KEP-P2 Treatment Inspiration

At the current treatment facility, inpatient continuous ketamine infusion was delivered as a standard of care treatment for patients with intractable Complex Regional Pain Syndrome (CRPS), Type I and Type II. In 2014, a 29 year old Hispanic male patient with previously diagnosed PTSD was admitted to the Medical Intensive Care Unit (MICU) for a 5 day continuous ketamine infusion to treat upper extremity CRPS, Type II secondary to a combat-induced gunshot wound. During the infusion, medical staff noted an uncharacteristic lability and verbal expressiveness of the patient talking about his combat experiences during regular nursing check-ins. This revelation prompted the treatment team to consider the possibility of interdisciplinary care that included psychotherapy. This began a process of integrating psychotherapeutic interventions for patients on short-term ketamine infusion for the treatment of both chronic pain and PTSD. While research investigating pharmacolgical interventions for PTSD has mixed findings, there has been some theoretical proposals and evidence for the use of ketamine for reduction of symptom severity (1-3).

KEP-P2: Patient 1

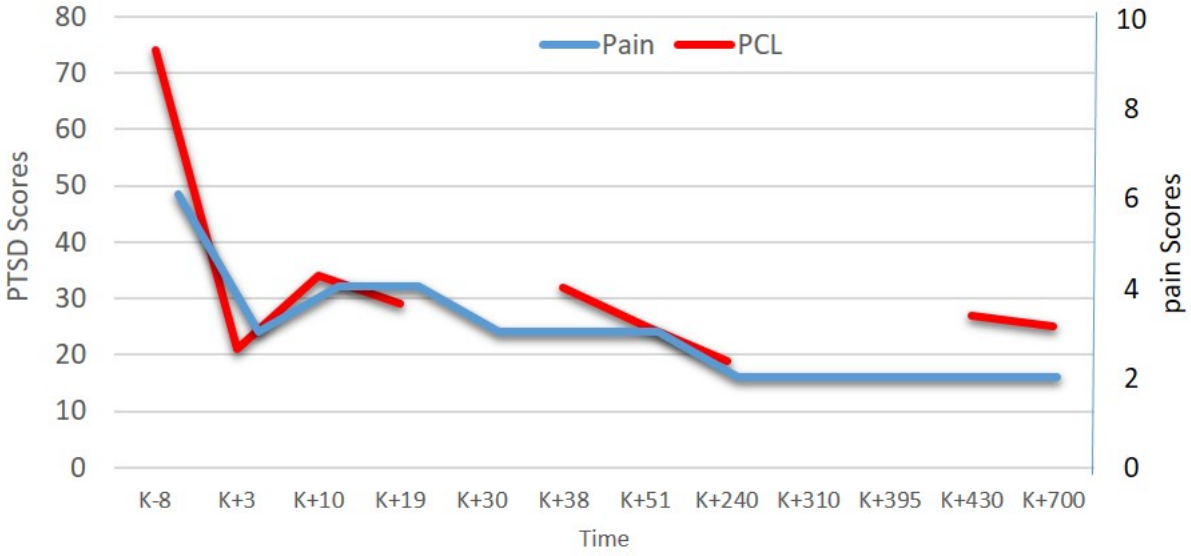
The first case was a 33 year old Caucasian female civilian spouse of a US Army service member admitted for a disabling lower left extremity CRPS and chronic lower back pain that preceded the onset of PTSD secondary to a subsequent sexual assault. Her medical history included L4-L5 spinal fusion, a left knee micro fracture surgery for a torn meniscus, two failed Spinal Cord Stimulator (SCS) trials, and spondylolisthesis and herniated disc from a cheerleading accident. She had bronchiectasis with a right upper-lobectomy and had been oxygen dependent for more than five years resulting in her placement on a lung transplant list approximately two weeks prior to admission. She also suffered from Reynaud's syndrome from childhood, bulimia, and bradycardia associated with syncope spells. She had been unable to work for two years at the time of the treatment due to pain severity. At admission the patient was maintained on fentanyl patch (75 mcg/hr/72 hrs) and oral hydromorphone (32 mg/day). Before beginning ketamine treatment, this patient's PCL-C was a 74 and her average pain rating ranged 6-8 out of 10 on the NPRS.

Over the four days of ketamine enhanced psychotherapy, she was able to discuss her sexual assault and change her previous cognitive distortion involving a sense of worthlessness. By the final day of the ketamine enhanced psychotherapy, her PCL scores dropped to only 21 (i.e., below a diagnostic threshold) and her pain ratings maintained at 0 of 10 points for the duration of the ketamine infusion. Following discharge, her PCL scores remained fairly stable and continued below a diagnostic threshold, with a final PCL score of 25 approximately 23 months post-ketamine. See Figure 1 for pain

and PCL scores as measured in psychotherapy sessions pre-ketamine and 23 months post-ketamine. In terms of pain medications, she was discharged on methadone (5mg/day) and tizanidine (4mg tab, as needed) for pain management and was regularly monitored by her pulmonologist for respiratory therapy. She also continued psychotherapy with the first author focused on changing maladaptive beliefs, insomnia reduction, and behavioral activation.

Patient 1 completed 11 psychotherapy sessions in the 23 months after ketamine discharge, including 6 sessions in the first two months following the ketamine infusion and then another 5 booster psychotherapy sessions over the final 21 months before she was discharged from psychotherapy. The purpose of the psychotherapy booster sessions was to assess progress in terms of the patient's coping strategies, resilience, and quality of life. Throughout the approximately two years of follow-up, the patient's PCL scores remained low (ranging from 19-34) indicating a true remission from PTSD. The only noteworthy medical event for this patient occurred on Day 31 after ketamine discharge when the patient was hospitalized for syncopal fainting and loss of consciousness related to a medically unexplained pulmonary comorbidity. However, by Day 52 her pulmonary function had improved sufficiently for the pulmonologist to recommend oxygen supplementation on an as needed basis and the patient was removed from the lung transplant list. At approximately 9 months after the ketamine protocol oxygen supplementation was discontinued completely. At 13 months after the ketamine protocol the patient returned to part-time work and by 14 months she had discontinued the use of methadone. The patient remained off of opioids through a final post-ketamine follow-up at 23 months, returning to work full time for the first time in over four years.

Figure 1: Patient #1 PTSD and pain scores pre and post-ketamine



K=time of ketamine infusion discharge; +/ - represents number of days pre (-) or post (+) ketamine infusion discharge. PTSD Scores are from the PCL, and pain scores are from the NPRS.

Patients included in this case series were Active Duty Army (n=5), Retired Army (n=2), Active Duty Marine (n=2), Active Duty Air Force (n=1), and a civilian military spouse (n=1). Seven patients were previously diagnosed with Traumatic Brain Injury (TBI) and two were diagnosed with Bipolar II Disorder. In terms of education, seven of eleven patients had bachelor's degrees and five of these seven also had a Master's degree. With regard to trauma types, 10 reported combat related traumas, with nine of those occurring during deployment to Iraq, Afghanistan, or Syria and one from Vietnam. Of these 10 patients, one female reported a sexual assault trauma and another female reported physical and emotional abuse – both of which occurred prior to the combat trauma. Three of the eleven patients were female and the age of all patients ranged between 25 and 69 years old. Of note, three of the patients had lower extremity amputations and two were Special Forces operators.

The 11 patients in this case series are summarized below:

Patient 1	
Demographics	**33 year old Caucasian female; civilian spouse of military member**
Background	**Unable to work for two years due to multiple medical conditions**

Date of KEP-P2	**Summer, 2014**
Presenting Complaints	**Left lower extremity CRPS, Lower back pain, PTSD secondary to sexual assault**
Pre-ketamine pain medication	**Fentanyl patch (75mcg/hr/72hrs), oral hydromorphone (32 mg daily dose)**
Average daily pain	**6/10 (pre-ketamine); 3/10 (post-ketamine)**
PTSD Checklist (Civilian) score	**74 (pre-ketamine); 21 (post-ketamine)**
Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**10 (pre-ketamine); 7 (post-ketamine)**
Relevant Medical History	**Spondylolisthesis & herniated disc secondary to cheerleading accident** **Complex Regional Pain Syndrome, Type II** **Left knee micro-fracture surgery for torn meniscus** **Reynaud's syndrome (childhood)** **Bradycardia with periodic fainting (syncope)** **Bulimia** **L4-L5 spinal fusion** **Bronchiectasis with right upper lobectomy (oxygen-dependent since 2008)** ***Placed on lung transplant list prior to ketamine infusion**
Comments	**The patient remained off of opioids through a final post-ketamine follow-up at 23 months, returning to work full time for the first time in over four years.**

Patient 2	
Demographics	**25 year old Asian/Pacific Islander male; Active Duty Army infantryman**
Background	**Involved in Improvised Explosive Device (IED) explosion in Afghanistan in 2012 resulting in lower extremity limb salvage; he was pending elective below the knee amputation, which he received following the ketamine infusion**
Date of KEP-P2	**Fall, 2014**
Presenting Complaints	**Lower extremity and lower back pain, PTSD secondary to military trauma (IED explosion)**
Pre-ketamine pain medication	**oxycodone HCL (20mg daily dose), oxycodone HCL, Extended Release (30 mg daily dose), hydroxyzine (75 mg daily dose)**
Average daily pain	**8/10 (pre-ketamine); 6/10 (post-ketamine)**
PTSD Checklist (Military) score	**51 (pre-ketamine); 47 (post-ketamine)**

Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**41 (pre-ketamine); 34 (post-ketamine)**
Relevant Medical History	**Obstructive Sleep Apnea** **Complex Regional Pain Syndrome, Type 1** **Traumatic Brain Injury (secondary to IED blast)** **Hypertension** **Obesity**
Comments	**The second patient in the series had difficulty gaining the required analgesic effects, resulting in a high ketamine dosage that eliminated the possibility of effective psychotherapy past day two of the infusion. That is, although the ketamine dosage eventually reached a level that alleviated his pain, the patient became so sedated that he was unable to participate in psychotherapy on the MICU after the second psychotherapy session.**

Patient 3	
Demographics	**65 year old Caucasian female, retired Active Duty Army nurse**
Background	**Chronic over-use from three combat deployments to Iraq/Afghanistan resulted in severe radiating lower back pain**
Date of KEP-P2	**Spring, 2015**
Presenting Complaints	**Intractable radiating lower back pain, PTSD secondary to sexual, physical, and military trauma**
Pre-ketamine pain medication	**Fentanyl patch (25mcg/hr/72hrs), Gralise (300 mg daily dose), gabapentin (400mg daily dose)**
Average daily pain	**6/10 (pre-ketamine); 8/10 (post-ketamine)**
PTSD Checklist (Military) score	**76 (pre-ketamine); N/A (post-ketamine)**
Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**14 (pre-ketamine); 26 (post-ketamine)**
Relevant Medical History	**Hypertension** **Hyperlipidemia** **Lumbar Spondylosis** **Multiple spine surgeries including sacroiliac joint fusion** **Multiple failed percutaneous spinal cord stimulator trials** **Surgical lead implanted (paddle) spinal cord stimulator**
Comments	**This patient reported that she was able to "smell" stimuli from her traumatic event both during the ketamine infusion and**

	post-ketamine during times subsequent flashbacks of the traumatic event. This patient was upset with the first author and pain physician due to a misunderstanding that resulted in an unwanted overnight hospital stay post ketamine infusion, resulting in a failure to administer the PCL. Despite this, the patient continued psychotherapy after ketamine discharge focused on the depressive aspects of spousal physical and sexual abuse experiences prior to military service.

Patient 4	
Demographics	**69 year old Caucasian male, retired Active Duty Army infantry**
Background	**Injured by a command detonated rocket propelled grenade during combat operations in Vietnam in 1970 which resulted in a below the knee amputation. Prior to the injury he had been involved in multiple combat engagements.**
Date of KEP-P2	**Summer, 2015**
Presenting Complaints	**Residual limb and phantom limb pain, lower back pain, PTSD secondary to military trauma**
Pre-ketamine pain medication	**Lyrica (100 mg daily dose), lidocaine patch 5% (12 hours on/12 hours off), topiramate (100 mg daily dose)**
Average daily pain	**7/10 (pre-ketamine); 7/10 (post-ketamine)**
PTSD Checklist (Military) score	**34 (pre-ketamine); N/A (post-ketamine– see comments)**
Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**5 (pre-ketamine); 1 (post-ketamine)**
Relevant Medical History	**Hypertension** **Cataracts** **Erectile dysfunction** **Basal cell carcinoma** **Malaria**
Comments	**This patient did not complete a PCL in the psychotherapy session immediately post-ketamine, but clinically, the patient seemed to be somewhat improved. He was just below the diagnostic threshold for PTSD pre-ketamine and was in good spirits during post ketamine infusion psychotherapy follow-up. This focus of ketamine enhanced psychotherapy was addressing a moral injury combat incident that he had never discussed with anyone previously. This patient attended one post-ketamine infusion behavioral health appointment and never returned to clinic. The focus of the one outpatient**

	behavioral health session post-infusion was on managing his residual limb pain. Of note, he was the only the person treated for experiences related to combat in Vietnam and not related to current armed conflict in the Middle East.

Patient 5	
Demographics	**29 year old Caucasian male, Active Duty Marine Corps Special Forces Operator**
Background	**Slipped on ice and fell on his back and head with greater than 200 pounds of combat gear on his back while on a combat mission in Afghanistan in 2014. He experienced a loss of consciousness and sustained L1 and L2 compression fractures and bilateral knee meniscal degenerative changes and tears.**
Date of KEP-P2	**Summer, 2015**
Presenting Complaints	**Bilateral lower extremity pain, PTSD secondary to military trauma, difficulty concentrating, insomnia**
Pre-ketamine pain medication	**Norco 5mg/325mg (25mg/1625mg daily dose); Lyrica (450 mg daily dose), venlafaxine (300 mg daily dose), naproxen (1000 mg daily dose); Topamax (25 mg daily dose); Butrans patch (15 mcg per hour)**
Average daily pain	**9/10 (pre-ketamine); 4/10 (post-ketamine)**
PTSD Checklist (Military) score	**48 (pre-ketamine); 31 (post-ketamine)**
Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**95 (pre-ketamine); 89 (post-ketamine)**
Relevant Medical History	**Traumatic Brain Injury** **Complex Regional Pain Syndrome, Type II in lower extremity (treated with a spinal cord stimulator)** **Bilateral lower leg compartment syndrome (treated with bilateral fasciotomies)** **Chronic Migraine headaches** **Lower extremity instability and gait disturbance** **Insomnia**
Comments	**On the morning of day three of ketamine infusion, he received two fellow service member visitors from the local unit detachment (not his assigned unit) who were checking on the patient. They started telling "war stories" that caused the patient to become alert and excited about a perceived impending return to combat duty. The patient became so enthusiastic that he stood up and pulled out his peripheral intravenous (PIV) lines with the belief that he was going to be able to go on a combat mission with his two combat**

	uniformed visitors. The medical staff quickly intervened and asked the patient to return to his hospital bed. He complied without resistance and the PIV lines were re-inserted into the patient and his ketamine infusion resumed. Following this event we enacted a policy where we forbade outside visitors that were not immediate family without treatment team approval and chaperone.

Patient 6	
Demographics	**31 year old Caucasian male, Active Duty Army Logistics Officer**
Background	**He suffered a right lower extremity injury** (**anterior talofibular ligament tear) secondary to a fall and mild Traumatic Brain Injury during fire fight in Iraq in 2008, finishing the rest of the deployment in an ankle brace. The pain and function diminished over the next five years, requiring multiple ankle surgeries and complications, including the development of Complex Regional Pain Syndrome, Type II. The patient also suffered a second traumatic brain injury with approximately five minute loss consciousness during a second combat incident in Iraq approximately nine days after his initial fall.**
Date of KEP-P2	**Summer, 2015**
Presenting Complaints	**Lower extremity pain, PTSD secondary to military trauma**
Pre-ketamine pain medication	**Oxycodone Hydrochloride, extended release (30mg daily dose); Hydromorphone hydrochloride (16 mg daily dose); Lyrica (450 mg daily dose); Flexeril (30 mg daily dose); Celebrex (200 mg daily dose)**
Average daily pain	**5/10 (pre-ketamine); 2/10 (post-ketamine)**
PTSD Checklist (Military) score	**58 (pre-ketamine); 25 (post-ketamine)**
Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**34 (pre-ketamine); 22 (post-ketamine)**
Relevant Medical History	**Traumatic Brain Injury** **Complex Regional Pain Syndrome, Type II** **Spinal Cord Stimulator (failed trial)** **Erectile Dysfunction** **Chronic Migraine headaches** **Lower extremity instability and gait disturbance** **Gastroesophageal reflux disease (GERD)** **Bipolar II Disorder** **Attention-Deficit/Hyperactivity Disorder (ADHD)**

	Obstructive Sleep Apnea (OSA) **Periodic Limb Movement Syndrome**
Comments	**The patient was not diagnosed with, and treated for, Bipolar II Disorder until after the ketamine infusion.**

Patient 7	
Demographics	**50 year old Caucasian male, Active Duty Army Chaplain**
Background	**Severely sprained ankle twice while deployed to Afghanistan in 2012 but refused medical care. Injured same ankle one year later and developed Complex Regional Pain Syndrome, Type II. In 2014, MRI revealed anterior tibiofibular and calcaneofibular ligament tear, which was surgically addressed.**
Date of KEP-P2	**Winter, 2016**
Presenting Complaints	**Lower extremity, shoulder, and elbow pain, PTSD secondary to military trauma, insomnia**
Pre-ketamine pain medication	**Norco 5mg/325mg (15mg/975mg daily dose); Lyrica (900 mg daily dose); Naproxen (500 mg daily dose);**
Average daily pain	**5/10 (pre-ketamine); 1/10 (post-ketamine)**
PTSD Checklist (Military) score	**64 (pre-ketamine); 36 (post-ketamine)**
Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**8 (pre-ketamine); 23 (post-ketamine)**
Relevant Medical History	**Complex Regional Pain Syndrome, Type II** **Chronic Migraine headaches** **Lower extremity instability and gait disturbance** **Hypogonadism** **Erectile Dysfunction** **Obstructive Sleep Apnea (OSA)** **Bipolar II Disorder**
Comments	**When compared to his pre-ketamine behavioral health visits, he utilized a high number of behavioral health interventions post-ketamine infusion even though his PTSD was remitted. This patient utilized a high number of cycling group appointments, a behavioral activation model treatment group administered by another behavioral health provider at the rehabilitation facility. This contrasts with the year prior to ketamine infusion, where all of his behavioral health visits consisted of traditional psychotherapy.**

Patient 8	
Demographics	**37 year old Caucasian female, Active Duty Army Nurse**
Background	**Developed lower extremity synovial sarcoma treated with radiation and surgical intervention in 2013. Suffered from severe chronic pain during a failed limb salvage process that eventually resulted in a lower extremity below the knee amputation in 2016. Had difficulty wearing the socket and prosthetic due to multiple painful neuromas.**
Date of KEP-P2	**Spring, 2017**
Presenting Complaints	**Lower extremity residual limb pain, PTSD secondary to military trauma**
Pre-ketamine pain medication	**Gabapentin (900 mg daily dose); Amitriptyline (25 mg daily dose);**
Average daily pain	**4/10 (pre-ketamine); 4/10 (post-ketamine)**
PTSD Checklist 5 (PCL-5) score	**38 (pre-ketamine); 41 (post-ketamine)**
Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**24 (pre-ketamine); 40 (post-ketamine)**
Relevant Medical History	**Below the knee amputation** **Chronic neck and shoulder pain** **Major Depressive Disorder** **Traumatic Brain Injury** **Hypothyroidism**
Comments	**This patient had been a high utilizer of behavioral health visits prior to seeking out care with the first author. That is, from 2013 thru 2017 she attended 115 individual psychotherapy sessions with another clinical psychologist to address issues related to acute life stressors, including divorce and subsequent custody battle, sleep disturbances, adjustment to cancer diagnosis, work related stressors, and body image with little progress in terms of treating her PTSD. Post ketamine, she continued treatment with the first author focused primarily on the multiple, complex and intertwined combat traumas identified during the ketamine infusion. Once the effects of the combat traumas had minimized in post-ketamine psychotherapy sessions, the patient began to focus on a variety of issues related to emotional and physical abuse from her previous marriage and her family of origin. Three months following ketamine infusion the patient was discharged from treatment with the first author and later sought out treatment from another behavioral health provider to address issues**

	related to her family of origin. We posit that KEP-P2 accelerated the psychotherapeutic progress of this complicated patient and created the conditions for psychotherapeutic progress where little existed previously. We believe it likely that this patient under-reported the true severity of her PTSD symptoms prior to KEP-P2. This patient seemed to have the strongest opinion in stating how unpleasant and difficult the KEP-P2 experience was for her.

Patient 9	
Demographics	**38 year old Caucasian male, Active Duty Army Special Forces**
Background	**The patient was originally injured during combat operations in 2009 while deployed in Afghanistan, where he fell from a building and injured his ankle. This injury became more severe after he suffered a 50 foot fall during a subsequent combat deployment in 2014. He received multiple failed surgical procedures and a failed limb salvage process before receiving a below the knee amputation in 2015. He continued to have trouble managing his pain, including a failed Spinal Cord Stimulator trial and multiple opioid medications.**
Date of KEP-P2	**Summer, 2017**
Presenting Complaints	**Lower extremity residual limb pain, PTSD secondary to military trauma**
Pre-ketamine pain medication	**Oxycodone Hydrochloride (30 mg daily dose); dronabinol (15 mg daily dose); Gabapentin (900 mg daily dose); Amitriptyline (25 mg daily dose)**
Average daily pain	**3/10 (pre-ketamine); 4/10 (post-ketamine)**
PTSD Checklist 5 (PCL-5) score	**42 (pre-ketamine); 15 (post-ketamine)**
Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**20 (pre-ketamine); 10 (post-ketamine)**
Relevant Medical History	**Below the knee amputation** **Traumatic Brain Injury** **Irritable Bowel Syndrome** **Major Depressive Disorder** **Chronic Migraine headaches**
Comments	**This was the patient's second inpatient ketamine infusion in six months, the first with no complications. During the third day of KEP-P2 and following an emotionally challenging psychotherapy session the patient reported that he had spent the majority of the night in prayer "asking God to take me"**

	(i.e., kill him) as an atonement for a perceived moral failure sustained in the deployed combat experience addressed in the previous psychotherapy session. The patient subsequently experienced an acute, but variable tachycardia experience that began two hours after the bedside KEP-P2 session and lasted most of the night. At approximately 0430 the next morning the nursing staff noted a prolonged heartrate around 160 heartbeats per minute. The attending physician discontinued ketamine and administered a bolus of Ativan. The patient's tachycardia diminished and he was able to fall asleep for several hours. The ketamine was re-started at approximately 1100 the next day and he was able to complete the rest of the protocol with no further complications.

Patient 10	
Demographics	**29 year old Caucasian male, Active Duty Air Force Combat Controller**
Background	**Patient injured in a military vehicle roll-over accident during combat operations in Syria that resulted in 13 fractured spinous processes (C6 thru T2, T11, and T12) in 2018. Patient had previously experienced a hard jump landing during airborne training, resulting in a C5-C7 discectomy and fusion in 2016.**
Date of KEP-P2	**Spring, 2018**
Presenting Complaints	**PTSD secondary to military trauma; difficulty concentrating and memory problems; facial tics (6-10 times per minute when stressed); and chronic pain (left hip, abdominal, lower/mid/upper back, neck, and left sided head)**
Pre-ketamine pain medication	**Oxycodone Hydrochloride (40 mg daily dose); acetaminophen (975 mg daily dose)**
Average daily pain	**5/10 (pre-ketamine); 7/10 (post-ketamine)**
PTSD Checklist 5 (PCL-5) score	**63 (pre-ketamine); 12 (post-ketamine)**
Behavioral Health Visits (1 year pre / 1 year post ketamine infusion)	**17 (pre-ketamine); 8 (post-ketamine)**
Relevant Medical History	**Traumatic Brain Injury** **Attention-Deficit/Hyperactivity Disorder (ADHD)** **Major Depressive Disorder**
Comments	**During a pre-ketamine individual psychotherapy session in March 2018 the patient was experiencing what appeared to be anxiety related physical manifestations (upper back/neck twitching/jerking) while discussing riding as a passenger in a vehicle with his wife on the interstate. He stated that this response was connected with vigilance related to the roll-over**

	accident in Syria that resulted in his injuries. These tic-like responses occurred approximately 6-10 times per minute during this session and continued until the ketamine infusion. Although the patient had recently discontinued wearing a neck brace, he was once again required to wear his neck brace by his physical medicine providers for fear of re-injury after this incident. The patient's jerking/twitching had reduced significantly post-ketamine to the point that it was only periodic. However, this jerking/twitching continued to be positively correlated with perceived stressors.

Patient 11	
Demographics	**31 year old Hispanic male, Active Duty Marine Corps Infantryman**
Background	**The patient was subjected to greater than 15 explosions during three separate combat deployments to the Middle East. He experienced loss of consciousness on multiple occasions during these deployments. He suffered a gunshot wound to the ankle during a firefight in Afghanistan in 2009. In 2017 he suffered 3rd degree burns over 30% of his body, most prominently to his face, arms and hands, as well as loss of consciousness. He required more than 15 surgeries (and counting) following this event. In spring 2019, he was inpatient hospitalized for making suicidal statements to his spouse while intoxicated. He subsequently completed an Intensive Outpatient Program (mood emphasis) prior to being discharged to the first author for KEP-P2.**
Date of KEP-P2	**Summer, 2019**
Presenting Complaints	**Chronic pain, PTSD, and major depression**
Pre-ketamine pain medication	**Oxycodone Hydrochloride (60 mg daily dose); dronabinol (10 mg daily dose); Gabapentin (2400 mg daily dose); hydroxyzine (75 mg daily dose); celecoxib (200 mg daily dose); acetaminophen (1500 mg daily dose);**
Average daily pain	**6/10 (pre-ketamine); 2/10 (post-ketamine)**
PTSD Checklist 5 (PCL-5) score	**60 (pre-ketamine); 16 (post-ketamine)**
Behavioral Health Visits (1 year pre / 6* months post ketamine infusion)	**47 (pre-ketamine); 17* (post-ketamine)**
Relevant Medical History	**Traumatic Brain Injury** **Major Depressive Disorder (since childhood)** **Headaches** **Tinnitus**

	Chronic pain in lower back, shoulder, bilateral hands, and hips
Comments	**The daily KEP-P2 sessions initially addressed previous combat traumas and secondarily the physical trauma of being burned. The patient tapered himself off of all pain medications except for dronabinol and Gabapentin following KEP-P2.**

Discussion/Conclusion

We report herein encouraging results of Ketamine-Enhanced Psychotherapy-PTSD and Pain (KEP-P2) with clinically and statistically significant reductions in PTSD symptoms and meaningful, though not statistically significant reductions in pain. Ten of the 11 patients were able to effectively engage trauma-focused therapy while under the influence of ketamine and six of those patients showed immediate reductions in PCL scores suggestive of clinical remission. These results were obtained in patients who generally had received a number of behavioral health inventions prior to ketamine infusion and post-treatment assessment clearly suggest that ketamine-enhanced treatment resulted in a clinically meaningful improvement in the lives of these patients.

During ketamine treatment, every patient experienced some form of visual perception alteration, which took many forms and ranged from the relatively benign sensory disturbances (e.g., double vision) to more emotionally disturbing frank hallucinations (e.g., observing a combat deceased military friend). The visual disturbances were of variable frequency and affected each patient uniquely and tended to become more frequent as the infusion progressed. These alterations could be classified as occurring in combinations of three forms: current realistic (i.e., seeing the MICU nurse in the corner staring at the patient); past realistic (i.e., dead friend from combat trauma in chair looking at the patient); and/or symbolic (i.e., Grim Reaper flying around the room swinging scythe at patient's head).

Although it was not systematically assessed, these patients were not deemed delirious or delusional since they were able to understand that these visual alterations were not real. Patients had been warned of this potential side effect of ketamine prior to the treatment and most of the patients seemed to understand that the hallucinations were drug-induced and temporary. Perhaps because of the dissociative aspects of ketamine intoxication, patients generally tended not to exhibit or report excessive fear during or after these visual alterations and hallucinations. However, psychotherapeutic techniques similar to dealing with true clinical psychosis were needed and employed for one patient who experienced a simultaneous past realistic (i.e., dead friends from a

combat trauma sitting next to him in the hospital room) and symbolic visual hallucinations (i.e., Grim Reaper flying around hospital room) on day four of the ketamine infusion.

As previous research has shown that benzodiazepines can negatively impact trauma focused treatment outcomes (4, 5), our standard procedures were very conservative regarding the use of benzodiazepines to control agitation or arousal. Another study indicated that combining lorazepam and ketamine resulted in a spectrum of interactive effects, including worsening attention, learning, and memory (6).

In the current case series, ketamine almost uniformly reduced the patient's pain intensity during the ketamine infusion to between 0-2 out of 10 within 24 hours. However, several patient's NPRS pain intensity scores were observed to increase a couple points on the days where the most intense psychotherapy also occurred -- typically the third and fourth day of the five day ketamine infusion.

While pain severity scores decreased after ketamine infusion for six of the eleven patients, this change did not reach statistical significance for the sample. Although clinical impressions suggest some relationship between PTSD symptom improvement and pain severity reduction for some patients, two our patient's showing the greatest PTSD symptom reduction actually showed an increase in pain level.

Opioid reduction or discontinuation may account for some of the lack of change or an increase in pain levels by the end of treatment, as most patients were receiving a new pain medication regimen following the infusion. Of note, several patients who discontinued opioids during the ketamine infusion also experienced some opioid withdrawal-like symptoms, which included insomnia. Poor sleep the weekend following the ketamine infusion protocol also seemed to be a contributing factor as the previous night's sleep is a known predictor of the next day's pain severity level (7). The most common patient complaints about life during the first weekend post-ketamine were insomnia-related fatigue, grogginess, difficulty returning to a normal day-night schedule, and a difficulty adjusting back to 'normal life.'

The majority of the patients in this sample had suffered severe orthopedic injuries and reported multiple areas of chronic pain. Tracking long term pain outcomes and delineating between variable pain conditions (e.g., CRPS, phantom limb pain, lower back pain, etc.) would be suggested for future research. Unfortunately, this case series did not assess physical function during physical and/or occupational therapy follow-up treatment, which was an important factor affecting their utilization of the newly formed interdisciplinary treatment program for the majority of patients in this case series.

The psychotherapeutic experience of patients on ketamine appears unique when compared with regular, trauma-focused psychotherapy in the absence of ketamine. This can best be understood by considering the altered state of consciousness (ASC) effects of ketamine. ASCs are temporary non-ordinary, wakeful states where an individual becomes aware of altered experiences in cognition, sensation, perception, and/or emotion (8). ASCs are non-psychiatric by definition and examples include hallucinogenic drug induced states, meditation, hypnosis, dream, and any dissociative state. Pooled data from 43 experimental studies used to create a new factor analysis (OAV-11) of the already existing Altered States of Consciousness Rating Scale indicated that some of the most common ketamine ASC phenomena include a high degree of disembodiement (e.g., I had the feeling of being outside of my body), experience of unity (e.g., conflicts and contradictions seemed to dissolve), and impaired control and cognition (e.g., I had difficulty in distinguishing important from unimportant things)(9)

Predictably, patient experience of ASCs increased dramatically from day one to day four of the infusion. Simultaneously, the highest level of therapeutic progress occurred during infusion day three and four when patients exhibited the highest levels of ASCs. Clearly, the cause and effect relationships between therapeutic progress and ASCs are confounded by the onset and process of therapy in this compressed 5-day intervention. This anectdotal observation is congruent with previous studies that found that stronger ASC-like effects of ketamine predicted a stronger and more sustained antidepressant effect (10, 11). Additionally, a recent report showed a positive relationship between specific ketamine induced ASCs (i.e., feeling of lightness) and amelioration of the subjective experience of depression (12).

The most common expression of emotion we observed were sadness, regret/guilt, shame, love/gratitude (directed toward family and/or fellow service members), and self-directed-anger. Common themes during ketamine enhanced psychotherapy included the perception of being a failure to themselves, failing or bringing shame to their family, grief, moral injury, and letting down/failing fellow combat deployed unit members.

From a psychobiological perspective, PTSD can be thought to induce a conflict within the brain between the bottom-up mind (i.e., lower brain/limbic system) that constantly alerts the patient with PTSD to exaggerate danger (e.g., smell of diesel fuel or burned steak = impending danger), and the intentional top-down mind (i.e., neo-cortex) that attempts to rationalize/reassure the person that the current environment is not actually dangerous. In our opinion and experience, the dissociative effects of ketamine seem ideally-suited to help the patient to resolve this conflict (3). We do not

suggest that ketamine diminished emotionality in this series of patients – rather, that it allowed them to experience it.

Importantly, most of our patients had significant behavioral health engagement and psychotherapy in the year prior to ketamine, and yet five days of KEP-P2 seemed to achieve remarkable and sudden results and breakthroughs in terms of helping patients to focus on trauma memories. Nonetheless, most of these patients continued to need psychotherapy after the KEP-P2 intervention. The fact that KEP-P2 did not significantly reduce behavioral health visits post infusion is explained by multiple factors. Seven of the ten patients attended 7.3 fewer behavioral health sessions in the year after the ketamine (the eleventh patient was not one year post treatment at the time of publication and is excluded). The three who attended more sessions in the year post-ketamine averaged 14.3 more sessions. Nine of the ten patients during and after ketamine were more dedicated to treatment, relieved to finally unmask what had previously been buried, and desired to continue treatment because of the progress during the KEP-P2 intervention. The topic of post-ketamine psychotherapy tended to be focused on enhancing interpersonal relationships with family and friends and managing health conditions (especially sleep and pain) and was less focused on PTSD symptom management. In other cases, post-KEP-P2 relief of combat related PTSD symptoms changed the clinical focus to pre-combat sexual and/or physical abuse and the accompanying symptoms (i.e., depression) and subsequent life experiences and consequences. These findings suggest that KEP-P2 accelerated the psychotherapeutic progress of very complicated patients and created the conditions for psychotherapeutic progress where little existed previously.

Limitations

The information presented describes our clinical observations of the first eleven patients participating in a new program providing psychotherapy for PTSD during a ketamine infusion for patients with severe chronic neuropathic pain conditions. However, conclusions from this case series are limited to due to the lack of a randomized comparison to a control condition and the lack of standardized procedures, assessments, and psychotherapy manuals that would normally be used in an experimental protocol. This prevents firm conclusions about the efficacy of our combined treatment program itself or that of any of its components involving either ketamine or psychotherapy treatment for either PTSD or for pain. Nonetheless, the clinical experience presented does show that most patients were able to meaningfully engage trauma-focused therapy over a 5-day inpatient ketamine infusion protocol. Although we present data suggesting that the psychotherapy experiences during ketamine infusion were qualitatively different than usual care

therapy in a patient population who had not responded to psychotherapy previously, the lack of randomization to a placebo control prevents a conclusion that ketamine actually enhanced the psychotherapy process or outcome. Another limitation is our reliance on elevated PCL scores and a clinical diagnosis of PTSD rather than use of the gold-standard Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Though we report clinically and statistically significant reductions in PTSD symptom severity, a lack of statistical power due to small sample size could explain some of our negative results on the other measures of pain and consequent behavioral health service utilization. We believe future clinical trials should also include the administration of an ASC scale (e.g., OAV-11) in an attempt to better understand the role of ASC in optimal treatment outcomes. We hope that our data can guide future controlled clinical trials evaluating the effectiveness of ketamine to facilitate trauma-focused therapy.

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