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Review

Pharmacotherapy for the Secondary Prevention of Suicide: Leads from the Social Pain Hypothesis

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Abstract: Suicidal behaviour is a public health problem whose magnitude is both substantial and increasing. Since many individuals seek medical treatment following a suicide attempt, strategies aimed at reducing further attempts in this population are a valid and feasible secondary prevention approach. An evaluation of the available evidence suggests that existing treatment approaches have limited efficacy in this setting, highlighting the need for innovative approaches to suicide prevention. Existing research on the neurobiology of social pain has highlighted the importance of this phenomenon as a risk factor for suicide, and has also yielded several attractive targets for pharmacological preventive strategies. In this paper, the available evidence related to these targets is synthesized and critically evaluated. The way in which social pain is related to the "anti-suicidal" properties of recently approved treatments, such as ketamine and psilocybin, is also examined. Such strategies may be effective for the short-term reduction of suicidal ideation and behaviour in individuals who have made a suicide attempt suicide prevention, particularly in cases where social pain is identified as a contributory factor. These pharmacological approaches may be effective regardless of the presence or absence of a specific psychiatric diagnosis.

Keywords: suicide; social pain; psychache; endogenous opioid system; oxytocin; serotonin; endocannabinoids; buprenorphine; psilocybin; ketamine

1. Introduction

Suicide is one of the leading global causes of premature mortality. It is estimated that around 750,000-800,000 people lose their lives to suicide each year, and suicide rates appear to be rising in several low- and middle-income countries [1, 2]. Suicide is a complex phenomenon, representing the result of non-linear interactions between innate genetic or developmental vulnerability [3-5], current life stressors or events [6], and individual or social protective factors [7]. Suicide attempts are preceded by suicidal ideation and planning, but suicidal ideation is relatively common in the general population, and many individuals with such ideas do not progress to making a suicide attempt [8-10]. A suicide attempt is one of the most robust predictors of future suicide risk; therefore, the provision of interventions in the aftermath of an attempt is one of the key secondary suicide prevention strategies [11]. Several psychological interventions to reduce suicidal ideation and behaviour have been evaluated in controlled trials. A critical evaluation of these strategies found that the benefits from such interventions are modest, and that there is no evidence for the superiority of one approach over another [12, 13]. Likewise, in view of the association between mental illness and suicide, several pharmacological agents have been assessed for "anti-suicide" effects. There is no significant evidence that existing pharmacotherapies have robust and replicated effects on suicide risk, with the exception of two drugs – lithium in patients with bipolar disorder, and clozapine in patients with treatment-resistant schizophrenia. Neither of these drugs is useful as a suicide prevention strategy in the absence of these specific diagnoses, and both are associated with significant adverse effects and a narrow therapeutic index [14]. Furthermore, there is evidence that some pharmacological agents may slightly but significantly increase the risk of suicide,

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particularly in youth [15]. These findings suggest that there is an urgent need for approaches to suicide prevention, particularly following a suicide attempt, which have greater efficacy and a better risk-benefit ratio than existing pharmacological or psychological therapies.

In recent years, much has been learned about the neuroanatomical, neurophysiological and biochemical correlates of suicidal ideation and behaviour. There is little evidence for gross structural abnormalities in the brains of individuals attempting suicide. Instead, functional imaging studies have revealed evidence of reduced activity in the prefrontal cortices, left insula and right putamen, possibly related to altered serotonergic transmission, and increased activity in the superior and middle temporal gyri and right occipital cortex [16, 17]. Biochemical studies have revealed evidence of alterations related to monoaminergic transmission [18], hypothalamic-pituitary-adrenal (HPA) axis activity [19], immune-inflammatory pathways [20], and neural plasticity [21]. Recent genome-wide analyses of individuals who have made a suicide attempt are consistent with these findings, suggesting that several biological pathways are related to suicidality, including monoaminergic, glutamatergic and peptidergic neurotransmission, the HPA axis and circadian rhythms [22]. Likewise, psychological factors such as decision-making ability, executive functioning, neuroticism, impulsivity and aggression have been identified as candidate endophenotypes for suicidal behaviour [23]. Though each of these findings is valuable and could serve as a potential lead for the development of pharmacological or psychological suicide prevention strategies, it is unclear to what extent they apply to individual cases encountered in a "real-world" setting such as a clinic, emergency room or community treatment centre. It is also unclear to what extent these individual pathways are interrelated. The existing literature highlights the need for an overarching theory – or at least a hypothesis – that could link these findings and highlight discrete targets for suicide prevention strategies that can be tested in controlled trials. In this paper, evidence for one such hypothesis – the social pain model of suicide – is critically evaluated using the available evidence. Next, potential targets for pharmacological intervention, based on our existing knowledge of the phenomenon of social pain, are identified, and their potential benefits and risks are explored.

2. Materials and Methods

For the purpose of this review, a literature search of the PubMed, Scopus and ScienceDirect literature databases was conducted, using the key words "social pain" along with "suicide", "suicide attempt", "suicidal ideation", "suicidal behaviour", "suicide risk" or "suicidality". A total of 152 citations were retrieved using this method. After the exclusion of duplicates (n = 26), the remaining 126 citations were examined for their relevance to the current review. Papers were included in this review only if they discussed theoretical models or presented the results of original research – translational, observational or interventional – that could be of relevance in elucidating the links between social pain and suicide-related phenomena. A total of 67 articles were included via this process. In addition, the reference lists of the included articles were examined for relevant citations. A total of 95 papers were included in the final review. This process is depicted graphically in **Figure 1**.

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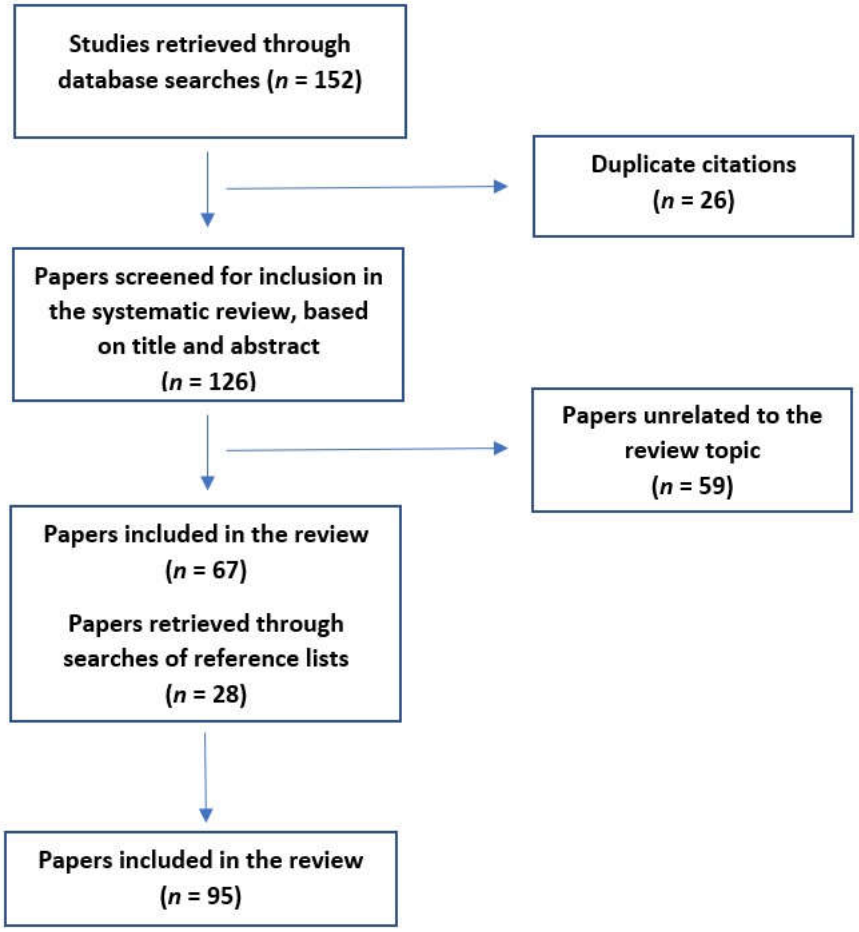

Figure 1. Flow diagram depicting the selection of articles for inclusion in this review.

In view of the heterogeneous nature of the included studies, the results of this review were organized conceptually under the following headings:

- Neurobiology of social pain
- Relationship between social pain and suicide
- Relationship between social pain and factors related to suicide (e.g., depression, substance abuse, stress)
- Existing secondary suicide prevention strategies in relation to the social pain model
- Novel pharmacological targets for secondary suicide prevention

Following this, the implications of these findings for research and clinical practice, as well as the potential risks and benefits associated with these approaches, were examined.

3. Results

a. Neurobiology of social pain

Negative emotional states, particularly those occurring in response to social exclusion or rejection, are often described using words that refer to pain or tissue damage: for example, we speak of being "broken-hearted" or of having "hurt feelings". Recent neurobiological research suggests that there is a deeper reality behind such metaphors. Stated in brief, the social pain hypothesis postulates that social pain – that is, the distressing responses to conflict or disruption in social relationships – shares neural mechanisms with physical pain [24]. From a neuroanatomical perspective, social pain appears to be strongly correlated with altered patterns of activation in distinct areas of the anterior cingulate cortex (ACC); for example, self-reported distress caused by social exclusion is associated with increased activation of the subgenual ACC, while the length of exclusion is associated

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with a ventral-to-dorsal gradient in ACC activation [25]. Other components of the "physical" pain pathway that have also been implicated in the experience social pain include the thalamus, sensory cortex, and periaqueductal gray area of the midbrain [26]. Neurochemically, social pain appears to be most strongly linked to alterations in the activity of the endogenous opioid system, particularly to changes in the activation of μ-opioid receptors [27-29]. This pathway is known to be crucially involved in the modulation of physical pain [30], again supporting the hypothesis of an overlap between the two. Other neurotransmitters that have been linked to the perception of social pain include serotonin [31], the neuropeptide oxytocin [32], and endogenous cannabinoids [33]. Pro-inflammatory cytokines, which are known to increase sensitivity to physical pain, have also been associated with increased neural activation in key brain regions when exposed to an experimental situation that induces social pain; this suggests a certain degree of cross-talk between the immune-inflammatory and social pain pathways [34]. Though this hypothesis assumes an overlap between the neural substrates of physical and social pain, it does not require a perfect correspondence between the two. Functional brain imaging studies have found that, though both phenomena involve alterations in the functioning of common brain regions, the patterns of altered activation in these regions can reliably distinguish between the two [35]. Variations in specific genes, such as the *OPRM1* gene which encodes the μ-opioid receptor, appear to be associated with alterations in sensitivity to experimentally-induced social pain [36]. Exposure to severe adversity in childhood may also influence social pain perception through alterations in ACC structure and oxytocin-related neural transmission [37]. More generally, experiences of social rejection in early life may alter the "calibration" of the neural pathways discussed above, resulting in altered sensitivity to specific types of social pain [38].

From an evolutionary perspective, the overlap between social and physical pain is understandable if one considers social pain an adaptation that promotes an individual's safety. Just as physical pain serves as an "alarm", leading to behavioural changes such as avoidance of painful stimuli and decreased use of an injured body part, the aversive nature of social pain can be thought of as an "alarm" that prevents the separation of an individual from a larger group [39]. In line with this, evidence for an overlap between social and physical pain has been documented even in other mammalian species, such as dogs and monkeys [40]. In ancestral environments, separation from a group would have been associated with a higher rate of injury or death (for example, due to starvation or attacks from predators) [41, 42], and even in "modern" settings, loneliness is associated with a significantly elevated risk of mortality from all causes [43]. In this sense, the social pain hypothesis can be viewed as an extension of attachment theory, elucidating the mechanism by which social pain elicits distress and stimulates efforts to avoid separation [44]. Along these lines, Meier et al. have proposed a "μ-opioid feedback" model of human social behaviour, in which the endogenous opioid system influences social affiliation, empathy and bonding in response to positive and negative social experiences [45].

b. Social pain and suicide

In 1993, Edwin Shneidman suggested that, regardless of the role of specific triggering factors, the ultimate reason for suicide was an attempt to put an end to "unbearable mental pain", which he termed *psychache* [46]. Subsequent research has confirmed Shneidman's hypothesis [47], and has found that mental or psychological pain may be a stronger predictor of suicide than other known risk factors, such as the presence of depression [48]. Though there are relatively few studies of the neural correlates of psychological pain, the available evidence suggests that it shares several a common neural circuit with physical pain, involving regions such as the prefrontal cortex, ACC and thalamus [49]. These regions are almost identical to those that have been associated with social pain, raising the possibility of an overlap between the two; more precisely, social pain may represent a subtype of psychological pain [50].

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From an empirical perspective, conditions associated with social pain are frequently cited as motives for suicide. These include conflicts between family members (such as parent-child conflict), marital conflict, infidelity by a spouse, a lack of close friends, a perceived lack of support or affection from significant others, loneliness, bullying (including "cyber-bullying"), and social ostracism [51-55]. These factors appear to play a significant role regardless of the age or geographical location of the populations being studied, suggesting that they may all act through the final common pathway of causing intolerable social pain. The available evidence suggests that social pain is, in fact, a key mediator between exposure to such situations and suicidal behaviour [56].

These neurobiological and epidemiological findings were synthesized by Gunn [57], who proposed the *social pain model* of suicide. According to this model, experiences such as rejection or exclusion in a social or interpersonal setting lead to social pain. Generally speaking, the experience of social pain is much more common than suicide attempts or completed suicide, and social pain does not lead to suicidality in the majority of cases. However, in vulnerable individuals, social pain is associated with "suicidogenic cognitions", such as ideas of hopelessness, of being a burden to others, or of feeling trapped in a situation from which one cannot escape. Social pain can also be associated with "negative social cognitions" which, while not directly suicidogenic, can reinforce suicidogenic cognitions; these may include ideas of oneself as inferior, inept and being unable to sustain social relationships. Social pain, suicidogenic cognitions and negative social cognitions may then create a positive feedback loop, which – if left uninterrupted – can lead to an increase in social pain to an intolerable level, which triggers suicidal behaviour. Though Gunn's formulation is based on a consideration of psychological intermediate variables, it is supported by neuroimaging studies of individuals with a recent or past suicide attempt. When exposed to an experimental state of social exclusion, these individuals were found to have reduced activation in specific cortical regions and decreased oxytocin levels; alterations in regional brain activity were correlated with levels of cytokines such as interleukin-1 beta (IL-1β) and interleukin-2 (IL-2) [58]. Similarly, a study of individuals with low social integration and acute suicidal ideation found evidence of increased activity in the dorsal ACC and anterior insula, which appear to play a role in the experience of social pain [59], while a study of women with a past history of suicidal behaviour showed evidence of reduced activity in the left insula and supramarginal gyrus, in contrast with healthy controls, when experiencing social exclusion in an experimental setting [60]. Though these findings require replication, they provide a support for alterations in the neural substrates of social pain perception in relation to suicide.

Along similar lines, it has been suggested that the endogenous opioid system may play a central role in the link between exposure to adverse social experiences, social pain and suicide. There is evidence from both animal and human research that the distress caused by separation or social exclusion is related to altered signalling at the μ-opioid receptor; these changes may be linked to the severity of social pain experienced by a given person, and may vary in relation to genetic polymorphisms of the μ-opioid receptor gene (*OPRM1)* [61, 62]. If this pain crosses a certain threshold, suicidal behaviour is more likely to occur according to the social pain model. In line with this proposal, there is evidence that a specific functional polymorphism of the *OPRM1* gene is associated with an increased risk of suicide [63, 64]. Post-mortem studies of suicidal deaths found evidence for increased functional coupling of the μ-opioid receptor in the anterior insula [65] and increased μ-opioid receptor density in the prefrontal cortex [66], which may reflect compensatory changes in the face of a high level of social pain.

In summary, the social pain model postulates that exposure to certain adverse experiences triggers social pain, which can result in negative cognitions and form a self-reinforcing process, resulting in suicidal behaviour; this process may be mediated at a neural level by alterations in opioidergic transmission. While this model may not account for all suicide attempts, it may be of particular relevance to two subsets of suicide attempters. The first, as discussed above, is those individuals whose suicide attempts occur in the context of an event or events that trigger social pain [67]. The second, which follows from

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the sharing of a neural substrate between physical and social pain, is suicide occurring in the context of chronic physical pain. Physical pain is associated with a significant increase in suicidal ideation, behaviour, and completed suicide [68], and there is evidence of cross-talk between the processes involved in physical and social pain [69]. Therefore, it is possible that social stressors can exacerbate the impact of physical pain on suicide risk, and that physical pain can increase sensitivity to social pain [70]. This reasoning can also be extended to more complex social problems in which there is an interplay between physical and social pain, such as victims of intimate partner violence [71]. In at least some of the cases mentioned above, pharmacological or psychological therapies aimed at altering social pain perception or sensitivity may represent valid suicide prevention strategies.

The social pain model and its functional correlates are summarized in **Figure 2**.

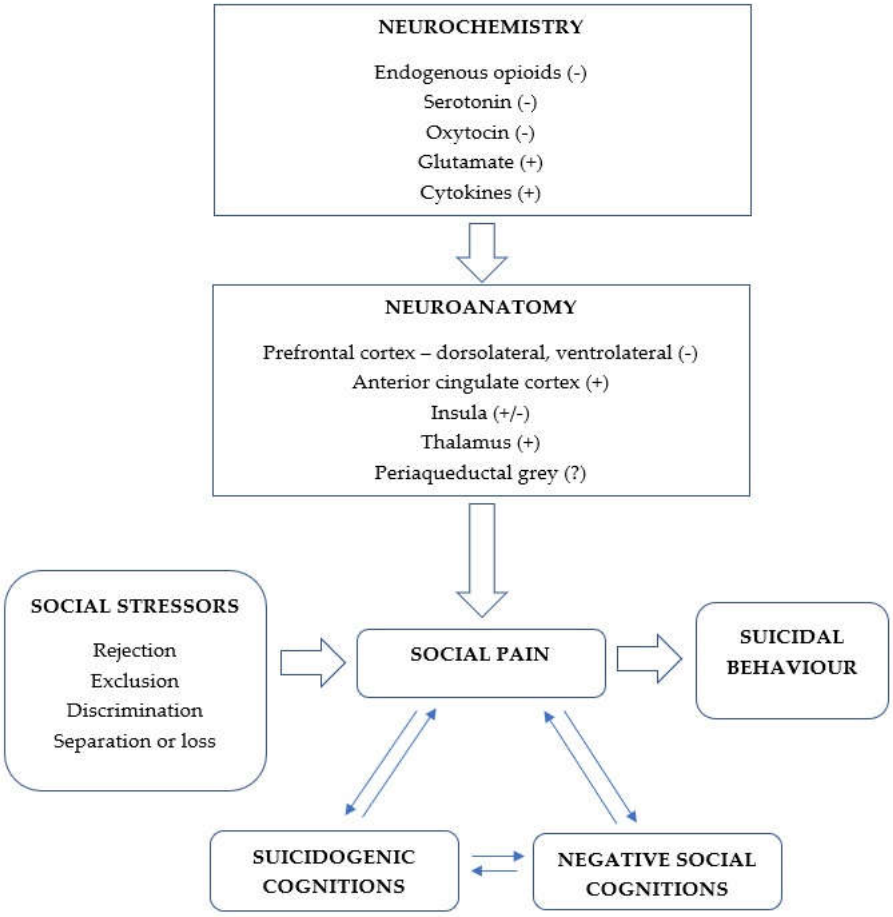

Figure 2. The social pain model of suicide and its biological substrates. (+) indicates a transmitter or region that may be associated with an increase in social pain; (-) indicates a transmitter or region that may attenuate social pain; (+/-) indicates evidence of mixed effects; (?) indicates an uncertain effect.

c. Social pain and other risk factors for suicide

The risk of suicide in a given individual is significantly increased by the presence of certain comorbid psychiatric disorders. These include depression, substance use disorders, and personality disorders [72, 73]. While there is ample evidence for links between these disorders and suicide in their own right, there is also evidence of altered sensitivity to social pain in individuals suffering from these disorders. Such alterations might represent one of the mechanisms linked to increased suicidal behaviour in these individuals. For example, patients with major depression had reduced μ-opioid receptor activation in several key brain areas, in comparison with healthy controls, when exposed to a social feedback task that simulated social rejection [74]. Similarly, patients with opioid misuse

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show altered HPA axis reactivity and increased anger when exposed to experimental situations that triggers social pain [75], and patients with borderline personality disorder show evidence of a link between social and physical pain perception [76]. While it is simplistic to assume that altered social pain perception is the chief cause of suicidal behaviour in people with these diagnoses, it may contribute to their increased risk of suicide to a significant extent.

Similar considerations may extend to other risk factors for suicide. For example, chronic stress is associated with suicide risk via alterations in neuroendocrine, inflammatory and serotonergic pathways *inter alia* [4]. These pathways are also involved in social pain responses [31, 34, 77], and there is evidence that chronic stress influences the relationship between social and physical pain [78]. Likewise, impulsivity, which is an important endophenotype for suicidal behaviour, has been found to interact with social pain in complex ways. Individuals with high impulsivity may be at a higher risk of facing social rejection, and hence of experiencing social pain, in early life [79]; on the other hand, social pain may increase impulsive behaviour in some individuals [80]. These findings suggest that the concept of social pain can be fruitfully incorporated into other, broader models of suicide risk, and that it may be of relevance in a significant number of suicide attempts [81].

d. The social pain hypothesis and existing strategies for secondary suicide prevention.

Existing approaches to suicide prevention following an attempt can be broadly divided into two categories: pharmacological or psychological treatment of an underlying psychiatric diagnosis (such as depression), and psychological interventions specifically targeted at reducing suicidal ideation and behaviour. When examining the first of these, it is noteworthy that though antidepressants have been available for over five decades, trends in their prescription do not appear to correlate significantly with changes in suicide rates [82, 83]. Moreover, in children, adolescents and young adults, the use of antidepressant therapy is associated with a modest but significant *increase* in suicidal ideation and behaviour [15, 84]. Thus, though these drugs appear to be effective for the treatment of moderate to severe depressive episodes, they do not appear to have robust "anti-suicidal" properties. Several social and biological explanations for this phenomenon have been proposed, but have not been tested systematically. In this context, it is worth considering the possibility that this finding may be related to the lack of effect of antidepressants on social pain. A clinical trial of patients with fibromyalgia receiving the antidepressant duloxetine – which acts via both serotonergic and noradrenergic mechanisms – found no evidence that this drug has a significant effect on social pain when given over a period of one month [85]. It has also been observed that patients with depression show an increased activation of the prefrontal cortex, amygdala and insula when facing social rejection, even when they are receiving antidepressant therapy [86]. Other drugs used in the management of depression, such as mirtazapine and atypical antipsychotics, are antagonists of serotonin type 2A ($5HT_{2A}$) receptors [87]; there is evidence that activation of these receptors can attenuate social pain [31]. Patients with a specific polymorphism of the *OPRM1* gene, known to be associated with social pain sensitivity, may experience a paradoxical increase in suicidal ideation when treated with the antidepressant tianeptine [87]. Thus, the lack of a meaningful effect on the neural substrates of social pain may be one reason why the commonly used antidepressants do not exhibit consistent "anti-sucide" effects.

When considering pharmacological therapies that have been shown to reduce suicidal behaviour, it is notable that though lithium and clozapine act through diverse pharmacological mechanisms, they both appear to have effects on endogenous opioid receptor activity. Lithium has been shown to reduce pain sensitivity in a rat model of neuropathic pain, and this effect appears to be mediated by increased activation of the μ-opioid receptor by the endogenous peptide β-endorphin [88]. N-desmethylclozapine, a metabolite of clozapine, has been shown to act as an agonist at δ-opioid receptors, which are co-expressed with μ-opioid receptors and also play a role in pain perception [89]. These

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pharmacological properties may explain why lithium and clozapine have a significant effect on suicidal behaviour, while other drugs that are effective in the management of bipolar disorder or schizophrenia apparently do not.

Among the various psychological interventions that have been tested following a suicide attempt, it has been observed that cognitive-behavioural approaches show a significant superiority over "control" interventions, while approaches such as dialectical behaviour therapy and problem-solving therapy are not significantly superior to "controls" [12]. Though a number of explanations may exist for these findings, one possibility is that cognitive-behavioural therapy (CBT), which aims to correct dysfunctional beliefs and appraisals, may interrupt the positive feedback loop between social pain and negative cognitions that leads to suicide [57, 81]. CBT is also effective in the management of chronic physical pain [90], and imaging studies have shown that CBT is associated with changes in the functioning of specific brain areas that form part of the shared pathway for physical and social pain [91]. Therefore, it is possible that psychological therapies such as CBT derive at least some of their "anti-suicidal" properties from their effects on the perception and appraisal of social pain.

e. Novel pharmacological targets for suicide prevention based on the social pain model

From the foregoing section, it can be seen that the social pain model of suicide may explain some of the differences in "anti-suicide" properties among existing pharmacological and psychological therapies. However, research into the pharmacological substrates of social pain perception also provides valuable leads for novel suicide prevention strategies, particularly in individuals who have made a suicide attempt or are experiencing active suicidal ideation in relation to social exclusion, rejection or isolation. These are summarized in **Table 1** and discussed in more depth below.

Table 1. Pharmacological targets for secondary suicide prevention, based on the social pain model of suicide.

Pharmacological target	Mechanism for the reduction of social pain	Potential drug therapies
Opioid receptors	μ-opioid receptor partial agonism; κ-opioid receptor antagonism (?)	Buprenorphine
Serotonin receptors	Activation of $5HT_{2A}$ and $5HT_{1A}$ receptors	Psilocybin MDMA (?)
Glutamate receptors	Blockade of NMDA receptors; modulation of metabotropic glutamate receptors (?)	Ketamine Agmatine (?)
Cannabinoid receptors	Blockade or partial agonism of CB_1 receptors (?)	No specific agent available for clinical use to date
Oxytocin receptors	Agonism of oxytocin receptors	Intranasal oxytocin (?)
Immune-inflammatory pathways	Reduction in the levels of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α)	NSAIDs (?) Infliximab (?)
Others	Reduction of social pain perception or sensitivity	Acetaminophen (paracetamol) (?) rTMS (?)

Abbreviations: (?), uncertain or inconsistent evidence; 5-HT, serotonin; CB, cannabinoid; IL-1β, interleukin-1 beta; IL-6, interleukin-6; MDMA, 3, 4-methylenedioxymethamphetamine; NMDA, *N*-methyl d-aspartate; NSAIDs, non-steroidal anti-inflammatory drugs; rTMS, repetitive transcranial magnetic stimulation

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e1. Opioid receptor agonists and antagonists

Endogenous opioid peptide transmission, and signalling at the μ-opioid receptor in particular, appears to play a central role in the perception of social pain. Therefore, it is possible that cautious pharmacological manipulation of this receptor could reduce the severity of social pain, and thereby reduce suicidal cognitions and behaviours related to this parameter [27-29, 36, 45, 61-66]. Though there is anecdotal evidence of an effect of opioid agonists in suicide prevention in certain cases [92], this must be balanced against the significant evidence for an increased risk of suicide related to high-dose opioid therapy or to its discontinuation [93, 94]. There is some evidence that buprenorphine, a partial μ-agonist with high receptor affinity, may be associated with a lower risk of abuse and suicide than other opioid analgesics [95]. Thus, it is possible that therapy with buprenorphine – but not other commonly used opioids – could be effective in the reduction of suicidality through its effects on social pain.

To verify this hypothesis, Yovell et al. conducted a multi-centre, placebo-controlled trial of low-dose buprenorphine (0.1 – 0.8 mg/day; the standard analgesic dose is 4-24 mg/day) in patients with significant suicidal ideation and no past or current history of substance abuse [96]. It was found that buprenorphine was significantly superior to placebo in reducing suicidal ideation after 2 and 4 weeks, and was also superior in reducing self-reported mental pain. These results were not influenced by concurrent antidepressant treatment, and buprenorphine did not cause a significant reduction in symptom scores for depression, suggesting that its suicide-specific effect was independent of any antidepressant property. Though these results are promising, they should be interpreted with caution, as the rates of suicide attempts did not differ significantly across treatment groups. Subsequently, a controlled trial of a single high dose of buprenorphine (32, 64, 96 mg) found that this treatment was associated with a significant reduction in suicidal ideation in patients with comorbid major depression and opioid dependence; all three doses were equally effective in terms of the primary outcome, and no suicide attempts were reported [97]. In this trial, the effect of a single dose appeared to be maintained when patients were followed up after two weeks; however, the lack of a placebo group in this study was a significant limitation. These results suggest that μ-opioid receptor agonism is a potentially valid strategy for the reduction of suicidal ideation, though its effect on suicidal behaviour remains uncertain and its long-term effects remain unclear. Further randomized control trials of buprenorphine or related agents with a focus on outcomes beyond suicidal ideation are required, both to establish real-world efficacy and to determine the effective dose range and the risk/benefit ratio of this approach.

The effects of buprenorphine on suicidal ideation or behaviour may not be confined to its μ-opioid receptor partial agonism: there is some evidence that blockade of κ-opioid receptors may also attenuate suicide risk, and that this property contributes to the putative "anti-suicidal" effect of buprenorphine [98]. In animal models, δ-opioid agonists reduce the affective component of experimentally induced pain [99]; as mentioned earlier, clozapine may exert its effects on suicide risk through the actions of its active metabolite at this receptor. These receptors may represent useful alternate targets for the pharmacological reduction of suicide risk through the attenuation of social pain.

e2. Serotonin receptor agonists

The monoamine transmitter serotonin has been hypothesized to play a key role in the neurobiology of suicidal behaviour. Low levels of the serotonin metabolite 5-hydroxyindole-acetic acid (5-HIAA) have been consistently reported in suicide attempters [18], and variations in serotonin-related genes, such as the serotonin transporter gene (*SLC6A4*) and the tryptophan hydroxylade-2 gene (*TPH2*) have been associated with suicide attempts [100]. More generally, serotonin has been implicated in the regulation of a number of fundamental biological processes, such as appetite, the sleep-wake cycle, perception, the regulation of emotions, and cognition, including social cognition [101-103]. These effects are mediated through 14 known subtypes of serotonin receptors [104]. Serotonin is

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also hypothesized to play a role in the pathogenesis of depression, and drugs acting on serotonergic pathways are the most commonly used antidepressants [105].

Recent evidence suggests that the serotonergic system plays a role in the modulation of social pain. A functional polymorphism of the *SLC6A4* gene is associated with the perception of interpersonal problems in depressed individuals [106] and with the level of anxiety experienced during an experimental task involving social exclusion [107]. Administration of an agonist of serotonin type 2A and 1A receptors appears to reduce social pain processing [31]. *d*-fenfluramine, which increases serotonin release, is associated with reduced distress when performing a socially stressful task, as is the serotonin type 1A partial agonist ipsapirone. On the other hand, stimulation of serotonin type 1B receptors, or blockade of type 2A receptors, appeared to increase anxiety during such tasks [108]. Thus, it is possible that pharmacological therapies which selectively target specific types of serotonin receptors can reduce the perception of social pain.

A promising lead for a serotonergic drug that might reduce suicidal ideation or behaviour was obtained from epidemiological studies of individuals taking psychedelic and related drugs for recreational purposes. These drugs, which include psilocybin, lysergic acid diethylamide (LSD), dimethyltryptamine and mescaline, all act either through an increase in presynaptic serotonin release or through agonism of serotonin type 1 and type 2 receptor subtypes. Initially, a class effect was observed for these drugs, with lifetime psychedelic use associated with lower rates of suicidal ideation, planning, and attempts [109, 110]. Further research led to the emergence of a more fine-grained picture, in which LSD was associated with an increase in the risk of depression and suicidal ideation, while psilocybin was associated with reduced suicidal ideation and behaviour [111, 112]. Psilocybin was also found to reduce social pain in a controlled trial conducted in healthy volunteers [31]. Subsequently, the use of a single dose of psilocybin, in combination with psychotherapy, was noted to cause a significant reduction in suicidal ideation in patients with advanced cancer. This effect was sustained up to 6 months [113]. These results suggest that psilocybin may be an effective means of targeting the social pain pathway and causing an acute reduction in suicide risk [114]. Nevertheless, caution is required when using psychedelic drugs in this manner, as they can also be associated with undesirable psychological effects ("bad trips") such as anxiety, aggression and dysphoria [115].

3,4-methylenedioxymethamphetamine (MDMA), commonly referred to as "Ecstasy", is a drug that is sometimes grouped together with psychedelics or hallucinogens because of an overlap in their pharmacological properties and perceived effects [112]. The mechanism of action of MDMA appears to involve an increase in the release of serotonin, though it also has effects on dopamine and noradrenaline release [116]. MDMA, like psilocybin, appears to be associated with reduced suicidal ideation in community surveys [117], and MDMA appears to reduce social pain both in animal models and in humans by blunting the response to social rejection [118]. Recently, MDMA has been investigated as a potential treatment for patients with post-traumatic stress disorder in combination with psychotherapy, and appeared to be associated with a reduction in suicide risk at trial completion [119]. However, given the numerous reports of suicide attempts or suicidality associated with MDMA outside a clinical context [116], as well as consistent reports of neurotoxicity and other end-organ damage associated with excessive MDMA use [120, 121], the risk-to-benefit ratio of this approach requires careful evaluation.

e3. Glutamate receptor antagonists

The amino acid transmitter glutamate is the main excitatory neurotransmitter in the brain [122]. Glutamate plays a key role in pain perception, and functional imaging studies have demonstrated elevated levels of glutamate in patients with chronic pain syndromes [123, 124]. Glutamate also interacts with opioid receptor functioning, particularly with the μ-opioid receptor, to influence sensitivity to pain [125]. The effects of glutamate on pain are mediated through its actions on specific receptors, including the *N*-methyl d-aspartate (NMDA) receptor and metabotropic receptors [126, 127]. Pharmacological blockade of the

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glutamate receptor reduces central pain perception, and this effect appears to be mediated by the actions of endogenous opioids at μ receptors [128]. In rodent models, glutamate plays a key role in the response to social stressors, such as exclusion or exposure to hostile behaviours, and this effect appears to be related to alterations in the activity of NMDA and metabotropic type 5 (mGlu5) glutamate receptors [129, 130]. These findings suggest a plausible association between glutamatergic transmission and the perception of social pain. A study of adolescents with suicidal ideation found evidence of altered glutamate metabolism in the ACC, a region strongly associated with the experience of social pain [131]. Based on these findings, it has been suggested that glutamate-related therapies may represent a novel approach to the reduction of suicidality [132].

A short-term clinical trial of pregabalin, a drug that inhibits the release of glutamate, found that this drug did not reduce social pain in patients with chronic physical pain [85]. On the other hand, the NMDA receptor antagonist ketamine, previously used as a general anaesthetic and analgesic, has recently been approved for use in patients with resistant depression [133]. Apart from its rapid antidepressant properties, ketamine and its enantiomer esketamine (S(+)-ketamine) also appear to exert a significant early effect on suicidal ideation in patients with mood or anxiety disorders [134]. A subsequent clinical trial involving 32 patients with a history of chronic suicidal thoughts found that ketamine was associated with a reduction in suicidal ideation over a 6-week period, with over two-thirds of participants reporting a significant benefit. These effects were independent of the patients' formal diagnosis or concurrent treatment with other medications, and were associated with increased grey matter volumes in brain regions that form part of the "social pain circuit", such as the thalamus and periaqueductal gray [135, 136]. Crucially, it has also been observed that the anti-suicidal effects of ketamine in humans are blocked by the administration of naltrexone, a drug that acts primarily as a μ-opioid receptor antagonist [137]. A synthesis of these results is consistent with the hypothesis that ketamine may reduce suicidal ideation through its effects on social or psychological pain, mediated by increased activation of the μ-opioid receptor. However, the specific effects of ketamine on suicidal behaviour have not been evaluated independently.

Given the known risks of misuse associated with ketamine [138], the polyamine molecule agmatine has also been investigated as a safer alternative. Agmatine appears to act at least partially through blockade of the NMDA receptor [139], and a post-mortem study has documented reduced agmatine levels in the cerebral cortex of completed suicides, independent of the presence of depression [140]. Agmatine has also been shown to have antidepressant-like effects in animal models of depression [141], and could share anti-suicidal effects with ketamine; however, these properties have not yet been evaluated in controlled trials in humans.

e4. Cannabinoid receptor agonists

The endogenous cannabinoid or endocannabinoid system has been identified as playing a significant role in several psychiatric disorders, as well as in suicidal behaviour [142, 143]. These effects appear to be mediated primarily through the cannabinoid type 1 (CB_1) receptor, which is expressed at high levels in several key brain regions, including the prefrontal cortex and limbic system [144]. In a rat model, changes in social behaviour and sensitivity to physical or social pain caused by rejection were associated with an upregulation of CB_1 receptors. These changes could be reversed by administration of rimonabant, a CB_1 receptor inverse agonist [145]. The administration of another CB_1 inverse agonist, AM-251, was associated with antidepressant effects in a mouse model, and these effects were potentiated by the opioid antagonist naltrexone, suggesting a link between opioid system activity and these effects [146]. Post-mortem studies have found evidence of increased cannabinoid receptor density and functional coupling in the brains of individuals with depression who committed suicide [147, 148], while chronic cannabis use in adults leads to an increase in the associations between physical pain, depression and anxiety [149]. The endocannabinoid system also interacts significantly with several of the

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molecular pathways implicated in social pain, including the endogenous opioid system [146, 150], serotonergic transmission [151], and the HPA axis [152]. Therefore, the endocannabinoid system appears to be implicated in social pain as well as in suicide, most probably through signalling at the CB_1 receptor.

Despite what would be expected from the results of animal studies, administration of rimonabant in humans is associated, not with a reduction in suicidality, but with an increase in depression, anxiety and even suicide risk; these effects were severe enough to necessitate its withdrawal from several markets [153]. It has been suggested that these effects may be the result of functional polymorphisms in the CB_1 receptor gene *CNR1*, or in serotonergic genes that influence the interaction between serotonergic and endocannabinoid systems [154]. It is also noteworthy that the CB_1 receptor is down-regulated rather than up-regulated following exposure to chronic stress, suggesting that there may not be a simple linear relationship between CB_1 receptor activity and suicide-related risk factors [152]. Alternately, these effects may result from the specific "inverse agonist" properties of rimonabant, in which case they could be minimized or even avoided entirely through the development of pure antagonists, partial agonists or allosteric modulators of the CB_1 receptor [155].

e5. Oxytocin receptor agonists

The neuropeptide oxytocin functions both as a hormone and a neurotransmitter, and plays a key role in the regulation of social behaviour in animals as well as humans [156]. These effects are mediated through the oxytocin receptor (OXTR), which is present in high density at several regions of the brain, including the cerebral cortex, hippocampus, and nucleus accumbens [157]. Oxytocin and endogenous opioid peptides appear to interact with each other in a reciprocal manner [158], and oxytocin reduces pain perception through effects that are mediated by increased opioid receptor activation [159]. In rodents, oxytocin receptor levels decrease with social isolation, and the administration of oxytocin partially reduces the behavioural problems seen in socially isolated mice or rats [160]. In healthy human volunteers, oxytocin reduces the social pain caused by romantic rejection [161], and a functional polymorphism of the *OXTR* gene influences changes in HPA axis functioning in individuals exposed to social rejection [162]. In individuals who had made a suicide attempt, exposure to social rejection in an experimental setting resulted in a decrease in plasma oxytocin levels, and serum oxytocin and cerebrospinal fluid (CSF) levels of oxytocin were lower than in controls. CSF oxytocin levels were negatively correlated with the intent associated with a suicide attempt [163-165]. These findings are consistent with a significant relationship between oxytocin and suicidal behaviour which may be mediated, at least in part, by the effects of oxytocin on social pain.

The intranasal administration of oxytocin has been evaluated as a therapeutic option in several psychiatric disorders, including depression and anxiety; however, evidence of efficacy has been inconclusive to date [166]. Studies examining the effects of intranasal oxytocin on responses to social rejection suggest that its effects on social pain are variable, and depend crucially on factors such as sex, attachment style and social context [167-169]. Besides these individual factors, methodological limitations related to sample size, study design, treatment duration, and the definition of specific outcomes may account for the inconsistent responses seen in clinical trials of intranasal oxytocin [170]. Given its favourable adverse effect profile, and its lack of potential for misuse compared to many of the drugs discussed above, well-designed short- to medium-term clinical trials of oxytocin in individuals with suicidal ideation or behaviour may still be warranted.

e6. Immune-inflammatory modulators

Suicidality is associated with significant alterations in the levels of several cytokines. Levels of interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) are significantly increased in both peripheral blood samples and in postmortem brain tissue in relation to completed suicides or suicide attempts, and persons with suicidal behaviour also show reduced

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interleukin-2 (IL-2) production by peripheral mononuclear cells and reduced interleukin-8 (IL-8) in cerebrospinal fluid [20]. At a central level, upregulation of tumor necrosis factor alpha (TNF-α) has been demonstrated in the prefrontal cortex of suicide victims [171]. Changes in the levels of these inflammatory markers are also significantly associated with social pain. In individuals exposed to social rejection in a laboratory setting, increased levels of IL-6 and soluble tumour necrosis factor-alpha receptor type II (sTNFαRII) were observed, and these changes were correlated with increased activity in brain regions linked to social pain [172]; in a similar study involving only female participants, exposure to criticism in an experimental setting was associated with increases in brain amygdala activity that correlated with increases in IL-6 levels and self-reported social feelings of rejection [173]. The induction of an inflammatory response through the administration of low-dose endotoxin was also associated with elevated IL-6, depressed mood, and social pain when healthy individuals were exposed to social rejection in an experimental setting. These changes were correlated with alterations in brain regions hypothesized to be related to social pain, such as the dorsal ACC and anterior insula, particularly in female participants [34]. These findings suggest a certain degree of similarity between the inflammatory correlates of social pain and those seen in suicide attempters.

Clinical trials in patients with depression, who often exhibit similar alterations in inflammatory markers, may provide clues for potential suicide prevention therapies targeting the relationship between social pain and inflammation. The available evidence suggests that some, but not all, patients with depression have elevated levels of inflammatory markers such as IL-6 and TNF-α, and it is this specific group of patients that shows an antidepressant response to anti-inflammatory therapies, such as non-steroidal anti-inflammatory drugs (NSAIDs) and the TNF-α antagonist infliximab [174, 175]. It is possible that, in patients with a suicide attempt occurring in relation to social pain, and in association with elevated levels of these markers, therapies such as NSAIDs or infliximab may reduce suicidal ideation or behaviour. However, given the complex and homoeostatic role often played by cytokines, such therapies may not always work in a linear manner [176]: a trial of the IL-6 antagonist tocilizumab in medically ill patients found a worsening of depressed mood instead of the expected improvement in depression [177].

e7. Other therapeutic targets

Research on the neural and molecular mechanisms of social pain has identified certain other approaches that may reduce social pain in an experimental setting. Acetaminophen (paracetamol), a commonly used analgesic and antipyretic, has been shown to reduce social pain in response to rejection in experimental settings [178], and was also found to reduce social pain in a 3-week clinical trial [179]. On the other hand, in a study designed to examine whether acetaminophen could increase the capacity for suicide in healthy volunteers, no evidence was found for such an effect [180]. The exact mechanisms underlying these properties are unknown, but may involve inhibition of prostaglandin synthesis at a central level, as well as the activation of serotonergic and endocannabinoid pathways [181].

In a controlled trial conducted in healthy college students, it was observed that repetitive transcranial magnetic stimulation (rTMS) over the ventrolateral and dorsolateral prefrontal cortices led to a decrease in the social pain caused by viewing images of social exclusion; this effect was sustained for around one hour after each rTMS session. This result suggests that the lateral prefrontal cortex may play a role in the "down-regulation" of social pain, and offers an alternative target for somatic therapy [182]. However, it is not known if either of these approaches show similar results in a clinical setting.

4. Discussion

Suicide often appears to be the result of intolerable psychological pain, and such pain often arises in the context of social rejection, exclusion, isolation, or the disruption of established social bonds – social pain. Though it cannot account for all cases of completed

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suicide, the social pain hypothesis is a useful heuristic both in terms of understanding the contributions of psychosocial factors related to suicide, and in terms of identifying potential targets for intervention. The evidence covered in the current review suggests that a number of potentially useful pharmacological approaches to suicide prevention, particularly in individuals with suicidal ideation or a recent suicide attempt, can be derived from this hypothesis. In many cases, this evidence is limited and inferential in nature, and has not yet been subjected to rigorous evaluation in the actual populations of interest. Nevertheless, it is important to note that at least two of the recently advocated treatments for the rapid reduction of depression and suicidality – ketamine and psilocybin – appear to exert their effects, at least in part, through a reduction in social pain. Positive results obtained in controlled clinical trials of buprenorphine, though they cannot be generalized, provide further support for the potential value of targeting the "social pain pathway" as an approach to secondary suicide prevention.

Much remains unknown about the "anti-suicidal" properties of these drugs. Are they achieved after a single dose, or after repeated dosing? How long are these effects sustained? Do reductions in suicidal ideation translate into meaningful reductions in suicidal attempts or deaths? What are the potential interactions between these drugs and other treatments that a suicidal patient might receive, such as antidepressants? Are there any long-term adverse effects of these treatments that may not be evident in short-term trials? A definitive answer to these questions can be obtained only through carefully designed controlled clinical trials [183, 184]. The essential components of these trials would be: (a) the inclusion of subjects with a recent suicide attempt and active suicidal ideation, even if these subjects do not qualify for a formal diagnosis such as "major depression" or "anxiety disorder"; (b) the operationalization and measurement of the key variables of interest – social pain, suicidal ideation and suicidal behaviour – before and after treatment; (c) the administration of specific doses of a given agent, either singly or repetitively; (d) comparisons with "treatment as usual", given the paucity of established pharmacological strategies for suicide prevention; (e) a reasonable duration of follow-up, to ensure that any observed effect is sustained over weeks or months and is not a transient and naturally-occurring fluctuation; and (f) appropriate ethical safeguards to handle unexpected or paradoxical medication effects and to protect individual participants. The measurement of surrogate markers, such as changes in peripheral blood markers or the activity of specific brain regions, may help in confirming mechanistic hypotheses, but should not be considered a primary outcome in trials of this sort. If specific agents are found efficacious in trials of this sort, they would merit further evaluation in more naturalistic or "real-world" settings. It should also be noted that, given the rarity of suicide attempts in comparison with suicidal ideation, an accurate evaluation of this outcome would require fairly large samples and a lengthy follow-up period, or the use of alternative strategies to improve trial efficiency [185].

Several precautions should be mentioned in this context. These are summarized in **Table 2**. First, though the drugs covered in this review may be effective in the reduction of suicidal ideation and behaviour, they are also associated with significant risks, such as misuse or abuse (ketamine, buprenorphine, psilocybin, MDMA) [93, 115, 116, 138], a narrow therapeutic index and a risk of toxicity in overdose (acetaminophen) [186] or other undesirable systemic adverse effects (NSAIDs, infliximab) [187, 188]. A careful evaluation of the risk-benefit ratio should precede the initiation of any of these therapies, even if they are found effective, and practitioners prescribing these drugs should take appropriate precautions to ensure that these drugs are not diverted for misuse or prescribed in patients with significant contraindications to their use.

A further note of caution is in order. Apart from the known hazards associated with these drugs, there is some concern that pharmacological manipulation of the social pain pathway may have undesirable social effects. This concern has been voiced most specifically with regard to acetaminophen and NSAIDs, which may reduce an individual's empathy to others' pain while reducing their own perception of, or sensitivity to, social pain. This may result in a decrease in prosocial behaviour [189, 190]. Likewise, as discussed

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above, seemingly "prosocial" drugs such as psilocybin and MDMA have both been associated with undesirable and unpredictable effects such as anxiety, dysphoria, and even suicide attempts [115, 116]. Whether such concerns will be an issue in the setting of time-limited treatments for suicide prevention is unknown; however, these findings highlight the need to assess behavioural adverse effects when evaluating the efficacy of these drugs.

Even in the absence of adverse effects, there may be significant variations in the efficacy of these drugs across patients. In some cases, this may reflect the influence of pharmacogenomic factors, such as functional polymorphisms in target receptors or downstream molecular pathways. Secondary analyses of trial data may help in identifying these variants (e.g., *OPRM1* rs1799971, *OXTR* rs53576, *5-HTTLPR*) and lead to the development of pharmacogenomic testing, which would facilitate a personalized medicine-based approach to the use of these agents [154, 191]. Alternately, the measurement of specific biomarkers may help in identifying subgroups of suicidal patients who would respond to specific therapies, as is already being attempted in the case of depression [174, 175, 192].

Table 2. Limitations and safety concerns associated with novel pharmacological strategies for suicide prevention.

Concern	Drug	Cause of mechanism	Risk reduction strategy
Lack of evidence	All except ketamine	Lack of controlled clinical trials; variations in definition of suicidal phenotype	Well-designed phase II and III trials with clear operational definitions of suicide-related outcomes
Abuse or dependence	Buprenorphine, ketamine, psilocybin, MDMA	Activation of mesolimbic dopamine and opioid pathways; toxicity from accidental or intentional overdoses	Careful selection of subjects for treatment; limited dispensing; screening for misuse at follow-up; legislation.
Narrow therapeutic index	Acetaminophen	Various; e.g. liver damage by active metabolites for acetaminophen	Limited dispensing; supervision by healthcare providers and caregivers
Systemic adverse effects	NSAIDs, infliximab	Various; e.g. gastric ulceration or haemorrhage with NSAIDs; hypersensitivity reactions with infliximab	Identification of clinical risk factors; education of patients and caregivers regarding potential adverse effects; use of alternate agents
Behavioral toxicity	Acetaminophen, NSAIDs, MDMA, psilocybin	Modification of social pain perception (analgesics); challenging experiences ("bad trips") leading to negative emotional responses and suicidality (MDMA, psilocybin)	Careful monitoring of mental status; use of alternate agents; education of patients and caregivers regarding potential adverse effects.
Variable efficacy	All	Pharmacogenomic variations in molecular targets or downstream mediators	Genetic analysis of data from controlled trials; pharmacogenomic testing and personalized medicine

Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine; NSAIDs, non-steroidal anti-inflammatory drugs

Finally, it should be noted that these drugs – even if found effective in the reduction of suicidal ideation and behaviour – should not be viewed as "cures" for suicidality. As mentioned earlier, suicide is a complex phenomenon resulting from the interplay of biological, psychological and social factors. It is naïve to assume that a single drug can address the deeper psychological or social roots of suicidal behaviour, even if these have

identifiable biological substrates. These drugs should best be viewed as short-term, acute-phase interventions, in the same way as analgesics are used for the management of acute or post-operative pain [193]. They are probably best used as part of a multidisciplinary treatment approach that includes psychological or social interventions tailored to an individual's needs [194].

5. Conclusions

Despite certain limitations in the existing evidence base, the social pain hypothesis holds promise for the development of novel suicide prevention strategies. It is hoped that the findings summarized in this review, though requiring replication and extension, will be of use to those involved in the development and testing of pharmacological therapies for this indication. These therapies may prove to be most effective in the reduction of suicidal ideation and behaviour immediately after a suicide attempt, but should be evaluated carefully for both efficacy and safety prior to their use in clinical settings.

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