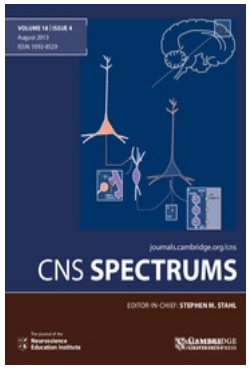


# Serotonergic modulation of glutamate neurotransmission as a strategy for treating depression and cognitive dysfunction

Alan L. Pehrson and Connie Sanchez

CNS Spectrums / *FirstView* Article / August 2013, pp 1 - 13
DOI: 10.1017/S1092852913000540, Published online: 01 August 2013

*CNS Spectrums*, page 1 of 13. © Cambridge University Press 2013
doi:10.1017/S1092852913000540

REVIEW ARTICLE

# Serotonergic modulation of glutamate neurotransmission as a strategy for treating depression and cognitive dysfunction

**Alan L. Pehrson, and Connie Sanchez***

*External Sourcing and Scientific Excellence, Lundbeck Research USA, Inc., Paramus, New Jersey, USA*

Monoamine-based treatments for depression have evolved greatly over the past several years, but shortcomings such as suboptimal efficacy, treatment lag, and residual cognitive dysfunction are still significant. Preclinical and clinical studies using compounds directly targeting glutamatergic neurotransmission present new opportunities for antidepressant treatment, with ketamine having a surprisingly rapid and sustained antidepressant effect that is presumably mediated through glutamate-dependent mechanisms. While direct modulation of glutamate transmission for antidepressant and cognition-enhancing actions may be hampered by nonspecific effects, indirect modulation through the serotonin (5-HT) system may be a viable alternative approach. Based on localization and function, 5-HT can modulate glutamate neurotransmission at least through the 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_3$, and 5-$HT_7$ receptors, which presents a rational pharmacological opportunity for modulating glutamatergic transmission without the direct use of glutamatergic compounds. Combining one or more of these glutamate-modulating 5-HT targets with 5-HT transporter inhibition may offer new therapeutic opportunities. The multimodal compounds vortioxetine and vilazodone are examples of this approach with diverse mechanisms, and their different clinical effects will provide valuable insights into serotonergic modulation of glutamate transmission for the potential treatment of depression and associated cognitive dysfunction.

*Received 28 May 2013; Accepted 2 July 2013*

**Key words**: α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), glutamate, metabotropic glutamate receptors (mGluRs), N-methyl-D-aspartate (NMDA), selective serotonin reuptake inhibitor (SSRI), serotonin (5-HT), serotonin transporter (SERT), vilazodone, vortioxetine.

## Clinical Implications

- Significant unmet needs exist in the treatment of major depressive disorder, such as suboptimal efficacy and residual cognitive dysfunction.
- A paradigm shift from the traditional monoamine therapeutics to approaches integrating glutamatergic function has occurred recently in antidepressant research, and has been especially fueled by the surprising rapid and sustained antidepressant effect of ketamine.
- We review the evidence that glutamate neurotransmission can be modulated indirectly by the 5-HT system through the 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_3$, and 5-$HT_7$ receptors, and discuss the therapeutic potential of a multimodal approach, combining one or more 5-HT receptor mechanisms with 5-HT reuptake inhibition.
- We review the available information for the two multimodal compounds vortioxetine and vilazodone, which are examples of this approach.

*Address for correspondence: Dr. Connie Sanchez, External Sourcing and Scientific Excellence, Lundbeck Research USA, Inc., 215 College Road, Paramus, NJ 07652, USA.
(Email: CS@lundbeck.com)

The authors thank Dr. Huailing Zhong of U-Pharm Laboratories LLC (Parsippany, NJ) for insightful and very valuable help with writing the manuscript, and Dr. David Simpson for helpful insights and comments.

## Introduction

Over the past 50 years, pharmacological treatments for major depressive disorder (MDD) have evolved from the older tricyclic antidepressants and monoamine oxidase inhibitors, to selective serotonin (5-HT) reuptake inhibitors (SSRI) and serotonin and norepinephrine (NE) reuptake inhibitors (SNRIs). In recent years, antidepressant combination therapies with multifunctional pharmacologic mechanisms have been used to enhance therapeutic outcomes.[1] Some combinations include an SSRI plus the 5-$HT_{1A}$ receptor and β adrenergic receptor antagonist pindolol,[2] or SSRIs augmented with atypical antipsychotics.[3] Despite these therapeutic evolutions, significant unmet needs still exist in treating depression, including improving suboptimal treatment response and remission rates, and cognitive impairments in domains such as memory, attention, executive function, and speed of processing.[4,5] Moreover, some cognitive disturbances may predict the development of mood disorders,[6] and furthermore may persist beyond remission.[7] Since cognitive dysfunction in

depression contributes significantly to disability in some patients,[8] its alleviation is an important goal.

The glutamate system is the major excitatory neurotransmitter system in the brain and is essential for cognitive processing. In depressed patients, neurochemical assessments have found increased basal glutamate levels in serum or plasma,[9–11] though changes in its levels in cerebrospinal fluid[12,13] and brain tissue[14,15] are somewhat inconsistent. Recent studies using magnetic resonance spectroscopy (MRS) in depressed patients have generally found reductions in GLX, a combined measure of glutamate and glutamine, possibly suggesting that the total glutamatergic pool available for synaptic and metabolic activities is reduced in depression.[16] However, studies that have directly measured glutamate using MRS have also found inconsistent results, with some groups finding increases, decreases, or no change in glutamate concentrations.[16] There is also evidence from studies of post-mortem brain tissue in depressed patients or suicide victims for altered expression of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors.[17–20] Given the complexity of glutamatergic neurotransmission and the diversity of these results, it is difficult to come to a definitive conclusion on the role of glutamate in the etiology of major depression at this time. In the future, information on functional single nucleotide polymorphisms related to the glutamate system may provide another valuable method of examining glutamate's role in this disease.

Nonetheless, interest in the role of glutamate in depression is quickly accreting, primarily due to the observation that the noncompetitive NMDA receptor antagonist ketamine engenders a fast and relatively long-lasting antidepressant effect.[21] This observation has prompted a new focus in antidepressant development toward integrating glutamatergic function,[22] leading to the suggestion of a wide range of glutamate targets for the treatment of depression.[23,24]

5-HT neurotransmission is regulated both by the serotonin transporter (SERT),[25] which has been a target of antidepressants for the past 30 years, and by modulation via 5-HT receptor subtypes,[26] some of which (such as the 5-$HT_{1A}$ receptor) may be independent therapeutic targets for the treatment of depression.[27] A substantial body of data shows that, in addition to modulating 5-HT neurotransmission, multiple 5-HT receptor subtypes can also modulate glutamate neurotransmission. This may be reflected in results from a recent preclinical study, which found that ketamine's fast antidepressant activity was abolished by 5-HT depletion,[28] suggesting that these effects may be serotonin-dependent. Thus, there may be an opportunity to integrate monoamine and glutamate strategies for treating depression. A new class of multimodal antidepressants has emerged, which, in addition to inhibiting the SERT, also modulate 5-HT receptors,[29,30] and may represent an example of this integrative strategy.

In this review, we summarize the current knowledge of putative glutamatergic antidepressants, 5-HT receptor-mediated glutamate modulation, and current evidence that multimodal serotonergic antidepressants with indirectly modulating roles on glutamate transmission are active in treating lowered mood and impaired cognition.

## Antidepressant Effects by Modulation of Glutamate Transmission

The glutamate receptors are divided into two major families: ionotropic and metabotropic glutamate receptors (mGluRs). The ionotropic family includes NMDA, AMPA, and kainate receptors. The metabotropic family consists of Group I receptors (mGluR1 and mGluR5), which potentiate both presynaptic glutamate release and postsynaptic NMDA currents, and group II (mGluR2 and mGluR3) and Group III receptors (mGluR4, mGluR6, mGluR7, and mGluR8), which in general suppress glutamate function.[31,32] Glutamate receptors are widely expressed in the brain, and some of them have been implicated in the treatment of depression.[33] Preclinical and clinical compounds acting via these targets and showing potential antidepressant activity are listed in Table 1.

Over-activation of extrasynaptic NMDA receptors is one of several hypothesized glutamate-related pathophysiologies for depression.[34] In support of this idea, the noncompetitive NMDA receptor antagonist ketamine at a single i.v. dosing shows rapid (~4 h) antidepressant effect that is sustained for up to 7 days in therapy-resistant depressed patients.[35] This rate of onset is extremely fast compared to the 2-3 weeks that approved antidepressants require. A single infusion of a subtype selective NMDA NR2B antagonist traxoprodil has shown a robust separation from placebo in treatment-resistant depression (60% vs 20% response) with sustained effects up to 1 week.[36] However memantine, a use-dependent NMDA receptor antagonist, has not demonstrated the same efficacy as ketamine, though it was not tested in the same paradigm as ketamine.[37] Part of the mechanism for the antidepressant effect of ketamine may involve disinhibition of pyramidal cell firing as a result of the antagonism of NMDA receptors located on interneurons.[38] However, it remains to be seen whether the NMDA receptor blockade alone mediates this fast antidepressant activity.

In support of a role for AMPA receptors in treating depression, preclinical studies suggest that ketamine

**Table 1.** *Examples of glutamatergic compounds with antidepressant or antidepressant-like properties*

| Compound examples | Mechanism of action | Development stage | Effects | References |
|---|---|---|---|---|
| Ketamine | NMDA antagonist | Clinical use | Rapid (~4 h) antidepressant effect; sustained for up to 1 week | 35,149 |
| Memantine | NMDA antagonist | Clinical use | No effect | 37 |
| Lamotrigine | Inhibition of glutamate release | Clinical use | Antidepressant properties in unipolar patients | 46,47 |
| Riluzole | Increase in glutamate uptake | Clinical use | Antidepressant efficacy in treatment-resistant and bipolar depression | 48,49 |
| Traxoprodil | NR2B antagonist | Clinical development | Antidepressant effect in treatment-resistant depression after a single infusion, sustained up to 1 week | 36 |
| Aniracetam | AMPA potentiator | Clinical development | Memory-enhancing effects, antidepressant-like behavioral effects | 43,44,150 |
| LY392098 | AMPA potentiator | Preclinical | Antidepressant-like effects in the tail suspension and forced-swim tests | 151 |
| MPEP | mGluR5 antagonist | Preclinical | Antidepressant-like effects in the mouse tail-suspension and rat forced swim tests | 50 |
| LY341495 | mGluR2/3 antagonist | Preclinical | Antidepressant-like effects; enhanced spatial memory | 52,152 |
| MGS0039 | mGluR2/3 antagonist | Preclinical | Antidepressant-like effects | 51 |
| GlyX13 | NMDA receptor glycine site partial agonist | Preclinical | Antidepressant-like effects | 153 |

exerts its antidepressant-like effect through AMPA receptors,[39] and that fast action is accompanied by rapid neuronal and synaptic adaptation.[32,40] It is widely believed that neuroadaptive changes represent a key event during antidepressant treatment, and may play a role in the delayed onset of efficacy in traditional antidepressants.[41,42] Thus, ketamine's rapid effects on neuroadaptation may be a key mechanism in its antidepressant effects, and may converge with the general actions of antidepressant treatments suggested in the past decades. Furthermore, the AMPA receptor potentiator aniracetam has shown an antidepressant-like profile.[43,44] However, the clinical benefit of AMPA receptor potentiation in depression remains unsubstantiated.

Lamotrigine, a modulator of glutamate release via its action on sodium and calcium channels, is approved for relapse prevention in bipolar disorder in the United States, and may have antidepressant properties in unipolar patients.[45] Additionally, it may accelerate the rate of onset in combination with traditional antidepressants.[46,47] Riluzole, which acts to rebalance glutamate levels by enhancing glutamate transport in astrocytes, has shown efficacy in treatment-resistant and bipolar depression.[48,49] Further examples of targets in the glutamate system with antidepressant-like implications include mGluR2/3 and mGluR5 antagonists or negative allosteric modulators.[50–52]

Thus, although there is evidence that drugs that negatively modulate some aspects of glutamate neurotransmission have antidepressant-like effects,[50–52] there is also evidence that increasing other aspects of glutamate signaling can have antidepressant-like effects.[43,44] It remains to be seen which variables are the true mediators of these effects. In comparison, the prominent role of glutamatergic neurotransmission in cognitive function is better understood. Antagonism of NMDA receptors[53] as well as other experimental manipulations that reduce aspects of glutamatergic neurotransmission, such as antagonism at AMPA[54] or mGlu5 receptors,[55] are known to consistently impair function across a range of cognitive domains. Accordingly, the glutamatergic neurotransmitter system has become a common target in developing cognition-enhancing drugs,[56] with the broad theme that increasing synaptic glutamate neurotransmission, for example using positive allosteric modulators at AMPA (AMPAkines[57]), mGluR5 (CDPPB[58]), or NMDA receptors (D-cycloserine[59]), improves cognitive function in rodent models. However, improving mood and cognition by directly modulating glutamatergic neurotransmission may be difficult, as excessive glutamatergic activation can lead to excitotoxic effects[60] and cognitive impairment.[61] Furthermore, the near-ubiquitous expression of glutamatergic receptors in the brain may hamper the specificity of drug development.

Thus, a strategy to indirectly modulate glutamatergic neurotransmission in selected brain regions may be more advantageous. A recent preclinical report

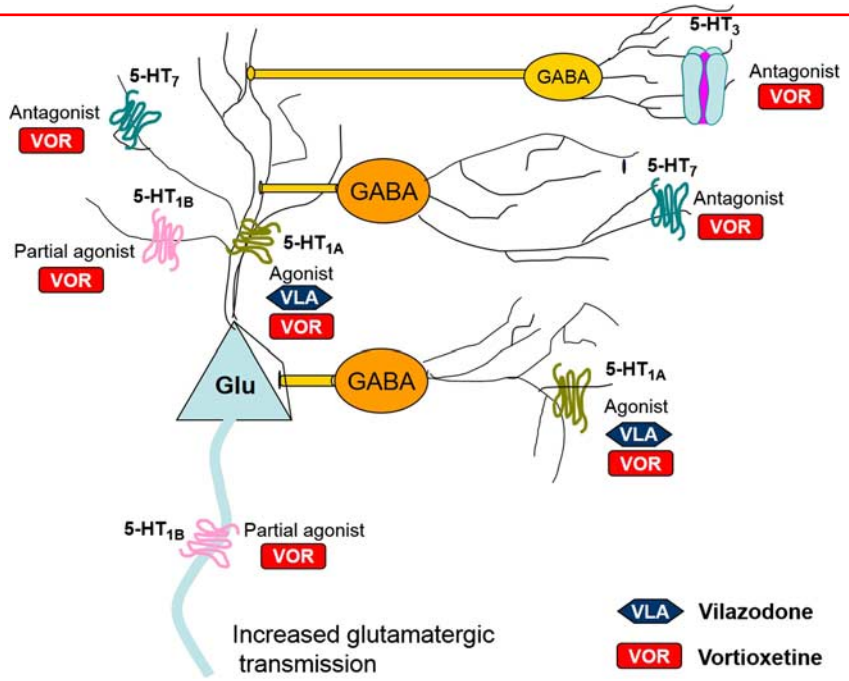


**Figure 1.** A schematic diagram of the hypothesized modulatory role of 5-HT receptors on glutamatergic neurotransmission. A glutamatergic pyramidal neuron and several GABA interneurons expressing the 5-$HT_3$, 5-$HT_{1A}$, 5-$HT_7$, and 5-$HT_{1B}$ receptors on either dendrites or axon terminals are shown. The multimodal compounds vortioxetine and vilazodone and their possible sites of action are also shown. Note that 5-$HT_{1A}$, 5-$HT_{1B}$, and 5-$HT_7$ receptors may be localized on different neuronal populations. Symbols used: VLA, vilazodone; VOR, vortioxetine.

demonstrated that 5-HT depletion abolished ketamine's antidepressant-like activity, suggesting that 5-HT plays an important role in its action.[28] Furthermore, multiple 5-HT receptors modulate glutamate neurotransmission. Taken together, these data make it reasonable to explore a strategy in which 5-HT receptor modulation can be used to alter glutamate neurotransmission in a manner that may improve both mood and cognitive function.

## Modulation of Glutamate Transmission by 5-HT Receptors

Here we discuss four 5-HT receptors known to be involved in the action of multimodal antidepressants that have been approved or are in the approval process, and which have the potential to modulate the glutamate system based on their localization and function.

### *5-$HT_{1A}$ receptors*

The 5-$HT_{1A}$ receptor is an inhibitory autoreceptor or heteroceptor located on serotonergic and other neurons, whose activation typically results in suppression of neuronal activity. The main function of presynaptic autoreceptors localized in the midbrain raphe nuclei is to self-regulate the function of the serotonergic system.[62] Desensitization of these autoreceptors is believed to play an important role in the onset of action of SERT inhibitors.[63,64] The antidepressant potential of 5-$HT_{1A}$ receptor agonism or partial agonism has been studied in both preclinical and clinical settings.[65,66]

As postsynaptic heteroreceptors, 5-$HT_{1A}$ is localized in the hippocampus, septum, amygdala, and corticolimbic areas.[67,68] Based on immunocytochemical studies, the 5-$HT_{1A}$ receptor is expressed in both pyramidal cells and GABAergic interneurons in the cortex and hippocampus.[69] Unlike presynaptic 5-$HT_{1A}$ receptors, which mainly act through inhibition of adenylate cyclase, postsynaptic 5-$HT_{1A}$ receptors exert their inhibitory action through G protein-coupled inwardly rectifying $K^+$ channels.[70] Due to the inhibitory nature of GABAergic interneurons, stimulation of 5-$HT_{1A}$ receptors located on interneurons can paradoxically increase cortical pyramidal cell firing, although higher doses can suppress it, probably due to the action of 5-$HT_{1A}$ receptors on the pyramidal cells.[71–73] Similarly, 5-$HT_{1A}$ receptor stimulation resulted in inhibition of GABAergic interneurons in the hippocampus.[74] Thus, based on the localization of 5-$HT_{1A}$ receptors on both GABA and glutamate neurons (Figure 1), their activation may lead to either an increase or a decrease in glutamate neurotransmission depending on which subpopulations of 5-$HT_{1A}$ receptors are activated.

Based on the above interaction between effects mediated through the 5-$HT_{1A}$ receptor and glutamatergic neurons, agonists of the 5-$HT_{1A}$ receptor are predicted to have a memory-modulating role, and this has been demonstrated in various preclinical studies.[75–77] The 5-$HT_{1A}$ receptor full agonist flesinoxan impairs working memory in a delayed conditional discrimination task in normal rats.[78] Mixed results have been shown in a passive avoidance test in mice, in which pretreatment with flesinoxan either decreased or increased memory function, depending on when it was administered.[79] In contrast, a memory-enhancing profile was consistently observed with 5-$HT_{1A}$ agonism in animals with learning and memory deficits. For example, the 5-$HT_{1A}$ receptor agonist 8-OH-DPAT reversed learning deficits induced by scopolamine and MK-801 in an autoshaping learning task.[77] Interestingly, a postsynaptic-selective 5-$HT_{1A}$ receptor agonist F15599 was reported to improve working and reference memory in rats with phencyclidine-induced memory deficits.[76,80] This seems consistent with the glutamatergic modulatory role of postsynaptic 5-$HT_{1A}$ heteroreceptors. Last, 5-$HT_{1A}$ receptor agonists, such as tandospirone, seem also to be able to alleviate the memory deficits induced by subchronic phencyclidine treatment.[80]

Thus, based on the localization and function of 5-$HT_{1A}$ heteroreceptors, 5-$HT_{1A}$ receptor stimulation has the potential to enhance or suppress glutamatergic neurotransmission, and thus may also have biphasic effects on mood or cognitive function.

### *5-$HT_{1B}$ receptors*

Like the 5-$HT_{1A}$ receptors, 5-$HT_{1B}$ receptors are distributed as autoreceptors or heteroreceptors throughout the brain, in areas such as the ventral pallidum, globus pallidus, substantia nigra, dorsal subiculum cerebral cortex, and the hippocampus.[81] Unlike the 5-$HT_{1A}$ autoreceptors, which are localized in somatodendritic regions of 5-HT neurons, 5-$HT_{1B}$ receptors are localized either presynaptically at nerve terminals or postsynaptically on dendrites.[81–83] Postsynaptic 5-$HT_{1B}$ receptors are co-localized with NMDA or AMPA receptors on dentrites, and are thus well-positioned to modulate glutamate transmission.[82,83] Recently, Cai et al[84] demonstrated that 5-$HT_{1B}$ receptor agonism increases hippocampal excitatory field potentials through a CaM kinase-dependent pathway. In the dorsal subiculum, however, 5-$HT_{1B}$ receptors are localized on CA1 pyramidal axon terminals as inhibitory heteroceptors,[85] and activation of these receptors attenuates glutamate transmission in the hippocampus due to its negative coupling to adenylate cyclase.[86–88]

The 5-$HT_{1B}$ receptor has been implicated in the pathophysiology and treatment of depression.[89,90] It has been shown that the 5-$HT_{1B}$ receptor agonist CP-94253 can modulate 5-HT synthesis in the Flinders Sensitive Line rat, an animal model of depression.[91] In intracerebral microdialysis studies, stimulation of 5-$HT_{1B}$ receptors by RU 24969 potentiated the antidepressant-like effects of SSRIs and imipramine.[92] Additionally, 5-$HT_{1B}$ receptor stimulation with the selective agonist CP-94253 in mice displayed an antidepressant-like profile in the forced swim test.[90]

The 5-$HT_{1B}$ receptor may modulate learning and memory through a glutamatergic mechanism. Intrahippocampal microinjection of the 5-$HT_{1B}$ receptor agonist CP-93129 impairs spatial learning performance in the radial maze task.[93] On the other hand, the 5-$HT_{1B}$ receptor antagonist SB-224289 enhanced memory consolidation during learning in an associative autoshaping learning task, and reversed the cognitive deficits induced by either the cholinergic inhibitor scopolamine or the NMDA receptor antagonist MK-801.[94] In an aversive contextual learning task in mice, the 5-$HT_{1B}$ receptor antagonist NAS-181 dose-dependently improved passive avoidance retention.[95]

Thus, 5-$HT_{1B}$ receptors may be able to positively or negatively modulate glutamate transmission and may be linked to the pathophysiology of depression. Due to the somewhat contrasting antidepressant-like properties of 5-$HT_{1B}$ receptor agonism and memory deficit-reducing effect of 5-$HT_{1B}$ receptor antagonism, a balance of stimulation versus blockade of this receptor may be needed. Based on this idea, a partial agonist for the 5-$HT_{1B}$ receptor may be a reasonable approach, although at the time of writing, the authors are not aware of any empirical investigations of the effects of 5-$HT_{1B}$ partial agonism on mood and cognitive function.

### *5-$HT_3$ receptors*

Among 5-HT receptors, the 5-$HT_3$ receptor is the only known excitatory ion channel, and is expressed throughout the brain, including the following regions: (1) hippocampus; (2) amygdala; and (3) entorhinal, frontal, and cingulate cortices.[96] Immunohistochemical studies show that 5-$HT_3$ receptors are localized in postsynaptic dendrites, especially of GABAergic interneurons in cortical and hippocampal regions.[97,98] These receptors function as a mechanism of 5-HT-mediated excitation of GABA neurons.[97] In freely moving rats, the 5-$HT_3$ receptor antagonist ondansetron significantly suppressed the firing rate of CA1 hippocampal GABAergic interneurons and concomitantly increased the firing rate of glutamatergic pyramidal cells by disinhibition.[99] Consistent with the above, activation of 5-$HT_3$ receptors can suppress both the spontaneous firing and NMDA-evoked responses of the pyramidal neurons in the rat medial

prefrontal cortex.[100,101] Thus, 5-$HT_3$ receptor antagonism enhances glutamate transmission by reducing GABA-mediated inhibition, as illustrated in Figure 1.

This mechanism may explain previous reports that 5-$HT_3$ receptor antagonism by ondansetron enhances long-term potentiation (LTP) and hippocampal and cortical theta rhythms.[102,103] Likewise, 5-$HT_3$ receptor antagonists also improve memory[102,104–107] in preclinical studies. For example, the 5-$HT_3$ receptor antagonist itasetron showed memory-enhancing effects in a multiple-choice avoidance behavioral task,[104] and ondansetron blocks scopolamine-induced deficits in learning.[108] In addition to the previously mentioned effects on cognition, 5-$HT_3$ receptor antagonists have antidepressant-like effects. The antagonists such as zacopride and ondansetron reversed helpless behavior in rats.[109] Newer antagonists also show antidepressant-like activities in the forced swim test and in olfactory bulbectomized rats.[110] 5-$HT_3$ receptor antagonists also augment the effects of SSRIs.[111,112]

In conclusion, 5-$HT_3$ receptor antagonism shows antidepressant-like activity and increased cognitive function in preclinical studies, possibly through facilitation of glutamate neurotransmission by reducing the activity of inhibitory GABA neurons.

### *5-$HT_7$ receptors*

The 5-$HT_7$ receptor is a G-protein-coupled receptor (GPCR) with positive coupling to adenylate cyclase, and is highly expressed in the brain, including the thalamus, hypothalamus, hippocampus, and cortex.[113] In midbrain slices of rat brain containing the dorsal and median raphe nuclei, the mixed 5-HT receptor agonist 5-carboxamido-tryptamine inhibited glutamate release, and this was reversed by the 5-$HT_7$ receptor antagonist SB-258719.[114] Thus, 5-$HT_7$ receptors in the axon terminals of the glutamatergic cortico-raphe neurons may serve as heteroreceptors that inhibit glutamate release.[114,115] The 5-$HT_7$ receptor is also expressed on the cell bodies of pyramidal neurons.[116] In normal animals, activation of the 5-$HT_7$ receptor leads to increased firing of glutamatergic neurons in the cortex[117] and hippocampus.[118] However, these effects on glutamatergic neurotransmission may be accompanied by increased inhibitory GABAergic transmission, likely due to expression in both pyramidal neurons and GABAergic interneurons. These concomitant effects were demonstrated in the hippocampus with an increase in the frequencies of both spontaneous inhibitory postsynaptic currents recorded in pyramidal neurons and spontaneous excitatory postsynaptic currents recorded in interneurons.[119] Based on these data, 5-$HT_7$ receptor activation has mixed effects on glutamatergic neurotransmission, but the overall effect in normal rodents appears to be excitatory.[117] Importantly, this relationship may be altered in disease states, as 5-$HT_7$ receptor activation in 6-hydroxydopamine-lesioned animals led to a net inhibition, rather than excitation, of pyramidal cell firing in the same study.[117] Based on these results, 5-$HT_7$ receptor antagonism may result in either increases or decreases in glutamatergic neurotransmission within the context of depression.

Although the effects of 5-$HT_7$ receptor modulation on glutamatergic neurotransmission are currently somewhat unclear, clear antidepressant-like activities of 5-$HT_7$ antagonism have been reported in a number of preclinical studies. Treatment with the 5-$HT_7$ receptor antagonist SB-269970 reduced immobility in the forced swim and tail suspension tests, and there was a further synergistic effect on extracellular 5-HT release in the frontal cortex when SB-269970 was combined with the SSRI citalopram.[120] Therefore, the results from preclinical studies suggest that 5-$HT_7$ receptor antagonism might be a novel strategy for treating depression.[121,122]

Additionally, memory-enhancing effects of 5-$HT_7$ antagonists have been shown in preclinical models[123–126] and have been reviewed elsewhere.[122] In cases where learning or memory was disrupted by NMDA antagonists such as phencyclidine or MK-801, 5-$HT_7$ receptor antagonism consistently improved performance.[123–125,127] Interestingly, combined 5-$HT_7$ receptor antagonism and SERT inhibition produced a synergistic effect in a preclinical test of executive function.[128]

These data support a modulatory role of 5-$HT_7$ receptors on glutamate transmission as mentioned above. 5-$HT_7$ receptor antagonism might be beneficial to cognitive function and antidepressant activity.

## Multimodal Antidepressants

There are currently two multimodal compounds with clinically documented antidepressant activity: vilazodone, which is approved for clinical use in the U.S., and vortioxetine, which is undergoing regulatory review. Given the complexity of the serotonergic modulation of glutamate, it is not possible to predict the net effect that multimodal serotonergic compounds will have on glutamate neurotransmission. Thus, the need for empirical data on the effects of these compounds on glutamate neurotransmission is paramount.

Vilazodone is a recently approved antidepressant with high affinities for the SERT ($IC_{50}$ 0.5 nM) and 5-$HT_{1A}$ receptor ($EC_{50}$ 0.2 nM)[129,130] (Table 2). Vilazodone is a partial agonist at the 5-$HT_{1A}$ receptor, but with a relatively high intrinsic activity—69% of the magnitude of the full 5-$HT_{1A}$ receptor agonist 8-OH-DPAT.[130] In preclinical studies, vilazodone seems to

**Table 2.** *Clinical compounds with serotonin (5-HT) transporter (SERT) inhibition plus activity at one or more 5-HT receptors linked to glutamatergic modulation*

| | | Vilazodone | Vortioxetine | |
|---|---|---|---|---|
| Target | Type of activity | Human $IC_{50}$ (nM) | Human $K_i$ (nM) | Rat $K_i$ (nM) |
| 5-$HT_3$ | Antagonist | | 3.7 | 1.1 |
| 5-$HT_7$ | Antagonist | | 19 | 200 |
| 5-$HT_{1B}$ | Partial agonist | | 33 | 16 |
| 5-$HT_{1A}$ | Agonist | 0.2 (69%) | 15 (full) | 230 |
| SERT | Inhibitor | 0.5 | 1.6 | 8.6 |
| References | | 129 | 112, 134, 135 | |

The *in vitro* pharmacological activities were from either binding or functional measurements. Numbers in parentheses denote agonist efficacy.

outperform the SSRIs paroxetine and fluoxetine, as measured by 5-HT release and ultrasonic vocalization. However, the fact that antidepressant-like effects are observed at moderate but not higher doses in the rat and mouse forced swim test may suggest that its 5-$HT_{1A}$ receptor partial agonism may inhibit the expression of rodent antidepressant-like behaviors.[130,131] Vilazodone's potential to interact with glutamate neurotransmission is illustrated in Figure 1. The antidepressant efficacy of vilazodone was seen only in some of the clinical trials, partly due to the need to balance the higher dose (40 mg) needed versus the high rate of gastrointestinal side effect, and thus its efficacy and safety profiles in comparison to current antidepressants require further clinical evaluation.[132,133]

Vortioxetine is an investigational multimodal antidepressant that acts as a 5-$HT_3$, 5-$HT_7$, and 5-$HT_{1D}$ receptor antagonist; 5-$HT_{1B}$ receptor partial agonist; 5-$HT_{1A}$ receptor agonist; and SERT inhibitor in vitro[112,134,135] (Table 2). Its pharmacological profile indicates that vortioxetine has the potential to modulate glutamate transmission through all of the four 5-HT receptor pathways discussed above (Figure 1). Multiple reports of preclinical studies have shown the antidepressant-like activities of vortioxetine.[112,134–138] Further, in clinical studies, its efficacy as an antidepressant has been demonstrated in several studies to date,[139–145] although statistically significant separation from placebo has not been observed in every clinical trial.[146,147] Recently, it was reported that vortioxetine enhanced time-dependent contextual fear memory and object recognition memory in rats.[148] Additionally, 5-HT depletion-induced memory deficits were dose-dependently reversed by vortioxetine treatment,[106] while escitalopram and duloxetine were inactive. These data strongly suggest that the receptor activities of vortioxetine contribute to its cognition-improving properties in rats.[106] In further support of the relevance of the receptor mechanism, this study reported improved memory performance in rats by a selective 5-$HT_{1A}$ receptor agonist and a 5-$HT_3$ receptor antagonist.[106] Furthermore, a recent clinical study in elderly depressed patients showed a beneficial effect of vortioxetine compared to placebo in cognitive tests of processing speed, verbal learning, and memory.[140] It should be noted that vortioxetine has a 10-fold lower in vitro affinity for rat 5-$HT_7$ ($K_i$ = 200 nM) compared with human 5-$HT_7$ receptors ($K_i$ = 19 nM), and a ~15-fold lower affinity at rat 5-$HT_{1A}$ ($K_i$ = 230 nM) compared with human 5-$HT_{1A}$ receptors ($K_i$ = 15 nM)[112] (Table 2). Thus, the contribution of the 5-$HT_7$ and 5-$HT_{1A}$ receptors in the clinic may be underestimated by evaluation of preclinical models. Based on the current preclinical understanding of the mechanisms and the preclinical and clinical results, we hypothesize that vortioxetine's multimodal profile including 5-$HT_3$ and 5-$HT_7$ antagonism, 5-$HT_{1B}$ partial agonism, and 5-$HT_{1A}$ agonism could result in enhanced glutamate transmission and contribute to its antidepressant and cognitive enhancing properties (Figure 1). However, the way in which vortioxetine modulates glutamate transmission remains to be empirically determined.

## Conclusions

Pharmacological treatments for major depressive disorder have evolved from monoamine-based therapies to integration of glutamatergic mechanisms. Data from current clinical and preclinical compounds targeting NMDA, AMPA, and mGluR receptors and glutamate transport present new opportunities for the treatment of depression. The serotonergic system can modulate glutamate transmission through 5-$HT_3$, 5-$HT_{1A}$, 5-$HT_7$, and 5-$HT_{1B}$ receptors. These 5-HT receptor targets present opportunities for integrating glutamatergic modulation into monoamine-based therapies, without the direct use of glutamatergic compounds. The multimodal compounds vilazodone and vortioxetine

are examples of this approach with diverse mechanisms, to indirectly modulate glutamate transmission by respectively targeting the 5-$HT_{1A}$ receptor, or 5-$HT_3$, 5-$HT_{1A}$, 5-$HT_7$, and 5-$HT_{1B}$ receptors along with the SERT. Clinical results with these multimodal compounds will provide valuable insights into whether exploiting serotonergic modulation of glutamate transmission is an effective strategy in treating depression.

## Disclosures

The work by both authors was performed as full-time employees of Lundbeck at the time of the study. Vortioxetine is currently under development by H. Lundbeck A/S and the Takeda Pharmaceutical Company, Ltd.

## References


1. Stahl SM. Enhancing outcomes from major depression: using antidepressant combination therapies with multifunctional pharmacologic mechanisms from the initiation of treatment. *CNS Spectr*. 2010; **15**(2): 79–94.
2. Artigas F, Adell A, Celada P. Pindolol augmentation of antidepressant response. *Curr Drug Targets*. 2006; **7**(2): 139–147.
3. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry*. 2009; **166**(9): 980–991.
4. Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropathology. *Br J Psychiatry*. 2001; **178**: 200–206.
5. Lee RS, Hermens DF, Porter MA, Redoblado-Hodge MA. A meta-analysis of cognitive deficits in first-episode major depressive disorder. *J Affect Disord*. 2012; **140**(2): 113–124.
6. Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. *Annu Rev Clin Psychol*. 2005; **1**: 167–195.
7. Hasselbalch BJ, Knorr U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect Disord*. 2011; **134**(1–3): 20–31.
8. Naismith SL, Longley WA, Scott EM, Hickie IB. Disability in major depression related to self-rated and objectively-measured cognitive deficits: a preliminary study. *BMC Psychiatry*. 2007; **7**: 32–38.
9. Altamura CA, Mauri MC, Ferrara A, *et al*. Plasma and platelet excitatory amino acids in psychiatric disorders. *Am J Psychiatry*. 1993; **150**(11): 1731–1733.
10. Kim JS, Schmid-Burgk W, Claus D, Kornhuber HH. Increased serum glutamate in depressed patients. *Arch Psychiatr Nervenkr*. 1982; **232**(4): 299–304.
11. Maes M, Verkerk R, Vandoolaeghe E, Lin A, Scharpe S. Serum levels of excitatory amino acids, serine, glycine, histidine, threonine, taurine, alanine and arginine in treatment-resistant depression: modulation by treatment with antidepressants and prediction of clinical responsivity. *Acta Psychiatr Scand*. 1998; **97**(4): 302–308.
12. Levine J, Panchalingam K, Rapoport A, Gershon S, McClure RJ, Pettegrew JW. Increased cerebrospinal fluid glutamine levels in depressed patients. *Biol Psychiatry*. 2000; **47**(7): 586–593.
13. Pangalos MN, Malizia AL, Francis PT, *et al*. Effect of psychotropic drugs on excitatory amino acids in patients undergoing psychosurgery for depression. *Br J Psychiatry*. 1992; **160**: 638–642.
14. Francis PT, Poynton A, Lowe SL, *et al*. Brain amino acid concentrations and Ca2+-dependent release in intractable depression assessed antemortem. *Brain Res*. 1989; **494**(2): 315–324.
15. Hashimoto K, Sawa A, Iyo M. Increased levels of glutamate in brains from patients with mood disorders. *Biol Psychiatry*. 2007; **62**(11): 1310–1316.
16. Yuksel C, Ongur D. Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biol Psychiatry*. 2010; **68**(9): 785–794.
17. Beneyto M, Meador-Woodruff JH. Lamina-specific abnormalities of NMDA receptor-associated postsynaptic protein transcripts in the prefrontal cortex in schizophrenia and bipolar disorder. *Neuropsychopharmacology*. 2008; **33**(9): 2175–2186.
18. Beneyto M, Kristiansen LV, Oni-Orisan A, McCullumsmith RE, Meador-Woodruff JH. Abnormal glutamate receptor expression in the medial temporal lobe in schizophrenia and mood disorders. *Neuropsychopharmacology*. 2007; **32**(9): 1888–1902.
19. Bleakman D, Alt A, Witkin JM. AMPA receptors in the therapeutic management of depression. *CNS Neurol Disord Drug Targets*. 2007; **6**(2): 117–126.
20. Mathew SJ, Manji HK, Charney DS. Novel drugs and therapeutic targets for severe mood disorders. *Neuropsychopharmacology*. 2008; **33**(9): 2080–2092.
21. Kendell SF, Krystal JH, Sanacora G. GABA and glutamate systems as therapeutic targets in depression and mood disorders. *Expert Opin Ther Targets*. 2005; **9**(1): 153–168.
22. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology*. 2012; **62**(1): 63–77.
23. Hashimoto K. The role of glutamate on the action of antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; **35**(7): 1558–1568.
24. Skolnick P, Popik P, Trullas R. Glutamate-based antidepressants: 20 years on. *Trends Pharmacol Sci*. 2009; **30**(11): 563–569.
25. Schloss P, Williams DC. The serotonin transporter: a primary target for antidepressant drugs. *J Psychopharmacol*. 1998; **12**(2): 115–121.
26. Smythies J. Section V. Serotonin system. *Int Rev Neurobiol*. 2005; **64**: 217–268.
27. Artigas F. Serotonin receptors involved in antidepressant effects. *Pharmacol Ther*. 2013; **137**(1): 119–131.

28. Gigliucci V, O'Dowd G, Casey S, *et al*. Ketamine elicits sustained antidepressant-like activity via a serotonin-dependent mechanism. *Psychopharmacology (Berl)*. 2013; **228**(1): 157–166.
29. Nutt DJ. Beyond psychoanaleptics—can we improve antidepressant drug nomenclature? *J Psychopharmacol*. 2009; **23**(4): 343–345.
30. Stahl SM, Lee-Zimmerman C, Cartwright S, Morrissette DA. Serotonergic drugs for depression and beyond. *Curr Drug Targets*. 2013; **14**(5): 578–585.
31. Javitt DC, Schoepp D, Kalivas PW, *et al*. Translating glutamate: from pathophysiology to treatment. *Sci Transl Med*. 2011; **3**(102): 102mr2.
32. Li N, Lee B, Liu RJ, *et al*. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010; **329**(5994): 959–964.
33. Catena-Dell'Osso M, Fagiolini A, Rotella F, Baroni S, Marazziti D. Glutamate system as target for development of novel antidepressants. *CNS Spectr*. In press.
34. McCarthy DJ, Alexander R, Smith MA, *et al*. Glutamate-based depression GBD. *Med Hypotheses*. 2012; **78**(5): 675–681.
35. Zarate CA Jr, Singh JB, Carlson PJ, *et al*. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006; **63**(8): 856–864.
36. Preskorn SH, Baker B, Kolluri S, *et al*. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J Clin Psychopharmacol*. 2008; **28**(6): 631–637.
37. Zarate CA Jr, Singh JB, Quiroz JA, *et al*. A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am J Psychiatry*. 2006; **163**(1): 153–155.
38. Anticevic A, Gancsos M, Murray JD, *et al*. NMDA receptor function in large-scale anticorrelated neural systems with implications for cognition and schizophrenia. *Proc Natl Acad Sci U S A*. 2012; **109**(41): 16720–16725.
39. Maeng S, Zarate CA Jr, Du J, *et al*. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry*. 2008; **63**(4): 349–352.
40. Tripp A, Oh H, Guilloux JP, Martinowich K, Lewis DA, Sibille E. Brain-derived neurotrophic factor signaling and subgenual anterior cingulate cortex dysfunction in major depressive disorder. *Am J Psychiatry*. 2012; **169**(11): 1194–1202.
41. Murphy SE, Norbury R, O'Sullivan U, Cowen PJ, Harmer CJ. Effect of a single dose of citalopram on amygdala response to emotional faces. *Br J Psychiatry*. 2009; **194**(6): 535–540.
42. Norbury R, Mackay CE, Cowen PJ, Goodwin GM, Harmer CJ. The effects of reboxetine on emotional processing in healthy volunteers: an fMRI study. *Mol Psychiatry*. 2008; **13**(11): 1011–1020.
43. Knapp RJ, Goldenberg R, Shuck C, *et al*. Antidepressant activity of memory-enhancing drugs in the reduction of submissive behavior model. *Eur J Pharmacol*. 2002; **440**(1): 27–35.
44. O'Neill MJ, Bleakman D, Zimmerman DM, Nisenbaum ES. AMPA receptor potentiators for the treatment of CNS disorders. *Curr Drug Targets CNS Neurol Disord*. 2004; **3**(3): 181–194.
45. Hahn CG, Gyulai L, Baldassano CF, Lenox RH. The current understanding of lamotrigine as a mood stabilizer. *J Clin Psychiatry*. 2004; **65**(6): 791–804.
46. Obrocea GV, Dunn RM, Frye MA, *et al*. Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry*. 2002; **51**(3): 253–260.
47. Normann C, Hummel B, Scharer LO, *et al*. Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled, double-blind study. *J Clin Psychiatry*. 2002; **63**(4): 337–344.
48. Zarate CA Jr, Payne JL, Quiroz J, *et al*. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry*. 2004; **161**(1): 171–174.
49. Sanacora G, Kendell SF, Fenton L, Coric V, Krystal JH. Riluzole augmentation for treatment-resistant depression. *Am J Psychiatry*. 2004; **161**(11): 2132.
50. Belozertseva IV, Kos T, Popik P, Danysz W, Bespalov AY. Antidepressant-like effects of mGluR1 and mGluR5 antagonists in the rat forced swim and the mouse tail suspension tests. *Eur Neuropsychopharmacol*. 2007; **17**(3): 172–179.
51. Chaki S, Yoshikawa R, Hirota S, *et al*. MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity. *Neuropharmacology*. 2004; **46**(4): 457–467.
52. Higgins GA, Ballard TM, Kew JN, *et al*. Pharmacological manipulation of mGlu2 receptors influences cognitive performance in the rodent. *Neuropharmacology*. 2004; **46**(7): 907–917.
53. Riedel G, Platt B, Micheau J. Glutamate receptor function in learning and memory. *Behav Brain Res*. 2003; **140**(1–2): 1–47.
54. Teixeira CM, Pomedli SR, Maei HR, Kee N, Frankland PW. Involvement of the anterior cingulate cortex in the expression of remote spatial memory. *J Neurosci*. 2006; **19**(29): 7555–7564.
55. Homayoun H, Stefani MR, Adams BW, Tamagan GD, Moghaddam B. Functional interaction between NMDA and mGlu5 receptors: effects on working memory, instrumental learning, motor behaviors, and dopamine release. *Neuropsychopharmacology*. 2004; **29**(7): 1259–1269.
56. Moghaddam B. Targeting metabotropic glutamate receptors for treatment of the cognitive symptoms of schizophrenia. *Psychopharmacology (Berl)*. 2004; **174**(1): 39–44.
57. Hamlyn E, Brand L, Shahid M, Harvey BH. The ampakine, Org 26576, bolsters early spatial reference learning and retrieval in the Morris water maze: a subchronic, dose-ranging study in rats. *Behav Pharmacol*. 2009; **20**(7): 662–667.

58. Fowler SW, Walker JM, Klakotskaia D, *et al*. Effects of a metabotropic glutamate receptor 5 positive allosteric modulator, CDPPB, on spatial learning task performance in rodents. *Neurobiol Learn Mem*. 2013; **99**: 25–31.
59. Ozawa T, Kumeji M, Yamada K, Ichitani Y. D-Cycloserine enhances spatial memory in spontaneous place recognition in rats. *Neurosci Lett*. 2012; **509**(1): 13–16.
60. Choi DW, Maulucci-Gedde M, Kriegstein AR. Glutamate neurotoxicity in cortical cell culture. *J Neurosci*. 1987; **7**(2): 357–368.
61. Zajaczkowski W, Frankiewicz T, Parsons CG, Danysz W. Uncompetitive NMDA receptor antagonists attenuate NMDA-induced impairment of passive avoidance learning and LTP. *Neuropharmacology*. 1997; **36**(7): 961–971.
62. Sprouse JS, Aghajanian GK. Electrophysiological responses of serotoninergic dorsal raphe neurons to 5-HT1A and 5-HT1B agonists. *Synapse*. 1987; **1**(1): 3–9.
63. Blier P, de Montigny C. Serotonin and drug-induced therapeutic responses in major depression, obsessive-compulsive and panic disorders. *Neuropsychopharmacology*. 1999; **21**(2 suppl): 91S–98S.
64. El Mansari M, Sanchez C, Chouvet G, Renaud B, Haddjeri N. Effects of acute and long-term administration of escitalopram and citalopram on serotonin neurotransmission: an in vivo electrophysiological study in rat brain. *Neuropsychopharmacology*. 2005; **30**(7): 1269–1277.
65. Kennett GA, Dourish CT, Curzon G. Antidepressant-like action of 5-HT1A agonists and conventional antidepressants in an animal model of depression. *Eur J Pharmacol*. 1987; **134**(3): 265–274.
66. Robinson DS, Rickels K, Feighner J, *et al*. Clinical effects of the 5-HT1A partial agonists in depression: a composite analysis of buspirone in the treatment of depression. *J Clin Psychopharmacol*. 1990; **10**(3 suppl): 67S–76S.
67. Martinez D, Hwang D, Mawlawi O, *et al*. Differential occupancy of somatodendritic and postsynaptic 5HT(1A) receptors by pindolol: a dose-occupancy study with [11C]WAY 100635 and positron emission tomography in humans. *Neuropsychopharmacology*. 2001; **24**(3): 209–229.
68. Santana N, Bortolozzi A, Serrats J, Mengod G, Artigas F. Expression of serotonin1A and serotonin2A receptors in pyramidal and GABAergic neurons of the rat prefrontal cortex. *Cereb Cortex*. 2004; **14**(10): 1100–1109.
69. Aznar S, Qian Z, Shah R, Rahbek B, Knudsen GM. The 5-HT1A serotonin receptor is located on calbindin- and parvalbumin-containing neurons in the rat brain. *Brain Res*. 2003; **959**(1): 58–67.
70. Luscher C, Jan LY, Stoffel M, Malenka RC, Nicoll RA. G protein-coupled inwardly rectifying K+ channels (GIRKs) mediate postsynaptic but not presynaptic transmitter actions in hippocampal neurons. *Neuron*. 1997; **19**(3): 687–695.
71. Llado-Pelfort L, Santana N, Ghisi V, Artigas F, Celada P. 5-HT1A receptor agonists enhance pyramidal cell firing in prefrontal cortex through a preferential action on GABA interneurons. *Cereb Cortex*. 2012; **22**(7): 1487–1497.
72. Llado-Pelfort L, Assie MB, Newman-Tancredi A, Artigas F, Celada P. Preferential in vivo action of F15599, a novel 5-HT(1A) receptor agonist, at postsynaptic 5-HT(1A) receptors. *Br J Pharmacol*. 2010; **160**(8): 1929–1940.
73. Wang S, Zhang QJ, Liu J, *et al*. The firing activity of pyramidal neurons in medial prefrontal cortex and their response to 5-hydroxytryptamine-1A receptor stimulation in a rat model of Parkinson's disease. *Neuroscience*. 2009; **162**(4): 1091–1100.
74. Levkovitz Y, Segal M. Serotonin 5-HT1A receptors modulate hippocampal reactivity to afferent stimulation. *J Neurosci*. 1997; **17**(14): 5591–5598.
75. Newman-Tancredi A, Martel JC, Assie MB, *et al*. Signal transduction and functional selectivity of F15599, a preferential post-synaptic 5-HT1A receptor agonist. *Br J Pharmacol*. 2009; **156**(2): 338–353.
76. Depoortere R, Auclair AL, Bardin L, *et al*. F15599, a preferential post-synaptic 5-HT1A receptor agonist: activity in models of cognition in comparison with reference 5-HT1A receptor agonists. *Eur Neuropsychopharmacol*. 2010; **20**(9): 641–654.
77. Meneses A, Hong E. 5-HT1A receptors modulate the consolidation of learning in normal and cognitively impaired rats. *Neurobiol Learn Mem*. 1999; **71**(2): 207–218.
78. Herremans AH, Hijzen TH, Olivier B, Slangen JL. Serotonergic drug effects on a delayed conditional discrimination task in the rat; involvement of the 5-HT1A receptor in working memory. *J Psychopharmacol*. 1995; **9**(3): 242–250.
79. Tsuji M, Takeda H, Matsumiya T. Modulation of passive avoidance in mice by the 5-HT1A receptor agonist flesinoxan: comparison with the benzodiazepine receptor agonist diazepam. *Neuropsychopharmacology*. 2003; **28**(4): 664–674.
80. Horiguchi M, Meltzer HY. The role of 5-HT1A receptors in phencyclidine (PCP)-induced novel object recognition (NOR) deficit in rats. *Psychopharmacology (Berl)*. 2012; **221**(2): 205–215.
81. Sari Y. Serotonin1B receptors: from protein to physiological function and behavior. *Neurosci Biobehav Rev*. 2004; **28**(6): 565–582.
82. Peddie CJ, Davies HA, Colyer FM, Stewart MG, Rodriguez JJ. A subpopulation of serotonin 1B receptors colocalize with the AMPA receptor subunit GluR2 in the hippocampal dentate gyrus. *Neurosci Lett*. 2010; **485**(3): 251–255.
83. Peddie CJ, Davies HA, Colyer FM, Stewart MG, Rodriguez JJ. Dendritic colocalisation of serotonin1B receptors and the glutamate NMDA receptor subunit NR1 within the hippocampal dentate gyrus: an ultrastructural study. *J Chem Neuroanat*. 2008; **36**(1): 17–26.

84. Cai X, Kallarackal AJ, Kvarta MD, *et al*. Local potentiation of excitatory synapses by serotonin and its alteration in rodent models of depression. *Nat Neurosci*. 2013; **16**(4): 464–472.
85. Ait AD, Segu L, Naili S, Buhot MC. Serotonin 1B receptor regulation after dorsal subiculum deafferentation. *Brain Res Bull*. 1995; **38**(1): 17–23.
86. Boeijinga PH, Boddeke HW. Activation of 5-HT1B receptors suppresses low but not high frequency synaptic transmission in the rat subicular cortex in vitro. *Brain Res*. 1996; **721**(1–2): 59–65.
87. Mlinar B, Falsini C, Corradetti R. Pharmacological characterization of 5-HT(1B) receptor-mediated inhibition of local excitatory synaptic transmission in the CA1 region of rat hippocampus. *Br J Pharmacol*. 2003; **138**(1): 71–80.
88. Stepien A, Chalimoniuk M, Strosznajder J. Serotonin 5HT1B/1D receptor agonists abolish NMDA receptor-evoked enhancement of nitric oxide synthase activity and cGMP concentration in brain cortex slices. *Cephalalgia*. 1999; **19**(10): 859–865.
89. Svenningsson P, Chergui K, Rachleff I, *et al*. Alterations in 5-HT1B receptor function by p11 in depression-like states. *Science*. 2006; **311**(5757): 77–80.
90. Tatarczynska E, Klodzinska A, Stachowicz K, Chojnacka-Wojcik E. Effects of a selective 5-HT1B receptor agonist and antagonists in animal models of anxiety and depression. *Behav Pharmacol*. 2004; **15**(8): 523–534.
91. Skelin I, Kovacevic T, Sato H, Diksic M. The opposite effect of a 5-HT1B receptor agonist on 5-HT synthesis, as well as its resistant counterpart, in an animal model of depression. *Brain Res Bull*. 2012; **88**(5): 477–486.
92. Redrobe JP, MacSweeney CP, Bourin M. The role of 5-HT1A and 5-HT1B receptors in antidepressant drug actions in the mouse forced swimming test. *Eur J Pharmacol*. 1996; **318**(2–3): 213–220.
93. Buhot MC, Patra SK, Naili S. Spatial memory deficits following stimulation of hippocampal 5-HT1B receptors in the rat. *Eur J Pharmacol*. 1995; **285**(3): 221–228.
94. Meneses A. Could the 5-HT1B receptor inverse agonism affect learning consolidation? *Neurosci Biobehav Rev*. 2001; **25**(2): 193–201.
95. Eriksson TM, Madjid N, Elvander-Tottie E, *et al*. Blockade of 5-HT 1B receptors facilitates contextual aversive learning in mice by disinhibition of cholinergic and glutamatergic neurotransmission. *Neuropharmacology*. 2008; **54**(7): 1041–1050.
96. Thompson AJ, Lummis SC. 5-HT3 receptors. *Curr Pharm Des*. 2006; **12**(28): 3615–3630.
97. Puig MV, Santana N, Celada P, Mengod G, Artigas F. In vivo excitation of GABA interneurons in the medial prefrontal cortex through 5-HT3 receptors. *Cereb Cortex*. 2004; **14**(12): 1365–1375.
98. Morales M, Bloom FE. The 5-HT3 receptor is present in different subpopulations of GABAergic neurons in the rat telencephalon. *J Neurosci*. 1997; **17**(9): 3157–3167.
99. Reznic J, Staubli U. Effects of 5-HT3 receptor antagonism on hippocampal cellular activity in the freely moving rat. *J Neurophysiol*. 1997; **77**(1): 517–521.
100. Ashby CR Jr, Minabe Y, Edwards E, Wang RY. 5-HT3-like receptors in the rat medial prefrontal cortex: an electrophysiological study. *Brain Res*. 1991; **550**(2): 181–191.
101. Liang X, Arvanov VL, Wang RY. Inhibition of NMDA-receptor mediated response in the rat medial prefrontal cortical pyramidal cells by the 5-HT3 receptor agonist SR 57227A and 5-HT: intracellular studies. *Synapse*. 1998; **29**(3): 257–268.
102. Staubli U, Xu FB. Effects of 5-HT3 receptor antagonism on hippocampal theta rhythm, memory, and LTP induction in the freely moving rat. *J Neurosci*. 1995; **15**(3 pt 2): 2445–2452.
103. Sanchez C, Robichaud PJ, Pehrson A, Leiser SC. The effects of the multimodal antidepressant Lu AA21004 on attention and vigilance measured as EEG activity in the rat. *Eur Neuropsychopharmacol*. 2012; **22**(suppl 2): S243–S244.
104. Pitsikas N, Borsini F. Itasetron (DAU 6215) prevents age-related memory deficits in the rat in a multiple choice avoidance task. *Eur J Pharmacol*. 1996; **311**(2–3): 115–119.
105. Roychoudhury M, Kulkarni SK. Effects of ondansetron on short-term memory retrieval in mice. *Methods Find Exp Clin Pharmacol*. 1997; **19**(1): 43–46.
106. Pehrson A, Gaarn du Jardin Nielsen K, Jensen JB, Sanchez C. The novel multimodal antidepressant Lu AA21004 improves memory performance in 5-HT depleted rats via 5-HT3 and 5-HT1A receptor mechanisms. *Eur Neuropsychopharmacol*. 2012; **22**(suppl 2): S269–S269.
107. Fontana DJ, Daniels SE, Henderson C, Eglen RM, Wong EH. Ondansetron improves cognitive performance in the Morris water maze spatial navigation task. *Psychopharmacology (Berl)*. 1995; **120**(4): 409–417.
108. Carey GJ, Costall B, Domeney AM, *et al*. Ondansetron and arecoline prevent scopolamine-induced cognitive deficits in the marmoset. *Pharmacol Biochem Behav*. 1992; **42**(1): 75–83.
109. Martin P, Gozlan H, Puech AJ. 5-HT3 receptor antagonists reverse helpless behaviour in rats. *Eur J Pharmacol*. 1992; **212**(1): 73–78.
110. Mahesh R, Bhatt S, Devadoss T, *et al*. Antidepressant potential of 5-HT3 receptor antagonist, N-n-propyl-3-ethoxyquinoxaline-2-carboxamide (6n). *J Young Pharm*. 2012; **4**(4): 235–244.
111. Kos T, Popik P, Pietraszek M, *et al*. Effect of 5-HT3 receptor antagonist MDL 72222 on behaviors induced by ketamine in rats and mice. *Eur Neuropsychopharmacol*. 2006; **16**(4): 297–310.
112. Mørk A, Pehrson A, Tottrup BLT, *et al*. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J Pharmacol Exp Ther*. 2012; **340**(3): 666–675.
113. Hedlund PB, Sutcliffe JG. Functional, molecular and pharmacological advances in 5-HT7 receptor research. *Trends Pharmacol Sci*. 2004; **25**(9): 481–486.

114. Harsing LG Jr. The pharmacology of the neurochemical transmission in the midbrain raphe nuclei of the rat. *Curr Neuropharmacol*. 2006; **4**(4): 313–339.
115. Duncan MJ, Congleton MR. Neural mechanisms mediating circadian phase resetting by activation of 5-HT(7) receptors in the dorsal raphe: roles of GABAergic and glutamatergic neurotransmission. *Brain Res*. 2010; **1366**: 110–119.
116. Bickmeyer U, Heine M, Manzke T, Richter DW. Differential modulation of I(h) by 5-HT receptors in mouse CA1 hippocampal neurons. *Eur J Neurosci*. 2002; **16**(2): 209–218.
117. Fan LL, Zhang QJ, Liu J, *et al*. In vivo effect of 5-HT(7) receptor agonist on pyramidal neurons in medial frontal cortex of normal and 6-hydroxydopamine-lesioned rats: an electrophysiological study. *Neuroscience*. 2011; **190**: 328–338.
118. Tokarski K, Zahorodna A, Bobula B, Hess G. 5-HT7 receptors increase the excitability of rat hippocampal CA1 pyramidal neurons. *Brain Res*. 2003; **993**(1–2): 230–234.
119. Tokarski K, Kusek M, Hess G. 5-HT7 receptors modulate GABAergic transmission in rat hippocampal CA1 area. *J Physiol Pharmacol*. 2011; **62**(5): 535–540.
120. Bonaventure P, Kelly L, Aluisio L, *et al*. Selective blockade of 5-hydroxytryptamine (5-HT)7 receptors enhances 5-HT transmission, antidepressant-like behavior, and rapid eye movement sleep suppression induced by citalopram in rodents. *J Pharmacol Exp Ther*. 2007; **321**(2): 690–698.
121. Hedlund PB. The 5-HT7 receptor and disorders of the nervous system: an overview. *Psychopharmacology (Berl)*. 2009; **206**(3): 345–354.
122. Stahl SM. The serotonin-7 receptor as a novel therapeutic target. *J Clin Psychiatry*. 2010; **71**(11): 1414–1415.
123. Meneses A. Effects of the 5-HT7 receptor antagonists SB-269970 and DR 4004 in autoshaping Pavlovian/instrumental learning task. *Behav Brain Res*. 2004; **155**(2): 275–282.
124. McLean SL, Woolley ML, Thomas D, Neill JC. Role of 5-HT receptor mechanisms in sub-chronic PCP-induced reversal learning deficits in the rat. *Psychopharmacology (Berl)*. 2009; **206**(3): 403–414.
125. Horiguchi M, Huang M, Meltzer HY. The role of 5-hydroxytryptamine 7 receptors in the phencyclidine-induced novel object recognition deficit in rats. *J Pharmacol Exp Ther*. 2011; **338**(2): 605–614.
126. Waters KA, Stean TO, Hammond B, *et al*. Effects of the selective 5-HT(7) receptor antagonist SB-269970 in animal models of psychosis and cognition. *Behav Brain Res*. 2012; **228**(1): 211–218.
127. Bonaventure P, Aluisio L, Shoblock J, *et al*. Pharmacological blockade of serotonin 5-HT(7) receptor reverses working memory deficits in rats by normalizing cortical glutamate neurotransmission. *PLoS One*. 2011; **6**(6): e20210.
128. Nikiforuk A. Selective blockade of 5-HT7 receptors facilitates attentional set-shifting in stressed and control rats. *Behav Brain Res*. 2012; **226**(1): 118–123.
129. Heinrich T, Bottcher H, Gericke R, *et al*. Synthesis and structure–activity relationship in a class of indolebutylpiperazines as dual 5-HT(1A) receptor agonists and serotonin reuptake inhibitors. *J Med Chem*. 2004; **47**(19): 4684–4692.
130. Page ME, Cryan JF, Sullivan A, *et al*. Behavioral and neurochemical effects of 5-(4-[4-(5-cyano-3-indolyl)-butyl)-butyl]-1-piperazinyl)-benzofuran-2-carboxamide (EMD 68843): a combined selective inhibitor of serotonin reuptake and 5-hydroxytryptamine(1A) receptor partial agonist. *J Pharmacol Exp Ther*. 2002; **302**(3): 1220–1227.
131. De Paulis T. Drug evaluation: vilazodone—a combined SSRI and 5-HT1A partial agonist for the treatment of depression. *IDrugs*. 2007; **10**(3): 193–201.
132. Guay DR. Vilazodone hydrochloride, a combined SSRI and 5-HT1A receptor agonist for major depressive disorder. *Consult Pharm*. 2012; **27**(12): 857–867.
133. Wang SM, Han C, Lee SJ, Patkar AA, Pae CU. A review of current evidence for vilazodone in major depressive disorder. *Int J Psychiatry Clin Pract*. In press.
134. Bang-Andersen B, Ruhland T, Jørgensen M, *et al*. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. *J Med Chem*. 2011; **54**(9): 3206–3221.
135. Westrich L, Pehrson A, Zhong H, *et al*. In vitro and in vivo effects of the multimodal antidepressant vortioxetine (Lu AA21004) at human and rat targets. *Int J Psychiatry Clin Pract*. 2012; **5**(suppl 1): 47–47.
136. Pehrson AL, Cremers T, Betry C, *et al*. Lu AA21004, a novel multimodal antidepressant, produces regionally selective increases of multiple neurotransmitters—a rat microdialysis and electrophysiology study. *Eur Neuropsychopharmacol*. 2013; **23**(2): 133–145.
137. Bétry C, Pehrson AL, Etievant A, *et al*. The rapid recovery of 5-HT cell firing induced by the antidepressant vortioxetine involves 5-HT3 receptor antagonism. *Int J Neuropsychopharmacol*. 2013; **16**(5): 1115–1127.
138. Li Y, Pehrson AL, Budac DP, Sanchez C, Gulinello M. A rodent model of premenstrual dysphoria: progesterone withdrawal induces depression-like behavior that is differentially sensitive to classes of antidepressants. *Behav Brain Res*. 2012; **234**(2): 238–247.
139. Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2012; **15**(5): 589–600.
140. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol*. 2012; **27**(4): 215–223.
141. Baldwin DS, Loft H, Dragheim M. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive

disorder (MDD). *Eur Neuropsychopharmacol*. 2012; **22**(7): 482–491.

142. Baldwin DS, Loft H, Florea I. Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. *Int Clin Psychopharmacol*. 2012; **27**(4): 197–207.
143. Boulenger JP, Loft H, Florea I. A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. *J Psychopharmacol*. 2012; **26**(11): 1408–1416.
144. Henigsberg N, Mahableshwarkar AR, Jacobsen P, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry*. 2012; **73**(7): 953–959.
145. Baldwin DS, Hansen T, Florea I. Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. *Curr Med Res Opin*. 2012; **28**(10): 1717–1724.
146. Mahableshwarkar AR, Jacobsen PL, Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. *Curr Med Res Opin*. 2013; **29**(3): 217–226.
147. Jain R, Mahableshwarkar AR, Jacobsen PL, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *Int J Neuropsychopharmacol*. 2013; **16**(2): 313–321.
148. Mørk A, Montezinho LP, Miller S, *et al*. Vortioxetine (Lu AA21004), a novel multimodal antidepressant, enhances memory in rats. *Pharmacol Biochem Behav*. 2013; **105C**: 41–50.
149. Berman RM, Cappiello A, Anand A, *et al*. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000; **47**(4): 351–354.
150. Koliaki CC, Messini C, Tsolaki M. Clinical efficacy of aniracetam, either as monotherapy or combined with cholinesterase inhibitors, in patients with cognitive impairment: a comparative open study. *CNS Neurosci Ther*. 2012; **18**(4): 302–312.
151. Li X, Tizzano JP, Griffey K, *et al*. Antidepressant-like actions of an AMPA receptor potentiator (LY392098). *Neuropharmacology*. 2001; **40**(8): 1028–1033.
152. Bespalov AY, van Gaalen MM, Sukhotina IA, *et al*. Behavioral characterization of the mGlu group II/III receptor antagonist, LY-341495, in animal models of anxiety and depression. *Eur J Pharmacol*. 2008; **592**(1–3): 96–102.
153. Burgdorf J, Zhang XL, Nicholson KL, *et al*. GLYX-13, a NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects without ketamine-like side effects. *Neuropsychopharmacology*. 2013; **38**(5): 729–742.