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EDITORIAL

Increased Demand for Ketamine Infusions and Associated Complexities

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There has been a significant recent trend toward offering ketamine therapies for a multitude of medical and mental health diagnoses.[1] The treated conditions have included major depressive disorder,[2–5] post-traumatic stress disorder,[6–10] postpartum and peripartum depression,[11–14] anxiety,[15–18] substance abuse disorders,[19–22] eating disorders,[23–25] chronic pain,[26–31] and mood disorders[32] among others, in a continually expanding list.[33] This interest has been associated with widespread openings of clinics in the United States and world-wide that offer ketamine therapies. In addition to variability of guidelines and organizational oversight on a state-by-state basis, patients may experience a vastly different standard of care between individual treatment sites. Although a growing body of evidence does support potential benefits of ketamine for some of the disorders above, a prospective evaluation and retrospective analysis should be conducted in order to support the safe, widespread, and clinically effective use of this controlled substance.

Ketamine infusions are associated with several complexities that make them challenging to offer broadly to patients, particularly if they are to be considered safe and effective. Ketamine treatment, by definition, includes an active pharmacologic infusion with recognized hemodynamic and physiologic implications that can vary widely based on total delivered dosage, rate of infusion, consideration of medical comorbidities (particularly cardiovascular), patient volume and catecholaminergic status, and individual pharmacodynamic response.[34] Studies have suggested that discrete pharmacogenomic factors are involved in response to ketamine including a brain derived neurotrophic factor (BDNF) gene Val66Met polymorphism, cytochrome P450 family 2 subfamily B member 6 (CYP2B6) levels, and particular allelic variants.[35–37] The clinical impact of the treatment may potentially be affected by the route of administration, utilization of a racemic versus enantiomeric compound, and augmentation of secondary pharmacologic agents such as benzodiazepines or antiemetics.[38–40] In addition, there are staffing, resource, safety, and cost issues that require consideration. Each of the factors above should be weighed when planning and administering therapeutic interventions involving ketamine.

An initial requirement in considering ketamine therapy is the setting of the treatment. From a safety standpoint, one might consider inpatient administration if higher or bolus dosing is needed. Academic or inpatient facilities may have more regulatory oversight, have undergone more extensive evaluation by medical governing bodies, and have restrictive policies and procedures regarding appropriate candidates and safe administration of ketamine treatments. Unfortunately, while there are currently no data, our suspicion is that healthcare insurers are and will likely remain reluctant to cover inpatient hospitalization for ketamine treatments. Outpatient settings offering ketamine infusions can vary immensely, ranging from experienced centers that have previously specialized in infusions such as chemotherapy, to established mental healthcare facilities that may or may not have offered infusions previously, to completely de novo ketamine specialized centers employing staff with a wide range of experience and competencies. Even within the realm of inpatient care, site of service can vary from intensive care and post-anesthesia care to step-down units and general medical floors. To date, no comparative studies examining various clinical settings for these infusions have been published, and it should be recognized that inpatient

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management alone likely does not have the same impact as the training and experience of the providers administering the infusion, the resources and preparation of the individual site, and the parameters of the infusion itself. Therefore, inpatient versus outpatient status of a patient for ketamine infusions, or more specifically the defined clinical setting, warrants further examination.

Another facet that warrants discussion is the associated cost and financial structuring of the infusions. An infusion billed as an inpatient service for a patient actively managed in an Intensive Care Unit will likely fall within the monetary jurisdictions of reimbursed insurance coverage. An infusion for a chronic pain patient in the community who has severe neuropathic peripheral pain secondary to prior chemotherapy nonresponsive to traditional conservative and pharmacologic care may fall within a personal out-of-pocket payment structure. Therefore, infusions may be more financially feasible and should be considered earlier for patients managed in an inpatient setting who require multimodal pain management or those with preexisting histories of complex pain presentations. This example addresses only neuropathic pain and not the newly developing mental health indications, and these generalities do not apply to all individuals and insurance coverage plans. Review of the current outpatient landscape for medical and mental health indications for ketamine infusions has demonstrated that patients are often required to pay a higher proportion of the associated cost matched to comparative therapies, creating a substantial financial barrier to access. The FDA-recognized indications for intranasal Spravato® (S-ketamine)[41,42] offer valuable support to the efficacy of the enantiomeric formulation, but the drastically more cost-effective generic racemic ketamine lacks FDA on-label recognition for the same indication. As research has demonstrated, both mental health diagnoses and chronic pain are not limited to a particular socioeconomic class or patient population. Ensuring equal and equitable access is imperative for maximizing the theoretical benefit of this treatment[43,44]; such a lack of equitable access may be interpreted as a violation of the bioethical principle of "justice".

A third factor associated with ketamine therapy that should be acknowledged is that the drug has historically been used primarily for intraoperative anesthetic management of patients undergoing surgical intervention and secondarily for pain management, neurologic conditions, and mental health indications.[45] Understandably, due to this imbalance, there is disparate volume and quality of scientific medical literature comparing infusion protocols for these varied medical and mental health diagnoses suggested to be responsive to ketamine.[46] Research concerning mental health conditions including several depressive disorders, anxiety, suicidality, and post-traumatic stress disorder have provided a growing body of concordant evidence, while secondary indications such as substance abuse, addiction, and eating disorders are still in very early stages of scientific exploration. Routes of administration, including oral tablets, intranasal sprays, intramuscular injections, and intravenous infusions or boluses have been individually presented in various case reports without larger powered, controlled scientific trials comparing outcomes. Arguably, certain routes of administration, such as intranasal delivery, are fraught with more potential for variable drug delivery, with issues such as nasal scar tissue or patient competence in operating inhaler devices resulting in decreased exposure with already limited bioavailability.[47,48]

Unique concerns for ketamine therapy for mental health indications bring additional complexity for study, including the efficacy and durability of outcomes when offering the infusion alone versus pairing it with traditional mental health therapies such as cognitive behavioral therapy and motivational interviewing. It is paramount that we develop a standard of care to ensure patient safety and optimal outcomes. Cardiovascular complications, psychosis, or death attributed to ketamine administration outside of an inpatient setting are rare, although have been reported.[49–52] A more recent trend is home mail-order prescribing of ketamine capsules for oral administration in non-healthcare settings, which creates another host of ethical and legal issues.[53]

The United States has witnessed significant growth in ketamine clinics by a wide and diverse group of clinicians, treating disorders ranging from depression to PTSD to pain. To advance the science and protect patient safety, the scientific community must collect and publish meaningful data to better elucidate optimal dosages, infusion rates, clinical settings, adjuvant therapeutics, expected side effects, relative contraindications, and further prospective responsive conditions amenable to treatment. It is likely that there will be a need for treatment in both inpatient and outpatient settings, and whether there are any advantages to either will certainly depend on the training and experience of the providers. As the virgin fields of Psychedelic Medicine and Psychedelic-Assisted Therapy expand, maintaining a high degree of scientific ethics and standards represents a viable pathway to the most sustainable and beneficial practices.

Ketamine therapy is not and should not be touted as first-line treatment without impartial investigation and study. It would be helpful if the health insurance industry supported this potential emerging therapy while the evidence basis expands. Although scarce, research related to the administration of ketamine is underway and should help frame safe treatment guidelines and promote payor policies to support patient access. Arthur Schopenhauer is quoted as opining, "all truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident"[54] (p. 451). Only time – and scientific effort – will determine whether ketamine treatments and ketamine assisted therapy will be recognized as viable medical and psychological treatments.

Disclosure

Dr Evan Peskin is a co-founder of a mental healthcare organization that treats depression, PTSD, anxiety and uses ketamine-assisted therapy. He does not actively participate in any direct clinical care through this company. Dr Michael E Schatman is a research consultant for Modoscript and a member of the scientific Steering Committee of Collegium Pharmaceutical, outside the submitted work. The authors report no other conflicts of interest in this work.

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