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REVIEW ARTICLE

Cognition and depression: the effects of fluvoxamine, a sigma-1 receptor agonist, reconsidered

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Cognitive impairment is a primary feature of patients with major depressive disorder (MDD) and is characterised by stress-induced neural atrophy. Via alpha-adrenergic, anti-cholinergic and anti-histaminic activities, several antidepressants can cause significant counter-therapeutic cognitive impairment. Evidence is emerging of the involvement of sigma-1 receptor agonism in the mechanism of action of some antidepressants, notably fluvoxamine. Sigma-1 receptors are abundant in areas affected by depression/stress-induced cerebral atrophy and their ligands have a unique pharmacological profile; they may promote neurogenesis and initiate adaptive neural plasticity as a protection/reaction to stress. Fluvoxamine, as a potent sigma-1 receptor agonist, has shown ameliorating effects in animal models of psychosis, depression, stress, anxiety, obsessive-compulsive disorder (OCD) and aggression and has been shown to improve cognitive impairments. In humans, fluvoxamine may repair central nervous system (CNS) atrophy and restore cognitive function. The current review explores the mechanisms through which sigma-1 receptors can modulate cognitive function and examines how antidepressant therapy with fluvoxamine may help improve cognitive outcomes in patients with depression.

KEY WORDS — cognition; depression; fluvoxamine; neurogenesis; sigma-1 receptor

INTRODUCTION

Major depressive disorder (MDD) is the most common and widespread of all psychiatric disorders; it has a lifetime prevalence of 16.2%, a 12-month prevalence of 6.6% in developed countries (Trivedi *et al*., 2007) and is a leading cause of disability worldwide (WHO, 2008). The significant unmet therapeutic need in MDD is evidenced by increased levels of mortality and morbidity and reduced quality of life in patients with depression and up to 850 000 cases of suicide per annum (WHO, 2008).

Good cognitive function is fundamental to psychological well-being and for dealing with perceived stresses. Cognitive impairment is a ubiquitous and characteristic feature of patients suffering from MDD (Widlöcher, 1983) and causes not only aberrant coping with stress, a prime aetiological factor in the development of depression, but also reduced brain metabolism and neural atrophy, particularly in the hippocampus, amygdala and prefrontal cortex. These problems may be symptoms of depressive illness and persist (as residual symptoms) despite otherwise effective antidepressant therapy. They may also, however, emerge as adverse effects of some antidepressants (Fava, 2003). Residual symptoms (including anxiety, sleep disturbance, somnolence/fatigue and apathy) are common in individuals treated for MDD and they are associated with an increased risk of relapse and poor psychosocial functioning (Fava, 2006).

The first principle of pharmacotherapy is to 'do no harm' and it is particularly important that antidepressant therapy should cause no further cognitive impairment in patients with depression. This is especially so for elderly patients or those with an already reduced cognitive ability and also those patients where an intact cognitive function is an essential prerequisite for safe or optimal everyday functioning, e.g. students, car drivers, machine operators, etc.

This paper considers the role and mechanisms of the sigma-1 receptor in facilitating cognition and promoting neurogenesis and examines the potential for sigma-1 receptor agonists, e.g. fluvoxamine, to improve cognitive outcomes in patients with depression.

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A Medline search for peer-reviewed publications was conducted from 1975 to August 2008 using the keywords and subjects 'depression', 'MDD', 'cognition', 'cognitive', 'fluvoxamine', 'SSRI', 'impairment', 'neurogenesis', 'sigma' and 'antidepressant'. Further articles were found using the reference citations from articles identified in the Medline search.

COGNITION, DEPRESSION AND STRUCTURAL CHANGES IN THE BRAIN

Cognitive impairment broadly disrupts human behaviour and functioning and is both a cause and a symptom of depressive illness. Cognitive impairment is manifest in many ways in patients with MDD, including psychomotor retardation, memory loss, confused thought, impaired judgement, increased fear and psychotic thought, risky decision making and reduced learning competence (Silva and Larach, 2000; Porter *et al*., 2003; Campbell and Macqueen, 2004; Elderkin-Thompson *et al*., 2004; DeLuca *et al*., 2005; Thomas *et al*., 2008). In some individuals with a history of MDD, cognitive deficits (notably problem solving difficulties) also appear to be linked to suicidality (Crane *et al*., 2007).

It has long been hypothesised that the cognitive structures which enable the individual to represent the environment have a neuroanatomical underpinning (Sherwood *et al*., 2008). Whilst exposure to acute everyday stress can facilitate memory formation and consolidation, chronic stress and anxiety impairs cognitive performance (Reagan *et al*., 2008). Furthermore, 'depressogenic cognitions' are activated by chronic distress in MDD subjects, leading to stress exacerbation, anxiety and a poorer treatment outcome (Candrian *et al*., 2007).

It is now believed that chronic stress may elicit neurochemical, neuroanatomical and cellular changes that may have deleterious consequences on higher brain functioning. Significant neurobiological consequences involving structural, functional and molecular alterations occur in several areas of the brain, particularly in the hippocampus, amygdala and prefrontal cortex during depression (Bremner, 1999; Sapolsky, 2001; Maletic *et al*., 2007).

Atrophy of the human hippocampus is seen in a variety of psychiatric and neurological disorders such as recurrent depression, schizophrenia, bipolar disorder, post-traumatic stress disorder, epilepsy, head injury and Alzheimer's disease. Several studies using volumetric magnetic resonance imaging have found decreases in left hippocampal volumes (Bremner *et al*., 2000; Mervaala *et al*., 2000; Frodl *et al*., 2002; Vythilingam *et al*., 2002), right hippocampal volumes (Steffens *et al*., 2000) and total hippocampal volumes (Sheline *et al*., 1999; MacQueen *et al*., 2003; Dhikav and Anand, 2007) in patients with depressive illness. Decreases in hippocampal volume were associated with deficits in hippocampal-dependent measures of cognitive function. Imaging studies have revealed that the amygdala is a further site for neuroanatomical alterations in depressive illness (McEwen, 2003; Reagan *et al*., 2008).

Over a 3-year prospective study period, MDD patients showed significant grey matter density reductions within hippocampus, anterior cingulum, left amygdala and right dorsomedial prefrontal cortex compared with controls. Patients who experienced stable remission during this period had less volume decline than non-remitted patients in the left hippocampus, left anterior cingulum, left dorsomedial prefrontal cortex, and bilaterally in the dorsolateral prefrontal cortex (Frodl *et al*., 2008).

BEHAVIOURAL TOXICITY OF ANTIDEPRESSANTS

Clinical remission of the symptoms of depression is influenced by the degree of integrity of the cognitive system. It is therefore important that the drugs used to treat depression are free from untoward effects on cognitive and psychomotor competence.

Antidepressant agents can be broadly classified according to the extent to which they impair cognitive function because of their intrinsic pharmacological activity. This, so-called, behavioural toxicity (Hindmarch *et al*., 1990) is independent of the class of drug and differences exist between antidepressants irrespective of their attributed therapeutic class. As regards behavioural toxicity, antidepressants can be sedative, excitatory or neutral (Spring *et al*., 1992; Hindmarch, 1995; Wadsworth *et al*., 2005).

The broad receptor binding spectrum of antidepressants confers specific secondary pharmacodynamic properties and adverse behavioural effects. For example, paroxetine (selective serotonin reuptake inhibitor; SSRI) has significant anticholinergic properties and appreciable affinity for the noradrenaline transporter. Anticholinergic activity can lead to clinically significant cognitive impairment including forgetting, confusion and problems with concentration (Stein and Strickland, 1998; Ridout et al., 2003). A disruption of memory caused by paroxetine was evident in a clinical trial (Schmitt *et al*., 2001) where memory recall was impaired after 7 days of treatment at 20 mg/day. Cognitive and psychomotor impairment may occur regardless of the class of antidepressant. In a retro-

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spective study of 2428 nursing home residents there was little difference in rates of falls between those treated with tricyclic antidepressants and those treated with the SSRI sertraline (Thapa *et al*., 1998).

The secondary binding profile of the SSRI fluvoxamine includes potent agonist activity at sigma-1 receptors (Narita *et al*., 1996; Hashimoto, 2009). This may be of potential clinical significance as the (largely preclinical) evidence suggests that sigma-1 agonist activity may help reverse deleterious effects on brain function and cognitive faculties (Monnet, 2005; Hashimoto, 2009) and improve cognitive impairments in a patient with schizophrenia (Iyo *et al*., 2008).

CLINICAL SIGNIFICANCE OF SIGMA RECEPTORS

Sigma receptors, discovered in 1976 (Martin *et al*., 1976), have a unique pharmacological profile (Su and Hayashi, 2003) and are located in the cell membrane, although they are also dynamic endoplasmic reticulum (ER) proteins thought to affect intracellular second messenger systems, particularly calcium mobilisation. Sigma-1 receptors are found mainly in regions of the cerebellum, cingulate nucleus, hippocampus, hypothalamus and pones (Stahl, 2005). A recent study by Hayashi and Su (2007) identified the sigma-1 receptor as a novel ER chaperone. Sigma-1 receptors are predominantly expressed at the mitochondrial-associated ER membrane, thereby regulating the IP3 receptor-mediated Ca^{2+} influx from the ER to the mitochondria (Hayashi and Su, 2007). Because mitochondrial Ca^{2+} originating from the ER is a key activator of three dehydrogenases in the tricyclic acid (TCA) cycle, the sigma-1 receptors are assumed to serve as a regulator of ATP production and bioenergetics within the cell (Hayashi and Stahl, 2009).

Sigma-1 receptors have been shown to regulate a number of neurotransmitter systems, including the glutamatergic, dopaminergic, serotonergic, noradrenergic, and cholinergic systems. Glutamate modulation has the effect of promoting neurogenesis via nerve growth factor which initiated adaptive neural plasticity as a protection or reaction to stress (Takebayashi *et al*., 2002; Nishimura *et al*., 2008). The accumulated evidence also suggests that the activation/up regulation of sigma-1 receptors promotes neuronal differentiation as well as a robust anti-apoptotic action (Hayashi and Su, 2008). As reviewed by Stahl (2005), sigma-1 receptor ligands have been linked to the improvement of memory and learning processes (Debonnel and de Montigny, 1996; John *et al*., 1997; Waterhouse *et al*., 1997; Takebayashi *et al*., 2002; Guitart *et al*., 2004; Hashimoto *et al*., 2007), depression (Senda *et al*., 1996; Phan *et al*., 2002; Urani *et al*., 2002; Wang *et al*., 2003; Ishikawa and Hashimoto, 2010), anxiety (Ucar *et al*., 2002; Ishikawa and Hashimoto, 2010), psychosis (Kamei *et al*., 1998; Urani *et al*., 2002; Ishikawa and Hashimoto, 2010), stress (Bergeron and Debonnel, 1997; Maurice and Lockhart, 1997; Maurice *et al*., 2001), aggression (Phan *et al*., 2002) and pharmacodependence (Ucar *et al*., 1997; Maurice *et al*., 2001; Phan *et al*., 2002).

The action of sigma-1 receptor agonists on the function via NMDA receptors may be important as another mechanism of enhancement of glutamatergic function. It is known that sigma-1 receptor agonists do not bind to the glycine site on the NMDA receptors (located on post-synaptic neurons) because sigma-1 receptors located on the ER. However, it is well known that sigma-1 receptors might play a role in the central nervous system (CNS) as a modulator of signal transduction in neurotransmitter systems such as NMDA receptors (Hashimoto and Ishiwata, 2006). Thus, it seems that sigma-1 receptors might have important roles in glutamatergic function indirectly via NMDA receptors.

Various sigma-ligands have been investigated over the years for potential clinical applications. Preclinical and clinical studies have encompassed, for example, functional diarrhoea as a model of somatoform disorder (involving igmesine [also known as JO, 1784], a potent and selective ligand and one of the earliest tested [Roman *et al*., 1990]), depression (igmesine, opipramol), anxiety (opipramol, siramisine), schizophrenia (panamasine, rimcazole) and somatoform disorders (opipramol). In many cases, however, further development of these agents was stopped for commercial reasons (Volz and Stoll, 2004). Clinical investigations into the potential sigma receptor-related effects of fluvoxamine, however, continue.

FLUVOXAMINE

Several lines of evidence support the important role of the sigma-1 receptor agonism in the mechanism of action of fluvoxamine. Of a number of antidepressants tested, fluvoxamine was a ligand and had the highest affinity for the sigma-1 receptor in rat brain (Table 1; Narita *et al*., 1996; Hayashi and Su, 2004; Hashimoto, 2009).

Consistent with these findings, high occupancy of sigma-1 receptors has also been observed in living human brain following the administration of therapeutic doses of fluvoxamine (i.e. 50–200 mg) to 15 healthy male volunteers. A single administration of fluvoxamine (200 mg) but not paroxetine (20 mg) markedly decreased

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Table 1. *In vitro* affinity of various agents for rat sigma-1 binding sites (Narita *et al*., 1996; Hayashi and Su, 2004)

Drug	Ki (nM)		Ki ratio (sigma-2/sigma-1)
	Sigma-1	Sigma-2	
SSRIs			
Fluvoxamine	36	8439	234
Sertraline	57	5297	93
S(+)Fluoxetine	120	5480	46
(±)Fluoxetine	240	16 100	68
Citalopram	292	5410	19
Paroxetine	1893	22 870	12
Tricyclic antidepressants			
Imipramine	343	2107	6
Desipramine	1987	11 430	6

the distribution volume of [^{11}C]SA4503, a selective positron emission tomography (PET) ligand for the sigma-1 receptor in the brain (Figure 1). Also revealed by dynamic PET, fluvoxamine significantly and dose-dependently bound to sigma-1 receptors in all brain regions (i.e. frontal cortex, parietal cortex, occipital cortex, head of the caudate nucleus, thalamus and cerebellum). The dose-dependency also appeared to occur at the temporal cortex, anterior cingulated gyrus and putamen (correlation at these sites not statistically significant) (Ishikawa *et al*., 2007).

The relatively high affinity of fluvoxamine for the sigma-1 receptor may result in a variety of clinically relevant activities and may explain the ameliorating effects observed with fluvoxamine in animal models of psychoses, depression, stress, anxiety, obsessive-compulsive disorder (OCD), aggression, memory and learning (Kamei *et al*., 1998; Maurice *et al*., 1999a,b; Mamiya *et al*., 2000; Urani *et al*., 2001; Egashira *et al*., 2007; Hashimoto *et al*., 2007).

Phencyclidine-induced cognitive deficits in mice were significantly improved by sub-chronic (2-week) administration of fluvoxamine (20 mg/kg b.w./day), but not paroxetine (10 mg/kg b.w./day) or sertraline (10 or 20 mg/kg b.w./day) (Hashimoto *et al*., 2007; Ishima *et al*., 2009). Co-administration of NE-100 (1 mg/kg b.w./day) antagonised the effect of fluvoxamine, suggesting that the effects of fluvoxamine are mediated via agonistic activity at sigma-1 receptors (Hashimoto *et al*., 2007).

Fluvoxamine, via sigma-1 receptor agonism, was found to potentiate nerve-growth factor (NGF)-induced neurite outgrowth in PC12 cells (Figure 2). The potentiation by fluvoxamine was blocked by co-administration of the selective sigma-1 receptor antagonist NE-100, suggesting that sigma-1 agonists play a role in blocking the enhancement of NGF-induced neurite outgrowth. Unlike fluvoxamine, sertraline, which has a moderate affinity for

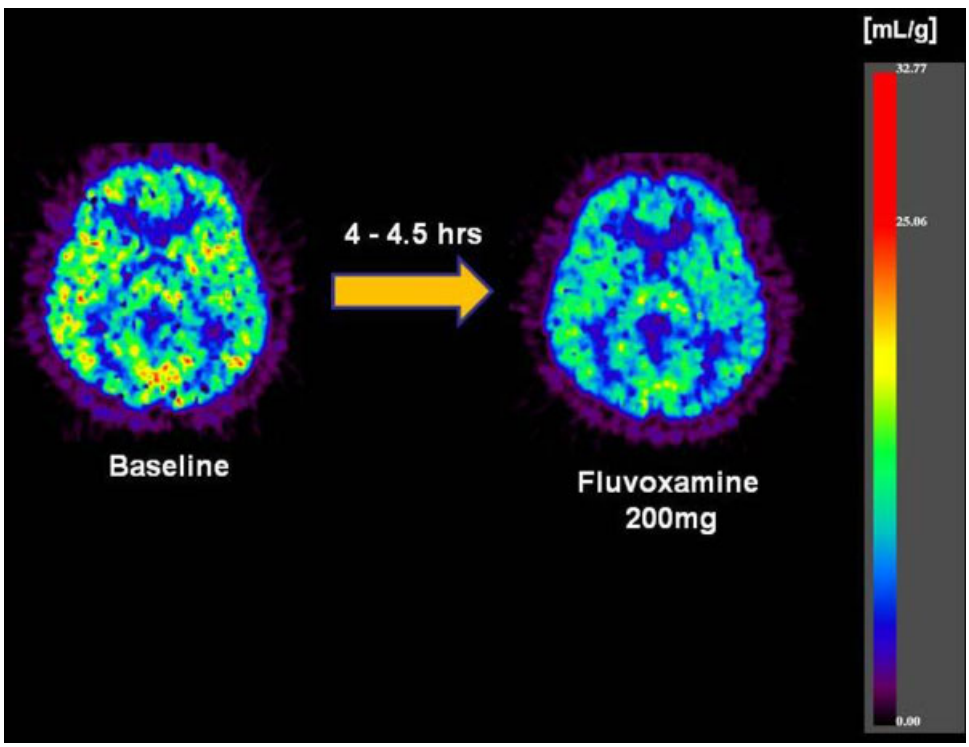

Figure 1. High occupancy of sigma-1 receptors in human brain by fluvoxamine, but not paroxetine; shown are distribution volume images of [11C]SA4503-PET before and after a single oral administration of each agent (reproduced with permission from Ishikawa *et al*., 2007)

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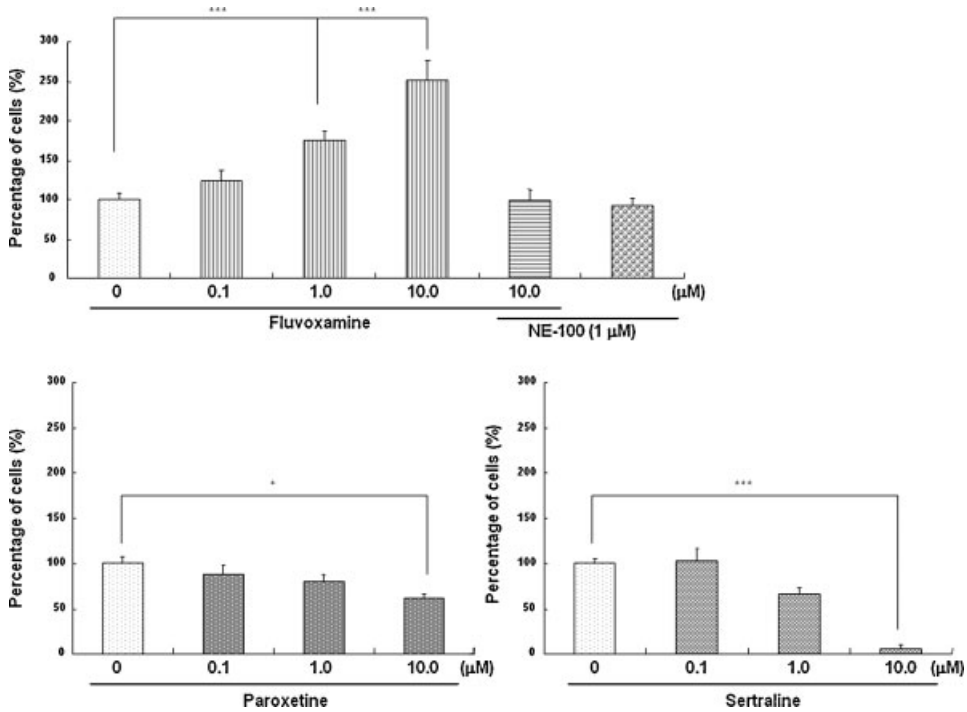

Figure 2. Effects of three SSRIs (fluvoxamine, sertraline, paroxetine) on NGF-induced neurite outgrowth in PC12 cells. Fluvoxamine (data show the mean ± SEM [$n = 6$]), paroxetine (mean ± SEM [$n = 6$]), sertraline (mean ± SEM [$n = 6$]). $^{*}p < 0.05$, $^{***}p < 0.001$ compared with control (NGF alone group). $^{+++}p < 0.001$ compared with fluvoxamine (10.0 μM) plus NE-100 group. The figure is a slight modification from the article (Nishimura *et al*., 2008)

sigma-1 receptors, did not alter NGF-induced neurite outgrowth. The reasons underlying this discrepancy between these two agents are currently unclear, although one possibility may involve the difference in pharmacological actions (agonist vs. antagonist) between them at sigma-1 receptors. Another possibility may be that other pharmacological activities of sertraline mask the effects of sigma-1 receptor agonism (Takebayashi *et al*., 2002; Nishimura *et al*., 2008). These findings suggest a potential sigma-1 receptor-mediated involvement of fluvoxamine in mechanisms of neuroplasticity (Hashimoto, 2009).

Although less well defined, the range of observed clinical effects is also consistent with sigma-1 receptor agonism and there are preliminary suggestions that fluvoxamine may also help to improve learning mechanisms.

Fluvoxamine significantly improved performance in the digit symbol substitution test ($p = 0.02$ vs. baseline) in a double-blind, randomised study (Perez and Ashford, 1990). In another study in 51 patients hospitalised for a major depressive episode, 4 weeks treatment with fluvoxamine resulted in significant symptomatic remission with higher total Wechsler IQ scores and a lower incidence of cognitive impairment in treatment responders (Mandelli *et al*., 2006). More recently, fluvoxamine improved cognitive impairments in a patient with schizophrenia an observation putatively linked to sigma-1 receptor agonism (Iyo *et al*., 2008).At present, it is difficult to assess the relevance of evidence that a sigma-1 receptor agonist fluvoxamine has beneficial effects on cognition in particular patient groups, such as the elderly. There are no reports showing that fluvoxamine has clinical superiority over other SSRIs in elderly patients with significant cognitive dysfunction although case reports may exist. Nonetheless, it is shown that sertraline is a sigma-1 receptor antagonist, and that paroxetine does not bind to sigma-1 receptors. In order to assess the role of sigma-1 receptor agonism in the mechanism of action, further detailed, randomised, double-blind controlled studies of SSRIs (fluvoxamine vs. sertraline or fluvoxamine vs. paroxetine) will be necessary.It is suggested that sigma-1 receptor agonists can serve as a regulator of ATP production and bioenergetics with the cell, suggesting that sigma-1 receptor agonists might have beneficial effects on the cell (Hayashi and Su, 2007; Hayashi and Stahl, 2009). Therefore, in terms of patients with dementia with or without depression, we, therefore, believe that a SSRI (e.g. fluvoxamine) with sigma-1 receptor agonist activity might have beneficial effects on cognition as compared with an SSRI with no sigma-1 receptor agonism.

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CONCLUSIONS

Patients with MDD experience a variety of symptoms consistent with cognitive impairment, and it is important for any selected antidepressant therapy to cause no further cognitive impairment. A normally functioning cognitive system is an important defence mechanism against stress and can be fundamental to minimising residual symptoms that impair remission and recovery.

The secondary binding properties of antidepressants may contribute differential positive and negative effects on cognitive function. Accumulated preclinical and clinical data support an antidepressant-like action of selective sigma-1 receptor agonists. It is thought that, overall, the activation of sigma-1 receptors may contribute to the proper functioning of active ion channels and signal transductions essential for physiological functions of neurons (e.g. neurotransmitter release). The activation of sigma-1 receptors may also induce potentiation of neurotrophic factor signalling, cellular differentiation and cell survival. Sigma-1 receptor ligands can modulate neurotransmitter release through interactions with muscarinic, dopaminergic, noradrenergic, serotonergic and histaminergic receptors along with intracellular kinase and phospholipase pathways. Chronic sigma-1 receptor activation also contributes to the formation and recomposition of membrane lipid rafts, with direct consequences for neuroplasticity (Hayashi and Su, 2008).

Certain ligands of the sigma-1 receptor are neuroprotective and appear to exert a potent neuromodulatory role in the brain that may have relevance in the response to anxiety and stress, depression, learning, cognition and antipsychotic activity. Fluvoxamine is a potent sigma-1 receptor agonist that may have particular benefits in the treatment of patients with severe MDD, those with psychotic depression, those with comorbid anxiety and those where any cognitive impairment could well compromise the performance of their everyday tasks or where a risk of cognitive failure would increase non-compliance or raise the risk of accident.

The clinical potential of sigma-1 receptor agonists (including fluvoxamine) is only just beginning to be explored. The primary clinical targets of sigma-1 receptor agonists in ongoing research include stroke, neurodegenerative disorders, depression, bipolar disorder and schizoaffective disorders (Hayashi and Su, 2008; Iyo *et al*., 2008; Stahl, 2008).

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