognitive dysfunction in Schizophrenia, Major Depressive Disorder and Bipolar Disorder is a relevant determinant of patient clinical and functional outcomes. Clinical studies evaluated several compounds to estimate their positive impact and their efficacy profiles on cognitive domains.

### Key words

Cognition • Psychopharmacology • Schizophrenia • Major Depressive Disorder • Bipolar Disorder

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## Introduction: cognitive impairment and actual pharmacological target

Cognitive dysfunction is a relevant dimension of psychiatric disorders, such as Schizophrenia, Bipolar Disorder and Depression. Cognitive impairment is associated with different genetic, epigenetic, developmental and environmental factors. Although some of these factors may be compensated, others are not reversible, so prevention and early treatment are crucial <sup>1</sup>.

As regards Schizophrenia, cognitive impairment represents a core feature of the disorder <sup>2</sup>. A considerable proportion of patients with Schizophrenia performs an average of 1.0 to 2.0 standard deviations below the population norms on standardized psychometric tests <sup>3</sup>. Neurocognitive impairment is detectable before the first episode of psychosis <sup>4</sup> and it has been reported to be one of the strongest predictors of functional outcome in Schizophrenia <sup>5</sup>; this form of deficit is not only present in patients, but also in their first degree relatives <sup>6</sup>. Most patients with Schizophrenia show deficits in at least one cognitive domain, including working memory, attention, processing speed, reasoning and problem solving, social cognition, visual learning and memory <sup>7</sup>, with a significant impact on functioning <sup>8</sup>, quality of life <sup>9</sup>, success in psychosocial rehabilitation programs and employment <sup>10</sup>. Understanding of cognitive deficits' neural bases is limited. Since the discovery of chlorpromazine's antipsychotic properties in 1952, treatments to date have mainly targeted the dopamine type 2 receptor, mostly via direct antagonism of the receptor. Although this mechanism is relatively effective on positive symptoms, both first and second-generation antipsychotic drugs minimally impact negative and cognitive aspects. The use of already-approved drugs and already-available complementary medications to enhance cognition has been proposed <sup>11</sup>. Also, several agents have been developed and tested to improve neurocognition in Schizophrenia. It is possible that the heterogeneity of mechanisms responsible for cognitive deficits in Schizophrenia may be at the heart of the lack of success of any single pharmacological approach. Promising results obtained with cognitive remediation have suggested that promotion of neuroplasticity could be an effective approach. Although most efforts have focused on dopaminergic, cholinergic, glutamatergic, noradrenergic, GABAergic and serotonergic mechanisms, the impact of neuroinflammation and oxidative stress and their downstream effects on neuroplasticity and D1 and NMDA receptors suggest that they may be treatment targets for neurocognition in Schizophrenia <sup>12</sup>. Similarly, regarding Major Depressive Disorder (MDD), cognitive deficits are considered core symptoms of the disorder, and appear to be broadly associated with functional outcome. Until now, they have been gener-

ally considered a direct consequence of depressive symptoms <sup>13</sup>, but it is still debated whether they are independent of mood. In fact, cognitive symptoms have been demonstrated not only during depressive episodes, but also during remission. Studies investigating cognitive functioning in MDD have focused on patients with a history of more than one Major Depressive Episode (MDE) <sup>14</sup>. Deficits have been identified in the areas of psychomotor speed, attention, learning and memory, executive functioning, cold cognition, hot cognition and social cognition. In addition, brain abnormalities in regions related to these functions have been demonstrated <sup>15</sup> even during the early stages of the illness.

To date, although inconsistent but positive effects of conventional treatments on cognitive impairment are observed, no single antidepressant agent has received approval for the treatment of cognitive symptoms associated with MDD. Data across new agents are preliminary and are promising for EPO, SAME, insulin, NAC and antidiabetic agents <sup>16</sup>. Several mechanisms may contribute to cognitive dysfunction in MDD, including, but not limited to, over-activation of the hypothalamic-pituitary-adrenal axis, oxidative and nitrosative stress, imbalances in pathways involved in cell survival and death and immune activation. These pathways may offer a basis for the development of novel drugs and/or the repurposing of existing agents for the treatment of cognitive impairment in Depression <sup>17</sup>.

Regarding the cognitive profile of patients with Bipolar Disorder (BD), the existence of cognitive impairment has been well demonstrated by several studies <sup>18</sup>, with impairment in psychomotor speed, declarative memory, executive function, visual memory and attention <sup>19</sup>. These deficits are present during all phases of BD <sup>20</sup>, including euthymia <sup>21</sup>, with significant consequences on functioning and quality of life <sup>22</sup>. BD has a substantial genetic component, with estimated heritability ranging from 70% to 80% <sup>23</sup>. Unaffected relatives and offspring of BD patients exhibit mild deficits in memory, visuospatial and executive function domains. A meta-analysis revealed executive functions and verbal memory deficits of small effect size in first-degree relatives of BD patients <sup>24</sup>. Despite the negative impact of cognitive deficits on the functional status of BD patients, there is no specific pharmacological agent for the management of cognitive symptoms among bipolar patients. The variability of available findings suggests that medications might be of marginal benefit in the treatment of this impairment, and it is still unclear which deficits are more likely to respond to therapeutic interventions.

## Psychopharmacological treatment to improve cognitive deficits in Schizophrenia

Treatment of Schizophrenia is often limited to the reduction of positive symptoms, while negative symptoms

and cognitive impairment may persist throughout life, in spite of treatment with antipsychotics<sup>25</sup>. First Generation Antipsychotics (FGAs) have relatively little influence on cognitive and negative symptoms and may cause adverse side effects, such as extrapyramidal motor symptoms, tardive dyskinesia, weight gain and sedation<sup>26</sup>. Recently, second-generation antipsychotics drugs (SGAs) have been used as first-line medications to treat patients with Schizophrenia. It has been indicated that SGAs may partially improve cognitive dysfunction, which may be related to their relatively high affinity for serotonin 5HT<sub>2A</sub> receptors compared with D<sub>2</sub> receptors<sup>27</sup>. The apparent cognitive enhancement may be related to one or more of the following effects of atypical antipsychotics agents, not shared by typicals: increased release of dopamine (DA) and acetylcholine (ACh) in the prefrontal cortex and hippocampus<sup>28</sup>; antagonism of 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> or 5-HT<sub>6</sub> receptors<sup>29</sup> and stimulation of 5-HT<sub>1A</sub> receptors<sup>30</sup>. An increased release of DA may particularly lead to stimulation of D<sub>1</sub> and D<sub>3</sub> receptors, which might have a beneficial effect on cognition, assuming that these receptors are understimulated in Schizophrenia. An increased release of ACh might lead to enhancement of M<sub>1</sub>, M<sub>4</sub>, or  $\alpha$ 7 nicotinic acid post-synaptic receptors, all of which have been indicated as potentially involved in cognitive impairment in Schizophrenia<sup>31</sup>.

However, several investigators have speculated that the cognitive improvements observed with SGAs may reflect an avoidance of potentially deleterious effects associated with FGAs rather than a specific enhancement of cognition<sup>32</sup>. A meta-analysis by Woodward et al. demonstrated that SGAs improved overall cognitive function to a greater extent than FGAs<sup>33</sup>. McGurk et al. demonstrated a significant improvement in several cognitive domains (selective attention, executive functioning, verbal learning and memory and verbal fluency) in partial responders to typicals antipsychotics who had been switched to olanzapine<sup>34</sup>. Furthermore, Wang et al. reported that olanzapine could significantly improve short-term memory, immediate memory and memory quotient in first-episode schizophrenic patients<sup>35</sup>. Some findings suggest that aripiprazole may offer advantages over olanzapine in improving neurocognitive function<sup>36</sup>. Furthermore, a systematic review of eleven comparative studies revealed that paliperidone resulted in significantly greater improvements in social functioning compared to those achieved with comparative antipsychotics, including risperidone, olanzapine and aripiprazole<sup>37</sup>.

In an independent systematic review, Houthoofd et al. reported positive effects of risperidone on neurocognitive function in patients with Schizophrenia and Schizoaffective Disorder in processing speed, attention/

vigilance, verbal and visual learning and memory and in reasoning and problem-solving<sup>38</sup>. However, the effect of risperidone on social cognition in patients with Schizophrenia remains controversial due to conflicting results<sup>39</sup>. Regarding long acting injection (LAIs) treatments, patients who switched from risperidone to paliperidone long acting showed greater improvements in attention and processing speed compared to those who continued on risperidone<sup>40</sup>. Davidson et al. reported small advantages of SGAs compared to FGAs in terms of cognitive performance<sup>41</sup>. In conclusion, the studies that have focused on the possible differential effects of specific SGAs were not conclusive. Given that individual SGAs show different pharmacological profiles and that cognitive function consists of different domains, it is possible that the effects on cognitive function may differ among drugs. Treatment with antipsychotic medication is associated with moderate improvement in cognitive performance among patients with Schizophrenic form Disorder or at first episode of Schizophrenia.

To stimulate cognition in Schizophrenia, a number of GABAergic agents have been studied. Dysfunction of  $\gamma$ -aminobutyric acid (GABA) interneurons has been suggested in the pathophysiology of Schizophrenia, as the result of an imbalance between excitation and inhibition in the cerebral cortex. There is histological evidence of the reduction of GABA interneuron density in the frontal cortex<sup>42</sup> and it has been suggested that a developmental deficit of inhibitory GABA interneurons may underlie neurodegeneration through the exaggerated activation of glutamatergic neurons<sup>43</sup>. In this context, an imbalance between excitatory and inhibitory (E-I) activity, induced by low activity of glutamatergic projections and GABA interneurons in the prefrontal cortex, may lead to impaired working memory in Schizophrenia<sup>44</sup>. These observations led to the "GABA hypofunction" theory<sup>45</sup> and to the development of novel compounds to treat negative symptoms and cognitive deficits, correcting the "E-I imbalance"<sup>46</sup>, including agonists of the glycine site of NMDA receptor, DA-D<sub>1</sub> receptor, metabotropic glutamate receptor and 5-HT<sub>1A</sub> receptors<sup>47</sup>. Clinical evidence suggests that serotonin 5-HT<sub>1A</sub> receptor agonists improve cognitive deficits in Schizophrenia, through the correction of the E-I imbalance via the suppression of GABA neural function<sup>48</sup>. Several compounds have been developed to influence GABA activity, but most of these compounds have failed to demonstrate neurocognitive benefits in large clinical trials<sup>49</sup>. The effects of glutamatergic agents on cognitive deficits were also investigated. Glutamate is the major excitatory neurotransmitter in the central nervous system. Glutamate receptors include NMDA and AMPA receptors, which are G-protein coupled receptors that trigger second-messenger cascades upon glutamate

binding. NMDA receptor antagonists, such as ketamine and phencyclidine, can produce clinical and cognitive symptoms of Schizophrenia in healthy individuals, leading to the hypothesis that the NMDA receptor could be involved in the pathophysiology of psychosis. This hypothesis has gained traction based on findings of altered glutamate levels in cerebrospinal fluid and cortex of patients with Schizophrenia and of genetic risk factors in genes for the NMDA receptor. Drugs can modulate the NMDA receptor through different mechanisms, such as binding the NMDA glycine co-agonist site, increasing glycine concentration (glycine transporter inhibitors) and influencing the NMDA receptor via glutathione, the major anti-inflammatory molecule in the central nervous system<sup>50</sup>. Several clinical trials have examined the neurocognitive enhancement benefits of a group of amino acids that act as glutamate agonists by binding to the glycine site on NMDA receptors. These NMDA receptor agonists include glycine, D-cycloserine, and D-serine but none of the currently published studies produced evidence that the adjunctive use of these compounds improves neurocognition. D-cycloserine, currently approved for treatment of Tuberculosis, binds to the glycine site and acts as a partial agonist of the NMDA receptor. In an initial exploratory study, a single dose of D-cycloserine improved performance on a delayed recall task, but later studies were not able to replicate this initial finding of improved cognition. Glycine has shown a beneficial effect as an adjunctive agent to antipsychotics for negative and cognitive symptoms.

Cholinergic agents act on the central cholinergic system. This innervates a diverse range of cortical and sub-cortical structures, interacting with two structurally diverse families of receptors, the nicotinic and muscarinic receptors, through coordinated acetylcholine (ACh) release<sup>51</sup>. The administration of anti-cholinergic and anti-muscarinic agents was once common practice among schizophrenic patients due to the capacity of these drugs to alleviate extrapyramidal side effects commonly caused by typical antipsychotic medications. Besides worsening the severity of positive symptoms, it was discovered that the administration of muscarinic antagonists potentiated the cognitive impairments prevalent amongst patients<sup>52</sup>. With the advent of atypical antipsychotic medications, the concurrent administration of anti-muscarinic drugs ceased. In healthy subjects, the acute administration of anti-muscarinic agents can produce cognitive impairments that mimic the deficits observed in schizophrenic patients<sup>53</sup>. Significant reductions in the expression of M1 and M4 receptors have been consistently reported in the postmortem brains of schizophrenic patients in regions linked to cognitive function, including the hippocampus, frontal and prefrontal cortex, superior temporal gyrus and the anterior

and posterior cingulate cortex<sup>54</sup>. Conversely, the expression of M2 and M3 receptors has been reported as unaltered in the brains of patients with Schizophrenia across a number of cortical regions<sup>55</sup>. In accordance with this evidence, it is apparent that a dysfunctional muscarinic system is contributing to the symptoms of Schizophrenia and thus this system might thus represent a therapeutic target<sup>56</sup>. In this regard, clozapine was the first atypical medication to show nootropic attributes inducing mild improvements across a number of cognitive functions, including learning and memory<sup>57</sup>, eventually attributed to its effects on the muscarinic system. Galantamine is a competitive and reversible cholinesterase inhibitor that also acts as a M1 muscarinic acetylcholine receptor agonist or a modulator of  $\alpha 4$  and  $\alpha 7$  nicotinic receptors, and has been used primarily in the treatment of early-stage of Vascular Dementia and Alzheimer's Disease<sup>58</sup>: this drug produced neurocognitive benefits in schizophrenic patients<sup>59 60</sup>.

The five muscarinic receptors share considerable orthosteric binding site homogeneity. As a consequence, it is very difficult to target a specific muscarinic receptor at this site without manipulating any of the remaining four receptors and producing unwanted side-effects and/or receptor down-regulation/drug desensitization. Fortunately, it has been discovered that M1, M2, M3, M4 and M5 receptors all exhibit a secondary, allosteric binding site. Unlike the orthosteric binding sites, the allosteric binding sites demonstrate substantial heterogeneity across the five muscarinic receptors, thus becoming the target for most recently developed drugs. Positive allosteric modulators (PAMs) are a class of allosteric agonist that do not directly activate the receptor. By binding to the allosteric site, muscarinic PAMs increase the receptor's affinity for ACh at the orthosteric binding site and consequentially potentiate the receptor's response to ACh<sup>61</sup>. BQCA<sup>62</sup> and PQCA<sup>63</sup> are potent, highly selective M1 receptor PAM reported to produce pro-cognitive responses, including enhancing memory function and increasing spontaneous prefrontal brain activity in pre-clinical trials. In addition to antipsychotic like qualities, the M4 receptor PAM, VU0467154<sup>64</sup> and VU1052100<sup>65</sup> have been reported to enhance cognition. Although more detailed investigations are required to determine the suitability of muscarinic PAMs as novel treatments against psychotic and cognitive symptoms of Schizophrenia, the already available evidence is promising. Regarding nicotinic agents, the hypothesis that nicotine might improve cognition derived from the observation that smoking rates in patients, whether taking an antipsychotic or not, are significantly higher (40-90%) compared to general population (15-25%)<sup>66</sup>. Drug development strategies mostly focused on the  $\alpha 7$ -subtype of the nicotinic acetylcholine receptor. Interest in this re-

ceptor subtype is based on genetic links between this subunit and Schizophrenia, on its high expression rates in key cognitive processing areas (e.g., hippocampus, thalamus, and prefrontal cortex) and on the evidence of a decreased expression in post-mortem studies on patients' brains. The  $\alpha 7$  nicotinic acetylcholine receptors ( $\alpha 7$  receptors) have been shown to play an important role in cognition and have potential therapeutic applications in cognitive impairment in Schizophrenia as well as in Alzheimer's Disease <sup>67</sup>.

Encenicline demonstrated clinically meaningful improvements in cognition and functioning in patients with Schizophrenia <sup>68</sup>. Varenicline, an  $\alpha 7$ -subtype of the nicotinic acetylcholine receptor agonist originally approved for smoking cessation, and tropisetron, a 5-HT<sub>3</sub> receptor antagonist and  $\alpha 7$ -subtype of the nicotinic Ach receptor partial agonist, approved as antiemetic agent, showed the same inconsistent effects on cognition in Schizophrenia. Several cognitive enhancers approved for Alzheimer's Disease such as antidementia agents including donepezil, rivastigmine, galantamine and memantine, have been tested for their potential to improve cognition in Schizophrenia. Since they have always been the only cognition-enhancing agents available on the market their potential effects on cognition in Schizophrenia were obviously examined. Findings, however, have painted a different picture, suggesting that cognitive deficits in Schizophrenia most likely arise from different mechanisms, if compared to the ones involved in Alzheimer's Disease. Studies on the acetylcholinesterase inhibitors, donepezil, rivastigmine and galantamine have been mixed <sup>69</sup> or negative <sup>70</sup>. Memantine, typically prescribed to enhance neurocognition in Alzheimer's Disease, has several mechanisms of action. Studies on the possible procognitive benefits of memantine in Schizophrenia are available <sup>71</sup>, but Authors found that adjunctive memantine (in patients with atypical APDs therapy) did not produce any benefits on neurocognition in Schizophrenia <sup>72</sup>.

Oxytocin is a hypothalamic peptide contributing to maternal infant bonding. There have been several smaller studies on the effects of intranasal oxytocin on social cognitive functioning in people with Schizophrenia. Further testing is needed to explain whether oxytocin has therapeutic potential for social cognitive deficits and/or negative symptoms in people affected by Schizophrenia. Three noradrenergic compounds have been evaluated for their putative procognitive benefits in people with Schizophrenia; however, in published clinical trials, all three compounds (guanfacine <sup>73</sup>, atomoxetine <sup>74</sup> and reboxetine <sup>75</sup>) have demonstrated no sign of possible efficacy in schizophrenic patients.

Some published studies on serotonergic agents have evaluated tandospirone <sup>76</sup>, buspirone <sup>77</sup> and ondansetron <sup>78</sup>.

However, no study has suggested robust procognitive effects of these compounds. Also, interest emerged about the possible procognitive effects of histaminergic agents. Modafinil, a wakefulness-promoting medication, has a yet unclear mechanism of action. Modafinil appears to show therapeutic effects by increasing the expression of histamine in the hypothalamus <sup>79</sup> and seems to act as a dopamine agonist, inhibiting the reuptake of dopamine by the dopamine transporter <sup>80</sup>. In some studies, modafinil was shown to improve attention, memory and executive functioning in people with Schizophrenia; however, several studies found no benefits of modafinil.

Authors studied several drugs targeting neuroinflammation and oxidative stress, following the hypothesis that inflammation plays a role in the pathogenesis of Schizophrenia. In fact, increased rates of Schizophrenia were observed after infectious events, such as maternal exposure to influenza and upper respiratory infections. Studies revealed that in pregnant women, an augmented expression of inflammatory cytokines in the second trimester increased the risk of Schizophrenia in their offspring <sup>81</sup>. Viral exposure can reduce the density of receptors relevant for neurocognition, such as D1 receptors in the frontal areas and NMDA receptors in the hippocampus, it can decrease protein kinase B expression and impair axonal integrity <sup>82</sup>. Levels of proinflammatory cytokines, such as interleukin IL-6, are elevated in Schizophrenia <sup>83</sup> and have been shown to influence specific brain regions, including prefrontal cortex, medial temporal regions and long-term potentiation in the hippocampus <sup>84</sup>. IL-6 increases oxidative stress, which may interfere with the expression of inhibitory GABA interneurons and impact executive functioning <sup>85</sup>; levels of C-reactive protein (CRP), an inflammatory biomarker, are associated with neurocognitive deficits, but not necessarily with symptom severity in people with Schizophrenia <sup>86</sup>. Neuroinflammation impacts the activity-dependent transport of brain-derived neurotrophic factor (BDNF), a neuroplasticity-regulating protein that promotes neurogenesis, synaptogenesis and dendritic growth <sup>87</sup>. Given their impact on neurocognition, neuroinflammation and oxidative stress are potential targets for psychopharmacological enhancement of neurocognition. Minocycline, a broad-spectrum antibiotic, is a long-acting tetracycline traditionally prescribed as treatment of bacterial infections.

There has been recent interest about possible anti-inflammatory, anti-oxidative and neuroprotective benefits of minocycline in people with neurodegenerative disorders and in people with Schizophrenia. Acetylsalicylic acid (aspirin), traditionally used as an analgesic and an antipyretic medication, has gained recent interest as an anti-inflammatory agent. Particular atten-

tion has been paid to the anti-inflammatory properties of simvastatin and rosuvastatin; however, evidences are sparse<sup>88</sup>. Omega-3 fatty acids are known to be essential for normal cortical expansion and maturation and functional integrity during prenatal and postnatal phases and during adult development<sup>89</sup>. It has been demonstrated that omega-3 fatty acids may be beneficial to decrease the risk of a frank psychotic disorder in ultra high-risk individuals, suggesting possible neuroprotective effects<sup>90</sup>. However, very few clinical studies on omega-3 fatty acids have examined their neurocognitive benefits. Some studies demonstrated that the adjunctive use of N-Acetylcysteine, a precursor of glutathione with antioxidant effects, improved the negative symptoms of Schizophrenia, although there was no direct examination of its neurocognitive benefits<sup>91</sup>. Cannabis sativa is the most widely used drug in the world. It contains over 70 different constituents, including delta-9-tetrahydrocannabinol ( $\Delta$ 9-THC) and cannabidiol (CBD)<sup>92</sup>. CBD can interfere with the detrimental actions of  $\Delta$ 9-THC in terms of psychotic proneness and cognitive dysfunction<sup>93</sup>. On the other hand, CBD is a particularly interesting target as a novel approach for cognitive improvement in Schizophrenia, in part, due to its strong anti-inflammatory properties<sup>94</sup>. CBD has the potential to limit  $\Delta$ 9THC-induced cognitive impairment and to improve cognitive function in different pathological conditions, but there is limited evidence investigating the therapeutic efficacy of CBD as treatment for cognitive deficits in Schizophrenia. However, evidences suggesting cognitive improvement in neurological disorders with CBD treatment emerged<sup>95</sup>.

### Psychopharmacological treatment to improve cognitive deficits in major depressive disorder

Several clinical studies have primarily evaluated the effects of conventional antidepressants on cognitive performance in individuals with MDD. Conventional antidepressants are generally associated with beneficial effects on cognitive impairment in individuals with MDD, which may be mediated at least in part by the improvement obtained in affective symptoms, making it a partially indirect effect. For example, it was reported that SSRI treatment led to a significant improvement in memory performance in individuals with MDD<sup>96</sup>. Studies showed that treatment with sertraline is associated with significant improvements in psychomotor speed and executive functions<sup>97</sup>. On the other hand, other findings indicated that sertraline, citalopram or paroxetine were not associated with significant changes in cognitive performance in patients with Major Depression, whereas a beneficial effect was observed in pa-

tients with Minor Depression<sup>98</sup>. Interventions targeting multiple neurochemical systems simultaneously (e.g. SNRIs) might be more likely to improve cognitive performance than treatments targeting only a single system (e.g. SSRIs)<sup>99</sup>. For instance, a trial including adults with MDD treated with escitalopram or duloxetine showed that SNRIs were superior to SSRIs in ameliorating memory performance. Despite both escitalopram and duloxetine improved measures of working memory, attention, executive functions processing speed and motor performance, the improvement induced by duloxetine was greater than the one induced by escitalopram in episodic and working memory<sup>100</sup>. However, duloxetine did not differ from placebo in several assessed cognitive domains in a study on elderly individuals with MDD<sup>101</sup>. A recent meta-analysis further indicates that standard antidepressant drugs may ameliorate certain cognitive domains in patients with MDD, namely psychomotor speed and delayed recall. However, the evidence base remains limited, and the effect sizes derived from this meta-analysis were small in magnitude (standard mean difference was 0.16 for psychomotor speed and 0.24 for delayed recall, respectively)<sup>102</sup>. These results might be encouraging; however, the extrapolation of a class effect on cognition based on results from a single medication within that class should be a very cautious operation. Long-term therapy with certain antidepressants may also be linked to cognitive side effects in adult subjects with MDD. For instance, in depressed individuals reaching partial or full remission, the treatment with antidepressants has been associated with increased cognitive deficits, such as apathy, inattentiveness, forgetfulness, word-finding difficulty and mental slowing<sup>103</sup>. Vortioxetine is an antidepressant agent that acts as an antagonist of the 5-HT<sub>3</sub> and 5-HT<sub>7</sub> serotonin receptors, as a partial agonist of the 5-HT<sub>1B</sub> serotonin receptor, as an agonist of the 5-HT<sub>1A</sub> receptor, and that inhibits the serotonin transporter<sup>104</sup>. Vortioxetine may influence learning and memory processes by improving hippocampal synaptic plasticity and increasing the output of pyramidal cells<sup>105</sup>. Furthermore, it has been postulated that vortioxetine may improve the cognitive symptoms of MDD through its effects on cognate serotonergic receptors which may modulate glutamatergic neurotransmission<sup>106</sup>. McIntyre et al. evaluated the efficacy of vortioxetine on cognitive function (executive functions, processing speed, attention, learning and memory) and depression in adults with recurrent moderate-to-severe Major Depressive Disorder (MDD). In terms of primary endpoint, Vortioxetine significantly improves cognitive functions. Analyses indicate that the beneficial effect of vortioxetine on cognition is largely a direct effect of the treatment. Vortioxetine significantly improved objective and subjective measures of cognitive function in adults

with recurrent MDD and these effects were largely independent from the improvement of depressive symptoms. The clinical relevance of the significant effect of vortioxetine on objective neuropsychological test scores was supported by the magnitude of the standardized effect sizes, which ranged from 0.23 to 0.52 [Cohen's *d*] <sup>107</sup>. The 5-HT system not only plays a critical role in the regulation of mood, but it is also intimately involved in the regulation of cognitive function, as evidenced by preclinical and clinical studies <sup>108</sup>. Vortioxetine activates cortical networks associated with cognitive processes; 5-HT<sub>1A</sub> receptor agonism and 5-HT<sub>3</sub> and 5-HT<sub>7</sub> receptor antagonism contribute to these activating effects of vortioxetine <sup>109</sup>. Furthermore, vortioxetine is associated with the disinhibition of GABA interneurons <sup>110</sup> that plays an important role in the activation of the cortical and hippocampal networks involved in cognitive processes and with 5-HT<sub>3</sub> receptor antagonism <sup>111</sup>. In addition, vortioxetine exerts its antidepressant and beneficial effect on cognitive function via a distinct mechanism. There is evidence that cognitive function may vary independently of mood state in MDD. In particular, improvements in cognitive performance do not necessarily follow improvement in mood symptoms, which may reflect the distinct neural basis of cognitive control and emotion regulation related to depression <sup>112</sup>.

To date it is a high priority to identify new compounds to develop an effective treatment for Major Depressive Disorder. Lisdexamfetamine dimesylate (LDX) is a pharmacologically inactive pro-drug of D-amphetamine approved for ADHD. Augmentation therapy with LDX administration seems to be effective in reducing depressive symptoms <sup>113</sup> and improving the executive functions <sup>114</sup>. Erythropoietin (EPO) exerts antidepressant-like and neuroprotective effects, enhancing hippocampus-dependent memory and neuroplasticity <sup>115</sup>. Clinical evidence suggests that EPO may have cognitive-enhancing effects in MDD. Minocycline, as in Schizophrenia, has been proposed to play a role in the neuroprogressive nature of MDD and there is some evidence that pro-inflammatory status may also correlate with poor neurocognitive performance. Results obtained from preclinical <sup>116</sup> and clinical <sup>117</sup> studies have supported the potential of intranasal insulin in improving memory performance and executive functions. SAME is obtained from the essential amino acid methionine and from adenosine triphosphate. SAME is a major methyl donor required for the synthesis of several neurotransmitters and serves as a precursor molecule to the transsulfuration pathway, leading to the synthesis of glutathione <sup>118</sup>. The procognitive potential of SAME was preliminarily documented in SSRI-resistant outpatients with MDD <sup>119</sup>. Authors described inconsistent results about Acetyl-L-carnitine <sup>120</sup>, omega-3 polyunsaturated fatty acids <sup>121</sup>,

melatonin <sup>122</sup>, modafinil <sup>123</sup>, galantamine <sup>124</sup>, scopolamine <sup>125</sup>, N-acetylcysteine <sup>126</sup>, curcumin <sup>127</sup>, statins <sup>128</sup> and coenzyme Q10 <sup>129</sup>.

### Psychopharmacological treatment to improve cognitive deficits in bipolar disorder

The literature findings regarding the effects of lithium on cognition are equivocal. Although some studies reported cognitive deficits in attention and memory <sup>130</sup>, others failed to detect any impact of lithium treatment on cognitive performance <sup>131</sup>. Furthermore, studies did not find any cognitive difference between bipolar patients treated with different agents (including lithium) and drug-naïve BD subjects <sup>132</sup>. The cognitive impairment associated with medications appears to be present in BD patients who did not receive monotherapy with lithium. Therefore, the results might suggest that lithium only has minor side effects on cognition, at least in a clinically stable subgroup of BD patients. BD patients taking anticonvulsants as mood stabilizers other than lithium also showed deterioration in several cognitive domains. Furthermore, several cognitive functions are compromised in BD. In particular processing speed, sustained attention and emotion recognition are impaired in all BD patients regardless of the prescribed medication <sup>133</sup>.

Anticonvulsant medications, such as valproic acid, lamotrigine and carbamazepine, have well-established mood stabilizing and cognitive enhancing properties. A follow-up study found that lamotrigine-treated BD patients obtained better scores on verbal fluency and verbal memory compared with patients treated with valproic acid and carbamazepine <sup>134</sup>. Little is known about the neurocognitive effects of valproic acid and carbamazepine in BD, but studies in healthy volunteers and epileptic patients have shown that anticonvulsants generally lead to psychomotor retardation and memory and attentional decline <sup>135</sup>.

Compared to lithium and anticonvulsants, findings on the cognitive effects of second-generation antipsychotics in the treatment of BD are limited. Quetiapine and risperidone in euthymic BD patients showed adverse effects on cognitive domains <sup>136</sup>. Further analyses revealed that quetiapine, olanzapine and risperidone had no robust evidence regarding their beneficial properties <sup>136</sup> on cognitive aspects. Recently, Yatham et al. indicated some preliminary evidence about the efficacy of lurasidone in improving cognition in euthymic patients with Bipolar I Disorder. Overall, the evidence supporting a possible role of cholinesterase inhibitors in the treatment of BD-related cognitive impairment is very limited. In conclusion, the pathophysiological mechanisms involved in the cognitive deficits found among bipolar patients may result from disruption in noncho-

linergic neurotransmitter systems. If confirmed by future studies, this hypothesis would explain the reason why BD patients are less likely to respond to this class of medications.

Mifepristone is a glucocorticoid receptor antagonist; authors observed significant improvements in spatial working memory, spatial recognition memory and verbal fluency in bipolar patients receiving mifepristone<sup>136</sup>; however, the side-effect profile of this medication restricts its clinical routine use in the clinical setting.

Growing evidence points to a possible role of insulin on neuroplasticity regulation and the presence of insulin receptors in the hippocampus suggests that insulin may be involved in processes associated with memory consolidation<sup>137</sup>.

Authors evaluated several compounds to estimate their

positive impact on cognitive domains. Studies were conducted to examine pramipexole<sup>138 139</sup>, N-acetyl cysteine<sup>140</sup>, omega-3 polyunsaturated fatty acids<sup>141</sup>, L-carnosine<sup>142</sup> and erythropoietin<sup>143</sup>. To date, no study has suggested robust procognitive effects of these compounds. Finally, growing evidence points to the role of inflammatory processes in the pathophysiology of BD and some studies have evaluated the correlations between inflammatory cytokines and cognitive impairment in BP. Therefore, the possible role of antiinflammatory agents in the treatment of cognitive impairment in BP seems to be a promising target for future studies<sup>144</sup>.

## Conflict of Interest

None.

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