

Review

Optimized Clinical Strategies for Treatment-Resistant Depression: Integrating Ketamine Protocols with Trauma- and Attachment-Informed Psychotherapy

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Abstract: Strategically timed trauma- and attachment-informed psychotherapy to address underlying emotional wounds, paired with ketamine administered in precision-calibrated doses to ensure high-entropy brain states, may be key to improving the quality and duration of ketamine's therapeutic efficacy for treatment-resistant depression. This approach optimizes the opportunities for change created by ketamine's known effects as a rapid antidepressant that stimulates synaptogenesis, normalizes neural connectivity and coherence, enhances neuroplasticity, reduces inflammation, and induces high-entropy brain states with associated subjective psychedelic experiences. Ketamine, a non-selective N-methyl-D-aspartate (NMDA) receptor antagonist is a safe, effective, fast-acting dissociative anesthetic that, as a standalone treatment, also exhibits rapid sustained antidepressant effects, even in many patients with treatment-resistant depression. A prior history of developmental trauma and attachment injuries are known primary factors in the etiology of treatment resistance in depression and other mental disorders. Thus, the adjunct of targeted psychotherapy attuned to trauma and attachment injuries may enhance and prolong ketamine efficacy and provide an opportunity for lasting therapeutic change. Psychotherapy engagement during repeated ketamine sessions for patient safety and integration of altered states, paired with separate individualized psychotherapy-only sessions timed 24–48 h post ketamine induction, takes advantage of peak ketamine-induced dendritic spine growth in the prefrontal cortex and limbic system, and normalized network connectivity across brain structures. This strategically timed paired-session approach also exploits the therapeutic potential created by precision-calibrated ketamine-linked high-entropy brain states and associated psychedelic experiences that are posited to disrupt overly rigid maladaptive thoughts, behaviors, and disturbing memories associated with treatment-resistant depression; paired sessions also support integration of the felt sense of happiness and connectivity associated with psychedelic experiences.

Keywords: ketamine; treatment-resistant depression; glutamate modulator; synaptogenesis; induced neuroplasticity; entropic brain states; psychedelic experience; developmental trauma; attachment injury; trauma- and attachment-informed psychotherapy; ketamine-assisted psychotherapy; inflammation-related depression



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1. Introduction

The relationship between depression and stress, with its accompanying brain changes, has been well established over the last 20 years in both preclinical and clinical trials (Taylor et al., 2005; Stepanichev et al., 2014; Young et al., 2003 [1–3]). Chronic stress influences depression and affective behavior, is associated with inflammation, and disrupts neuroplasticity, brain connectivity, interhemispheric excitatory homeostasis and associated cellular and molecular systems (Pittenger and Duman, 2008 [4]). In particular, the consequences

of chronic stress suffered in early childhood during critical periods of brain development and maturation are profound and may last a lifetime (Joseph, 1999; Schore, 2005; Siegel, 2006 [5–7]). TRD is a complex psychiatric disorder influenced by genetic, biological, and environmental factors that is typically, although not always, co-morbid with complex early childhood developmental stress and trauma (Chapman et al., 2004; Nemeroff, 1998; Palazidou, 2012 [8–10]). Developmental trauma and associated attachment injuries that occur during critical stages of child development are associated with treatment resistance in mental disorders including depression. While a variety of therapeutic approaches can be effective for TRD, treatments with trauma- and attachment-informed psychotherapy are designed specifically for the needs of this population (Dore et al., 2019 [11]). When this form of psychotherapy is timed to occur 24–48 h after paired ketamine-only sessions precision dosed to ensure high-entropy brain states and psychedelic experiences, it will coincide with the likely peak of dendritic spine growth and the therapeutic disruption of negative thoughts and beliefs induced by ketamine administration. This strategy may optimize the opportunities for change created by ketamine's glutamate modulation, normalization of neural connectivity and coherence, and stimulation of synaptogenesis and neuroplasticity—and may be key to improving the quality and duration of ketamine's therapeutic efficacy with TRD individuals.

2. Ketamine Treatment for Treatment-Resistant Depression: Efficacy and Mechanisms of Action

Ketamine, a non-selective N-methyl-D-aspartate (NMDA) receptor antagonist, has been studied over the past two decades as a promising treatment modality for treatment-resistant depression (TRD); as a glutamate modulator, it is a fast-acting antidepressant capable of relieving suicidality within hours of a single infusion of 0.5 mg/kg (Zanos and Gould, 2018 [12]). Ketamine has been in use for over five decades as an effective short-acting anesthetic, has a well-documented safety record for patients of all ages, and typically does not interfere with respiration or cardiovascular stability even at maximum effect. There is evidence that ketamine selectively induces adult synaptogenesis, normalizes neural connectivity and coherence, and enhances neuroplasticity in brain systems and structures impacted by depression-related neuronal atrophy [13]. Ketamine is also a powerful anti-inflammatory with neuroprotective factors, with potential to decrease inflammation-related depressive symptoms (Wang et al., 2018 [14]; Zanos et al., 2018 [15]). Through induction of high-entropy brain states and the accompanying psychedelic experiences, ketamine therapeutically disrupts entrenched habitual cognitive frames and neural activation patterns associated with traumatic memories, negative thoughts, and disempowering beliefs (Barthas et al., 2015 [16]; Carhart-Harris et al., 2014 [17]).

A key factor in ketamine's efficacy with mental disorders is its role as a powerful and efficient glutamate modulator—the only known psychedelic substance with this effect. Glutamate is the main excitatory neurotransmitter in the mammalian central nervous system, is present in over 60% of all brain synapses, and is the primary mediator of neurosystem plasticity (Javitt, 2004 [18]). Glutamate levels are tightly regulated by homeostatic excitatory and inhibitory neurotransmission through a complex system of ionotropic and metabotropic receptors throughout the whole neuraxis. Any abnormality in glutamate function or in the regulation of glutamatergic transmission can disrupt nerve health and communication and is a major influence on the presentation and progression of many neurodegenerative and psychiatric diseases (Brunton et al., 2011 [19]; Javitt, 2004 [18]). Beginning with Berman et al.'s work in 2000, research has demonstrated ketamine's efficacy in treating major depressive disorder (MDD) and in providing rapid resolution of suicidal ideation (<4 h), an acute symptom associated with MDD (Diazgranados et al., 2010; Dolgin, 2013; Thakurta et al., 2012; vande Voort et al., 2017 [20–23]; Zanos et al., 2018 [15]).

2.1. Evidence of Ketamine's Efficacy for Treatment-Resistant Depression

In research on the core factors of depression with animal models, ketamine is acknowledged to rapidly reverse the atrophy of neurons in the prefrontal cortex (PFC) caused by complex stress and other factors intrinsic to TRD (Duman and Li, 2012 [24]). The association between childhood or developmental trauma and TRD and the efficacy of ketamine with these conditions is illustrated by ketamine treatment of rodents exposed to the chronic unpredictable stress model (CUS) condition for 3 weeks (N. Li et al., 2011 [25]). CUS is a behavioral model that induces symptoms most analogous of the symptoms of TRD in humans, as well as the animal model most reflective of stress from childhood developmental trauma (Höfllich et al., 2018 [26]; Kraus et al., 2017 [27]). In response to the CUS condition, rodents exhibited decreased density of spines in layer V pyramidal neurons and decreased 5HT and hypocretin induced EPSCs in the same neurons; developed anhedonia—a core symptom of depression often associated with TRD—as measured by a decreased preference for sweetened solution in the sucrose preference test; and displayed an increase in the latency to feed in the novelty suppressed feeding test (anxiety model). Li and colleagues (2011 [25]) administered a single infused ketamine dose of 10 mg/kg, which rapidly (within hours) reversed all CUS impacts—structural, functional, and behavioral—with effects sustained for seven days.

In another rodent chronic stress study, ketamine selectively restored the number and function of PFC and hippocampal dendritic spines lost in mice during chronic corticosterone stress (CORT), rescuing only the dendritic spines clustered on specific dendrite branches eliminated by chronic CORT treatment (Moda-Sava et al., 2019 [28]); researchers found that 47.7% of newly formed spines were located <2 μm from a spine lost during chronic CORT exposure. While spinogenesis occurred long after the positive behavior effects of ketamine were present, and therefore could not be involved in the initial rapid behavioral antidepressant response, behavioral differences measured at 27 days post ketamine treatment correlated with spinogenesis activity at the same time mark, suggesting that spinogenesis is likely intrinsic to ketamine's profile of sustained antidepressant effects after ketamine has vacated the body.

In a pivotal study, Elhussiny et al. (2021 [29]) demonstrated that the CUS mouse model of depression produced rat brain atrophy and maladaptive remodeling of dendrites in the same brain regions affected in humans with TRD, and ketamine treatment reversed these effects. In this study, stress-vulnerable male rats were exposed to CUS for five weeks to induce symptoms associated with TRD. Effects of this stress included hypofunction of activity-dependent glutamatergic synaptic transmission chains of events, and selective downregulation of mGlu2. Researchers demonstrated that ketamine dosed at 10 mg/kg in CUS-vulnerable animals produced modulations of AMPA GluA2 expression at synaptic membranes that reversed the effects of CUS exposure. This evidence confirms that ketamine effects are targeted, established AMPA GluA2 functional role in regulating stress vulnerability, and for the first time proposed an mGlu2 involvement in the fast-acting antidepressant effect of ketamine.

The fact that ketamine's rapid antidepressant effects can be attributed to a different mechanism than ketamine's antidepressant effects of longer duration illustrates that ketamine's multiple avenues of efficacy can contribute synergistically to its unique therapeutic profile. To date, five distinct therapeutic mechanisms of action have been demonstrated or proposed in the literature. The following section presents each of these mechanisms in brief, along with representative evidence; for a more extensive review of literature on the topic of this section, see Muscat et al., 2021a, 2021b [13,30].

2.2. Ketamine's Therapeutic Mechanisms of Action

As with most conventional antidepressants, one of ketamine's mechanisms is neurotransmitter regulation. However, in contrast with the reuptake inhibition strategies of traditional monoamine and tricyclic antidepressants in which the levels of target neurotransmitters are augmented, ketamine is a glutamate modulator that upregulates or

downregulates as needed to normalize glutamate metabolism in the neural system, including the brain. Ketamine's rapid reduction in depressive symptoms even with depression considered treatment resistant is of additional value for individuals with developmental trauma, as these individuals typically exhibit an impaired capacity to build the trust required for compliance with extended treatment schedules.

Ketamine's fast-acting antidepressant effect is also associated with its rapid temporary activation of neural plasticity through selective induction of synaptogenesis and normalization of connectivity in multiple brain structures and systems impacted by depression-related neuronal atrophy and altered brain connectivity (Moda-Sava et al., 201 [28]; Abdallah et al., 2017 [31]). These processes initiate restoration of the neurological architecture needed to support the new neural pathways and adaptive changes in belief and behavior afforded by the psychotherapeutic process, while also supporting the high-entropy therapeutic disruption of entrenched neural activation patterns associated with negative thoughts and beliefs (Carhart-Harris et al., 2014 [17])—an invaluable adjunct for increasing the efficacy of trauma-informed psychotherapy in the treatment of developmental trauma.

A less studied mechanism of action by which ketamine impacts symptoms of depression is through its powerful anti-inflammatory effect induced by downregulation of pro-inflammatory cytokines (Wang et al., 2018 [14]; Zanos et al., 2018 [15])—a mechanism that is activated when chronic stress-induced inflammation is present (Maydych, 2019 [32]). Inflammation and associated immunologic processes are thought to play a pivotal role in the emergence and persistence of some psychiatric disorders (Zanos et al., 2018 [15]; Wang et al., 2012 [14]) by creating dysfunction in brain networks through disruption of glutamate release, transmission, and metabolism; this results in accumulation of extracellular glutamate in the central nervous system. While depression is not strictly an inflammatory disorder, some forms—particularly treatment-resistant forms—may be caused or exacerbated by chronic low-level inflammation from multiple sources such as childhood stress, psychological distress, chronic stress, and chronic inflammatory diseases such as autoimmune disorders (Zanos et al., 2018 [15]; Wang et al., 2012 [14]; Kim et al., 2018 [33]).

Another therapeutic mechanism of ketamine at certain dosages is the induction of a high-entropy brain state. In this context, brain entropy is the degree of disorder or randomness in brain activity at any given moment (Carhart-Harris et al., 2014 [17]; Li and Mashour, 2019 [34]; Schartner et al., 2017 [35]). Carhart-Harris et al. (2014 [17]) developed an entropic brain theory, a neuroscientific explanation of mind and mental states. The authors associated low entropy with greater organization of brain activity, correlated with mature and awake adult states of mind. High-entropy states were associated with more randomness of brain activity and correlated with pre-adult, unconscious, primitive, and sleeping states of consciousness. When high-entropy brain states are induced by psychedelics such as ketamine, psilocybin, and lysergic acid diethylamide (LSD), they appear to aid in the disruption of depression-related neural pathways and associated rigid negative and self-critical thoughts, behaviors, and beliefs that may result in feelings of helplessness, hopelessness, isolation, and anhedonia (Carhart-Harris, 2018 [36]; Nikiفورuk and Popik, 2013 [37]).

While research on entropic brain states and their impact has been conducted primarily with traditional psychedelic substances such as psilocybin (Carhart-Harris, 2018 [36]), ketamine may be preferred for clinical use as it is a legal substance, is comparatively short acting (45 min), has a 50 year medical safety profile, and at higher subanesthetic doses also induces high-entropy brain states (Li and Mashour, 2019 [34]; Schartner et al., 2017 [35]) that provide a similar opportunity for adaptive neural reorganization critical for recovery from developmental trauma.

High-entropy brain states are associated with psychedelic phenomenology, and there is evidence that these subjective experiences may provide benefits beyond the neural effects of increased brain entropy (Dakwar et al., 2014 [38]). Ketamine's psychoactive effects offer some individuals reconnection with, or even discovery of, a meaningful experience of

connectedness, hope, and happiness (Watts et al., 2017 [39]; Wolfson, 2014 [40]), similar to those found to occur with more traditional psychedelics (Majic' et al., 2015 [41]). Furthermore, the quality or intensity of the psychedelic experience appears to be associated with better therapeutic outcomes (e.g., Dakwar et al., 2014 [38]; Kolp et al., 2014 [42]; Wolfson, 2014 [40]). However, the inherent therapeutic value of the ketamine-induced mystical or peak experience as an effective tool to accelerate and enhance the psychotherapeutic process is underrepresented in the literature. A more comprehensive examination of this mechanism of action is addressed in the section that follows.

2.3. Therapeutic Impacts of Ketamine-Induced Peak and Mystical-Type Experiences

Both glutamatergic and serotonergic psychedelics appear to induce structural and functional neuroplasticity through identical Trkb, BDNF, and mTOR signaling pathways. As with classic psychedelics, ketamine stimulates neural plasticity by means of boosting BDNF expression caused by mTOR activation, producing high-level changes in network connectivity. These changes occur particularly within the default mode network (DMN), which is associated with executive functioning; such changes may facilitate long-lasting cognitive and psychological flexibility, which in some senses is a definition of psychological health (Bahi, 2020 [43]). Ketamine induces phenomenological experiences in altered states of consciousness that are similar to those reported with classic psychedelics. In addition, ketamine shares similar downstream mechanisms of action with serotonergic psychedelics (Kadriu et al., 2020 [44]). Despite this, caution must be exercised when generalizing from serotonergic psychedelics to ketamine until research can show whether such extensions are warranted. With this caveat, it can be noted that double-blind studies of high-dose psilocybin administered in a supportive therapeutic setting have demonstrated important correlations between improved therapeutic outcomes and peak psychedelic-induced mystical-type experiences.

A series of two studies reported profound positive personality changes after a psilocybin-induced mystical experience in 32 and 17 adult subjects, respectively, who had no previous experience of psychedelics. Longitudinal data from these studies confirmed that positive personality changes were durable over a period of 14 months (Griffiths et al., 2006, 2008, 2011 [45–47]).

Relevant results with ketamine were obtained by Sos et al. (2014) in a double-blind, placebo-controlled crossover study that examined the relationship between antidepressant efficacy and psychotomimetic symptoms. Twenty-seven hospitalized TRD patients were infused with a single 0.5 mg/kg dose of ketamine and subsequently monitored over a 2 week period. Higher intensity of reported psychotomimetic symptoms during ketamine treatment correlated with higher ratings of mood alleviation throughout the monitoring period, with peak effects at day 7. Researchers proposed that ketamine's efficacy with TRD may initiate with its action on NMDA receptors, an effect that is subsequently enhanced by psychotomimetic effects.

A double-blind randomized study of ketamine's effects on cocaine dependency with eight cocaine-dependent inpatient subjects who had a history of cue-induced cravings, and who were not actively seeking treatment, indicated a correlation between mystical-type phenomena and the motivation to stop cocaine use (Dakwar et al., 2014 [38]). Subjects received three infusions separated by 48 h: one with 2 mg of lorazepam as active placebo, one with 0.41 mg/kg ketamine, and one with 0.71 mg/kg ketamine. Subjects completed an adaptation of the Hood Mysticism Scale to measure mystical effects, and the Clinically Administered Dissociative Symptoms Scale (CADSS), at baseline, within 15 min of infusion, and at 24 h post infusion. No mystical phenomena were generated with lorazepam, few such effects resulted at 0.41 mg/kg ketamine, but a substantially greater number of such effects were reported at 0.71 mg/kg ketamine (Dakwar et al., 2014 [38]). The intensity of the temporary mystical phenomena mediated the therapeutic effects of ketamine and the motivation to quit cocaine at 24 h post infusion, but did not impact cue-induced cravings. These results confirmed previous evidence that experiencing a psychedelic peak experience

is dose dependent, and also demonstrated dose-dependent efficacy with an aspect of addiction in a small sample.

Roseman and colleagues (2018 [48]) found additional evidence of a relationship between improved therapeutic outcomes with TRD and peak psychedelic or mystical-type experiences induced by psilocybin. Twenty TRD subjects received two psilocybin treatments one week apart, the first with 10 mg and the second with 25 mg. TRD symptoms were measured using the Self-Report Quick Inventory of Depressive Symptoms (SRQIDS). Measures were taken at 1 day, 1 week, and 5 weeks. Participants had overall positive therapeutic outcomes ($p = 0.001$) across all time periods ($p = 0.002$). An altered states of consciousness questionnaire was used to rate the incidence and intensity of two dimensions of experience: oceanic boundlessness (which correlated to mystical experiences), and dread of ego state dissolution (which correlated to anxiety). Both of these dimensions predicted positive therapeutic outcomes, while dimensions of sensory and perceptual effects did not. These results supported the study's hypothesis that "the quality of the acute psychedelic experience is a key mediator of long-term change in mental health" (Roseman et al., 2018, p. 974, [48]).

The dissociative effects of ketamine have been found to correlate with its antidepressant effect even without reference to mystical dimensions or peak experiences—sometimes in a dose-dependent manner (Ionescu et al., 2018 [49]). Dissociative effects during ketamine administration may be markers of therapeutic impact on brain activity associated with rumination (Lehmann et al., 2016 [50]), self-monitoring and autobiographical memory (Bonhomme et al., 2016 [51]; Deakin et al., 2008 [52]; Stone et al., 2011 [53]), and emotionally valenced processing (Evans et al., 2018 [54]; Murrough et al., 2013 [55]; Scheidegger et al., 2016 [56])—areas often related to key symptoms of depression such as excessive self-focus and rumination and negative bias in emotional processing.

While there is evidence supporting the therapeutic impact of ketamine's psychedelic effects, empirical research specific to this aspect of ketamine treatment for TRD is lacking as compared with other peer-reviewed studies of ketamine for depression. Moreover, not all results are uniformly supportive. For example, in a study with 82 participants undergoing ketamine treatment for TRD, no association was found between the dissociative experience of "floating" during ketamine treatment, and subsequent antidepressant efficacy (Acevedo Diaz et al., 2020 [57]). However, given that ketamine has a wide range of subjective effects, the absence of association between efficacy and one particular dimension of experience does not preclude possible correlations with other dimensions or impacts of psychedelic experience (e.g., Sos et al., 2014 [58]).

For example, a study of 32 subjects with MDD treated with either a single ketamine dose of 0.44 mg/kg or remifentanyl as active placebo (Sumner et al., 2021 [59]) found that dimensions of experience associated with insight, spirituality, and a sense of unity correlated with enhanced antidepressant response. In contrast with this, a study by Liechti et al. (2016 [60]) called into question the description of peak psychedelic experiences with LSD as mystical in nature. This two-trial double-blind placebo-controlled crossover study used 100 and 200 mcg doses of LSD with 24 and 16 healthy subjects, respectively. Participants completed the Altered States of Consciousness 5 Dimensions Edition (5D-ASC) and the Mystical Experiences Questionnaire (MEQ). While few participants reported full mystical experiences, those who received the higher dose of 200 mcg had higher scores on insightfulness, bliss, empathogenic effects, and meaning enhancement than those who received 100 mcg. The higher LSD dose produced high scores in the positive mood domains on the MEQ, which correlated with high ratings on the 5D-ASC dimension of bliss. From this, the authors concluded that previous characterizations of the LSD experience as mystical in nature did not universally reflect its most prominent features. However, this conclusion is based on a narrow definition of mystical experience. Given that LSD induced a set of experiential qualities strongly associated with mystical experiences (e.g., [61,62]), and did so in a dose-dependent manner, such an inference seems unwarranted.

The preponderance of preliminary evidence suggests that when prescribed at higher subanesthetic doses, the experiential effects of ketamine offer a unique therapeutic opportunity for TRD subjects—regardless of how those effects are characterized. Becker (2014 [63]) postulated that ketamine’s beneficial and sustained psychological effects may be greatly enhanced by the brief transformational state of consciousness that is induced, and by the positive impact this experience has on subsequent psychotherapy sessions. Wolfson (2014) agreed that “ketamine assisted psychotherapy’s value is inextricably linked with the psychedelic experience that ketamine induces” (p. 37, [63]).

Despite the variety of positive impacts of ketamine on neurotransmitters, synaptogenesis, brain connectivity, neural plasticity, inflammatory cytokines, brain states, and elevated experiences, these positive effects are typically of short duration. More durable change often requires the incorporation of psychotherapy—in the case of TRD, preferably trauma- and attachment-informed psychotherapy.

3. Trauma- and Attachment-Informed Psychotherapy

The importance of healthy attachment during critical periods of childhood development can hardly be overstated. As social creatures, the ability to function within society is intrinsic to human health, happiness, and quality of life, and adults with healthy, organized early attachment appear to establish elements of interpersonal physiological synchrony during naturalistic social interactions. For example, a study using hyperscanning EEG (Kinreich et al., 2017 [64]) measured the brain-to-brain synchrony during male–female social interactions in 104 adults, comparing strangers with romantic couples; neural synchrony was measured between romantic couples but not between strangers. Within couples, neural synchrony appeared to be anchored in positive affect and social gaze. Findings of neural synchrony were positively correlated with an increased degree of social connectedness and important non-verbal social behaviors and highlighted the key role of attachment in neural synchrony between individuals. One major approach to trauma- and attachment-informed psychotherapy involves the development of emotional self-regulation through neural synchrony established within a therapeutic relationship.

3.1. Stress and the Etiology of TRD

As noted earlier, the relationship between depression and stress, with its accompanying brain changes, has been well established over the last 20 years in both preclinical and clinical trials (Stepanichev et al., 2014 [2]; Taylor et al., 2005 [1]; Young et al., 2003 [3]). The hypothalamic–pituitary–adrenal (HPA) axis is one of the crucial mechanisms involved in an organism’s response to stress (Liberzon et al., 1997 [65]; Müller et al., 2002 [66]; Young et al., 2003 [3]). Dysfunction of the HPA axis has been implicated as a major contributor to TRD and other mental disorders such as anxiety and post-traumatic stress disorder (PTSD). Simplistically, the HPA axis is a tightly regulated feedback system that influences the release, transmission, and metabolism of glutamate—the major excitatory neurotransmitter in the mammalian neural system. Under chronic stress conditions, HPA axis dysregulation can occur, consequently affecting metabolism, cognitive processing, and emotions—especially fear and anxiety (Liberzon et al., 1997 [65]; Müller et al., 2002 [66]; Taylor et al., 2005 [1]; Young et al., 2003 [3]).

Excessive stresses on the brain from external or internal environments are known precursors of mood disorders, including depression. The type, intensity, and duration of the stressor, and at what brain developmental stage it occurs, are factors in depression pathology. Stress in the form of attachment injury during childhood is associated with treatment resistance in depression and other disorders. When factors necessary for healthy attachment are absent during critical stages of neurobiological developmental—particularly due to neglect, abuse, abandonment, or narcissistic parenting—the developmental trauma may prevent normal development of certain neural pathways in the child’s brain (Schoore, 2005 [6]; Siegel, 2006 [7]).

3.2. Treatment-Resistant Depression and Complex Trauma

As previously indicated, TRD is a complex psychiatric disorder with known and unknown contributing factors comprised of genetic, biological, and environmental variables. Individuals diagnosed with TRD often have a comorbid diagnosis of complex early childhood developmental stress and/or trauma and frequently suffer from an attachment injury (Chapman et al., 2004 [8]; Nemeroff, 1998 [9]; Palazidou, 2012 [10]; Pittenger and Duman, 2007 [4]). Adverse childhood events are strong risk factors for the development of mental disorders, particularly of anxiety, depression, and PTSD in adults (Chapman et al., 2004 [8]; Grossman et al., 2017 [67]; Heim et al., 2010 [68]). Untreated developmental trauma and injury are associated with the etiology of treatment resistance, not only in TRD but also in other mental disorders (Chapman et al., 2004 [8]; Heim et al., 2010 [68]). As such, trauma- and attachment-informed psychotherapy appears a necessary addition to any antidepressant drug treatment protocol for TRD in order to increase the likelihood of long-term psychological health and well-being (Grossman et al., 2017 [67]).

Developmental trauma refers primarily to attachment injury; attachment trauma and injury are best understood within the context of modern attachment theory. Modern attachment theory is a biopsychosocial framework for human development. It is a multidisciplinary collaborative model that integrates genetics, biology, physiology, and developmental neuroscience with psychological, emotional, cognitive, societal, and cultural development. The foundation of attachment theory is the principle that brain maturation is experience dependent and shaped by the mother–child dyadic attachment relationship, and that brain-to-brain synchrony and attunement between mother and child are vital for the optimal health and development of children (Schoore and Schoore, 2014 [69]). Critical stages of development refer to periods of brain growth and neural plasticity that occur periodically throughout the life span. However, neurobiological research has determined that the rapid brain growth in the first two years of life is a critical stage of development that may be of importance in laying down the affective neural pathways that are the blueprint for interpersonal relationships over the lifespan (Schoore, 2005 [6]).

Although born with hardwired neural circuitry, infant brain maturation is experience dependent (Schoore, 2005) [6]. Thus, the cellular architecture of the infant neocortex may be sculpted by input from early dyadic attachment relationships. These dyadic relationships may influence the shape of the brain by altering the strength of the synaptic connections within the brain. Thus, synapses formed from primarily genetic encoded information may be strengthened, weakened, or eliminated (pruned). Within this context, the parent–child dyadic relationship is thought to be instrumental in the formation of new synapses and the production of myelin that functionally enhances neural connectivity by increasing the speed of conduction of the electrical action potential down the axon length (Ran and Zhang, 2018 [70]; Schoore, 2005 [6]; Siegel, 2006 [7]).

Regardless of the origin of the synapse, genetic information, toxic substances, and stressful or absent experiences can lead to the elimination of synapses (Siegel, 2006 [7]). Thus, infant brain development is dependent upon biopsychosocial stimulation via the interactive dyadic integration of the infant’s right hemisphere and the mother’s right hemisphere, biologically encoding affect strategies at a non-verbal implicit unconscious level. These non-verbal communications are transmitted through eye-gaze, facial expression, emotional tone, intonation, attention, and tactile information (Schoore, 2005 [6]).

Furthermore, there is evidence that the biopsychological basis of the synchrony and attunement of the attachment bond are also bidirectional. Swain et al.’s (2007 [71]) research demonstrated that infant stimuli activate basal forebrain regions in mothers, which regulate brain circuits that handle specific nurturing and caregiving responses and activate the brain’s neural circuitry for handling emotions, motivation, attention, and empathy, all of which are critical for effective parenting. Moreover, the quality of this early dyadic attachment encodes and informs the future health of intimate relationships and the successful interaction with one’s culture, community, and society.

Physical evidence offering a mechanism for neuronal brain-to-brain synchrony was discovered in 1994 in the form of highly specialized cells—mirror neurons that internally reflected the experience of another person—located in the cerebral cortex (Bastiaansen et al., 2009 [72]; Wolf et al., 2000 [73]). This discovery contributed to the understanding of the physiology of attachment. Mirror neurons facilitate neural mimicking of the actions of others. Bastiaansen et al. (2009 [72]) demonstrated that “observation of an action in another individual directly triggers the activation of matching neural substrates in the observer through which the action can be understood” (p. 2392, [73]). Mirror neurons, primarily located in the premotor cortex, may be the neurobiological underpinning of social engagement and interaction (Jeon and Lee, 2018 [74]), and crucial to attachment between child and parent.

3.3. *Developmental Trauma and Attachment Injury*

If synchrony/attachment between parent/caregiver and child does not occur during these critical stages in neurobiological development, particularly due to neglect, abuse, abandonment, or narcissistic parenting, developmental stress and trauma may ensue; vital neural paths may not develop in the child’s brain. Indiscriminate neural circuitry may remain and develop abnormally, and limbic system nuclei may atrophy. Neurons, synapses, dendrites, and neural pathways essential to normal development may be sheared away throughout the brain. The loss of presynaptic vesicles, glia, interneurons, neurons, axons, synapses, and cortical thickness, in the septal nuclei, amygdala and hippocampus, combined with the failure to generate new neurons and circuitry during critical developmental periods, may cause immeasurable brain and developmental damage and dysfunction in daily living during childhood that will follow into adulthood and beyond (Abrous et al., 2005 [75]; Joseph, 1999; [5]; Schore, 2005 [6]; Siegel, 2006 [7]).

The negative effects of attachment injury on child development are profound. A strong association has been identified between adverse childhood events and the development of mood and anxiety disorders, including unipolar depression, bipolar disorder, generalized anxiety disorder, panic disorder, phobias, and PTSD (Heim et al., 2010 [68]). Ultimately, these children’s emotional and social development may be severely impaired. They may not develop a sense of safety, trust, security, or foundation. Furthermore, they may never develop a sense of self, or self-agency. These children are often unable to regulate their autonomic and central nervous systems, or regulate their emotions, and may have difficulty forming relationships in the future. This state of underdevelopment may lead to lifelong psychopathologies including anxiety, depression, aggression, violence, suspiciousness of other’s motivations, paranoia, personality disorders, and a lack of sympathy and empathy towards others. Without therapeutic intervention, the impact of disorganized parent–child attachment may last a lifetime (Abrous et al., 2005 [75]; Grossman et al., 2017 [67]; Heim et al., 2010 [68]; Joseph, 1999 [5]).

3.4. *Psychotherapy for Developmental Trauma*

When first-line treatments of depression with antidepressant medication fail, typical clinical strategies include switching to a different class of antidepressants, psychotherapeutic or pharmacological augmentation, or combination strategies [76,77]. A 2018 systematic review and meta-analysis of psychotherapeutic and pharmacological augmentations found both forms to be more effective for TRD than drug or psychology placebo [78], and combination strategies using both drug and psychotherapy treatment have been shown by meta-analyses to yield generally better results than pharmacological treatment alone (Ijaz et al. [79,80]); psychotherapy approaches measured included cognitive behavior therapy (CBT), cognitive behavioral analysis interpersonal psychotherapy, and mindfulness-based cognitive therapy. Another meta-analysis showed CBT alone to be more effective at reducing symptoms and increasing response and remission rates in TRD than standard pharmacological treatment [81].

While various types of psychotherapy are effective, treatment modalities for trauma-related conditions typically center on trauma-informed care as best practice (Kezelman and Stavropoulos, 2012 [82]; Courtois, 2004 [83]). There is consensus in the trauma field that developmental trauma impacts both the neurobiology of the developing brain and the beliefs and narratives of the psyche (Abrous et al., 2005 [75]; Joseph, 1999 [5]; Schore, 2005 [6]; Siegel, 2006 [7]). Developmental trauma, sometimes referred to as complex trauma (cPTSD) in psychiatric literature, is caused by repeated or prolonged exposure to traumatic events that are interpersonal and from which escape is difficult, such as childhood abuse, domestic violence, genocide, and institutions of organized violence (Lee-Evoy and Hershler, 2021 [84]).

There are six clusters of cPTSD symptoms encountered in therapy: (1) re-experiencing through nightmares, traumatic memories, and flashbacks, associated with emotional distress and physical symptoms; (2) avoidance of thoughts or feelings that are reminders of the trauma, including avoiding people, places, and activities; (3) feeling a sense of current threat, associated with hypervigilance, exaggerated startle response, and irritability; (4) problems with emotion regulation such as rapid mood changes, persistent sadness, dissociation, emotional numbing, suicidal thoughts, and difficulty experiencing pleasure or positive emotions that may lead to maladaptive tension reduction behaviors such as self-harm and substance abuse; (5) relational difficulties such as difficulty maintaining long-term relationships, difficulty feeling close to others, avoidance or disinterest in social connections, and repeated seeking for a rescuer; and (6) a rigidly negative self-concept, including negative self-worth or self-value and the belief of being wrong or broken (Lee-Evoy and Hershler, 2021 [84]).

Trauma-focused CBT uses an informational approach about the effects of trauma and coping mechanisms, alongside CBT principles [85]. Yet there is also evidence that attachment dimensions predict response to treatment [86], and that attachment both moderates and mediates psychotherapeutic efficacy [87]. Given the association between developmental trauma and treatment resistance, the addition of attachment-informed approaches for TRD would appear advisable. In trauma- and attachment-informed psychotherapy, the therapist becomes a temporary attachment figure (Levy, 2013 [88]). Within this framework, the therapist's main task is to establish trust, care, and support. This allows for the safe examination of past attachments and relationships, even those with painful aspects related to expectations, feelings, and behaviors; the understanding of dynamics from past relationships can then be linked to current relationships. The therapist then guides the patient through a revision of their internal working model based on the new healthy relationship template that is based on the alliance of the therapeutic relationship. Recognition of the patient's attachment to the therapist enables the therapist to better moderate and adapt their interpersonal style and choice of therapeutic techniques.

3.5. Efficacy of Trauma- and Attachment-Informed Psychotherapy

Current treatment options for complex childhood trauma are limited, whether through traditional pharmacology (Liriano et al., 2019 [89]) or trauma-informed therapeutic modalities (van der Kolk and Courtois, 2005 [90]). Moreover, research has shown only partial efficacy in approximately 50% of participants with evidence-based trauma-informed psychotherapy treatment modalities, with that efficacy linked more to the therapeutic relationship than to the treatment modality (Grossman et al., 2017 [67]; Heim et al., 2010 [68]; Muskett, 2014 [91]).

Even when therapeutic progress is achieved, the process is lengthy, requiring a multimodal, multidisciplinary, integrative approach (Grossman et al., 2017 [67]). Additionally, therapeutic gains achieved with an in-hospital multimodal approach quickly reverted to baseline when individuals re-entered their community (Muskett, 2014 [91]), and the addition of conventional antidepressants to trauma-informed therapy has yielded little additional improvement. However, when trauma-informed care is proactively incorporated into foster care systems, child welfare systems, and other forms of institutional care, treated

individuals have shown significant gains in positive adaptive behavior, lowered frequency of removal, and fewer instances of reported abuse (Barto et al., 2018 [92]; Murray et al., 2019 [93]).

4. Ketamine and Psychotherapy as Adjunctive Interventions for TRD

Given the considerable challenges of treating developmental trauma and associated disorders such as TRD, the advances with ketamine as a novel antidepressant that also normalizes brain connectivity and neural coherence, induces synaptogenesis, enhances neural plasticity, downregulates stress-related cytokines, and interrupts habitual patterns of brain activity and negative thought patterns make ketamine a potentially promising treatment for these disorders. However, while shown to be immediately effective in reducing negative symptoms, ketamine retains its potency for relatively brief periods of time. It has been suggested that ketamine efficacy might be improved through the addition of multi-modal individually tailored trauma-informed psychotherapies focused directly on rewiring the underlying disrupted attachment, and targeting associated autonomic and sympathetic system dysregulation, neural incoherence, and inhibited or abnormal interpersonal relational patterns (Doblin et al., 2019 [94]; Grossman et al., 2017 [67]; Rosenthal, 2017 [95]), as well as assisting in the development of self-identity, self-regulation, and self-agency necessary for long-term stability, psychological growth, and well-being (Abrous et al., 2005 [75]; Joseph, 1999 [5]; Schore, 2005 [6]). Concurrently, the addition of ketamine treatment to trauma- and attachment-informed psychotherapy appears to facilitate and increase the efficacy of this standard treatment.

4.1. History and Evidence for Combined Efficacy

Experiences of developmental trauma and attachment injuries impact both the neurobiology of the brain as well as the beliefs and narratives of the psyche. This may explain why novel antidepressant medications in standalone treatment models show short-term efficacy in reducing negative symptoms of TRD but only retain their potency for relatively brief periods of stability (Schore, 2005 [6]); the antidepressant is the opportunity for new experience, but if not supported by long-term psychosocial engagement, the gains are likely to be transient. Without the addition of psychotherapies focused directly on reprocessing the underlying disrupted attachment, attending to the consequential autonomic and sympathetic system dysregulation, disrupted neural coherence, and inhibited or abnormal interpersonal relational patterns, these individuals soon return to their baseline. Although psychedelics are also effective in disrupting habitual cognitive patterns, adjunct psychotherapy is imperative for the healing of underlying emotional wounds, forging new neural pathways, attaining improved self-regulation and neural coherence, and achieving self-agency for long-term stability, psychological growth, and well-being (Abrous et al., 2005 [75]; Joseph, 1999 [5]; Schore, 2005 [6]; Siegel, 2006 [7]).

4.1.1. History of Ketamine as an Adjunct to Psychotherapy

Since the discovery of LSD in 1943 by Swiss chemist Albert Hoffman, a prolific body of literature, including thousands of publications, conference reports, and psychedelic treatment modalities, has extolled the merits and advantages of psychedelics as an adjunct to psychotherapy (Carhart-Harris et al., 2014 [17]; Crockett et al., 1963 [96]; Garcia-Romeu et al., 2016 [97]; Grof, 1970 [98]; Osmond, 1957 [99]; Pahnke, 1970 [100]). Among these were the 1971–1975 reports by Salvatore Roquet, an established psychotherapist in Mexico, who published clinical findings from his work with ketamine-assisted psychotherapy (Kolp et al., 2014 [42]). Roquet administered a dose of 1.5 mg/kg ketamine (amongst other psychedelics such as LSD, mescaline, and psilocybin) with a combination of psychoanalytic psychotherapy and traditional shamanic healing practices of the indigenous people of Mexico. His treatment population, while predominantly neurotic, also included the personality disordered and a few cases of psychosis. Roquet reported an improvement in symptoms in 85% of approximately 150 patients treated between the years 1969 and 1973. Roquet was

also credited with the development of an operative hierarchical classification system of four distinct categories of ketamine experiences along a continuum.

The first category is comprised of the mildest experiences, described as moderate perceptual distortion. The second category includes pleasant fantasies of wish fulfillment, possibly some mild mystical experiences, with the potential to effect some minor personality reorganization in the patient. The third category is that of existential anxiety, wherein subjects experience a psychological death and rebirth. This level of response frequently produces a powerful abreaction and eventual healing catharsis in the patients. The fourth, most intense category was the experience of complete ego dissolution characterized by a total loss of personality, identity, and all previous points of reference, and transformative mystical experiences that provoked profound personality reorganization. Roquet emphasized that the attainment of the fourth category was essential to the maximization of favorable therapeutic outcomes (Kolp et al., 2014 [42]).

Roquet was considered a maverick, revered by some and ostracized by others. His were not standard methodical clinical trials. He incorporated many different psychedelics, sometimes in combination with each other, other times combined sequentially over months. Set and setting were important to the therapy, including shamanic rituals, group therapy, music, art, film, and even the inclusion of family members. His reasoning was based on the premise that the medicine (a) initiated a disruption of the psyche, (b) the patient would then experience deep insights, and (c) gain understanding within interpersonal contexts, particularly from childhood and later trauma. He termed his therapeutic method psychosynthesis (Kolp et al., 2014 [42]).

In 1974, Fontana y Col [101], a well-known Argentinian researcher, authored another landmark study of the successful application of ketamine-assisted psychotherapy on depressed patients. Fontana hypothesized, analogous to Roquet's third category of experience, that ketamine facilitated a deep regression to a prenatal state, with a journey through death and rebirth, thereby allowing the therapist an entry point to interject and correct primitive experiences through the therapeutic process. His was a very psychodynamic orientation, and his methods are still a component of the modern ketamine-assisted psychotherapy process today. Unfortunately, the number of patients, the dosages administered, and the specific procedure of the psychotherapy utilized were not published. Ketamine-assisted psychotherapy was popular during this period in history and was applied to many diverse mental illnesses by clinicians around the world (Khorramzadeh and Lofty, 1973, 1976 [102,103]; Kolp et al., 2014 [42]).

Unfortunately, much of the research and clinical application from this earlier era did not have the scientific rigor required of research today. Thus, these earlier studies, though they were extensive and reported remarkable recovery rates, are difficult to verify or replicate. At the time, the outcomes and conclusions inferred by the research and researchers, though plausible in the light of current ketamine-assisted psychotherapy literature, were deemed suspect (Carhart-Harris et al., 2014 [17]; Friedman, 2006 [104]; Kolp et al., 2014 [42]). While there were a few exceptions to the above generalization—in particular, the noteworthy effectiveness of ketamine with alcohol and heroin addictions (Krupitsky and Grinenko, 1997 [105]; Krupitsky et al., 2007 [106])—ketamine-assisted psychotherapy was marginalized and distrusted.

4.1.2. Evidence for Combined Efficacy

Research evidence for combining ketamine treatment and psychotherapy is as yet limited. However, there are a few older and current studies pointing to improved response and duration of ketamine's efficacy for various disorders when psychotherapy was added to treatment, and vice versa. For example, a review of 10 years of controlled clinical research that compared the impact of psychotherapy with ketamine treatment to treatment as usual for individuals with alcoholism found that more than 1 year of abstinence was reported by 73 out of 111 patients in the ketamine plus psychotherapy group, compared with 24 out of 100 patients in the treatment as usual group (Krupitsky and Grinenko, 1997 [105]). This

literature suggests that cautious optimism may be warranted for ketamine treatment with trauma- and attachment-informed psychotherapy in addressing developmental trauma, and that further exploration and systematic investigation appears worthwhile.

A randomized, placebo-controlled crossover clinical study with 10 adults suffering from chronic symptoms of PTSD combined ketamine treatment with a mindfulness-based cognitive behavioral therapy targeting trauma memories for extinction and reconsolidation (TIMBER; Pradhan et al., 2017 [107]). The goal of the study was to determine whether the addition of ketamine treatment would increase the duration of TIMBER's therapeutic effects on individuals suffering from PTSD—some with comorbid depression—as compared with a placebo/TIMBER group. Patients were randomly assigned to either a ketamine/TIMBER group that received a protocol of 12 therapy sessions combined with a single infusion of 0.5 mg/kg ketamine or a control group that received the TIMBER protocol plus a saline infusion. Members of the placebo/TIMBER group who experienced a sustained relapse were switched to the ketamine/TIMBER group. Psychometric instruments measuring PTSD, depression, and anxiety symptoms were used, as well as a measurement of cognition, and an assessment for a personalized mindfulness intervention program.

The addition of ketamine prolonged the effectiveness of the TIMBER protocol, with symptom reduction lasting a mean of 33 ± 29.98 days compared to the placebo/TIMBER group (25 ± 16.8 days). After subjects from the placebo group switched to the ketamine group, they experienced a significantly prolonged response (49 vs. 25 days, $p = 0.028$). There were no intolerable side effects or dropouts during the 18-month follow-up period.

A small open-label trial with 16 self-selecting patients diagnosed with TRD examined whether the addition of cognitive behavioral therapy would extend ketamine's antidepressant effects (Wilkinson et al., 2017 [108]). Patients participated in a 12 session, 10 week course of cognitive behavioral therapy concurrent with a 4 treatment, 2 week course of intravenous ketamine provided under a standardized clinical protocol of 0.5 mg/kg infused over 40 min. Subjects were previously identified as ketamine responders and ketamine non-responders.

The overall response rate of 8 ketamine responder subjects to treatment was 70.8%. The Montgomery-Åsberg Depression Rating Scale score measured a significant decrease at 2 h post first ketamine infusion (18.9 ± 6.6 , $< p = 0.001$), and that response was sustained throughout the infusion phase. It was notable that experiencing an early (within 4 h) positive response was predictive of an overall greater treatment efficacy.

Of patients who achieved a remission diagnosis, the mean time to relapse was 12 weeks; this compared with mean time of 18–19 days to relapse in studies of repeated ketamine infusion without psychotherapy, leading the researchers to conclude that the addition of cognitive behavioral therapy may increase the duration of ketamine antidepressant treatment effects. Although the sample size was small, controlled trials with larger sample groups were recommended to further investigate this extended treatment-responding pattern with TRD subjects.

The strongest evidence to date comes from a landmark retrospective study of ketamine-assisted psychotherapy by Dore and colleagues (2019 [11]) with 235 adult patients (mean age 42.7; 115 F/120 M) from three distinct private general psychiatric practices located in Northern California. This was the first published study of ketamine-assisted psychotherapy clinical data in situ, with real-world outcome data of the efficacy of ketamine-assisted psychotherapy on individuals diagnosed with mental disorders common to a general psychiatry practice. The authors reported that their ketamine-assisted psychotherapy protocol evolved naturally over the course of this study, based on clinical experience and patient outcome measures, into a fairly standardized, replicable treatment modality, when administered by well-trained professionals.

The Dore et al. (2019 [11]) study yielded both quantitative and qualitative results: psychometric testing included the patient self-reported measures of depression, anxiety, PTSD, presence of adverse childhood events, mystical experience and out-of-body experiences, along with correlating clinician observation measures. Patient and clinician

change of state measures confirmed internal consistency and inter-rater reliability. Results included decreases in anxiety and depression symptoms. Importantly, subset analysis of the improvement in depression and anxiety demonstrated that patients with chronic PTSD or developmental trauma experienced the greatest improvement in depression and anxiety scores.

A higher number of visits was correlated with greater improvements in depression post treatment. Longer treatment duration also showed greater improvements in depression and anxiety. Patients with the most severe symptom burdens—including higher suicidality at intake, more frequent hospitalizations in the previous year, and higher adverse childhood events scales—had the most significant improvements across all measured domains. The authors noted that ketamine-assisted psychotherapy appeared to be effective with a wide range of diagnoses encountered in a general psychiatry private practice.

The protocol employed by Dore and colleagues (2019 [11]) presupposed the importance of the relationship between treatment resistance, historical complex trauma, and the interpersonal neurobiology of the therapeutic alliance. According to the authors, breaking trust and consequent lack of trust acquisition is the fundamental element of trauma persistence and treatment resistance. Therefore, the authors agreed that tailoring the therapeutic alliance towards relationship bonding and trust building in a supportive, reliable, and compassionate environment that recognizes the patient's vulnerable state is best practice for healing emotional wounds. Additionally, the therapist must be well versed in maintaining awareness of the interpersonal biological synchrony and attunement of the therapy relationship, while also maintaining healthy boundaries that encourages psychological growth towards autonomy and self-reliance.

Regarding ketamine treatment, Dore et al. (2019 [11]) noted that oral, intramuscular, or intranasal administration appeared to be just as effective as IV ketamine induction—a substantial advantage in a community-based practice that avoids the risks associated with intravenous administration and the necessity of the more expensive and less inviting clinical atmosphere of hospital-based programs. In this context, a therapeutic modality was developed based on the notion of two levels of ketamine dosage, resulting in either trance or transformation. The trance state of consciousness is dose dependent, and easily controlled by the therapist with sublingual oral route administration of an average of 200–250 mg (bioavailability of 10%). The trance state appeared to promote a time-out from the ordinary rigid, negative, and distorted cognitive processes associated with the depressive mind state, offering the individual relief from negativity, replaced with a felt sense of openness and mind expansion that enhanced the individual's ability to engage in meaningful therapy, improve affect regulation, increase the ability to self soothe through meditation, process trauma, and progress in depression recovery.

The transformational state was effectively induced through intramuscular administration of 80–90 mg with a bioavailability of 93–95%, often inducing a full out-of-body experience, providing a more intense therapeutic experience. The transformation state was seen as most effective when positioned as an escalating secondary phase of treatment, used at pivotal therapeutic moments to accelerate the journey to psychological growth and well-being. What the evidence in this section points towards generally is the enhanced value of ketamine treatment with psychotherapy as compared with either ketamine-only treatment or psychotherapy-only treatment. Of specific relevance here are findings from the retrospective clinical study by Dore et al. (2019 [11]) in which individuals with developmental trauma who received ketamine treatment with psychotherapy actually showed greater improvement in depression and anxiety scores than other populations—an outcome that stands in stark contrast to the typically low response rates with developmental trauma.

5. Ketamine Risks, Adverse Effects and Contraindications

Along with ketamine's excellent safety record, it is important to note short-term effects that may cause patient discomfort, abuse risk, long-term effects of ketamine dependency, and contraindications for ketamine treatment based on lack of evidence for efficacy or risks

related to comorbid conditions. Existing evidence suggests that there is a high incidence of short-term effects that should be managed and monitored, the risk of conversion from therapeutic to recreational use is quite low, there are potentially serious effects related to long-term ketamine use, ketamine appears to lack efficacy for schizophrenia-related depression, and ketamine is contraindicated in limited circumstances for patients with certain comorbidities.

Ketamine is known to cause transient increases in heart rate, blood pressure, intracranial and intraocular pressure, and increases in liver enzymes; at subanesthetic doses these effects are likely insignificant (Gorlin et al., 2016 [109]). A high percentage of patients receiving subanesthetic doses of ketamine for depression experienced transient psychotomimetic or other adverse neuropsychological effects such as dissociation, intoxication, decreased concentration, perceptual distortions, and impaired memory; these effects occur at the time of administration and resolve within hours of infusion, and evidence is absent for long-term adverse psychiatric side effects (Katalinic et al., 2013; Perry et al., 2007; Short et al., 2018 [110–112]). Other common transient effects included headache, dizziness, light-headedness, blurred vision, abnormal sensations, tingling or numbness, nausea, and drowsiness (Dugar et al., 2018 [68]; Katalinic et al., 2013 [110]; Short et al., 2018 [112]). While these effects may cause discomfort when understood as drug treatment side effects, some may be experienced more constructively when ketamine is used in accordance with its classification as a psychedelic—along with appropriate management of the treatment context and the patient’s mental stance (set and setting; Hartogsohn, 2017 [113]; Muscat et al., 2021 [13,30]).

With respect to abuse risk, the state-altering properties of ketamine have proven attractive to illicit drug users in many countries (Bonaventura et al., 2021 [114]; Kleczkowska and Zaremba, 2021 [115]). The fact that ketamine is not considered highly addictive (Kolp et al., 2014 [42]; Li et al., 2011 [116]; Zanos et al., 2018 [12]) may contribute to the virtual absence of evidence for conversion from therapeutic to illicit use (e.g., Acevedo-Diaz et al., 2019 [117]; Perry et al., 2007 [111]). However, when abused, the chronic long-term use of ketamine is associated with gastrointestinal toxicity, hepatic dysfunction, impaired gallbladder function, bladder inflammation, renal toxicity, and renal failure (Bokor and Anderson, 2014 [118]). A very small number of cases of urinary tract disorders have been reported with longer-term (usually 5+ months) ketamine prescribed for analgesia (Katalinic et al., 2013 [110]); however, to date, few studies of ketamine have assessed effects of long-term medical use (Short et al., 2018 [112]).

Contraindications for subanesthetic ketamine treatment include poorly-controlled coronary or vascular disease, pregnancy, liver dysfunction, and kidney dysfunction; injuries or conditions associated with elevated intracranial or intraocular pressure may also be contraindications depending on severity (Gorlin et al., 2016 [109]; Schwenk et al., 2018 [119]). In addition, there has been concern regarding the use of ketamine with psychotic disorders, given its tendency to increase psychosis-like symptoms (e.g., Beck et al., 2020 [120]). However, multiple studies suggest that these effects are transient and have no lasting effect (Lahti et al., 1995 [121]; Malhotra et al., 1997 [122]) and are distinctly different in nature than psychotic illnesses (Rajpal et al., 2022 [123]). More relevant for ketamine treatment of depression is evidence of its limited short-term effects and subsequent failure in patients with comorbid schizophrenia (Ye et al., 2019 [124]; Zhuo et al., 2020 [125]).

6. Discussion

As a legal substance that modulates neurotransmitter levels and brain connectivity, reduces stress-related inflammation, and induces synaptogenesis, brain plasticity, high-entropy brain states, and psychedelic experiences, ketamine as a standalone treatment has multiple mechanisms of action that are effective for treatment-resistant depression (TRD). However, given the intractable nature of TRD, ketamine treatment alone is often insufficient to produce lasting change. Treatment solely with psychotherapy demonstrates similar shortcomings, but for different reasons: psychotherapy provides new adaptive cognition

and behavior experiences, but progress is significantly inhibited by the rigid, entrenched, negative, and maladaptive response patterns with TRD patients. Ketamine disrupts these rigid patterns of neural and associated cognitive activity and provides resources for novel pathways, but requires the addition of psychotherapy to cultivate new ways of thinking and acting.

Together, trauma- and attachment-informed psychotherapy with ketamine treatment that is optimized for its multiple mechanisms of action hold considerable potential for the treatment of TRD. In combination, ketamine treatment can provide neurological and experiential disruption and reorganization of the fixed response patterns that typically inhibit psychotherapeutic progress with TRD, while psychotherapy can capitalize on these therapeutic shifts to implement a revitalized adaptive narrative in collaboration with the TRD patient. With TRD, lifelong beneficial change cannot be induced through biological, neurological, or cognitive changes alone—ketamine treatment facilitates, and also requires, a new relationship template or a new story (Castrén and Antila, 2017; Castrén and Kojima, 2017; Hajszan et al., 2005 [126–128]; Miskolczi et al., 2018; Olson, 2018; Popova, 2015; Umemori et al., 2018 [129–132]).

Clinical implementation of optimization strategies calls for some modifications to current clinical protocols. In the simplest form of ketamine treatment for depression, the patient is situated in a treatment area and ketamine is administered by some route—typically intravenous infusion, intramuscular injection, or intranasal spray, but sometimes by insufflation or orally. For comfort, dosage is calibrated to produce no more than mild to moderate dissociative effects. After a brief period of post treatment observation, the client or patient goes home. If additional treatments are scheduled, these proceed in a similar manner. This approach relies on the demonstrated biochemical actions of ketamine as a glutamate neurotransmitter modulator that also normalizes brain connectivity, stimulates synaptogenesis, and induces greater neural plasticity.

Such approaches fall short of utilizing all of ketamine’s mechanisms of action, and do not integrate ketamine treatment with needed psychosocial engagement. Changes in protocol likely to improve TRD outcomes substantially include precision calibration of ketamine dosage to ensure high-entropy brain states and the associated dissociative or mystical-type psychedelic experiences, inclusion of psychoeducation, ensuring the patient’s sense of psychological safety and conscious intentionality, attention to set and setting in the preparation for treatment, and proper timing of adjunct trauma- and attachment-informed psychotherapy to take advantage of peak ketamine-induced neurological and biological changes that support new adaptive cognition, behavior, and belief.

A simple step toward improving ketamine efficacy would be to revise basic ketamine treatment protocols by adjusting dosage toward the higher end of the subanesthetic range to ensure the induction of entropic brain states. While more research on this topic is needed, brief high-entropy states that increase brain signal diversity show promise in disrupting depression-related neural pathways and the associated rigid negative and self-critical thoughts, behaviors, and beliefs that contribute to symptoms of depression (Carhart-Harris, 2018 [36]; Carhart-Harris et al., 2014 [17]; Nikiforuk and Popik, 2013 [37]; Schartner et al., 2017 [35]). The induction of a high-entropy brain state also ensures the presence of dissociative experiences, which with proper attention to set and setting may take the form of positive, peak, or even mystical-type experiences. As previously discussed, increases in such experiences have been associated with improved therapeutic outcomes. In addition, such experiences may at times constitute deeply meaningful and transformative experiential aspects of ketamine treatment.

As there is a low end to the dose range for ketamine that is optimal in the sense that all of its mechanisms of action are operational, there also appears to be a high end. In a rodent study by Li et al. (2010 [133]), activation of mTOR signaling associated with increased neural plasticity and with ketamine’s rapid antidepressant effect was present at subanesthetic doses of 5–10 mg/kg, but not at anesthetic doses of 80 mg/kg. This suggests

that the optimal ketamine dose range is above the level that induces high-entropy brain states and below the level that induces anesthesia.

This view of ketamine dosage suggests a shift away from treatment priorities proposed by Berman et al. in 2000 [134]—who saw ketamine’s dissociative effects as a negative to be minimized and an abuse risk to be avoided. In light of evidence that ketamine’s dissociative effects and its therapeutic impacts appear to be somewhat linked, that the risk of conversion from therapeutic ketamine use to drug abuse is quite low (Acevedo-Diaz et al., 2019 [117]; Kolp et al., 2014 [42]; Li JH et al., 2011 [116]; Zanos et al., 2018 [15]), and that a higher subanesthetic dose confers the benefits of all of ketamine’s known mechanisms of action, the field of ketamine treatment should consider revising its priorities.

At the same time, because this proposed optimal dose range is narrowed by the exclusion of sub-entropic doses, and because the optimal dose for any given individual will be affected by their level of sensitivity to ketamine, improved methods will be needed to identify and deliver optimal ketamine dosage. If this approach to ketamine dosage is adopted, it is likely that multiple dosage strategies will be developed; standardized mg/kg formulas, while imprecise, may still serve some role in approximating dosage. One method for precision dosing that has been proposed by Morin (2018 [135]) employs neural imaging to track the onset, maintenance, and duration of entropic brain states in real time.

With higher subanesthetic doses and activation of deeper ketamine experiences comes need for greater attention to set and setting—referring to the mindset of the client or patient, and the context in which treatment is provided. Psychoeducation about ketamine’s multiple mechanisms of action, along with assistance that aids the client or patient choose an intention for the outcome of their ketamine treatment, will aid in the creation of a positive mental attitude. Important aspects of setting include a comfortable and welcoming and soothing treatment context, the supportive presence of a therapist during and after the ketamine experience, and an appropriate selection of music to help ensure that the experiential phenomena will retain a positive tone.

The presence of an experienced and ketamine therapy trained psychotherapist during ketamine sessions is an essential component in patient psychological safety and comfort while providing an anchor for meaningful exploration. Furthermore, psychotherapy serves to apply and integrate the ketamine experience into everyday life, while taking advantage of the disruption of negative core self-beliefs and associated narratives to install new adaptive interpersonal relationship templates, patterns of thinking and feeling, and for the support of new behaviors and beliefs.

Trauma- and attachment-informed psychotherapy can also be timed in a way that maximizes the transient biological effects of ketamine. Induced synaptogenesis peaks at 24–48 h post ketamine induction, so timing adjunct psychotherapy in this window takes full advantage of increased dendritic growth and improved neural coherence as a structural foundation for the new adaptive relational experiences to create or rewire durable adaptive neural pathways.

The introduction of ketamine as an adjunct to a safe therapeutic environment may herald the advent of scientifically informed psychotherapy. In the opinion of Carhart-Harris et al. (2014 [17]), “Mainstream psychiatry and psychology have underestimated the depth and complexity of the human mind by discounting the unconscious” (p. 18, [17]). This evaluation is evocative of the earlier theorizing of Stanislav Grof, a pioneer in the field of transpersonal psychology and an early researcher in the pursuit of using altered states of consciousness as a means of understanding the human psyche. Grof hypothesized that psychedelic research is valuable because it may serve as a direct means of examining extraordinary human experience and altered states of consciousness (Friedman, 2006 [104]). Rather than a side effect to be avoided, ketamine’s dissociative effects may be a therapeutic mechanism to be embraced as part of optimized protocols that integrate well with trauma- and attachment-informed psychotherapy.

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