PALLIATIVE CARE
CASE OF THE MONTH

"Ketamine – A promising antidepressant?"
by
April Christensen, MD

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Case:

Mr. S is an 81-year-old man with Stage IV non-small cell lung cancer who was admitted to inpatient hospice in a pain crisis. During his time at the inpatient unit, he reported months of ongoing depression interfering with his sleep and his ability to enjoy time with his family. He had a history of recurrent depression, most recently two years ago, for which he had previously been on sertraline and duloxetine of unknown doses without clear benefit. He had not been on any recent antidepressants and had never seen a psychiatrist or psychologist in the past.

In the two weeks prior to admission, Mr. S had experienced a precipitous decline in functional status. At the time of inpatient admission, he was no longer able to ambulate and was becoming fatigued with sitting on the side of the bed. His appetite had also decreased dramatically during this same period.

Discussion:

Depression affects people with cancer at approximately two to three times the rate of the general population.[1] Cancer patients receiving palliative care or hospice may have an even higher rate, with a 20% prevalence in one study and other data suggesting a prevalence as high as 42%.[2-3] Despite the impact of depression on cancer patients, a 2015 Cochrane Review found little evidence that typical antidepressants are more effective than placebo.[4]

Over the past two decades, ketamine received increasing attention as a potential rapid-acting antidepressant, particularly for treatment-resistant depression with suicidal ideation, and more recently for hospice paitents.[2,5] While ketamine is not appropriate for routine clinical care at this time given insufficient data, preliminary results suggest it may be highly effective in specific populations.

It was first synthesized in 1962 through attempts to create a shorter-acting analog of phencyclidine with similar anesthetic effects and less delirium.[6] Ketamine's primary mechanism of action is as a N-methyl D-aspartate (NMDA) receptor antagonist, although it also is an agonist of mammalian target of rapamycin (mTOR), blocks muscarinic acetylcholine receptors, interacts with CN1 channels, inhibits serotonin reuptake, and has affinity for σ receptors.[7,8] At an epigenetics level, ketamine inhibits histone deacetylase and has variable activity on microRNAs.[8] Due to its multifaceted effects, it has been dubbed the "pharmacologist's nightmare.[8]"

Despite its approval in 1970 by the Food and Drug Administration for anesthesia, it was not until the 1990s that researchers became aware of its potential as an antidepressant.[5] An early study published in 1990 demonstrated the effectiveness of other NMDA antagonists in animal models.[9] Based on this and additional animal studies in the mid-90s, researchers at Yale completed the first study of ketamine's effectiveness in humans.[10] In the randomized, placebo-controlled, crossover study, four of eight patients demonstrated a greater than 50% decline in their Hamilton Depression Rating Scale (HDRS) scores three days after a ketamine infusion compared to only one in the saline placebo group. Mood returned to baseline within one-two weeks after the infusion.

Another randomized, placebo crossover study published by Zarate et. al. in 2006 demonstrated response rates to a single ketamine infusion of 71%; this rate was higher than that in studies of traditional antidepressants, which ranged from 62-65%.[11-12] In the Zarate study, symptom improvement was demonstrated within two hours and was maintained for a week. These unexpected findings compelled further research into ketamine as an antidepressant.

The majority of randomized controlled trials (RCTs) on ketamine since the Zarate study have examined only one-time infusions with a follow-up of less than two weeks, particularly for those with resistant depression. In two meta-analyses of these studies, ketamine significantly reduced depressive symptoms on both day one and day seven post-infusion.[5,13] The number needed to treat (NNT) to achieve a clinical response on day one was 3 while the NNT for a clinical remission was 5.[13] This occurred with minimal side effects, including psychotomimetic effects which abated within a couple hours after infusion and no adverse events in the majority of studies.[13]

Given the lack of sustained response following a single infusion, a few studies have started to explore repeat infusions.[13,14] One study that examined three infusions per week for two weeks had a 71% response rate with a median relapse of 18 days after the final infusion.[14] At 83 days, 25% of those who responded remained in remission. As this study highlights, appropriate induction and maintenance protocols for IV ketamine have yet to be elucidated.

While repeat infusions of ketamine for depression have multiple financial and practical constraints, other methods of administration have been limited by bioavailability.[13] Intranasal ketamine has a bioavailability of 45% while oral ketamine undergoes extensive first-past metabolism to the less-potent norketamine.[6,15] These varied approaches to ketamine administration have contributed to mixed literature on dosing, frequency of administration, and effectiveness.

The first paper to examine the potential use of oral ketamine for depression in hospice patients reviewed two cases from an open-label study at San Diego Hospice.[16] In these two cases, patients who had failed to respond to typical antidepressants were given a single dose of 0.5mg/kg of oral ketamine.[16] Both patients experienced significant improvement of anxiety within a few hours after administration and decreased depression within the first three days; the effects were maintained for several weeks.[16]

(Discussion continued)

These results prompted further examination of oral ketamine and its potential use for depression at the San Diego Hospice.[2] In the first published open-label study, 14 patients were started on oral ketamine at a 0.5mg/kg dose for 28 days. Four patients withdrew after day 14 due to lack of response and two withdrew for unrelated reasons. Of the eight who completed the study, all showed a greater than 30% decrease in the Hospital Anxiety and Depression Scale (HADS). The response rate per intention-to-treat analysis was 57% with a novel finding of 100% response rate in anxiety, including the four who withdrew at 14 days. Despite the promising quick onset in the previous paper, this study noted time to response was longer than for IV infusion, one-two weeks rather than hours.

In total, these studies suggest that oral ketamine may have a unique role in depression, including for those with resistant depression or limited life expectancy, with relatively few potential side effects. Nevertheless, given the varied dosing strategies employed by the available studies, small sample sizes, lack of RCTs in hospice patients, and challenges associated with route of administration, significantly more research is needed in this area prior to clinical use.[17]

Resolution of the Case:

Given his rapid functional decline with limited life expectancy, we considered starting oral ketamine totaling 30mg/day as a more rapid-acting antidepressant. In discussion with Mr. S, he ultimately decided not to pursue treatment for his depression due to his concern about taking too many medications. He also expressed that he was an independent person and did not want to be reliant on medication for his mood. He was subsequently transitioned to home and passed away approximately a week later.

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