

# Patient-Controlled Analgesia: Therapeutic Interventions Using Transdermal Electro-Activated and Electro-Modulated Drug Delivery

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**ABSTRACT:** Chronic pain poses a major concern to modern medicine and is frequently undertreated, causing suffering and disability. Patient-controlled analgesia, although successful, does have limitations. Transdermal delivery is the pivot to which analgesic research in drug delivery has centralized, especially with the confines of needle phobias and associated pain related to traditional injections, and the existing limitations associated with oral drug delivery. Highlighted within is the possibility of further developing transdermal drug delivery for chronic pain treatment using iontophoresis-based microneedle array patches. A concerted effort was made to review critically all available therapies designed for the treatment of chronic pain. The drug delivery systems developed for this purpose and non-drug routes are elaborated on, in a systematic manner. Recent developments and future goals in transdermal delivery as a means to overcome the individual limitations of the aforementioned delivery routes are represented as well. The approval of patch-like devices that contain both the microelectronic-processing mechanism and the active medicament in a small portable device is still awaited by the pharmaceutical industry. This anticipated platform may provide transdermal electro-activated and electro-modulated drug delivery systems a feasible attempt in chronic pain treatment. Iontophoresis has been proven an effective mode used to administer ionized drugs in physiotherapeutic, diagnostic, and dermatological applications and may be an encouraging probability for the development of devices and aids in the treatment of chronic pain. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 103:353–366, 2014

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## INTRODUCTION

Although hailed as a medical breakthrough for pain treatment, the risks and limitations of patient-controlled analgesia (PCA) outweigh the benefits associated with its use, the main risk being overdose and subsequent death and the main limitation being high costs. Many clinicians believe that analgesic doses need to be increased to provide adequate pain relief, yet they fail to see the underlying problem related to drug delivery. Although numerous pain treatment therapies are available on the market, a point regarding drug delivery made by Stapleton et al.<sup>1</sup> still holds true:

“The plethora of new parenteral agents which the pharmaceutical companies have introduced over the past 20 years is not a reminder that we have not found the right drug but a

reminder that we have not found the optimal mode of administration of perfectly adequate analgesic drugs.”

Pain according to the International Association for the Study of Pain can be defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”<sup>2</sup> Three classifications of chronic noncancer pain (CNCP) are identified: nociceptive, neuropathic, and functional.<sup>2</sup> The management of CNCP has proven to be challenging to both the clinician and patient, resulting in time-consuming, complex, and sometimes unsuccessful or inadequate treatment.<sup>3,4</sup> Chronic pain may result from numerous medical conditions and although there are corresponding large numbers of specific injections, rehabilitation programs, and pharmacological treatments available, many patients are still left with continued pain even after repeated treatment attempts, necessitating controlled delivery of analgesic drugs.

As CNCP causes sleeplessness and depression, and interferes with normal physical and social functioning,<sup>5</sup> the impact and prevalence of chronic pain warrants serious attention as the condition may influence the overall quality of life.<sup>3,4</sup>

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Approximately 3%–4.5% of the 1.5 billion people suffering from chronic pain worldwide also suffer from neuropathic pain, with the incidence rate increasing complementary to age. Major adjustments that chronic pain patients usually make include changing jobs altogether or taking disability leave from work, moving to a more manageable home and getting assistance with daily living activities. Because numerous patients in routine practice settings feel they have some or no control over their pain or fail to achieve adequate pain relief, chronic pain is now considered to be a public health problem of major proportions.<sup>6</sup> In America alone, chronic pain affects more than 50 million people,<sup>3</sup> causing significant physical and emotional disability, ultimately leading to substantial declines in many other areas of living. The economic consequences of long-term pain are thought to be vast, with the annual cost of chronic pain in the United States, including lost income, lost productivity, and healthcare expenses, being estimated to be \$100 billion<sup>7</sup> and the cost to the patient in terms of lost earnings, lost ambitions, lost potential, lost life quality, and lost relationships being immeasurable. CNCP poses a major societal problem with an urgent need for more advanced treatment options, thereby offering a large and attractive market potential. The search for pain relief has taken on many variations through the ages resulting in some atypical methods and some worthy of further investigation. The past 40 years has seen numerous developments that have improved available medications, clinical understanding, and pain management related patient outcomes<sup>8</sup> with inherent advantages and disadvantages as highlighted in Table 1.

Transdermal delivery systems (TDSs) offer a laudable alternative to these conventional drug delivery methods. In addition to avoiding hepatic first-pass metabolism and gastrointestinal degradation, TDSs are advantageous in that they increase patient compliance as a result of convenience, being challenged only by the *stratum corneum*, which limits skin penetration.<sup>10</sup> In this review, CNCP treatment therapies will be discussed, highlighting the therapeutic interventions using transdermal electro-activated and electro-modulated (TEAM) drug delivery as a potential platform for PCA.

## PATIENT-CONTROLLED ANALGESIA

Patient-controlled analgesia has rapidly become a popular and effective means of providing analgesia to patients with various aetiologies of pain. PCA is a welcomed advancement in the treatment of pain, and for the first time, the actual patients are empowered to control their own pain relief treatment. Patients are no longer required to receive analgesics by intramuscular injection, often long after the healthcare professional had been beckoned for assistance. Also, patients are not subjected to the lengthy process of procuring and preparing the medication, which ultimately delays patient access to pain relief. Traditional oral or parenteral drugs do not always provide adequate therapeutic effects to treat chronic pain.

### Benefits and Adversities Associated with PCA Infusion Pumps

Currently, PCA is mostly limited to infusion pumps as a mode of drug delivery.<sup>11</sup> The concept of PCA presented herein is not restricted to a single administration route or analgesic class but rather an overview on the concept of the PCA infusion pump device and its relevant aspects. PCA has been shown to im-

prove pain management with less opioid consumption, potentially fewer adverse effects, such as respiratory complications and less sedation, in noncritically ill patients<sup>12</sup> being hailed as a major advancement both in the medical and pharmaceutical field alike with many different types of infusion pump devices being available today (Fig. 1). This concept of PCA offers numerous benefits to patients, which include: patient autonomy allowed with safe individualized dosing, improved analgesia with less sedation, and enhanced satisfaction; have earlier mobilization and better respiratory function resulting in less risk of pneumonia and pulmonary emboli and a reduced length of stay; reduced length of stay results in patients not being subjected to nosocomial infections. In addition, the pumps offer several safety features to prevent the administration of excessive amounts of analgesic medication. Although PCA has resulted in relief to many patients, it is not without shortcomings, which could be listed as: (1) incorrect drug or drug concentration, (2) triggering in error by the proxy (i.e., family member and nurse), (3) false triggering (various reasons), (4) hardware or software/malfunction, (5) drug accumulation, siphoning, or retrograde flow because of dead space or catheter blockage, (6) duplicate analgesic orders or poorly written orders, (7) accidental misprogramming at the caregiver–pump interface, (8) anaphylaxis/countless drug interactions, (9) extraordinary drug sensitivity, (10) reprogramming with criminal or “mercy” intent, (11) high-cost implications, and (12) overuse because of misunderstanding that PCA is a magic black box for pain relief. In addition to using many drugs for pain relief, it has become evident that continuous, demand-independent background infusions usually did not improve the quality of analgesia but increased overall opioid consumption with the risk of higher incidences of respiratory depression.<sup>13</sup> Thus, newer, advance systems need to be developed to prevent any unwanted adversities and provide rapid, effective pain relief.

### Effective Pain Treatment

As its introduction years ago, PCA has become the gold standard for severe pain management, the pioneering PCA technology has led to its routine use for postsurgical pain management today.<sup>13,14</sup> The concept of pain management using the notion of so-called “PCA” or “on-demand analgesia” by intravenous administration of opioids was published in the late 1960s,<sup>15</sup> yet evidence suggests that PCA was first used experimentally by Sechzer.<sup>16</sup> Sechzer<sup>16</sup> evaluated the analgesic response to small intravenous opioids doses given on patient demand first by a nurse and then by a machine. Further advances in PCA led to the development of electronic programmable pumps making the PCA safe and efficient in clinical practice.<sup>17</sup>

### Effortless Use of the PCA Infusion Pumps

The concept of obtaining analgesic from the infusion device is easily understood from the patient’s perspective. When the patient is in pain, or foresees pain because of an activity like getting out of bed, the PCA infusion pump push button is switched on. Without waiting for the nurses to answer a call button, analgesics can be conveniently delivered intravenously via a computerized pump. The computerized pump is capable of confirming, preparing, and administering the analgesic treatment depending on the patient’s eligibility to receive the

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