Sigma-1 Receptor Agonists as Therapeutic Drugs for Cognitive Impairment in Neuropsychiatric Diseases

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Abstract: Cognitive impairment is a core feature of patients with neuropsychiatric diseases such as schizophrenia and psychotic depression. The drugs currently used to treat cognitive impairment have significant limitations, ensuring that the search for more effective therapies remains active. Endoplasmic reticulum protein sigma-1 receptors are unique binding sites in the brain that exert a potent effect on multiple neurotransmitter systems. Accumulating evidence suggests that sigma-1 receptors play a role in both the pathophysiology of neuropsychiatric diseases, and the mechanistic action of some therapeutic drugs, such as the selective serotonin reuptake inhibitors (SSRIs), donepezil and neurosteroids. Among SSRIs, fluvoxamine, a potent sigma-1 receptor agonist, has the highest affinity at sigma-1 receptors. Sigma-1 receptor agonists greatly potentiate nerve-growth factor (NGF)-induced neurite outgrowth in PC12 cells, an effect that is antagonized by treatment with the selective sigma-1 receptor antagonist NE-100. Furthermore, phencyclidine (PCP)-induced cognitive impairment, associated with animal models of schizophrenia is significantly improved by sub-chronic administration of sigma-1 receptor agonists such as fluvoxamine, SA4503 (cutamesine) and donepezil. This effect is antagonized by co-administration of NE-100. A positron emission tomography (PET) study using the specific sigma-1 receptor ligand [^{11}C]SA4503 demonstrates that fluvoxamine and donepezil bind to sigma-1 receptors in the healthy human brain. In clinical studies, some sigma-1 receptor agonists, including fluvoxamine, donepezil and neurosteroids, improve cognitive impairment and clinical symptoms in neuropsychiatric diseases. In this article, we review the recent findings on sigma-1 receptor agonists as potential therapeutic drugs for the treatment of cognitive impairment in schizophrenia and psychotic depression.

Keywords: Sigma-1 receptor, Cognition, Schizophrenia, Psychotic depression, Delirium.

1. INTRODUCTION

Cognitive impairment is a common symptom in patients with neuropsychiatric disorders such as schizophrenia and major depressive disorder. Schizophrenia is characterized by three distinct symptom clusters: positive symptoms (*e.g.*, hallucinations and delusions), negative symptoms (*e.g.*, affective flattening, alogia and avolition), and cognitive impairment (*e.g.*, severe deterioration of working memory and attention). Cognitive impairment is a core feature of schizophrenia and its presence predicts both vocational and social disabilities for patients [1-4]. While positive symptoms are greatly improved with atypical antipsychotic medication, cognitive impairment is not greatly improved by therapy [5].

Cognitive impairment is also a ubiquitous and characteristic feature of major depressive disorder [6], often persisting despite otherwise effective antidepressant therapy. In addition, cognitive impairment can also be an adverse effect ("cognitive toxicity"), as a direct consequence of some antidepressant therapy [7]. The severity of major depression also has a bearing on the extent and magnitude of cognitive, psychomotor and memory impairment [8, 9]. Given the relative commonality of this disorder, and the lack of highly effective therapy, there is still a strong need for the development of pharmacological agents to improve cognitive impairment associated with neuropsychiatric disorders [10-14].

Sigma-1 receptors, discovered in 1976 by Martin and coworkers [15], were cloned in 1996 [16], and characterized as having an endoplasmic reticulum (ER) retention signal. Sigma-1 receptors on the ER regulate Ca^{2+} signaling *via* inositol 1,4,5-triphsphate (IP_3) receptors on the ER [17]. Interestingly, the ER protein sigma-1 receptors are Ca^{2+}-sensitive and are ligand-operated receptor chaperones at the mitochondrial associated ER membrane [18, 19]. The ER lumeral domain of the sigma-1 receptor possesses robust chaperone activity that prevents the aggregation of a variety of proteins *in vitro,* which stabilizes the ER Ca^{2+} channel IP_3 receptor *in vivo* [18, 20]. Sigma-1 receptors are predominantly expressed at the mitochondrial associated ER membrane, thereby regulating the IP_3 receptor-mediated Ca^{2+} influx from the ER to the mitochondria [18]. Sigma-1 receptors modulate ATP production and bioenergetics within cells [20].

Sigma-1 receptors regulate a number of neurotransmitter systems, including the glutamatergic, dopaminergic, serotonergic, noradrenergic, and cholinergic systems. Several lines of evidence implicate the role of sigma-1 receptors in the pathophysiology of neuropsychiatric disorders, such as mood disorders, anxiety disorders, and schizophrenia, and suggest that the receptor ligands may be potential therapeutic agents for these diseases [21-34]. This article reviews and discusses the role of sigma-1 receptor agonists as therapeutic agents, to improve cognitive impairment in neuropsychiatric disorders, particularly schizophrenia and major depressive disorder.

2. SIGMA-1 RECEPTOR AGONISTS AND NEUROPLASTICITY

Sigma-1 receptors play a role in synaptogenesis and myelination in the brain [35, 36], processes implicated in the pathology of schizophrenia [37-40] and depression [41, 39].

Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) are widely used as therapeutic drugs for major depressive disorder. Although all SSRIs share the common function of the blockading serotonin transporters, leading to elevated serotonin levels throughout the central nervous system (CNS), it is well known that their secondary pharmacology is heterogeneous [42-44]. We have reported that some SSRIs possess high to moderate affinity for sigma-1, but not for sigma-2 receptors Table **1** [45]. *In vitro* experiments suggest that the affinity of SSRIs for sigma-1 receptors is as follows: fluvoxamine > sertraline >

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Table 1. ***In Vitro*** **Affinity of Various Antidepressants for Rat Sigma-1 Binding Sites (from Ref. [45])**

Drug	Ki (nM)		Ki ratio
SSRIs	**Sigma-1**	**Sigma-2**	**(Sigma-2/Sigma-1)**
Fluvoxamine	36	8,439	234
Sertraline	57	5,297	93
S(+)Fluoxetine	120	5,480	46
(±)Fluoxetine	240	16,100	68
Citalopram	292	5,410	19
Paroxetine	1,893	22,870	12
Tricyclic antidepressants			
Imipramine	343	2,107	6
Desipramine	1,987	11,430	6

fluoxetine > citalopram >> paroxetine. It is highly likely that some SSRIs such as fluvoxamine, utilize sigma-1 receptors in its mode of action [45].

Antidepressants are thought to exert their effect by inducing adaptive neuroplasticity such as neurite outgrowth [46-48, 30, 49]. The prototypic sigma-1 receptor agonist (+)-pentazocine, as well as the antidepressants imipramine and fluvoxamine, enhance nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells, in a concentration dependent manner [50]. The selective sigma-1 receptor antagonist, NE-100 [51], blocks these enhancements [50]. Recently, we reported that fluvoxamine, but not sertraline or paroxetine, significantly potentiates NGF-induced neurite outgrowth in PC12 cells, in a concentration dependent manner Fig. (**1**) [52]. Similarly, the sigma-1 receptor agonists, 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl) piperazine dihydrochloride (SA4503: cutamesine) [53], 4-phenyl-1-(4-phenylbutyl) piperidine (PPBP) [54-56], dehydroepiandrosterone–sulfate (DHEA-S) [57, 58], and donepezil also potentiate NGF-induced outgrowth in PC12 cells, in a concentration-dependent manner [59, 52]. This outgrowth is greatly attenuated if NE-100 is co-administered Fig. (**1**) [59, 52]. All these findings suggest that sigma-1 receptors play an important role in NGF-induced neurite outgrowth, and that in the brain, selected antidepressants and compounds facilitate this neurite outgrowth, *via* sigma-1 receptors. However, the precise cellular and molecular mechanisms underlying these processes are not fully understood.

3. SIGMA-1 RECEPTOR AGONISTS AND COGNITION

Sigma-1 receptor agonists can improve acetylcholine (an anti-muscarinic drug)-related deficits in memory and cognition in rodent models [24, 25, 27, 60]. Selective receptor agonists, including igmesine and SA4503, reverse amnesia induced by muscarinic and nicotinic receptor antagonists [61, 62]. Furthermore, sigma-1 receptor agonists, such as (+)-SKF 10,047 and SA4503, release acetylcholine in the rat brain [63, 64]. Recently, methyl (1*R*,2*S*/1*S*,2*R*)-2-[4-hydroxy-4-phenylpiperidin-1-yl)methyl]-1-(4-methylphenyl) cyclopropanecarboxylate ((±)-PPCC) , a novel sigma-1 receptor agonist, has been shown to ameliorate cognitive impairment induced by selective cholinergic lesions in rats [65]. These findings suggest that sigma-1 receptor agonists can improve acetylcholine-related cognitive impairments through a mechanism of acetylcholine in the brain [27, 60].

Multiple lines of evidence suggest that aberrant glutamatergic neurotransmission *via* the *N*-methyl-D-aspartate (NMDA) receptors may precipitate the cognitive impairment associated with schizophrenia and major depression [66-71]. The NMDA receptor antagonists, such as phencyclidine (PCP), induce schizophrenia-like symptoms including cognitive impairment in healthy subjects [66]. As a consequence, the NMDA receptor antagonists, including PCP, are widely used to generate animal models of cognitive impairment. We have shown that PCP-induced cognitive impairment in a novel object recognition test is significantly improved by subsequent sub-chronic (2-week) administration of the atypical antipsychotic drug clozapine, but not the typical antipsychotic drug haloperidol [72]. Thus, the reversal of PCP-induced cognitive impairment as measured by the novel object recognition test, may be a potential animal model for atypical antipsychotic activity, in the amelioration of schizophrenia associated cognitive impairment [72]. Furthermore, we have found that repeated administration of PCP causes a significant reduction of sigma-1 receptors in the mouse hippocampus [73, 74], suggesting that a decrease in sigma-1 receptors may precipitate PCP-induced cognitive impairment.

4. POTENTIAL THERAPEUTIC DRUGS FOR COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

4.1. Fluvoxamine as a Sigma-1 Receptor Agonist

We have reported that PCP-induced cognitive impairment is significantly improved by subsequent sub-chronic (2-week) administration of fluvoxamine (20 mg/kg/day), but not paroxetine (10 mg/kg/day) [48] or sertraline (10 or 20 mg/kg/day) [73]. The effect of fluvoxamine on PCP-induced cognitive impairment is antagonized by co-administration of NE-100. Unlike fluvoxamine, sertraline which is an SSRI with a high affinity at sigma-1 receptors, does not attenuate PCP-induced cognitive deficits in mice. In addition, sertraline does not enhance NGF-induced neurite outgrowth in PC12 cells [52]. These findings suggest that fluvoxamine and sertraline may act as an agonist and an antagonist respectively, at sigma-1 receptors [52, 30, 73]. Also, it is likely that the agonistic activity of fluvoxamine at sigma-1 receptors mediates its therapeutic effect in PCP-induced cognitive impairment in mice.

4.2. Donepezil as a Sigma-1 Receptor Agonist

Donepezil is the most widely prescribed drug for Alzheimer's disease. It is thought to influence cognition and function by inhibiting acetylcholinesterase (AChE) in the brain, however, it has also been reported that donepezil binds sigma receptors in the brain [75]. This sigma-1 receptor binding is thought to promote the antidepressive, anti-amnesic and neuroprotective effects of donepezil in

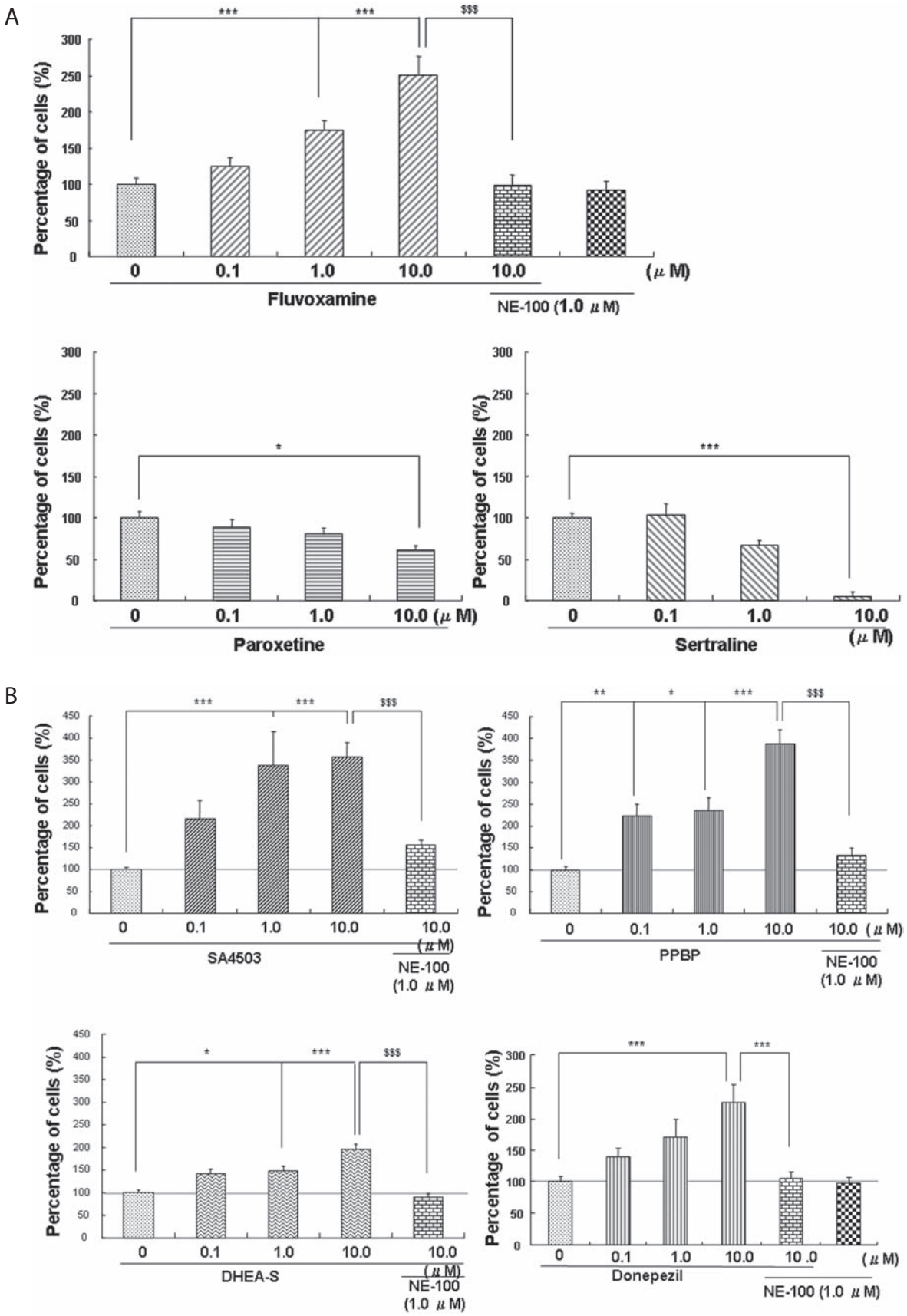

Fig. (1). Effects of SSRIs (fluvoxamine, paroxetine, sertraline) and sigma-1 receptor agonists (SA4503, PPBP, DHEA-S) on NGF-induced neurite outgrowth in PC12 cells. *P<0.05, **P<0.01, ***P<0.001 as compared with control (NGF alone) group. $^{\$\$\$}$P<0.001 as compared with drugs plus NE-100 group. The data are from Ref. [52] and Ref. [59].

the mouse forced swim test [76], and CO gas-induced [77] and amyloid $\beta_{25\text{-}35}$-induced neurotoxicity [78].

We have reported that PCP-induced cognitive impairment is significantly improved by subsequent, sub-chronic (2-week) administration of donepezil (1.0 mg/kg/day) [74]. This effect is antagonized by co-administration of the sigma-1 receptor antagonist NE-100. In contrast, PCP-induced cognitive impairment is not improved by subsequent, sub-chronic (2-week) administration of a different AChE inhibitor, physostigmine, that has no affinity to sigma-1 receptors [74]. These findings suggest that when treating mouse, PCP induced cognitive deficits, the therapeutic effect of donepezil is mediated *via* agonistic activity at sigma-1 receptors.

4.3. Neurosteroids as Sigma-1 Receptor Agonists

Neurosteroids, hormones produced in central and peripheral neurons, were first reported by Baulieu [79]. In the brain, concentrations of the neurosteroids, DHEA, DHEA-S, pregnenolone (PREG) and PREG-sulfate are far greater than in the circulatory system. Furthermore, concentrations in the brain remain high after adrenalectomy and orchiectomy, suggesting that these steroids do not originate from steroidogenic tissue but rather through local brain synthesis. As these neurosteroids do have moderate affinity towards sigma-1 receptors, they are considered endogenous ligands.

Neurosteroids may influence neuronal survival, neurite outgrowth and neurogenesis [80], as well as having varied effects on NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), γ-aminobutyric acid type A ($GABA_A$), kainate, glycine, serotonin and nicotinic acetylcholine receptors [81]. In addition, several neurosteroids have affinity for the sigma-1 receptor; for example, DHEA, DHEA-S and PREG are all sigma-1 receptor agonists, while progesterone is an antagonist [21, 82, 20]. Neurosteroids therefore, appear to be highly relevant to the pathophysiology and pharmacological treatment of mood disorders, psychosis and dementia [83]. We have previously shown that DHEA-S significantly attenuates PCP-induced cognitive impairment in mice, and that these effects are antagonized by co-administration of NE-100, suggesting that DHEA-S activity is generated through sigma-1 receptors [48].

5. CLINICAL REPORTS OF SIGMA-1 RECEPTOR AGONISTS IN SCHIZOPHRENIA

A previous positron emission tomography (PET) study demonstrated that in the healthy human brain, fluvoxamine (50-200 mg) and donepezil (5 or 10 mg) bind sigma-1 receptors in a dose-dependent manner, after oral administration [84, 85]. Studies on post-mortem brains from schizophrenic patients, report a greatly reduced density of sigma receptors, compared with controls [86, 87], consistent with pre-clinical reports showing a lower level of sigma-1 receptors in PCP-treated mouse brains [73, 74].

Studies show that fluvoxamine adjunctive therapy improves negative symptoms in patients with schizophrenia [88-90] Table **2**. We recently, reported that fluvoxamine is effective in correcting cognitive impairment in patients with schizophrenia [91, 92]. There is also a case demonstrating the effectiveness of fluvoxamine in treating a patient with schizoaffective disorder for whom therapy with the SSRI, escitalopram, failed [93], suggesting a possible antipsychotic effect for fluvoxamine. Both pre-clinical and clinical evidence points to fluvoxamine being a promising therapeutic drug for cognitive and clinical symptoms in patients with schizophrenia. Recently, we performed a randomized double-blind trial of fluvoxamine adjunctive therapy in patients with schizophrenia and found that fluvoxamine was effective in restoring executive functions in patients [94].

Despite small sample sizes, clinical evidence suggests that the sigma-1 receptor agonists, donepezil [95-97], PREG [98, 99], and DHEA [100-104, 98, 105], could also be promising therapeutic agents for cognitive and clinical symptoms in patients with schizophrenia Table **2**, although these results are inconclusive [106, 107]. Further studies on sigma-1 receptor agonism using large cohorts need to be conducted.

Cognitive impairment is also a common feature in the prodromal state of psychosis [108]. Considering that sigma-1 receptors mediate neuroprotection and neuronal plasticity, it is likely that agonists such as fluvoxamine could reduce the risk of subsequent transition to schizophrenia in susceptible patients [109]. Very recently, we reported a case that fluvoxamine was effective in preventing persons at ultra-high risk of psychotic disorder from the onset of psychosis [110]. Randomized, double-blind, placebo-controlled studies of fluvoxamine in this group of patients will be necessary to determine the drug's clinical efficacy.

6. POTENTIAL THERAPEUTIC DRUGS FOR MAJOR DEPRESSIVE DISORDER

In the late 1990s, it was demonstrated that sigma-1 receptor ligands have antidepressant-like action in animal models of depression. The selective sigma-1 receptor agonist, SA4503 [53], decreases immobility time in the forced swim test without any effect on open-field locomotion [111]. Interestingly, the antidepressant-like effect of SA4503 is achieved after a single dose of the drug. A Phase II study of SA4503, in patients with major depression is currently underway. The rapid antidepressant-like action of SA4503 has more recently been replicated by different agonists such as OPC-14523, igmesine (JO1784), (+)-SKF-10,047 and DHEA-S [112, 113]. Electrophysiological studies demonstrate a rapid antidepressant-like action for sigma-1 receptor agonists [114]. In addition, sigma-1 receptor knock-out mice show longer immobility times in the forced swim test, an indicator of a depression-like phenotype in mice [115]. These results point towards rapid antidepressant-like activity for sigma-1 receptor agonists [20].

The NMDA receptor antagonist ketamine exerts a rapid antidepressant action in patients with refractory major depression and bipolar depression [116, 117]. It is possible that this activity is triggered by sigma-1 receptor agonist binding [70, 71], since ketamine has moderate affinity for this receptor [118, 119].

7. CLINICAL REPORTS OF SIGMA-1 RECEPTOR AGONISTS IN PSYCHOTIC DEPRESSION

Psychotic (or delusional) major depression is a severe illness typified by marked depressive symptoms and accompanied by delusions, and sometimes, by hallucinations. Patients with psychotic depression tend to experience longer episodes, psychomotor impairment, guilt, suicidal pre-occupation, and cognitive impairment [120-122]. In addition, they have a significantly higher mortality than patients with nonpsychotic major depression [121, 123, 124]. Several reports link psychotic depression with higher cortisol levels and more severe cognitive impairment, relative to non-psychotic depression sufferers [125-127].

Unfortunately for patients, psychotic depression frequently proves difficult to treat. Clinical studies demonstrate the efficacy of combined antidepressant (either a TCA or an SSRI) and atypical antipsychotic or electroconvulsive therapy (ECT) in treating psychotic depression [120, 124]. However, combinations of antipsychotics can lead to severe side effects such as extrapyramidal symptom or tardive dyskinesia [124]. Additionally, several antidepressants, *e.g.* TCAs, can produce significant cognitive impairment [128]. Several case reports have found that fluvoxamine monotherapy, in contrast to other SSRIs, is effective in treating patients with psychotic depression [129-131]. Furthermore, fluvoxamine monotherapy has a superior efficacy in alleviating both the psychotic and depressive symptoms of this disorder [132-136] Table **3**, while paroxetine has a lesser effect [137].

Sigma-1 receptors have been implicated in the pathophysiology of depression and in the therapeutic action of antidepressants [18, 30]. Unlike paroxetine, with an inhibition constant (Ki) of 1,893

Table 2. Clinical Studies Using Sigma-1 Receptor Agonists in Schizophrenia

Compound	Study Design	Sample Size	Dose (mg)	Positive Symptoms	Negative Symptoms	Cognitive Symptoms	Ref.
Fluvoxamine	DBT, RCT	30	100	→	↑	NA	[88]
	DBT, RCT	25	100	→	↑	NA	[89]
	DBT, RCT	53	100	→	↑	NA	[90]
	DBT, RCT	44	150	→	→	↑	[94]
Donepezil	DBT, RCT, COT	15	5	↑ (PANSS total score)		↑	[95]
	DBT, RCT, COT	13	5-10	NA	↑(depressive symptom)	NA	[96]
	DBT, RCT, COT	13	5-10	→	↑	NA	[97]
DHEA	DBT, RCT	27	100	→	↑	NA	[100]
	DBT, RCT, COT	55	200	→	→	↑	[102]
	DBT, RCT	31	150	→	↑	→	[103]
PREG	DBT, RCT	18	500	→	↑	→	[98]
PREG DHEA	DBT, RCT	44	30 200 400	↑ → →	→ → →	↑ → →	[105]

DBT: Double-blind trial, RCT: Randomized controlled trial, COT: Cross-over trial, ↑: Effective, →: No change, NA: Not assessed, PANSS: The Positive and Negative Syndrome Scale.

nM, fluvoxamine is a potent sigma-1 receptor agonist with a Ki of 36 nM [45]. Fluvoxamine, but not paroxetine, binds to sigma-1 receptors in the intact human brain [84], suggesting that sigma-1 receptors are involved in fluvoxamine's mode of action. Supporting this is the evidence that fluvoxamine, but not paroxetine, improves PCP-induced cognitive impairment in mice [48] and cognitive impairment in some schizophrenics [91, 92]. As in schizophrenia, patients with psychotic depression have a greater level of cognitive impairment compared with non-psychotic depression [125-127]. In summary, the superior efficacy of fluvoxamine monotherapy in psychotic depression may be due to its sigma-1 receptor agonist property [138, 139, 30]. Again, further studies are needed to confirm the role of sigma-1 receptors in the efficacy of fluvoxamine treatment of psychotic depression.

8. CLINICAL REPORTS OF FLUVOXAMINE IN DELIRIUM

Delirium, a common and deleterious complication in patients, is thought to be a neurobehavioral manifestation of imbalances in the synthesis, release, and inactivation of the neurotransmitters that normally control cognitive function, behavior, and mood [140]. Recently, Furuse and Hashimoto [141-143] reported that fluvoxamine is effective in treating the delirium associated with Alzheimer's disease and patients in intensive care units, and postoperative delirium, although these reports are case reports. Given the role of sigma-1 receptors in the regulation of neurotransmitters as well as in cognition [27, 30, 20], it is likely that again, they are the target of fluvoxamine's therapeutic action [144]. In order to confirm the role of sigma-1 receptors in the treatment of delirium, a randomized double-blind, placebo-controlled study of selective sigma-1 receptor agonists (for example, SA4503) in patients with delirium would be of interest.

9. CONCLUSION

As discussed here, sigma-1 receptors play a role in neuroplasticity and regulation of various neurotransmitter systems, and may be implicated in the pathophysiology of cognitive impairment in neuropsychiatric diseases. This would make sigma-1 receptor agonists attractive therapeutic drugs in the improvement of cognitive impairment, especially in schizophrenia and psychotic depression. The evolution of more selective sigma-1 receptor agonists and the analysis of their efficacy in the treatment of cognitive impairment associated with neuropsychiatric diseases are still needed.

ABBREVIATIONS

AChE	=	Acetylcholinesterase
AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP	=	Adenosine triphosphate
CNS	=	Central nervous system
DHEA	=	Dehydroepiandrosterone
DHEA-S	=	Dehydroepiandrosterone-sulphate

Table 3. Clinical Studies Using Fluvoxamine in Psychotic Depression

Study Design	Analyzed Sample Size	Duration of Administration	Dose (mg)	Evaluation Criteria	Efficacy (%)	Ref.
Open	59	6 weeks	300	HAM-D<=8 DDERS=0	84.2	[133]
Open	25	6/ 24 months (30 months)	300/ 200	Rate of recurrence	0/ 20	[134]
DBT, RCT	Flu+Pla: 36 Flu+Pin: 36	6 weeks	Flu: 300 Pin: 7.5	HAM-D<=8 DDERS=0	80.0 80.5	[135]
DBT, RCT	Flu: 14 Ven: 14	6 weeks	Flu: 300 Ven: 300	HAM-D<=8 DDERS=0	Flu: 78.6 Ven: 58.3	[136]
DBT, RCT	Flu+Pla: 13 Flu+Hal: 11 Des+Pla: 10 Des+Hal: 14	6 weeks	Flu: 300 Des: 150 Hal: 0.1mg/kg	HAM-D<=50% DDERS=0	Flu+Pla: 69 Flu+Hal: 45 Des+Pla: 40 Des+Hal: 64	[132]

DBT: Double-blind trial, RCT: Randomized controlled trial, HAM-D: Hamilton rating scale for depression, DDERS: Dimensions of delusional experience rating scale, Flu: Fluvoxamine, Pla: Placebo, Pin: Pindolol, Ven: Venlafaxine, Des: Desipramine, Hal: Haloperidol.

ECT = Electroconvulsive therapy
ER = Endoplasmic reticulum
$GABA_A$ = γ-aminobutyric acid type A
IP_3 = Inositol 1,4,5-triphsphate
NGF = Nerve-growth factor
NMDA = *N*-Methyl-D-aspartate
PCP = Phencyclidine
PET = Positron emission tomography
PPBP = 4-phenyl-1-(4-phenylbutyl)piperidine
(±)-PPCC = Methyl (1*R*,2*S*/1*S*,2*R*)-2-[4-hydroxy-4-phenylpiperidin-1-yl)methyl]-1-(4-methylphenyl) cyclopropanecarboxylate
PREG = pregnenolone
SA4503 = 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride
SSRI = Selective serotonin reuptake inhibitor
TCA = Tricyclic antidepressant

CONFLICT OF INTEREST

Dr. Hashimoto reports having received the speakers' bureau honoraria from Abbott Pharmaceuticals. Other authors report no competing interests.

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