# *Psilocybin as a novel treatment for chronic pain*



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THEMED ISSUE REVIEW

# Psilocybin as a novel treatment for chronic pain

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## Abstract

Psychedelic drugs are under active consideration for clinical use and have generated significant interest for their potential as anti-nociceptive treatments for chronic pain, and for addressing conditions like depression, frequently co-morbid with pain. This review primarily explores the utility of preclinical animal models in investigating the potential of psilocybin as an anti-nociceptive agent. Initial studies involving psilocybin in animal models of neuropathic and inflammatory pain are summarised, alongside areas where further research is needed. The potential mechanisms of action, including targeting serotonergic pathways through the activation of 5-$HT_{2A}$ receptors at both spinal and central levels, as well as neuroplastic actions that improve functional connectivity in brain regions involved in chronic pain, are considered. Current clinical aspects and the translational potential of psilocybin from animal models to chronic pain patients are reviewed. Also discussed is psilocybin's profile as an ideal anti-nociceptive agent, with a wide range of effects against chronic pain and its associated inflammatory or emotional components.

KEYWORDS

neuropathic pain, neuroplasticity, nociplastic pain, psychedelic drugs, psilocybin, serotonergic signalling

## 1 | INTRODUCTION

Psychedelic substances such as **lysergic acid diethylamide** (LSD), **N,N-dimethyltryptamine** (DMT)—the psychoactive component of ayahuasca—**mescaline** and **psilocybin** have long been studied for their psychoactive properties, including ritualistic use. Systematic research into their cognitive effects and potential in pain management began in the 1960s (see Krebs & Johansen, 2013). The modern use of psychedelics emerged from the 1960s counterculture, which embraced them as a way to 'turn on, tune in, and drop out.' Aldous Huxley's call to use hallucinogens to 'cleanse the doors of perception', inspired by William Blake, further fuelled their popularity. Anecdotally, some individuals have used psychedelics to alleviate unwanted pain perceptions, whether from physical or mental trauma. Given that these substances affect a range of sensory functions, they hold potential for treating conditions like chronic pain. Reports of beneficial effects under monitored psychedelic use have been linked to psychological factors, such as an enhanced sense of well-being and spirituality — likely to be important components in a multifactorial therapeutic response.

This review will examine the pharmacological foundations of psychedelic drugs, particularly psilocybin, in the context of chronic pain treatment. Chronic pain can be categorised as neuropathic (because

**Abbreviations:** ACC, anterior cingulate cortex; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CeA, central nucleus of the amygdala; CIPN, chemotherapy-induced peripheral neuropathy; DMT, N,N-dimethyltryptamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; DRG, dorsal root ganglia; DRN, dorsal raphe nucleus; fMRI, functional magnetic resonance imaging; IBS, irritable bowel syndrome; LSD, lysergic acid diethylamide; PAG, periaqueductal grey; PET, positron emission tomography; PFC, pre-frontal cortex; RVM, rostral ventromedial medulla; SNI, spared nerve injury; SNL, spinal nerve ligation; TrkB, tropomyosin receptor kinase B.

of direct nerve damage or chemotherapy-induced nerve injury), inflammatory (often seen in conditions like osteoarthritis), or nociplastic (a newer classification for pain without clear tissue damage, such as lower back pain, migraines, irritable bowel syndrome [IBS] and fibromyalgia). Each of these categories represents an unmet clinical need, and evidence suggests that psychedelics might address this need in the near future. This review will concentrate on psilocybin, a tryptamine alkaloid naturally produced by *Psilocybe* mushrooms, which has garnered significant attention in both clinical and preclinical research.

During the 'first wave' of psychedelic research, clinical evidence for pain treatment emerged with Dr. Eric Kast's work in the 1960s, where LSD was administered to cancer patients experiencing pain. Kast reported that LSD had analgesic effects, superior to those of commonly used drugs (Kast & Collins, 1964). Similar studies in cancer patients revealed positive outcomes, often framed as 'medication-assisted psychotherapy' to emphasise the importance of a supportive environment in achieving therapeutic results (Cavarra et al., 2022). Building on this foundation, interest in psychedelics for pain therapy has grown, and the current 'second wave' of psychedelic research has seen psilocybin emerge as a promising therapeutic agent. Although much of the focus has been on conditions such as treatment-resistant depression and major depressive disorder, it is important to note that pain frequently co-exists with these affective disorders, further exacerbating the patient's condition.

In this review, we consider human case studies and clinical trials that are beginning to uncover the further potential anti-nociceptive properties of psilocybin in different areas, offering promise for individuals who experience inadequate relief of chronic pain from conventional analgesics. In line with our expertise and recent work, we focus on the role of preclinical animal models of pain in investigating anti-nociceptive effects of psilocybin. Thus, on-going clinical work sets a precedent as to why animal model work needs to accelerate towards understanding the mechanistic biology of the nociceptive potential of psilocybin. Such preclinical evidence can also be instrumental in evaluating evidence that psilocybin might have potential as an adjunctive agent to augment the actions of such existing analgesics. Finally, we consider the research areas in preclinical models that should be prioritised to support more fully the potential translation of psilocybin to clinical efficacy in chronic pain management.

## 2 | THE PHARMACOLOGY OF PSILOCYBIN

Psilocybin exerts its pharmacological effects through its active metabolite, psilocin. Upon ingestion, psilocybin is rapidly dephosphorylated by alkaline phosphatase enzymes in the liver and gut, converting it to **psilocin**, which can then cross the blood–brain barrier. The elimination half-life of psilocin is approximately 50 min, with psychoactive effects typically lasting 4–6 h, depending on the dose and metabolism (Dinis-Oliveira, 2017). The bioavailability of psilocybin is variable, but oral administration leads to rapid absorption and high conversion to psilocin. Peak plasma concentrations of psilocin occur approximately 2 to 3 h after ingestion of psilocybin (Dodd et al., 2023). Metabolism of psilocin occurs primarily in the liver, where it is conjugated with glucuronic acid and subsequently excreted mostly in the urine (Dodd et al., 2023). Psilocin is structurally similar to **5-HT (serotonin)** and therefore exhibits high affinity for 5-HT receptors. There are seven major families of **5-HT receptors** (5-$HT_{1\text{-}7}$, as designated by IUPHAR; Alexander et al., 2023) currently subdivided into up to 15 subtypes. All are G protein-coupled receptors, with the exception of the ligand-gated **5-$HT_3$ receptor** family, and all are excitatory in nature. Psilocin has nanomolar affinity at **5-$HT_{2A}$ receptors**, but it also has (lower) affinity for other 5-HT receptor subtypes including **5-$HT_{1A}$**, **5-$HT_{2B}$**, **5-$HT_{2C}$** and **5-$HT_7$**, receptors as well as interacting with **dopamine**, **adrenaline** and **histamine** receptors. Moreover, psilocin has (lower) micromolar affinity at the 5-HT transporter (**SERT**) (Rickli et al., 2016). There is consensus that 5-$HT_{2A}$ receptors represent the predominant pharmacological target of psychedelics drugs such as psilocybin (Wallach et al., 2023). For example, 5-$HT_{2A}$ receptor occupancy of psilocybin correlate with the psychedelic experience, as assessed by PET scans in humans (Madsen et al., 2019). Moreover, psilocin mediates the 'head-twitch' response, considered a behavioural proxy of the psychedelic drug response in animal models (Matsumoto et al., 1997) and such head twitch responses can by blocked by 5-$HT_{2A}$ receptor antagonists and are absent in 5-$HT_{2A}$ receptor knockout mice (Halberstadt et al., 2011).

## 3 | TARGETING PUTATIVE PATHWAYS OF CHRONIC PAIN WITH PSILOCYBIN

Pain, defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage', is experienced subjectively, and influenced by individual factors and prior experiences (Kumar & Elavarasi, 2016). Nociceptive signalling, initiated by various noxious stimuli, activates primary afferent fibres (nociceptors) in the periphery, which transmit signals via dorsal root ganglion neurons to the dorsal horn of the spinal cord. Projection neurons then relay ascending signals to higher brain centres involved in pain processing, which respond via descending inhibitory and facilitatory pathways (see Figure 1).

### 3.1 | Anti-nociceptive effects via the serotonergic system

The pharmacological actions of psilocybin, both immediate and enduring, are predominantly due to activation of 5-HT receptors (see Inserra et al., 2021; Nichols, 2016). Equally, serotonergic pathways represent key modulators of nociceptive signalling (see Bardin, 2011; Cortes-Altamirano et al., 2018; Liu et al., 2020; Viguier et al., 2013). However, there is an on-going and serious debate as to whether a psychedelic 'trip' is necessary for the potential therapeutic effects of drugs such as psilocybin.

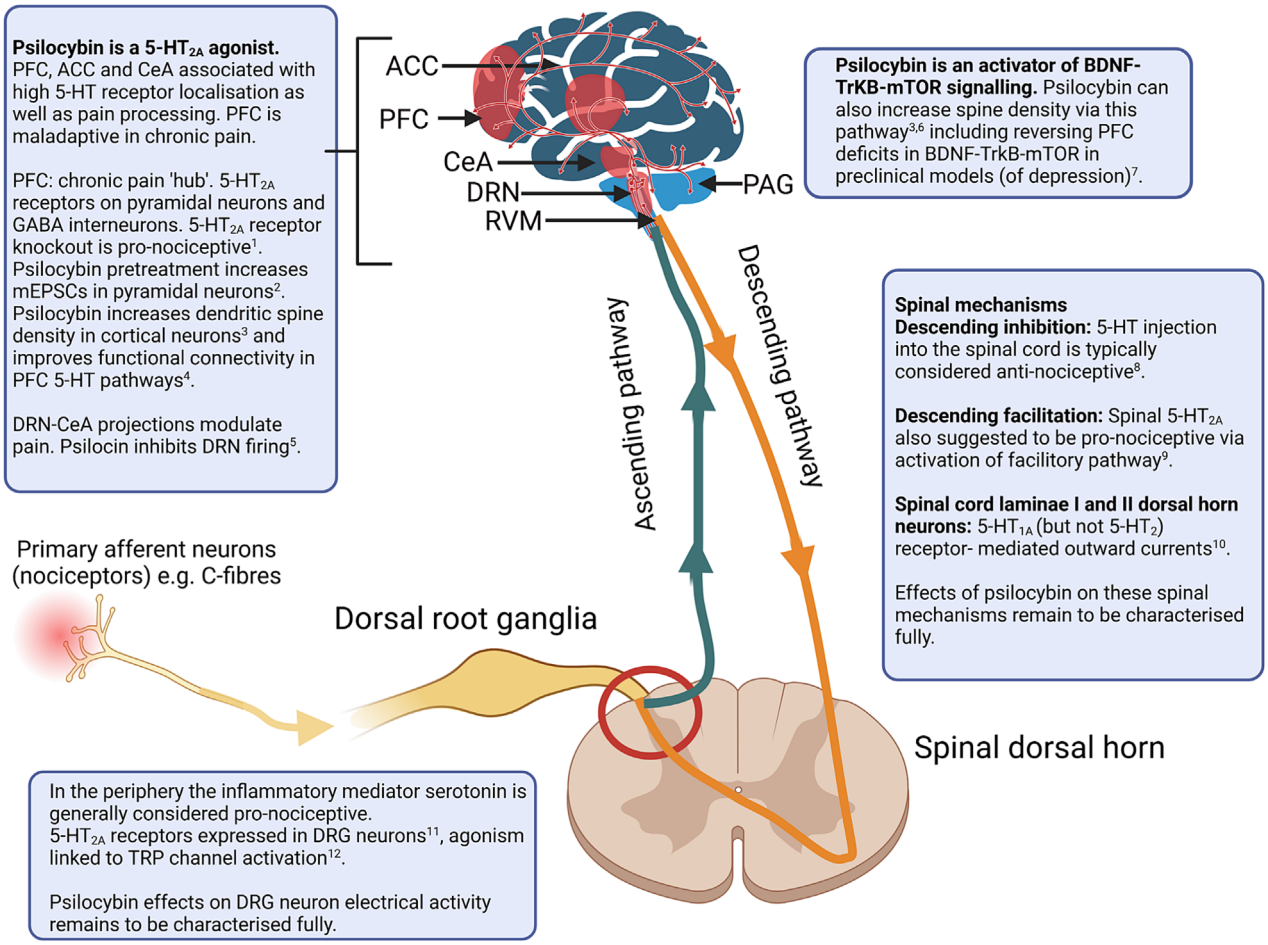


**FIGURE 1** **Potential sites of action for psilocybin anti-nociceptive effects.** This diagram outlines the major mammalian nociceptive pathways and summarises major theories by which psilocybin has been proposed to act as an anti-nociceptive agent. We also highlight areas where further research is warranted. ACC: anterior cingulate cortex, PFC: prefrontal cortex, CeA central nucleus of the amygdala, DRN: dorsal raphe nucleus, RVM: rostral ventromedial medulla. [1]Yuan et al., 2022; [2]Shao et al., 2021; [3]Ly et al., 2018; [4]Grandjean et al., 2021; [5]Aghajanian & Hailgler, 1975; [6]Moliner et al., 2023; [7]Zhao et al., 2024; [8]Viguier et al., 2013; [9]Van Steenwinckel et al., 2008; [10]Abe et al., 2009; [11]Nicholson et al., 2003; [12] Sanjel et al., 2022. Created with BioRender.com.

Central effects: In the CNS, 5-HT receptors are highly expressed in regions such as the prefrontal cortex (PFC), anterior cingulate cortex (ACC) and the central nucleus of the amygdala (CeA), areas highly associated with both mood regulation and pain processing (see Figure 1). This overlap might explain the high rates of comorbidity between chronic pain and depression, with approximately 50% of chronic pain sufferers also experiencing symptoms of major depressive disorder (Doan et al., 2015). The PFC is often described as a 'hub' for chronic pain control (Ong et al., 2019). People with chronic pain reportedly have a decreased grey matter volume within the PFC (Kang et al., 2019) and reduced functional connectivity within corticolimbic circuits (Vachon-Presseau et al., 2016; Yang & Chang, 2019). Preclinical models of pain have been instrumental in revealing serotonergic mechanisms underlying pain-like behaviours but are not always consistent. In the mouse spared nerve injury (SNI) model of pain, activity of serotonergic projections from the dorsal raphe nucleus (DRN) to somatostatin neurons in the CeA was shown to reduce depression-like behaviour and to partly reverse SNI-induced reduction in pain threshold (Zhou et al., 2019). This was assigned to a 5-HT$_1$ receptor-mediated effect, with activation of a 5-HT$_{2A}$ receptor pathway proposed to cause excitation via synapses onto non-somatostatin CeA neurons (Zhou et al., 2019). In the rat SNI model, Xu et al. (2020) reported that microinjection of agonists of 5-HT$_{2A}$, 5-HT$_{2B}$ and **5-HT$_{2C}$** receptors into the PFC rat ventrolateral orbital region had an anti-allodynic action. Yuan et al. (2022) also reported that knockdown of 5-HT$_{2A}$ receptors in the mouse ventrolateral orbital cortex aggravated spontaneous pain and mechanical hypersensitivity, using chronic constriction injury of the infraorbital nerve as a pain model. These data are consistent with a beneficial anti-nociceptive effect of 5-HT$_{2A}$ receptor agonists in the PFC and its projection pathways. However, Vizcarra et al. (2022) reported that intracranial PFC injection of the 5-HT$_{2A}$ receptor antagonist **volinanserin** (2.68 mmol per injection site) reduced mechanical hypersensitivity in the rat SNI model via a pathway that was linked to inhibitory **K$_V$7.x** channel activity.

In rat PFC, 5-HT$_{2A}$ receptors are highly expressed on excitatory layer V pyramidal neurons, and also on inhibitory fast-spiking

interneurons (Andrade, 2011; Puig et al., 2010); such expression provides potential for differential control of PFC output. Early findings indicate that psilocin decreases 5-HT firing in rat DRNs (Aghajanian & Hailgler, 1975). Here, it was proposed that psilocin activated presynaptic 5-HT receptors to inhibit DRN neurons and thus relieve an inhibitory serotonergic tone. There is evidence that psilocybin can act on serotonergic pathways to influence release of other transmitters to engender final functional effects. In a human PET scan study, activation by psilocybin (0.25 mg $kg^{-1}$) of 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors was reported to increase striatal dopamine release (Vollenweider et al., 1999). Using dual regression analysis, psilocybin (1–2 mg $kg^{-1}$) was shown to increase functional connectivity in mouse 5-HT pathways amongst the cortex, thalamus and midbrain (Grandjean et al., 2021). These data were correlated with increased expression of 5-$HT_{2A}$ receptor genes. Of interest was that psilocybin decreased connectivity in dopaminergic ventral striatum pathways. As above, USE OF action of psilocybin on 5-$HT_{2A}$ receptors expressed on **GABA**ergic interneurons in the PFC is another prominent potential central mechanism whereby psilocybin could reduce functional output in this major region involved in chronic pain signalling (see Smausz et al., 2022).

Spinal/supraspinal effects: Within the ascending pain pathway, serotonergic neurons project from the brainstem to the CeA, which forms part of the limbic system believed to control our emotional perception of pain and also to play a key role in depression and anxiety responses (Wilson et al., 2019). Moreover, descending inhibitory and facilitatory pathways, projecting from regions expressing high levels of 5-HT receptors to the brainstem rostral ventromedial medulla (RVM) and terminating at the dorsal horn of the spinal cord (Bardin et al., 2000), also represent an important modulatory component of pain (Ossipov et al., 2014) (see Figure 1). Direct injection of 5-HT into the spinal cord results in an overall anti-nociceptive action in animal models of pain (see Viguier et al., 2013). Earlier studies reported that intrathecal injections of the 5-HT receptor agonists, **α-methyl 5-hydroxytryptamine maleate** (α-m-5-HT) (30 μg) and **2,5-dimethoxy-4-iodoamphetamine** (DOI) (100 μg), were anti-nociceptive in the rat spinal nerve ligation (SNL) model, with effects blocked by the 5-$HT_{2A}$ receptor antagonist **ketanserin** (30 μg) (Obata et al., 2004). Bardin et al. (2000) also reported that intrathecal injection of ketanserin (10 μg) ameliorates 5-HT (1 μg)-induced anti-nociception in naïve rats. These data suggest that 5-$HT_{(2A)}$ receptor agonism can combat hyperalgesia in models of neuropathy, potentially via activation of descending inhibitory pathways. By contrast, spinal injection of 5-$HT_{2A}$ and 5-$HT_{2B}$ receptor agonists enhanced nociceptive C fibre-evoked spinal field potentials, whereas the injection of 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{2C}$ or 5-$HT_3$ receptor agonists depressed responses in the rat SNL model (Aira et al., 2010). Moreover, increased expression of 5-$HT_{2A}$ receptors in the dorsal horn of the spinal cord in animal models of chemotherapy-induced peripheral neuropathy (CIPN) has been associated with sensitising pain pathways (Thibault et al., 2008; Van Steenwinckel et al., 2008). In these studies, it was proposed that agonism of spinal 5-$HT_{2A}$ receptors was associated with activation of descending facilitatory pathways. These reports further highlight the complexity of the serotonergic system in pain and suggest that responses are dependent on activating specific serotonergic pathways. At present, the effects of spinal injection of psilocybin on pain-like behaviours in an appropriate range of animal models is largely unknown and such experiments will be useful to elucidate potential spinal mechanisms further. Earlier studies in ex vivo rat spinal cord slices reported that 5-HT (10 μM) induced outward currents in subpopulations of superficial laminae I and II dorsal horn neurons (Lu & Perl, 2007), such responses were reported to be mediated by 5-$HT_{1A}$ receptor, but not by 5-$HT_2$, 5-$HT_3$ or **5-$HT_4$ receptor** agonists (Abe et al., 2009). At present, the effects of psilocybin on electrical properties of dorsal horn neurons also remain to be clarified.

Peripheral effects: It is generally accepted that 5-HT is pro-nociceptive when applied peripherally in humans and in preclinical models. 5-HT is amongst the well-known inflammatory mediators of pain and modulation, by 5-HT, of peripheral inflammatory cells, such as mast cells (Imamdin & van der Vorst, 2023), is a key aspect to chronic pain development. In rat peripheral dorsal root ganglia (DRGs), early studies reported high expression of **5-$HT_{1B}$**, **5-$HT_{1D}$**, 5-$HT_{2A}$, 5-$HT_{2B}$, **5-$HT_{3B}$** and 5-$HT_4$ receptor transcripts within the small to medium diameter neurons that are typically involved in the processing of nociceptive information (Nicholson et al., 2003). Several studies have confirmed functional effects mediated by 5-$HT_{2A}$ receptors in rodent DRGs (Ohta et al., 2006; Sanjel et al., 2022), potentially via the subsequent activation of **TRP** receptors. These actions would be consistent with an excitatory, pro-nociceptive action for psychedelic drugs that act via 5-$HT_{2A}$ receptor agonism. It has been proposed that the 5-$HT_{(2A)}$ receptor mediated central/spinal anti-nociceptive effects discussed above outweigh possible peripheral actions of 5-HT (Viguier et al., 2013). However, it has also been reported that when 5-HT (250 ng—a lower dose than that causing pain) was injected peripherally, an anti-nociceptive effect, mediated predominantly via activation of 5-$HT_{1B}$, 5-$HT_{2A}$ and 5-$HT_3$ receptors, can be seen (Diniz et al., 2015). At present, there is scant evidence regarding the effect of psychedelic drugs, including psilocybin, on electric firing properties of DRGs, and it will be of interest to determine these in the near future.

Overall, it is clear that the predicted role of 5-HT receptor subtypes, and not least 5-$HT_{2A}$ receptors, can be contradictory between pain models and brain regions/pathways. Such inconsistencies might also reflect differences in 5-HT receptor subtype and distribution and circuitry. Any psilocybin-mediated anti-nociceptive effects might also be dependent on ligand dose, duration and/or route of administration, as well as the model of pain investigated. In general, these data highlight the complex nature of the serotonergic system in pain and the need to confirm involvement in psilocybin action in a complete and systematic manner at multiple levels along this axis. Animal models of pain can be of major benefit in this regard.

## 3.2 | BDNF/TrkB/mTOR and neuroplasticity

A prominent theory in the field of psilocybin research that is often used to explain the positive long-term effects of psilocybin on mood

is that of neuroplasticity (Ly et al., 2018; Olson, 2022) and this is an attractive hypothesis for management of chronic pain. Thus, neuroplasticity, namely, the reorganisation of neuronal pathways within the brain and spinal cord, is a process that is often disrupted in patients with mood disorders and is maladaptive in chronic pain conditions (Kuner & Flor, 2017). Psilocybin (1–2 mg $kg^{-1}$) has been shown to increase functional connectivity in brain regions associated with pain control including the PFC and ACC, as well as in the limbic system (Grandjean et al., 2021; Liu et al., 2023). Support for a neuroplasticity mechanism comes from several animal studies reporting that a single dose of psilocybin (0.5–20 mg $kg^{-1}$) increased the release of plasticity markers in different brain regions, notably the PFC (Jefsen et al., 2021), reversing maladaptive connections and priming the brain for improved globalisation. Psilocybin (4.4 mg $kg^{-1}$) also increased immediate early gene expression in mouse somatosensory cortex via both 5-$HT_{2A}$ receptor-dependent and 5-$HT_{2A}$ receptor-independent pathways (Lerer et al., 2024). In different animal models, the psilocybin (1 mg $kg^{-1}$)-induced release of plasticity markers preceded a persistent increase in dendritic spine growth in the cortex (Ly et al., 2018; Shao et al., 2021), which has been associated with increased density of the presynaptic marker synaptic vesicle protein 2A (Raval et al., 2021). This persistent effect has been proposed to explain some of the enduring anti-depressant effects of psilocybin (Zhao et al., 2024). In this regard, many dendritic spines represent functional glutamatergic synapses, which also express 5-$HT_{2A}$ receptors (Jakab & Goldman-Rakic, 1998). Recent studies report that pretreatment with psychedelic drugs such as DMT (1–10 mg $kg^{-1}$) (Ly et al., 2018) and psilocybin (1 mg $kg^{-1}$) (Shao et al., 2021) increases miniature excitatory postsynaptic currents in rodent layer V pyramidal neurons, providing a useful readout of increased functional activity. These effects mirrored the 5-$HT_{2A}$ receptor-mediated effects of 5-HT on spontaneous excitatory postsynaptic currents in rat layer V pyramidal neurons (Aghajanian & Marek, 1999). Moreover, it has been proposed that membrane-permeant ligands such as psilocin (1 μM) may activate intracellular 5-$HT_{2A}$ receptors to increase dendritic spine density in rat neurons (Vargas et al., 2023). Here, it was speculated further that a decoupling of effects of some 5-$HT_{2A}$ receptor agonists on hallucinogenic/neuroplastic versus behavioural effects (see Cameron et al., 2021) may be explained by targeting intracellular or cell surface 5-$HT_{2A}$ receptors, respectively. Psilocybin (1 mg $kg^{-1}$) strengthened cortico-hippocampal synapses in chronically stressed mice, demonstrating that psilocybin is pro-neuroplastic (Hesselgrave et al., 2021). Of further interest in this study, pre-treating mice with the 5-$HT_{2A}$ receptor antagonist ketanserin (2 mg $kg^{-1}$) did not impede psilocybin-induced synaptic strengthening or anti-depressant-like behaviour in an animal model (Hesselgrave et al., 2021). Similarly, ketanserin (1 mg $kg^{-1}$) was reported not to inhibit psilocybin-induced dendritogenesis in mice by Shao et al. (2021). These studies suggest the involvement of receptors/pathways other than those involving 5-HT in mediating psilocybin's effects on plasticity. Ly et al. (2018) further showed that inhibiting **TrkB** and **mTOR** signalling pathways using rapamycin (100 nM) prevented neuroplasticity induced by psilocin (and other psychedelic drugs) in rat neurons, and authors suggest a mechanism involving both TrkB and 5-$HT_{2A}$ receptor signalling (Ly et al., 2018). In mouse models of depression, the resultant negative structural effects on the hippocampus and PFC can be reversed by a single dose of psilocybin (1–5 mg $kg^{-1}$), promoting neurogenesis via activation of a **BDNF**-TrkB-mTOR signalling pathway within hours of psilocybin administration (Zhao et al., 2024). A recent study by Moliner et al. (2023) showed that psilocin (100 nM) upregulates cell surface levels of TrkB via endogenous BDNF release at active synapses; this action being independent of 5-$HT_{2A}$ receptors. There is also evidence that psychedelics can cause **glutamate** release and activation of **AMPA** receptors, together with effects on TrkB, to induce plasticity (Olson, 2022).

There is limited research showing an effect of psilocybin specifically on functional connectivity in chronic pain conditions. Interestingly however, upregulation of the BDNF-mTOR-TrkB pathway has been shown to play a significant role in the development and persistence of chronic pain conditions, affecting both the brain and spinal cord (Ren & Dubner, 2007). Dysregulation of BDNF, TrkB and mTOR has been linked to increased neuroinflammation, central sensitisation and maladaptive changes in the nervous system, exacerbating and perpetuating chronic pain states. Inhibition of the BDNF pathway within the ACC, using **rapamycin**, reduced mechanical allodynia in nerve injury models of pain (Um et al., 2019), and it is believed that upregulation of BDNF/TrkB in the descending pain pathway is important in the development of inflammatory pain conditions (Ye et al., 2023). Generally, in human chronic pain conditions, serum levels of BDNF are increased, compared to those in healthy controls (Thakkar & Acevedo, 2023), causing increased hyperexcitability of neurons within the spinal dorsal horn and DRGs. Therefore, it remains to be established how psilocybin activation of the BDNF–TrkB-mTOR pathway may be relevant in nociceptive pathways.

Overall, there is evidence that psilocybin may act via 5-$HT_{2A}$ receptor activation and/or as a positive allosteric modulator at the BDNF-TrkB-mTOR pathway, with the potential subsequent involvement of further receptor pathways, to promote neuroplasticity and improved functional connectivity. Such actions have potential to be beneficial in anti-nociceptive responses. Thus, psilocybin may improve dysfunctional synaptic connectivity within the key areas of pain processing, such as the PFC, and 'reset' the brain back to its healthy state. Psilocybin-induced dendritic spine growth persists for weeks following injection. Such long-term neuronal changes might explain how psilocybin improves symptoms of depression long after the hallucinogenic effects of the drug have worn off and may apply equally to chronic pain.

### 3.3 | Anti-inflammatory role

It is widely known that psychedelic drugs promote anti-inflammatory effects not only in the periphery, most likely through 5-$HT_{2A}$ receptors, but also in the brain, with evidence suggesting an anti-inflammatory effect of psilocybin in appropriate animal models (Flanagan & Nichols, 2018; Nichols, 2016). Such anti-inflammatory

actions are consistent with a prominent mechanism associated with analgesic drugs. Inflammation within the CNS, termed neuroinflammation, is believed to trigger 'central sensitisation' within the CNS, resulting in increased excitability of neurons here and leading to the chronification of pain (Fang et al., 2023). Psilocybin (45–315 μg $kg^{-1}$) was reported to increase plasma concentrations of anti-inflammatory **adrenocorticotropic hormone**, **cortisol**, **prolactin** and **thyroid-stimulating hormone** in human volunteers (Hasler et al., 2004). More recently, psilocybin in mushroom extracts was shown to reduce concentrations of pro-inflammatory cytokines, such as **TNF-α** and **IL-1β** in **lipopolysaccharide** (LPS)-stimulated macrophage cell cultures in vitro (Nkadimeng et al., 2021). Psilocybin (0.88 mg $kg^{-1}$) also reduced cytokines in mouse brains following LPS injection (Zanikov et al., 2023). In the latter study, combining psilocybin treatment with **eugenol** (an anti-inflammatory agent) was more efficacious in reducing inflammation than with either treatment alone. These and other data suggest that use of psilocybin alongside complementary treatments could augment therapeutic benefit and support the use of psilocybin as an adjunctive therapy, as discussed below.

### 3.4 | Emotional processing

Pain, according to its widely accepted definition, is not only the result of nociceptive signals transmitted from damaged tissues; it also encompasses a substantial emotional experience, heavily influenced by an individual's mood and psychological state. One key factor that may determine whether a person fully recovers from an injury or develops chronic pain is their level of psychological vulnerability. Chronic pain patients, in particular, are more likely to experience pain catastrophising, a psychological tendency to ruminate excessively on pain, which can exacerbate and prolong the pain experience (Edwards et al., 2011). Moreover, although the PFC is associated with the pain state, this region is also important in maintaining fear associated with pain, and emotional components of chronic pain have been linked with PFC dysfunction (Yang & Chang, 2019). As described above, 5-HT receptors contribute to amygdala circuitry and activation of such pathways is also a potential mechanism by which psilocybin may alleviate emotional pain. Equally, increased plasticity and functional connectivity in limbic areas can induce changes in emotional processing, thereby alleviating the emotional burden of pain (Stoliker et al., 2024). A second region which is primarily associated with the emotional processing of pain is the ACC, a region rich in serotonergic signalling pathways (Xiao & Zhang, 2018). Lesion of the ACC has been reported to attenuate many affective pain-associated behaviours in multiple animal models of pain (Fuchs et al., 2014). Psilocybin (2 mg in 10 ml saline, infused over 60 s) reduced neuronal firing in human studies, with fMRI imaging showing decreased blood oxygen-level dependent signalling within the ACC and PFC (Carhart-Harris et al., 2012). In mice, psilocybin (2 mg $kg^{-1}$) similarly reduced activity within the ACC (Golden & Chadderton, 2022). The psychedelic drug experience is explicitly associated with both sensory and emotional effects. It is, therefore, tempting to speculate that therapeutic use of psychedelic drugs such as psilocybin for chronic pain might have additional utility in treating aspects of emotional or existential pain.

Dysfunction of the insula cortex has also been implicated in various chronic pain conditions, such as fibromyalgia, migraine and neuropathic pain. Such studies show increased activation of the anterior insula and increased functional connectivity, correlating with heightened pain sensitivity and emotional distress (Alves et al., 2023; Mandloi et al., 2023). This abnormal insula connectivity may lead to an exaggerated perception of pain. Similarly, in migraine, altered insula activity has been linked to the emotional and sensory dysregulation that exacerbates pain intensity, with fMRIs often showing increased functional connectivity within the insula (Labrakakis, 2023; McBenedict et al., 2024). These conditions highlight how insular dysfunction disrupts pain processing, integrating sensory input with emotional states, resulting in chronic pain. Psilocybin may offer therapeutic potential for these conditions by targeting insula dysfunction. By promoting neuroplasticity, psilocybin could provide long-lasting improvements in pain-related affective and sensory dysfunction in nociplastic and neuropathic pain.

## 4 | PRECLINICAL EVIDENCE FOR USE OF PSILOCYBIN IN CHRONIC PAIN CONDITIONS

The data presented so far have set the scene for the consideration of how research using animal models may be extended to investigate opportunities for psilocybin to manage different types of neuropathic or inflammatory pain and to also interrogate mechanisms of action. At present, there are only a limited number of such preclinical investigations, although recent preliminary studies suggest that this is an area of emerging interest. A study by Kolbman et al. (2023) presents some compelling preclinical data regarding the anti-nociceptive effect of psilocybin in the formalin model of inflammatory pain as tested in 42 male (21) and female (21) adult Sprague–Dawley rats. Here, a single intravenous injection of psilocybin (1–10 mg $kg^{-1}$) caused a significant reduction in mechanical sensitivity 3 h post-injection, with this reduction persisting throughout the entire 28 days of the experiment (Kolbman et al., 2023). Although the study describes a persistence of effect size that is unparalleled in current chronic pain treatments, potential mechanistic theories were not tested. Because of the long-term effects that greatly outlast the ~2-h half-life of psilocybin, it was suggested that the reduction in mechanical sensitivity might be caused by long-term neuroplastic changes to the CNS. In abstract communications, researchers at Virginia Commonwealth University report that psilocybin (0.1–1 mg $kg^{-1}$) and DOI (0.3–2 mg $kg^{-1}$) reversed mechanical and cold hypersensitivity for up to 14 days, both in a mouse model of CIPN (Koseli et al., 2023) and a Complete Freund's Adjuvant model of chronic inflammatory pain (Damaj et al., 2024). Moreover, these effects were reported to be sensitive to the 5-$HT_{2A}$ receptor antagonist volinanserin. We have recently investigated the effects of psilocybin for the first time in the mouse SNI model of neuropathic pain, with our initial results submitted as an abstract communication to IASP (Askey et al., 2024). We found that a

single intraperitoneal injection of psilocybin (0.3–1 mg $kg^{-1}$) caused a persistent reduction in pain-like behaviours in male mice in the SNI model. Thus, psilocybin caused a significant reduction in mechanical hypersensitivity, reduced dynamic allodynia (hypersensitivity to light brush) for up to 10 weeks post-injection and reduced cold hypersensitivity in the acetone evaporation test. Such a single dose of psilocybin was also without any deleterious effect on locomotor performance, suggesting that there were no potentially confounding effects on motor function (Askey et al., 2024). Taken together, these initial studies are very encouraging and begin to develop an evidence base and provide the opportunity to further explore the gaps in our knowledge highlighted in the current review, not least is the question of anti-nociceptive mechanism of action of psilocybin. These aspects are discussed further, below.

## 5 | CLINICAL EVIDENCE FOR PSILOCYBIN EFFECTS IN CHRONIC PAIN CONDITIONS

The emerging preclinical evidence discussed above offers primary support for human case studies and larger clinical trials. Thus, there have been several recent case studies with psychedelic drugs that have fuelled an increased number of human clinical trials, in particular using psilocybin. These areas and recent updates are summarised below.

### 5.1 | Case studies with psilocybin

Initial research into the anti-nociceptive effects of psychedelic drugs focussed on the effects of LSD in patients with phantom limb pain and cancer-related pain. These historic 'first wave' case studies are covered in some depth in recent reviews (Castellanos et al., 2020; Jevotovsky, Chopra, Pak, et al., 2024; Robinson et al., 2024). While clinical evidence of psilocybin utility in chronic pain remains limited at present, we provide an updated summary of recent and most relevant case studies in this area. In an interesting proof of concept study, Ramachandran et al. (2018) demonstrated that psilocybin (0.2–3 g dried mushroom) can augment the effects of mirror visual feedback therapy in phantom limb syndrome, a debilitating form of neuropathic pain. Here, patient 'AL' found neither opioids nor mirror visual feedback therapy alone to be adequate treatments, but psilocybin alone could provide significant, albeit temporary, relief from chronic pain. Increasing doses of psilocybin alongside mirror visual feedback therapy produced stronger, more immediate and prolonged pain relief. These authors proposed that psilocybin increases cross-modal communication via a neuroplastic increase in crosstalk between the visual and somatosensory systems. In another case study (Gonzales et al., 2024), psilocybin also provided relief in a patient with autoimmune lupus-related pain, whereby a 'one-time macrodose' of 6 g *Psilocybe cubensis* significantly improved their pain levels for an extended period of at least 12 months. An area of recent increased interest with particular relevance to psychedelic drugs is that of "microdosing"; this procedure involves using more regular, sub-hallucinogenic, doses to achieve therapeutic effects, while attempting to decouple the psychedelic experience. A case study in three patients with complex regional pain syndrome (CRPS) showed that psilocybin microdosing (500 mg of *Psilocybe cubensis* mushroom daily for 7–10 days) provided a nearly complete resolution in pain levels for many hours to several weeks and, importantly, reduced the use of opioids (Lyes et al., 2023). A recent case study further supports use of psilocybin in CRPS, whereby a 54-year-old female with a long treatment history that failed to resolve the condition, found significant and prolonged pain relief via a macrodose (2 g) of *Psilocybe cubensis* mushroom with follow-up dose of 5.5 g 3 days later and 2.5 g 2 days later (Jevotovsky, Chopra, Wing, et al., 2024).

### 5.2 | Clinical trials with psilocybin

As discussed elsewhere, there has been a steady increase in clinical trials investigating potential therapeutic benefits of psychedelic drugs, in particular psilocybin. Whereas early trials often suffered from a lack of randomisation and blinding and/or appropriate placebo controls, recent gold standard randomised controlled trials are beginning to provide a stronger evidence base. Outcomes of human trials with psychedelic drugs were reviewed recently by Ross et al. (2022) and by Schindler (2022) and these reviews are updated here and represent human trials with psilocybin currently listed on clinicaltrials.org (Table 1).

There is some focus on nociplastic pain conditions within the trials listed earlier. Such conditions include IBS, fibromyalgia, headaches and chronic lower back pain. Nociplastic conditions have been particularly associated with CNS neuronal reorganisation as well as decreased inhibitory modulation from the descending pathway (Bułdyś et al., 2023), factors which are known to be targeted by psilocybin. There are several encouraging findings among those studies with reported and analysed data. Efficacy of psilocybin both on attack frequency in people with migraine and cluster headaches and on associated chronic pain measures has been reported from two major groups (Madsen et al., 2024; Schindler et al., 2021, 2024). Another prominent finding is that psilocybin reduced pain measures in people with cancer (Agrawal et al., 2024); this study also indicates that psilocybin might also improve quality of life in conditions such as demoralisation syndrome. As indicated in Table 1, the NCT06206265 trial indicates that psilocybin has further potential utility in conditions of visceral pain.

It is of general interest that these studies vary between single or (a small number of) repeat-dosing regimen. Much preclinical focus is currently on single dose effects of psilocybin, for example, in Phase II trials for different forms of depression, where psilocybin was administered at 1–25 mg (Goodwin et al., 2022) or 0.215 mg $kg^{-1}$ (von Rotz et al., 2023). However, published data on pain measures in Table 1 are exclusively from studies using repeat-dosing regimen; it will be of interest to discover if single dosing proves as efficacious for pain. All trials in Table 1 also use a macrodosing experimental design. As mentioned earlier, microdosing may be an attractive alternative for those

**TABLE 1** Human trials on effects of psilocybin on measurements of chronic pain.

| Chronic pain condition | Psilocybin dose/regime | Phase | Dates (start-end) | Study ID | Comments |
|---|---|---|---|---|---|
| Phantom limb pain | 25 mg (single dose) | Phase 1 Double-blind placebo-controlled pilot study | 2022–2024 | NCT05224336 | Primary outcome: phantom limb pain intensity. Secondary outcomes: visual analogue scale. Data to be reported. |
| Cancer-related pain and major depressive disorder | 25 mg (single dose) | Phase 2 Open-label trial | 2020–2022 | NCT04593563 | Significant reduction in visual analogue scale pain rating and in the pain subscale of the EuroQoL-5-dimension 5-level scale reported for 30 subjects (Agrawal et al., 2024). |
| Chronic lower back pain | 1–30 mg (single dose) | Phase 2 Double-blind, randomised trial | 2023–2024 | NCT05351541 | Primary outcome: brief pain inventory-interference subscale. Data to be reported. |
| Chronic lower back pain and depression | 25 mg (single dose) | Phase 1 Double-blind, randomised, active control study | 2024–2026 | NCT06355414 | Primary outcomes include effect on pain catastrophising and changes in positive affective pain inhibition. Data to be reported. |
| Fibromyalgia | 15 mg then 25 mg dose 2 weeks later | Phase 2 Open-label trial | 2023–2024 | NCT05128162 | Secondary outcome: Chronic pain interference and intensity. Data to be reported. |
| Fibromyalgia | 0.36 mg $kg^{-1}$ (single dose) | Phase 1 Double-blind, placebo- controlled clinical trial | 2023–2025 | NCT05068791 | Primary outcome: visual analogue scale. Secondary outcomes: Patient global impression of change and brief pain inventory. Data to be reported. |
| Fibromyalgia | Up to 25 mg × 2 doses 4 weeks apart | Observational mechanistic trial | 2022–2024 | NCT05548075 | Secondary outcome: brief pain inventory interference subscale. Data to be reported. |
| Migraine | 0.0143 mg $kg^{-1}$ or 0.143 mg $kg^{-1}$ × 2 doses 2 weeks apart | Phase 1 double-blind, placebo-controlled clinical trial | 2017–2021 | NCT03341689 | Significant reduction in weekly migraine days, significant reduction in pain severity reported for 10 subjects followed for 2 weeks post-treatment; psilocybin was well tolerated (Schindler et al., 2021). |
| Migraine | 10 mg single versus repeat dose ~7 days later | Phase 1 Double-blind, placebo-controlled clinical trial | 2021–2023 | NCT04218539 | Frequency and duration of attacks; pain intensity. Data to be reported. |
| Cluster headache | 10 mg per 70 kg × 3 doses 5 days apart | Phase 1 Blinded extension to double-blind, placebo-controlled clinical trial | 2016–2022 | NCT02981173 | Cluster headache attack frequency was significantly reduced by 50%, significant reductions baseline versus 3 weeks in attack pain severity in 10 subject cohort; psilocybin was well tolerated (Schindler et al., 2024). |
| Cluster headache | 0.14 mg $kg^{-1}$ × 3 doses 1 week apart | Phase 2 Open label trial | 2020–2022 | NCT04280055 | Increased hypothalamus functional connectivity correlated with a reduction in the frequency of attacks and reduction in pain intensity in 10 subject trial; treatment well tolerated (Madsen et al., 2024) |
| IBS | 25 mg × 2 doses up to 15 days apart | Phase 2 Open label trial | 2024–2025 | NCT06206265 | Measures of safety and tolerability with secondary measures of IBS-related pain changes and affective state. Data to be reported. |

*Note*: Current trials where pain is a primary or secondary endpoint, for example, in conditions with pain as an associated but significant co-morbidity, are summarised.

concerned about experiencing an unwanted, full blown, psychedelic experience. Microdosing might also find favour in terms of regulatory drug approvals. However, there are concerns that this is a relatively new concept and potential safety issues, for example, that more chronic psychedelic dosing might cause cardiotoxicity (Rouaud et al., 2024; Wsół, 2023), remain to be considered more fully.

Although the data in Table 1 supports the current review and suggests clear and appropriate interest in the anti-nociceptive effects of psilocybin in several areas of chronic pain, it will be imperative to evaluate data yet to be communicated fully from ongoing trials. It will also be vital to advance these findings to more advanced stages of clinical trials with larger cohort sample size where true therapeutic utility can be appreciated more fully.

## 6 | CONCLUSIONS AND FUTURE INSIGHTS

It can be argued that psilocybin may represent a 'perfect' anti-nociceptive pharmacotherapy. Thus, an agent that can combine effective treatment of physical pain with that of existential or emotional pain is so far lacking in our therapeutic armoury. It is of interest that, largely for such reasons, psilocybin is being proposed as a new player in management of pain associated with terminal or life-threatening disease and palliative care (Ross et al., 2022; Whinkin et al., 2023). Psilocybin has an attractive therapeutic profile: it has a fast onset of action, a single dose can cause long-lasting effects, it is non-toxic and has few side effects, it is non-addictive and, in particular, psilocybin has been granted FDA breakthrough therapy status for treatment-resistant depression and major depressive disorder, both intractable conditions co-morbid with chronic pain. A further potential advantage is that the sustained action of psilocybin may have additional effects on longer-term inflammatory pain, often a key component of the types of nociplastic pain that psilocybin has been targeted against in clinical trials.

Given the above potential, what are the questions that need to be asked in on-going and future preclinical studies with psilocybin for pain treatment? As discussed, there are several potential mechanisms by which psilocybin may mediate effects against chronic pain. This area is key to the further development of psilocybin and is particularly suited to preclinical analysis. Activation of 5-$HT_{2A}$ receptors (potentially via subsequent effects on pathways expressing other receptors) has anti-nociceptive potential. The plasticity-promoting effects of psilocybin are a further attractive property. Such neuroplastic effects can occur rapidly, for example, via the upregulation of BDNF, and be prolonged, for example, leading to persistent changes in spine density, far outlasting the clearance of psilocybin from the body. These mechanisms provide potential for any anti-nociceptive effects of psilocybin to be much more effective and sustained than current chronic pain treatments.

We found that a single dose of psilocybin leads to a prolonged reduction in pain-like behaviours in a mouse model of neuropathy following peripheral nerve injury (Askey et al., 2024). It will be important to characterise the effects more fully in other models of neuropathic pain such as those induced by chemotherapeutic agents and inflammatory pain (see Damaj et al., 2024; Kolbman et al., 2023). Our model investigated intraperitoneal injection of psilocybin (Askey et al., 2024), and Kolbman et al. (2023) injected psilocybin intravenously. It will be of interest to determine actions at the spinal, supraspinal and peripheral levels using different routes of administration such as intrathecal, or perhaps direct CNS delivery. In terms of further options of drug administration, it will also be important to determine if repeat dosing of psilocybin can further prolong changes in pain-like behaviour in animal models. There is also the possibility to determine the effects of microdosing in terms of repeat application of low doses of psilocybin on behavioural efficacy.

An area of general pharmacological interest is an appreciation that sex is an important biological variable (Docherty et al., 2019); this is of particular relevance in regard to chronic pain (Ghazisaeidi et al., 2023) and for psychedelic drug treatment (Shadani et al., 2024). Closing the gender pain gap is vital for developing future anti-nociceptive agents that are effective in all people with chronic pain. Some interesting sex differences were reported by Shao et al. (2021) in that psilocybin-mediated increases in cortical spine density were more prominent in female mice. We have shown that psilocybin has anti-nociceptive effects in male mice (Askey et al., 2024), but it will be vital to include both sexes in future work.

Alongside the significant societal, economical and clinical cost associated with chronic pain, there are well-documented concerns with those drugs that are available. For example, although opioids are commonly used to manage acute pain, their effectiveness diminishes with chronic use, often leading to issues of tolerance and addiction (Jamison & Mao, 2015). Moreover, the use of opioids has clearly been the subject of intense clinical and societal debate in the wake of the on-going 'opioid crisis'. In addition, a gold standard treatment for neuropathic pain, **gabapentin**, is often associated with side effects and poor compliance (Wiffen et al., 2017). Because of these key issues associated with current analgesics, concerted effects are being made to develop novel chronic pain treatments with fewer side effects and greater efficacy for long-term use. Although not without its own social stigma, psilocybin, with a comparatively low addiction potential (Johnson et al., 2008), might represent a safer alternative to current drugs. A final attractive possibility is that psilocybin treatment may not only have useful anti-nociceptive effects in its own right but might also enhance the effect of other treatments, as shown in preclinical (e.g. Zanikov et al., 2023) and human studies (e.g. Ramachandran et al., 2018). Thus, psilocybin may act to 'prime' the nociceptive system to create a favourable environment to improve efficacy of co-administered analgesics. Overall, psilocybin, with the attractive therapeutic profile described earlier, represents a potential alternative, or adjunct, to current treatments for pain management. It will now be important to expand preclinical investigation of psilocybin in a fuller range of preclinical models and elucidate its mechanisms of action in order to realise fully the anti-nociceptive potential of psilocybin.

### 6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander, Christopoulos, Davenport, Kelly, Mathie, Peters, Veale, Armstrong,

Faccenda, Harding, Davies, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Amarosi, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Annett, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Beuve, et al., 2023; Alexander, Mathie, Peters, Veale, Striessnig, Kelly, Armstrong, Faccenda, Harding, Davies, Aldrich, et al., 2023).

## AUTHOR CONTRIBUTIONS

**T. Askey:** Conceptualization (equal); data curation (supporting); writing—original draft (supporting). **R. Lasrado:** Conceptualization (supporting); writing—original draft (supporting). **M. Maiarú:** Conceptualization (equal); funding acquisition (equal); project administration (equal); supervision (equal); writing—original draft (supporting). **G. J. Stephens:** Conceptualization (equal); funding acquisition (equal); project administration (equal); supervision (equal); writing—original draft (lead).

## CONFLICT OF INTEREST STATEMENT

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N/A-Review.

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