

# Clinical Pharmacists' Pharmaceutical Care for Postoperative Pain in Guangdong Province

## Expert Consensus by Guangdong Pharmaceutical Association

Pain is an unpleasant feeling and emotional experience caused by tissue injury or potential tissue injury, or a painful experience with sensory, emotional, cognitive and social dimensions. According to the healing time and the duration of pain, it can be divided into acute pain and chronic pain.<sup>[1]</sup> The American Pain Society (APS) and the American Academy of Pain Medicine (AAPM) define acute pain as the physiological response and experience to harmful stimuli that may become pathological, usually sudden and time-limited, and can stimulate behavior to avoid potential or actual tissue injury.<sup>[2]</sup> Postoperative pain is an acute pain that occurs immediately after surgery, including physical and visceral pain, which usually lasts for 7 days and sometimes several weeks.<sup>[2]</sup> According to Buvanendran,<sup>[3]</sup> 66% of patients report moderate, severe, or extreme pain after surgery, and 59% report moderate, severe, or extreme pain within 2 weeks after discharge. If the pain after surgery is not fully controlled, it will bring a series of adverse effects on the body, such as increasing oxygen consumption and affecting ischemic organs, triggering harmful spinal reflex arcs, reducing pulmonary function and gastrointestinal peristalsis, and delaying the recovery of gastrointestinal function. Acute pain not only increases the pain and complications of patients, but also evolves into chronic pain, reducing the patients' quality of life.<sup>[4]</sup> Perioperative acute pain remains a challenge for both doctors and patients. Taking active and effective analgesic measures to relieve pain can not only accelerate postoperative recovery, but also improve the comfort, the quality of life, and the satisfaction of patients.

Clinical pharmacists in Guangdong Province provide pharmaceutical services for postoperative pain by combining the acute pain service (APS) team,<sup>[5]</sup> multi-disciplinary treatment (MDT),<sup>[6]</sup> and postoperative pain management in medical institutions in China. Although there is no global standard for the working pattern of clinical pharmacists in pharmaceutical care for postoperative pain, clinical pharmacists in Guangdong Province have gradually formed their processes and requirements for pharmaceutical care for postoperative pain, such as comprehensive evaluation of pain-pharmacy, drug treatment plan, pharmaceutical care for postoperative pain, individualized medication for special populations, and pharmaceutical education.

### 1. Working Patterns

#### 1.1 Responsibilities of Postoperative Pain Management Team

Establishing a team for MDT in the hospital can be effective for postoperative pain management. All members should receive professional training before taking up their posts, and their work should be supervised and controlled by medical institutions or quality control departments.<sup>[5,6]</sup>

Clinical pharmacists provide team members with pharmaceutical services such as comprehensive assessment training on pain-medication risk, suggestions on analgesic drug schemes and evidence-based medicine,<sup>[7-9]</sup> as well as pharmaceutical services such as health education on pain and analgesic drug monitoring to patients and their families,<sup>[10-13]</sup> and are engaged in the quality control of the team.<sup>[14]</sup>

#### 1.2 Common Working Patterns of Clinical Pharmacists in Postoperative Pain Management

Clinical pharmacists in Guangdong Province follow two types of working patterns for pharmaceutical care for postoperative pain.

One is to start with the surgical ward as the breakthrough point<sup>[9,11,15-18]</sup> and adopt the pattern suitable for this medical institution in postoperative acute pain management. Clinical pharmacists first select a pilot department, gradually establish and improve the daily work focus and the working pattern of clinical pharmacists, and then extend it to all surgical departments in the hospital.<sup>[19,20]</sup>

Clinical pharmacists, anesthesiologists, doctors, and nurses in pilot departments set up a DMT team for APS and work out the workflow of perioperative pain service for patients. According to the team's guidelines and literature, the team develops a graded medication plan for common postoperative pain in this specialty.<sup>[6]</sup> For example, orthopedic surgery is divided into three grades (mild, moderate, and severe) according to the predicted degree of postoperative pain, and subsequently 3-5 analgesic medication plans are formulated for each grade with one of them adopted according to the patient's condition.

According to the needs of team members for knowledge of analgesic drugs, clinical pharmacists carry out pharmaceutical training, such as evaluation of pain medication, safe use of analgesic drugs, and monitoring of adverse reactions after analgesic medication, so as to enhance their theoretical knowledge.<sup>[2]</sup> Clinical pharmacists should evaluate the curative effect of postoperative analgesia and inquire about the adverse reactions of patients during multidisciplinary rounds, and make pharmaceutical intervention in time.<sup>[21]</sup>

Clinical pharmacists educate patients and their families on pain, reduce medication errors, guide patients to use assessment tools, and participate in self-pain management<sup>[8, 12, 16]</sup>

Clinical pharmacists' engagement in quality control is conducive to DMT,<sup>[18]</sup> and ultimately ensures the quality of postoperative acute pain management.

The other pattern starts with patients who use patient-controlled analgesia (PCA).<sup>[14,22-26]</sup> Clinical pharmacists take part in optimizing the PCA administration scheme from multiple perspectives, such as incompatibility and different PCA administration methods according to the drug properties.<sup>[24, 27, 28]</sup> Patients with PCA are followed up continuously for postoperative pain, the operation of PCA is checked, and whether the analgesic drugs are sufficient or excessive is evaluated according to the change of pain intensity scores of the patients.<sup>[29-32]</sup> Clinical pharmacists monitor patients for and evaluate and deal with adverse drug reactions, adjust the off-pump analgesic plan, and conduct medication education according to the patient's conditions.<sup>[33-35]</sup>

Clinical pharmacists can choose the working pattern of pharmaceutical care for postoperative pain according to the actual conditions of the medical institution.

## **2. Working Content**

### **2.1 Health Education on Pain**

Individuals have different understanding of pain, and most misunderstand postoperative pain. So it is necessary to establish a correct concept of postoperative pain treatment. For example, postoperative pain can be treated;<sup>[1,6,20]</sup> Effective analgesic treatment can reduce postoperative complications;<sup>[36-39]</sup> The use of analgesic drugs under the guidance of professionals can reduce the incidence of adverse drug reactions.<sup>[40-43]</sup> At the same time, clinical pharmacists need to carry out health education on pain for different groups so that everyone can realize that relieving pain is the basic right of human beings to promote the recovery of patients.<sup>[6,37]</sup>

Clinical pharmacists first provide pharmaceutical training to doctors and nurses in the team, and individualized health education to patients, which should run through hospital treatment.<sup>[6,21]</sup> For example, clinical pharmacists should introduce correct concept of analgesia and simple pain assessment methods, improve patients' medication compliance, and instruct them to report in time when there is intolerable pain or adverse drug reactions; Clinical pharmacists should explain the basic properties of the analgesic drugs to be used by patients after operation, so that they understand the necessity of analgesic drugs and remind them to report pain or adverse drug reactions in time again; Clinical pharmacists should educate patients on the correct use of drugs and relevant precautions after discharge.

## 2.2 Pain Assessment

Pain assessment includes the evaluation of pain intensity, pain causes, possible changes in vital signs, treatment effects and side effects, and the patients' satisfaction.<sup>[2,6]</sup> It is an important step in the effective management of postoperative pain, and clinical pharmacists should participate in the formulation of postoperative analgesia efficacy record.

### 2.2.1 Evaluation Principles

Clinical pharmacists evaluate the pain intensity of patients during rest and activities.<sup>[2]</sup> One of the difficulties in pain assessment is the pain intensity in the active state. Patients will perform rehabilitation exercises after surgery only when their pain is tolerable in the active state.<sup>[44, 45]</sup> Clinical pharmacists and team members should develop operational methods for pain assessment in the active state for patients according to different postoperative functional exercise requirements.<sup>[46]</sup>

Clinical pharmacists regularly evaluate the analgesic schemes used by patients and their therapeutic effects, including adverse reactions.<sup>[42,43]</sup> If the patient has poor pain control, they should discuss the causes with team members and adjust the analgesia plan; When patients have adverse drug reactions, corresponding measures should be taken and the results of adverse drug reactions recorded.<sup>[39]</sup>

Team members should promptly evaluate and deal with sudden and severe pain (breakthrough pain) of patients, and clinical pharmacists evaluate the effectiveness of analgesic medication.

At the end of pain treatment, a survey should be conducted on the patients' satisfaction of pain treatment and clinical pharmacists.<sup>[37]</sup>

### 2.2.2 Scoring Method of Pain Intensity

Numerical Evaluation Scale (NRS) marks different degrees of pain on a scale of 0 to 10: 0 for no pain; 1-3 for mild pain; 4-6 for moderate pain; 7-10 for severe pain. The medical staff or the patients themselves choose the number for pain degree.

Visual Analog Scale (VAS) is a scale with a length of 10cm with one end representing no pain and the other severe pain. Patients are asked to mark the position on the scale that best reflects their pain degree.

Facial Expression Scoring consists of six facial pictograms with different expressions from smiles to tears. The pain degree of patients is rated by selecting a similar pictogram according to their expressions.

FLACC is for children aged 7 years and below.<sup>[21,47]</sup> Observe the child's face, legs, activity, cry, and consolability, and score 0-2 points for each item. Calculate the total score to evaluate their degree of pain. 0 for relaxed, 1-3 for mild pain, 4-6 for moderate pain, and 7-10 for severe pain and/or discomfort.

### 2.2.3 Nature of Pain

The nature of pain is directly related to the choice of analgesic drugs and formulation of analgesia schemes, so it is necessary to accurately describe and comprehensively consider the nature of pain and its causes.<sup>[6,44]</sup>

### 2.2.4 The Best Time for Postoperative Pain Assessment

Currently, no consensus has been reached on the best time for postoperative pain assessment.<sup>[48, 49]</sup> Some scholars<sup>[20]</sup> recommend that patients' pain be assessed every 2h within 6h after surgery, every 4h within 6-24h after surgery, and every 12h after 24h. Clinical pharmacists can determine the time for evaluation according to the patient's symptoms of pain and the actual conditions of the clinical department.

In the case of a sudden and severe pain (breakthrough pain), it is necessary to assess immediately,

and to assess the therapeutic effect in due course after drug treatment. The evaluation should focus on the dynamic process of assessment, treatment and re-assessment, and make timely records for burst pain (Table 2).

### **3. Postoperative Analgesia and Pharmaceutical Care**

Clinical pharmacists are engaged in the formulation of analgesic schemes and conduct pharmaceutical monitoring on the efficacy and adverse reactions of patients using analgesic drugs, which is the key content of clinical pharmacists' participation in postoperative pain management.<sup>[20,50]</sup>

#### **3.1 Common Analgesic Drugs and Pharmaceutical Care**

Opioid analgesics exert an analgesic effect by combining with opioid receptors in peripheral and central nervous systems (spinal cord and brain). Opioids commonly used clinically can be divided into weak and strong opioids according to their analgesic intensity.<sup>[1]</sup> Strong opioids have strong analgesic and non-ceiling effects, and their analgesic effects and adverse reactions are dose-dependent.<sup>[51]</sup> Attention should be paid to strengthening the monitoring of adverse reactions to opioids.<sup>[52]</sup>

Common adverse reactions of opioids<sup>[53,54]</sup> include nausea and vomiting, respiratory depression, pruritus, urinary retention, sedation, cognitive dysfunction, etc. Respiratory depression is the most serious adverse reaction of opioid analgesics.<sup>[55]</sup> Elderly patients, patients with chronic obstructive pulmonary disease (COPD) or those with combined use of sedatives are prone to respiratory depression. If the patient's respiratory rate  $\leq 8$  times/min, SpO<sub>2</sub> <90%, or shallow breathing occurs, he/she should be alert to respiratory depression and be treated immediately.<sup>[56]</sup> The treatment includes immediate cessation of opioids, oxygen inhalation and strong pain stimulation, establishing an artificial airway or mechanical ventilation when necessary, and intravenous injection of naloxone.<sup>[57]</sup> Adverse reactions of nausea and vomiting will occur with a high probability after patients use opioids after operation.<sup>[54,58]</sup> The high risk factors include adult female, non-smoking, previous history of postoperative nausea and vomiting, or motion sickness.<sup>[59]</sup> Glucocorticoids, droperidol, and 5-HT<sub>3</sub> receptor antagonists are the drugs to prevent postoperative nausea and vomiting.

Paracetamol exerts antipyretic and analgesic effects by inhibiting prostaglandin synthesis in the central nervous system.<sup>[60]</sup> It is effective for mild-to-moderate pain when applied alone, and the combination of opioids, tramadol, or NSAIDs can exert additive or synergistic analgesic effect.<sup>[61-63]</sup> APS<sup>[6]</sup> recommends that patients be given acetaminophen orally before operation, which not only reduces the postoperative pain, but also the dosage of opioids after surgery. However, overdose of such drugs can increase the risk of severe liver injury and acute tubular necrosis.<sup>[60]</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs) exert antipyretic, analgesic, anti-inflammatory, and anti-rheumatic effects by inhibiting the synthesis of cyclooxygenase and prostaglandins.<sup>[64]</sup> APS recommends<sup>[6]</sup> that patients be given celecoxib orally before operation to reduce postoperative pain and the dosage of opioids after surgery. After operation, patients are treated with NSAIDs orally or by injection to treat mild and moderate pain, or multi-mode analgesia plans for severe pain.<sup>[63, 65]</sup> NSAIDs have a ceiling effect, and should not be overused, and their plasma protein binding rate is high, so the combination of two NSAIDs is not recommended. Another NSAID can be considered when the therapeutic effect of one NSAID is not good.<sup>[6]</sup>

The main adverse reactions of NSAIDs include gastrointestinal tract irritation, cardiovascular disease, platelet dysfunction, and kidney injury.<sup>[66-69]</sup> Clinical pharmacists should evaluate the gastrointestinal injury and cardiovascular risks of patients before using NSAIDs, and take different plans according to different risk levels. With regard to the possible risk of NSAIDs delaying bone healing, APS suggests<sup>[6]</sup> that there is not enough evidence to oppose the use of NSAIDs in patients undergoing orthopedic fracture and spinal fusion surgery, but acknowledges its potential harm.

Tramadol is an analgesic that acts on the central nervous system by inhibiting the re-uptake of 5-hydroxytryptamine and norepinephrine and by binding to opioid receptors. It can be used alone or

combined with acetaminophen and NSAIDs for postoperative analgesia, and has a synergistic effect.<sup>[70,71]</sup> Clinical pharmacists should pay attention to possible adverse reactions, such as nausea, vomiting, dizziness, lethargy, dry mouth and sweating,<sup>[72]</sup> especially measures to keep from falling should be taken for elderly patients. The medicine helps prevent and treat postoperative shivering at the analgesic dosage,<sup>[73]</sup> and is more suitable for patients with postoperative pain and chills. Tramadol is mainly metabolized by CYP2D6 liver enzymes, and CYP2D6 activity differs among races.<sup>[74]</sup> The dosage can be optimized through genotype detection to achieve the best analgesic effect while minimizing adverse reactions.

Local anesthetics are mainly used for postoperative analgesia through intraspinal administration, peripheral nerve tissue, and local infiltration.<sup>[75]</sup> They are commonly used for postoperative analgesia, including bupivacaine, ropivacaine, lidocaine, etc. Bupivacaine is widely used for postoperative analgesia<sup>[76, 77]</sup> because of its long acting time and low price, but, drug overdose can easily lead to the toxicity to central nervous system and heart.<sup>[78]</sup> Ropivacaine has a relatively weak effect on motor nerve block,<sup>[79-81]</sup> “kinesthetic separation” phenomenon is more obvious than that of bupivacaine, and its toxicity is lower than that of bupivacaine and levobupivacaine, making it an ideal local anesthetic for postoperative analgesia.<sup>[6]</sup>

Gabapentin and pregabalin are calcium channel regulators that control  $\alpha 2\delta$  subunit, which reduces the release of glutamate, noradrenaline, and substance P, and has an analgesic effect<sup>[6,82]</sup>. As part of the multimodal analgesia, it can reduce the dosage of opioids and postoperative pain of patients.<sup>[83-86]</sup> The common adverse reactions include dose-dependent dizziness and lethargy.<sup>[82]</sup> Clinical pharmacists should inform patients and caregivers to take measures to prevent falls.

Ketamine is a receptor antagonist of N-methyl-D-aspartate acid (NMDA). Intravenous injection before and after surgery plays an important role in relieving pain and preventing the central and peripheral sensitization,<sup>[87-89]</sup> and at the same time it can reduce the dosage of opioids.<sup>[6,90]</sup> It should be noted that such drugs can cause hallucinations, nightmares, sleepwalking, and other adverse reaction,<sup>[91,92]</sup> and patients with a history of mental illness should use it with caution.

Dexmedetomidine<sup>[93]</sup> is a highly selective  $\alpha 2$ -adrenergic receptor agonist with sedative, analgesic, anti-inflammatory, anti-sympathetic, anti-anxiety, and organ-protective effects. When combined with other sedative and analgesic drugs, it has a good synergistic effect and can significantly reduce the dosage of other sedative and analgesic drugs. The most common adverse reactions are hypertension, hypotension, bradycardia, and dry mouth.

### 3.2 Multi-mode Analgesia

Multi-mode analgesia<sup>[6,94-99]</sup> refers to the combined use of analgesic drugs or techniques that act on different targets and mechanisms in the pain pathway, so as to obtain additive or synergistic analgesic effects, reduce drug dosage and related adverse reactions, and achieve the maximum effect/risk ratio. It is the most common type of postoperative analgesia.

The combination of analgesic drugs includes the following five categories: First, the combination of opioids or tramadol with acetaminophen can reduce the dosage of opioids;<sup>[100-104]</sup> Second, acetaminophen combined with NSAIDs can exert additive or synergistic analgesic effect;<sup>[101,105,106]</sup> Third, opioids or tramadol combined with NSAIDs after major surgery can save the dosage of opioids, especially can achieve good analgesia in patients' awake state.<sup>[94, 95]</sup> Fourth, opioids, especially highly liposoluble fentanyl or sufentanil, are combined with local anesthetics for PCA;<sup>[107-109]</sup> Fifth, preoperative application of ketamine, tramadol, gabapentin, pregabalin, and  $\alpha 2$  adrenergic receptor agonist clonidine or low-dose dexmedetomidine<sup>[84,88,94,101,111]</sup> can reduce postoperative pain and the dosage of opioids. APS<sup>[6]</sup> strongly recommends NSAIDs such as acetaminophen and celecoxib as part of the multimodal analgesia. However, it should be noted that when acetaminophen is combined with opioids, the maximum daily dose of the former should be reduced.<sup>[103]</sup>

Although local anesthetic infiltration, ultrasound-guided regional block, or peripheral nerve block

can be used alone for postoperative analgesia, it is likely that the analgesic effect will be poor, so it is suggested to combine it with systemic analgesics.<sup>[94,95]</sup> Combined with systemic medication based on local medication, it can not only significantly reduce the demand of analgesic drugs, but also the incidence of adverse drug reactions.<sup>[98]</sup>

Clinical pharmacists can formulate individualized multi-mode analgesia plans according to the expected pain intensity, clinical factors, and patients' conditions after different types of operations.

### **3.3 Patient Controlled Analgesia (PCA)**

PCA<sup>[6,112]</sup> boasts the advantages of quick effect, no blind area, relatively stable blood drug concentration, and timely control of burst pain through impact dose, making it the most commonly used and ideal method for postoperative analgesia and is applicable for moderate to severe postoperative pain.<sup>[113-116]</sup>

Clinical pharmacists should evaluate the rationality of drug administration from many aspects, such as incompatibility, drug properties, patients' conditions, and different PCA administration methods.<sup>[14,117]</sup> When choosing PCA plans, it is necessary to comprehensively evaluate the patient's condition, such as liver and kidney function, infection risk and drug contraindications. Although several guidelines have recommended the use of multiple drugs in postoperative PCA, clinical pharmacists are required to comprehensively analyze whether there are incompatibilities in the combinations of these drugs, especially the stability of long-term mixing.<sup>[118-120]</sup>

## **4. Postoperative Analgesia for Special Populations**

### **4.1 Postoperative Analgesia in Elderly Patients**

Aging leads to the decrease of blood supply to human organs, the weakening of drug metabolism and clearance function, especially kidney metabolism and active metabolites. For example, a low dose of morphine should be administered for the first time.<sup>[121-123]</sup> Therefore, it is suggested that drugs with no clinical significance and little influence on liver and kidney function should be selected. The proportion of muscle in elderly patients decreases while that of fat increases, which leads to the change of drug distribution volume and makes lipophilic drugs such as fentanyl<sup>[123]</sup> easy to accumulate in fat, resulting in a prolonged half-life of drugs.

The elderly often have other chronic diseases, including hypertension, coronary heart disease, diabetes, and chronic obstructive pulmonary disease, which are more likely to lead to adverse cardiovascular events and respiratory depression. Gastrointestinal injury and cardiovascular risk assessment should be conducted before medication.<sup>[66,68]</sup> Clinical pharmacists should strengthen the monitoring of vital signs of elderly patients during postoperative analgesia..

### **4.2 Postoperative Analgesia in Children**

It is difficult to assess pain in children because they cannot complain of pain, and some analgesic drugs are restricted for use in children, or their parents are overly worried about the side effects. As a result, postoperative pain in children is seriously overlooked.<sup>[124]</sup> Therefore, clinical pharmacists should choose appropriate pain assessment methods according to the age of children,<sup>[21,125]</sup> and analgesic drugs, dosages, and administration routes according to the pain assessment results. The European Society for Paediatric Anesthesiology (ESPA) recommends several analgesic drugs and methods that can be used for children,<sup>[126]</sup> such as opioid analgesic drugs and NSAIDs according to the weight of children. Other guidelines<sup>[127]</sup> also suggest that children and their families should be educated about the safe use of opioids before and after surgery.

### **4.3 Postoperative Analgesia for Patients with Renal Insufficiency**

Most of the analgesic drugs are metabolized by kidney, and some of them are nephrotoxic, especially NSAIDs, which have a great impact on renal function;<sup>[69,128]</sup> Clinical pharmacists should adjust the dosage and administration of drugs and monitor the renal function regularly according to the renal function of patients. It is recommended to evaluate the renal function before taking drugs according to the chronic kidney disease (CKD) grading standard, glomerular filtration rate (GFR) and creatinine clearance (Ccr).<sup>[129-131]</sup>

#### **4.4 Postoperative Analgesia for Patients with Hepatic Insufficiency**

The liver is the largest organ of the human body, and liver insufficiency affects the pharmacokinetics of most analgesic drugs.<sup>[132]</sup> At the same time, the use of analgesic drugs increases the metabolic burden of the liver, and further aggravate the liver damage.<sup>[133]</sup> Clinical pharmacists should work out individualized analgesia schemes for patients with hepatic insufficiency, and regularly monitor liver function. It is recommended to use Child-Pugh grading standard and model for end-stage liver disease (MELD) to evaluate liver function.<sup>[134,135]</sup>

#### **5. Conclusion**

Postoperative pain control can reduce postoperative stress, weaken postoperative immunosuppression, accelerate the recovery of intestinal function, and promote the early recovery of patients. Clinical multi-disciplinary team members, such as anesthesiologists, surgeons, specialist nurses and clinical pharmacists, can cooperate to enhance postoperative pain management. Clinical pharmacists, as important members of the group,<sup>[136]</sup> can play an important role in effectively relieving patients' pain and improving their satisfaction by participating in the pain assessment and health education of patients with postoperative pain; They can use their expertise to assist doctors in formulating and monitoring the efficacy of analgesic schemes, so as to effectively control pain, reduce adverse reactions and promote safe medication, as well as to further reduce the incidence of postoperative complications, shorten postoperative hospital stay and reduce medical expenses.

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**Acknowledgements:**

Special thanks to Zhou Juan, Jiang Xiaofeng, Wang Guoqiang, Chen Binwei, Xu Xiaoyan, Wu Xuelian, Ji Cuihong, Yin Xuexia and Zhong Shanjiao for their contributions to this consensus

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