Received: July 17, 2020 Revised: August 18, 2020 Accepted: September 22, 2020

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13335

EDITORIAL

Practice Choices in Targeted Intrathecal Drug Delivery: An Online Survey Conducted by the Polyanalgesic Consensus Committee

INTRODUCTION

Intrathecal drug delivery (IDD) has evolved over the past 40 years to treat intractable pain and spasticity not successfully managed with other treatment modalities or routes of drug delivery. The overall lack of substantial evidence initially suggested the need for expert review and guidance that led to a series of consensus guidelines from a panel of specialists in conjunction with the International Neuromodulation Society (INS). Beginning in 2000, the Polyanalgesic Consensus Conference (PACC) conducted surveys and published recommendations for appropriate medical practice relating to IDD, with the most recent guidelines published in 2017 (1-15).

Recently, the INS surveyed its members to describe current practice trends and contrast the outcomes to the previous recommendations of the PACC publications, as new guidelines are planned for 2021. Inasmuch as 80% of intrathecal therapy drug use is considered ''off-label'' per regulatory approval, it is helpful to understand current practice when formulating new recommendations.

MATERIALS AND METHODS

The current survey was commissioned by the PACC and members were chosen based on their expertise, demographics and publications. The authors of the 2020 PACC survey reviewed the prior surveys and updated questions to assess current IDD treatment practices and concerns. After initial development, the survey was reviewed by four independent physicians for question clarity and appropriate breadth of topics. The final survey was agreed upon by those authors and it was decided the survey period would last approximately 30 days.

The survey consisted of 44 questions in an online format that was sent via email to the 2736 active members of INS for invited participation. Survey questions were all multiple choice. The survey had three major groupings: 1) participant demographics, 2) application of PACC guidelines, and 3) IDD clinical questions (see Supporting Information Appendix S1A for survey questions). Participants answered anonymously and were not offered compensation for their time. The active membership of INS were contacted via email with a link to the survey on April 17, 2020 with follow-up reminders on April 24, 28, and May 10. Members who

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: This project was supported and funded by the International Neuromodulation Society (INS). No corporate funding was received for this project. No corporate entities had any direct input into the contents of this manuscript or the conclusions of the collaborators. As an INS contractor, Sarah Staples, MA, ELS, assisted with survey deployment, data collection, and manuscript preparation.

[Correction added on 13 January 2021, after first online publication: Dr. Alyson Engle was added as co-author.]

Conflict of Interest: Dr. Deer has equity options in Bioness, Vertiflex, Axonic, Vertos, SpineThera, Saluda Medical, Nalu, Cornerloc, PainTeq and SPR Therapeutics; is a member of the advisory board for Abbott, Vertos, Flowonix, Nalu, SPR Therapeutics and Vertiflex; is a consultant for Abbott, Axonics, Flowonix, Saluda Medical, Vertos, SpineThera, Nalu, Medtronic, Nevro, SI Bone, Stimgenics, SPR Therapeutics, Cornerloc Boston Scientific, PainTeq and Vertiflex; and has a patent pending for the DRG paddle lead with Abbott. Dr. Abd-Elsayed is a consultant of Medtronic, StimWave, and Avanos. Dr. Falowski consults for Abbott, Vertiflex, Boston Scientific, Vertos, Medtronic, Saluda, and SPR; has equity in Thermaquil, SPR, CornerLoc, PainTeq, SpineThera, Saluda, Stimgenics, AGR, Neural Integrative Solutions, Celeri; and conducts research for Medtronic, Abbott, Saluda, Vertiflex, Boston Scientific, and Stimgenics. Dr. Hagedorn has no conflicts to disclose. Dr. Abejon consults for Abbott, Boston Scientifics, Medtronic, PRIM, Cardiva2, and Grünenthal. Dr. Russo has no financial conflicts to declare. He served as INS Congress Scientific Chair and received Medtronic travel support in 2019. Dr. Hah has no conflicts to disclose. Dr. Lamer has no conflicts to disclose. Dr. Carayannopoulos consults for Pain Spine & Rehabilitation Consulting Inc., has grant/research support from Boston Scientific, Medtronic, DARPA, Nevro, Aspen, Nuvectra, NIH-Heal, Asahi, and Mainstay, is on the advisory board of Saluda. Dr. Hunter has ownership in Axonics, PainTEQ, Nalu, Spine BioPharma, and Mainstay; consults for Saluda and Genecentrix; is on the speaker's bureau for Tersera; has research funding from Abbott, Biotronik, DiscGenics, Mesoblast, Saluda, TissueGene, and Vivex; and serves on the advisory boards of Abbott, Mainstay, Nalu, Spine BioPharma, and Vertiflex. Dr. Steegers has no conflicts to disclose. Dr. Pope reports other from Ethos Labs, other from Flowonix, other from Saluda, other from PainTeq, other from Aurora Spine, other from Thermaquil, other from Celeri Health, other from Spine Thera, other from AGR, other from NIS, other from Abbott, other from Medtronic, other from Vertiflex, other from Boston Scientific, other from Vertos, other from SPARK, other from WISE, other from Tersera, other from Neural Integrative Solutions, outside the submitted work.

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did not respond or who opened the email request but did not respond were not contacted further. Any partially completed survey was included. It is unknown if recipients who skipped questions did not have expertise to answer the questions or merely left the survey. The survey was closed on May 15, 2020; responses were tallied using Survey Monkey and reviewed by the authors.

RESULTS

Participant Demographics

The survey invitation email was opened by 1551 respondents (56.7%) with 211 total responses (7.7% response rate); 174 (82.5%) were complete and 37 (17.5%) were partial. The average time to complete the survey was 7 min. The survey had a strong international presence, with North America and Europe accounting for 87% of respondents and responses from Australia/New Zealand/Oceania, Asia, South America and Africa (Table 1).

Table 1 describes survey respondents. Most specialized in anesthesiology (135/211, 64%), were board-certified (159/211, 75.4%), practiced pain medicine full-time (120/210, 57.1%), and had been in practice for longer than ten years (126/210, 52.9%). Most respondents worked in academic medicine (80/210, 38.1%), followed by private practice (71/210, 33.8%) or private hospital (25/210, 11.9%), with the rest splitting time between private/academic and other practice environments. The majority of participants (167/209, 79.9%) implanted fewer than 20 pumps per year. The most common IDD practice size was 25 patients or less (80/210, 38.1%), but results varied with 16.7% (35/210) having 26–50 patients, 20% (42/210) having 51–100 patients, 12.9% (27/210) having 101–200 patients, 11% (23/210) having 201–400 patients, and 1.43% (3/210) having 400+ patients. The majority of practices were treating patients ranging from 51 to 75 years of age (145/210, 69.1%).

Table 1. Characteristics of Survey Respondents.

	Respondents, *N* (%)
Practice specialty	*N* = 211
Anesthesiology	135 (64%)
Neurosurgery	49 (23.2%)
Physical medicine and rehabilitation	11 (5.21%)
Neurology	4 (1.9%)
Other	12 (5.7%)
Board certification	*N* = 211
Yes	159 (75.4%)
No	52 (24.6%)
Practice environment	*N* = 210
Academic, full-time pain management	47 (22.4%)
Academic, part-time pain management	33 (15.7%)
Private practice, full-time pain management	56 (26.7%)
Private practice, part-time pain management	15 (7.1%)
Private hospital, full-time	17 (8.1%)
Private hospital, part-time	8 (3.8%)
Private/academic hybrid	17 (8.1%)
Other	17 (8.1%)
Years practicing pain management	*N* = 210
<1 year	11 (5.2%)
1–2 years	7 (3.3%)
3–5 years	22 (10.5%)
6–10 years	44 (21%)
>10 years	126 (60%)
Years implanting pumps	*N* = 206
<1 year	16 (7.8%)
1–2 years	13 (6.3%)
3–5 years	30 (14.6%)
6–10 years	38 (18.5%)
>10 years	109 (52.9%)
Pumps implanted per year	*N* = 209
0–5	83 (39.7%)
6–20	84 (40.2%)
21–50	33 (15.8%)
51–75	6 (2.9%)
76–100	3 (1.44%)
>100	0
Pump patient population size	*N* = 210
25 patients or less	80 (38.1%)
26–50	35 (16.7%)
51–100	42 (20%)
101–200	27 (12.9%)
201–400	23 (11%)
400+ patients	3 (1.43%)
Practice location	*N* = 211
North America	105 (49.8%)
Europe	78 (37%)
Australia/New Zealand/Oceania	11 (5.2%)
Asia	11 (5.2%)
South America	5 (2.4%)
Africa	1 (0.5%)

PACC Experience and Usefulness

Most respondents reported having read the 2017 PACC guidelines (83%, 161/194) and using the guidelines always or often (72.7%, 141/194), finding them helpful (73%, 142/193) and beneficial to patient care (87.6%, 170/194). Respondents reported making many (12.4%) or some changes (49.2%) to their practice based on the updated guidelines (119/193).

More than 70% of respondents reported following PACC guidelines for trial dosing ranges (always 27% and often 46%, 143/194), maximum daily dosage (always 42% and often 34%, 146/193) and maximum concentrations (always 46% and often 33%, 162/192). The anticoagulation recommendations are followed by 86% (166/191) of the respondents, as are the infection prevention guidelines (91.6%, 176/192).

Respondents felt that PACC guidelines were less helpful with regard to insurance concerns or denials of mono- and multi-drug therapy and off-label drug use. With regard to insurance coverage of mono- or multi-drug therapy, 29.47% (56/190) responded that the PACC guidelines were "not very" or "not at all" helpful; similarly, off-label medication questions were not meeting the needs of the group; 30.36% (58/191) responded having found the guidelines seldom or never helpful.

Clinical Questions

Indications (*n* = 172)

The most common indication for IDD was failed back surgery not responding to spinal cord stimulation (SCS) (40.12%, *n* = 69). However, cancer pain (25.58%, *n* = 44) and spasticity (21.51%, *n* = 37) were also common indications for IDD. Chronic noncancer pain without previous SCS (8.72%, *n* = 15) and chronic low back pain without surgical interventions (2.33%, *n* = 4) accounted for most of the remaining responses.

Trialing (*n* = 171)

Nearly half of the respondents reported trialing intrathecal opioids with a single intrathecal injection (46.78%, *n* = 80). On

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the other hand, continuous intrathecal catheter infusion (22.81%, $n = 39$) and no trial (13.45%, $n = 23$) were also relatively common responses. Less common responses were multiple single-shot intrathecal injections (9.36%, $n = 16$), continuous epidural catheter infusion (5.26%, $n = 9$), and single epidural injection (2.34%, $n = 4$). The location for opioid trialing was split between inpatient (43.27%, $n = 74$) and outpatient (43.86%, $n = 75$) settings, with the remaining respondents not trialing (12.87%, $n = 22$).

Survey responses for trialing of intrathecal ziconotide were different from intrathecal opioids. Seventy physicians (40.94%) stated they do not use ziconotide. Of those physicians who do use ziconotide, the most common method was a single intrathecal injection (21.64%, $n = 37$). Other responses included no trial (12.28%, $n = 21$), continuous intrathecal catheter infusion (11.11%, $n = 19$), and multiple single-shot intrathecal injections (7.60%, $n = 13$). Less common responses included using ziconotide, but not as a first-line agent, so no trial was performed (5.26%, $n = 9$), and single epidural injection (1.17%, $n = 2$).

Neuropsychological Evaluation ($n = 172$)

The majority of physicians reported that all of their patients undergo a psychological evaluation before IDD implantation (56.98%, $n = 98$). The next most common responses were <50% of patients undergoing psychological evaluation (18.02%, $n = 31$), >75% (9.30%, $n = 16$), no evaluation (9.30%, $n = 16$), and 50–75% (6.40%, $n = 11$).

Most physicians felt that neuropsychological screening has increased success rates of IDD within their practice (54.65%, $n = 94$). Fifty-three physicians were undecided (30.81%) and 25 physicians disagreed/strongly disagreed (14.54%) that screening has increased success rates.

Oral Opioid Management ($n = 170$)

The approach to oral opioid management before trialing varied, with the most common strategy being to wean oral opioids by at least 50% prior to trialing (30.59%, $n = 52$). This was followed by reducing oral opioids during the trial (22.35%, $n = 38$), weaning oral opioids completely prior to trialing (17.06%, $n = 29$), continuing usual oral opioids doses during the trial (15.88%, $n = 27$), and holding oral opioids during the trial (14.12%, $n = 24$).

On the topic of oral opioid elimination, 169 physicians responded, and most reported that they eliminate systemic opioids after implantation (39.05%, $n = 66$). Other responses included elimination of opioids before trialing (17.75%, $n = 30$) and during trialing (8.88%, $n = 15$). Some physicians reported not eliminating systemic opioids before IDD (13.61%, $n = 23$) or eliminating for some, but not all, patients (20.71%, $n = 35$).

Medications ($n = 169$)

The majority of physicians surveyed reported using opioid-only (56.80%, $n = 96$) or opioid with local anesthetic (24.85%, $n = 42$) regimens. Ziconotide (7.10%, $n = 12$) and ziconotide combined with other drugs (2.37%, $n = 4$) were used less frequently. Fifteen physicians reported using other regimens (8.88%).

When considering choice of opioid, 170 physicians responded. Overwhelmingly, morphine was the most common choice (75.29%, $n = 128$). This was followed by hydromorphone (16.47%, $n = 28$) and fentanyl (2.94%, $n = 5$).

Catheters ($n = 171$)

Most practitioners reported using both subjective and objective assessments in deciding catheter tip location, with decision-making about the specific vertebral level along the spinal cord being dependent upon diagnosis of patient-specific anatomical alterations. Other factors affecting catheter tip location included the type of drug being used, the location of pathology, and desire to cover one or multiple painful regions. The most common location reported for catheter tip placement was at T9-10 (53.22%, $n = 91$); other common areas were T10-11 (18.71%, $n = 32$) and placement above the most rostral pain dermatome (16.96%, $n = 29$). Objectively, tip location depends most commonly on pathology type and location, as well as the drug type being used in conjunction with the pathology type and location.

Assessment Tools ($n = 169$)

The use of validated measures to determine response to IDD varied widely with 13% ($n = 22$) of respondents noting that all patients in their practice participate in assessment, although assessment is tailored to the patient. Use of Oswestry Disability Index (ODI) or Neck Disability Index (NDI), the Short Form 12 (SF-12), and EuroQol-5D (EQ-5D) was reported by 11.2% ($n = 19$) and VAS/NRS use as the sole measure by 20.1% ($n = 34$). The majority reported using both subjective (NRS/VAS) and objective (ODI, etc.) measures in combination (47.9%, $n = 81$).

Morbidity and Mortality

The majority of respondents strongly agreed (29.6%, 50/169) or agreed (36.6%, 62/169) that therapy with intrathecal opioids results in less morbidity and mortality compared to systemic opioid therapy; 27.8% (47/169) were undecided or neutral and approximately 6% (10/169) disagreed with this concept.

Granuloma formation remains a significant, albeit rare, outcome. Forty percent of respondents have never seen a granuloma (40.6%, 69/170), and another 42.9% (73/170) estimate it occurring in <1% of their population; 1–5% prevalence is suggested by 12.9% (22/170) of respondents. The remaining prevalence groupings (5–10% and > 10%) were rare according to survey results (2.3% and 1.1%, respectively). Diagnosis of granuloma was via MRI in the vast majority of cases (46.7%, 79/170). CT and CT myelogram were seldom used (1.8% and 2.9%, respectively).

When asked specifically about granuloma management, 38.46% (65/169) of respondents reported never having seen a granuloma. For those who had encountered a granuloma, management was by catheter removal or removal and replacement (19.52%, 34/169), neurosurgical resection (14.7%, 25/169), or leaving the catheter in place with medication change (12.4%, 21/169).

IDD Process and Procedures

Most respondents do not prescribe postoperative antibiotics (39.5%, 68/172) or do so for only 24 hours (22.09%, 38/172). However, significant numbers of respondents still prescribe for greater than 96 hours (13.4% prescribe 4–5 days and 15.1% prescribe >5 days; $n = 172$). In the operating room, 22% (38/172) always place antibiotics at the surgical site (antibiotic powder, antibiotic-impregnated pouch, or antibiotic beads).

With regard to IDD system refills, nurse or nurse practitioner/physician assistants performed refills 44.4% of the time, while physicians refilled 49.6% of the time ($n = 171$). Image-guided refill is seldom used (34.1%, 59/173) or sometimes used (17.3%, 30/173), suggesting manual palpation-guided refill remains the

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Table 2. Comparison of Survey Results from 2000, 2009, and 2020 (%).

	2000 (n = 413)	2009 (n = 87)	2020 (n = 211)
Anesthesiologists	76	77	64
Neurosurgeons	15	6	23
Academic	25	21	38
Private Practice	78	61	46
Ten or more years implant experience	41	61	46
Cancer indication	16	NA	26
Granuloma experience	NA	64	59
Morphine as first drug	99	81	75

modality of choice. The minority of physicians, 13.3%, always uses image guidance (n = 173).

DISCUSSION

Over the past 20 years, there have been some consistencies in the survey responses. In general, the respondents were experienced clinicians, were anesthesiologists, were in private practice, treated mostly noncancer pain, used morphine as the most common medication, and had experience managing catheter tip granuloma(s). Trends in the 2020 data compared to 2000 and 2009 demonstrate that an increasing percentage of implanters are neurosurgeons, are in academic practice, and are treating cancer-related pain (Table 2).

During the past two decades, IDD users are still mainly comprised of anesthesiologists, although their representation has decreased from 77% to 63% of respondents, with a compensatory increase in neurosurgeons. In the latest survey 12.8% of physicians came from physical medicine and rehabilitation, neurology, and other specialties. Another notable change has occurred in practice location, with private practice decreasing from 78% in the first survey to 46% in the most recent survey, and academics rising from 25% to 38%. This observed shift in medical specialty could represent demographic changes to the INS membership population, or perhaps more use of multidisciplinary treatment teams. It may also be that neurosurgeons were more likely to respond and were disproportionately represented among the overall low percentage of responders.

The practitioners who participated in the three surveys had a similar profile with respect to time in practice, implant numbers, and the number of IDD patients within individual practices. Thus, the three surveys provide an idea of therapy evolution. The most common indications in 2000 were chronic noncancer-related pain (84% of cases) and cancer-related pain (16%), while the main indications in the most recent survey were failed back surgery syndrome not responding to SCS (40.1%), cancer pain (25.6%), and spasticity (21.5%).

As in previous surveys, morphine continues to be the most widely used opioid medication, although its use has slowly decreased from 99% of the cases in the first survey to 75% in the 2020 survey. The typical starting regimen has continued to be mostly a single drug and typically an opioid (12).

Most respondents acknowledged having read and used the most recent 2017 PACC guidelines and this may partially explain the declining trend of granuloma occurrence over time. In the most recent survey, 40.6% of respondents reported never having seen a granuloma and another 42.9% reported granuloma formation in less than 1% of their patients. This is compared to 63.9% in 2007, with no change in the diagnostic method. This decrease may be explained by physician adherence to the dose and concentration recommendations in the 2017 PACC guidelines. Previously, more than half of participants (57.1%) infused morphine concentrations that exceeded the PACC recommended concentration limits (20 mg/mL) (5).

Recommendations for Safe Care Based on 2020 Survey Results

First, the survey results suggest that many clinicians do not perform intrathecal trials before proceeding to pump implantation and of those who do, some do not use validated tools to assess response to the trial, instead relying on clinical judgment alone. Similarly, a number of physicians reported they do not require a psychological evaluation before implantation. This approach is concerning given that uncontrolled psychiatric illness is a contraindication to IDD system implantation, as significant behavioral abnormalities in a candidate may place undue stress on the managing clinicians and may increase the prospect of a suboptimal outcome by unchecked or unrealistic expectations (12,14). These observations suggest significant appropriateness, safety, and efficacy concerns. Another safety concern is that 5–10% of clinicians do not follow infection or anticoagulation guidelines. Given that up to 30% of clinicians consider the PACC guidelines as ''not very'' or ''not at all'' helpful with insurance processes, these inconsistencies in clinical practices may increase rates of insurance denials and may be perpetuating the perception that the guidelines are not helpful.

Second, the number of respondents who did not use ziconotide was somewhat unexpected, given that it has been recommended as a first-line choice for more than a decade (Supporting Information Appendix S1B). The exact reason for this could not be ascertained from this survey. Financial constraints or availability may limit the use of this agent, as may potential side effects. A meta-analysis of ziconotide monotherapy for the treatment of chronic neuropathic pain included randomized controlled trials (RCTs) and 586 patients (15). While ziconotide treatment was associated with a significant reduction in pain, serious adverse events were more common in patients receiving ziconotide, including dizziness, confusion, somnolence, urinary retention, nausea and vomiting, visual disturbances, abnormal gait, ataxia, and memory impairment. Perhaps the known central nervous system (CNS) adverse effects of ziconotide and further variability in reported dosing and titration schedules serve as significant barriers to using ziconotide in routine practice. The disparity between the position of ziconotide within the latest PACC algorithm and its use in clinical practice represents a potential deficit in clinical care, particularly given the possible safety concerns with opiates, and the finding that up to 10% of clinicians are not following maximum opioid dose guidelines. This could be an important question to address in future surveys.

On a larger scale, the results of this survey suggest that IDD is being underutilized among younger physicians and is not being adopted with the same frequency with recent/new graduates. Ostensibly, this result could be swayed by selection bias since the survey targeted exclusively INS membership. Other concerns about selection bias arise from the findings that up to 45% of pump management may be performed by nurses and physician assistants and not early career or experienced physicians. Assuming the results are

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indicative of the global pain medicine community and if this trend were to continue, there could be limitations in access to IDD as older physicians retire. Additionally, younger and less experienced physicians may be encountering unfamiliar situations, which could have an impact on patient safety. It will be important for training programs and continuing medical education to provide IDD training and experience to address these potential concerns.

Recommendations for Future Work

The Institute of Medicine (IOM) defines clinical practice guidelines as ''statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options'' (16). The PACC guidelines represent the most comprehensive set of evidence-based clinical practice guidelines for the practice of IDD. The results of this survey showed that the majority of respondents (83%) read the most recent PACC reports. Further, a majority (73%) always or often used the guidelines to guide clinical practice and 94% found the guidelines to be at least somewhat helpful. To help improve and strengthen future guidelines, it would be valuable to understand why 10% of the survey respondents seldom or never used the guidelines and 6% found them ''not very'' or ''not at all'' useful.

Identification of systematic and significant differences between survey respondents who find the guidelines to be at least somewhat helpful, and those who do not find them helpful would help tailor the utility of the PACC guidelines. For example, approximately 26% of respondents identified cancer pain as the most common indication for IDD therapy. Clinicians primarily focused on the palliative care of patients with end-stage cancer are likely to discuss risks and benefits of IDD therapy in a different context than those focused on treating patients with chronic noncancer pain conditions. At the extreme, consideration of life expectancy and primary intended outcomes of IDD in the treatment of patients with end-stage cancer pain may outweigh routine consideration of PACC guidelines. When considering the rising indication of cancer pain-related treatment, focusing on the quality of life in addition to length of life is important.

Another consideration is that roughly 40% of respondents perform between 0–5 pump implants yearly. Perhaps those responders who seldom or never use the guidelines do not find them helpful as IDD therapy is not a focus of their practice. Focused surveys of trainees, or those who have been implanting pumps for less than 5 years, may help to identify trends in pain management education. Perhaps clinicians may be less likely to adapt PACC guidelines or to find the guidelines helpful if less pain training and education is focused on the use of IDD therapy.

While the 2017 PACC guidelines have reasonably good penetrance (83%), a significant number of pain physicians are still not utilizing these recommendations. A future survey designed with the objective of understanding why some clinicians currently choose not to follow the guidelines or at least some aspects of the guidelines would help guide future development and hopefully make future guidelines more inclusive. Such a survey should be designed to identify (1) the rationales and barriers for not following specific guidelines, (2) elicit questions of interest from the respondents' perspective, and (3) ascertain what resources, including education, would be most helpful for those uncomfortable making decisions regarding IDD (12). The questionnaire should address common survey problems such as sample bias, which limits the generalizability of the results. Importantly, the answers to the survey questions should provide enough information to address the issues at hand (17). A pretest survey discussion with members representative of the reader base can help identify ambiguous answers to optimize face validity of survey questions. Benchmarking survey results over time will help predict healthcare trends, training gaps, and lack of access to care.

In addition, significant gaps in the literature exist, such that some of the guideline recommendations rely heavily on expert opinion rather than published evidence. In the 2017 PACC publications, Level III Evidence was defined as ''clinical experience-based opinions, descriptive studies, clinical observations or reports of expert committees,'' and Degree of Recommendation I was defined as ''insufficient, low quality or contradictory evidence; the balance between benefit and harms cannot be determined.'' In the first 2017 PACC manuscript (12), there were 20 recommendations that had an Evidence Level of III and 10 that had Degrees of Recommendation that were Level I. It is conceivable that such significant gaps in the evidence could be a factor in some clinicians' decisions not to follow some of the guidelines. It would be useful to identify some of the most important literature gaps and issues and then work with investigators and industry partners to design studies and trials to address these gaps. In addition, research regarding the comparative efficacy of various pain interventions, including IDD therapy, will help to further define the role of IDD therapy in the treatment pathways of various pain conditions. Reasonably designed studies exploring the clinical effectiveness and/or safety of IDD would be a welcome addition to this body of literature. By way of example, relatively high-level clinical investigations into intrathecal hydromorphone use were completed but the results have not been published (18,19).

The conclusions of this survey are interesting but very limited based on the response rate of 7%. This is in many ways not surprising since those who were invited to participate in the survey, the general membership, in a vast majority, do not perform IDD and therefore did not respond. The actual response rate of those involved in the use of intrathecal therapies is most likely much higher, but a much greater response rate would be needed to increase the reliability and validity of the conclusions. In the future, we would recommend the INS consider a special interest group in intrathecal therapies to better analyze the practice and habits of our members.

CONCLUSIONS

In this third iteration of the PACC survey, modern trends within IDD were identified from a sizable group of experienced pain management physicians (n = 211). The survey results suggest that most physicians find the PACC guidelines beneficial (87%) and they are almost universally used to some extent in IDD clinical practice (94%). Importantly, the results will be used to shape future PACC guidelines and identify gaps in the current recommendations and literature, all with the goal of improving efficacy and patient safety.

Acknowledgements

We would like to thank additional members of the PACC Survey Workgroup, including: Dr. Michael Saulino for consulting on the survey questions and reviewing the manuscript and Drs. Jay S. Grider, Alyson Engle, and Luz Elena Caceres for reviewing the manuscript.

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Authorship Statements

Authors Deer, Hagedorn, Pope, Lamer, Hunter, and Abd-Elsayed developed the survey questions. All authors were assigned to draft portions of the manuscript (Introduction, Methods, Results of the 44 questions, and Discussion) and reviewed the final manuscript. Dr. Deer and Steegers served as senior editors.

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