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Interventional Psychiatry Associates

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Making Ketamine Work in the Long Run

Terrence S. Early¹

Interventional Psychiatry Associates
Santa Barbara, CA, USA

Treatments such as ketamine psychotherapy face substantial financial and regulatory obstacles to dissemination into widespread use. Newly patented medications are able to generate enough capital to pay for studies required for FDA approval, personnel to apply for coverage on insurance plans, and marketing to establish a successful launch. Ketamine is an older drug with considerable evidence of efficacy for treatment resistant depression, and almost 50 years of data concerning safety as an anesthetic agent. However, it can no longer be patented, so there is no incentive for pharmaceutical companies to help get it into widespread use. In this paper we discuss some of the complex issues surrounding use of ketamine in the outpatient setting and share information and practice pearls that have been gathered through communication with other practitioners and through direct experience with over 1000 treatments involving 120 patients in the last eight years. The safety and appropriateness of intramuscular ketamine treatment in the outpatient psychiatric office is discussed. We hope to help proponents of effective mental health interventions navigate the actual and potential challenges involved in safe application of this treatment option outside of hospital-based programs.

Keywords: *Ketamine, psychotherapy, treatment-resistant depression, post traumatic stress disorder, facilitated psychotherapy, dissemination*

Ketamine shows considerable efficacy for rapid symptom relief in treatment resistant depression, as well as an exceptional safety record as an anesthetic agent with over nearly 50 years of clinical use. Based on this evidence, ketamine appears to be a safe and effective treatment for depression in outpatient settings. At the same time, there are financial and regulatory obstacles to dissemination of ketamine into widespread use as a psychoactive medication. Newly patented medications that show promise are typically able to attract capital investment to pay for studies required by the Food and Drug Administration (FDA) in order to be approved for a specific use that will then be covered by insurance plans. However, since ketamine can no longer be patented, there is little financial incentive for pharmaceutical for psychiatric applications. Given the great need for effective new antidepressant strategies, and the regulatory situation of ketamine treatment for mood disorders, the dissemination of information regarding its promising efficacy will necessarily proceed through channels that are professional rather than commercial.

This report is based on the experience of the author and a colleague (Jeffrey Becker) who have had direct experience with over 1000 ketamine treatments

conducted with 120 patients over the past eight years; in addition, the author is in communication with other practitioners involved in ketamine treatment. Based on this clinical experience, the current paper reports on the actual and potential challenges involved in safe application of intramuscular ketamine treatment for psychological conditions such as depression in outpatient settings.

Early's interest in ketamine for depression began after studying another anesthetic treatment approach that never became mainstream—halothane isoelectric therapy, using sevoflurane. Langer, Neumark, Koinig, Graf, and Schoenbeck (1985) originally reported that a related anesthetic agent, isoflurane, had a robust antidepressant effect comparable to electroconvulsive therapy (ECT) in an open-label trial. These results were later replicated in a double-blinded trial (Langer et al., 1995). Early found similar results with an open label trial of sevoflurane therapy and a blinded comparison to ECT (Early et al., unpublished results). Langer's isoflurane results were recently replicated by Weeks et al. (2013). Halothane isoelectric therapy produces a period of isoelectric electroencephalography (EEG) similar to the state that follows an ECT-induced seizure,

but without seizure-related cognitive side effects. Early found it impossible to disseminate the technique, since there was no mechanism to pay for anesthesiology and hospital time to provide the treatment and no way to obtain insurance coverage. Ketamine offered a less expensive and less invasive alternative, and Early began using it in 2007.

Becker examined the potential of ketamine on depression in medical school and psychiatric residents at UCLA. While looking at the NMDA receptor related neurological substrates of transcendent experience it became clear that ketamine might provide relief from depression. Multiple clinical studies now confirm this (Mathews & Zarate, 2013).

A Mandate for New Treatment Options

Ketamine represents the first new receptor-based treatment for depression in decades and has the potential to provide profound relief from great suffering. In contrast with monoamine oxidase inhibitors and tricyclic antidepressants that typically take weeks or months to reach full effectiveness—and too often are not effective at all—ketamine appears to provide rapid relief from symptoms of depression, even in treatment-resistant cases (Zarate et al., 2006; Diazgranados et al., 2010). Ketamine may represent a breakthrough in the broader treatment of depression by offering a novel pharmacological strategy focused on the glutamatergic system, which may be more central to the neurobiological mechanisms of mood disorders than the serotonergic, noradrenergic, and dopaminergic systems typically targeted in conventional pharmacological treatments for mood disorder (Sanacora, Zarate, Krystal, & Manji, 2008). There is evidence that ketamine impacts the N-methyl-D-aspartate (NMDA) receptor complex, which may itself mediate the delayed relief in conventional treatment strategies; targeting this system directly may represent a significantly more efficient approach to the treatment of depression, and of mood disorders more broadly, with a potentially large impact on public health (Zarate et al., 2010).

The use of medications as psychotherapeutic adjuncts has a long history in psychiatry (Kolb, 1985). Barbiturate-facilitated psychotherapy, introduced by Blackwenn (1930), was practiced for over 80 years to treat conversion symptoms and *traumatic war neurosis* or PTSD. The amytal and pentothal interviews were developed later, along with other forms of drug-facilitated psychotherapy (Grinker & Spiegel, 1945;

Horsely, 1943; Lindemann, 1932). Sometimes called abreactive psychotherapy, this approach was reported to produce rapid relief of classic symptoms such as flashbacks, nightmares, hypervigilance, and autonomic hyper-reactivity (Hoch, 1946). Shovrin and Sargant (1947) introduced an excitatory abreactive therapy using ether and a variety of other agents, which later were used to facilitate learning during psychotherapy (Sargant & Slater, 1972).

Clearly the psychological effects that occur with ketamine use as an antidepressant treatment touch similar themes. While these older treatment techniques were in danger of becoming a simple footnote in psychiatric history, the improved safety and efficacy of ketamine may eventually provide PTSD patients with a viable treatment model in this mode. Indeed, Feder et al. (2014) recently reported a robust effect on core symptoms of PTSD with ketamine treatment.

However, perception of safety is likely to be one of the largest challenges to broader acceptance of ketamine's role in psychiatry and the adoption of this treatment within outpatient psychiatric offices. Despite the fact that the outpatient psychiatric office is likely to be the most efficient and effective in delivering treatment to those in need, currently the majority of participating practitioners are anesthesiologists or are at hospital-based programs. The author hopes to clarify issues that will allow broader adoption of this effective treatment option in outpatient psychiatric clinics. Fear regarding safety, both founded and often unfounded, should be balanced by clinical evidence and an awareness of the immense need for effective treatment delivery.

Safety of Low-Dose Ketamine Therapy

Intramuscular ketamine is generally considered safe at subanesthetic doses, even in non-medical settings. When used to induce general anesthesia, ketamine is generally administered at a dose range of 3-8 mg/kg IM or 1-4.5 mg/kg IV. The usual maintenance dose for ketamine is an IV bolus of 0.1-0.5 mg/kg/minute. Ketamine is often combined with other anesthetic agents (such as propofol), and the dose is typically less in this situation. Even at doses used for general anesthesia, ketamine is associated with normal pharyngeal-laryngeal reflexes, and usually cardiovascular and respiratory stimulation, though there may occasionally be a transient and minimal respiratory depression. In the low-dose range 0.5-1 mg/kg, patients experience *conscious sedation*, which means they remember the experience and respond

to stimuli during the session. The physiologic effects of subanesthetic ketamine provide a large margin of safety in the treatment of depression through preservation of responsivity to the practitioner, cardiac stimulation, and maintenance of respiratory function and the gag reflex (Hass & Harper, 1992).

Early and Becker have found use in the outpatient setting to be remarkably free of adverse effects. Nausea and occasional vomiting are the most common negative effects, which are minimized by fasting 4-6 hours prior to treatment or through the use of ondansetron. Anxiety upon arrival at a session is common and is managed through pretreatment discussion, clonidine and/or, if needed, oral lorazepam. Blood pressure increases of 5-10 mm/hg diastolic and 5-15 mm/hg systolic are routine while heart rate increases of 10-20 bpm are seen less commonly. We have not seen laryngospasm, severe hypertension, respiratory distress, or severe agitation in any of our cases. Our experience is consistent with the experience of other clinicians with whom we consult and with existing research.

Ketamine's large safety margin provides reassurance in settings where anesthesiologists and monitoring are not available, such as the battlefield, veterinary medicine, dentistry, and pediatric anesthesia. O'Hara, Ganeshalingam, Gerrish, and Richardson (2014) reported no adverse cardiac or respiratory events after 131 sedation procedures by nursing with oral ketamine, which is known to be more unpredictable than IM or IV routes. In this study, an anesthesiology consult was only required to further deepen sedation or deal with excessive sedation. The National Clinical Guideline Centre recommends that anesthesiology be present only when ketamine is administered with opiates (National Institute for Health and Care Excellence [NICE], 2010). Even in full anesthesia, reflecting doses up to 10 times those used for depression (e.g., 2 mg/kg IV to 5 mg/kg IM), ketamine is remarkably safe. A review of over 70,000 published anesthesia cases reported only one ketamine-related fatality occurring in a seriously medically compromised individual (Strayer & Nelson, 2008).

Given the confusion between full anesthesia and conscious sedation a few issues do deserve further clarification.

Respiratory Drive

Bourke, Malit, and Smith (1987) reported minimal changes in respiratory drive with low-dose

IV ketamine and a 5% drop in minute ventilation (l/min) at 1.08 mg/kg. Mankikian, Cantineou, Sortene, Clergue, and Viars (1986) reported no significant change in respiratory functional residual capacity and minute ventilation or tidal volume after full anesthetic induction with 3 mg/kg. Morel, Forster, and Gemperle (1986) reported increased respiratory drive, stable arterial oxygen saturation, and end-tidal carbon dioxide concentration with 1 mg/kg delivered IV. In addition, bronchodilatory effects of ketamine, likely second to circulating catecholamines, have been observed in canine models. Ketamine has been used successfully in pediatric status asthmaticus to facilitate intubation (Reich & Silvy, 1989). While salivary secretions increase with ketamine-induced full anesthesia this does not appear to be a problem in conscious sedation due to intact swallow reflexes and the vastly lower doses involved. In short, respiratory drive remains intact with low dose (and even high dose) ketamine (Hass & Harper, 1992).

Blood Pressure and Intracranial Pressure

It is understood that ketamine can increase heart rate and arterial pressure (Hass & Harper, 1992) at least partially through increases in free norepinephrine (Zsigmond, Kelsch, & Kothary, 1973). Hypertension should therefore be well controlled prior to treatment. Mild increases in intracranial pressure have been noted with ketamine, and Haas and Harper (1992) saw this as a contraindication for use in vulnerable individuals.

Emergence Reaction

Ketamine's psychological effects are often reported in anesthesia and surgery research as an adverse effect. While these effects may actually be inherent to antidepressant effects, ketamine and other dissociative drugs have been reported to exacerbate psychotic symptoms in schizophrenia. While Carpenter (1999) reported a lack of significant negative effects after administration to 12 subjects with stable schizophrenia, ketamine is not likely to be indicated for treatment in cases involving primary psychosis.

Screening and Contraindications

Given physical safety considerations and the unique psychological effects of ketamine, treatment with minimal monitoring is relatively contraindicated in the following physical and psychiatric conditions:

- Uncontrolled Hypertension
- Congestive Heart Failure
- Other impaired cardiac status

Making Ketamine Work

Severe Chronic Obstructive Pulmonary Disease (COPD)
Severe Obesity
Increased intracranial or cerebrospinal (CSF) pressure
Schizophrenia and Schizoaffective Disorder
Severe or Primitive Personality Disorders

Patient Selection and Evaluation

During an initial evaluation, psychiatric and medical history is reviewed along with lab work, past treatment history, and history of substance abuse. Issues relating to cardiac and pulmonary history, prior adverse response to anesthesia, evidence of sleep apnea, and history of primary psychosis are assessed. The patient is considered a candidate for a ketamine session if they have already failed multiple antidepressant trials and specific contraindications do not exist. If the patient is severely ill or suicidal, ketamine may be the treatment option most likely to produce rapid, if temporary remission.

Consent for Treatment

A thorough informed consent process educates patients to the psychological effects of treatment and addresses the expectations and questions of the patient and their family. Topics for discussion include acute and residual side effects, potential risks and benefits, the off-label nature of the treatment, and the research supporting ketamine's use in the treatment of depression. The scope and duration of potential positive effects should be discussed with every patient. Discussion regarding the frequency and number of treatments required can be informed by the naturalistic outcomes seen in ECT, in that some patients respond after relatively few treatments while others require a longer course of treatment.

The consent process helps to set realistic but positive expectations, which may be an essential element to success. With proper control of the physical environment (e.g., dim light, music, reclining position) the treatment experience is usually described by patients as meaningful and positive. Psychotherapy is an essential part of the process of recovery and is recommended to every patient receiving ketamine treatment. Our considerations regarding therapy are beyond the scope of this paper, however, and will be provided in another forum (see Becker, this issue, p. ____).

The Ketamine Treatment

Patients are advised to take morning medications, particularly antihypertensive medication given

ketamine's tendency to increase arterial pressure. Our list of medications that are held off from use for at least 24 hours prior to a ketamine session include:

Lamotrigine – due to its ability to block the psychological effects of ketamine
Bupropion – due to observed anxiety and mild agitation during treatment
Stimulants – for similar reasons as bupropion and blood pressure elevation

These medications may be resumed later in the day after the treatment session concludes.

When patients arrive there is discussion as to their current psychiatric status and any appropriate psychological assessments are completed (e.g., Beck Depression Inventory), though particularly anxiety-provoking discussions are avoided. Patients are asked to recline and spend time deep breathing as the treatment is made ready and blood pressure is taken. Lights are dimmed and soft music is provided if the patient has not opted to bring their own. We remain with the patient monitoring status, blood pressure and safety considerations for 60-90 minutes during the active period of the treatment, and patients will spend additional time as needed to fully recover.

The setting is designed to facilitate a sense of safety, comfort, and warmth. This is a lesson well learned during early studies of psychedelic psychotherapy that found the setting to contribute much to the effect of treatment. There is stark contrast between ketamine experienced in a florescent hospital setting surrounded by detached strangers with a clinical stance versus a warm and comfortable setting accompanied by loved ones. This may be in part why we rarely see anxiety or dysphoria to any significant degree. Patients usually lie quietly during the session as we sit nearby to offer assistance as needed.

Monitoring and Safety During Therapy

Ketamine produces conscious sedation within 3-5 minutes at 0.5 mg/kg IM, which means that patients are responsive to verbal and physical prompts. Intravenous infusions over 45 minutes are associated with a more gradual alteration in consciousness, with altered awareness usually reported within 10 minutes. In every patient, vital signs and mental status should be monitored before, at least once during the session, and after the treatment concludes with an auto-inflatable pressure cuff. To reduce the incidence of nausea

and vomiting we recommend fasting for eight hours before the initial treatment, reducing to four hours for subsequent treatments in individuals without evidence of delayed gastric emptying and who establish tolerance to treatment side effects. Patients are advised to arrange for other transportation home and agree not to drive after treatment until they have slept a full night.

Some patients with controlled hypertension will present with elevations due to anticipatory anxiety. In these cases treatment is rescheduled and a prescription for clonidine 0.1 or 0.2 mg PO 1-2 hours before arrival is given. Clonidine is generally sufficient to reduce blood pressure within protocol range, consistent with Tanaka and Nishikawa (1994) who reported that administration of clonidine 5 mcg/kg with ketamine in full anesthesia abolished increases in arterial pressure seen in controls. While it is also possible to use propranolol in these situations, this may diminish the bronchodilatory effect of ketamine (Reich & Silvey, 1989) and thus is an inferior option and should not be used in patients with asthma.

While we have not witnessed severe anxiety or agitation in our clinic lorazepam or alprazolam available for oral or IM administration is always available. Ondansetron 4-8 mg ODT or 2 mg liquid for IM injection is also available for patients who experience nausea despite fasting. Patients are advised to use acetaminophen or ibuprofen for any headaches that may occur after treatment. We also recommend that patients take 500 mg of n-acetyl cysteine (NAC) prior to arrival to support glutathione production.

Dosing and Duration of Effect

A target dose of 0.5 mg/kg IM may be initiated in the first session at the clinician's discretion or the initial dose may be reduced by 25-50% in potentially sensitive individuals. The total dose may also be divided and separated by 10-15 minutes to reduce the speed of onset and peak blood levels. Some patients have required increased doses to improve efficacy.

Peak effects are felt within the first 10-20 minutes and patients are usually mostly recovered 90 minutes after injection. Some cognitive fog and fatigue may linger for some hours, or until sleep resets brain function.

Beneficial Effects

The medical literature now provides extensive reports of clinical efficacy. The following are clinical impressions based upon a broad range of patients and treatment outcomes. Beneficial psychiatric effects on

depression, anxiety, and pain are usually seen during and immediately following treatment, though some patients begin to notice effects up to 48 hours later. Patients who ultimately respond will almost always have a robust antidepressant effect with the first treatment, though this is not always the case.

In our experience, the duration of the effect on depression is generally from one to four weeks. For unclear reasons in some cases the effect fades after only a few days while in others it may last for months. As such, frequency of treatment must be adjusted to effect—some patients only require a single session to resolve a depressive episode while others may require a series of treatments over a few weeks or months, similar to the frequency of acute and maintenance ECT. We generally treat patients once every 2-4 weeks to maintain remission if depression recurs, concurrently adjusting medications and psychotherapy to achieve a lasting remission.

Patients with both unipolar (typical and atypical) and bipolar depression often respond to ketamine offered in our clinic. We have seen patients with psychotic depression improve with resolution of psychosis. But, we have also observed a tendency for mania to become more pronounced with ketamine. On two occasions, we have had patients who failed to respond to low dose treatment go on to respond to a higher dose (3-8 mg/kg) received during an unrelated surgical procedure. We have repeatedly seen rapid and robust remission of severe suicidal ideation, consistent with reports from preliminary research on ketamine treatment (Price, Nock, Charney, & Mathew, 2009).

It is notable that even when the strong acute effect on depression fades there tends to be residual improvement in mood that persists. In addition, we suspect that it is helpful for patients to experience an interval of recovery, however brief, after prolonged periods of depression. They are generally encouraged to know that recovery is possible. Our patients routinely report that ketamine provides them hope, reminding them what it feels like to be free of depression.

Storage and Documentation

Ketamine and syringes for IM delivery may be ordered for office use through a pharmacy or a medical supply company. Ketamine should be stored under double lock-and-key as per Drug Enforcement Administration (DEA) regulations for in-office storage of scheduled medications. A log should be kept recording receipt and use of medication including: date, amount received,

amount used, amount wasted, expired medication that is destroyed, vial number, patient name, indication, and any other relevant comments.

Towards a Mechanism of Action-Facilitated Emotional Learning

Enduring psychological change often requires facing emotionally painful topics, and exposure can be a powerful treatment technique. We have found that ketamine therapy facilitates this process in the days following treatment, when patients encounter anxiety cues during exposure therapy with reduced anxiety and defensive responses. They discuss difficult areas in psychotherapy with notably improved comfort and insight.

It seems likely that ketamine may intervene specifically at the crossroads of extinction and reconsolidation, two processes capable of altering the response to fearful memory (Centonze, Siracusano, Calabresis, & Bernardi, 2005; Schiller, Raio, & Phelps, 2012; Soeter & Kindt, 2010).

Extinction of the response to fearful memory can occur through prolonged exposure within a safe environment. This allows a competing extinction memory associated with safety rather than fear to become associated with the trauma cues. However, short exposure to fearful memory can instead initiate reinforcement of a pathologic response through reconsolidation (Schiller et al., 2012). With severe PTSD, recall of the fearful memory during therapy often produces freezing and dissociation, and the resulting brief recall may reconsolidate and reinforce the memory, rather than produce extinction (Centonze et al., 2005; Myers, Carlezon, & Davis, 2011; Schiller et al., 2012).

In the days following ketamine therapy patients typically find it easier to discuss and encounter reminders of previous trauma. They do not generally experience the extreme anxiety and freezing produced by previous recall of the traumatic memory. Ketamine attenuates the anxiety response produced by recalling the traumatic memory, and thus patients engage in more extended discussions of the traumatic memory, potentially allowing for the development of extinction memory.

A Second Mechanism of Action-Accelerated Self-Reliance

Treatment-resistant patients often show complex medical and psychiatric co-morbidity, social isolation and avoidant behaviors that point toward attachment difficulties. Attachment trauma, a common

feature of PTSD (Courtois, Ford, Herman, & Van der Kolk, 2009), and perhaps of treatment resistant patients in general, inhibits recovery through its detrimental effects upon interpersonal intimacy and trust, self-conception, and life-perspective. It has become clear in the last few decades that the neurobiological substrate of change through psychotherapy includes improvements in attachment patterns (Cozolino, 2010).

An important aspect of psychotherapy is the provision of a mature psychological model as an attachment structure that permits the development of new and secure attachment patterns within and, eventually, outside of the therapeutic relationship. The therapeutic bond acts as proxy for the patient's relation to the Self (the personal and transpersonal subconscious—capitalized here on in the tradition of Jung to distinguish as the counter to ego) until authentic restitution can develop, bringing this process inward to allow a new orientation toward the outside world. Unfortunately, this process often advances so slowly as to be inconsistent with the resources of the patient. We have come to see ketamine treatment as an accelerant to this mysterious process. Perhaps through its capacity to engender self-acceptance, intuition, and awareness, patients more rapidly begin the process of relying upon themselves, in a deep sense, rather than the therapeutic bond.

Group Therapy

We provide a didactic component in a group therapy setting, discussing topics such as the neurobiology of depression, pain, and anxiety, as well as an introduction to effective psychotherapy and pharmacotherapy techniques for addressing psychological symptoms. As an organizing principle, ketamine patients participating in group therapy are asked to focus their efforts in four areas.

1. Automatic Scripts

The depth of each patient's experience with ketamine therapy usually exposes some of the cognitive distortions they experience on a daily level. Patients often have the nature of their limited and disengaging programmatic scripts revealed to them by the experience. They may appreciate a new venue to consider and practice new scripts. Patients complete a script/schema inventory and the group may be educated about cognitive-behavioral links as leverage points for growth.

2. *Mindfulness*

Mindfulness meditation has been shown to improve attention and emotional self-regulation, as well as enhancing white matter integrity around the anterior cingulate gyrus, a cortical component of the voluntary attention system (Tang, Lu, Fan, Yang, & Posner, 2012; Tang & Posner, 2009). Mindfulness skills are an important part of effective psychotherapy for a broad variety of psychiatric conditions (Omidi, Mohammadi, Zargar, & Akbari, 2013; Teasdale, Segal, & Williams, 1995), and we find them helpful in this setting as well. We commonly use the book, *Mindfulness: A Practical Guide to Finding Peace in a Frantic World* (Williams & Penman, 2011) to educate about daily practice techniques. In addition, we practice ten-minute mindfulness meditation techniques during the group session.

3. *Attachment / Compassion*

We find that education regarding attachment theory can help patients identify their specific attachment patterns and facilitate insight-oriented change. After years of observing treatments with ketamine therapy, we believe that identifying the effect of attachment issues on symptoms such as depression and social detachment is particularly valuable. Here, we find discussions on compassion and the use of loving-kindness or Metta Bhavana Meditation helpful (Hofmann, Grossman, & Hinton, 2011). We also discuss self-compassion, using exercises detailed by Paul Gilbert (2009) in *The Compassionate Mind: A New Approach to Life's Challenges*.

4. *Life Narrative / Mythic Reframing*

Patients often experience substantial changes in areas such as self-concept, life goals, and personal understanding of life-meaning. We encourage discussion of authentic truth and meaning and support efforts to reframe major themes and archetypal forces within their lives. Some patients experience this process as occurring within a particular religious tradition, but others do not. We do not think it is the role of the therapist to indoctrinate patients into any particular religious tradition, but it is important to acknowledge the spiritual nature of their efforts to gain a deeper understanding of who they are. Ketamine permits a “panoramic” view of life, not only one’s own life but the life of others.

Treatment Beyond Depression

Major depression is a significantly heterogeneous disorder that is often co-morbid with other psychiatric conditions. As such we have been able to observe the positive effect of ketamine upon a number of other disorders.

Use in Pain

Chronic pain frequently becomes associated with depression and anxiety. Fortunately, ketamine has numerous beneficial effects on pain and many of our patients report that ketamine is the most effective treatment they have used for chronic pain. Complex regional pain disorder (CRPS), also known as reflex sympathetic dystrophy, is notoriously difficult to treat but sometimes responds to high-dose ketamine protocols offered in the United States and Germany (Schwartzmann et al., 2009). In five CRPS patients we have also observed low-dose ketamine providing noticeable acute pain relief. Three of these patients gradually experienced a permanent overall reduction in pain intensity over several months. We have seen ketamine improve chronic daily headaches, new daily persisting headache, neuropathic pain, and chronic pelvic pain.

Use in PTSD and Anxiety Disorders

Following ketamine sessions, our patients with PTSD often report reduced reaction to trauma cues, with effects usually lasting from one to four weeks. During this “grace period” patients seem to be more capable of tolerating graded exposure. One patient, who was abused and tormented with rodents as a child, could not be near a rodent without experiencing dissociative anxiety and flashbacks. Following ketamine, she was able to enter a pet store and touch pet rats without severe anxiety. We have seen patients tolerate discussion of emotionally distressing events without feeling overwhelmed, and therapists often report making considerable headway in sessions scheduled a few days after ketamine treatment. Patients with social phobia and generalized anxiety disorder have generally reported benefits distinct from the antidepressant effect as well. While we have not treated enough patients with obsessive-compulsive disorder (OCD) to have an opinion, two patients with body dysmorphic disorders did not show any appreciable effect with over six sessions.

Eating Disorders

We have observed one patient with severe mixed anorexia and bulimia of 12 years duration recover over the course of 12 months with treatments occurring

once per week for a total of 48 treatments. Purging and restriction patterns resolved completely. Psychological growth was demonstrated through increasingly meaningful and rewarding interpersonal relationships and an ability to tolerate a healthy romantic dyad for the first time. Mills, Park, Manara, and Merriman (1998) reported a 70% response rate with multiple, 10 hour extended infusions of a low dose of ketamine in a group of patients hospitalized with anorexia and bulimia.

Conclusion

Ketamine treatment shows great potential as a new pharmacological strategy in the treatment of depression in that it produces relief of symptoms rapidly, even in treatment resistant cases. Ketamine appears to target the glutamatergic system that may be central to the neurobiology of mood disorders, and may represent a more direct treatment strategy than that offered by more conventional approaches. Its excellent safety record has been demonstrated over decades. Despite potential regulatory hurdles given that the drug cannot be patented, and thus poses little opportunity for pharmacological industry profit, the clinical observations presented here are offered with the hope that ketamine treatment for depression may find its way into more widespread use in outpatient settings.

Note

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About the Author

Terrence Early, MD, is a 1982 graduate of the Duke University School of Medicine and completed his psychiatric residency at the Washington University School of Medicine in 1986. He became interested

in novel treatments involving anesthetic agents for refractory mood and anxiety disorders, and initially studied high dose sevoflurane therapy as an alternative to ECT while at the University of Texas Medical Branch in Galveston. He received grants from Narsad and the Stanley Foundation to study this beginning in 1999. He became interested in ketamine in 2007, when he was on the faculty at the Baylor College of Medicine department of psychiatry. At Baylor, he collaborated with a pain specialist, Dr. Everett Edmundson, to provide IV ketamine to patients with pain and psychiatric illness. Since 2007, he has been in Santa Barbara, California, where he began doing intramuscular ketamine in a private psychiatric practice in 2009. His goal has been to provide ketamine in a safe, effective, and affordable manner for psychiatric illness, and to disseminate this extremely valuable treatment.