Current Ketamine Practice: Results of the 2016 American Society of Pain Management Nursing Survey on Ketamine

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ABSTRACT:

BACKGROUND:
Ketamine is increasingly utilized for a variety of pain management challenges. Audience comments from a ketamine presentation at the 2015 American Society of Pain Management Nursing (ASPMN) Conference reflected wide variation in ketamine practices as well as barriers to use.

AIM:
The goal was to gain a greater understanding of ASPMN member practice patterns and barriers related to ketamine as adjunctive therapy for pain management.

DESIGN:
A questionnaire survey design was used.

SETTINGS:
Respondents represented 35 states and 2 countries.

PARTICIPANTS:
The participants were 146 respondents from ASPMN membership (1,485 members).

METHODS:
The survey was distributed by ASPMN on SurveyMonkey. Practice setting and ketamine administration practices were assessed with areas for comments. Results were reviewed using frequencies to

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describe responses and formatted into tables. Comments were individually reviewed and grouped into common themes.

**Results:**

Administration of ketamine as an analgesic was reported by 63% of respondents. Continuous intravenous ketamine infusions were the most common route of administration (65%); however, wide variability in dosing and length of therapy was reported. A wide variety of practices and challenges related to ketamine utilization were noted.

**Conclusions:**

Numerous studies have indicated the analgesic benefits of ketamine in pain management. The lack of practice standardization has created challenges to its consistent use and outcome measurement. Additionally, the off-label use of ketamine for pain management creates its own unique challenges. However, given the current national climate with intense focus on pain management, interdisciplinary practitioners have an ideal opportunity to evaluate ketamine’s use in a comprehensive approach to pain management.

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As the United States grapples with the ramifications of chronic opioid use, the need for non-opioid modalities to manage pain becomes more urgent. More than 100 million Americans have chronic pain (Institute of Medicine [IOM], 2013), raising the likelihood that patients with chronic pain conditions and opioid tolerance will be seen by providers in all health care settings. Traditional management of chronic pain with antidepressants, anticonvulsants, and opioids has limited efficacy, with only 30% to 40% of patients reporting improved pain management with these modalities (Niesters, Martini, & Dahan, 2013). In the 2016 Guidelines for Prescribing Opioids, the Centers for Disease Control and Prevention (CDC) recommends use of non-pharmacologic and non-opioid therapies for chronic pain, and when used, these should be used in combination with an opioid (CDC, 2016). It is increasingly clear that utilization of innovative therapies is required to provide comprehensive pain management for our patients (IOM, 2013).

The anesthetic properties of ketamine have been extensively studied over the last three to four decades. There is a growing body of research on ketamine for other indications including analgesia, antidepressant, anti-inflammatory, neuroprotective, and antitumor effects (Niesters et al., 2013). Studies of low-dose ketamine report analgesic effects caused by pain impulse inhibition at the N-methyl-D-aspartate (NMDA) receptor (Himmelscher & Durieux, 2005), as well as activation of descending modulation pathways (Niesters et al., 2013). Many studies indicate the efficacy of ketamine for chronic pain and acute on chronic pain including reduction in postoperative opioid administration. However, details for non-operative administrative dosing are lacking.

Despite 50 years of research and clinical use, there exists a lack of information on nursing care of the patient receiving ketamine; of additional concern is the lack of dosing guidelines. At the 2015 American Society of Pain Management Nursing (ASPMN) conference, participant comments during a presentation on ketamine as an adjuvant for pain suggested that although ketamine is used extensively, practice varies relative to dosing, patient selection, indications for use, and clinical practice area. The purpose of this article is to review the 2016 ASPMN membership survey results on ketamine practice patterns and barriers related to ketamine as adjunctive therapy for pain management and provide recommendations for steps to remove barriers to use.

**Literature Review**

**Mechanism of Action**

Ketamine provides analgesia by blocking the NMDA receptors (Persson, 2013), and new evidence indicates ketamine influences descending inhibitory pain pathways (Niesters et al., 2013). Side effects from the clinical use of ketamine may affect the cardiovascular, neurologic, and central nervous systems. The central nervous system side effects could include hallucinations, anxiety, and vivid dreams. These psychedelic effects explain why ketamine has become a drug of abuse (Niesters et al., 2013).

Ketamine was developed in the 1960s by a Parke-Davis scientist searching for an ideal anesthetic for veterinary medicine that would be a safer alternative to phencyclidine (PCP) (Mion & Villevicilie, 2013). The first systematic reviews exploring the analgesic properties of low-dose ketamine occurred in the 1970s (Persson, 2013). Discovery of the NMDA receptor in 1987, and its role in pain processing, generated renewed interest in ketamine as a potential anti-hyperalgesic agent (O’Brien, Pangarkar, & Prager, 2013).
The hallucinatory side effects made it a popular recreational drug, prompting ketamine to be classified as a Schedule III Controlled Substance in 1999 (Dong, Mellin-Olsen, & Gelb, 2015). In 2003, Hocking and Cousins published the first systematic review on the effectiveness of ketamine in chronic pain management, which included 11 controlled trials, 2 uncontrolled trials, 9 case reports, and 2 case series from 1966 to 2002 (O’Brien et al., 2014).

Because of its analgesic effects, ketamine is increasingly utilized for a variety of pain management challenges including neuropathic pain, acute on chronic pain, and persistent postsurgical pain. There are two commercial formulations of ketamine (Niesters et al., 2013). The racemic mixture (Ketalar by Pfizer) has been available since 1966 in the United States. The S(þ) enantiomer formulation (S-ketamine or Ketanest-S, Pfizer, Inc.) is available in the European community (Himmelscher & Durieux, 2005).

The U.S. Food and Drug Administration (FDA) classifies ketamine as a general anesthetic providing dissociative anesthesia with a wide margin of safety. Therefore, the use of ketamine as an analgesic is considered an off-label use in the United States (FDA, 2015) and by many commercial insurers. This off-label designation has far-reaching implications and affects many areas of health care, including nursing practice, practice setting utilization, and reimbursement. Interestingly, ketamine is listed as an option for the management of acute pain in remote areas (Russell et al., 2014), as well as for analgesia in combat areas (Butler et al., 2014). Ketamine is noted to be essential in low- and middle-income countries as an anesthetic because of its ease of administration (Dong et al., 2015).

**Peri-Operative Pain**

Early studies on the analgesic properties of ketamine date back to the 1970s and are not detailed here. Rather, more recent publications related to ketamine as an analgesic are highlighted. A 2006 Cochrane review of peri-operative subanesthetic dosing of ketamine indicated reduced rescue analgesic requirements or pain intensity, or both, in 27 of the 37 trials (Bell, Dahl, & Kalso, 2006). A 2009 study reported that ketamine produced a morphine-sparing effect after total hip arthroplasty, even when morphine was combined with multimodal systemic analgesia. These patients received a bolus of ketamine followed by a 24-hour infusion. Additionally, rehabilitation was facilitated at 1 month, and postoperative chronic pain was decreased up to 6 months for patients receiving ketamine (Remerand et al., 2009).

**Cancer Pain**

More recent studies on ketamine as an adjuvant for cancer pain (Bell, Eccleston, & Kalso, 2012) and comparison of daily intravenous ketamine with placebo for chronic regional pain syndrome (O’Connell, Wand, McAuley, Marston, & Moseley, 2013) have noted insufficient evidence to assess the benefits, potential for harm, and effectiveness of ketamine for these conditions. However, a study on the use of daily ketamine infusions for refractory cancer pain indicated improvement in reported pain scores and reduction in the use of morphine (Lo, Sze, Yuen, Wong, and Tung (2012). Brediau et al. (2013) noted the efficacy of oral ketamine in children with chronic pain has not been proven; however, oral dosing up to 14 days was noted to be safe in this population. In contrast, Chaparro, Smith, Wifen, Moore, and Gilron, (2013) reported that treatment with ketamine produced a statistically significant reduction in the development of chronic pain in postsurgical patients up to 3 months after surgery. A retrospective study of 460 patients who received intravenous ketamine for analgesia noted a significant decrease in pain scores (Kator et al., 2016).

**Emergency Department**

Emergency departments (EDs) have been studying ketamine extensively. Adult patients in an urban ED received IV hydromorphone and IV ketamine for severe pain, resulting in a 46% reduction in pain (Ahern, Herring, Stone, & Frazee, 2013). Intranasal ketamine resulted in a significant reduction in moderate to severe visual analog scale pain scores when used with adult patients in an ED (Andolfatto et al., 2013). Another study (Ahern et al., 2015) of 500 adult ED patients found that low-dose ketamine was a safe and feasible treatment for many types of pain.

**Chronic Pain**

Ketamine provides benefit for patients with chronic pain. A significant reduction in average pain scores was reported for patients receiving intravenous ketamine at 0.2 mg/kg/h in addition to opioids (Barrevel et al., 2013). Subcutaneous ketamine infusions given over 3 to 7 days, followed by sublingual ketamine lozenges, provided significant reduction in pain intensity that was sustained for 3 months to 6 years and reduced opioid use by 59% (Zekry, Gibson, & Aggrawal, 2016). An in vitro study (Bassani & Banov, 2015) evaluated the absorption of analgesics administered via a transdermal base. Ketamine, gabapentin, clonidine, and baclofen were compounded and had rapid penetration (1 hour for gabapentin and baclofen; dual peaks of 1 and 40 hours for clonidine; and a peak for ketamine at 6-
Methods and Analysis
Surveys are a useful tool determining practice and establishing knowledge within professional organizations (Willens, Junquist, Cohen, & Polomano, 2013). In response to the 2015 conference remarks, a 34-item ketamine usage survey was developed by the authors. Demographic and practice area information was elicited to determine if practice setting and prescribing authority affected ketamine use. It was important to understand the specifics of the practice variability; therefore, questions included area of practice, indicators for ketamine use, age range of patients, dosing, route, and frequency of administration, as well as side effects and management of these effects. Ketamine is administered primarily as a component of multimodal therapy, and the survey was designed to elicit information on these therapies as well as non-pharmacologic modalities in pain management. Many of the 2015 conference participant comments focused on barriers to the utilization of ketamine; therefore, 4 of 34 survey questions focused on the barriers with opportunity for respondent comments.

Following development of the questions and responses, the survey was formatted in SurveyMonkey. A sample survey was distributed to pain management nursing experts who provided feedback on questions. The survey questions and responses were revised based on this information. The survey was distributed to the ASPMN membership (1,485 members) and was available from December 2015 to March 2016.

RESULTS
Results were reviewed using frequencies to describe responses. Open-ended comments were individually analyzed for themes and titled to reflect key topics. A total of 146 surveys from 35 states and 2 countries were returned. The majority of respondents were MSNs (n = 70, 49%), followed by BSNs (n = 39, 28%). Most (69%) were not prescribers. Practice settings varied, with 26% of respondents working in outpatient clinics; the majority practiced in acute care settings (Table A2).

Direct Patient Care
The majority of respondents were involved in direct patient care, and more than half (53%) specialized in pain management activities. Specialty areas included pain service/management (34%), chronic pain clinic (26%), post-anesthesia care unit (PACU, 11%), palliative care (11%), pediatrics (5%), anesthesia/operating room (5%), oncology (4%), and medicine (3%). Remaining areas included emergency department, intensive care unit, family practice, and psych.

Interdisciplinary Services
A variety of interdisciplinary personnel and resources were available in the practice settings. These included a pain service (74%), anesthesia (79%), internal medicine pain specialists (11%), palliative care (55%), pain clinical nurse specialist (27.4%), pain nurse practitioner (40.7%), stress management (16%), and aromatherapy (11%). The use of an interdisciplinary team approach combined with complementary and integrative therapies was common in both inpatient and outpatient settings.

Pain Modalities
Nearly 100% of respondents reported using non-steroidal anti-inflammatory agents and acetaminophen (98%), as well as oral opioids (99%), for pain management. Other modalities included patient-controlled analgesia (PCA, 78%), intravenous opioids (76.6%), anticonvulsants (82%), anxiolytics (81%), epidural catheters (72%), peripheral nerve catheters (61%), and transverse abdominis plane (TAP) blocks (53%). Massage was utilized in 29% of practice areas. Other modalities offered (28%) included healing touch, reflexology, lidocaine infusions, acupuncture, Reiki, physical therapy, music, and behavioral medicine, as well as outpatient procedures, injections, implantable pumps and spinal cord stimulators.

Ketamine Usage
Sixty-six of respondents (63%) reported using ketamine in their practice setting, but the setting (inpatient versus outpatient) did not appear to be a defining factor (Table A3). Respondents from Australia and Canada reported ketamine is used in acute care and outpatient clinics. Within the United States, regional differences were not apparent. There was inconsistency within many states in which some of the states’ hospitals administered ketamine and others did not. This variability was independent of hospital size or academic affiliation. In other states, ketamine was administered in acute care settings but not in outpatient settings. In many organizations it was evident the use of ketamine was restricted to the operating room, PACU or intensive care unit (ICU) as well as by provider type.

In many settings, orders for ketamine are managed by more than one provider such as: anesthesia (71%), pain teams (53%), ICU/intensivists (25%), palliative care, and nurse practitioners (24%). Some settings require pharmacy consultation or review by anesthesia practice, indicators for ketamine use, age range of patients, dosing, route, and frequency of administration, as well as side effects and management of these effects. Ketamine is administered primarily as a component of multimodal therapy, and the survey was designed to elicit information on these therapies as well as non-pharmacologic modalities in pain management. Many of the 2015 conference participant comments focused on barriers to the utilization of ketamine; therefore, 4 of 34 survey questions focused on the barriers with opportunity for respondent comments.

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or an acute pain provider, whereas other areas have no such restrictions. Others who may order ketamine include physician assistants, emergency department physicians, clinical nurse specialists, and surgeons. More than 44% of practice settings use standing order sets for ketamine administration.

Ketamine is administered across the age continuum, with the majority of patients between the ages of 18 and 65 (91%). Interestingly, patients older than 65 accounted for 55% of those receiving ketamine followed by 12- to 18-year-olds (27%), 8- to 12-year-olds (14%), 3- to 8-year-olds (12%), and those younger than 3 years (5%). Monitoring (oversight) of patients while on ketamine was provided by anesthesia groups (57%), pain teams (54%), ICU/intensivists (28%), and palliative care (26%), as well as nurse practitioners and clinical nurse specialists.

Side effects related to ketamine administration are common and included vivid dreams (61.8%), hallucinations (54%), increased sedation (37%), and feelings of intoxication (35%), nausea (28%), nystagmus (24%), hypertension (20%), tachycardia (19%), diplopia (12%), and headache (11%). Rarely reported were occurrences of urinary incontinence or frequency anxiety, tunnel vision, dizziness, and excessive salivation. Respondents mentioned few side effects with oral administration. Premedication with an anti-emetic and/or benzodiazepine, as well as a lower infusion rate, was reported to decrease the intensity of the side effect. Thirty-eight percent routinely administered unspecified anxiolytics in conjunction with ketamine; a benzodiazepine was utilized in 50% of the practice settings, and midazolam (Versed), in 47%. There were many participant inquiries related to best practice management of side effects (stop infusion, decrease and/or administer anxiolytic), dosing, and level of monitoring.

Dosing Practices
There exists wide variation in ketamine dosing. Continuous IV ketamine infusion is the most common route of administration of ketamine (65%). Alternate administration methods included a one-time IV bolus of several minutes (55%), one-time IV administration (40%), and oral administration (31%). Length of one-time IV administration varied from 60 minutes to several hours. Outpatient clinics typically utilized oral, IV bolus, or one-time IV administration. One respondent noted that their clinic utilized ketamine as a 1-day intravenous treatment. Hospice utilized oral administration and continuous infusions. Acute care hospitals and academic centers utilize primarily one-time IV administration and continuous infusions.

To determine duration of ketamine therapy, respondents were asked how ketamine was administered to their patient population and the duration of therapy. This was a multiple-selection question. Results indicate a variety of infusion practices, as well as a wide range in duration of ketamine treatment (see Table A4).

To develop a comprehensive picture of ketamine dosing practices, a series of questions were asked related to starting dose and maximum. Responses indicate a lack of standardization as noted in Table A5. Starting doses were variable as was the manner in which regimens were calculated. Some were weight based, whereas others were milligrams/hour or time limited. Maximum dose was also variable and ranged from no maximum dosing to total amount infused on maximum infusion rates. Analgesia is obtained by administration of 0.2-0.75 mg/kg intravenously (Reich & Silvay, 1989). Most respondents noted that a provider was required to administer ketamine boluses and one-time IV doses.

Barriers to Ketamine Use
Respondents who do not use ketamine work in both outpatient clinics and acute care hospitals of varying size. Barriers to use include lack of provider knowledge (52%), lack of provider availability (35%), practice setting issues (27%), lack of nursing staff to monitor (20.97%), and lack of nursing knowledge (38.71%). Comments related to barriers were categorized into the following areas: practice setting/monitoring barriers, boards of nursing barriers/regulatory, insurance/reimbursement barriers, knowledge barriers, and provider barriers. Even for practice areas that utilize ketamine, there were barriers affecting utilization including challenges for policy development, intensity of monitoring, and limited utilization outside of ICUs or PACUs. Policy development and approval were noted to be a barrier to implementation in many practice settings.

Practice setting and monitoring barrier comments included the inability of outpatient clinics to offer conscious or deep sedation; increased level of care for those receiving ketamine; and lack of interprofessional coordination (see Appendix B for detailed comments). Additionally, there was a lack of resources such as space, RNs, and providers.

Regulatory barriers included state nurse practice acts limiting administration of ketamine by RNs (ketamine considered an anesthetic) and lack of licensed personnel to administer ketamine (CRNAs, PAs, NPs). Additionally, many state laws prohibit NPs and/PAs from prescribing ketamine. Insurance barriers included the following:
• Restrictions related to insurance coverage; academic center regulations versus private practice
• Payment and reimbursement
• Insurance company procedures resulting in difficulty in obtaining authorization
• Statements by insurance companies that ketamine was “experimental”
• Locating a physician to prescribe

Knowledge barriers included nursing, physician, and organizational knowledge deficits. These were related primarily to the indications for ketamine use, its benefits, its side effects, and appropriate practice setting. There were a number of free text comments about best practice for infusion rates in specific areas and administration of IV boluses, as well as administration of oral ketamine.

The positive impact of ketamine on patients’ pain was cited as a reason for continued and expanded use. In one outpatient clinic, the medical management team had years of experience with oral ketamine and found it to be very effective for some patients with chronic regional pain syndrome (CRPS). Others noted that repeated education, as well as one-on-one education, was successful in overcoming knowledge deficits related to ketamine use.

DISCUSSION

The ASPMN ketamine survey offers a small, initial analysis of practice related to the use of ketamine as an adjunct for pain management. Limitations of the survey include a relatively small sample size and limited geographic representation. Of particular note, the majority of respondents were not prescribers; all were nurses. However, the majority of those responding were engaged in pain practice and, therefore, were assumed to have expertise in this specialty. Administration of ketamine occurs in acute care and outpatient settings, independent of academic affiliation.

Consistent with the literature, the ASPMN survey results clearly indicate a lack of practice standardization. There is wide variation in dosing regimens, length of therapy, and management of side effects. The implications for use of ketamine in pain practice are influenced by the designation of ketamine as a dissociative anesthetic, which limits universal use. This designation determines which providers order and monitor the patients who are receiving ketamine and influences the perceived level of care required for patients receiving ketamine. Survey responses indicate frustration from respondents who have witnessed the analgesic benefits of ketamine for patients, but are constrained by barriers in administration.

Although studies have clearly revealed the benefit of ketamine as an analgesic, dosing of sub-dissociative ketamine has not been established (Persson, 2013). Dosing, routes of administration, and length of ketamine therapy vary in studies and in practice, with no widely accepted guidelines, making standardization of practice difficult (Kator et al., 2016). These findings are not unusual; a survey of providers in France (Martinez et al., 2015) reported that although ketamine was being used to treat acute and chronic pain, administration routes, dosing, duration of therapy, and location of patient during ketamine treatment varied greatly. Many of the studies also have small sample sizes, making generalizations and thus development of practice standards difficult in some patient populations such as pediatrics. The ASPMN survey reveals similar practice variability with dosing and length of therapy.

The long-term effects of ketamine, such as ulcerative cystitis and memory deficits, have been noted in persons who have utilized ketamine as a drug of abuse (Niesters et al., 2013). Therefore, ketamine at low therapeutic dosing for analgesic reasons should not cause concern; however, longitudinal studies are needed to assess this further and to determine if long term, sub-dissociative dosing produces similar effects. Although ketamine is metabolized by the liver and excreted by the kidneys, recommendations for adjustments in dosing for impaired hepatic and renal function are not available. A study of ketamine’s effect on experimental pain and cardiac output noted increased ketamine metabolism by females and higher drug plasma concentrations in men, suggesting a possible need for dosing adjustment based on sex (Sigtermans et al., 2009). Additional studies are also needed to define this further.

The IOM (2013) report noted addressing our country’s pain burden would necessitate a transformation in the way pain is understood, assessed, and treated. The current national dialogue related to opioid use underscores the urgency of examining pain management options. This survey can be utilized as a springboard for future research and initiatives. Clearly, additional data are needed from physicians and advanced practice providers related to prescribing of ketamine. Survey respondents described physician and prescriber knowledge deficits and fears related to utilization of ketamine as an adjunct for pain management. It is imperative to develop education addressing knowledge gaps including guidance on patient selection.

There is overwhelming evidence in the literature of the efficacy of ketamine infusions for the management of pain. However, the FDA does not list pain as an approved use. The ASPMN survey respondents indicated many barriers to use of ketamine because of its designation as an anesthetic. There is a tremendous
need for this to be reviewed because of the implications for pain management, board of nursing guidelines, nursing practice, and reimbursement.

The literature notes current research into alternate routes of ketamine administration, dosing, and length of therapy. The APSMN survey highlighted the lack of ketamine standardization. The development of ketamine administration, dosing, monitoring, and length of therapy guidelines, in conjunction with physician and advanced practice provider groups, is needed to address this gap in practice. Guidelines ideally should include inpatient/acute care for malignant and nonmalignant pain including chronic and refractory pain. Outpatient, emergency department, home, and hospice guidelines are also indicated. These should include ketamine dosing guidelines including bolus, short-term infusion, and continuous infusion.

Side effect management including appropriate use of anxiolytics has not been clearly established. The APSMN survey notes great variability in side effect management. Because of the consistent occurrence of some degree of side effects, management guidelines are important. With proliferation of electronic medical records, the use of standing orders for ketamine administration would assist with standardization. Finally, the development of administration and monitoring guidelines would assist policy development in practice settings. Such an evaluation would aid in defining measurable outcomes that should naturally lead to the establishment of practice standards.

CONCLUSIONS

The APSMN ketamine practice survey clearly reflects the necessity for and utilization of an interprofessional approach. As the United States grapples with the ramifications of opioid use, there is an urgent need for closer examination of non-opioid pain management strategies, particularly ketamine. This will require standardization of dosing and length of therapy and improved education of the health care team. An interprofessional dialogue is necessary in determining who can initiate, administer, and monitor patients, as well as the practice areas where patients can receive this medication. Furthermore, the current focus on non-opioid pain management provides an ideal platform for interprofessional groups to evaluate the role of ketamine in pain management strategies and remove barriers to use.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.pmn.2018.02.063.

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