The concept of intrathecal drug therapy arose from the landmark work of Wang et al.1 who first injected morphine into terminally ill cancer patients and demonstrated that it achieved profound pain relief. From this simple case series arose the practice of both intrathecal and epidural infusion of opiates and local anesthetics, and the concept of long-term in-dwelling catheters. Because of advances in mechanical pumps, electronic controls, and newer agents, it is now possible to provide profound analgesia to a wide variety of patients.

The process of choosing which agents to employ is not without controversy; however. This article serves to review the evidence upon which this algorithm is based so that practitioners can assess the quality of the data and be aware of the potential conflicts of interests that may have affected the development of the algorithm. In addition, the article delineates the steps in the algorithm and describes the complications of implantable intrathecal devices.

Opiates

Morphine, Hydromorphone, Fentanyl, Sufentanil, Meperidine, and Buprenorphine

Opiate receptors are present throughout the central nervous system (CNS). In the spinal cord, opioid receptors are located in the substantia gelatinosa of the dorsal horn2 (Rexed lamina II). Opiates act through multiple mechanisms, including presynaptic inhibition of release of excitatory neurotransmitters, coupling with various G proteins to open up K+/H+ channels, which produces

Learning Objectives: After participating in this activity, the physician should be better able to:
1. Use the intrathecal drug algorithm.
2. Classify 3 off-label medications that are included in the algorithm.
3. Diagnose and treat complications of implantable intrathecal devices.

The author has disclosed that intrathecal medications such as hydromorphone, meperidine, fentanyl, sufentanil, gabapentin, midazolam, ropivacaine, ketamine, adenosine, ketorolac, octreotide, neostigmine, XEN 2174, CGX 1160, resiniferatoxin, and P-saporin are discussed in off-label use within the context of the algorithm published in this article.
neuronal hyperpolarization. Spinal opiates also act on the descending inhibitory pathways and may cause the release of other neurotransmitters such as acetylcholine and adenosine.

Morphine is the gold standard of intrathecal therapy and is usually started at a dose as low as 0.1 mg/d, which can then be titrated up to as much as 15 mg/d. Hydromorphone is also a very popular drug for intrathecal analgesia. It is equianalgesic in a dose of just 20% of the equivalent in morphine. Hydromorphone acts primarily on the mu receptor, but also on the kappa and delta receptors. Hydromorphone is more lipid-soluble and has less active primary metabolite than morphine, while having a smaller supraspinal distribution and an overall lower incidence of adverse effects.

The potency of fentanyl and sufentanil administered intrathecally is approximately 10 to 20 times greater than when administered systemically, which indicates high lipophilicity and also results in less rostral spread and fewer adverse effects.

It is important to note that these 2 drugs—fentanyl and sufentanil—are not associated with granuloma formation. Meperidine alone or with clonidine has been determined to be helpful in treating patients with intractable neuropathic cancer pain. However, prolonged use of meperidine can cause neurotoxicity of the CNS.

Buprenorphine is a partial mu receptor agonist with long duration of action. There is not enough published evidence to determine the safety of its use in long-term intrathecal therapy.

**Alpha-2 Agonist: Clonidine**

Alpha-2 agonists act on alpha-2 adrenoreceptors reducing noradrenaline release by a negative feedback mechanism. They...
also activate descending inhibitory pathway and act synergistically with local anesthetics, opiates, and neostigmine. Clonidine was originally approved by the FDA for epidural use in patients with cancer. However, it is actually most often used clinically via the intrathecal route rather than epidurally for the treatment of chronic neuropathic pain.

The intrathecal dose of clonidine typically needs careful incremental titration and is commonly started with 50 to 75 mcg/d. The dose may be titrated up to 300 mcg/d. Adverse effects include bradycardia (especially when the catheter tip is in upper thoracic region), hypotension, and dry mouth.

**GABA Receptor Agonists**

**Midazolam**

γ-aminobutyric acid (GABA) A is an amino acid that functions as an inhibitory neurotransmitter in the CNS. Intrathecal midazolam and gabapentin, are GABA A agonists currently being investigated in clinical trials.

Gabapentin, a GABA analogue, is thought to act on voltage-dependent calcium channels and resulting in inhibition of glutamate release in the spinal dorsal horn and effective in neuropathic pain. It activates the noradrenergic system after nerve injury.

**Baclofen**

The GABA B receptor agonist baclofen is approved by the FDA for intrathecal use and is the drug of choice for spasticity.

**Calcium Channel Antagonist: Ziconotide**

Ziconotide, which has been reviewed in *Topics in Pain Management* (21(1):1–6, August 2005) is a highly selective reversible blocker of the N-type of voltage-dependent calcium channels that are active in the dorsal horn of spinal cord, cerebral cortex, and neurohypophysis. Ziconotide is effective in both nociceptive and neuropathic pain. Clinical experience suggests that ziconotide should be started at the low dose of 2.4 mcg/d (0.1 mcg/h). The clinician should slowly titrate up the dose once per week and use an overall period longer than 3 weeks, up to a recommended maximum of 19.2 mcg/d (0.8 mcg/hr).

**Local Anesthetic Drugs**

**Bupivacaine**

Local analgesic drugs, when given neuraxially, block autonomic sensory motor function, depending upon dosage and concentration. They cause axonal membrane blockade predominantly of spinal nerve roots. Bupivacaine, when given in a very low dose with morphine, shows analgesic improvement and sometimes a reduced tolerance to morphine. The still unproven hypothesis is that low-dose bupivacaine acts mainly by membrane stabilization inhibiting calcium channels rather than sodium channels. Sodium channel blockade is seen with high-dose administration.

Bupivacaine doses that are less than 20 mg/d are well tolerated, whereas high-dose administration is associated with tachyphylaxis, motor paralysis, urinary retention, and orthostatic hypotension.

**Ropivacaine**

There is no long-term study that demonstrates the safety of ropivacaine, but it has been widely adopted.

**NMDA Antagonist: Ketamine**

The intrathecally administered N-methyl D-aspartate (NMDA) antagonist ketamine produces antinociception in patients with neuropathic pain. Ketamine seems to prevent spinal “wind up” and helps to prevent development of chronic pain syndromes. Although this drug has a long history of safe IV use, there are only anecdotal reports of its use intrathecally, and it is not approved by the FDA for this route of administration.

**Miscellaneous Drugs**

**Adenosine**

Adenosine is an endogenous ligand that acts on 4 types of receptors. Adenosine receptors are found in substantia gelatinosa of the spinal cord. The antinociceptive effect is mediated by A1 receptor subtype. Intrathecal adenosine is more effective at reducing allodynia and hyperalgesia than spontaneous pain. Intrathecal adenosine 500 to 2000 mcg in human volunteers was shown to decrease allodynia in phase I clinical trials. The major adverse effect reported was transient lumbar pain after a dose of 2000 mcg. Adenosine can be given as a bolus dose between 1 and 2 mg or infusion of 0.05 to 0.1 mg/h. Again, adenosine is not approved by the FDA for intrathecal use.

**Ketorolac**

Prostaglandins mediate the local signaling for pain and inflammation. Spinally synthesized prostaglandin effects can be reversed with the nonselective cyclooxygenase inhibitor ketorolac, which produces analgesia and may reverse the hypersensitivity seen with chronic spinal opiate exposure. However, these are entirely anecdotal reports, and ketorolac is not FDA-approved for intrathecal use.

**Octreotide**

Octreotide is a synthetic octapeptide of somatostatin. Somatostatin is a neurotransmitter found within the substantia gelatinosa and mitigates nociception. Octreotide has been documented to have a similar effect. But again this is only anecdotal evidence, and this medication is not FDA-approved for intrathecal use.

**Neostigmine**

Neostigmine administered intrathecally inhibits nociception by increasing endogenous acetylcholine, an inhibitory neurotransmitter, and can be an adjunct to other spinal medications. There is an increased incidence of vomiting, which may preclude its routine use. It is not approved by the FDA for use via this route.

The committee recommends a 6-step progression of drug therapy for patients with chronic pain.


XEN 2174/CGX 1160

These drugs are conopeptides that, like ziconotide, inhibit norepinephrine (NE) transport and activate NE inhibitory pathways.

XEN 2174 targets the norepinephrine transporter. Inhibition of this transporter elevates the levels of NE in the spinal cord to prevent pain signals from reaching the brain.

Resiniferatoxin

Resiniferatoxin is a naturally occurring, ultrapotent capsaicin analog that activates the vanilloid receptor in a subpopulation of primary afferent sensory neurons involved in nociception. It causes an ion channel in the plasma membrane of sensory neurons—the transient receptor potential vanilloid 1—to become permeable to cations, most particularly the calcium cation; this evokes a powerful irritant effect followed by desensitization and analgesia. Resiniferatoxin desensitizes dorsal root ganglion.

P-Saporin

P-saporin (SP-SAP) is a targeted neurotoxin, produces selective destruction of superficial neurokinin 1 receptor (NK1r)-bearing cells in the spinal dorsal horn. In rats, SP-SAP prevents the formation of hyperalgesia and can reverse established neuropathic pain behavior in rodents. Intrathecal delivery of SP-SAP produces a significant reduction in the number of superficial NK1r-positive neurons. This depletion had no effect upon acute nociceptive thresholds but blocked the facilitated state initiated by persistent small afferent input and resulted in a potent and persistent loss of hyperalgesia in rats. Thus, SP-SAP apparently prevents the development of hyperalgesia without producing anesthesia or acute analgesia.

Conclusions and Recommendations of Polyanalgesic Conference 2007

Portenoy and Hassenbusch reviewed 413 physicians who use intraspinal infusion devices and determined that physicians who had used intrathecal analgesia and devices for years did not have a universal drug protocol, and that their usage of various drugs in different painful conditions varied according to their knowledge and experience, without clear indication.

To make a uniform drug policy for intrathecal administration, 3 Polyanalgesic Consensus Conferences of expert panelists have been convened since 2000. These guidelines were published in 2000, 2003, and 2007 and were based on “best evidence” and expert opinion.

This algorithm is for treatment of chronic pain refractory to conventional therapies. The authors have taken into account new molecules designed specifically for intrathecal therapeutic use, new intrathecal delivery devices, compatibility of the medication with the drug delivery system on “best available evidence”—inclusive of both an updated literature review and expert consensus, and not necessarily by “type A evidence” of large “gold-standard” randomized clinical trials. The stated goal was to help treating physicians formulate knowledge-based decisions when using intrathecal analgesic therapies.

If a lower-tier drug fails, then the patient should progress to the drugs at the next tier.

Algorithm: Selection of Medications for Long-Term Intrathecal Infusion

The consensus and recommendation of a panel of experts on intrathecal polyanalgesia is to follow a definite protocol on the basis of preclinical and available clinical data. The committee recommends a 6-step progression of drug therapy for patients with chronic pain. If a lower-tier drug fails, then the patient should progress to the drugs at the next tier (Figure 1).

The conference explains the progression as follows:

“Line 1: Morphine and ziconotide are approved by the Food and Drug Administration of the United States for intrathecal analgesic use and are recommended for first-line therapy for nociceptive, mixed, and neuropathic pain. Hydromorphone is recommended based on clinical widespread usage and apparent safety.”

“Line 2: Because of its apparent granuloma-sparing effect and because of its wide apparent use and identified safety, fentanyl has been upgraded to a Line 2 agent by the consensus conference when the use of the more hydrophilic agents of Line 1 result in intractable supraspinal side-effects. Combinations of opioid + ziconotide or opioid + bupivacaine or clonidine are recommended for mixed and neuropathic pain and may be used interchangeably. When admixing opioids with ziconotide, attention must be made to the guidelines for admixing ziconotide with other agents.”

“Line 3: Clonidine alone or opioids such as morphine/hydromorphone/fentanyl with bupivacaine and/or clonidine mixed with ziconotide may be used when agents in Line 2 fail to provide analgesia, or side-effects occur when these agents are used.”

Line 1: Morphine ↔ hydromorphone ↔ ziconotide;

Line 2: Fentanyl ↔ morphine/hydromorphone + ziconotide ↔ morphine/hydromorphone + bupivacaine/clone dine;

Line 3: Clonidine ↔ morphine/hydromorphone/fentanyl + bupivacaine + clonidine + ziconotide;

Line 4: sufentanil ↔ sufentanil + bupivacaine + clonidine + ziconotide;

Line 5: ropivacaine, buprenorphine, midazolam, meperidine, ketorolac;

Line 6: gabapentin, octreotide, neostigmine, adenosine, XEN 2174/CGX 1160.

Figure 1. Intrathecal agents recommended by the Polyanalgesic Consensus panelists, 2007.
“Line 4: Because of its proven safety in animals and humans and because of its apparent granuloma-sparing effects, sufentanil alone or mixed with bupivacaine and/or clonidine plus ziconotide is recommended in this line. The addition of clonidine, bupivacaine, and/or ziconotide is to be used in patients with mixed or neuropathic pain. In patients at the end of life (less than 6 months), the panelists felt that midazolam and octreotide should be tried when all other agents in lines 1–4 have failed.”

“Line 5: These agents, although not experimental, have little information about them in the literature and their use is recommended with caution and obvious informed consent regarding the paucity of information regarding the safety and efficacy of their use.”

“Line 6: Experimental agents must only be used experimentally and with appropriate Independent Review Board (IRB)-approved protocols.”

It is interesting to note that baclofen was not included in the algorithm at all. Although it is not an analgesic, its use in pain management has been noted beyond treating spasticity.

Under new federal guidelines, virtually none of the panelists would have been able to vote on the medications listed on the algorithm.

Conflicts of Interest

To their credit, all of the participants disclosed a detailed list of conflicts of interest. In reviewing the list, it is important to point out that under new federal guidelines governing appointments to FDA-approval review panels, virtually none of the panelists would have been able to vote on the medications listed on the algorithm. As an example, the placement of ziconotide as a first-line drug is based on a study that was conducted by a panelist who received funding from the manufacturer. This study has not been repeated by any other researcher who does not have a potential conflict of interest. In organizations that specialize in the development of evidence-based studies and protocols, such as the Cochrane consortium, significant conflicts of interest preclude participation in writing and publishing reports.

Furthermore, rather than using available polling technology to achieve a broad consensus from the pain medicine community (eg, conduct a free online poll on Sermo.com or Survey Monkey), the conference relied on only the members present to rank and order the drugs according to their experience. It is important to understand that there are no data on the numbers of patients that have gone through this progression or measured their degree of pain relief or improved quality of life. Similarly, there are no rates of complication listed for each step.

In addition, it is not clear whether the line 6 clinical trials are still enrolling patients.

And finally, the algorithm also does not address the cost-effectiveness of its recommendations.

The placement of ziconotide as a first-line drug is based on a study that was conducted by a panelist who received funding from the manufacturer.

The Machine: Implantable Intrathecal Delivery Device

The first implanted continuous epidural infusion system was reported by Harbaugh et al in 1982, where 2 patients received epidural morphine by implanted pump. The system worked well without infection or respiratory complication. Soon afterward, the first FDA-approved implantable pump (Infusaid Model 400) was launched by its manufacturer. The first generation of pumps were gas driven and delivered a constant flow. It rapidly became apparent that patients with chronic pain of varying intensity accompanied by sudden increases of pain level could not be effectively managed with a constant-flow type of pump. Programmable pumps were then in development to give a bolus dose along with constant flow. A combination of patient-controlled analgesia (PCA) and implantable device was needed.

The device that met this need was the SynchroMed EL, manufactured by Medtronic Inc., which allows the patient to administer a bolus infusion in advance of expected increase of pain (prophylactic) or in response to sudden breakthrough pain (therapeutic).

As in the usual PCA devices, the dose, infusion time, lockout interval, and maximum repetitions of boluses can be programmed. Each bolus is counted as either successful, rejected, or unsuccessful, and stored in pump memory for readaptation of basic infusion dose and bolus dose for “individualization of therapy.”

The next generation of pumps (Synchromed II and Patient Therapy Manager [PTM], Medtronic Inc.) have additional features such as registering visual analog pain scale (VAS) before and after a bolus. The values are stored and analyzed for reprogramming of daily doses. Optimum dose range is reflected by a reduction in daily bolus calls. In a multicenter open-level registry recording 168 patients, the authors documented that 85% patients were satisfied with PTM.

Although a full discussion of pump-related complications is beyond the scope of this article, 2 types of complications bear on the algorithm: intrathecal granuloma at the tip of the spinal catheter and misses of the port when refilling with medication.

Intrathecal granuloma at the tip of the spinal catheter has the potential to cause spinal cord compression with all its sequelae. More than 100 cases have been reported since the first one in 1991.

Granuloma formation is most commonly seen with morphine and seems to be a function of concentration (>25 mg/mL),...
dosage (>10 mg/d), and duration of therapy. Among the opioids, fentanyl and sufentanil have apparent granuloma-sparing effect.

Cases have been recorded of physicians missing the refill port while refilling the instrument’s reservoir with medicine, resulting in extravasation of the medicine.

Physical symptoms and signs suggestive of granuloma formation include loss of analgesic effect and progressive neurologic symptoms. Small granulomas that are diagnosed early require cessation of drug and observation, along with pulling back of the spinal catheter by 2 segments or changing the catheter. Large granulomas must be removed surgically.

Cases have been recorded of physicians missing the refill port while refilling the instrument’s reservoir with medicine, resulting in extravasation of the medicine.

On January 14, 2011, the manufacturer issued a recall, which the FDA classified as Class I, for specific lots of implantable infusion pumps manufactured by Medtronic. The recall was issued for Medtronic SynchroMed II (model no. 8637) and SynchroMed EL Implantable Infusion Pump (model nos. 8626 and 8627) and Refill Kits (model nos. 8551, 8555, 8561, 8562, 8564, 8565, and 8566). The problem with the devices is the potential for “pocket fills” to occur, in which the drug is injected into the pump pocket (the area under the skin where the pump is placed) instead of the pump. Between 1996 and 2010, 8 deaths and 270 events requiring medical intervention were reported related to the occurrence of pocket fills, according to the FDA. The rate of occurrence per refill opportunity is estimated at 1 per 10,000 refills.

A pocket fill can result in either overdose or underdose of drugs, both of which are dangerous and require immediate attention. In underdose, the patient presents with withdrawal symptoms and increased pain. Baclofen withdrawal may be fatal as the patient presents with fever, altered mental status, and profound muscular rigidity. With opiate drugs, an overdose can cause respiratory depression, hypotension, and death. Prompt diagnosis of unexpected pain or other symptoms are important to prevent complications.

Conclusion

The panel opined that clinical research on intrathecal analgesics that meets the gold standard of evidence-based studies has not kept pace with the growing need for innovative approaches to pain management. They sought to fill this void with best evidence and experience. However, the vast majority of clinical experience is with the off-label use of various agents, and large multicenter studies are required to establish the safety and efficacy of the suggested approach. By reading this article, clinicians should be prepared to weigh the existing evidence, algorithms, and expert opinions about treating patients with these medications in a safe and effective manner.

References

Conversation: Institute of Medicine Pain Report Committee
Members Philip Pizzo, Lonnie Zeltzer, Robert Kerns, Kenneth Follett, and Sean Mackey Discuss a Blueprint for Transformation

The Institute of Medicine (IOM) report “Relieving Pain in America: A Blueprint for Transforming Prevention, Treatment, and Research,” released in June 2011 includes recommendations for what the IOM committee that drafted it has called a “cultural transformation.”

The report was commissioned by the Congress through Section 4305 of the 2010 Patient Protection and Affordable Care Act. That legislation required the secretary of the Department of Health and Human Services (HHS) to work with the IOM “to increase the recognition of pain as a significant public health problem in the United States.”

A group of scientists was appointed by the IOM as the Committee on Advancing Pain Research, Care, and Education, part of the Board on Health Sciences Policy. The chairman was Philip A. Pizzo, MD, dean of the Stanford University School of Medicine, as well as the Carl and Elizabeth Naumann Professor of Pediatrics and professor of microbiology and immunology. Vice chair was Noreen M. Clark, PhD, the Myron E. Wegman Distinguished University Professor and the director of the Center for Managing Chronic Disease, at the University of Michigan in Ann Arbor.

Pizzo and several members of the committee answered a series of questions through an e-mail interview with Topics in Pain Management (TPM). Those interviewed in addition to Pizzo were:

• Lonnie Zeltzer, MD, director of the Pediatric Pain Program at Mattel Children’s Hospital and professor of pediatrics, anesthesiology, psychiatry, and biobehavioral sciences at the David Geffen School of Medicine at University of California, Los Angeles. Zeltzer is also a member of the Topics in Pain Management editorial advisory board and the president of the Special Interest Group on Pain in Childhood for the International Association for the Study of Pain.

• Robert D. Kerns, PhD, professor of psychiatry, neurology and psychology at Yale University; national program director for pain management for the Veterans Health Administration; and director of the Pain Research, Informatics, Medical Comorbidities, and Education Center at the VA Connecticut Healthcare System.

• Kenneth A. Follett, MD, PhD, the Nancy A. Keegan and Donald R. Voelte Jr. Chair of Neurosurgery and interim chair of anesthesiology at the University of Nebraska; and chief of neurosurgery at the University of Nebraska Medical Center in Omaha.

• Sean Mackey, MD, PhD, associate professor of anesthesia, neuroscience, and neurology, and chief of the Division of Pain Management at Stanford University School of Medicine. Mackey’s special areas of expertise include neuroimaging of pain and spinal cord mechanisms. He provided input on research, clinical care, and educational aspects of the report.

TPM: Who do you hope will read the report?

Pizzo: We hope all medical professionals, health care policy experts, state and federal legislators, and leaders—as well as state and federal funding and regulatory agencies—will read this report. We also hope that the American public, especially those suffering from chronic pain, will be aware of this report and its conclusions.

Zeltzer: The public and Congress.

Kerns: Multiple stakeholder groups are likely to find the report of interest, especially persons with pain, health care providers and administrators, educators, scholars, and scientists, as well as Congress and employees of the NIH, the sponsors of the report.

Follett: The report is addressed to all stakeholders in the “pain arena,” including those people who have pain or who are affected directly or indirectly by pain—such as family members and friends—or who participate directly or indirectly in the delivery of pain care—healthcare professionals, payors, regulatory agencies, researchers, and educators.

Mackey: Everyone. Pain is such a ubiquitous experience that touches every single human on this planet. The importance of it cannot be underestimated.

TPM: What impact and specific outcomes do you hope to see?

Pizzo: We hope that this report will foster a cultural transformation in the way that pain is experienced, treated, and prevented in the USA. The committee outlined both immediate and near-term recommendations, as well as who is responsible for addressing them. We hope that these recommendations are responded to promptly and as completely as possible.
This narrow perspective on pain needs a cultural change to be multi-focused, often called the “bio-psycho-social model of pain.”

This purely biological, singular view of pain has inhibited the spread of treatments that impact the physical, emotional, and cognitive aspects of the pain experience that—in total—impact suffering and function. This mind-versus-body unidirectional understanding of pain has had a major negative impact on pain care in health care coverage, training and education, and clinical practice.

This narrow perspective on pain needs a cultural change to be multi-focused, often called the “bio-psycho-social model of pain.” Science has documented the validity of this model, and yet health care is not delivered within this model of care to people with pain.

This is the cultural change needed to reduce pain-related suffering, health care costs, and burden on the country as a whole.

Kerns: The report specifies multiple specific recommendations with identified stakeholders who we hope will share responsibility in addressing them. It is my hope that the recommendations will serve as a roadmap for strategic and tactical plans for our key professional and patient advocacy groups.

Ultimately, the challenges are large, so enactment of the recommendations will require a sustained and coordinated effort.

Follett: I hope—and expect—the report will increase awareness of: (1) the burden of pain and the impact of pain on individuals and on society; (2) the under-diagnosis and under-treatment of pain, and disparity in care among special populations; (3) the need for individualized care—and the roles of various stakeholders in providing that care; (4) the complexity of diagnosis and treatment and the need for comprehensive, multidisciplinary assessment, and treatment for people with complicated pain disorders; and (5) the need for better education and research to allow better assessment, treatment, and prevention of pain.

Mackey: A greater appreciation for the impact of pain on the individual and society as a whole. I am hopeful that the report will be an instrument of change that will help us to better care for patients with chronic pain, to better educate our health care providers about pain, and to help advance our research mission to develop improved therapies for pain.

The prevalence of chronic pain is significant and rivals that of cardiac disease, cancer, and diabetes combined.

TPM: How long did the committee work on the report?

Zeltzer: The committee was assembled by invitation to ensure broad and targeted areas of expertise. We began our first meeting in November 2010. We met monthly for 2 days after that until the report came out in June 2011.

There was significant subcommittee and individual member work throughout that entire time period, with much information-gathering, writing, e-mail and phone discussions, and other forms of effort. As major holes in information were determined, specific papers were commissioned to appropriate experts to provide those missing pieces that were needed for final recommendations.

TPM: Starting out, what were the easiest things to agree on?

Pizzo: The committee fully concurred that pain in America was not well cared for, that perceptions about pain impacted its diagnosis, treatment, and prevention, and that it represented both a public-health issue as well as a deeply individual one for those affected by pain.

Zeltzer: Pain is a major health care problem in America and causes significant suffering, time lost from work, and major health care costs to families as well as to third-party health care payors.

The prevalence of chronic pain is significant and rivals that of cardiac disease, cancer, and diabetes combined.

Research on pain is underfunded in relation to the public health problem of pain in America.

Part of the problem in poor pain care in America is the result of insufficient education of health care providers.

Kerns: I recall that the committee readily agreed on the enormous scope of the problem and the need for a comprehensive approach to raise society’s awareness of the number of persons affected by pain and the costs associated with it. I think that we quickly defined the challenge as one that will require a cultural transformation in terms of how pain is viewed and how it
should be managed. The core principles that are asserted in the report were similarly endorsed with little disagreement.

**Follett:** Committee members agreed unanimously that the impact of pain—from the individual to the societal level—is much larger than what is typically recognized and agreed that the healthcare and societal burden of pain warrants a comprehensive evaluation of the delivery of pain care, education, and research in the United States.

**TPM:** Were there any issues that raised controversy? If so, what were they, and how did the group reach a consensus about how to treat these issues in the report?

**Pizzo:** While the committee’s expertise was broad and varied, and while committee members had many different options and beliefs, they responded to the issues in a remarkably thoughtful and unified manner. There are many controversial issues around the diagnosis and treatment of pain—but the committee used knowledge and data to overcome bias and work in unified way to prepare the report.

**Zeltzer:** One of the most controversial issues initially was both defining “chronic pain” and calling it a “disease.” Discussions under the good leadership of Drs. Pizzo and Clark led to consensus with all the pros and cons and definitions discussed and debated.

**One of the most controversial issues initially was both defining “chronic pain” and calling it a “disease.”**

**Kerns:** I can’t say that any issues were particularly controversial. More extensive discussion focused on several issues, including how to best define the magnitude of the problem and associated costs, how to frame the stepped or tiered approach to pain care, the assertion of pain as a disease, how to find a desired balance in representing the extensive background literature given the broad scope of the problem, how to frame the “opioid conundrum,” and the prioritizing and wording of key recommendations.

**Follett:** Several issues addressed by the committee were considered controversial among people and patients in the “pain arena.” For example, the role of opioids in pain care. The committee was populated intentionally to have representation by a broad cross-section of people who deal with pain, from health care providers (including neurologists, anesthesiologists, neurosurgeons, oncologists, pediatricians, nurses, and complementary and alternative health care providers) to epidemiologists, to people who suffer with pain. The spectrum of expertise of committee members allowed the committee to explore each area of concern from multiple perspectives. The committee reached consensus by relying upon the expertise of its members, evidence presented in published literature, evidence presented by specialists brought in to address topics before the committee, and public commentary solicited as part of the committee’s activities.

**TPM:** If you didn’t mention opioids in the previous question, did this topic divide the committee in any way?

**Pizzo:** The committee fully understood the controversies surrounding opioids but was not divided in its recommendations.

**Zeltzer:** The main issue related to debate over opioids was not in their value, but rather in how much of the report was going to cover the opioid legal, political, and clinical issues, since an entire report could be focused on the opioid issues alone, including legislation and the legal system in relation to opioid prescribing and use.

**Kerns:** In my view, a particularly important aspect of the committee’s work was its ability to constructively address the diversity of views of a strong, multispecialty membership. The committee members did discuss the issue of long-term opioid therapy in some detail, but also recognized that it was only one of many specific topics that could distract the committee from other “big picture” questions. Ultimately, although the report speaks to this issue, we clarified that it was not a specific focus of the committee’s task.
The committee members did discuss the issue of long-term opioid therapy in some detail, but also recognized that it was only one of many specific topics that could distract the committee from other “big picture” questions.

Follett: Committee members recognized that opioid medications have a role in the management of pain, but acknowledged that appropriate and successful opioid therapy is complicated by a variety of factors, including the stigma of opioid therapy and concern about abuse and diversion, among others. Committee members’ consensus on this topic is reflected in the report.

TPM: The summary says the report was based on evidence and expertise. Was that because of a lack of good evidence or clinical trials in certain areas? If so, which ones?

Pizzo: The committee recognized the need for more data about the incidence and prevalence of pain and its demography, as well as many gaps in our knowledge of the neuroscience of pain and the treatments that could be used for its management. The committee recommended that much more needs to be learned to address the problem of pain in America.

Zeltzer: We based our recommendations on the scientific data and noted when those data were not available. For example, there were major holes in our scientifically acquired knowledge about the extent and type of disparities across individuals and groups in factors influencing pain and pain-related disability, and thus there remain gaps in pain disparities research aimed at reducing such disparities in pain care.

Similarly, even with recent advances, there remain significant knowledge gaps in pain care of infants, children, and adolescents, especially as they emerge into young adulthood.

We lack sufficient data comparing different types of treatment for specific pain conditions, especially with lack of information for clinicians on which patient would benefit most from which type of treatment for pain.

Finally, the long-term pain impact of the war experience on veterans is unknown, and there are early steps to understand and treat pain in veterans and in our military personnel.

Kerns: This question draws attention to core principles in the field of pain management, including the concept that pain is an individual experience that comprises the biological, psychological, and social dimensions of human experience, and that effective management most often requires an individually tailored, comprehensive, interdisciplinary, and multimodal approach.

Thus, the field of pain management is particularly challenged by our capacity to conduct relevant clinical research that can adequately integrate these multiple dimensions.

Although the committee called on continued research using randomized controlled trials and comparative effectiveness research methods, it seems clear that the field will continue to be challenged with limitations of the science of pain and pain management.

TPM: How do you, in particular, feel about the report—does it contain what you hoped it would, whether from your own area of expertise or another?

Pizzo: Given the charge to the committee and the timeline we faced, I believe the group did an excellent and comprehensive job.

Zeltzer: I think that the report was quite thorough, especially given that our committee had half the usual time period to research, write the report, and make final recommendations that we hoped would have impact on changing the culture of pain care in America.

Kerns: I am truly gratified by the opportunity to serve as a member of the committee, and I am genuinely pleased with the report. I look forward to working with my colleagues in multiple venues to enact its several important recommendations.

The report sets the stage for a new approach to pain care by virtue of its call to develop a national, population-level strategy to improve pain care, education, and research.

Follett: I am pleased with the report and honored to have been part of the development of this important document. It sets the stage for a new approach to pain care by virtue of its call to develop a national, population-level strategy to improve pain care, education, and research.

Mackey: This is a wonderful report that brings together expertise from a variety of different disciplines with a clear and compelling vision for where we as a nation should be doing to improve the care, education, and research in the area of pain.

TPM: If you could add or remove anything, what would that be?

Zeltzer: If we had more time, it would have been helpful to examine more specifics about pain research—specifically, to categorize topic areas that have been well covered and others where there remain significant gaps. Such a carefully constructed list would have been useful to the National Institutes of Health, National Science Foundation, and other private foundations that fund health care research.
1. Fentanyl and sufentanil are not associated with granuloma formation.
   A. True
   B. False

2. None of the following drugs is approved by the FDA for intrathecal use except
   A. bupivacaine
   B. ropivacaine
   C. ketamine
   D. adenosine

3. Which one of the following drugs has been approved by the FDA for intrathecal use?
   A. Meperidine
   B. Fentanyl
   C. Sufentanil
   D. Baclofen

4. Baclofen is not part of the polyanalgesic algorithm.
   A. True
   B. False

5. The algorithm presented in this article does not address the cost effectiveness of its recommendations.
   A. True
   B. False

6. Ziconotide is effective in both nociceptive and neuropathic pain.
   A. True
   B. False

7. Line 6 agents, which are experimental and should be used only as part of a registered clinical trial, include all of the following except
   A. gabapentin
   B. octreotide
   C. neostigmine
   D. sufentanil

8. Spinally synthesized prostaglandin effects can be reversed with the cyclooxygenase inhibitor ketorolac, which produces analgesia.
   A. True
   B. False

9. P-saporin, which is a targeted neurotoxin, destroys NK1r-bearing cells in the spinal dorsal horn. It seems to prevent the development of hyperalgesia without producing anesthesia or acute analgesia.
   A. True
   B. False

10. Granuloma formation is most commonly seen with morphine and seems to be a function of concentration, higher dosage, and longer duration of therapy.
    A. True
    B. False
Researchers Find Continuous Hydromorphone Hydrochloride Not Superior to Placebo in Treating Hip, Knee Osteoarthritis

A team of European researchers, led by Jozef Vojtassak, MD, of Orthos Paidion in Bratislava, Slovakia, found that patients treated with hydromorphone hydrochloride (a 24-hour, extended-release opioid formulation) with moderate to severe osteoarthritis (OA) pain of the knee or hip did not fare any better than those treated with placebo. The authors note that opioid therapy is increasingly being used in treating chronic noncancer pain. Further, opioid therapy is included in the treatment guidelines for the symptomatic management of hip or knee OA.

Vojtassak et al. write that “Weak opioids may be considered for the treatment of refractory pain where other pharmacologic agents have been ineffective, whilst strong opioids should only be used for managing severe chronic pain in exceptional circumstances.”

In Europe, hydromorphone hydrochloride, or, more simply, hydromorphone, is indicated for moderate to severe chronic pain that needs continuous treatment. The formulation is available in five strengths: 4, 8, 16, 32, and 64 mg. Not all dosage strengths are available in all countries. However, long-term opioid use remains controversial. This is due to concerns about long-term effectiveness and safety, especially the risk of developing tolerance, dependence, or abuse.

These drugs are also associated with a number of adverse effects (AEs), including nausea, vomiting, constipation, itching, and sedation. A Cochrane review, conducted by Evaline Nuesch, PhD, a research fellow at the University of Bern in Switzerland and colleagues, reported that opioids were more effective than control intervention in relieving pain and improving function. However, Nuesch et al. state that the small to moderate benefits of opioids are outweighed by large increases in the risk of AEs.

Nuesch et al.’s phase IIIb, multicenter, randomized, parallel-group, placebo-controlled, double-blind study was carried out at 18 cites in four European countries (Czech Republic, Romania, Slovakia, and the United Kingdom). The primary objective was to compare the analgesic effect of flexibly titrated hydromorphone and placebo in subjects with moderate to severe OA pain in the hip or knee that had not been adequately controlled with nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol [measured by “pain on average” on the brief pain inventory (BPI) scale].

Secondary objectives included assessing the dropout rate due to AEs; the effect of treatment on subjects’ functionality using the total score of the Western Ontario and McMaster Universities (WOMAC) OA index; the effect of treatment on pain using the pain subscales of the WOMAC OA index, the Health-Related Quality of Life (HRQoL) short form (SF)-36, and pain-related items measured on the BPI scale; and the overall safety and tolerability of the drug. Secondary objectives also included assessing the effect of treatment on subjects’ HRQoL using all other subscales, except pain, of the instrument SF-36; the effect of treatment on subjects’ functional impairment and stiffness using the subscales of the WOMAC OA index; the effect of treatment on subjects’ quality of sleep using a medical outcome study sleep sub-scale score; and the dropout rate due to inefficacy.

The study included 288 subjects who were randomized to the hydromorphone group (n = 139) or the placebo group (n = 149). At the screening visit (week 1), subjects taking weak opioids discontinued their medication; subjects taking NSAIDs or paracetamol remained on a stable dose. The mean age of study subjects was 65 years, and more (74%) suffered from knee OA than hip OA. (See Vojtassak J et al. A phase IIIb, multicentre, randomised, parallel-group, placebo-controlled, double-blind study to investigate the efficacy and safety of OROS hydromorphone in subjects with moderate-to-severe chronic knee pain induced by osteoarthritis of the hip or the knee. Pain Research and Treatment, 2011. doi:10.1155/2011/239501; and Nuesch E et al., Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Systemic Reviews, 2009;(4):CD003115.)