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Low Dose Ketamine Infusion for Comorbid Posttraumatic Stress Disorder and Chronic Pain Patients

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Low Dose Ketamine Infusion for Comorbid Posttraumatic Stress Disorder and Chronic Pain Patients

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Specific Aims/Purpose

The purpose of the study is to investigate the effectiveness of low dose IV ketamine infusion in the treatment of patients with PTSD and comorbid chronic pain.

Hypothesis: A single ketamine infusion should be associated with significantly greater reduction in core PTSD symptom levels after the treatment and such an effect is not only due to its analgesic properties but also through unknown mechanism of action that maybe related to NMDA/AMPA receptor modulation.

Scientific Rationale and Significance

It is well established that the prevalence of PTSD is substantially greater in patients with chronic pain. In a sample of chronic pain patients, PTSD prevalence was 35%[1], compared to 3.5% in the general population[2]. To-date, the treatment options for patients suffering from PTSD among our veterans remain largely unchanged and novel therapies continue to gain interest among researchers and treating providers. Ketamine infusion has been shown to be safe and effective treatment option for such patients. Feder et al. have reported that single dose of IV ketamine infusion is associated with significant and rapid reduction in PTSD symptom severity compared with midazolam[3]. The observed effect is present 24 hours after infusion. This primary outcome remained for at least 7 days. Additional comorbid depressive symptoms were also reduced and persisted up to a week later at the end of the study. Among the studied 41 patients, it is possible that some may have had comorbid chronic pain. It is still not known whether the observed effect of ketamine was due to its analgesic and/or antidepressant properties.

More recently Albott et al. reported that repeated IV ketamine infusion was effective in treating patients with comorbid PTSD and highly treatment resistant major depression. This was an open

study of 16 VA patients given six 0.5 mg/kg IV ketamine infusions on 3 days per week schedule over 2 weeks period. The median time to relapse of PTSD was 41 days and to depression 26 days[4].

Clinical studies have evaluated the use of ketamine for different chronic pain conditions. In a double-blind, randomized, placebo-controlled parallel-group trial of 60 patients with chronic regional pain syndrome type I treated with low dose IV ketamine infusion for 4.2 days, Sigtermans et al showed significant spontaneous pain relief without functional improvement[5]. Patients were treated with placebo (n = 30) or a low dose IV infusion of ketamine (n = 30), which was titrated to effect from a minimum dose of 5 mg/hr to a maximum dose of 30 mg/hr. Significant reduction in spontaneous pain that was maintained for 11 week has been observed.

Noppers et al studied 24 fibromyalgia patients treated with an IV infusion of ketamine (0.5 mg/kg over 30 minutes, n = 12) or placebo (midazolam 5 mg, n = 12) in a randomized double blind, active placebo-controlled trial and concluded that short-term infusion of ketamine is insufficient to induce long-term analgesic effects in these patients[6]. The study patients were followed for 8 weeks with initial VAS score and FIQ measured for 2.5 hours post-infusion and weekly. Fifteen minutes post-infusion the number of patients showing a reduction in pain scores > 50% was 8 in the treatment group vs. 3 in the control group ($P < 0.05$), at t = 180 minutes, 6 vs. 2 (not statistically significant), at the end of the first week, 2 vs. 0 (nonsignificant), and at end of the eighth week, 2 vs. 2 in the ketamine and midazolam groups, respectively[5]. Both of these studies indicate that single doses of ketamine produce short term pain relief probably related to its plasma concentration.

Patients with PTSD and chronic pain have the complexity of two syndromes with overlapping brain connectivity circuits. PTSD symptoms are reduced by ketamine for a longer period beyond its presence in the brain[3]. The hypothesis of the present research is that some of the chronic pain symptoms in PTSD patients will also be reduced for a longer period. The iv-nonsteroidal anti-inflammatory drug ketorolac will be used as a positive control. The second research hypothesis is that ketorolac will produce pain relief only related to its short-term pharmacokinetics in contrast to ketamine. In as much as ketamine is effective in PTSD, this study will also confirm in PTSD volunteers possible therapeutic agent for the large number of VA patients.

Preliminary Studies

The proposed research will be a pilot study that will enable PI to apply for funding through DoD or VA as well as pursue career development award in the near future. Dr. Dadabayev is Board Certified Anesthesiologist and Pain Medicine physician who has an extensive experience with the use of ketamine infusion for chronic pain patients. With his collaboration with world renowned leader in PTSD, Dr. Liberzon, Dr. Dadabayev is hoping to conduct a novel clinical trial that might help patients with PTSD to find new treatment options for their symptoms.

Research Design and Methods

The study will be randomized, controlled, double-blind trial comparing ketamine with active placebo control ketorolac. Eligible participants with primary diagnosis PTSD assessed with the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders–Patient Version and comorbid diagnosis of chronic pain as defined by having any chronic pain beyond 6 months in duration

will be identified and recruited from the Pain Clinic. More specifically, all eligible patients that meet eligibility criteria will be identified in the Clinic by Dr. Dadabayev the same day when he sees his patients in the Pain Clinic for their chronic pain. All new patients complete the standard Pain Clinic Questionnaire that in addition to chronic pain profile screens for PTSD symptoms. These patients are new patients for him and are scheduled as new patient consult. Those eligible patients will be given a recruitment letter at the end of the visit by a clinic nurse (notice, attached). To avoid coercion, Dr. Dadabayev will not be involved in any discussion of the study design with potential candidates. Instead, if patient is interested in the study, he/she will contact RA (Hedieh Briggs) by phone who will arrange a visit to VA to go over the study and sign the consent form. To recruit all eligible patients, Dr. Dadabayev will review a cohort of his chronic pain patients who see him infrequently in the Pain Clinic as a follow-up patients and those patients will be sent a recruitment letter by mail. Again, if patient is interested in the study, he/she will contact RA (Hedieh Briggs) by phone who will arrange a visit to VA to go over the study and sign the consent form. Again, Dr. Dadabayev will not be involved in any discussion of the study design with potential candidates.

Sample size and power calculation

Based on Feder et al study we estimated an effect size d=0.75 between the Ketamine and Midazolam group. A sample size of 24 patients per group was calculated to be necessary for 80% power to detect this effect size with alpha = 0.05. We expect larger difference between our groups, since Midazolam used in Feder study is sedative and anxiolytic and Ketorolac has no such properties. So, we anticipate that 20 subjects per group (20 for ketamine and 20 for ketorolac infusion) will be sufficient to generate 80% power.

Dr. Dadabayev sees on average 20-25 patients per week/1000-1200 patients/year. As previously mentioned, in a sample of chronic pain patients, PTSD prevalence was 35% and this is also consistent with what he encounters in his practice. We plan to screen and enroll at least 60 patients. We hope to have at least 10 patients in each sub-group (table 1) prior to analyzing the data. We believe we can recruit eligible patients from Dr. Dadabayev's clinic based on such rationale.

Arms and assigned interventions.

The entire study will be conducted in an outpatient settings. Patients will be asked to fast overnight and be accompanied by a driver on the day of the infusion. They will be admitted to PACU where an indwelling catheter will be placed in the antecubital vein of the nondominant arm. Monitoring of pulse and blood pressure, pulse oximetry, and electrocardiographic monitoring will be instituted. Participants will be required to stay at the clinical site for 4 hours after the medication has been given. Follow-up visits will occur at different time points over the course of 1 week after the infusion period has been completed (Figure 1).

There will be 4 groups of patients. The first group will comprise of patients with PTSD and chronic pain diagnoses who will be assigned to receive a single IV infusion of ketamine hydrochloride (0.5 mg/kg) and administered over 40 minutes. The second group will comprise of patients with PTSD and chronic pain diagnoses who will be assigned to receive a single IV

infusion of ketorolac 15 mg reconstituted in 500 cc of normal saline and administered over 40 minutes. The third and fourth groups will be randomized as above, namely to receive either IV ketamine or ketorolac infusion, however the cohort of patient will have chronic pain diagnosis only without PTSD symptoms. Table 1 outlines the arms and assigned interventions.

To prevent the development of nausea and vomiting, a known side effect associated with ketamine infusion, 4 mg IV ondansetron will be administered to patients. To avoid potential bias ondansetron will be administered to all patients. Following the infusion, a total of 10 cc of blood will be withdrawn from peripheral vein of the patient into a standard 10 cc capped tube with EDTA anticoagulant. The samples will then be transferred to Dr. Liberzon's Lab on ice and undergo centrifugation to separate plasma. After careful aspiration of plasma from the buffy coat and red blood cell, plasma will be placed in a separate container and capped. Original buffy coat and red blood cell tube will be capped and stored at -80C. At the end of the study the samples will be sent to an off-site laboratory to document plasma concentration of the drug.

Only the research pharmacy will be aware of drug identity, and all study personnel, including raters, patients, and data analysts, will be blinded to randomization order. Only anesthesiologist performing the infusion will not be blinded as to prepare for possible development of side effects of the medication. A trained rater will administer ratings at preinfusion baseline, 15 minutes, 40 minutes, 120 and 240 minutes, 24 hours (day 1), 48 hours (day 2) after infusion, and 7 days (day 7) after infusion. Figure 1 illustrates the timeline of the infusion and assessment of the patients prior, during and after the infusion.

The anticipated side effects and possible development of dissociative, psychotomimetic, and manic symptoms will be measured with the Patient-Rated Inventory of Side Effects (PRISE20) (Table 4) and Clinician-Administered Dissociative States Scale (Table 5).

Outcomes

The primary outcome will be PTSD symptom severity assessed with the Impact of Event Scale–Revised (IES-R) and Visual Analogue Scale for pain administered by a study clinician 24 hours post infusion.

Secondary outcome measures will include Impact of Event Scale–Revised (IES-R) (See Table 2), Visual Analogue Scale (See Figure 2) and Brief Pain Inventory (Short Form) (See Table 3) for pain 1 week after the infusion.

Study Population

Eligibility

The following inclusion criteria will be utilized when recruiting patient for the research study: male or female veterans aged 18 to 65 years; veterans with chronic pain as defined by having any chronic pain beyond 6 months in duration with and without PTSD diagnoses (participants must meet DSM-V criteria for current post-traumatic stress disorder (PTSD) and have received a

diagnosis of PTSD greater than or equal to 3 months prior to assessment); they also will be either free of concomitant use of psychotropic and/or pain medications for at least 6 weeks or on stable doses of those medications within the last 6 weeks prior to randomization and for the duration of the study; if applicable, current frequency and duration of psychotherapy sessions must remain stable for at least 6 weeks prior to beginning of the study.

Exclusion criteria will include inability to speak English, inability or unwillingness to provide written informed consent; moderate-to-severe cognitive impairment (Mini-Mental State Examination scores<20)[7]; current or lifetime history of psychotic or bipolar disorder; current bulimia or anorexia nervosa, alcohol abuse or dependence in the previous 3 months; serious unstable medical illness or sleep apnea; HTN, prolonged QT interval, peptic ulcer disease or recent history of GI-bleed, renal insufficiency, active substance use disorder, active suicidal or homicidal ideation on presentation; for women: pregnancy (confirmed by baseline lab test), the initiation of female hormonal treatments within 3 months of screening, or inability or unwillingness to use a medically accepted contraceptive method for the duration of the study.

Informed Consent

All eligible patients will be approach and consented within 4 weeks prior to offering them the treatment. The waiting period between informing the potential participant and obtaining informed consent is necessary for proper planning as we do not anticipate performing more than 2-3 patients per week due to PACU spacing and availability. The informed consent and the session addressing patients' questions will be conducted in English. Every reasonable effort will be made to minimize possible coercion or undue influence. The informed consent can be withdrawn by patient at any point.

Risks, Benefits and Side Effects:

In clinical practice, ketamine is considered safe, and in general, side effects are well tolerated. Ketamine is linked to the following side effects: CNS-related symptoms (development of a schizoid-like state, somnolence, dizziness, drug high, memory defects), cardiovascular stimulation (development of hypertension and tachycardia) and in a minority of patients liver injury. The use of B-adrenoceptor blockers to combat sympathetic overactivity and the use of benzodiazepines, such as midazolam will be considered for all patients who develop untoward symptoms within the first 15 minutes of infusion. Immediate cessation of the infusion and maintenance of patient's vital signs will always be a priority.

We anticipate significant benefit for patients with PTSD symptoms from this novel therapeutic approach who unfortunately have been limited to available treatment options thus far. It is the impression of the treating physicians and to some degree many patients that ketamine infusion is safe and effective treatment for patient with specific medical problems. Among the most recent studies, there is an increasing body of evidence that ketamine infusion should be offered to patients with PTSD. To date there is limited pharmacotherapies available for these patients who continue to suffer from this disabling condition. Hence, we believe that there are substantial benefits to investigate such therapy and these benefits outweigh the risks associated with the medication.

Resources Available

The treatment protocol will take place in PACU. Every reasonable effort will be made in coordination with the leadership of the unit as to not disrupt the clinical care of the unit while the research study takes place. We anticipate a total of 4-5 hours per patient needed including admission, infusion and recovery of the patient. The PI of the study will be directly involved in the initiation, monitoring and completion of the infusion along with direct one-on-one clinical care by the RN of the unit. The time needed for PI to complete the infusion will be protected from other clinical duties and is agreed upon with his Service Chief.

The research study will also utilize a rater whose compensation will be partially offset by the grant from the University of Michigan, Dr. Domino.

Costs To Subjects and Compensation:

Since the proposed protocol may potentially offer therapeutic benefit for the patient with PTSD symptoms, the cost associated with the study will be covered by VA, including admission, initiation of the medication, monitoring and recovery in PACU. There will be no compensation offered to the patient.

Transfer of Data Ownership
A copy of any electronic data, and originals of paper records will be maintained concurrently at VA Ann Arbor over the course of the study

Data and Safety Monitoring Plan

Risk assessment
There are several risks associated with participation in this study.
These include:
Risks related to infusion of ketamine
In clinical practice, ketamine is considered safe, and in general, side effects are well tolerated. Ketamine is linked to the following side effects:
CNS-related symptoms (development of a schizoid-like state, somnolence, dizziness, drug high, memory defects), cardiovascular stimulation (development of hypertension and tachycardia) and in a minority of patients liver injury. The use of B-adrenoceptor blockers to combat sympathetic overactivity and the use of benzodiazepines, such as midazolam will be considered for all patients who develop untoward symptoms within the first 15 minutes of infusion.

Risks related to loss of confidentiality

a) There is a small risk in telling us sensitive information about you, such as a history of abusing substances. You also may feel uncomfortable with certain questions in our interview. To minimize any discomfort, only highly trained interviewers will be asking these sensitive questions. We will hide your identity on all of our research records, except for what is necessary to properly organize this information. We keep all information in locked file drawers in locked rooms, in parts of the hospital where only those persons directly involved in this research have access.

b) Subjects may become upset while providing personal information. A psychiatrist will be available in the event that they need to discuss any emotional distress experienced. If the subject elects to stop the study or has continued feelings of discomfort after the study is completed, a follow-up telephone call will be made within 1-3 days to check in and ensure that they are not still experiencing emotional reactions related to the study.

Protections against risks associated with this study:

Precautions to minimize risk associated with ketamine

In order to monitor and minimize side effects from ketamine, all patients will undergo an infusion in the monitored settings including pulse oximeter, BP, HR monitoring every 5 minutes under direct RN and MD Anesthesiologist supervision. Typically, it has been shown that ketamine is well tolerated under supervised conditions. However, the use of B-adrenoceptor blockers to combat sympathetic overactivity and the use of benzodiazepines, such as midazolam will be considered for all patients who develop untoward symptoms within the first 15 minutes of infusion. Immediate cessation of the infusion and maintenance of patient's vital signs will always be a priority.

Precautions to minimize risks associated with loss of confidentiality

a) Participants will each be issued a unique subject number. All experimental records will bear no personal identifying information, only the subject number. With the exception of a crosswalk file there will be no way to link subject numbers and personal identifying information. The crosswalk file will be kept separate from all other experimental records. After data analysis has been completed, the links between subject names and research records will be destroyed. Furthermore, upon the event of a subject's participation being terminated, all information collected prior to the subject being removed from the study, will be destroyed.

b) Data integrity - Questionnaire and interview data will be recorded on paper forms and entered into an electronic database. All data will be linked to each other by sequentially assigned subject numbers, and linked to the subject by a single electronic crosswalk file, stored apart from the research data. Erasing this file when analysis is complete will anonymize research files. All research files reside on password-protected, secure servers within the AAVA to which only trained study personnel will have access.

Data Safety Monitoring Plan

Plan to avert harms

In order to monitor and minimize side effects from ketamine, all patients will undergo an infusion in the monitored settings including pulse oximeter, BP, HR monitoring every 5 minutes under direct RN and MD Anesthesiologist supervision. Typically, it has been shown that ketamine is well tolerated under supervised conditions. However, the use of B-adrenoceptor blockers to combat sympathetic overactivity and the use of benzodiazepines, such as midazolam will be considered for all patients who develop untoward

symptoms within the first 15 minutes of infusion. Immediate cessation of the infusion and maintenance of patient's vital signs will always be a priority.

All data is coded by research ID only. All data is kept on a secure network with password protection and a crosswalk file is kept separately on this network. Only trained study personnel have access to the passwords which are located at the AAVA.
No subjects will be recruited or run until the protocol receives full review and approval by the VA IRB. During the performance of the studies subjects will be monitored at all times by the study coordinator, research personnel associated with the project (research assistants, project manager, radiology technologists) and/or the investigators themselves. All research personnel with subject or subject data contact will complete human subjects training (i.e., PEERRS, Citi-program, TMS, HIPPA, etc.). They are also fully informed of all the possible side-effects that could be encountered during the study. Every measure will be taken to protect subjects against even the rarest possible side effects. The investigators and study coordinator have extensive prior experience with all of the medications and challenges utilized in this study. Subjects will be encouraged to contact the investigators or study coordinator if they notice any symptoms or untoward side effects. All subjects will have direct access to the phone numbers of the study coordinator and the responsible physician (Dr. Dadabayev) as well as a 24-hour contact number. This information is included in the copy of the consent forms provided to the subjects.

Reporting of adverse events
An adverse event is any experience that has taken place during the course of a research project, which was harmful to a subject participating in the research, increased the risks of harm in the research, or had an unfavorable impact on the risk/benefit ratio. Adverse events (AEs) will be recorded and tracked and will be reported per VA IRB guidelines.

The assessment of adverse events associated with the infusion of medication will be initially recorded by the investigator and later on either reported by the patient or the rater. On the day of the infusion patients must meet Discharge Criteria Phase II of the PACU as outlined below.

A. Patient is awake, alert, responds to commands appropriate to age, or returned to pre-procedure status.
B. SpO2 greater than 95% or pre-procedure baseline on room air for 30 minutes without airway support. Breathing even and unlabored. Respiratory rate greater than 10 and less than 30 for adults.
C. Able to sit in an upright position without signs and symptoms of orthostatic hypotension. BP +/- 20 Hq mm of pre-procedure range or within patient's stated normal range. No active bleeding. D. Able to ambulate with minimal assistance or at pre-procedure level.
E. Pain score at rest is < 4 or at pre-procedure level at rest and patient states adequate pain control. No IV opioids or sedatives given within 30 minute, any IM agents within 1 hour.
F. Patient is not actively vomiting and nausea is mild in severity.
G. Patient is able to void if patient had spinal or epidural anesthesia, or use of contrast media.
H. IV/ saline lock is discontinued unless ordered to the contrary.
I. Arrangements have been confirmed for a responsible adult to drive the patient home.
J. Discharge medication prescriptions are given to the patient.

K. Patient discharge teaching and written instructions are provided to the patient and/or companion
L. Patient is informed that the rater will make a post-procedure telephone call within 24 hrs of procedure, unless specified differently by the physician, or per patient's request and on day 2 and day 7 after the infusion.
M. Patient is discharged to a responsible adult and escorted out of the hospital.

The PI will oversee all safety data and monitoring weekly. Any development of untoward side effects, including worsening signs, symptoms of the PTSD will be assessed promptly, possibly, same day appointment with RA and/or PI and addressed accordingly.

References & Literature Cited

1. Asmundson, G.J., Bonin, M.F., Frombach, I.K., & Norton, G.R. (2000). Evidence of a disposition toward fearfulness and vulnerability to posttraumatic stress in dysfunctional pain patients. Behaviour Research and Therapy, 38, 801-812.
2. Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K.R., & Walters, E.E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry, 62(6): 617-627.
3. Feder A., Parides M.K., Murrough J.W., Perez A.M., Morgan J.E., Saxena S., Kirkwood K., Aan Het Rot M., Lapidus K.A., Wan L.B., Iosifescu D., Charney D.S. (2014). Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA Psychiatry. 2014 Jun;71(6):681-8.
4. Albott C.S. et al. (2017). Ketamine Infusions for PTSD and Treatment-Resistant Depression. Conference proceedings and personal communication.
5. Sigtermans MJ, van Hilten JJ, Bauer MCR, Arbous MS, Marinus J, Sarton EY, Dahan A. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. (2009). Pain. 145:304–311.
6. Noppers I, Niesters M, Swartjes M, Bauer M, Aarts L, Geleijnse N, Mooren R, Dahan A, Sarton E (2011). Absence of long-term analgesic effect from a short-term S-ketamine

infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur J Pain. 15:942–949.
7. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res 1975;12:189-198.

Appendix

Table 1: The arms and assigned interventions.

Cohort	Intervention	
Chronic pain patients with PTSD	**IV ketamine infusion (n=10)**	**IV ketorolac infusion (n=10)**
Chronic pain patients without PTSD	**IV ketamine infusion (n=10)**	**IV ketorolac infusion (n=10)**
Total	**N=20**	**N=20**

Table 2.

IMPACT OF EVENT SCALE-REVISED

Instructions: **The following is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you *during the past 7 days* with respect to the disaster. How much were you distressed or bothered by these difficulties?**

		Not at all	A little bit	Mod erat e-ly	Quite a bit	Ex-trem e-ly
1	**Any reminder brought back feelings about it.**	**0**	**1**	**2**	**3**	**4**
2	**I had trouble staying asleep.**	**0**	**1**	**2**	**3**	**4**
3	**Other things kept making me think about it.**	**0**	**1**	**2**	**3**	**4**
4	**I felt irritable and angry.**	**0**	**1**	**2**	**3**	**4**
5	**I avoided letting myself get upset when I thought about it or was reminded of it.**	**0**	**1**	**2**	**3**	**4**

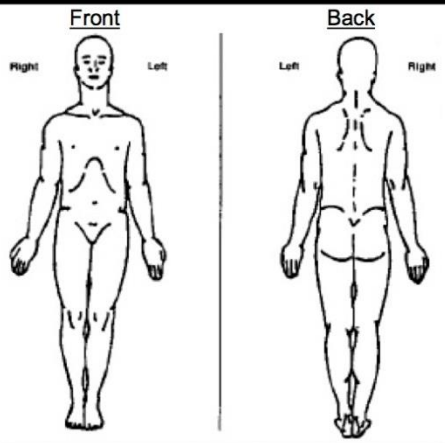
6	**I thought about it when I didn't mean to.**	**0**	**1**	**2**	**3**	**4**
7	**I felt as if it hadn't happened or wasn't real.**	**0**	**1**	**2**	**3**	**4**
8	**I stayed away from reminders about it.**	**0**	**1**	**2**	**3**	**4**
9	**Pictures about it popped into my mind.**	**0**	**1**	**2**	**3**	**4**
10	**I was jumpy and easily startled.**	**0**	**1**	**2**	**3**	**4**
11	**I tried not to think about it.**	**0**	**1**	**2**	**3**	**4**
12	**I was aware that I still had a lot of feelings about it, but I didn't deal with them.**	**0**	**1**	**2**	**3**	**4**
13	**My feelings about it were kind of numb.**	**0**	**1**	**2**	**3**	**4**
14	**I found myself acting or feeling like I was back at that time.**	**0**	**1**	**2**	**3**	**4**
15	**I had trouble falling asleep.**	**0**	**1**	**2**	**3**	**4**
16	**I had waves of strong feelings about it.**	**0**	**1**	**2**	**3**	**4**
17	**I tried to remove it from my memory.**	**0**	**1**	**2**	**3**	**4**
18	**I had trouble concentrating.**	**0**	**1**	**2**	**3**	**4**
19	**Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart.**	**0**	**1**	**2**	**3**	**4**
20	**I had dreams about it.**	**0**	**1**	**2**	**3**	**4**
21	**I felt watchful and on guard.**	**0**	**1**	**2**	**3**	**4**
22	**I tried not to talk about it.**	**0**	**1**	**2**	**3**	**4**

Table 3. Brief Pain Inventory Short Form.

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

B. Mood

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

C. Walking ability

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

E. Relations with other people

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

F. Sleep

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

G. Enjoyment of life

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

Table 4. **Patient related inventory of side effects (PRISE20)**

Have you had any of these side effects over the past two weeks? No Yes, but tolerable Yes – Distressing

	No	Yes, but tolerable	Yes-distressing
1. Dry mouth			
2. Nausea			
3. Diarrhea			
4. Constipation			
5. Dizziness			
6. Palpitations			
7. Sweating			
8. Headache			
9. Tremor			
10. Difficulty sleeping			
11. Sleeping too much			
12. Loss of sexual desire			
13. Trouble achieving orgasm			
14. Trouble with erections			
15. Anxiety			
16. Restlessness			
17. Decreased energy			
18. Increased appetite			
19. Increased weight			
20. Emotional indifference			

***Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA, for the STAR*D Investigators. Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract. 2006 Mar;12(2):71-9.**

Table 5. The Clinician Administered Dissociative States Scale (CADSS)
J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

Name_____ ID_____ Date_____

Subjective Items:

1. Do things seem to be moving in slow motion?
0= Not at all.
1= Mild, things seem slightly slowed down, but not very noticeable.
2= Moderate, things are moving about twice as slow as normally.
3= Severe, things are moving so slowly that they are barely moving.
4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.

2. Do things seem to be unreal to you, as if you are in a dream?
0= Not at all.
1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
2= Moderate, things seem dreamlike, although I know I am awake.
3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.

3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
0= Not at all.
1= Mild, I feel a little bit separated from what is happening, but I am basically here.
2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
4= Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.

4. Do you feel as if you are looking at things from outside of your body?
0= Not at all.
1= Mild, I feel somewhat disconnected from myself, but I am basically all together.
2= Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.

5. Do you feel as if you are watching the situation as an observer or a spectator?
0= Not at all.
1= Mild, I feel slightly detached from what is going on, but I am basically here.
2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.

3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in this room.
4= Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.

6. Do you feel disconnected from your own body?
0= Not at all.
1= Mild, I feel a little bit disconnected from myself, but I am basically all here.
2= Moderate, I feel somewhat detached from my own body, but I am basically all together.
3= Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.
4= Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.

7. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?
0= Not at all.
1= Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
2= Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
3= Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.
4= Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.

8. Do people seem motionless, dead, or mechanical?
0= Not at all.
1= Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
2= Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
3= Severe, people seem to be barely moving, or barely alive, or very mechanical.
4= Extreme, it's as if everyone were frozen or completely like machines.

9. Do objects look different than you would expect?
0= Not at all.
1= Mild, things seem slightly different than normal, although it is barely perceptible.
2= Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
3= Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.
4= Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.

10. Do colors seem to be diminished in intensity?
0= Not at all.
1= Mild, things seem slightly paler than usual if I think about it.
2= Moderate, colors are somewhat diminished, but still recognizable.
3= Severe, colors are extremely pale, in no way as vivid as they usually are.
4= Extreme, as if everything is in black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
0= Not at all.
1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.

12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?
0= Not at all.
1= Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
2= Moderate, it seems as if this interview has gone on for at least two hours.
3= Severe, it seems as if at least ten hours have gone on since the start of the interview.
4= Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.

13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
0= Not at all.
1= Mild, things are happening slightly faster than normal.
2= Moderate, things seem to be happening at least twice as fast as normal.
3= Severe, things seem to be happening at least 10 times faster than normal.
4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.

14. Have there been things which have happened during this interview [assessment] that now you can't account for?
0= Not at all.
1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.

2= Moderate, at least once there were things which happened which now I can't account for.
3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.

15. Have you spaced out, or in some other way lost track of what was going on during this experience?
0= Not at all.
1= Mild, I have had some episodes of losing track of what is going on, but I have followed everything for the most part.
2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3= Severe, I have lost several segments of time of one minute or more.
4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Have sounds almost disappeared or become much stronger than you would have expected?
0= Not at all.
1= Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem very real, as if there is a special sense of clarity?
0= Not at all.
1= Mild, things seem to be a little bit more real than normal.
2= Moderate, things seem to be more real than normal.
3= Severe, things seem to be very real or have a special sense of clarity.
4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
0= Not at all.
1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.

4= Extreme, I cannot make anything out around me.

19. Do colors seem much brighter than you would have expected?
0= Not at all.
1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
2= Moderate, colors seem brighter, about twice as bright as normal.
3= Severe, colors seem very bright, at least five times as bright as normal.
4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as bright as normal.

20. Do you feel confused about who you really are?
0= Not at all.
1= Mild, I feel a little bit confused about who I am.
2= Moderate, I feel confused about who I am, but I basically know who I am.
3= Severe, I feel very confused about who I am, and at times I wonder if I am a person, or if I am many people.
4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
0= Not at all.
1= Mild, I feel like there are different sides of myself, but they're basically part of myself.
2= Moderate, I feel like I have different parts which don't quite fit together.
3= Severe, there are two or more sides to myself which have unique characteristics.
4= Extreme, I have two or more parts to myself with unique personality characteristics.

22. Do you have gaps in your memory?
0= Not at all.
1= Mild, there are some recent things which I cannot remember.
2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.

23. Do you feel like you have more than one identity?
0= Not at all.
1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
4= Extreme, I have two or more personalities which are distinct and have their own

names and other unique characteristics.

Figure 1. The timeline of the infusion and assessment of the patients prior, during and after the infusion.

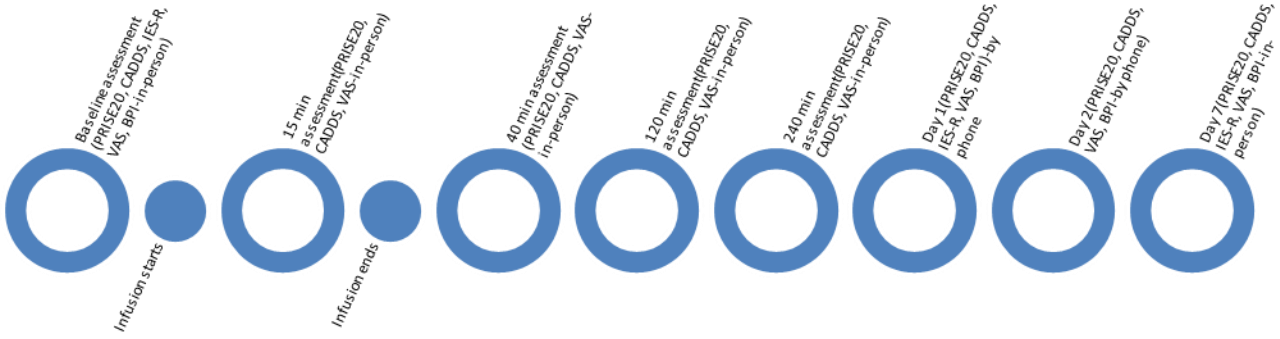


Figure 2. Visual Analog Scale

The Visual Analog Scale (VAS) is a 100-millimeter line with "no pain" on one end and "pain as bad as it can be" at the other end. This scale is a very simple form of assessment. Patients are expected to mark on the line the amount of pain they are experiencing.

Patients with visual impairment find this scale difficult to use, and some elderly patients have difficulty marking on the line (Herr 1993, AHCPR 1994, D'Arcy 2003).

|_____|

No pain **Pain as bad as it could possibly be**