**Review of Several Ketamine Studies**

**A consensus statement on the use of ketamine in the treatment of mood disorders.**

            A review of data from seven placebo-controlled, double-blind, randomized clinical studies on the treatment of depression with ketamine, showed “compelling evidence that the antidepressant effects of ketamine infusion are both rapid and robust, albeit transient” (Sancora, Frye, McDonald, Matthew, Turner, Schatzberg, Summergrad, & Nemeroff, 2017). The strongest data supporting ketamine’s clinical benefit in psychiatric disorders are in the treatment of major depressive episodes without psychotic features associated with major depressive disorder (MDD). Most studies on ketamine treatment have evaluated its efficacy only during the first week following a single infusion. The typical infusion doses of these studies were 0.5 mg/kg per 40 minutes IV.

            Studies of short term repeated administration of ketamine have limited data with small case reports and only a small number of randomized controlled trials available. One randomized, placebo-controlled clinical trial studied the efficacy of ketamine on 68 treatment-resistant MDD patients. Subjects were given ketamine 0.5 mg/kg IV over 40 minutes either two times a week or three times a week for two weeks. Results showed both dosing regimens were almost equal in efficacy. After two weeks, patients who received ketamine two times a week showed a 69% rate of response and 37.5 rate of remission, and those treated with ketamine three times weekly had a 53.8% rate of response and 23.1% rate of remission. In the open-label phase of the study, subjects were able to continue with ketamine infusions at the dose frequency they were originally assigned for an additional two week period. At the end of four weeks of treatment, the 13 patients who continued to receive twice a week dosing had a mean 27-point reduction in the Montgomery-Asberg Depression Rating Scale score compared with a 23-point decrease for the 13 patients who received ketamine three times weekly.

            In general, most reports showed the majority of benefits occurring early in the course of treatment, but some reports did show some cumulative benefits of continued treatment. Only one report showed that an increased dose of ketamine (greater than 0.5 mg/kg per 40 minutes) may lead to a response to treatment in patients who had previously not responded. There is limited published data on long term effectiveness of ketamine treatment in mood disorders.

**The promise of ketamine for treatment-resistant depression: Current evidence and future directions.**

Individuals with treatment resistant depression tend to be more depressed, more disabled, and more likely to experience relapses than non-TRD individuals. In a randomized, placebo-controlled trial, 64.8% of TRD patients were responsive after a single 40-minute ketamine infusion (DeWilde, Levitch, Murrough, Matthew, & Losivescu, 2015). Relapse after a single dose of ketamine often occurs within one week upon study review. In an open label study by Murrough et al., the effects of repeated ketamine infusions in unipolar depressive patients were examined. Patients received up to six ketamine infusions over two weeks and had a 70.8% response rate. The average relapse after the last infusion was 18 days. A pilot RCT of intranasal (IN) ketamine in TRD patients found that IN ketamine has a 44% response rate compared to a 6% response rate in the saline placebo-controlled patients. Response was sustained for 48 hours post ketamine administration. Minimal psychotomimetic and dissociative effects were found, and IN ketamine was well tolerated by participants. The difference in response rates between IV and IN ketamine may be related to the lower bioavailability of IN administration (25-50%).

**The use of ketamine in complex regional pain syndrome: Possible mechanisms. (A Randomized Controlled Trial)**

            A randomized, double-blind, placebo-controlled, parallel group trial of 60 CRPS patients conducted by Sigtermans et al. (2009) used a 4.2 day continuous low-dose ketamine infusion that was titrated to pain relief. Patients were evaluated for 12 weeks following the infusion and it was found that pain scores were significantly decreased for ten weeks. The mechanism hypothesized for ketamine’s effect was long-term desensitization of the NMDA receptor. Authors noted that ketamine’s effect was not related to length of disease. 90% of patients experienced mild to moderate hallucinations during the infusion and midazolam was used to dampen psychomimetic complications. Even though substantial pain relief was obtained, there was no functional improvement of patients.

            A randomized, placebo-controlled, double-blind outpatient study conducted by Schwartzman, Alexander, and Grotherson (2011) on 19 patients with CRPS also showed pain reduction after extended ketamine infusions. Patients were given ten consecutive infusions (4 h/day x 5 days; weekend off; 4 h/day for the next 5 days) at a maximum rate of 0.35 mg/kg/h not to exceed 100 mg over a 4-hour infusion period. It reduced the affective component of pain (McGill Pain Questionnaire) by 50% for three months. In 2011, Dahan et al. conducted a randomized, placebo-controlled trial on 60 CRPS patients. Subjects were given S-ketamine 5-20 mg/h over 4.2 days vs placebo. The ketamine infusion resulted in 50 days of significant pain relief.

            In 2008, Kiefer et al. conducted an open-label trial on 20 patients using anesthetic doses of ketamine, creating a ketamine coma. Patients were kept intubated for five days under a continuous infusion of ketamine at seven mg/kg/h, midazolam 0.4 mg/kg/h and a daily dose of 0.1 mg of clonidine. Results included complete remission from CRPS in all patients at one month, 17 out of 20 at three months, and 16 out of 20 at six months. Ten of the original patients have remained completely pain free from five to 11 years, returning to normal life in all aspects and taking no pain medication.

**Efficacy and safety of ketamine in patients with complex regional pain syndrome: A systematic review.**

            A 2012 review on ketamine in CRPS patients included three RCTs, seven observational studies, and nine case reports (Azeri, Lindsey, Briones, Clarke, Buchheit, & Pyati, 2012). These studies showed evidence that ketamine has both acute efficacy and long-term implications in the management of complex regional pain. Schwartzman et al.’s RCT showed a 27% decrease in pain scores on the numerical rating scale (NRS) for pain after IV ketamine therapy compared with 2% in the placebo group. There was also decreased night-time awakening and decreased spontaneous burning pain in the treatment group. The RCT conducted by Sigtermans et al. showed that pain scores on the NRS were significantly lower in the ketamine treatment group than in the placebo group over a 12-week period. The lowest pain scores were noted one week post ketamine treatment. In the third RCT conducted by Finch et al., CRPS patients were treated with topical 10% lidocaine twice in a period separated by one week. This study concluded that topical ketamine did not lead to pain reduction in these patients but it did reduce allodynia (pain response following normally non-painful stimuli).

            There is no consensus in the literature on the dose and duration required for systemic administration in the treatment of CRPS. This is because dosages and durations varied greatly between studies. The IV route of administration was most widely used. However, topical and oral routes showed some effectiveness. Adverse effects noted with ketamine administration included feelings of inebriation, nausea, psychotomimetic effects and headaches. Hypertension and elevated liver enzymes were also noted but resolved after termination of the ketamine infusion. Cognitive effects of ketamine were extensively evaluated in Koffler et al.’s study by several neuropsychological tests prior to ketamine infusion and at six weeks post infusion. Their study concluded there were no residual cognitive effects at six weeks.

**Effects of low-dose IV ketamine on peripheral and central pain from major limb injuries sustained in combat. (A Retrospective Case Series)**

            In a case series, 19 patients were given continuous low-dose (< 0.12 mg/kg/h) IV ketamine over three days (Polomano, Buckenmaier, Kwon, Hanlon, Rupprecht, Goldberg, & Galleger, 2013). These patients had inadequate pain control from previous multimodal analgesia and presented with neuropathic pain from major limb injuries sustained in combat. Over time, there was a significant decrease in present pain intensity (PPI) and improvement of global pain relief (GPR). Higher baseline worst pain intensity (WPI >7 on 1-10 scale) scores were associated with a significant decrease in WPI scores, whereas lower baseline WPI scores were not. Mean opioid requirements also decreased after 24 hours of ketamine therapy. This study concluded that low-dose ketamine infusions for complex combat injury pain were safe and effective. Ketamine appeared to have more significant effects on pain in those presenting with higher baseline pain scores.

**Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: A 5-year retrospective analysis.**

            Outpatient IV ketamine infusions were evaluated for efficacy in patients suffering from various chronic intractable pain syndromes (Patil, & Anitescu, 2012). Data from a university pain clinic was analyzed from 2004-2009. All patients reviewed had refractory pain for at least six months and received outpatient ketamine infusion treatments with no changes to their current medications over the previous month. Patients were pretreated with midazolam and ondansetron with an initial ketamine dose of 0.5 mg/kg over 30-45 minutes. Initial dose was continued for subsequent doses if deemed effective. If not, ketamine doses were increased in subsequent doses, as tolerated, to produce analgesia without unacceptable side effects. Ketamine infusions were discontinued when pain relief was not adequate.

            Results from 49 patients receiving a total of 369 outpatient ketamine infusions were reviewed. 37% of the patients were diagnosed with CRPS while the remaining 63% had refractory headaches, severe back pain, somatic pain, fibromyalgia, central neuropathic pain, and postherpetic neuralgia. All patients reported significant reduction in their visual analog score (VAS). For patients with CRPS, reduction in VAS score was 7.2, and a 5.1 reduction was noted for all others. Relief lasted for up to three weeks in half of the patients.

**Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial.**

            A randomized, double-blind, placebo-controlled, crossover trial compared ketamine to midazolam in 41 patients with chronic PTSD related to a range of trauma exposures (Feder et al., 2014). Effects were evaluated 24 hours post a single subanesthetic dose (0.5 mg/kg) of ketamine IV versus midazolam (0.045 mg/kg) IV. Compared to the placebo, ketamine was associated with significant and rapid reduction in PTSD symptom severity. Ketamine was also associated with reduction in comorbid depressive symptoms and with improvement in overall clinical presentation.

**Ketamine as a potential treatment for suicidal ideation: A systematic review of literature.**

            Six studies and three case reports were reviewed to assess the effects of subanesthetic ketamine administration on suicidal ideation (SI) (Reinstatler, & Youssef, 2015). Each study demonstrated a rapid and clinically significant reduction in SI, with results similar to previously described data on ketamine and TRD. The review included 137 patients with SI who were treated with ketamine. Seven studies used 0.5 mg/kg IV doses over 40 minutes, one study administered 0.2 mg/kg IV bolus, and another study administered a liquid suspension. Earliest significant results were observed after 40 minutes with longest results of up to ten days post infusion. In conclusion, ketamine resulted in rapid reduction in SI with minimal short-term side effects.

**Ketamine infusions for treatment of refractory headache. (A Retrospective Review)**

            A retrospective review was completed on 77 patients who underwent administration of subanesthetic dose ketamine for chronic migraine or new daily persistent headache (Pomeroy, Marmura, Hahas,& Viscusi, 2016). Records were reviewed from January 2006 to December 2014, and included only patients who had previously failed aggressive outpatient and inpatient treatments. Most patients had failed at least one series of nerve blocks and had been hospitalized for headaches several times before. Migraine preventative medications and medications for other conditions were continued during ketamine treatment.

            Ketamine treatment was administered via continuous IV for a maximum of 5 days. Initial doses were started at 0.1 mg/kg/h and increased by 0.05 mg/kg/h hourly until pain relief, nystagmus, or mild inebriation was present. When an infusion rate of 0.25 mg/kg/h was achieved the rate was maintained for six hours to assess side effects before further dose increases. If pain relief was inadequate, dose was titrated to effect as tolerated. Max dose was typically limited at 1 mg/kg/h. According to the numeric rating scale of 0-10, the average pain rating upon admission was 7.1. At discharge, the average pain score had dropped to 3.8. The majority of patients (71.4%) were classified as acute responders with at least a two point improvement in headache pain at discharge. 27.3% of acute responders maintained this benefit at their follow-up office visit within one month of their admission date, but sustained response was not significant.

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