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The role of patient-controlled analgesia in the management of chronic pain

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ABSTRACT

Patient-controlled analgesia (PCA) is a mainstay for postoperative and acute in-hospital pain management. Its role in the chronic pain setting, for example for palliative care as well as the care of ambulatory patients with chronic pain syndromes, is not well defined. Acute PCA typically involves intravenous PCA using morphine, although other opioid analgesics may be used. Chronic PCA may take advantage of emerging PCA technologies including transmucosal and transdermal delivery systems, novel dispensing units for oral tablets, and device-based therapies including implantable systems and external transcranial stimulation devices. Of particular concern in defining and developing chronic PCA systems are safety issues and concerns relating to long-term opioid therapy, whether administered via PCA or in oral form by prescription. Since chronic pain populations are diverse, chronic PCA solutions—if appropriate at all—may vary. Chronic PCA has been studied in palliative care cancer patients, but other groups who might benefit from chronic PCA are less thoroughly investigated.

Aim: This paper reviews the concept of the use of PCA as an option for the management of chronic pain in an appropriate patient population. It does so from the point of view of medical need, i.e., the optimal management of pain. We fully recognize, however, that there are also potential negatives and consequences that could arise from the point of view of misuse, abuse, and diversion. It is our hope that this paper stimulates not only a discussion of the use of PCA for chronic pain patients, but also a discussion about how best to balance medical need *vs.* inappropriate use.

1. Introduction

Patient-controlled analgesia (PCA) allows on-demand administration of pain medication to patients with or without continuous background infusions. Intravenous PCA of opioid analgesics is familiar in postoperative care, but PCA is a concept that may also include other analgesics (including nonopioids), other routes of administration (including transdermal, inhalation, oral and transmucosal, intrathecal, and brain stimulation technologies), and other settings (including chronic pain). Considerations for long-term PCA in the chronic pain setting include ease of use, device or system flexibility (to individualize PCA), safety features, and special requirements (for example, PCA for ambulatory and even active patients). The demonstrated benefits of PCA in the postsurgical setting suggest its potential utility in the chronic pain setting. Transitioning PCA from acute to chronic pain management requires considerable re-thinking of the PCA paradigm, which has been to date primarily defined by postsurgical PCA.

Chronic pain is an epidemic (Weiner, 2001). Since the incidence of chronic pain increases with advancing age (König et al., 2010; Pergolizzi et al., 2008), the aging population of developed nations are seeing a burgeoning chronic pain population. It has been estimated that about 80% of nursing home residents deal with chronic, under-treated pain (Weiner, 2001). Although there are diverse attitudes about pain (including some pervasive beliefs that chronic pain is a natural part of aging or that pain cannot be effectively treated), a growing population of chronic pain patients coupled with better understanding of chronic pain and its treatment has resulted in an increased demand for analgesia.

Wider use of PCA for the management of chronic pain will bring with it safety concerns, risks for drug abuse and diversion, and the need to understand its appropriate role. Chronic pain patients are not a homogeneous group. This large and growing population includes both cancer and noncancer patients, co-morbid and multi-morbid patients, and patients with mental health issues. It encompasses pediatric patients, geriatric patients, ambulatory and active patients, and those in palliative care. Thus, it is likely

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that PCA for chronic pain will be appropriate in some but not all chronic pain subpopulations.

2. The management of chronic pain

Chronic pain is often defined as pain that persists beyond three or six months from onset or beyond the point at which usual healing would reasonably have occurred (Turk and Okifuji, 2001). This temporal definition may be practical, but it is often inadequate to fully describe the nature of the pain syndrome. For example, chronic pain may be present in the absence of any discernible pathology (Manchikanti et al., 2009a,b). Chronic pathological processes may allow pain to persist continuously or intermittently for months or years. Some "chronic pain" patients actually experience intermittent pain that never completely resolves.

Chronic pain may be associated with cancer, terminal illnesses other than cancer, or chronification of pain (a process not clearly elucidated in which an acute pain syndrome transitions into chronic pain). Multiple pain mechanisms (nociception, neuropathy, etc.) may be involved in chronic pain, in particular, it may have nociceptive or neuropathic components or both (Varrassi et al., 2010), and may benefit from multimechanistic pain management. Chronic pain may have diverse etiologies and may be associated with sensitization syndromes (Kindler et al., 2011; Nijs et al., 2011). The management of chronic pain is frequently complicated by the presence of multiple comorbid conditions, including other disease states, obesity, and mental health disorders (Butchart et al., 2009). While acute postsurgical pain may be a single entity, chronic pain is not.

The emergence of pain management as a medical specialty, better understanding of the multiple mechanisms of pain, and a wide array of new pharmaceutical products has transformed adequate analgesia from a desirable goal into a "fundamental human right" (Brennan et al., 2007). Nevertheless, chronic pain remains so inadequately addressed even in developed nations that it has been termed a crisis (Giordano and Schatman, 2008). Even patients under close medical care may experience under-treated pain (Passik, 2009; Peppin, 2009). In light of under-treated chronic pain, PCA is worthy of exploration for the chronic pain patient even though chronic pain inherently differs from acute pain. Considerations for chronic PCA must include patient safety, flexibility for customized dosing, tamper resistance, usability, and versatility, such as allowing for ambulation or activity (Grass, 2005). Of particular concern is dosing for chronic PCA. A postsurgical patient with chronic pain typically requires higher doses of analgesics than a similar postsurgical patient without a chronic pain syndrome (Magnani et al., 1989). It is unclear whether a chronic pain patient with a PCA system would require similarly large doses, nor do we yet fully understand the ramifications of the factors which could affect dosing in chronic PCA, such as opioid tolerance, opioid-induced hyperalgesia, and toxicity concerns.

3. Intravenous PCA

In general, intravenous PCA involves an initial loading dose, on-demand bolus dosing also known as the incremental or PCA dose, lockout interval, and sometimes temporal limits (typically one- and four-hour limits). However, intravenous PCA is uniquely susceptible to analgesic gaps owing to kinked tubing, catheter dislodgement, infiltration of catheters, and safety issues (Panchal et al., 2007). Further, intravenous dosing provides for rapid high maximum plasma concentrations (C_{max}) of the analgesic agent followed by a trough in plasma concentration, which requires frequent dosing (Palmer and Miller, 2010). Intravenous PCA systems may limit patient mobility, which may be an issue in postsurgical patients (restricting early ambulation). For that reason, intravenous PCA may be appropriate for bedridden chronic pain patient, such as palliative cancer patients, but it would not be a useful model for the ambulatory patient suffering chronic neuropathic or osteoarthritic pain.

4. Intrathecal PCA

Intrathecal morphine infusion pumps have been available for more than a decade. A new patient control system has been introduced which can be used in tandem with an implantable infusion pump (Personal Therapy Manager used with SyncroMed pump, Medtronic, Inc., Minneapolis, MN). In a study of this device (n = 168), 85% of patients were satisfied with the PCA system (patient control device) with no serious adverse events observed (Ilias et al., 2008). Patients included both those who had a previously implanted infusion pump (without a PCA device) and those who first had the pump implanted upon enrollment into the study. Of those who had a previous pump without a PCA control system, 82% reported the patient control system was better at treating their pain fluctuations than the pump alone (Ilias et al., 2008). Intrathecal drug delivery allows for analgesia with lower doses than oral, intramuscular, or intravenous administration. However, infusion pump implantation is an invasive procedure that requires regular (monthly) refills and may complicate subsequent care in some patient populations because an implanted pump may contraindicate magnetic resonance imaging (Medtronic, 2011). Intrathecal morphine pumps with a PCA device as controller appear to be useful in a limited population of patients dealing with chronic severe pain.

5. Transdermal PCA

An innovative, noninvasive transdermal PCA system allows fentanyl to be delivered iontophoretically through the skin when the patient pushes a control button (IONSYS, Ortho-McNeil, Raritan, NJ) (Ortho-McNeil, 2006; Power, 2007). The delivered dose of fentanyl upon patch application is about 16 μg and the intended dose of 40 μg is achieved in about 10 h (Ortho-McNeil, 2006). This system is commercially available in certain European countries, but is not yet in the United States. Another transdermal PCA system involves a noninvasive electrotransport system, which provides transdermal fentanyl PCA, delivering 40 μg of fentanyl over 10 min on demand (E-TRANS®, ALZA Corporation, Mountain View, CA) (Chelly et al., 2004; Mystakidou, 2002). Such systems were designed for short-term pain management and have been evaluated and found safe and effective for postoperative patients (Bonnet et al., 2009; Hartrick et al., 2006; Mattia and Coluzzi, 2007; Minkowitz et al., 2010; Power, 2007; Viscusi et al., 2004). The role of a transdermal PCA system for a chronic pain patient has yet to be established. However, this technology may be useful for an active chronic pain patient in that it would not tether him to an intravenous type of PCA system.

6. Other forms of PCA

Various other forms of PCA may include inhalation, oral, and transmucosal systems. Inhalational systems for PCA, for example opioid nasal sprays, are under investigation (Thipphawong et al., 2003; Brull and Chan, 2008; Mystakidou et al., 2011). Oral and transmucosal systems currently include tablet dispensing systems (Avancen, 2011; Rosati et al., 2007; AcelRx Pharmaceuticals Inc., 2011) and lozenge like apparatuses (Cephalon Inc., 2011a,b), but current use may be limited to patients without dysphagia. In addition, some nonconventional methods (brain stimulation) for

treating chronic pain are being investigated and may eventually develop into PCA systems (Boggio et al., 2009; Borckardt et al., 2011; Fregni et al., 2006, 2007; Rosen et al., 2009; Williams et al., 2009).

7. PCA drugs

While PCA systems may (by definition) use any analgesic agent, the PCA analgesia systems most familiar to clinicians use opioids. All of the common opioid painkillers have been used in PCA analgesia, with morphine the most thoroughly studied (Grass, 2005). Pure mu-opioid agonists (e.g. morphine, fentanyl, hydromorphone, etc.) are often used for PCA because they offer full mu-opioid receptor binding and have no analgesic ceiling, although dose–dependent side effects produce what might be called a "clinical ceiling" (Grass, 2005). Meperidine should not be used for PCA because it produces an active neurotoxic metabolite (normeperidine) with no analgesic effects that can cause cumulative damage (Carr and Jacox, 1992; Simopoulos et al., 2002).

The agonist–antagonist opioids which include butophanol, nalbuphine, and pentazocine, have an analgesic ceiling and are not widely used in acute PCA. There appears to be a gender distinction with this group of opioid analgesics, in that women—but not men—often achieve effective analgesia with these agents (Gear et al., 1999). These opioids have been shown to be effective in acute PCA following gynecologic surgery (Ho et al., 1998).

Tramadol, a centrally acting analgesic with both opioid and nonopioid analgesic mechanisms, is used widely in Europe for postsurgical PCA (Raffa et al., 1992). The safe and effective use of tramadol in postsurgical PCA has been documented in the literature (Eroclay and Yuceyar, 2003; Ng et al., 1998; Ortner et al., 2011; Silvasti et al., 2000). It may be that tramadol will play an important role in chronic PCA in the future.

8. Safety of PCA

PCA systems have been associated with medication errors arising from both operator errors (human errors) and equipment malfunctions. Data from the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database report that of PCA-related adverse events, 76% were caused by a device malfunction (such as damaged wiring, cracked cartridges, and so on), while 7% could be attributed to operator error. However, only 8% of these types of errors results in harm to the patient (Cope et al., 2008; Hankin et al., 2007; Schein et al., 2009). Considering that an estimated 13 million postsurgical patients in the US will receive PCA every year (Meissner et al., 2007), this number is not unsubstantial. A cost study of postsurgical PCA errors found the annual error rate to be 407 intravenous PCA errors and 17 device-related errors per 10,000 people within the US. Depending on the database used, the average cost per error ranged from $552 to $733 (Meissner et al., 2007). In this retrospective database studies, more human-related errors occurred than device errors (Meissner et al., 2007).

Human factors are another main cause of most PCA errors (Hicks et al., 2008). A retrospective study of acute in-hospital PCA found an overall low error rate (<1%) but about a third of all errors had a negative effect on the patient (Paul et al., 2010) (see Table 1). New "smart pump" features may help to prevent operator errors for intravenous PCA systems (Lin et al., 1998; Moss, 2010) and other PCA systems may need to build in safety features to reduce the risk of operator or patient error (Paul et al., 2010). However, inappropriate programming of the PCA system remains a common PCA error, even when corrective precautions are in place (Moss, 2010).

PCA education and training for the healthcare provider is necessary in order to reduce the human error associated with PCA (Cohen and Smetzer, 2005; Ferrell et al., 1992; Ladak et al., 2007). Inadequate training of nurses for acute intravenous PCA accounted for 12.9% of PCA errors in a large retrospective study (n = 25,198) (Paul et al., 2010). In this study, 77.4% of PCA errors involved incorrect dose, 90% of which increased the dose (from 2-fold to 50-fold) (Paul et al., 2010). Inexperienced staff was considered a major contributing factor to intravenous acute PCA errors in a retrospective study of 919,241 medication errors in 801 centers (Hicks et al., 2008).

Of particular concern for PCA safety is "PCA by proxy", in which a person other than the patient activates the controls to obtain more analgesics. The Joint Commission issued a sentinel alert about PCA by proxy errors, encouraging patient education as a means of preventing such errors (The Joint Commission, 2004). Future incorporation of high tech security measures like fingerprint readers or voice recognition may be used to deter such abuse.

The rate of malfunctions and errors in the use of PCA equipment in the home setting have not been adequately studied, but represent an area of concern for the migration of PCA systems from the acute postsurgical setting to long-term care or the home setting. Ina study analyzing 168 patients using an implantable infusion pump with a patient control system, 69% of the pump related errors were due to memory errors and of the 16 patient–controller issues, 88% was related to device telemetry (Ilias et al., 2008). A case report of a woman with an implanted intrathecal morphine pump found that delayed pump refill was associated with a loss of consciousness. The patient allowed her implanted pump to exhaust the medication; she went about 12 days without morphine. In that time, she lost her degree of opioid tolerance and went into respiratory distress when the pump was refilled and her usual 4 mg/d dose suddenly resumed (Ruan et al., 2010). While this study did not involve a PCA system, it suggests that patients on opioid therapy must not be subjected to abrupt or prolonged cessation of opioid delivery followed by sudden resumption of a chronic dose. Chronic pain patients with opioid PCA would likely benefit from ambient opioid analgesia to prevent such events.

9. Opioid tolerance and misuse

An important issue in the consideration of long-term PCA is opioid tolerance. Patients on any type of chronic opioid therapy will eventually become opioid tolerant and, for that reason, need increasingly more opioids. Built-in safety features in a PCA system can prevent patients from self-administering dangerously high doses of analgesics, but it is possible that PCA will become functionally obsolete if the patient becomes too tolerant.

The relationship of tolerance to misuse poses another important consideration. Acute opioid PCA may be used safely and effectively in patients who are opioid experienced or opioid tolerant, but such patients typically require higher doses than similar opioid-naïve patients (Grass, 2005). Chronic PCA will ultimately result in tolerance; opioid tolerance has been associated with the increased risk of misuse (Ives et al., 2006; Spiller et al., 2009). However, these issues also occur in any form of long-term opioid therapy and are not unique to chronic PCA systems. It remains to be elucidated whether chronic PCA might result in more or less risk of tolerance and misuse/abuse to long-term opioid patients than conventional chronic opioid therapy.

10. Psychological factors associated with PCA

The benefits of PCA appear somewhat related to the patient's psychological status and attitudes about pain relief. When PCA is

Table 1
Safety of acute PCA systems.

Study	N	PCA	Study design	Results	Comments
Paul et al. (2010)	26,198 acute pain patients in-hospital	IV pump	Retrospective	Total PCA errors <1%. Most common errors were programming wrong drug concentration and improper tube set-up	Although error rate was low, negative effects occurred to patients as a result of these errors 34% of the time, including one case of respiratory arrest
Hicks et al. (2008)	919,241 medication error records from 801 facilities	Various	Retrospective	1% of medication errors involved PCA	Human factors caused the majority of PCA errors, of which 6.5% had harmful outcomes (including 2 deaths)
Salamonde et al. (2006)	93 home-based palliative care cancer patients	Oral methadone PCA system then titrated to oral opioid therapy	Retrospective	No significant side effects	Patients did experience mild to moderate opioid-associated side effects
Ahmad et al. (2010)	8240 acute pain patients in-hospital over 5 years	IV morphine PCA	Prospective observational	0.33% rate of critical incidents ($n = 27$)	89% of errors were due to human factors

administered in the acute postsurgical pain setting, a correlation between PCA demand by patients and pain scores as measured by a visual analog scale (VAS) can be determined ($p = 0.0001$) (McCoy et al., 1993). It is of great interest for the development of chronic PCA whether such correlations exist among chronic pain patients and, more specifically, whether chronic pain subpopulations may differ in how they use (and how well they use) PCA systems. Certain subpopulations of chronic pain patients (those with depression or other comorbid mental health disorders and those at risk for substance abuse) are challenging to treat and pose a particular challenge for any system of drug self-administration.

Chronic pain patients are known to accommodate themselves to a level of pain such that satisfactory analgesia may be obtained at a level an acute pain patient would consider intolerable (Magnani et al., 1989). Acute pain patients utilizing PCA for postsurgical pain have different expectations for analgesia than chronic pain patients. Furthermore, chronic pain patients may be susceptible to biochemical and psychological effects not present in acute pain patients, including lower endogenous endorphin levels (Almay et al., 1978, 1988; Buvanendran et al., 2010; Carlsson, 1986; Nicassio et al., 1985). A chronic pain patient with lower levels of endorphins would be presumed to need more opioid analgesics than a similar acute pain patient, but it has been shown that chronic and acute pain patients use similar amounts of narcotic analgesics. This finding has been interpreted in that chronic pain patients appear willing to accommodate to higher levels of pain than acute patients (Magnani et al., 1989). For example, in a study of knee replacement patients, PCA patients used analgesia but only to the point that they had moderate (rather than severe) levels of pain (Ferrante et al., 1988). This is presumably because such patients had chronic knee osteoarthritis and had accommodated themselves to a moderate level of pain. This has been described as chronic pain patients titrating their PCA to achieve "familiar levels" of pain (Magnani et al., 1989). Therefore, it must be assumed that patient's previous experiences and expectations of chronic pain will affect his or her use of a PCA system. How chronic pain may influence patient-controlled intake of opioid analgesics has not been thoroughly elucidated and more research is needed (Martin and Ewan, 2008).

11. PCA for cancer pain

The majority of cancer patients will experience a significant degree of pain in the last stages of the disease (Daut and Cleeland, 1982; Oster et al., 1978; Portenoy and Lesage, 1999). Pain in late-stage cancer patients is exacerbated by comorbidities, reduced mobility, lack of activity, and possible concomitant depression and anxiety (Ahles et al., 1983). Cancer pain differs markedly from noncancer pain, just as cancer patients are inherently different from noncancer patients. In particular, cancer pain patients typically have a poorer prognosis, reduced life span, less need for complete functional restoration and mobility, and may experience cancer pain simultaneously at multiple sites. It is not unusual for cancer pain patients to suffer with concurrent noncancer pain syndromes as well as depression and anxiety. Cancer pain patients may invest their suffering with a very different psychological meaning, interpretation, and emotional response than chronic pain patients with a non-life-threatening disease or disorder. Moreover, cancer pain is characterized by breakthrough pain, transitory episodes of exacerbated pain. Breakthrough cancer pain may be idiopathic, incident to an activity, or attributable to analgesic failure (Davies, 2005; Portenoy and Hagen, 1990). Advanced analgesic options for cancer pain are urgently needed (Deer et al., 2011) and PCA may be an important advance in the treatment of cancer pain.

In a study of 117 in-hospital patients with cancer pain given an intravenous or subcutaneous opioid PCA pump system, 95% of PCA patients reported excellent pain control (Swanson et al., 1989). Investigators in this study also observed that the PCA pumps appeared to reduce anxiety and depression in cancer patients, seemed to increase their mobility and decrease sedation, and were cost effective. A similar but smaller study ($n = 8$) of patients with severe cancer pain found all patients achieved significant pain relief with PCA, exhibited less sedation, and had a high degree of acceptance of the PCA system (Citron et al., 1986). Other studies of PCA for management of cancer pain have reported similar beneficial effects (Baumann et al., 1986; Citron et al., 1986, 1992; Kerr et al., 1988; Meuret and Jocham, 1996; Swanson et al., 1989).

Despite these good results, concerns remain around PCA for cancer patients. Delirium occurs in about 80% of late-stage cancer patients (Centeno et al., 2004; Lawlor and Bruera, 2002; Massie et al., 1983), and the literature reports that chronic opioid PCA in advanced cancer patients may cause or exacerbate delirium (Dev et al., 2011). A PCA-based analgesic model has been proposed in which initial PCA helps titrate the analgesic requirement (based on on-demand doses), which can then be administered by the clinical staff, who can monitor the patient for signs of delirium. Moreover, advanced cancer patients may develop encephalopathy or other conditions which make it impossible for them to understand and administer PCA (Ferrell et al., 1992). This indicates that PCA may be appropriate for cancer pain patients at some but not all stages of their disease progression.

12. Considerations for PCA in the management of chronic pain

To some extent, the technology that will allow for long-term PCA to treat chronic pain already exists or is in development. The

main innovation in chronic PCA is the paradigm shift as PCA moves from postsurgical in hospital use to home and long-term use. As even the concept of chronic PCA is new, there are few studies of various chronic PCA systems to help inform clinical decisions. Further study in this field is needed.

Acute postsurgical PCA experience provides valuable insights for the development of chronic PCA systems, but there are distinctions that must be considered. For example, chronic PCA may be administered in a home setting and could be used by active patients. Chronic PCA systems must be designed for long-term use and allow patients to use the system properly, confidently, and appropriately. Since PCA systems may administer potentially dangerous narcotic analgesic agents, safety features and safety-focused patient education must be incorporated into all such PCA systems to prevent overdose, withdrawal, or interruptions in opioid use (such as sudden cessation and abrupt resumption, which may result in intoxication). PCA systems must be rugged and resist tampering (see Table 2).

The long-term use of opioids has been associated with tolerance, addiction, pseudo-addiction, misuse, abuse, and diversion (Ives et al., 2006). Safe use of opioids and other drugs will no doubt be an important consideration in the development and evolution of PCA systems for chronic pain. Manufacturers should consider ways to prevent potential misuse of chronic PCA systems by tampering, misuse (using too much of the drug), and diversion (selling or putting the devices in the hands of recreational users or addicts).

Many chronic pain patients have a history of substance disorders, familial history of substance abuse, or active addictions (Manchikanti et al., 2010; Staines et al., 2001; Wright et al., 2008). The appropriate analgesic therapy for such chronic pain patients remains controversial (Volkow and McLellan, 2011). While it is tempting to reduce risk by withholding opioids to such patients, physicians have an ethical obligation to treat pain (Macpherson, 2010). In particular, if chronic PCA systems for this chronic pain subpopulation are developed, such systems must be designed to resist tampering and be deployed only under close medical supervision, ideally by a clinical team with experience and expertise in treating substance abuse. Chronic PCA represents the same "balancing act" as oral opioid analgesic therapy, in that prescribers must balance effective pain management with concerns about safety and potential drug misuse (Nathan, 2010).

Table 2
Considerations for PCA systems in the setting of chronic pain management.

PCAs for chronic pain should offer:	
Ease of administration	Patient-friendly features
	Patient education measures
	Portability (for ambulatory patients)
	Convenience
	Patient acceptance
System safety	Smart features to reduce human error
	Lockout
	Prevention of abrupt opioid cessation
	Dose limiting or time-limiting features
	System reliability
	Tamper-proof features
Efficacy	Reliable dosing
	Able to use with the right drugs
Long-term use	Safe for extended use
	Rugged design
Ambulatory use	Alternatives to intravenous systems for active patients
Versatility	Potential to use with other drugs (nonopioids and opioid combinations)
	Potential to work well with a variety of patients (ages, activity levels and diseases)
Safe use	Methods to prevent overdose, misuse, and abuse
	Patient education measures
	Abuse deterrent

13. Conclusion

The use of PCA is well established for the management of postsurgical pain. With rising concerns of the epidemic of chronic pain, which is often under-treated or entirely untreated, interest is growing in migrating PCA systems for the care of chronic pain patients. Considerations for such PCA systems include efficacy, safety, cost effectiveness, and patient-friendly features. PCA systems for the management of chronic pain, including but not limited to cancer pain, appear promising but have not yet been thoroughly studied. The development of the field of PCA systems is poised to expand in magnitude, variety, and complexity. Three factors will influence this phenomenon: the aging of the independent-minded baby-boomers, the increased incidence of diseases and conditions that trigger pain, and the explosion of technological approaches increasingly capable of self-managing pain. The question is not whether these systems will increase in use and popularity, but how the medical and regulatory community will manage their growth.

Conflict of interest statement

None.

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