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Ketamine for the Treatment of Depression in Patients Receiving Hospice Care: A Retrospective Chart Review of Thirty-One Cases

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Abstract

Background—Depression is prevalent in patients receiving hospice care. Standard antidepressant medications do not work rapidly enough in this setting. Evidence suggests that ketamine rapidly treats treatment refractory depression in the general population. Ketamine's role for treating depression in the hospice population warrants further study.

Methods—A retrospective chart review of 31 inpatients receiving hospice care who received ketamine for depression on a clinical basis was conducted. The primary outcome measure was the Clinical Global Impression Scale, which was used retrospectively to rate subjects' therapeutic

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improvement, global improvement, and side effects from ketamine over 21 days. Additionally, time to onset of therapeutic effect was also analyzed.

Results—Using the CGI, ketamine was found to be significantly therapeutically effective through the first week after ketamine dosing (p < 0.05), with 93% of subjects showing positive results for days 0 – 3 and 80% for days 4 – 7 post ketamine dosing. Subjects experienced global improvement during all four time periods post ketamine dosing (all p-values < 0.05). Significantly more subjects had either no side effects or side effects that did not significantly impair functioning at each of the four assessed time periods post ketamine dosing (all p-values < 0.05). Additionally, significantly more subjects experienced their first therapeutic response during days 0–1 post ketamine dosing (p < 0.001) than during any other time period.

Conclusions—These data suggest that ketamine may be a safe, effective, and rapid treatment for clinical depression in patients receiving hospice care. Blinded, randomized, and controlled trials are required to substantiate these findings and support further clinical use of this medication in hospice settings.

Introduction

Depression is one of the leading causes of disability worldwide (1) and is associated with increased morbidity and mortality (2–5). Standard antidepressants typically take four to six weeks to reach maximal effectiveness, and monotherapy with standard antidepressants is only effective approximately 35% of the time, often necessitating multiple trials of antidepressants (6, 7). Thus, there is mounting interest in possible treatments for depression that work more rapidly. This is especially true for populations with short prognoses, such as those receiving hospice care.

Psychostimulants, such as methylphenidate, are often used in hospice settings to rapidly treat depression, with some evidence to support this practice. (8–17) However, methylphenidate does not work for every patient, and its use can be limited by the development of anxiety, insomnia, agitation, and at times, mania. (18, 19)

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is another possible treatment. A growing body of literature, ranging from case reports to randomized controlled trials, supports the use of sub-anesthetic doses of intravenous (IV) infusions of ketamine at 0.5 mg/kg over 4 hours to treat depressive symptoms in individuals with treatment resistant depression (20–37). Ketamine's antidepressant properties are thought to be associated with its effects on the NMDA-receptor channel, glutamate transmission, mTOR-dependent synapse formation, cholinergic transmission, noradrenergic and serotonergic reuptake inhibition, as well as its interactions with other calcium and sodium channels (38–40).

Ketamine's antidepressant properties are of great interest for patients receiving hospice care. Up to 42% of hospice patients have symptoms of depression. (41–43) Untreated depression in patients receiving hospice care is associated with significant morbidity and mortality. (44,

45) Since the average time patients received hospice care in the US in 2012 was around 10 weeks, (with the median being less than 3 weeks)(46) and because standard pharmacologic treatments for depression take several weeks to reach maximal effect, many hospice patients will not live long enough to realize the benefits of standard treatments for depression. For these reasons, there is a growing interest in pharmacological treatments for depression with a rapid therapeutic effect such as ketamine.

Notably, a robust literature supports the safe and tolerable use of sub-anesthetic doses of ketamine for the treatment of pain in hospice patients (47–56). Furthermore, in both a small case series and an open label-trial, oral ketamine was found to be a fairly rapid, safe, and tolerable treatment for depression in patients receiving hospice care (57–59). In addition, these studies described a decrease in symptoms of anxiety with no insomnia or psychomimetic effects noted. In fact, most somatic symptoms improved.

Data from a retrospective chart review of the use of ketamine to clinically treat depression in patients receiving hospice care are presented in this paper. The objectives of this study are to provide preliminary data about the efficacy, tolerability, time to efficacy, duration of response, and side effects of ketamine for the treatment of depression in patients receiving hospice care. These results will inform future randomized controlled trials that are needed to definitively answer such questions.

Methods

The study was approved by the San Diego Hospice and The Institute for Palliative Medicine Institutional Review Board. Pharmacy data from 2005–2011 were used to identify patients who had received ketamine while being treated at an inpatient hospice care center. Thirty-three patients were prescribed ketamine for depression and 31 of these received ketamine for the first time during their inpatient admission. A retrospective review of these 31 charts was conducted.

Inter-rater reliability was established using three charts (10%). Each of these three charts was reviewed by all three raters, two of whom were board certified psychiatrists and one of whom was a board certified palliative care specialist. For the remaining 26 charts, each chart was reviewed by one of these three raters.

Each chart was evaluated for 1) demographic variables, 2) psychiatric diagnoses and treatments, 3) ketamine dosage, route, and frequency of dose, 4) time to first response of depressive symptoms, 5) time to maximal response of depressive symptoms, 6) duration of response to ketamine, and 7) ketamine related side effects. Data was collected for pre-determined time periods consisting of days 0–1, 2–3, 4–7, and 8–21 post-ketamine dosing. These time periods were chosen to capture possible rapid effects of ketamine, protracted effects, and longer-term effects based on the literature and our experience with an open-label trial. (58) In addition, we wanted to be vigilant about adverse events. Lastly, as this was a retrospective review, depression may not have been evaluated or commented on each day by the primary palliative care team.

The Clinical Global Impression (CGI) scale was completed retrospectively based on palliative care team charting to evaluate subjects' baseline clinical status pre-ketamine dosing and changes in the subjects' clinical outcomes/side effects post-ketamine dosing. (60) CGI ratings were determined based on the notes regarding depression written by psychiatric consultants, primary physicians, nurses, and social workers each day of the inpatient admission prior to ketamine dosing and each day during the four assessment time periods, as available. Depression was not necessarily commented on in the charts each day for each patient.

Global improvement ratings on the CGI reflect improvement, whether or not the improvement is due entirely to the drug treatment and range from "very much improved" (score of 1) to "very much worse" (score of 7) with (1) very much improved; (2) much improved; (3) minimally improved; (4) no change; (5) minimally worse; (6) much worse; and (7) very much worse. Scores of 1–3 were categorized as positive outcomes and scores of 5–7 were categorized as negative outcomes.

The Efficacy Index of the CGI has two components, the therapeutic effect and side effects, and is based specifically on the drug effect (i.e. response to ketamine). The therapeutic effect reflects how much the condition has improved related to the study medication and ranges from "unchanged or worse" (score of 1) to "marked" improvement (score of 4) with (1) unchanged to worse; (2) minimal; (3) moderate; and (4) marked improvement. Scores of 1 were categorized as negative outcomes and scores of 2–4 were categorized as positive outcomes.

Side effect ratings on the CGI's Efficacy of Index range from "none" (score of 1) to "outweighs therapeutic effect" (score of 4) with (1) none; (2) do not significantly interfere with patient functioning; (3) significantly interferes with patient functioning; and (4) outweighs therapeutic effect. Scores of 1–2 were categorized as positive outcomes and scores of 3–4 were categorized as negative outcomes.

Simple, formal, two-sided significance tests, based directly on binomial distribution and providing exact p – values, were performed for each CGI measure categorized into negative outcome versus positive outcome classifications and assumed as the null hypothesis that a subject had an equal chance of being classified in each.

For patients who only received one dose of ketamine, exact p – values, using a binomial distribution, were also obtained for the analyses of 1) time to first response, 2) time to maximal response, 3) time to fading of response, and 3) number of side effects, with the null hypothesis being that subjects had an equal chance of being in each cell (with the cells being the time periods of days 0–1, 2–3, 4–7, and 8–21 post-ketamine dosing for the analyses of "time to …"; and 0 side effects, 1 side effect, 2–3 side effects, and 4 or more side effects for "number of side effects").

Results

Sample

The sample was comprised of 11 male and 20 female subjects. The subjects ranged in age from 44 to 89 years, with a mean age of 68 years and a median age of 66 years (Table 1). The observed numbers of subjects for the CGI analyses were: 29 for days 0–1; 28 for days 2–3; 20 for days 4–7; and 10 for days 8–21 post ketamine dosing respectively, except that only 28 patients were noted to be observed for side effects during the days 0–1 post ketamine dosing period.

Ketamine Dosing

Twenty two patients received a single dose of ketamine at 0.5 mg/kg, and five received a single 0.5 mg/kg dose followed by a single repeat dose of 0.5 mg/kg. Four received three times a day dosing each day they were studied, each dose again at 0.5 mg/kg. Twenty nine patients received an oral formulation of ketamine, one received a single oral dose followed by a single subcutaneous dose, and one received a single subcutaneous dose (Table 2).

Inter-rater Reliability

For measuring Global Improvement, the three raters had substantial agreement with Fleiss's kappa = 0.65 ($p < 0.001$, 95% CI (0.45, 0.85)) and Kendall's coefficient of concordance of 0.99 ($p = 0.002$, 95% CI (0.91, 1)).

For the Efficacy Index, the three raters had almost perfect agreement with Fleiss's kappa = 1 ($p < 0.001$, 95% CI (0.80, 1)) and Kendall's coefficient of concordance of 1 ($p < 0.001$, 95% CI (0.93, 1)).

Response to Ketamine

Therapeutic Effect Scale of the CGI—For the therapeutic effect rating on the CGI, positive therapeutic outcomes were more common than negative therapeutic outcomes at time periods days 0–1 ($p < 0.001$), days 2–3 ($p < 0.001$), and days 4–7 ($p < 0.05$) post dosing (Table 3a). Overall, ketamine was therapeutically effective through the first week post dosing. Figure 1A shows the therapeutic effect scale of the CGI outcomes, in which 93% of the patients showed positive results during days 0–3, 80% during days 4–7, and 60% during days 8–21 post dosing (Figure 1A).

Global Improvement Scale of the CGI—For the global improvement measure of the CGI, which assesses overall clinical improvement whether or not it was thought to relate to ketamine administration, positive therapeutic outcomes were more common than were negative therapeutic outcomes at all assessed time periods post ketamine dosing ($p < 0.05$ at days 0–1, 2–3, 4–7, and 8–21 post ketamine dosing) (Table 3b). Figure 1B shows the outcomes for the CGI global improvement scale, in which 52%, 46%, 55%, and 80% of the patients had positive global improvement over the respective four post dosing assessment periods and no patients were classified as "much worse" or "very much worse" at any time point.

Time to First Response—Of the 22 subjects who received a single dose of ketamine, we were able to determine the time to first response for 14 subjects. Ten had their first response either on the day of ketamine dosing or day 1 post ketamine dosing and 4 had their first response on days 2–3 post ketamine dosing. None had their first response on days 4–21 post ketamine dosing. Significantly more subjects showed their first response on days 0–1 post ketamine dosing ($p < 0.05$) than at any other time point (Table 4).

Time to Maximum Response—Of the 22 subjects who received a single dose of ketamine, we were able to determine the time to maximum response for 11 subjects. Maximum response occurred for 4 subjects on days 0–1, 4 subjects on days 2–3, 2 subjects on days 4–7, and 1 subject on days 8–21 post ketamine dosing. There were no statistically significant differences indicating that maximal response occurred during one time period more commonly than any other (Table 4).

Fading of Response—Of the 22 subjects who received a single dose of ketamine, we were able to determine the time that the response started to fade for 6 subjects. The fading of response started in 5 subjects on days 2–3 and 1 subject on days 4–7 post ketamine dosing and was more common on days 2–3 post ketamine dosing ($p < .05$) than at any other time point (Table 4).

Side Effects

Side Effect Scale of the CGI—For the side effect measure of the CGI, the vast majority of subjects did not experience clinically significant side effects. More subjects had positive therapeutic outcomes (either no side effects or side effects that had no interference with functioning) than negative therapeutic outcomes (either significantly interfered with functioning or outweighed therapeutic effects) at all assessed time points post ketamine dosing ($p < 0.001$ at days 0–1 and 8–21 and $p < 0.05$ at days 2–3 and 4–7 post ketamine dosing) (Table 3c).

Figure 1C summarizes the data from the side effect scale of the CGI. Ninety-six percent, 71%, 85%, and 100% had either no side effects or side effects which did not interfere with functioning over the respective four post dosing assessment periods.

Side Effect Descriptions—Of those who received a single dose of ketamine, 9 experienced possible ketamine related side effects. All of the reported side effects were categorized as psychiatric: 7 subjects (45.5%) experienced disorientation, 4 (18.2%) had hallucinations, 4 (18.2%) had sedation, 1 (4.5%) had insomnia, 1 (4.5%) had delusions, and 1 (4.5%) had anxiety. Three (13.6%) had only 1 side effect, and 6 (27.3%) had 2–3 psychiatric side effects. Thirteen subjects (59.1%) had no side effects. Significantly more subjects had no side effects than any number of side effects ($p < 0.05$) (Table 4).

Discussion

This retrospective chart review represents a first step in providing preliminary data about the efficacy, tolerability, time to efficacy, duration of response, and side effects of ketamine for the treatment of depression in patients receiving hospice care. These results suggest the

utility of moving forward with randomized controlled trials. The overall findings support the potential for rapid efficacy and acceptable tolerability of ketamine in treating depression in this population. Ketamine, which was dosed orally the majority of the time, demonstrated rapid antidepressant properties, with efficacy typically occurring within 1 day of ketamine dosing.

The sustained effects of ketamine dosing were mixed. The vast majority of subjects in this study only received a single dose of ketamine and over half of those who experienced clinical benefit from ketamine started to show a fading of their response between days 2 and 7 post ketamine dosing, which is consistent with findings in the literature. (20–37) However, a recent open label trial indicates that daily dosing is associated with minimal side effects and a more sustained effect (58). Further study is required to determine when and how frequently ketamine dosing should be repeated, and by what route.

Ketamine was well tolerated by the subjects in this study. Most subjects did not appear to experience any side effects from ketamine. When side effects were present, they were all categorized as psychiatric rather than somatic. This fits the findings from the open label trial (58), which suggested that side effects were rare and somatic symptoms often lessened after ketamine dosing. Ratings indicate that when side effects were present, they rarely interfered with functioning, suggesting that they were mild and likely tolerable. However, caution should be used when considering these results given the high propensity for delirium in this population. (61)

The vast majority of subjects received ketamine by the oral route. The effectiveness and safety of ketamine use might theoretically improve with oral administration due to first pass metabolism to norketamine (62). Importantly, oral dosing is much more practical and less invasive than is intravenous dosing in many patient populations, especially hospice populations. It can be administered in ambulatory care settings and does not require advanced hospital resources or the presence of anesthesia services. Furthermore, complications of intravenous catheter placement are numerous, especially in medically ill populations and include placement difficulty, diminishing site availability, need for site rotation every few days, infection, malfunction, thrombosis, and extravasation--all of which decrease comfort and increase the cost of care (63–65). The ability to effectively dose ketamine orally would be beneficial for all patients, especially those with serious medical illness and those who prefer to receive treatment in settings other than a hospital.

A chart review comes with natural limitations. It is not randomized, controlled, blinded or prospective in nature. Symptoms and diagnoses are not always documented consistently in the medical chart, nor are they documented in a scientifically rigorous way. One must thus take caution in generalizing the results of this study, both within the hospice population as well as to other patient populations. Another limitation of this particular study is the average hospice length of stay of the patients who were included exceeded national averages. Thus, these results may be less generalizable to typical hospice populations. However, these subjects still represent an important medically ill sample of patients who benefited from palliative care provided in a hospice setting and were in need of rapid amelioration of their depressive symptoms.

Despite these limitations, the results of this exploratory chart review suggest that ketamine, which was most often orally administered, may be safe and effective for the rapid treatment of depression in a clinically diverse group of patients receiving hospice care. Further systematic study is needed to substantiate these results, as well as to determine the ideal dose, formulation, frequency of dosing, and clinical profile of patients who will best respond to and tolerate ketamine for the treatment of their depression.

A great need for a rapid acting antidepressant agent in patients receiving hospice care exists. This is a population that does not have time to wait for standard antidepressants to take effect. The treatment of depression has profound consequences on quality of life for both these patients and their families. This study helps set the stage for randomized controlled trials which can more definitively determine whether ketamine, which is inexpensive and easy to administer by multiple routes, may be an answer for this need.

Acknowledgments

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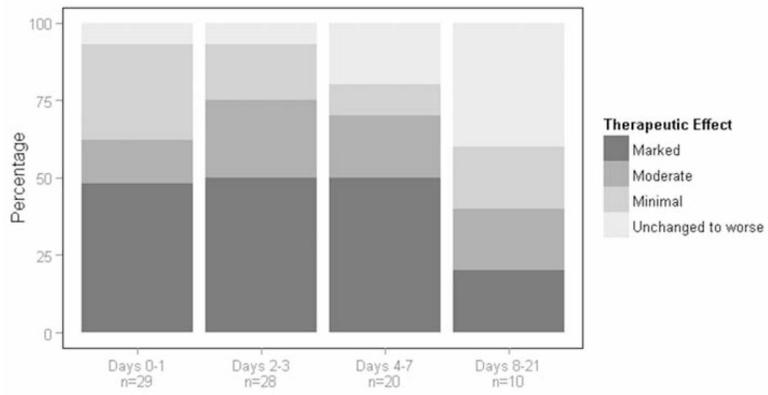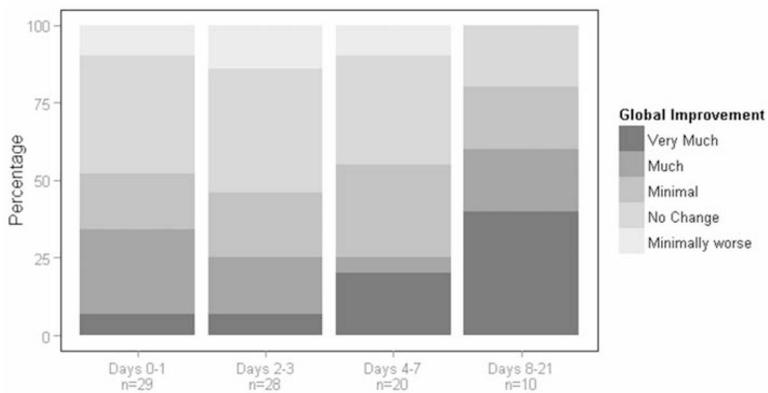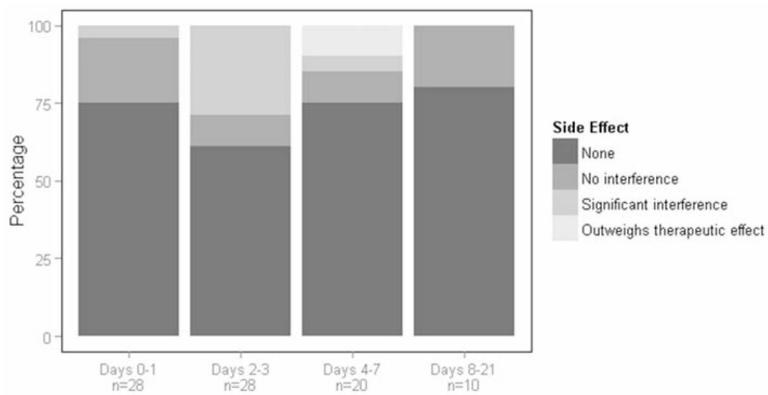
Figure 1A

Figure 1B

Figure 1C

Figure 1.
Figures 1A–C: Graphic summaries of the data. The four bars represent the four time periods post ketamine dosing and each bar goes from zero to 100 percent. Each bar designates

cumulative percentages going from the best to the worst category. Figure 1A is a graphic summary of the therapeutic index scale of the CGI and represents data from the best category of "marked improvement" to the worst category of "unchanged to worse". Figure 1B is a graphic summary of the global improvement scale of the CGI and represents data from the best category of "very much improved" to "very much worse". Since no subjects were rated as "very much worse", the worst category reflected in the figure is "minimally worse". Figure 1C is a graphic summary of the side effects scale of the CGI and represents data from the best category of "none" to the worst category of "outweighs therapeutic effect".

Table 1

Demographics

Gender	Number of Subjects
Male	11 (35.5%)
Female	20 (64.5%)
Age	**Years**
Average	68
Median	66
Range	44 – 89
Marital Status	**Number of Subjects**
Single	5 (16%)
Married	11 (35%)
Widowed	5 (16%)
Divorced	5 (16%)
Unknown	5 (16%)
Medical Diagnosis	**Number of Subjects**
Neoplasm	24 (77%)
Coronary artery disease	1 (3%)
Liver failure	1 (3%)
Failure to Thrive	2 (6%)
Debility	3 (10%)
Length of Stay on Hospice	**Number of Days**
Average	149
Median	89

Table 2

Ketamine Dosing

Dosing Route	Number of Subjects
Oral	29 (93.5%)
Subcutaneous	1 (3.2%)
Oral followed by Subcutaneous	1 (3.2%)
Dosing	**Number of Subjects**
TID dosing	4 (12.9%)
Single dose	22 (71%)
Repeat single dose	5 (16.1%)

Single Dose of Ketamine = 0.5 mg/kg

Table 3

Clinical Global Improvement Scale Results

A. Therapeutic Effect Scale of the CGI				
Classification	Days 0 – 1	Days 2 – 3	Days 4 – 7	Days 8 – 21
Positive outcome	27	26	16	6
Negative outcome	2	2	4	4
P - value	< 0.001	< 0.001	< 0.05	> 0.05

B. Global Improvement Scale of the CGI				
Classification	Days 0 – 1	Days 2 – 3	Days 4 – 7	Days 8 – 21
Positive outcome	15	13	11	8
Negative outcome	3	4	2	0
P - value	< 0.05	< 0.05	< 0.05	< 0.05

C. Side Effects Scale of the CGI				
Classification	Days 0 – 1	Days 2 – 3	Days 4 – 7	Days 8 – 21
Positive outcome	27	20	17	10
Negative outcome	1	8	3	0
P - value	< 0.001	< 0.05	< 0.05	< 0.001

Table 4

Responses to Ketamine Dosing

Days/Number of Side Effects						
Measure	**0–1**	**2–3**	**4-7**	**8-21**	**N**	**p - value**
Time to first Response (days)	10*	4	0	0	14	<0.05
Maximum response time (days)	4	4	2	1	11	>0.05
Fading Time (days)	0	5*	1	0	6	<0.05
Total # of side effects[1]	16	6	0	0	22	<0.05

*
Cell that is significantly different

[1]
For total number of side effects, the following categories were analyzed: 0, 1, 2–3, and 4 or more side effects, of which thirteen subjects had 0; three had 1; six had 2–3; and zero had 4 or more side effects.