Title: The Serotonin 1A ($5\text{-}HT_{1A}$) receptor as a Pharmacological Target in Depression

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Abstract

Clinical depression is a common, debilitating and heterogenous disorder. Existing treatments for depression are inadequate for a significant minority of patients and new approaches are urgently needed. A wealth of evidence implicates the serotonin-1A (5-HT_{1A}) receptor in the pathophysiology of depression. 5-HT_{1A} receptor stimulation is an existing therapeutic target for treating depression and anxiety, using drugs such as buspirone and tandospirone. However, activation of 5-HT_{1A} raphe autoreceptors has also been suggested to be responsible for the delay in the therapeutic action of conventional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs). This narrative review provides a brief overview of the 5-HT_{1A} receptor, the evidence implicating it in depression, and the effects of conventional antidepressant treatment. We highlight that pre-synaptic and post-synaptic 5-HT_{1A} receptors may have divergent roles in the pathophysiology and treatment of depression. To date, developing this understanding to progress therapeutic discovery has been limited, partly due to a paucity of specific pharmacological probes suitable for use in humans. The development of 5-HT_{1A} 'biased agonism', using compounds such as NLX-101, offers the opportunity to further elucidate the roles of pre-synaptic and post-synaptic 5-HT_{1A} receptors. We describe how experimental medicine approaches can be helpful in profiling the effects 5-HT_{1A} receptor modulation has on the different clinical domains of depression and outline some potential neurocognitive models that could be used to test the effects of 5-HT_{1A} biased agonists.

Key points

1. There is a breadth of pre-clinical and clinical evidence implicating serotonin 1A (5-HT_{1A}) receptors in the pathophysiology of depression
2. Pre-synaptic and post-synaptic 5-HT_{1A} receptors could have divergent roles in the causation and treatment of depression
3. The development of 5-HT_{1A} 'biased agonism' offers the opportunity to further elucidate the roles of pre-synaptic and post-synaptic 5-HT_{1A} receptors in the pathophysiology of depression, using human neurocognitive models.

1. Introduction

In 1979, using ligand binding approaches, Peroutka and Snyder identified two subtypes of serotonin (5-HT) receptors which were named 5-HT_1 and 5-HT_2 [1]. Subsequent work showed that the 5-HT_1 receptor could itself be subdivided into further subtypes with the 5-HT_{1A} receptor being characterised by the binding of spiperone and 8-OH-DPAT [2]. The aim of this review is to bridge the gap between the abundance of pre-clinical *in vitro* and *in vivo* evidence for a 5-HT_{1A} receptor role in depression to the study and treatment of patients with depression. Our approach will use the lens of experimental medicine, highlighting the currently available ligands for 5-HT_{1A} receptors and how novel pharmacological probes could help answer, and create, the most important and relevant questions to help patients with depression in the future.

5-HT_{1A} receptors have a wide distribution in the central nervous system and are found on post-synaptic sites in the frontal cortex, hippocampus, amygdala and hypothalamus (Figure 1) [3-5]. Another population of 5-HT_{1A} receptors is located on the cell bodies and dendrites of 5-HT neurons originating from the raphe nuclei [6, 7]. These 5-HT_{1A} receptors function as inhibitory autoreceptors and when activated they decrease 5-HT cell firing and diminish 5-HT release in terminal fields [8].

Activation of post-synaptic 5-HT_{1A} receptors is likewise inhibitory in nature and can modulate the release of other neurotransmitters such as GABA and acetylcholine [9-11]. Sometimes this can lead to a disinhibition of downstream neuronal activity. For example, stimulation of post-synaptic 5-HT_{1A} receptors on inhibitory GABAergic interneurons can lead to excitation of pyramidal neurons and increased glutamate release [12, 13]. This may be relevant to the intriguing observation that in animal models, the antidepressant-like effect of the NMDA receptor antagonist, ketamine is abolished by selective 5-HT_{1A} receptor blockade [14].

1.1 Intracellular signalling pathways of the 5-HT_{1A} receptor

The 5-HT_{1A} receptor is similar to most other 5-HT receptors in being G-protein coupled [15]. The 5-HT_{1A} receptor is typically coupled to the G_i intracellular protein, which when activated inhibits adenylate cyclase, decreasing cyclic adenosine 3′,5′-monophosphate (cAMP) formation [16]. 5-HT_{1A} receptor stimulation can also open G-protein-gated inwardly rectifying potassium channels, leading to neuronal hyperpolarisation and inhibition of voltage-gated calcium channels [17, 18].

It is now recognised that 5-HT_{1A} receptors can also signal through non-conventional, or non-canonical, intracellular pathways involving alternative G-proteins (such as $G\alpha_o$ or $G\alpha_z$ [16, 19]) or G-protein independent mechanisms [16, 20]. This includes activation of mitogen-activated protein

kinase (MAPK), particularly extracellular signal-regulated (ERK), pathways which can lead to induction of the cAMP response element-binding protein (CREB) transcription factor, a target of antidepressant treatments in animal models [21, 22]. New evidence has demonstrated that 5-HT_{1A} receptors can oligomerise with other membrane complexes to alter intracellular signalling, for instance 5-HT_7 receptors dimerising with 5-HT_{1A} receptors to inhibit signalling through G_i proteins [23].

This range of interactions allows the 5-HT_{1A} receptor to influence a wide repertoire of downstream responses including structural neuronal changes as well as alterations in synaptic plasticity [24]. It is not known how these alternative pathways are selected when activated by 5-HT. However, there seem to be differences based on brain localisation. For example, there are regional differences in the coupling of 5-HT_{1A} receptors to different G proteins, with 5-HT_{1A} receptors interacting exclusively with $G\alpha_{i3}$ in the anterior raphe, mainly with $G\alpha_o$ in the hippocampus and equally with $G\alpha_{i3\ and}$ $G\alpha_o$ in the cerebral cortex [25]. Furthermore, activation of raphe nucleus 5-HT_{1A} receptors causes downstream inhibition of ERK1/2 [26], whereas hippocampal 5-HT_{1A} receptors produce an increase in ERK1/2 signalling [27]. This regional variability opens the exciting possibility that pharmacological agents could selectively act on 5-HT_{1A} receptors in specific brain regions, as will be described later.

2. Are 5-HT_{1A} receptors affected in depression?

Clinical depression is a substantial health problem and the underlying biological is incompletely understood. The 5-HT theory of depression is over 50 years old but single neurotransmitter theories of pathophysiology are no longer regarded as tenable because of the complex nature and heterogeneity of depressive symptomatology [28-30].

Nevertheless, 5-HT pathways form a widely projecting, neuromodulatory system that influences neuropsychological processes of great relevance to depression including emotional responses, reward learning, anxiety, sleep and appetite [31-34]. Disturbances in 5-HT regulation are present in depression but are subtler and more complex than the originally proposed 5-HT deficit. Much work has focused on the possible role of the 5-HT_{1A} receptor in depression and this work will be briefly summarised here.

2.1 Post-mortem studies

Post-mortem studies of 5-HT_{1A} receptor binding in deceased individuals with depression were mainly conducted 10-20 years ago and the findings are rather contradictory [35]. Important confounding factors in these studies could lie in the characteristics of the sample used, including the presence of antidepressant treatment, mode of death (particularly suicide vs non-suicide) and co-morbid substance misuse.

In the raphe nuclei, both increased and decreased 5-HT_{1A} receptor binding were reported, perhaps representing a combination of some regional specificity of the observed changes and heterogeneity of the clinical samples used [36-38]. With the aforementioned reservations the overall picture is one of diminished 5-HT_{1A} receptor binding in cortical and subcortical post-synaptic regions in depression. Support for diminished post-synaptic 5-HT_{1A} receptor availability in depression comes from the post-mortem study of 5-HT_{1A} mRNA using in situ hybridisation. Levels of 5-HT_{1A} mRNA in patients with depression were significantly lower than those of controls in both dorsolateral prefrontal cortex and hippocampus [39]. This finding distinguished patients with major depression from those with schizophrenia or bipolar disorder [39].

2.2 Neuroimaging studies

Positon Emission Tomography (PET) ligand studies provide the opportunity to assess 5-HT_{1A} receptor binding in the living human brain. Whilst the literature indicates that there are changes in 5-HT_{1A} receptor binding in depression [3] there is inconsistency regarding the direction of these changes and where in the brain they occur.

Most studies have found that 5-HT_{1A} receptor binding exhibits a modest reduction in both post-synaptic and raphe regions in unmedicated patients with depression [40, 41]. Nevertheless, this apparent consensus is complicated by one group who have consistently found unmedicated patients with depression to have higher 5-HT_{1A} receptor binding in the raphe region, as well as cortical areas compared to control subjects [42, 43].

These contrasting findings could relate to technical and sample factors. The principal technical factor is believed to be the choice of reference tissue (usually the cerebellum) with which to compare 5-HT_{1A} receptor binding in regions of interest [44]. However, the matter is unresolved. Sample factors could include depression subtype, previous exposure to medication for depression and co-morbid diagnoses.

It is interesting to note that where studies have found a decrease in 5-HT_{1A} receptor binding, this decrease persists in people who have recovered from depression and are off medication, while the

binding in the raphe normalises. This suggests that that lower cortical 5-HT_{1A} receptor binding could represent a trait marker that predisposes to depression [45].

2.3 Pharmacological challenge studies

The availability of drugs that can be used in humans and possess some selectivity for 5-HT_{1A} receptors has led to studies that have probed the function of brain 5-HT_{1A} receptors in people with depression.

In studies of depression, a commonly-used agent has been buspirone, possibly because of its availability and familiarity in clinical settings [46, 47]. However, other agents, such as ipsapirone, gepirone and flesinoxan have also been used [46, 48]. Typical functional markers of 5-HT_{1A} receptor activation in humans include increased secretion of certain anterior pituitary hormones, such as adrenocorticotropic hormone (ACTH, with a consequent increase in plasma cortisol) and growth hormone [3, 49, 50], and a decrease in body temperature [50, 51]. Some agents, such as buspirone also increase plasma prolactin, but this is not thought to be mediated by 5-HT_{1A} receptors [52].

It is agreed that the ACTH and growth hormone responses to 5-HT_{1A} receptor challenge in humans is due to stimulation of post-synaptic 5-HT_{1A} receptors in the hypothalamus [53]. However, the location of the receptors involved in the hypothermic response has been debated [51]. There appear to be species differences, in that hypothermia in response to 5-HT_{1A} receptor activation is clearly mediated by 5-HT_{1A} autoreceptors in the mouse, while in the rat both pre- and post-synaptic receptors appear to be involved [54-56].

In humans, the location of the receptors relevant to 5-HT_{1A} receptor-related hypothermic responses is not clearly resolved. However, in healthy participants, cortisol treatment attenuates 5-HT_{1A} autoreceptor function as measured by EEG changes [57] and similar cortisol treatment blunts the hypothermic response, but not the growth hormone response, to buspirone challenge [58]. This suggest that in humans the hypothermic response to 5-HT_{1A} receptor agonist challenge at least involves 5-HT_{1A} autoreceptors.

In summary, the majority of studies investigating 5-HT_{1A}-mediated responses in unmedicated patients with depression have found blunted endocrine and/or hypothermic responses to pharmacological challenge though there is some disagreement [59-63]. Overall, this impaired functional response is consistent with post-mortem and PET binding studies suggesting that depression is associated with deficient 5-HT_{1A} receptor activity, both pre- and post-synaptically. Intriguingly, treatment with selective serotonin reuptake inhibitors (SSRIs) in patients with

depression and in healthy participants serves to decrease pre- and post-synaptic 5-HT_{1A} receptor function [63, 64].

This change in 5-HT_{1A} receptor sensitivity with SSRIs is presumably an adaptive response to elevated levels of synaptic 5-HT and reflects increased 5-HT neurotransmission in spite of the down-regulation of post-synaptic 5-HT_{1A} receptor sensitivity [63]. It also points to the need to study patients with depression who have been unmedicated for long periods of time, to avoid the possibility of abnormalities in 5-HT_{1A} receptors actually being a result of prior antidepressant treatment rather than the clinical disorder.

2.4 Genetic studies

In the era of candidate gene studies there was natural interest in the polymorphisms in the 5-HT_{1A} receptor gene as possible genetic risk markers of depression. Indeed, a single nucleotide polymorphism (SNP) at C(-1019)G was shown to regulate 5-HT_{1A} receptor gene expression in raphe neurons with this SNP influencing how transcription factors suppress 5-HT_{1A} receptor expression [65]. GG homozygotes exhibit a reduced ability to bind transcription factor, thus enabling greater expression of 5-HT_{1A} autoreceptors in raphe neurons [66]. Thus GG (-1019) homozygotes would in theory display increased raphe inhibition and a consequent decrease in 5-HT transmission throughout the brain.

Whether this relationship can be demonstrated in human PET studies of 5-HT_{1A} receptor binding is unclear. For example, one group found that in unmedicated patients with depression and healthy controls, 5-HT_{1A} receptor binding in the raphe increased with each G allele an individual possessed [67]. However two studies, each of 35 healthy volunteers, found no significant differences in raphe 5-HT_{1A} receptor binding between the different -1019 genotype groups (mean ± SD [^{18}F]MPPF BP_{ND} values of raphe nuclei C/C = 0.21 ± 0.07; C/G = 0.27 ± 0.11; G/G = 0.27 ± 0.19) [68] [69].

Studies have also explored whether the C/G polymorphism in the 5-HT_{1A} receptor gene is associated with an increased risk of major depression or the response to antidepressant treatment. Once again results from studies have been conflicting [43, 65, 70, 71]. While some investigations have suggested that the GG genotype is associated with an elevated risk of depression [65], the poor replicability of candidate gene studies and the lack of confirmation from GWAS investigations indicate that such findings should be received with caution. Similar comments apply to the possible poorer response of depressed G allele carriers to antidepressant treatment.

3. Conventional 5-HT_{1A} receptor ligands as possible antidepressants

3.1 Pharmacological probes for 5-HT_{1A} receptor activation in humans

The most widely available probe for assessing the clinical effects of 5-HT_{1A} receptor agonism is buspirone, which has an aryl-piperazine linked to an azaspirodecanedione moiety [47]. As the latter is a defining feature, buspirone is also referred to an azapirone. The 'azapirone' class includes gepirone, ipsapirone and tandospirone [46]. Flesinoxan is a phenylpiperazine derivative and unlike the azapirones is not metabolised to 1-(2-pyrimidinyl)piperazine (1-PP), an alpha$_2$-adrenoceptor antagonist [72].

Most of these drugs exhibit a degree of multimodality, that is activity at other neurotransmitter receptors (Table 1). This results in challenges in attributing particular behavioural or therapeutic effects specifically to 5-HT_{1A} receptor activation. For example, buspirone has affinity for dopamine D_2 and D_3 receptors [47] while tandospirone exhibits dopamine D_4 receptor engagement [73]. Gepirone has relatively weak affinity for dopamine D_2-receptors, making it a more useful probe of 5-HT_{1A} receptors [73].

Affinity and efficacy of agonists for the 5-HT_{1A} receptor varies, although all generally bind with high affinity with pKi < 10. However, this is not always paralleled with efficacy. For example, while flesinoxan and tandospirone have similar efficacy to 5-HT itself at the 5-HT_{1A} receptor [74], ipsapirone has half the efficacy of 5-HT (see Table 1) [75].

3.2 Evidence-based treatment for depression

Broadly, 5-HT_{1A} receptor agonists show antidepressant activity, alleviating depression more than placebo (RR 0.74, 95% CI 0.65-0.83) [46]. There may be within-class differences in antidepressant efficacy, with more robust effects seen with buspirone, gepirone and flesinoxan [46, 48, 76, 77], than agents such as ipsapirone [78-80]. Licensing does not reflect this directly, with buspirone and tandospirone approved for anxiety disorders rather than depression. Some 5-HT_{1A} receptor agonists are noted to have dose limiting side effects; for example, flesinoxan would likely produce unacceptable adverse effects at the doses required for adequate receptor occupancy in humans [75]. Ipsapirone has been found to be less well tolerated than SSRI comparators [78-80].

3.3 Pre/post synaptic 5-HT_{1A} receptor efficacy: implications for antidepressant action

Conventional 5-HT_{1A} receptor agonists act at both pre- and post-synaptic 5-HT_{1A} receptors to varying degrees. The azapirones such as buspirone and gepirone behave as full agonists at 5-HT_{1A} autoreceptors but as partial agonists at post-synaptic 5-HT_{1A} receptors [81]. These actions may provide a suboptimal pharmacological profile for the treatment of depression where the aim is to

facilitate overall neurotransmission at post-synaptic 5-HT_{1A} receptors. However, flesinoxan has greater agonist activity at post-synaptic 5-HT_{1A} receptors [73], and may have superior antidepressant activity, though as noted above with poor tolerability.

Some 5-HT_{1A} receptor antagonists have also been used in humans. The highly selective 5-HT_{1A} receptor antagonist, WAY-100635, has been widely employed as a radioligand in PET studies [44, 82, 83]. It binds similarly to both pre- and post-synaptic 5-HT_{1A} receptors. The beta-adrenoceptor antagonist, pindolol, also has a high affinity for 5-HT_{1A} receptors and has been used to block the neuroendocrine and hypothermic effects of buspirone [52].

The ability of pindolol to desensitise 5-HT_{1A} receptors, through its partial 5-HT_{1A} receptor agonism [84, 85], has been used to expedite the therapeutic action of SSRIs. The notion underlying this approach is that SSRIs are unable to exert their full therapeutic effect until 5-HT_{1A} autoreceptors have been desensitised, thereby freeing 5-HT neurons from inhibitory feedback control [86]. Desensitising the 5-HT_{1A} autoreceptor with pindolol should in theory allow the full effect of the SSRI on 5-HT neurotransmission to be expressed from the beginning of treatment.

There is some evidence that pindolol can speed the onset of the clinical antidepressant effect of SSRIs [87, 88], although it has been suggested that the dose of pindolol used in the clinical studies is probably too low to occupy 5-HT_{1A} autoreceptors in humans [89]. However *in vitro* work suggests the dose of pindolol does not alter G protein activation when 5-HT_{1A} receptor levels are moderate in density [90, 91]. Finally, in patients with depression, a more selective and classical 5-HT_{1A} receptor antagonist, DU-125530, failed to speed the therapeutic onset of action of the SSRI, fluoxetine [92].

3.4 Biased agonists of 5-HT_{1A} receptors

Biased agonism describes an agonist that activates a sub-population of receptors, through selective activation of specific intracellular pathways [93]. Through this selectivity, the biased agonist may then act preferentially on receptors located in particular brain regions (Figure 1) [24, 73].

As noted above it is now apparent that the intracellular responses to 5-HT_{1A} receptor activation include not only inhibition of adenylate cyclase but also a variety of 'non-canonical' pathways, in part, through selective binding of agonists to different G proteins [20, 25]. This property confers the potential ability to activate distinct subpopulations of 5-HT_{1A} receptors [94]. Two compounds available for human use are of particular interest, NLX-101 and NLX-112. Both drugs are selective for the 5-HT_{1A} receptor where they act as full agonists, but NLX-101 appears to preferentially activate cortical 5-HT_{1A} receptors while NLX-112 acts roughly equally at both 5-HT_{1A} autoreceptors and cortical receptors [73].

This distinction is supported by electrophysiological evidence in the rat. Specifically, whilst NLX-101 is able to suppress raphe 5-HT cell firing, consistent with 5-HT_{1A} autoreceptor activation, it is far more potent in increasing the firing of pyramidal neurons, an effect blocked by WAY-100635, suggesting these effects are 5-HT_{1A} specific [95]. This suggests a relative selectivity of NLX-101 for cortical 5-HT_{1A} receptors located on GABA interneurons. In contrast, NLX-112 showed a different pattern, with a similar dose needed to inhibit raphe firing and stimulate pyramidal neuron firing [96].

The differential effects of NLX-101 and NLX-112 on pre- and post-synaptic 5-HT_{1A} receptors is of interest when assessing their effects in animal models of depression. In the forced swim test both NLX-101 [97] and NLX-112 [98] reduced immobility with little difference between them in relative potencies of effect (Table 1). In the chronic mild stress (CMS) test, a single days' treatment with NLX-101 produced a prolonged reversal of the stress-induced decrease in sucrose consumption [99]. Sucrose consumption is considered a model of anhedonia, which suggests a possible activity of NLX-101 on this important clinical symptom. The effect of NLX-112 in the CMS test does not appear to have been reported.

Classically, activation of 5-HT_{1A} autoreceptors has been seen as an important mechanism in anxiety reduction. In the marble burying paradigm in mice, often used as a model of obsessive compulsive disorder and anxiety, NLX-112 was effective at a lower dose than NLX-101 [100]. In the elevated plus maze paradigm, a commonly used model of approach anxiety, NLX-112 0.1mg/kg elicited an anxiolytic effect in mice [101], compared to the higher dose of 5mg/kg of NLX-101 in rats (Wistar strain) (see Table 1) [102]. In summary, whilst drawn from different paradigms in different species, the evidence suggests that for the treatment of anxiety, NLX-112 may be a better candidate than NLX-101, which could be related to NLX-112's more potent, presynaptic 5-HT_{1A} receptor action.

Cognitive deficits are important in clinical depression and are not sufficiently addressed by current pharmacological treatments, even when an antidepressant response is obtained [103, 104]. The role of 5-HT_{1A} receptors in cognition is complex with both 5-HT_{1A} receptor agonists and antagonists reported to improve aspects of learning and memory in preclinical paradigms measuring spatial learning, aversive learning and working memory [105-107]. In healthy participants 5-HT_{1A} receptor agonists, such as buspirone and tandospirone, have little or no effect on cognition, though the data are somewhat inconsistent [108, 109]. In contrast, in patients with schizophrenia, the same agents have been reported to produce small improvements in some aspects of cognition [11]. Rather similarly, a single dose of ipsapirone reportedly impaired verbal learning in healthy participants but tended to improve it in patients with depression [62].

Studies in rats indicated that NLX-101 given as sole treatment had a largely pro-cognitive effect on a range of tasks [73]. NLX-101 also attenuated cognitive deficits produced by phencyclidine and scopolamine [110, 111]. These findings suggest that, likely through the activation of post-synaptic cortical 5-HT_{1A} receptors, NLX-101 has the potential to ameliorate cognitive deficits associated with clinical disorders such as depression.

4. Clinical translation of 5-HT_{1A} receptor biased agonists as antidepressant treatments: an experimental medicine approach

Experimental medicine has emerged as an important tool for translating findings from animal models into humans, and establishing the likely clinical profile of a drug in development. Whilst not required from a regulatory perspective, experimental medicine is valuable in 'de-risking' treatment development, thereby enabling the prioritisation of resources for intensive clinical trials [112]. As noted above, there are established physiological markers in humans for 5-HT_{1A} receptor activation; these include EEG changes [113], endocrine responses and body temperature alterations [114]. While measurements of these responses provide evidence of 5-HT_{1A} receptor activation at a given drug dose, they do not yield information about the possible utility of an agent in a psychiatric disorder such as major depression.

Experimental paradigms can tap into neurocognitive processes that are integral to the experience of the condition being targeted. A positive effect of a drug treatment in such a paradigm can provide useful evidence about the potential clinical utility of a novel compound in a particular disorder. When used in combination with biased agonists of the 5-HT_{1A} receptor, such paradigms may allow a more nuanced understanding of the role of 5-HT_{1A} receptors in human cognition. Here, we briefly describe three neurocognitive processes that are known to be core to major depression - emotional processing, reward processing and cognition – and the existing evidence of an involvement of 5-HT_{1A} receptions in these processes.

4.1 Emotional processing

Depression is associated with negative emotional biases which serve to maintain and reinforce the persistent low mood that characterises the clinical condition [115]. Conventional antidepressant drugs such as SSRIs produce rapid effects to shift emotional processing in a positive direction [116]. These effects are seen in both healthy volunteers and patients with depression where abnormal negative biases are reversed by antidepressant drugs from the very beginning of treatment [117]. These shifts in emotional processing is also seen with atypical antidepressants such as agomelatine

[118], and have been used by industry to screen for novel antidepressant compounds [119]. A typical task that measures biases in emotional processing is the recognition of emotional facial expressions [116]. This can be examined at both behavioural and neural levels and the effects of pharmacological agents assessed [120].

There is little work on the effect of 5-HT_{1A} receptor agonists on responses to emotional faces. However, in a cross-over study of 15 healthy participants, Bernasconi and colleagues (2015) reported that, relative to placebo, a single dose of buspirone (15mg) impaired the discrimination of fearful but not happy faces [121]. This reduction in sensitivity to fear is consistent with an anxiolytic effect and is also seen after repeated SSRI treatment. Using EEG, Bernasconi et al (2015) found that buspirone reduced activity in the right dorsolateral prefrontal cortex (dlPFC) in response to fearful faces, consistent with a role for 5-HT_{1A} receptor agonism in reducing cortical attention to negative stimuli [121].

Using combined PET & functional magnetic resonance imaging (fMRI), two healthy volunteer studies (with a total of 35 participants), reported an inverse correlation between 5-HT_{1A} receptor density in the raphe and amygdala activity in response to fearful faces [122, 123]. This suggests that higher availability of 5-HT_{1A} autoreceptors may be associated with reduced neural response to fear, which is consistent with an important role for pre-synaptic 5-HT_{1A} receptors in the control of anxiety and fear. Interestingly, pre-clinical evidence indicates that mice with high 5-HT_{1A} receptor expression in the raphe nuclei exhibit increased behavioural despair and poor response to antidepressants in behavioural models [124]. This could suggest the relative importance of post-synaptic 5-HT_{1A} receptor mechanisms in facilitating responses to antidepressant treatment.

4.2 Reward processes

The clinical symptoms relating to loss of interest and pleasure are often referred to ‘anhedonia’. As noted above, anhedonia is key symptom in the diagnosis of depression and is not well managed by current pharmacological approaches [125]. One reason for the great interest in the use of ketamine as an antidepressant is its ability to rapidly relieve anhedonic symptoms in patients with treatment resistant depression [126, 127]. In animal models, the antidepressant-like effect of ketamine can be reversed by drugs that block cortical 5-HT_{1A} receptors [14]. This, together with the ability of NLX-101 to rapidly reverse anhedonic-like behaviour in the chronic mild stress test in rats [99], makes the assessment of this biased agonist in reward processes in humans of particular interest.

Reward processing can be assessed in humans using neurocognitive models. These include measuring the hedonic response to a pleasurable stimulus, for example, the taste of chocolate [128]. In a somewhat different experimental medicine paradigm, participants can be assessed in reward

learning tasks, for example, the rate at which a response bias is developed towards a high-probability win in a probabilistic instrumental learning task [129]. As with emotional processing, responses in these tasks can be measured at both behavioural and neural levels.[130]

Interestingly, using a chocolate taste paradigm to test hedonic experience in healthy participants (N = 45), seven days' administration of the SSRI, citalopram, blunted the neural response to reward in the ventral striatum and orbitofrontal cortex [128]. Consistent with this, it was recently reported that chronic administration (at least 21 days) of the SSRI escitalopram reduces sensitivity to reward learning [131]. These findings are consistent with clinical observations that SSRIs are not helpful in reversing symptoms of anhedonia [132, 133].

At present there does not seem to be any work in humans that has investigated the effect of 5-HT_{1A} receptor agonism on behavioural or neural aspects of reward experience or reward learning. However, there is pre-clinical evidence for a role of post-synaptic 5-HT_{1A} receptors in dopamine release [134], which may suggest a role for this receptor subtype in reward processing. Thus, activation of cortical 5-HT_{1A} receptors, through inhibition of GABA interneurons, triggers disinhibition of pyramidal neurons projecting to the ventral tegmental area [135]. This in turn could lead to activation of mesocortical neurons and increased dopamine release in cortex. In rats, NLX-101 increased cortical dopamine levels at doses that did not lower 5-HT release, again suggesting preferential activation of post-synaptic 5-HT_{1A} receptors [95, 136].

4.3 Cognition

There is an unmet need for pharmacological treatments that can improve cognition in depression [104]. 'Difficulty in concentrating' is listed as a symptom contributing to the diagnosis of depression in ICD-11. In patients with depression, however, cognitive impairment is typically seen over a wide range of neuropsychological domains, including attention, learning, memory, and executive function, with some resolving as the patient enters remission and others persisting [137] . Such impairments can be assessed by cognitive tests in humans including well-established test batteries such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) [138].

It was noted above that conventional azapirone 5-HT_{1A} receptor agonists such as buspirone and tandospirone, do not reliably affect cognition in healthy participants, compared to placebo [108, 139]. However some studies have shown that the multimodal antidepressant agent, vortioxetine, has pro-cognitive effects in patients with depression [140]. This is of interest because vortioxetine has full agonist activity at 5-HT_{1A} receptors [141].

A study of vortioxetine in patients who had recovered from depression found that, compared to placebo, vortioxetine (20mg daily for 14 days) decreased self-reported cognitive deficits in the Perceived Deficits Questionnaire and improved performance on the Trail Making Test [142]. Also, in a working memory task in the same participants, vortioxetine reduced task-induced activation in the right dorsolateral prefrontal cortex (dlPFC) and left hippocampus. Vortioxetine has other pharmacological properties, for example 5-HT_3 receptor antagonism, which may contribute to its pro-cognitive profile. Therefore, a similar assessment of cognition with a selective, post-synaptic 5-HT_{1A} receptor agonist is important in elucidating the role of post-synaptic 5-HT_{1A} receptors in this effect.

4. Conclusions

5-HT_{1A} autoreceptors play a key role in the control of 5-HT release while post-synaptic 5-HT_{1A} cortical receptors are involved in the regulation of GABA interneurons and glutamatergic pyramidal cells. The significance of the role that 5-HT_{1A} receptors play in the pathophysiology of depression is not altogether clear but there is reasonable evidence for a decrease in 5-HT_{1A} receptor availability and function in patients with this condition. How this abnormality may relate to the symptomatology of the depressive syndrome is not established. However, biases in processing affective information may be a key cognitive process relating to 5-HT_{1A} receptor availability. This is supported by PET imaging work suggesting lower 5-HT_{1A} receptor availability in the raphe nuclei may be linked to increased amygdala activity in response to negative emotional stimuli [123]. .

5-HT_{1A} receptor agonists have been available for human use for over 20 years and buspirone continues to be widely prescribed in the United States for the treatment of generalised anxiety disorder. Data from controlled trials suggest that azapirone drugs, such as buspirone, have some efficacy in the treatment of depression [46] but no azapirone has yet been licensed for this purpose thus far. Buspirone is often used off-label to augment the antidepressant effects of SSRIs but the clinical efficacy of this approach is not established [143].

Conventional 5-HT_{1A} receptor agonists such as buspirone are full agonists at the 5-HT_{1A} autoreceptor but partial agonists at postsynaptic 5-HT_{1A} receptors [47]. It has long been thought that these pharmacological effects may lessen the ability of such agents to treat clinical depression because they would not increase overall neurotransmission at post-synaptic 5-HT_{1A} receptors with full effectiveness. This pharmacological profile also limits their use as a probe to test the role of post-synaptic 5-HT_{1A} receptor agonist as a therapeutic target in depression. The development of biased agonists, such as NLX-101 which appear to have selective and full agonist effects at cortical post-

synaptic 5-HT_{1A} receptors, may enable this role to be tested. Prior to a full-scale clinical trial, it is often appropriate to use experimental medicine methods to provide evidence that a particular agent may indeed be efficacious in a clinical disorder. In this review, we have outlined some potential models suitable for testing the potential antidepressant efficacy of biased 5-HT_{1A} receptor agonists in both healthy participants and patients with depression.

1

Figure 1 Title

5-HT_{1A} receptors in the brain

Figure 1 Legend

Serotonin (5-HT) neurons, originating from the raphe nucleus, release 5-HT when activated. This 5-HT release has a dual effect on 5-HT_{1A} receptors. Firstly it activates 5-HT_{1A} auto-receptors on the 5-HT neuron cell body and dendrites, leading to an inhibition of 5-HT cell firing. Secondly 5-HT release activates post-synaptic 5-HT_{1A} receptors in several regions of the brain, which play a role in a range of physiological and cognitive functions. The biased agonist NLX-101 preferentially activates post-synaptic 5-HT_{1A} receptors. Created with BioRender.com.

Declarations

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1. Peroutka, S.J. and S.H. Snyder, *Multiple serotonin receptors: differential binding of [3H]5-hydroxytryptamine, [3H]lysergic acid diethylamide and [3H]spiroperidol.* Mol Pharmacol, 1979. **16**(3): p. 687-99.
2. Peroutka, S.J., *5-Hydroxytryptamine receptor subtypes: molecular, biochemical and physiological characterization.* Trends Neurosci, 1988. **11**(11): p. 496-500 DOI: 10.1016/0166-2236(88)90011-2.
3. Savitz, J., I. Lucki, and W.C. Drevets, *5-HT(1A) receptor function in major depressive disorder.* Prog Neurobiol, 2009. **88**(1): p. 17-31 DOI: 10.1016/j.pneurobio.2009.01.009.
4. Celada, P., M. Puig, M. Amargos-Bosch, A. Adell, and F. Artigas, *The therapeutic role of 5-HT1A and 5-HT2A receptors in depression.* J Psychiatry Neurosci, 2004. **29**(4): p. 252-65.
5. Celada, P., A. Bortolozzi, and F. Artigas, *Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: rationale and current status of research.* CNS Drugs, 2013. **27**(9): p. 703-16 DOI: 10.1007/s40263-013-0071-0.
6. Kia, H.K., M.C. Miquel, M.J. Brisorgueil, G. Daval, M. Riad, S. El Mestikawy, et al., *Immunocytochemical localization of serotonin1A receptors in the rat central nervous system.* J Comp Neurol, 1996. **365**(2): p. 289-305 DOI: 10.1002/(SICI)1096-9861(19960205)365:2<289::AID-CNE7>3.0.CO;2-1.
7. Verge, D., G. Daval, A. Patey, H. Gozlan, S. el Mestikawy, and M. Hamon, *Presynaptic 5-HT autoreceptors on serotonergic cell bodies and/or dendrites but not terminals are of the 5-HT1A subtype.* Eur J Pharmacol, 1985. **113**(3): p. 463-4 DOI: 10.1016/0014-2999(85)90099-8.
8. Sharp, T., L. Boothman, J. Raley, and P. Queree, *Important messages in the 'post': recent discoveries in 5-HT neurone feedback control.* Trends Pharmacol Sci, 2007. **28**(12): p. 629-36 DOI: 10.1016/j.tips.2007.10.009.
9. Halasy, K., R. Miettinen, E. Szabat, and T.F. Freund, *GABAergic Interneurons are the Major Postsynaptic Targets of Median Raphe Afferents in the Rat Dentate Gyrus.* Eur J Neurosci, 1992. **4**(2): p. 144-153 DOI: 10.1111/j.1460-9568.1992.tb00861.x.
10. Ogren, S.O., T.M. Eriksson, E. Elvander-Tottie, C. D'Addario, J.C. Ekstrom, P. Svenningsson, et al., *The role of 5-HT(1A) receptors in learning and memory.* Behav Brain Res, 2008. **195**(1): p. 54-77 DOI: 10.1016/j.bbr.2008.02.023.
11. Meltzer, H.Y. and T. Sumiyoshi, *Does stimulation of 5-HT(1A) receptors improve cognition in schizophrenia?* Behav Brain Res, 2008. **195**(1): p. 98-102 DOI: 10.1016/j.bbr.2008.05.016.
12. Sprouse, J.S. and G.K. Aghajanian, *Responses of hippocampal pyramidal cells to putative serotonin 5-HT1A and 5-HT1B agonists: a comparative study with dorsal raphe neurons.* Neuropharmacology, 1988. **27**(7): p. 707-15 DOI: 10.1016/0028-3908(88)90079-2.
13. Sprouse, J.S. and G.K. Aghajanian, *Electrophysiological responses of serotoninergic dorsal raphe neurons to 5-HT1A and 5-HT1B agonists.* Synapse, 1987. **1**(1): p. 3-9 DOI: 10.1002/syn.890010103.
14. Fukumoto, K., M. Iijima, T. Funakoshi, and S. Chaki, *Role of 5-HT1A Receptor Stimulation in the Medial Prefrontal Cortex in the Sustained Antidepressant Effects of Ketamine.* International Journal of Neuropsychopharmacology, 2018. **21**(4): p. 371-381 DOI: 10.1093/ijnp/pyx116.
15. Raymond, J.R., Y.V. Mukhin, T.W. Gettys, and M.N. Garnovskaya, *The recombinant 5-HT1A receptor: G protein coupling and signalling pathways.* Br J Pharmacol, 1999. **127**(8): p. 1751-64 DOI: 10.1038/sj.bjp.0702723.
16. Masson, J., M.B. Emerit, M. Hamon, and M. Darmon, *Serotonergic signaling: multiple effectors and pleiotropic effects.* Wiley Interdisciplinary Reviews: Membrane Transport and Signaling, 2012. **1**(6): p. 685-713 DOI: 10.1002/wmts.50.
17. Luscher, C., L.Y. Jan, M. Stoffel, R.C. Malenka, and R.A. Nicoll, *G protein-coupled inwardly rectifying K+ channels (GIRKs) mediate postsynaptic but not presynaptic transmitter actions*

in hippocampal neurons. Neuron, 1997. **19**(3): p. 687-95 DOI: 10.1016/s0896-6273(00)80381-5.
18. Sun, Q.Q. and N. Dale, *G-proteins are involved in 5-HT receptor-mediated modulation of N- and P/Q- but not T-type Ca2+ channels.* J Neurosci, 1999. **19**(3): p. 890-9 DOI: 10.1523/JNEUROSCI.19-03-00890.1999.
19. Raymond, J.R., Y.V. Mukhin, A. Gelasco, J. Turner, G. Collinsworth, T.W. Gettys, et al., *Multiplicity of mechanisms of serotonin receptor signal transduction.* Pharmacol Ther, 2001. **92**(2-3): p. 179-212 DOI: 10.1016/s0163-7258(01)00169-3.
20. Albert, P.R. and F. Vahid-Ansari, *The 5-HT1A receptor: Signaling to behavior.* Biochimie, 2019. **161**: p. 34-45 DOI: 10.1016/j.biochi.2018.10.015.
21. Gould, T.D., H. Einat, R. Bhat, and H.K. Manji, *AR-A014418, a selective GSK-3 inhibitor, produces antidepressant-like effects in the forced swim test.* Int J Neuropsychopharmacol, 2004. **7**(4): p. 387-90 DOI: 10.1017/S1461145704004535.
22. Wang, J.Q. and L. Mao, *The ERK Pathway: Molecular Mechanisms and Treatment of Depression.* Mol Neurobiol, 2019. **56**(9): p. 6197-6205 DOI: 10.1007/s12035-019-1524-3.
23. Prasad, S., E. Ponimaskin, and A. Zeug, *Serotonin receptor oligomerization regulates cAMP-based signaling.* J Cell Sci, 2019. **132**(16) DOI: 10.1242/jcs.230334.
24. Sharp, T. and N.M. Barnes, *Central 5-HT receptors and their function; present and future.* Neuropharmacology, 2020. **177**: p. 108155 DOI: 10.1016/j.neuropharm.2020.108155.
25. Mannoury la Cour, C., S. El Mestikawy, N. Hanoun, M. Hamon, and L. Lanfumey, *Regional differences in the coupling of 5-hydroxytryptamine-1A receptors to G proteins in the rat brain.* Mol Pharmacol, 2006. **70**(3): p. 1013-21 DOI: 10.1124/mol.106.022756.
26. Kushwaha, N. and P.R. Albert, *Coupling of 5-HT1A autoreceptors to inhibition of mitogen-activated protein kinase activation via G beta gamma subunit signaling.* Eur J Neurosci, 2005. **21**(3): p. 721-32 DOI: 10.1111/j.1460-9568.2005.03904.x.
27. Adayev, T., Y. El-Sherif, M. Barua, N.J. Penington, and P. Banerjee, *Agonist stimulation of the serotonin1A receptor causes suppression of anoxia-induced apoptosis via mitogen-activated protein kinase in neuronal HN2-5 cells.* J Neurochem, 1999. **72**(4): p. 1489-96 DOI: 10.1046/j.1471-4159.1999.721489.x.
28. Menkes, D.B., *Putting serotonin in its place-again.* BMJ, 2022. **379**: p. o2357 DOI: 10.1136/bmj.o2357.
29. Moncrieff, J., R.E. Cooper, T. Stockmann, S. Amendola, M.P. Hengartner, and M.A. Horowitz, *The serotonin theory of depression: a systematic umbrella review of the evidence.* Mol Psychiatry, 2022 DOI: 10.1038/s41380-022-01661-0.
30. Jauhar, S., P.J. Cowen, and M. Browning, *Fifty years on: Serotonin and depression.* J Psychopharmacol, 2023. **0**(0): p. 2698811231161813 DOI: 10.1177/02698811231161813.
31. Dean, J. and M. Keshavan, *The neurobiology of depression: An integrated view.* Asian J Psychiatr, 2017. **27**: p. 101-111 DOI: 10.1016/j.ajp.2017.01.025.
32. Deakin, J., *The role of serotonin in depression and anxiety.* Eur Psychiatry, 1998. **13 Suppl 2**: p. 57s-63s DOI: 10.1016/S0924-9338(98)80015-1.
33. Kranz, G.S., S. Kasper, and R. Lanzenberger, *Reward and the serotonergic system.* Neuroscience, 2010. **166**(4): p. 1023-35 DOI: 10.1016/j.neuroscience.2010.01.036.
34. Merens, W., A.J. Willem Van der Does, and P. Spinhoven, *The effects of serotonin manipulations on emotional information processing and mood.* J Affect Disord, 2007. **103**(1-3): p. 43-62 DOI: 10.1016/j.jad.2007.01.032.
35. Kaufman, J., C. DeLorenzo, S. Choudhury, and R.V. Parsey, *The 5-HT1A receptor in Major Depressive Disorder.* Eur Neuropsychopharmacol, 2016. **26**(3): p. 397-410 DOI: 10.1016/j.euroneuro.2015.12.039.
36. Arango, V., M.D. Underwood, M. Boldrini, H. Tamir, S.A. Kassir, S. Hsiung, et al., *Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the*

brainstem of depressed suicide victims. Neuropsychopharmacology, 2001. **25**(6): p. 892-903 DOI: 10.1016/S0893-133X(01)00310-4.
37. Boldrini, M., M.D. Underwood, J.J. Mann, and V. Arango, *Serotonin-1A autoreceptor binding in the dorsal raphe nucleus of depressed suicides.* J Psychiatr Res, 2008. **42**(6): p. 433-42 DOI: 10.1016/j.jpsychires.2007.05.004.
38. Stockmeier, C.A., L.A. Shapiro, G.E. Dilley, T.N. Kolli, L. Friedman, and G. Rajkowska, *Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression-postmortem evidence for decreased serotonin activity.* J Neurosci, 1998. **18**(18): p. 7394-401 DOI: 10.1523/JNEUROSCI.18-18-07394.1998.
39. Lopez-Figueroa, A.L., C.S. Norton, M.O. Lopez-Figueroa, D. Armellini-Dodel, S. Burke, H. Akil, et al., *Serotonin 5-HT1A, 5-HT1B, and 5-HT2A receptor mRNA expression in subjects with major depression, bipolar disorder, and schizophrenia.* Biol Psychiatry, 2004. **55**(3): p. 225-33 DOI: 10.1016/j.biopsych.2003.09.017.
40. Wang, L., C. Zhou, D. Zhu, X. Wang, L. Fang, J. Zhong, et al., *Serotonin-1A receptor alterations in depression: a meta-analysis of molecular imaging studies.* BMC Psychiatry, 2016. **16**(1): p. 319 DOI: 10.1186/s12888-016-1025-0.
41. Drevets, W.C., M.E. Thase, E.L. Moses-Kolko, J. Price, E. Frank, D.J. Kupfer, et al., *Serotonin-1A receptor imaging in recurrent depression: replication and literature review.* Nucl Med Biol, 2007. **34**(7): p. 865-77 DOI: 10.1016/j.nucmedbio.2007.06.008.
42. Parsey, R.V., R.T. Ogden, J.M. Miller, A. Tin, N. Hesselgrave, E. Goldstein, et al., *Higher serotonin 1A binding in a second major depression cohort: modeling and reference region considerations.* Biol Psychiatry, 2010. **68**(2): p. 170-8 DOI: 10.1016/j.biopsych.2010.03.023.
43. Parsey, R.V., M.A. Oquendo, R.T. Ogden, D.M. Olvet, N. Simpson, Y.Y. Huang, et al., *Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study.* Biol Psychiatry, 2006. **59**(2): p. 106-13 DOI: 10.1016/j.biopsych.2005.06.016.
44. Shrestha, S., J. Hirvonen, C.S. Hines, I.D. Henter, P. Svenningsson, V.W. Pike, et al., *Serotonin-1A receptors in major depression quantified using PET: controversies, confounds, and recommendations.* Neuroimage, 2012. **59**(4): p. 3243-51 DOI: 10.1016/j.neuroimage.2011.11.029.
45. Bhagwagar, Z., E.A. Rabiner, P.A. Sargent, P.M. Grasby, and P.J. Cowen, *Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography with [11C]WAY-100635.* Mol Psychiatry, 2004. **9**(4): p. 386-92 DOI: 10.1038/sj.mp.4001401.
46. Kishi, T., H.Y. Meltzer, Y. Matsuda, and N. Iwata, *Azapirone 5-HT1A receptor partial agonist treatment for major depressive disorder: systematic review and meta-analysis.* Psychol Med, 2014. **44**(11): p. 2255-69 DOI: 10.1017/S0033291713002857.
47. Loane, C. and M. Politis, *Buspirone: what is it all about?* Brain Res, 2012. **1461**: p. 111-8 DOI: 10.1016/j.brainres.2012.04.032.
48. Ansseau, M., W. Pitchot, A.G. Moreno, J. Wauthy, and P. Papart, *Pilot-Study of Flesinoxan, a 5-Ht1a Agonist, in Major Depression - Effects on Sleep Rem Latency and Body-Temperature.* Human Psychopharmacology-Clinical and Experimental, 1993. **8**(4): p. 279-283 DOI: DOI 10.1002/hup.470080407.
49. Cowen, P.J., *Serotonin receptor subtypes in depression: evidence from studies in neuroendocrine regulation.* Clin Neuropharmacol, 1993. **16 Suppl 3**: p. S6-18.
50. Pitchot, W., J. Wauthy, M. Hansenne, E. Pinto, S. Fuchs, J. Reggers, et al., *Hormonal and temperature responses to the 5-HT1A receptor agonist flesinoxan in normal volunteers.* Psychopharmacology, 2002. **164**(1): p. 27-32 DOI: 10.1007/s00213-002-1177-0.
51. Voronova, I.P., *5-HT Receptors and Temperature Homeostasis.* Biomolecules, 2021. **11**(12): p. 1914 DOI: 10.3390/biom11121914.

52. Anderson, I.M., C.J. Ware, J.M. da Roza Davis, and P.J. Cowen, *Decreased 5-HT-mediated prolactin release in major depression.* Br J Psychiatry, 1992. **160**: p. 372-8 DOI: 10.1192/bjp.160.3.372.
53. Pan, L. and F. Gilbert, *Activation of 5-HT1A receptor subtype in the paraventricular nuclei of the hypothalamus induces CRH and ACTH release in the rat.* Neuroendocrinology, 1992. **56**(6): p. 797-802 DOI: 10.1159/000126332.
54. Goodwin, G.M., R.J. De Souza, and A.R. Green, *The pharmacology of the hypothermic response in mice to 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT). A model of presynaptic 5-HT1 function.* Neuropharmacology, 1985. **24**(12): p. 1187-94 DOI: 10.1016/0028-3908(85)90153-4.
55. Hutson, P.H., T.P. Donohoe, and G. Curzon, *Hypothermia induced by the putative 5-HT1A agonists LY165163 and 8-OH-DPAT is not prevented by 5-HT depletion.* Eur J Pharmacol, 1987. **143**(2): p. 221-8 DOI: 10.1016/0014-2999(87)90536-x.
56. Hillegaart, V., *Effects of local application of 5-HT and 8-OH-DPAT into the dorsal and median raphe nuclei on core temperature in the rat.* Psychopharmacology (Berl), 1991. **103**(3): p. 291-6 DOI: 10.1007/BF02244281.
57. McAllister-Williams, R.H., A.E. Massey, and G. Fairchild, *Repeated cortisol administration attenuates the EEG response to buspirone in healthy volunteers: evidence for desensitization of the 5-HT1A autoreceptor.* J Psychopharmacol, 2007. **21**(8): p. 826-32 DOI: 10.1177/0269881107078292.
58. Young, A.H., A.L. Sharpley, G.M. Campling, R.A. Hockney, and P.J. Cowen, *Effects of hydrocortisone on brain 5-HT function and sleep.* J Affect Disord, 1994. **32**(2): p. 139-46 DOI: 10.1016/0165-0327(94)90072-8.
59. Lesch, K.P., *5-HT1A receptor responsivity in anxiety disorders and depression.* Prog Neuropsychopharmacol Biol Psychiatry, 1991. **15**(6): p. 723-33 DOI: 10.1016/0278-5846(91)90001-h.
60. Meltzer, H.Y. and M. Maes, *Effects of ipsapirone on plasma cortisol and body temperature in major depression.* Biol Psychiatry, 1995. **38**(7): p. 450-7 DOI: 10.1016/0006-3223(94)00370-i.
61. Shapira, B., M.E. Newman, Y. Gelfin, and B. Lerer, *Blunted temperature and cortisol responses to ipsapirone in major depression: lack of enhancement by electroconvulsive therapy.* Psychoneuroendocrinology, 2000. **25**(5): p. 421-38 DOI: 10.1016/s0306-4530(99)00067-0.
62. Riedel, W.J., T. Klaassen, E. Griez, A. Honig, P.P. Menheere, and H.M. van Praag, *Dissociable hormonal, cognitive and mood responses to neuroendocrine challenge: evidence for receptor-specific serotonergic dysregulation in depressed mood.* Neuropsychopharmacology, 2002. **26**(3): p. 358-67 DOI: 10.1016/S0893-133X(01)00361-X.
63. Navines, R., R. Martin-Santos, E. Gomez-Gil, M.J. Martinez de Osaba, M.L. Imaz, and C. Gasto, *Effects of citalopram treatment on hypothermic and hormonal responses to the 5-HT1A receptor agonist buspirone in patients with major depression and therapeutic response.* Psychoneuroendocrinology, 2007. **32**(4): p. 411-6 DOI: 10.1016/j.psyneuen.2007.01.006.
64. Gray, N.A., M.S. Milak, C. DeLorenzo, R.T. Ogden, Y.Y. Huang, J.J. Mann, et al., *Antidepressant treatment reduces serotonin-1A autoreceptor binding in major depressive disorder.* Biol Psychiatry, 2013. **74**(1): p. 26-31 DOI: 10.1016/j.biopsych.2012.11.012.
65. Lemonde, S., G. Turecki, D. Bakish, L.S. Du, P.D. Hrdina, C.D. Bown, et al., *Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide.* Journal of Neuroscience, 2003. **23**(25): p. 8788-8799.
66. Albert, P.R. and S. Lemonde, *5-HT1A receptors, gene repression, and depression: guilt by association.* Neuroscientist, 2004. **10**(6): p. 575-93 DOI: 10.1177/1073858404267382.

67. Hesselgrave, N. and R.V. Parsey, *Imaging the serotonin 1A receptor using [11C]WAY100635 in healthy controls and major depression.* Philos Trans R Soc Lond B Biol Sci, 2013. **368**(1615): p. 20120004 DOI: 10.1098/rstb.2012.0004.
68. Lothe, A., C. Boni, N. Costes, S. Bouvard, P. Gorwood, F. Lavenne, et al., *5-HT1A gene promoter polymorphism and [18F]MPPF binding potential in healthy subjects: a PET study.* Behav Brain Funct, 2010. **6**: p. 37 DOI: 10.1186/1744-9081-6-37.
69. David, S.P., N.V. Murthy, E.A. Rabiner, M.R. Munafo, E.C. Johnstone, R. Jacob, et al., *A functional genetic variation of the serotonin (5-HT) transporter affects 5-HT1A receptor binding in humans.* J Neurosci, 2005. **25**(10): p. 2586-90 DOI: 10.1523/JNEUROSCI.3769-04.2005.
70. Lemonde, S., L. Du, D. Bakish, P. Hrdina, and P.R. Albert, *Association of the C(-1019)G 5-HT1A functional promoter polymorphism with antidepressant response.* Int J Neuropsychopharmacol, 2004. **7**(4): p. 501-6 DOI: 10.1017/S1461145704004699.
71. Serretti, A., P. Artioli, C. Lorenzi, A. Pirovano, V. Tubazio, and R. Zanardi, *The C(-1019)G polymorphism of the 5-HT1A gene promoter and antidepressant response in mood disorders: preliminary findings.* Int J Neuropsychopharmacol, 2004. **7**(4): p. 453-60 DOI: 10.1017/S1461145704004687.
72. Seletti, B., C. Benkelfat, P. Blier, L. Annable, F. Gilbert, and C. Demontigny, *Serotonin(1a) Receptor Activation by Flesinoxan in Humans - Body-Temperature and Neuroendocrine Responses.* Neuropsychopharmacology, 1995. **13**(2): p. 93-104.
73. Newman-Tancredi, A., R.Y. Depoortere, M.S. Kleven, M. Kolaczkowski, and L. Zimmer, *Translating biased agonists from molecules to medications: Serotonin 5-HT(1A) receptor functional selectivity for CNS disorders.* Pharmacol Ther, 2022. **229**: p. 107937 DOI: 10.1016/j.pharmthera.2021.107937.
74. Newman-Tancredi, A., S. Gavaudan, C. Conte, C. Chaput, M. Touzard, L. Verriele, et al., *Agonist and antagonist actions of antipsychotic agents at 5-HT1A receptors: a [35S]GTPgammaS binding study.* Eur J Pharmacol, 1998. **355**(2-3): p. 245-56 DOI: 10.1016/s0014-2999(98)00483-x.
75. Bantick, R.A., E.A. Rabiner, E. Hirani, M.H. de Vries, S.P. Hume, and P.M. Grasby, *Occupancy of agonist drugs at the 5-HT1A receptor.* Neuropsychopharmacology, 2004. **29**(5): p. 847-59 DOI: 10.1038/sj.npp.1300390.
76. Feiger, A.D., J.F. Heiser, R.K. Shrivastava, K.J. Weiss, W.T. Smith, J.M. Sitsen, et al., *Gepirone extended-release: new evidence for efficacy in the treatment of major depressive disorder.* J Clin Psychiatry, 2003. **64**(3): p. 243-9 DOI: 10.4088/JCP.v64n0304.
77. Bielski, R.J., L. Cunningham, J.P. Horrigan, P.D. Londborg, W.T. Smith, and K. Weiss, *Gepirone extended-release in the treatment of adult outpatients with major depressive disorder: a double-blind, randomized, placebo-controlled, parallel-group study.* J Clin Psychiatry, 2008. **69**(4): p. 571-7 DOI: 10.4088/jcp.v69n0408.
78. Heller, A.H., M. Beneke, B. Kuemmel, D. Spencer, and N.M. Kurtz, *Ipsapirone: evidence for efficacy in depression.* Psychopharmacol Bull, 1990. **26**(2): p. 219-22.
79. Lapierre, Y.D., P. Silverstone, R.T. Reesal, B. Saxena, P. Turner, D. Bakish, et al., *A Canadian multicenter study of three fixed doses of controlled-release ipsapirone in outpatients with moderate to severe major depression.* J Clin Psychopharmacol, 1998. **18**(4): p. 268-73 DOI: 10.1097/00004714-199808000-00002.
80. Stahl, S.M., L. Kaiser, J. Roeschen, J.M.K. Hesselink, and J. Orazem, *Effectiveness of ipsapirone, a 5-HT-1A partial agonist, in major depressive disorder: support for the role of 5-HT-1A receptors in the mechanism of action of serotonergic antidepressants.* International Journal of Neuropsychopharmacology, 1998. **1**(1): p. 11-18 DOI: 10.1017/s1461145798001059.

81. Yocca, F.D., *Neurochemistry and neurophysiology of buspirone and gepirone: interactions at presynaptic and postsynaptic 5-HT1A receptors.* Journal of clinical psychopharmacology, 1990. **10**(3 Suppl): p. 6S-12S.
82. Penttila, J., J. Hirvonen, L. Tuominen, V. Lumme, T. Ilonen, K. Nagren, et al., *Verbal memory and 5-HT1A receptors in healthy volunteers--A PET study with [carbonyl-(11)C]WAY-100635.* Eur Neuropsychopharmacol, 2016. **26**(3): p. 570-7 DOI: 10.1016/j.euroneuro.2015.12.028.
83. Hirvonen, J., H. Karlsson, J. Kajander, A. Lepola, J. Markkula, H. Rasi-Hakala, et al., *Decreased brain serotonin 5-HT1A receptor availability in medication-naive patients with major depressive disorder: an in-vivo imaging study using PET and [carbonyl-11C]WAY-100635.* Int J Neuropsychopharmacol, 2008. **11**(4): p. 465-76 DOI: 10.1017/S1461145707008140.
84. Clifford, E.M., S.E. Gartside, V. Umbers, P.J. Cowen, M. Hajos, and T. Sharp, *Electrophysiological and neurochemical evidence that pindolol has agonist properties at the 5-HT1A autoreceptor in vivo.* Br J Pharmacol, 1998. **124**(1): p. 206-12 DOI: 10.1038/sj.bjp.0701796.
85. Newman-Tancredi, A., C. Chaput, S. Gavaudan, L. Verriele, and M.J. Millan, *Agonist and antagonist actions of (-)pindolol at recombinant, human serotonin1A (5-HT1A) receptors.* Neuropsychopharmacology, 1998. **18**(5): p. 395-8 DOI: 10.1016/S0893-133X(97)00169-3.
86. Artigas, F., *5-HT and antidepressants: new views from microdialysis studies.* Trends Pharmacol Sci, 1993. **14**(7): p. 262 DOI: 10.1016/0165-6147(93)90125-4.
87. Portella, M.J., J. de Diego-Adelino, J. Ballesteros, D. Puigdemont, S. Oller, B. Santos, et al., *Can we really accelerate and enhance the selective serotonin reuptake inhibitor antidepressant effect? A randomized clinical trial and a meta-analysis of pindolol in nonresistant depression.* J Clin Psychiatry, 2011. **72**(7): p. 962-9 DOI: 10.4088/JCP.09m05827blu.
88. Whale, R., T. Terao, P. Cowen, N. Freemantle, and J. Geddes, *Pindolol augmentation of serotonin reuptake inhibitors for the treatment of depressive disorder: a systematic review.* J Psychopharmacol, 2010. **24**(4): p. 513-20 DOI: 10.1177/0269881108097714.
89. Rabiner, E.A., R.N. Gunn, M.E. Castro, P.A. Sargent, P.J. Cowen, M.J. Koepp, et al., *beta-blocker binding to human 5-HT(1A) receptors in vivo and in vitro: implications for antidepressant therapy.* Neuropsychopharmacology, 2000. **23**(3): p. 285-93 DOI: 10.1016/S0893-133X(00)00109-3.
90. Newman-Tancredi, A., D. Cussac, L. Marini, and M.J. Millan, *Antibody capture assay reveals bell-shaped concentration-response isotherms for h5-HT(1A) receptor-mediated Galpha(i3) activation: conformational selection by high-efficacy agonists, and relationship to trafficking of receptor signaling.* Mol Pharmacol, 2002. **62**(3): p. 590-601 DOI: 10.1124/mol.62.3.590.
91. Newman-Tancredi, A., D. Cussac, A.M. Ormiere, F. Lestienne, M.A. Varney, and J.C. Martel, *Bell-shaped agonist activation of 5-HT(1A) receptor-coupled Galphai(3) G-proteins: Receptor density-dependent switch in receptor signaling.* Cell Signal, 2019. **63**: p. 109383 DOI: 10.1016/j.cellsig.2019.109383.
92. Scorza, M.C., L. Llado-Pelfort, S. Oller, R. Cortes, D. Puigdemont, M.J. Portella, et al., *Preclinical and clinical characterization of the selective 5-HT(1A) receptor antagonist DU-125530 for antidepressant treatment.* Br J Pharmacol, 2012. **167**(5): p. 1021-34 DOI: 10.1111/j.1476-5381.2011.01770.x.
93. Smith, J.S., R.J. Lefkowitz, and S. Rajagopal, *Biased signalling: from simple switches to allosteric microprocessors.* Nat Rev Drug Discov, 2018. **17**(4): p. 243-260 DOI: 10.1038/nrd.2017.229.
94. Sniecikowska, J., A. Newman-Tancredi, and M. Kolaczkowski, *From Receptor Selectivity to Functional Selectivity: The Rise of Biased Agonism in 5-HT1A Receptor Drug Discovery.* Curr Top Med Chem, 2019. **19**(26): p. 2393-2420 DOI: 10.2174/1568026619666190911122040.

95. Llado-Pelfort, L., M.B. Assie, A. Newman-Tancredi, F. Artigas, and P. Celada, *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): p. 1929-40 DOI: 10.1111/j.1476-5381.2010.00738.x.
96. Llado-Pelfort, L., M.B. Assie, A. Newman-Tancredi, F. Artigas, and P. Celada, *In vivo electrophysiological and neurochemical effects of the selective 5-HT1A receptor agonist, F13640, at pre- and postsynaptic 5-HT1A receptors in the rat.* Psychopharmacology (Berl), 2012. **221**(2): p. 261-72 DOI: 10.1007/s00213-011-2569-9.
97. Assie, M.B., L. Bardin, A.L. Auclair, E. Carilla-Durand, R. Depoortere, W. Koek, et al., *F15599, a highly selective post-synaptic 5-HT(1A) receptor agonist: in-vivo profile in behavioural models of antidepressant and serotonergic activity.* Int J Neuropsychopharmacol, 2010. **13**(10): p. 1285-98 DOI: 10.1017/S1461145709991222.
98. Iderberg, H., A.C. McCreary, M.A. Varney, M.S. Kleven, W. Koek, L. Bardin, et al., *NLX-112, a novel 5-HT1A receptor agonist for the treatment of L-DOPA-induced dyskinesia: Behavioral and neurochemical profile in rat.* Exp Neurol, 2015. **271**: p. 335-50 DOI: 10.1016/j.expneurol.2015.05.021.
99. Depoortere, R., M. Papp, P. Gruca, M. Lason-Tyburkiewicz, M. Niemczyk, M.A. Varney, et al., *Cortical 5-hydroxytryptamine 1A receptor biased agonist, NLX-101, displays rapid-acting antidepressant-like properties in the rat chronic mild stress model.* J Psychopharmacol, 2019. **33**(11): p. 1456-1466 DOI: 10.1177/0269881119860666.
100. Depoortere, R., L. Bardin, A.L. Auclair, L.A. Bruins Slot, and A. Newman-Tancredi, *Marble Burying in NMRI Male Mice Is Preferentially Sensitive to Pre- Versus Postsynaptic 5-HT1A Receptor Biased Agonists.* Pharmacology, 2021. **106**(1-2): p. 114-118 DOI: 10.1159/000509729.
101. Powell, W.H., L.E. Annett, R. Depoortere, A. Newman-Tancredi, and M.M. Iravani, *The selective 5-HT(1A) receptor agonist NLX-112 displays anxiolytic-like activity in mice.* Naunyn Schmiedebergs Arch Pharmacol, 2022. **395**(2): p. 149-157 DOI: 10.1007/s00210-021-02183-2.
102. Jastrzebska-Wiesek, M., A. Partyka, J. Rychtyk, J. Sniecikowska, M. Kolaczkowski, A. Wesolowska, et al., *Activity of Serotonin 5-HT(1A) Receptor Biased Agonists in Rat: Anxiolytic and Antidepressant-like properties.* ACS Chem Neurosci, 2018. **9**(5): p. 1040-1050 DOI: 10.1021/acschemneuro.7b00443.
103. Ali, M., M. Fahmy, W. Haggag, A. El-Tantawy, and H. Hassan, *Evaluation of cognitive impairment in patients with major depressive disorder in remission.* Middle East Current Psychiatry-Mecpsych, 2021. **28**(1): p. 71 DOI: ARTN 71
10.1186/s43045-021-00149-x.
104. Douglas, K.M. and R.J. Porter, *Longitudinal assessment of neuropsychological function in major depression.* Aust N Z J Psychiatry, 2009. **43**(12): p. 1105-17 DOI: 10.3109/00048670903279887.
105. Warburton, E.C., A.A. Harrison, T.W. Robbins, and B.J. Everitt, *Contrasting effects of systemic and intracerebral infusions of the 5-HT1A receptor agonist 8-OH-DPAT on spatial short-term working memory in rats.* Behav Brain Res, 1997. **84**(1-2): p. 247-58 DOI: 10.1016/s0166-4328(96)00154-4.
106. Madjid, N., E.E. Tottie, M. Luttgen, B. Meister, J. Sandin, A. Kuzmin, et al., *5-Hydroxytryptamine 1A receptor blockade facilitates aversive learning in mice: interactions with cholinergic and glutamatergic mechanisms.* J Pharmacol Exp Ther, 2006. **316**(2): p. 581-91 DOI: 10.1124/jpet.105.092262.
107. Luttgen, M., E. Elvander, N. Madjid, and S.O. Ogren, *Analysis of the role of 5-HT1A receptors in spatial and aversive learning in the rat.* Neuropharmacology, 2005. **48**(6): p. 830-52 DOI: 10.1016/j.neuropharm.2005.01.007.

108. Chamberlain, S.R., U. Muller, J.B. Deakin, P.R. Corlett, J. Dowson, R.N. Cardinal, et al., *Lack of deleterious effects of buspirone on cognition in healthy male volunteers.* J Psychopharmacol, 2007. **21**(2): p. 210-5 DOI: 10.1177/0269881107068066.
109. Takahashi, M., K. Iwamoto, Y. Kawamura, Y. Nakamura, R. Ishihara, Y. Uchiyama, et al., *The effects of acute treatment with tandospirone, diazepam, and placebo on driving performance and cognitive function in healthy volunteers.* Hum Psychopharmacol, 2010. **25**(3): p. 260-7 DOI: 10.1002/hup.1105.
110. Depoortere, R., A.L. Auclair, L. Bardin, F.C. Colpaert, B. Vacher, and A. Newman-Tancredi, *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): p. 641-54 DOI: 10.1016/j.euroneuro.2010.04.005.
111. Depoortere, R.Y., A.L. Auclair, and A. Newman-Tancredi, *NLX-101, a cortical 5-HT(1A) receptor biased agonist, reverses scopolamine-induced deficit in the delayed non-matching to position model of cognition.* Brain Res, 2021. **1765**: p. 147493 DOI: 10.1016/j.brainres.2021.147493.
112. Paul, J., *Experimental Medicine Approaches in CNS Drug Development*, in *Translational Medicine in CNS Drug Development*, G.G. Nomikos and D.E. Feltner, Editors. 2019, Elsevier. p. 63-80.
113. McAllister-Williams, R.H. and A.E. Massey, *EEG effects of buspirone and pindolol: a method of examining 5-HT1A receptor function in humans.* Psychopharmacology (Berl), 2003. **166**(3): p. 284-93 DOI: 10.1007/s00213-002-1339-0.
114. Cowen, P.J., A.C. Power, C.J. Ware, and I.M. Anderson, *5-HT1A receptor sensitivity in major depression. A neuroendocrine study with buspirone.* Br J Psychiatry, 1994. **164**(3): p. 372-9 DOI: 10.1192/bjp.164.3.372.
115. Disner, S.G., C.G. Beevers, E.A. Haigh, and A.T. Beck, *Neural mechanisms of the cognitive model of depression.* Nat Rev Neurosci, 2011. **12**(8): p. 467-77 DOI: 10.1038/nrn3027.
116. Harmer, C.J., N.C. Shelley, P.J. Cowen, and G.M. Goodwin, *Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition.* Am J Psychiatry, 2004. **161**(7): p. 1256-63 DOI: 10.1176/appi.ajp.161.7.1256.
117. Harmer, C.J., R.S. Duman, and P.J. Cowen, *How do antidepressants work? New perspectives for refining future treatment approaches.* Lancet Psychiatry, 2017. **4**(5): p. 409-418 DOI: 10.1016/S2215-0366(17)30015-9.
118. Harmer, C.J., C. de Bodinat, G.R. Dawson, C.T. Dourish, L. Waldenmaier, S. Adams, et al., *Agomelatine facilitates positive versus negative affective processing in healthy volunteer models.* J Psychopharmacol, 2011. **25**(9): p. 1159-67 DOI: 10.1177/0269881110376689.
119. Harmer, C.J., P.J. Cowen, and G.M. Goodwin, *Efficacy markers in depression.* J Psychopharmacol, 2011. **25**(9): p. 1148-58 DOI: 10.1177/0269881110367722.
120. Norbury, R., M.J. Taylor, S. Selvaraj, S.E. Murphy, C.J. Harmer, and P.J. Cowen, *Short-term antidepressant treatment modulates amygdala response to happy faces.* Psychopharmacology (Berl), 2009. **206**(2): p. 197-204 DOI: 10.1007/s00213-009-1597-1.
121. Bernasconi, F., M. Kometer, T. Pokorny, E. Seifritz, and F.X. Vollenweider, *The electrophysiological effects of the serotonin 1A receptor agonist buspirone in emotional face processing.* Eur Neuropsychopharmacol, 2015. **25**(4): p. 474-82 DOI: 10.1016/j.euroneuro.2015.01.009.
122. Fisher, P.M., C.C. Meltzer, S.K. Ziolko, J.C. Price, E.L. Moses-Kolko, S.L. Berga, et al., *Capacity for 5-HT1A-mediated autoregulation predicts amygdala reactivity.* Nat Neurosci, 2006. **9**(11): p. 1362-3 DOI: 10.1038/nn1780.
123. Selvaraj, S., E. Mouchlianitis, P. Faulkner, F. Turkheimer, P.J. Cowen, J.P. Roiser, et al., *Presynaptic Serotoninergic Regulation of Emotional Processing: A Multimodal Brain Imaging Study.* Biol Psychiatry, 2015. **78**(8): p. 563-571 DOI: 10.1016/j.biopsych.2014.04.011.

124. Richardson-Jones, J.W., C.P. Craige, B.P. Guiard, A. Stephen, K.L. Metzger, H.F. Kung, et al., *5-HT1A autoreceptor levels determine vulnerability to stress and response to antidepressants*. Neuron, 2010. **65**(1): p. 40-52 DOI: 10.1016/j.neuron.2009.12.003.
125. Pizzagalli, D.A., *Toward a Better Understanding of the Mechanisms and Pathophysiology of Anhedonia: Are We Ready for Translation?* Am J Psychiatry, 2022. **179**(7): p. 458-469 DOI: 10.1176/appi.ajp.20220423.
126. Coyle, C.M. and K.R. Laws, *The use of ketamine as an antidepressant: a systematic review and meta-analysis*. Human Psychopharmacology-Clinical and Experimental, 2015. **30**(3): p. 152-163 DOI: 10.1002/hup.2475.
127. Lally, N., A.C. Nugent, D.A. Luckenbaugh, M.J. Niciu, J.P. Roiser, and C.A. Zarate, Jr., *Neural correlates of change in major depressive disorder anhedonia following open-label ketamine.* J Psychopharmacol, 2015. **29**(5): p. 596-607 DOI: 10.1177/0269881114568041.
128. McCabe, C., Z. Mishor, P.J. Cowen, and C.J. Harmer, *Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment.* Biol Psychiatry, 2010. **67**(5): p. 439-45 DOI: 10.1016/j.biopsych.2009.11.001.
129. Walsh, A.E.L., N.T.M. Huneke, R. Brown, M. Browning, P. Cowen, and C.J. Harmer, *A Dissociation of the Acute Effects of Bupropion on Positive Emotional Processing and Reward Processing in Healthy Volunteers.* Front Psychiatry, 2018. **9**: p. 482 DOI: 10.3389/fpsyt.2018.00482.
130. Admon, R. and D.A. Pizzagalli, *Dysfunctional reward processing in depression*. Current Opinion in Psychology, 2015. **4**: p. 114-118 DOI: https://doi.org/10.1016/j.copsyc.2014.12.011.
131. Langley, C., S. Armand, Q. Luo, G. Savulich, T. Segerberg, A. Sondergaard, et al., *Chronic escitalopram in healthy volunteers has specific effects on reinforcement sensitivity: a double-blind, placebo-controlled semi-randomised study.* Neuropsychopharmacology, 2023. **48**(4): p. 664-670 DOI: 10.1038/s41386-022-01523-x.
132. Nutt, D., K. Demyttenaere, Z. Janka, T. Aarre, M. Bourin, P.L. Canonico, et al., *The other face of depression, reduced positive affect: the role of catecholamines in causation and cure.* J Psychopharmacol, 2007. **21**(5): p. 461-71 DOI: 10.1177/0269881106069938.
133. Price, J., V. Cole, and G.M. Goodwin, *Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study*. Br J Psychiatry, 2009. **195**(3): p. 211-7 DOI: 10.1192/bjp.bp.108.051110.
134. Assié, M., V. Ravailhe, C. Benas, and A. Newman-Tancredi. *Differential effects of 5-HT1A receptor agonists on extracellular levels of 5-HT in hippocampus and of dopamine in frontal cortex of freely moving rats*. in *British Association for Psychopharmacology Summer Meeting. Harrogate, Poster ID*. 2008.
135. Llado-Pelfort, L., N. Santana, V. Ghisi, F. Artigas, and P. Celada, *5-HT1A receptor agonists enhance pyramidal cell firing in prefrontal cortex through a preferential action on GABA interneurons.* Cereb Cortex, 2012. **22**(7): p. 1487-97 DOI: 10.1093/cercor/bhr220.
136. Cabanu, S., F. Pilar-Cuellar, P. Zubakina, E. Florensa-Zanuy, J. Senserrich, A. Newman-Tancredi, et al., *Molecular Signaling Mechanisms for the Antidepressant Effects of NLX-101, a Selective Cortical 5-HT1A Receptor Biased Agonist.* Pharmaceuticals, 2022. **15**(3): p. 337 DOI: ARTN 337
10.3390/ph15030337.
137. Rock, P.L., J.P. Roiser, W.J. Riedel, and A.D. Blackwell, *Cognitive impairment in depression: a systematic review and meta-analysis.* Psychol Med, 2014. **44**(10): p. 2029-40 DOI: 10.1017/S0033291713002535.
138. CANTAB, C.C. *CANTAB® [Cognitive assessment software]*. . 2019; Available from: www.cantab.com.

139. Yasuno, F., T. Suhara, T. Nakayama, T. Ichimiya, Y. Okubo, A. Takano, et al., *Inhibitory effect of hippocampal 5-HT1A receptors on human explicit memory.* Am J Psychiatry, 2003. **160**(2): p. 334-40 DOI: 10.1176/appi.ajp.160.2.334.
140. Mahableshwarkar, A.R., J. Zajecka, W. Jacobson, Y. Chen, and R.S. Keefe, *A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder.* Neuropsychopharmacology, 2015. **40**(8): p. 2025-37 DOI: 10.1038/npp.2015.52.
141. D'Agostino, A., C.D. English, and J.A. Rey, *Vortioxetine (brintellix): a new serotonergic antidepressant.* P T, 2015. **40**(1): p. 36-40.
142. Smith, J., M. Browning, S. Conen, R. Smallman, J. Buchbjerg, K.G. Larsen, et al., *Vortioxetine reduces BOLD signal during performance of the N-back working memory task: a randomised neuroimaging trial in remitted depressed patients and healthy controls.* Mol Psychiatry, 2018. **23**(5): p. 1127-1133 DOI: 10.1038/mp.2017.104.
143. Henssler, J., D. Alexander, G. Schwarzer, T. Bschor, and C. Baethge, *Combining Antidepressants vs Antidepressant Monotherapy for Treatment of Patients With Acute Depression: A Systematic Review and Meta-analysis.* JAMA Psychiatry, 2022. **79**(4): p. 300-312 DOI: 10.1001/jamapsychiatry.2021.4313.
144. Cole, J.C. and R.J. Rodgers, *Ethological evaluation of the effects of acute and chronic buspirone treatment in the murine elevated plus-maze test: comparison with haloperidol.* Psychopharmacology (Berl), 1994. **114**(2): p. 288-96 DOI: 10.1007/BF02244851.
145. Koek, W., J.-F. Patoiseau, M.-B. Assié, C. Cosi, M.S. Kleven, E. Dupont-Passelaigue, et al., *F 11440, a Potent, Selective, High Efficacy 5-HT_{1A}Receptor Agonist with Marked Anxiolytic and Antidepressant Potential.* Journal of Pharmacology and Experimental Therapeutics, 1998. **287**(1): p. 266-283.
146. Koek, W., B. Vacher, C. Cosi, M.B. Assie, J.F. Patoiseau, P.J. Pauwels, et al., *5-HT1A receptor activation and antidepressant-like effects: F 13714 has high efficacy and marked antidepressant potential.* Eur J Pharmacol, 2001. **420**(2-3): p. 103-12 DOI: 10.1016/s0014-2999(01)01011-1.
147. Wieland, S. and I. Lucki, *Antidepressant-like activity of 5-HT1A agonists measured with the forced swim test.* Psychopharmacology (Berl), 1990. **101**(4): p. 497-504 DOI: 10.1007/BF02244228.
148. Chojnacka-Wojcik, E., E. Tatarczynska, K. Golembiowska, and E. Przegalinski, *Involvement of 5-HT1A receptors in the antidepressant-like activity of gepirone in the forced swimming test in rats.* Neuropharmacology, 1991. **30**(7): p. 711-7 DOI: 10.1016/0028-3908(91)90178-e.
149. Silva, R.C. and M.L. Brandao, *Acute and chronic effects of gepirone and fluoxetine in rats tested in the elevated plus-maze: an ethological analysis.* Pharmacol Biochem Behav, 2000. **65**(2): p. 209-16 DOI: 10.1016/s0091-3057(99)00193-8.
150. Brown, P.C., *APPLICATION NUMBER: 022567, NDA: 22-567*, in *Tertiary Pharmacology/Toxicology Review (PHARMACOLOGY REVIEW)*. 2010, CENTER FOR DRUG EVALUATION AND RESEARCH
151. Griebel, G., R.J. Rodgers, G. Perrault, and D.J. Sanger, *Risk assessment behaviour: evaluation of utility in the study of 5-HT-related drugs in the rat elevated plus-maze test.* Pharmacol Biochem Behav, 1997. **57**(4): p. 817-27 DOI: 10.1016/s0091-3057(96)00402-9.
152. Kasahara, K., S. Hashimoto, T. Hattori, K. Kawasaki, R. Tsujita, O. Nakazono, et al., *The effects of AP521, a novel anxiolytic drug, in three anxiety models and on serotonergic neural transmission in rats.* J Pharmacol Sci, 2015. **127**(1): p. 109-16 DOI: 10.1016/j.jphs.2014.11.008.
153. Guilloux, J.P., I. Mendez-David, A. Pehrson, B.P. Guiard, C. Reperant, S. Orvoen, et al., *Antidepressant and anxiolytic potential of the multimodal antidepressant vortioxetine (Lu AA21004) assessed by behavioural and neurogenesis outcomes in mice.* Neuropharmacology, 2013. **73**: p. 147-59 DOI: 10.1016/j.neuropharm.2013.05.014.

154. Sanchez, C., L. Westrich, H. Zhong, S. Nielsen, N. Boyle, M. Hentzer, et al., *P. 2. b. 008 In vitro effects of the multimodal antidepressant Lu AA21004 at human and rat 5-HT1A, 5-HT1B, 5-HT3 and 5-HT7 receptors, and 5-HT transporters.* European Neuropsychopharmacology, 2012(22): p. S245-S246.
155. Bang-Andersen, B., T. Ruhland, M. Jorgensen, G. Smith, K. Frederiksen, K.G. Jensen, 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): p. 3206-21 DOI: 10.1021/jm101459g.
156. Cao, B.J. and R.J. Rodgers, *Influence of 5-HT1A receptor antagonism on plus-maze behaviour in mice. I. Pindolol enantiomers and pindobind 5-HT1A.* Pharmacol Biochem Behav, 1997. **58**(2): p. 583-91 DOI: 10.1016/s0091-3057(97)00280-3.
157. Newman-Tancredi, A., J.C. Martel, M.B. Assie, J. Buritova, E. Lauressergues, C. Cosi, et al., *Signal transduction and functional selectivity of F15599, a preferential post-synaptic 5-HT1A receptor agonist.* Br J Pharmacol, 2009. **156**(2): p. 338-53 DOI: 10.1111/j.1476-5381.2008.00001.x.
158. Cao, B.J. and R.J. Rodgers, *Influence of 5-HT1A receptor antagonism on plus-maze behaviour in mice. II. WAY 100635, SDZ 216-525 and NAN-190.* Pharmacol Biochem Behav, 1997. **58**(2): p. 593-603 DOI: 10.1016/s0091-3057(97)00279-7.

1 Table 1: Currently available serotonin 1A (5-HT_{1A}) receptor agonists and antagonists

		Compound	Affinity for 5-HT_{1A} (pKi)	Efficacy E_{max} (as % of 10 µM 5-HT binding) mean ± S.E.M.	Pre- vs post-synaptic potency	Other receptors affinities (indicative pKi)	Pre-clinical effect on forced swim test (minimal effective dose used)	Pre-clinical effect in elevated plus maze test (minimal effective acute dose used, unless specified)	References
Licensed	Agonist	Buspirone	7.7-8.0	65.4 ± 4.4	Pre	D_2 (7.5) α_1 (6.2),	↑ immobility (40mg/kg po)	↑ % time in open arm entries (2.5mg/kg po, chronic)	[74, 75, 81, 144-147]
		Gepirone	7.2	32*	Pre	5-HT_{2A} (5.9) 5-HT_{2B} (5.8) D_2 (6.25) D_3 (6.5) D_4, (6.35) α_1 (6.35) α_2 (6.5)	↓ Immobility (5mg/kg ip)	↑ % time in open arm (10mg/kg po, chronic)	[81, 148-150]
		Ipsapirone	8.6-8.8	49 ± 3.6	-		↓ Immobility (10mg/kg sc)	NS effect on open arm entries	[74, 75, 147, 151]
		Flesinoxan	9.3	94.3 ± 10.4	-	D_2(7.1) D_3 (7.5) D_4 (6.8) α_1 (6.5)	↓ Immobility (40mg/kg po)	NS. Effect on open arm entries	[74, 75, 145, 151]

		Tandospirone	8.2	100.5 ± 0.7	-	D_2(6.9) D_3 (7.2) D_4, (7.2) α_1, (6.3) α_2 (6.5)	↓ Immobility (10 mg/kg sc)	NS effect on time spent in open arms	[74, 75, 147, 152]
		Vortioxetine	7.8	96†	-	SERT (0.2), 5-HT_7 (1.2) 5-HT_3 (0.6)	↓ Immobility (5mg/kg po)	In open field test: ↑ time in centre (2.5mg/kg po)	[153-155]
	Antagonist	Pindolol	8.1	20.3 ± 2.1	-		Not tested	↑ % time in open arm (0.1mg/kg ip)	[75, 156]
Unlicensed	Agonist	NLX-101 (F15599)	8.57	102 ± 3	Post	Nil	↓ Immobility (0.63mg/kg; po)	↑ % time in open arm (5mg/kg po)	[97, 102, 157]
		NLX-112 (F13640, Befiradol)	8.9	108 ± 3	Pre & post (equipotent)	Nil	↓ Immobility (0.16mg/kg po)	↑ % time in open arm (0.1mg/kg sc)	[101] [98]
	Anta-gonist	WAY-100635	7.9-9.2	-	-	Nil		↑ % time in open arm (0.05mg/kg ip)	[158]

Abbreviations α_1: alpha 1 adrenergic receptor; α_2: alpha 2 adrenergic receptor; D: dopamine receptor; SERT: serotonin transporter; 5-HT: serotonin; ip: intraperitoneal administration; po: oral administration; sc: subcutaneous administration; kg: kilogram; mg: milligram; ↓= decrease, ↑ = increase; pKi: negative logarithm of the dissociation constant of ligand -transporter complex; $E_{max:}$ maximum efficacy at human 5-HT_{1A} receptors in recombinant cell lines on G protein activation;. * = (5-HT reference concentration or S.E.M. not available); † =Intrinsic activity relative to 5-HT