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Review

Novel psychedelic interventions for post-traumatic stress disorder and their promise for precision medicine

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***Abstract*:** Novel interventions for post-traumatic stress disorder (PTSD) leverage the psychoactive properties of psychedelic compounds, such as ketamine, 3,4-methylenedioxymethamphetamine and psilocybin, which may overcome limitations of conventional treatments. Through the modulation of pathways involved in synaptic plasticity, psychedelic interventions are believed to enhance the mechanisms underlying memory processing and extinction. Multi-modal approaches to patient care can use existing treatments in combination with psychedelics to improve the efficacy of current psychotherapies, producing rapid and lasting improvement to chronic physiological and psychological symptoms. Modern methods for predicting treatment response will allow clinicians to personalise psychedelic interventions to the individual, capitalising on quantitative evidence to provide precision medical care. This review serves to identify limitations of the current treatment paradigm for PTSD, highlight how emerging psychedelic interventions may offer a solution to these considerations and explore the promise of precision medicine approaches for the future of PTSD treatment.

Plain language summary

Literature review of new psychedelic treatments for posttraumatic stress disorder (PTSD) and the potential to offer personalised, targeted approaches to care

New psychedelic treatments like ketamine, MDMA, and psilocybin offer new hope for people with PTSD, addressing the limitations of commonly prescribed drug therapies. These compounds work by enhancing brain processes involved in memory and emotional processing. When combined with existing psychotherapy treatments, psychedelics can improve therapeutic outcomes and provide faster, longer-lasting relief from symptoms. Advances in statistical techniques for predicting an individual's response to treatment aim to improve the effectiveness of treatments through the identification of treatments most appropriate to the unique needs of each person. This review highlights the limitations of current PTSD treatments, explores how psychedelics could help in overcoming these limitations, and discusses the potential for tailored, precision approaches in the future.

Keywords: ketamine, MDMA, post-traumatic stress disorder, precision medicine, precision psychiatry, psilocybin, psychedelics

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Introduction

Post-traumatic stress disorder (PTSD) is caused by exposure to a traumatic event and has an estimated lifetime prevalence of 3.9%,[1] with higher prevalence among populations with increased lifetime risk of trauma exposure, including veterans, military personnel, first-responders and survivors of war-related or interpersonal violence.[1–4] PTSD symptoms may be physiological and psychological and can have long-term negative effects on a person's physical, mental and social well-being.[5] PTSD is frequently reported as comorbid with at least one of many psychiatric disorders, including treatment-resistant depression (TRD), alcohol use disorder, substance use disorder, social phobia and insomnia, with comorbidity in older cohorts as high as 90%.[6,7] In these cases, the diversity of symptom presentation is compounded, increasing heterogeneity within cohorts and further diversifying observed responses to treatment. Additional factors, such as the nature of trauma experienced and the experience of the trauma as an isolated incident or series of incidents, also promote the unpredictability of treatment effect.[7,8] Individuals experiencing PTSD may have been exposed to a variety of stressful stimuli due to their occupation or interpersonal experiences, and symptom onset may follow a single traumatic event or a series of traumatic events.[9–11] As a result, cohorts typically present with a high degree of heterogeneity in both symptomology and condition severity.[12,13] The confounding nature of these factors highlights a key limitation of the current diagnostic and treatment paradigms, emphasising the importance of developing quantitative approaches for treatment selection.

Recent guidelines outlining the current paradigm of interventions for PTSD include the American Psychological Association,[14] the U.S. Department of Veterans Affairs and the Department of Defence,[15] Phoenix Australia[16] and the National Institute for Health and Care Excellence (UK).[17] The gold-standard treatments for PTSD include trauma-focused cognitive behaviour therapies, such as cognitive processing therapy (CPT),[18] cognitive therapy for PTSD,[19] eye movement desensitisation and reprocessing (EMDR)[20] and prolonged exposure (PE).[21] While these treatments differ, these interventions aim to reduce an individual's trauma-related psychological symptoms through the effective processing of trauma-related memories and sequelae.[22] There is ample evidence assessing the efficacy of trauma-focused psychotherapies,[22,23] though, treatment programs are plagued with highly varied treatment outcomes.[6,22]

Selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants are commonly prescribed for the management of chronic PTSD symptoms, providing benefit through the modulation of serotonergic signalling. Other medications, including antipsychotics and tricyclic antidepressants (TCAs), may also be prescribed to treat urgent behavioural and sleep-related concerns, though there is a comparative lack of evidence supporting their use.[24,25] Current pharmaceutical interventions moderate the dysregulation of neurotransmitter signalling pathways, primarily targeting serotonin and norepinephrine, and have been proven efficacious in reducing PTSD severity.[26,27] However, these interventions have been shown to have highly variable treatment responses, side effects and patient outcomes.[28]

Emerging psychedelic PTSD interventions, ketamine, 3,4-methylenedioxymethamphetamine (MDMA) and psilocybin, have been found to promote significant reductions in PTSD symptoms over short treatment periods, due to their rapid onset of effect.[29–31] These compounds are theorised to elicit psychoactive properties through novel biochemical cascades, including neural plasticity.[32] The use of psychedelic-assisted psychotherapy (PAP) leverages these properties to enhance current psychological interventions and can promote engagement with trauma-related material.[32,33] Such methods have demonstrated efficacy for the treatment of other conditions, including substance use disorders[34] and depression.[35,36] As the evidence supporting the safe and effective short-term use of psychedelic treatments continues to grow, the investigation of potential risks associated with long-term treatment has become an important direction for future research. Conversely, optimising for accessibility of early therapeutic intervention will improve treatment outcomes.[32,37]

Research on novel interventions has promoted the use of large dataset collection techniques such as neuroimaging, biomarker assays and genomic analysis, in combination with advanced statistical computing techniques.[38,39] These modalities will facilitate the development of predictive models for treatment response,[40] a quintessential step towards clinical treatment personalisation frameworks.

The current landscape of psychological treatments for PTSD

Trauma-focused psychotherapies

Current guidelines for the treatment of PTSD recommend trauma-focused psychotherapies, including cognitive processing therapy CPT, EMDR and PE in the treatment of PTSD.[14,15,17,41] A meta-analysis conducted by Cusack et al.[42] determined trauma-focused psychotherapies to have moderate strength of supportive evidence for the treatment of PTSD and associated symptoms. There was, however, insufficient evidence that any modality produces more desirable trajectories than another.

CPT focuses on beliefs about the trauma and the development of a new understanding of the trauma, reducing the long-term effects on psychological and physical health. RCTs have demonstrated that CPT can provide lasting reduction in PTSD-specific and associated (i.e. depression and anxiety) psychological symptoms in military and civilian cohorts of varied age and gender.[18,43,44] A recent study by Keefe et al.[45] determined that the treatment outcome for CPT is likely impacted by the proficiency of the clinician in delivering the intervention and the quality of their therapeutic relationship with the patient.

Conventional EMDR therapy utilises dual attention tasks (known as bilateral stimulation) as a means of reprocessing traumatic memories and aims to facilitate the connection of new neuronal networks in the brain to transform pre-existing dysfunctional beliefs into adaptive and functional beliefs.[46,47] While EMDR is efficacious in reducing PTSD symptom severity,[22,42,48] there is mixed evidence regarding the underlying mechanisms of action.[46] The adaptive information processing model of EMDR proposes that recollection of traumatic information during bilateral eye movement allows for the release of recalled information into the working memory for reprocessing.[49,50] Given its compatibility with other psychotherapies, EMDR is a highly adaptable modality for the treatment of heterogeneous PTSD, allowing for personalisation with combined forms of psychotherapy.[47,48,51]

PE therapy challenges avoidance behaviours through repeated exposure to traumatic memories, causing habituation of emotional responses to trauma-related stimuli.[21,46,52] PE therapy focuses on controlled modification of a fear structure, whereby the fear is activated by an exposure event and subsequently reprocessed.[52,53] The current treatment guidelines state that there is a high quality of evidence supporting the use of PE to treat PTSD.[14,15,17,41,46]

Other psychological interventions

The above trauma-focused psychotherapies are endorsed by the current treatment guidelines, with a specific recommendation by the U.S. Department of Veterans Affairs and Department of Defence for use before other psychotherapies and pharmaceuticals.[15] In consideration of the matter, several other psychotherapies have been explored for treatment of PTSD, including stress inoculation training,[54] transcendental meditation,[55] acceptance and commitment therapy[56] and present-centred therapy.[57] Meta-analyses have demonstrated psychotherapies without a focus on trauma-related material to be associated with a lower effect size but decreased risk of treatment discontinuation, when compared to trauma-focused psychotherapies.[22,58,59] These findings highlight an important clinical consideration for treatment selection and emphasise the need for data-driven methods for treatment selection and outcome prediction.[60]

Considerations for novel psychological treatment approaches

Despite the well-documented efficacy of trauma-focused psychotherapies, evidence suggests that therapies involving a high degree of emotional processing are less well tolerated than other interventions. In a recent meta-analysis, Edwards-Stewart et al. found that military populations had an average program dropout rate of 27.1% for trauma-focused psychotherapies and 16.1% for other psychotherapies.[8] The relative dropout rates of these intervention groups were found to be marginally higher than in an earlier study investigating civilian populations.[61] While trauma-focused psychotherapies are commonly recommended in treatment guidelines,[22,42,46] trauma-focused material may be harder for a patient to tolerate than other forms of therapy and may lead to a greater risk of treatment discontinuation.[22,58,59] Clinical approaches utilising the psychoactive properties of PAP are hypothesised to increase the ability of the individual to engage with trauma-focused therapies, thereby reducing treatment dropout rates. This is suggested to occur through the modification of

intrinsic unpleasantness and aversiveness that a patient may associate with events or traumatic memories.[30,33,62]

The current landscape of pharmacological treatments for PTSD

While current treatment guidelines promote psychotherapies as the gold-standard interventions for PTSD, some pharmacological interventions are also supported for their relative strength of literature evidence and greater accessibility, often prescribed synergistically to support the provision of psychotherapy. The primary pharmaceutical treatments, including SSRI and SNRI antidepressants, are frequently prescribed for the management of psychological and physiological symptoms. These common antidepressants are the most readily prescribed medications to address symptoms of anxiety and depression, and other medications are commonly prescribed off-label to address episodes of psychosis or sleep-related concerns.[63] Effective pharmacological intervention is confounded by the frequency of comorbidities, limiting treatment options.[6] Despite the heterogeneity of PTSD presentation, the range of pharmacological treatment recommended by current guidelines is limited to SSRIs, sertraline, paroxetine, and fluoxetine; and SNRI, venlafaxine.[14,15,41,64] While sertraline and paroxetine are the only two antidepressants approved by the United States Food and Drug Administration (FDA) for PTSD, fluoxetine and venlafaxine have demonstrated comparable efficacy.[65] Placebo-controlled trials investigating the use of antidepressants have demonstrated consistent reductions in PTSD severity regardless of presented symptom clusters, sex, or the nature of trauma experienced,[66–69] however, multiple weeks of treatment are required to achieve a significant reduction in chronic PTSD symptoms.[70]

Antidepressants

The dysregulation of serotonin has been implicated in the disruption of biological processes associated with changes in neurological function observed in psychiatric conditions relating to behaviour, mood and sleep.[71,72] For this reason, drugs that assist in the regulation of serotonin concentration are readily prescribed for conditions such as depression, anxiety, obsessive-compulsive disorder and PTSD. The most commonly prescribed PTSD antidepressants, SSRIs, competitively bind to the transmembrane serotonin transporter (SERT) protein, inhibiting the movement of serotonin from the postsynaptic cleft into the presynaptic neuron, preserving the concentration of serotonin available to postsynaptic receptors.[26,73,74] Paroxetine is commonly cited as the SSRI with the greatest binding affinity to SERT, followed by sertraline and fluoxetine.[26,73] It should be noted, however, that treatment with SSRIs is commonly associated with adverse side effects, which are managed by clinicians through adequate monitoring and treatment plan modifications.[74–76] We also note that SSRIs have demonstrated moderate reduction of PTSD symptoms, though effect sizes are generally larger for major depressive disorder cohorts.[28]

The final antidepressant supported by guidelines for the treatment of PTSD is the SNRI venlafaxine, which modulates the availability of serotonin and norepinephrine in the synaptic cleft. Venlafaxine is prescribed less commonly than the recommended SSRIs,[77] despite providing a comparable efficacy for symptom reduction and PTSD remission.[27,78] This is possibly due to considerable research on SSRIs for the treatment of PTSD. Despite the disparity in available data, the safety and efficacy of venlafaxine have been demonstrated in double-blind RCTs.[79–81] Inconsistent reporting of treatment side effects renders the relative tolerability of each antidepressant difficult to ascertain.[82,83]

Additionally, several factors have been identified to predict response to conventional antidepressants for PTSD. The time since trauma, and the chronicity of traumatic experience, have been associated with poorer treatment response. Conversely, the level of perceived support during treatment may improve outcomes.[84] We also note that the nature of trauma experienced may also predict treatment response, with combat and childhood trauma types associated with comparatively less response to pharmacotherapy interventions.[85]

Antipsychotics

The current treatment guidelines have conflicting recommendations for the use of antipsychotics in the treatment of PTSD.[77] The National Institute for Health and Care Excellence suggest that antipsychotics should only be prescribed for PTSD treatment in cases where primary psychological and pharmaceutical interventions fail to provide relief from debilitating symptoms, such as severe hyperarousal.[17] Antipsychotics have

been omitted from the American Psychological Association and Phoenix Australia guidelines,[14,41] and the United States Department of Veterans Affairs found there to be a weak level of evidence against use.[15] Medications such as risperidone, quetiapine, and olanzapine are frequently considered for the management of treatment-resistant psychiatric symptoms, with consideration of diverse side-effect profiles.[86]

Other medications

Tricyclic antidepressants (TCAs), such as amitriptyline and imipramine, are circumstantially prescribed for PTSD and function through the regulation of post-synaptic concentrations of serotonin and norepinephrine.[87] TCAs are secondary pharmacological interventions due to their relative risk of overdose and potential to cause unwanted side effects,[88,89] with no guideline recommendations for or against clinical use.[14] TCAs are also used for the treatment of nightmare disorder, which affects an estimated 4% of adults and has increased prevalence among individuals with PTSD.[90]

Another drug prescribed off-label for the management of PTSD-related sleep disturbance is prazosin, an alpha-1 receptor antagonist, and is conventionally used for the alleviation of nightmares, due to its inhibition of norepinephrine production in stress response signalling.[25] Like TCAs, however, the potency of side effects that can arise from prazosin treatment presents an important clinical consideration.[91]

Considerations of current pharmacological practices and the implications for novel treatments

Since the FDA approval of sertraline in the early 2000s,[92] SSRI antidepressants have remained the only government-approved pharmaceutical interventions for the management of chronic psychological symptoms of PTSD. This is despite findings that treatment outcomes are highly varied within studies (53%–62% response vs 22%–31% discontinuation),[66–69] and relapse is often observed following treatment discontinuation.[67,75] Individuals receiving SSRI treatment can experience an array of side effects leading to treatment discontinuation and/or undesirable health outcomes.[75] Transient SSRI and SNRI side effects can include gastrointestinal discomfort, sweating, nausea and dry mouth, while chronic side effects include insomnia, sexual dysfunction and weight gain.[74–76] Furthermore, there is evidence to suggest that children and young adults receiving SSRI treatment for depression symptoms may be at heightened risk of suicide ideation or self-harming behaviour.[70,74,75]

Another clinical consideration for conventional antidepressants in treating PTSD is the high incidence of comorbidities.[6,7] For example, PTSD cases are frequently comorbid with depression,[6] with prevalence estimates within cohorts as high as 62.5%.[93] Individuals experiencing PTSD with comorbid depression are at heightened risk of experiencing severe and exacerbated psychological symptoms[94,95] and may require adjunct pharmacological intervention to derive significant benefit from psychological treatment.[96] Additionally, an umbrella review of studies from the last 20 years found there to be no consistent evidence that reduced serotonin was associated with depression.[97] These concerns highlight a considerable need for novel interventions leveraging unique neurochemical pathways.[25,98–101] Intranasal ketamine has received FDA approval for the treatment of TRD and has demonstrated rapid, dose-dependent reductions in depression scores.[102–104] Recent studies using psilocybin have also yielded similar results.[64,105,106] This suggests that further investigation of the fast-acting mechanisms that underlie emerging pharmacotherapies could improve patient outcomes for depression-associated PTSD, addressing key limitations of current interventions such as increased risk of suicidality or delayed onset of action.

Novel pharmacological and combination treatment approaches

Over the last decade, literature has accumulated supporting the use of psychedelic treatments for PTSD, most commonly, ketamine, MDMA and psilocybin.[107,108] Through neurotransmitter signalling modulation, these chemical agents upregulate synaptic plasticity, promoting cortical function involved in processing of emotion, memory and pain.[109,110] These effects occur through novel biochemical pathways unutilised by current PTSD treatments and represent an opportunity to address limitations of current pharmacological treatment paradigms.

Psychedelics, or psychoplastogens, are of benefit due to their upregulation of biological mechanisms for neuromodulation. The associated

promotion in neuroplasticity is postulated to be a key contributor to the enhancement of psychotherapy, caused by the 'rewiring' of maladaptive neural circuits that reinforce the degenerative psychological features of PTSD.[32,109] The processing and extinction of trauma-related memories requires synaptic plasticity, cellular processes facilitating the long-term potentiation (strengthening) or depression (weakening) of neural circuits.[111] Psychedelic interventions target molecular signalling pathways implicated in these circuits, aiming to upregulate synaptic plasticity.[112–114] Through the promotion of mechanisms of neuromodulation, trauma-related cognitions maintaining PTSD can be challenged and adapted into healthier cognitions.

It should be noted that psychedelics may be subcategorised based on their effects on perception or affect. Ketamine, for example, is regarded as dissociative,[115] while MDMA is classified as an empathogen due to its promotion of prosocial behaviour.[116,117] Classic psychedelics, such as psilocybin or lysergic acid diethylamide (LSD), do not present dissociative or prosocial properties and are instead classified as hallucinogens.[118] The duration of subjective effects induced by psychedelic treatment varies between compounds and reflects the diversity in biochemical targets of each compound. Indeed, contemporary research suggests that the commonality of psychedelics to cause alteration of conscious states is not reflective of a ubiquitous biochemical mechanism, but rather a downstream upregulation of transcriptional mechanisms for neuroplasticity.[116]

The psychotropic effects elicited by these medications have been demonstrated to promote patient engagement and tolerance to trauma-focused psychotherapies,[119] hence, there is a growing interest in the potential of PAPs to overcome concerns regarding discontinuation of stand-alone psychotherapy treatment.[120] In contrast to current approved pharmacological interventions for PTSD, psychedelics elicit rapid, short-acting psychological effects and provide significant efficacy in reducing depression-related PTSD symptoms and TRD.[29–31,121]

Ketamine

Ketamine has established use as a dissociative anaesthetic, though contemporary research has focused on its antidepressant and analgesic properties at sub-anaesthetic doses.[122] Ketamine is positioned as an alternative to conventional antidepressants for cases of treatment-resistant PTSD and/or TRD. The primary hypothesis for the antidepressant activity of ketamine is its non-competitive antagonist action on ionotropic *N*-methyl-D-aspartate (NMDA) receptors located on GABAergic interneurons.[112,123,124] EEG studies and animal models have suggested that preferential reduction in the inhibitory signalling activity of forebrain GABAergic interneurons causes downstream elevations in the excitatory signalling and synaptic concentration of glutamate in the prefrontal cortex.[123] As outlined in Figure 1, this pathway underlies the disinhibition hypothesis for the antidepressant mechanism of ketamine, including increased activity of brain-derived neurotrophic factor (BDNF), tropomyosin receptor kinase B (TrkB), and mammalian target of rapamycin (mTOR). These enhanced elements of the cascade have been identified for their roles in promoting neurogenesis and synapse formation,[125,126] and, consequently, are considered prime candidates for the neural plasticity observed in early ketamine studies, particularly concerning the reprocessing of traumatic memories.

In view of the analogous symptomology of PTSD and depression, there is likely considerable overlap between the neural circuitry underpinning PTSD symptoms. While comorbidity poses a practical challenge for discernment between these states, it suggests that neurobiological findings for the use of ketamine therapy for depression may also be observed in PTSD cohorts.

Patient response to ketamine is greatly dependent on dosage and route of administration, factors which are controlled to promote contextual benefit. The most common dose parameters are 0.5 mg/kg over a 40-min infusion and correspond to desirable levels of treatment tolerance and patient coherence.[127] Given the discussed limitations of common antidepressants, early clinical trials of ketamine for depression symptom treatment aimed to leverage its unique mode of action and relatively fast-acting antidepressant and anti-suicidal properties.[128,129] Commonly reported side effects to intravenous ketamine include transient dissociation, visual distortion, nausea, and headaches.[130] Ketamine-induced urological toxicity has not been associated with therapeutic treatment as it has with chronic recreational use; however, urological data are limited, and

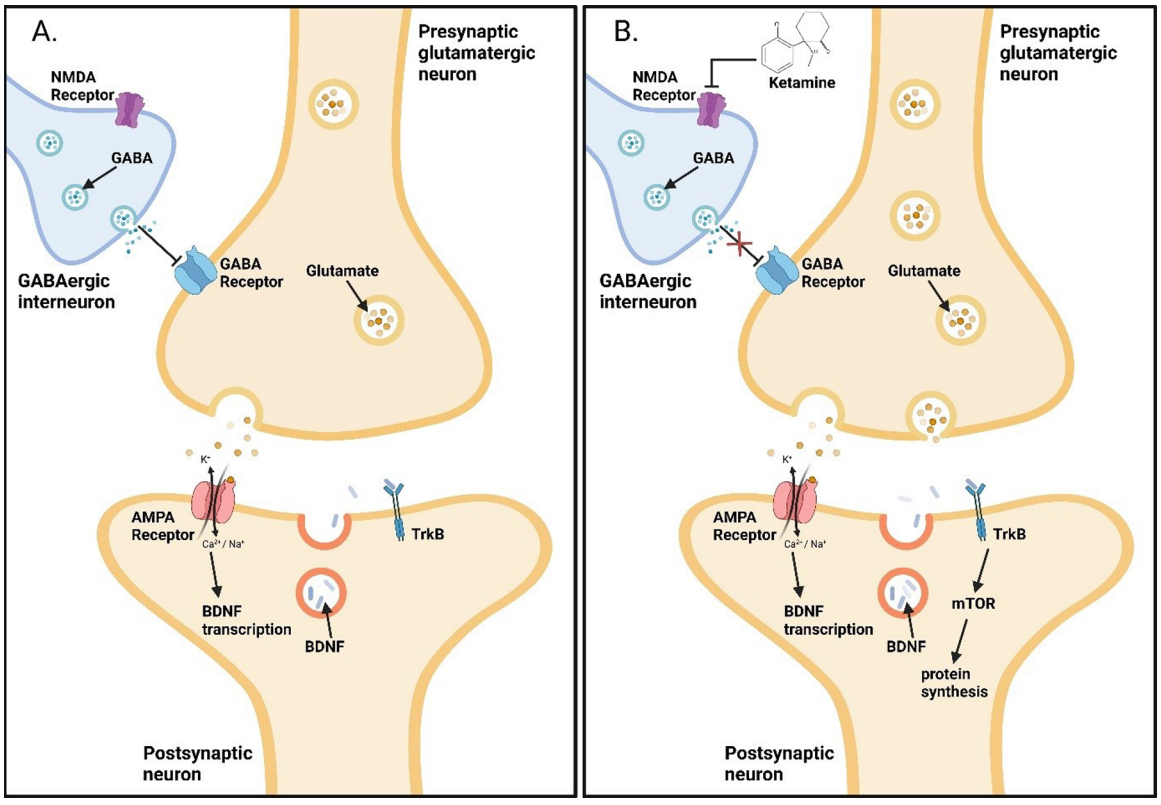

Figure 1. Outline of (a) the inhibitory effect of GABAergic interneurons and (b) the disinhibition hypothesis for the antidepressant effects of ketamine.
Ketamine exhibits antagonistic action through non-competitive binding to NMDA receptors located on GABAergic interneurons, preventing influx of Na2+ ions. This causes a reduction in the signalling potential of the interneuron. The inhibitory action of GABAergic interneurons has been blocked by the binding action of ketamine, characterising the disinhibition hypothesis. The release of synaptic glutamate from glutamatergic neurons is promoted. Glutamate is released from vesicles into the synaptic space, binding to post-synaptic AMPA receptors, and causes efflux of K+ ions and influx of Ca2+ and Na+ ions. BDNF synthesis and release are elevated, activating postsynaptic TrkB receptors. Upregulation of mTOR enhances protein synthesis. This pathway drives synaptic plasticity and long-term potentiation through the elevated expression of postsynaptic glutamate receptors.
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, Brain-derived neurotrophic factor; mTOR, mechanistic target of rapamycin; NMDA, N-methyl-D-aspartate; TrkB, tropomyosin receptor kinase B.

long-term investigation is required.[131,132] Studies of therapeutic ketamine treatment present limited evidence of chronic side effects, though there is a recognised need for further clinical investigation of long-term safety and efficacy.[133] Given the prevalence of ketamine as a drug of abuse,[134] there is notable concern regarding the addictive potential of therapy treatments, though preclinical and clinical evidence have suggested that sub-anaesthetic ketamine may have low addictive liability.[135,136] Accordingly, addiction risk is mitigated through the controlled implementation of clinical treatment protocols. Among other treatments leveraging mechanisms of neuroplasticity, ketamine has been explored for its use in the treatment of alcohol and substance use disorders, suggesting that treatment may reduce alcohol or drug seeking behaviours.[134,137] The first documented ketamine therapy clinical trial results were published by Berman et al.,[138] based on a pilot study in which seven participants with depression were observed after infusion of ketamine or saline solution. The study found ketamine infusions caused a significant and continual reduction in depressive symptoms over a period of 3 days, suggesting NMDA receptor dysfunction as an alternative to the predominant monoaminergic deficiency hypothesis.[127,138]

Another important characteristic of ketamine is its chemical structure, which features a chiral C-2 carbon on the cyclohexanone ring, resulting in

the existence of two enantiomeric species S(+)-ketamine ('esketamine') and R(−)-ketamine. Studies comparing the allosteric binding of these optical isomers with NMDAR have determined the S-enantiomer to have a binding affinity three to fivefold greater than the R-enantiomer.[127,139,140] This finding helped support the 2019 FDA approval of an S(+)-ketamine nasal spray, marking the first low-dose ketamine treatment approved for the management of TRD,[141] and has demonstrated rapid, dose-dependent reductions in depression scores.[102–104] While the difference in binding affinity between the two enantiomers is well established, continued research aims to provide a comparison of side-effect profiles, as well as treatment effect potency and duration.[140]

Recent clinical trials of intravenous ketamine have demonstrated reductions in PTSD symptom severity after the participants have received a single infusion[29,130,142–144] or repeated infusions over a given period.[115,145] A single ketamine infusion has demonstrated a fast onset of effect and a significant reduction in PTSD and depression related symptoms for an average response period of up to 7 days post-treatment. In a study of single infusions published by Pradhan et al.,[144] racemic ketamine outperformed placebo in producing an extended duration of response to mindfulness-based psychotherapy. Ketamine has been demonstrated to enhance fear processing and enhance tolerance of trauma-related material during psychotherapy. Clinical trials investigating PTSD treatment with ketamine-assisted psychotherapies have observed increased engagement with trauma-focused psychotherapies and reduced treatment discontinuation.[146]

3,4-Methylenedioxymethamphetamine

Like ketamine, MDMA (colloquially 'ecstasy'), has a well-documented history as a recreational drug, noted for its induced feelings of dissociation and elation.[147] However, despite concerns regarding substance abuse and dependence associated with recreational use, low-dose MDMA has shown significant clinical benefit in the context of PTSD treatment.[148,149] In 2017, the FDA designated MDMA-assisted psychotherapy as a 'breakthrough therapy' for PTSD,[148,150] sparking an international effort to investigate the suitability of low-dose MDMA (75–125 mg) in combination with trauma-focused psychotherapies for treatment of various patient cohorts and documented comorbidities, including depression and anxiety disorders.[151,152] The treatment is proposed to alleviate PTSD symptom severity by engaging a complex neurochemical cascade to enhance memory reconsolidation and fear extinction processes,[153] however, further investigation of this hypothesis is required if the exact mechanisms underlying its effect are to be understood.

Rat and non-human primate models have demonstrated that MDMA causes the simultaneous reuptake inhibition and release of serotonin from presynaptic vesicles into the synaptic cleft,[113,154] occurring through its binding to the primary and allosteric binding sites of the SERT protein.[113,154] This dual mechanism is postulated to promote the tolerability of traumatic memory exposure.[113] MDMA also exhibits inhibition of norepinephrine transporter and dopamine transporter, modulating synaptic concentrations of norepinephrine and dopamine.[149,155]

A continual effort to determine the suitability of MDMA for the treatment of PTSD has been demonstrated in phase II[31,156–158] and phase III trials.[159–161] However, clinical trials are limited in their ability to achieve blinding with placebo controls, due to the conspicuous dissociative effects of MDMA. To overcome the challenge of dissociative effects present in double-blinding, several trials have used low-dose controls.[158,161,162] In one such trial, Gorman et al.[158] determined the active-dose group to have a greater reduction in PTSD symptoms than the placebo/active control group. Perhaps most critically, 67% of the treatment cohort no longer met the criteria for PTSD diagnosis at 12 months post-treatment, supporting the long-term efficacy of MDMA-assisted psychotherapy.

A more recent study explored alterations in functional brain activity in patients after receiving MDMA-assisted psychotherapy for PTSD.[156] Singleton et al. conducted the first neuroimaging study for this intervention, observing the resting and autobiographical memory states of eight veterans and one first responder with PTSD. They found that the treatment led to significant ipsilateral strengthening of resting-state functional connectivity between the left amygdala and hippocampus, a network that is frequently associated with attenuation of psychological distress.[163,164] As with ketamine,

MDMA has been suggested to modulate fear response and avoidance behaviour, enhancing tolerability and engagement with trauma-focused psychotherapies.[62,153] This is supported by earlier evidence that resting-state amygdala connectivity was reduced in veterans with PTSD, in contrast to matched controls,[165] suggesting that resting-state network connectivity may be a suitable predictor of PTSD risk and/or response to MDMA-assisted psychotherapy. The most common side effects reported in clinical trials of therapeutic MDMA were headaches, nausea and vomiting, with occasional transient anxiety and elevated blood pressure.[118]

Psilocybin

Psilocybin is a psychedelic drug recognised for its effect on a person's senses, emotions and perception of reality.[166,167] Heavily regarded for its spiritual effects, psilocybin has been demonstrated to cause several dose-dependent acute psychological effects, including ego dissolution, an altered sense of time and sensory hallucinations.[168] To distil the therapeutic potential of psilocybin, current research explores its suitability in treating several psychiatric conditions, including PTSD,[115,169] depression,[64,105,170,171] and substance abuse.[172–174]

While the mechanisms underlying the dissociative and antidepressant properties of psilocybin are unclear, leading theories suggest that the psychoactive effects are elicited through serotonin receptor agonism, causing downstream neuroplasticity through altered expression of genes, including BDNF.[30,114] The psilocybin induced downstream expression of BDNF would be analogous to the proposed glutamate-driven BDNF mechanism for antidepressant action of ketamine,[112,123,124] likely suggesting some mechanistic overlap between their therapeutic pathways.

To our knowledge, there have been no published clinical trials investigating psilocybin for PTSD, although there is substantial clinical evidence supporting standalone and PAP treatment approaches for depressive disorders. As a novel approach to PTSD treatment, determining the efficacy and safety of psilocybin is a priority. In a recent phase II clinical trial, Goodwin et al. observed a drastic dose-dependent reduction in depression scores for up to 3 weeks post-treatment. Despite the clear reduction in mean depression scores, it was noted that the efficacious dose was also associated with a greater incidence of adverse side effects, including suicide ideation, intentional self-injury, headaches, and nausea.[64] Although psilocybin has demonstrated promise for clinical treatment of depressive symptoms, the variability of these findings highlights the importance of investigating therapeutic mechanisms using data-driven research methodologies such as neuroimaging.[175] In an earlier phase II study, Carhart-Harris et al. trialled psilocybin head-to-head with SSRI, escitalopram, over a 6-week treatment period. While there was no significant difference between the self-reported depression symptoms of the two groups, secondary depression-related outcomes were in favour of psilocybin.[176] The findings suggest that psilocybin may be a suitable alternative to SSRIs for the treatment of depression symptoms and highlight a need for a clinical trial of greater size and duration. It has been proposed that the risk of adverse psychological side effects during psilocybin trials can be mitigated through the provision of a carefully monitored research environment and patient psychoeducation before administration.[105,168] Current research aims to elucidate the therapeutic efficacy of psilocybin on individuals experiencing PTSD, despite concerns that psilocybin may exacerbate ego fragmentation experienced in response to trauma.[177,178]

Other psychedelic interventions

Most published evidence for psychedelic treatment approaches for PTSD focuses on ketamine, MDMA and psilocybin, though we would be remiss in failing to note other novel treatments of clinical interest. Alongside psilocybin, lysergic acid diethylamide (LSD) is another 'classical' psychedelic under investigation for its therapeutic potential in treating psychiatric disorders.[179–181] At present, there are no published clinical trial investigations of LSD as a standalone or assisted psychotherapy treatment for PTSD; however, there is considerable research focus on ascertaining the effects and safety of LSD for the management of anxiety, depression and pain.[119,179,182,183] LSD has demonstrated considerable effect for the treatment of alcohol use disorder and negative affect.[119] Studies suggest that the risk of severe side effects is low, although patient experiences of dissociation and distress are common areas of concern.

Another group of psychoactive drugs being explored for the treatment of PTSD are cannabinoids, which are derived from the cannabis plant

(*Cannabis sativa*). Certain derivatives, most notably cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), are observed to elicit improvements in anxiety, mood, and sleep.[184] These compounds are also considered to have therapeutic potential for PTSD, with consistent evidence suggesting benefit across metrics for physiological stress, including cardiovascular, inflammatory and metabolic response.[185] While the investigation of psychological benefits for PTSD is comparatively limited, one small study reported significant relief from nightmares for participants with military-related PTSD.[186] Despite the growing evidence in support of cannabinoids for PTSD treatment, contention regarding the mechanisms underlying the therapeutic action is a hindrance to implementation in clinical trials.[187,188] A deeper understanding of the mechanistic pathways producing dose-dependent alterations of mood and anxiety will be essential to validate clinical trials for PTSD.

Key areas of research for emerging psychedelic treatments

A key limitation of the emerging pharmacological interventions for PTSD is the lack of substantial data supporting the long-term safety of treatment.[102,148,167] Available research on the long-term safety of psychedelic interventions is seemingly sparse, though a recent meta-analysis on reported safety and efficacy of MDMA-assisted psychotherapy found there to be infrequent reporting of long-term effects, among other methodological inconsistencies such as intervention dosages and control groups.[189] The present absence of data supporting long-term safety and efficacy of psychedelics for PTSD is a major hindrance to the practical implementation of protocols to leverage the short-term pharmaceutical benefits that have been achieved in controlled environments. As such, consistent reporting and assessment of long-term treatment safety and tolerability must be a key consideration for future trials. Additionally, landmark trials of psychedelic treatments for PTSD have commonly listed concurrent suicidality, substance use disorders, and/or a lifetime history of psychotic disorders as exclusion criteria.[29,31,115] This limitation is of particular concern for the integration of psychedelic treatments into standard care, due to the clinical heterogeneity of cohorts with PTSD,[7] highlighting the need for further investigation of treatment suitability for frequent comorbidities. Other concerns for the implementation of psychedelic treatments include the variation of dissociative effects observed within trials and the documented risks of abuse.[112] Due to the sensitive dose–response profile associated with these substances, administration is performed to a high degree of consistency and supervision, presenting considerable demand for highly trained mental health clinicians and multidisciplinary clinical units.

Prediction of treatment outcomes for patients with PTSD

In consideration of the current treatment landscape, emerging approaches to PTSD treatment aim to employ multimodal techniques to predict patient responses to treatment and elevate existing methods of clinical care. By using quantitative data collection modalities and predictive modelling techniques, precision medicine approaches allow clinicians to assign treatment with a newfound statistical basis. In the case of PTSD treatment, we suggest that multimodal approaches using neuroimaging, genomic, blood biomarker and electrophysiology data may yield sufficient statistical evidence for individual-level risk predictions. In a recent study, Zhu et al. conducted a pooled analysis of brain MRI scans for 7925 individuals across multiple collection sites ($n = 32$) and tested the diagnostic performance of several statistical models. They demonstrated the suitability of advanced deep learning models in addressing variation between collection sites and potential for use in the investigation of PTSD pathophysiology.[190]

Neuroimaging studies on cohorts of varying trauma types have demonstrated structural and functional variation in the prefrontal cortex, hippocampus and amygdala[190,191]; brain regions implicated in neurological deficits of traumatic memory processing and emotional regulation.[192,193] Subsequent genetic studies exploring correlation with neuroimaging results have identified risk alleles associated with variation in these regions, providing a subset of genetic markers for PTSD risk.[194]

Other minimally invasive, data-rich sampling methods include blood biomarker and electrophysiology studies, which allow for combination as multimodal approaches. Through predictive modelling of physiological and neurobiological markers of PTSD, treatment protocols will be

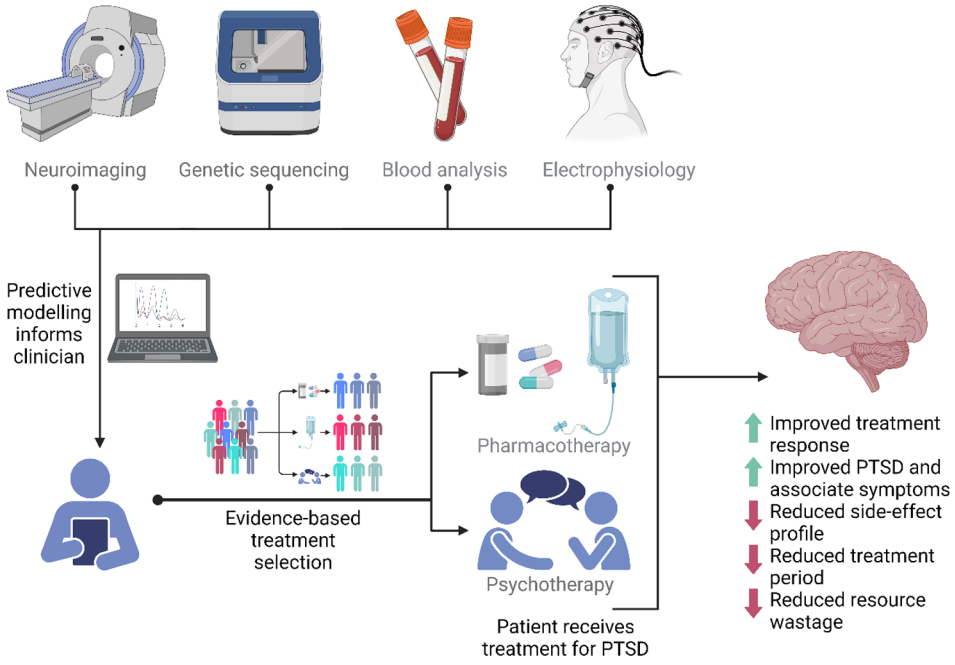

Figure 2. Data-driven treatment response prediction methods facilitate evidence-based treatment selection. Patient data are collected in the form of a brain scan, genetic sequencing, biomarker analysis or functional response. By applying predictive modelling techniques to patient data, clinicians will gain insight into likely treatment outcomes. This will assist in the selection of appropriate pharmacological and psychotherapy interventions and lead to improved patient outcomes.

tailored to the patient, allowing for selection of modular approaches targeting both biochemical and psychological mechanisms (see Figure 2).

Precision medicine and the future of PTSD treatment

Over the last decade, growing interest in precision medicine approaches toward the personalisation of patient care has driven the implementation of -omics (i.e. genomics, transcriptomics, proteomics, epigenomics or metabolomics) and imaging research methods for the development of improved therapeutics. These methodologies are not limited to any single human disease, organ or biological system, as analysis techniques can indiscriminately use data collected using varied methods across different fields of research. As an example, genome-wide association studies (GWAS) are now a common practice in the investigation of complex conditions, with polygenic risk determined for various PTSD cohorts.[195,196] However, the multifactorial nature of risk associated with PTSD symptomology and treatment response underpins the importance of capturing patient data beyond genetics. Recent studies have presented neuroimaging modalities such as T1-weighted, functional MRI (fMRI) or diffusion tensor imaging as appropriate methods for investigating features of brain structure and function associated with PTSD or depression symptoms. A systematic review conducted by Jiang et al. identified region-based differences in volume and functional activation, which were associated with PTSD and depression symptoms. Both conditions exhibit volumetric deficits in the prefrontal cortex, hippocampus and anterior cingulate cortex, while an elevated functional activity of the amygdala and insula were associated with PTSD only.[197] These findings demonstrate the potential of neuroimaging in the stratification of PTSD cohorts presenting with comorbidity.

Broadly, precision medicine approaches aim to overcome the limitations of population statistics-based one-size-fits-all models of treatment response. By moving from average effect sizes and rates towards patient-level statistics, treatment selection and parameter optimisation can be enhanced, improving outcomes on an individual basis. Figure 3 outlines key data available for health research at population-, group-, and patient-level. The stratification, or degree to which individuals within a cohort can be

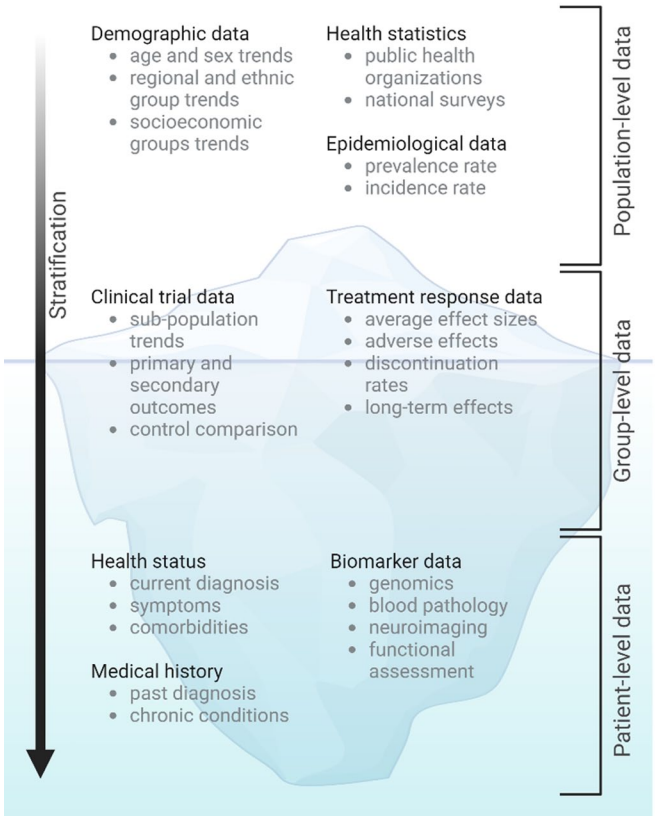

Figure 3. The various sources of medical data, arranged from population-level data to patient-level data. The degree to which individuals or groups of patients may be differentiated increases using data with greater specificity. Difficulty accounting for symptom or treatment response heterogeneity within a cohort can be addressed through adequate stratification of patients, leveraging the availability of large patient-level datasets to achieve computational prediction of individual risk.

meaningfully differentiated, is enhanced through the analysis of patient-level data such as health records and biomarkers. Through adequate risk stratification, selected treatment conditions can be tailored to the individual, facilitating reductions in adverse treatment effect risk and resource wastage.[198]

While there appears to be clear promise for such approaches in the treatment of psychiatric conditions (particularly in cases of front-line treatment resistance), there are ethical and logistical challenges to be addressed. Research on the use of precision medicine approaches in combination with psychological interventions (or precision psychiatry) is in a stage of relative infancy; by comparison to other disciplines, such as oncology.[199,200] This disparity between disease classifications has been primarily attributed to the multifactorial and dynamic nature of the biological systems implicated in psychiatric conditions.[201] The degree of variation in physical and psychological symptoms observed within and across study cohorts highlights the necessity of practical methods for patient stratification, while presenting a key consideration for the development of psychiatric nosology and healthcare methods.[7,202] Here, we present a pragmatic assessment of the current barriers to the design and implementation of precision medicine-based approaches to PTSD treatment (Figure 4).

Barriers to the design of precision approaches to PTSD treatment

Like precision medicine, precision psychiatry aims to leverage available objective biomarker data to estimate disease risk and assist in treatment selection to improve treatment response on an individual basis.[203] Outcome modelling also requires predetermination of metrics as representative proxies for patient health. As a result of the significant degree of symptom and pathological heterogeneity observed in conditions such as

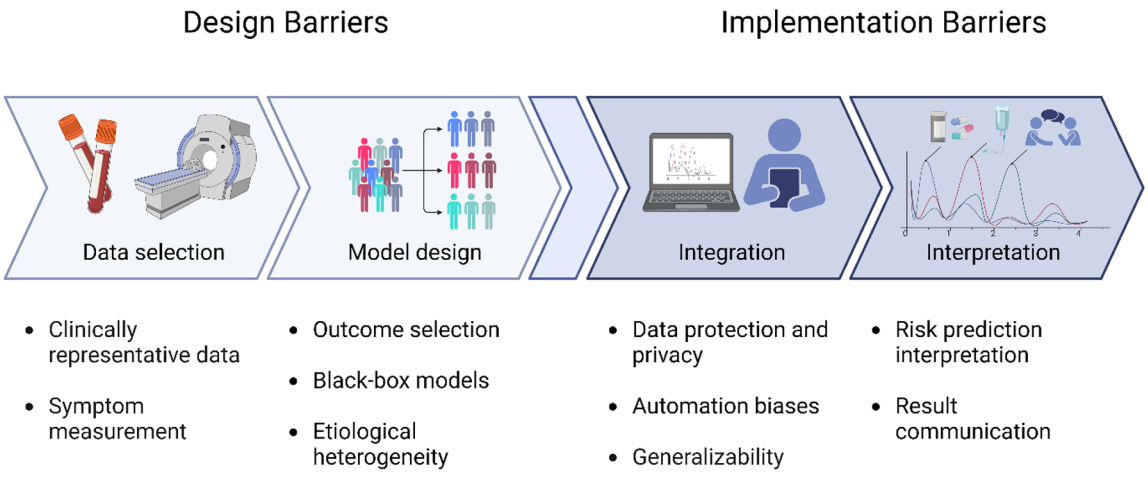

Figure 4. Outline of present barriers to the design and subsequent implementation of precision psychiatry approaches to PTSD treatment.
Primary concerns for the design of patient risk prediction models include the selection of clinically representative data and computational methods, balancing statistical accuracy with back-end interpretability. Implementation considerations regard the integration of advanced computational methods with conventional clinical practices, encompassing appropriate interpretation and communication of patient risk predictions. Addressing these barriers outlined will be necessary to achieve the successful application of precision psychiatry approaches for PTSD.
PTSD, post-traumatic stress disorder.

PTSD, defining health impact and recovery is an area demanding continual revision.[204] Moreover, the transcendence of PTSD symptomology beyond the binary states of disease or health presents added difficulty in measuring symptom severity and recovery. To capture and represent the multifaceted nature of PTSD recovery, studies on clinical data must use an array of primary and secondary metrics to allow for representative patient stratification across multiple health spectra.

PTSD symptom scores from the DSM-5, such as the PCL-5 or CAPS-5, are common primary outcome metrics for PTSD severity in research and clinical practice, allowing for observation of changes in symptomatic expression between timepoints. The PCL-5 is a 20-item, self-rated measure used to assess PTSD symptom severity according to the DSM-5 criteria and is commonly used in clinical research and practice. Item clusters focus on intrusions, avoidance, cognitive and emotional function, and hyperarousal.[204,205] The CAPS-5 is a 30-item, structured interview questionnaire to determine PTSD severity and observe symptom changes over time. Items target the 20 PTSD symptoms in the DSM-5 as well as their impact on related aspects of health.[205,206] Secondary outcome metrics are used to assess patients in areas of health that may not be captured by primary metrics. In clinical cases of PTSD, this will often mean observing for comorbid conditions, including depression, anxiety, and/or alcohol or substance use disorders,[7] or recognising previous experience with stressors.[207] Secondary outcome metrics capture information about symptoms that may be generalised to several conditions (i.e. suicidality, stress, sleep disturbance or social withdrawal); a parallel to the pleiotropic nature of gene variants underpinning mental health disorders.[208] Despite the potential inability for such metrics to delineate between conditions, the incorporation of PTSD-associated symptoms measures into a model design allows for a broader interpretation of patient health than would be achieved with a sole primary metric.

As previously highlighted, the heterogeneity of PTSD presentation and pathogenesis is both a rationale and barrier to the execution of precision medicine approaches for PTSD treatment. Therefore, researchers aim to use statistical prediction methods, such as linear mixed-effects (LME) modelling, to optimise for noise reduction and output relevance. In a recent publication, Smith and Held proved that an increase in the predictive accuracy of an LME model can be achieved using longitudinal data. Through continuous provision of outcome data during a CPT treatment period, the model was increasingly able

to explain variance across observed treatment responses. This study emphasises the importance of longitudinal data for the delineation of PTSD treatment response, addressing the non-linear and intercorrelated nature of variables observed. Cohorts receiving psychedelic treatment will exhibit variability in intensity and tolerability of dissociative experience, presenting an added layer of complexity to the interpretation and prediction of treatment response.[178] The impact of dissociative events on treatment response remains unclear, suggesting the need for further studies on dose–response variability and psychoeducation. Provided with adequate statistical grounding, precision medicine models will be better suited to simultaneously interpret multimodal datasets and generate predictions of response direction, intensity, and adverse event risk.

Barriers to the implementation of precision approaches to PTSD treatment

The implementation of precision psychiatry approaches is nuanced with considerations relating to their adaptability and accessibility.[209] For statistical prediction models to yield clinically reliable and accurate results, they must be trained on data from a representative population. While assumptions of causality in a risk prediction model can be informed by RCT data, training data must reflect the symptomological and pathophysiological diversity of the clinical population. The significant heterogeneity observed across individuals experiencing PTSD presents a substantial barrier to the determination of best treatment approaches. In acknowledging the uneven distribution of published treatment–response data across age, sex and ethnic demographics, separate models for defined subpopulations may be needed to outperform a unified PTSD prediction model. Obviously, a model to advance healthcare of a select subpopulation (i.e. veterans, children or sexual-assault victims) must be developed and integrated in the best interest of the target population. As such, the generalisability of precision approaches for PTSD risk prediction is a concern to both their design and their implementation. Should risk prediction modalities be limited in their benefit to the global PTSD population, ethical revision may be necessary to avoid systematic reinforcement of existing healthcare divides.[200,209]

The integration of predictive modelling for PTSD treatment into clinical practice will, initially, necessitate the use of patient data to inform and aid in the judgment of practitioners to enhance current treatment practices (Figure 2). This has been regarded as a barrier to the implementation due to automation biases and concerns regarding data use and privacy. An appropriate balance between statistical performance and model interpretability is required, as increasing performance at the cost of interpretability could hamper trust from patients and clinicians due to the 'black box' effect; the phenomenon in which the user knows the model inputs and outputs but lacks understanding of the logical processes between.[210] This occurrence is of particular concern due to the relative complexity of PTSD and the interactions of its variables.[211] To overcome the risk of automation biases, implementation will require preservation of key human elements of healthcare. This includes the therapeutic alliance between patients and clinicians, as well as the sense of personal agency regarding individual health.

While we have focused on the logistical considerations for the design and implementation of precision psychiatry approaches to PTSD, it is important to also acknowledge that systemic concerns influence the distribution of worldwide health resources, including geographical and financial constraints.[209] Thus, maintaining an understanding of how these factors can influence the potential benefit a proposed paradigm shift may offer is imperative to the development of novel medical practices that maximise health equality.

Limitations

As a non-systematic literature review, this paper is limited to the published literature within the chosen narrative scope. There are considerable legal and ethical barriers to the adoption and research of psychedelics as restricted substances with high potential for abuse.[212] However, these concerns are beyond the scope of this review, which is primarily focused on the clinical efficacy of psychedelics in PTSD treatment. This review encompasses contemporary research on prominent novel psychedelic treatments for PTSD and is not an exhaustive exploration of evidence for all psychedelic treatments, as such coverage would exceed the scope.

Conclusion

The forthcoming wave of research into novel PTSD treatment options presents growing evidence in support of a new clinical treatment

paradigm integrating data-driven approaches with best practices for psychiatry. As the catalogue of potential therapeutics for the treatment of severe psychiatric disorders continues to evolve, so do the technologies for the collection and analysis of quantitative patient data. The nexus of advanced data collection techniques for neuroimaging, biosampling, and -omic sequencing, and the growing capability of AI and machine learning algorithms, will facilitate the discovery of key predictors of treatment response. This has significant implications for the methodology of clinical research protocols, as neuroimaging and biosample analysis methods have become the gold standard for measuring treatment outcome. Ultimately, enacting evidence-based approaches to facilitate the stratification of treatment response across predictive biomarkers will assist clinicians in providing personalised treatment plans.

The heterogeneity of treatment responses and side-effect presentation demonstrates the need for personalisation of treatment. However, there are limited publications exploring the factors influencing treatment trajectories, suggesting a shift in research focus will be required for the development of personalised intervention practices. Future research into pharmacotherapies for PTSD must consider the psychological and biochemical factors influencing treatment response, in the hope of developing a compendium of therapeutic options that can transcend variability caused by factors such as comorbidity and symptom profiles.

Declarations

Ethics approval and consent to participate

Not applicable as this review is based solely on published literature.

Consent for publication

Not applicable as this review is based solely on published literature.

Author contributions

Charles Dodds: Conceptualisation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Rachelle Dawson: Supervision; Writing – review & editing.

Alexander Lim: Conceptualisation; Supervision.

Susannah Tye: Conceptualisation; Supervision; Writing – review & editing.

Fatima Nasrallah: Conceptualisation; Supervision; Writing – review & editing.

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Competing interests

The authors Charles Dodds, Rachelle Dawson and Alexander Lim are affiliated with the Zed3 Medical Group. Zed3 Medical Group is a health solutions provider for government and non-government agencies with extensive contractual and consultation work with the Australian Defence Force (ADF), Australian Federal Police (AFP) and former ADF servicemembers. One of Zed3 Medical Group's treatment programme includes ReviveMed, which centres around ketamine infusion therapy for treatment-resistant PTSD. Author Charles Dodds is currently a PhD candidate at the University of Queensland and is on a paid appointment with Zed3 Medical Group as a research assistant. Author Rachelle Dawson is currently a clinical psychologist and research associate with Zed3 Medical Group. Author Alexander Lim is currently the Director of Clinical Governance and Strategy at Zed3 Medical Group. No other member of Zed3 Medical Group had a role in approving the manuscript for publication.

Availability of data and materials

Not applicable.

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