

Review Article



All about pain pharmacology: what pain physicians should know

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From the perspective of the definition of pain, pain can be divided into emotional and sensory components, which originate from potential and actual tissue damage, respectively. The pharmacologic treatment of the emotional pain component includes anti-anxiety drugs, antidepressants, and antipsychotics. The anti-anxiety drugs have anti-anxious, sedative, and somnolent effects. The antipsychotics are effective in patients with positive symptoms of psychosis. On the other hand, the sensory pain component can be divided into nociceptive and neuropathic pain. Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are usually applied for somatic and visceral nociceptive pain, respectively; anticonvulsants and antidepressants are administered for the treatment of neuropathic pain with positive and negative symptoms, respectively. The NSAIDs, which inhibit the cyclo-oxygenase pathway, exhibit anti-inflammatory, antipyretic, and analgesic effects; however, they have a therapeutic ceiling. The adverse reactions (ADRs) of the NSAIDs include gastrointestinal problems, generalized edema, and increased bleeding tendency. The opioids, which bind to the opioid receptors, present an analgesic effect only, without anti-inflammatory, antipyretic, or ceiling effects. The ADRs of the opioids start from itching and nausea/vomiting to cardiovascular and respiratory depression, as well as constipation. The anticonvulsants include carbamazepine, related to sodium channel blockade, and gabapentin and pregabalin, related to calcium blockade. The antidepressants show their analgesic actions mainly through inhibiting the reuptake of serotonin or norepinephrine. Most drugs, except NSAIDs, need an up-dose titration period. The principle of polypharmacy for analgesia in case of mixed components of pain is increasing therapeutic effects while reducing ADRs, based on the origin of the pain.

Key Words: Analgesics; Anticonvulsants; Antidepressive Agents; Anti-Inflammatory Agents, Non-Steroidal; Carbamazepine; Gabapentin; Neuralgia; Nociceptive Pain; Opioids; Polypharmacy; Pregabalin; Serotonin.

INTRODUCTION

Pain can be treated with invasive or non-invasive methods. Pharmacologic treatment, mostly systemic administration, uses non-invasive methods. Definite targeted invasive treatments, such as a percutaneous osteoplasty

for metastasized bone fractures, or endoscopic discectomy for compressed nerves, have a definite advantage over broad-spectrum systemic analgesics in that they remove the source of the pain. If it is impossible to correct or remove the source of pain, non-invasive administration of systemic analgesics is the second choice.

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Table 1. Classification of Pain and Recommendable Appropriate Analgesics

Emotional pain	Anxiolytics (minor tranquilizers)	Benzodiazepines	Clonazepam, diazepam, midazolam
	Antidepressants	Etifoxine (etafenoxine)	
		Typical	Nortriptyline, amitriptyline,
Sensory pain	Antipsychotics (major tranquilizers)	Atypical	SSRIs, SSNRIs
		First generation	Haloperidol, chlorpromazine
	Nociceptive pain	Second generation	Quetiapine, risperidone, olanzapine
		Somatic (Superficial and deep ^a)	NSAIDs, APAP, ASA, and steroids
		Visceral ^a	Opioids: weak and strong
Neuropathic pain	Positive symptoms	Anticonvulsants	
	Negative symptoms	Antidepressants: nortriptyline, amitriptyline	

SSRIs: selective serotonin reuptake inhibitors, SSNRIs: selective serotonin norepinephrine reuptake inhibitors, NSAIDs: non-steroidal anti-inflammatory drugs, APAP: N-acetyl-para-aminophenol, ASA: acetyl salicylic acid.

^aDeep somatic and visceral pain may present referred pain or radiating pain including radicular pain.

First of all, recognition of the source of the pain is the first step in choosing analgesics. When the origin of the pain is classified, it is preferable to use the International Association for the Study of Pain definition of pain [1]. Therefore, it can be divided into the emotional component, caused by potential tissue damage, and the sensory component, caused by actual tissue damage. The sensory component of pain is also divided into nociceptive (somatic and visceral) and neuropathic pain (positive and negative) (Table 1).

Somatic nociceptive pain, which can be divided into superficial and deep categories, shows a good response to non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (Paracetamol[®], N-acetyl-para-aminophenol [APAP]), acetylsalicylic acid (ASA), and steroids. Visceral nociceptive pain usually responds to opioids. Deep nociceptive and visceral pain may sometimes present as referred pain and radiating pain, which create great confusion in deciding the origin of the pain.

Neuropathic pain can be divided into positive and negative symptom categories. Neuropathic pain with positive symptoms shows a good response to anticonvulsants, while neuropathic pain with negative symptoms responds well to antidepressants [2-5].

Most analgesics, except some which exhibit a therapeutic ceiling, such as NSAIDs, APAP, and ASA, need dose and dosage titration for seeking the appropriate analgesic blood level, which can control persistent pain, but not breakthrough pain.

The three steps for analgesic administration and pain management are pain relief at night, bed rest in the daytime, and active movement during daily life. In addition, the principle of polypharmacy is focused on increasing therapeutic effects (analgesia) while reducing adverse reactions (ADRs), based on the source of the pain.

This review provides appropriate choices of analgesics for the treatment of pain, based on the supposed origins of the pain.

MAIN BODY

1. Sensory component of pain

Nociceptive pain arises from actual or threatened damage to non-neural tissue, due to the activation of nociceptors. On the other hand, neuropathic pain is caused by a lesion or disease of the somatosensory nervous system, which exhibits abnormal function [6].

1) Nociceptive pain

Superficial somatic nociceptive pain exhibits well-demarcated, sharp, aching pain, while deep somatic nociceptive pain presents ill-demarcated, dull pain. Visceral pain shows poorly-demarcated, heavy, dull pain. Deep somatic and visceral nociceptive pain may have referred pain or radiating pain characteristics (including radicular pain).

Basically, the borders of the somatic and visceral structures are the dura in the head, the pleura and pericardium in the chest, the peritoneum in the abdomen, and the (potential) retroperitoneum (retroperitoneal space) behind the abdominal cavity in the pelvis.

Well-known referred pain from the visceral structures includes left shoulder pain from myocardial infarctions, and right supraclavicular pain from hepatobiliary disorders. Examples of representative referred pain from the deep somatic structures can be found in spinal joint pain from the atlanto-occipital and atlanto-axial joints, classic cervical, thoracic, and lumbar facet joints, and sacroiliac joints.

It has already been demonstrated that substance P, calcitonin gene-related peptide, and protein gene product 9.5 containing nerve fibers, exist in the cervical facet joints in a cadaveric study [7]. This means that anti-inflammatory drugs may be effective through either systemic administration or local infiltration. Therefore, in the case of inflamed knee joints, as with the diarthrodial joints, it seems more effective to use direct intra-articular injections than

innervating nerve branch blocks [8-10].

The medial branch also innervates bones, including the posterior lamina and spinous process, ligaments, including the supraspinous ligament, interspinous ligament, and ligament flavum, erect muscles, skin, and subcutaneous tissues, as well as the facet joints [11]. Therefore, the diagnostic value of medial branch blocks can be diluted, and the therapeutic effect may be lower than with facet joint injections.

(1) Non-steroidal systemic analgesics

① NSAIDs

The name NSAIDs includes analgesic drugs, which are not in the class of steroids and have an anti-inflammatory property. The NSAIDs reduce pain and inflammation, as well as fever. In addition, ASA also has the ability to reduce itching. However, APAP can only reduce pain and fever, not inflammation. Therefore, APAP is not an NSAID because it does not reduce inflammation. So, if there is inflammation, anti-inflammatory drugs which act by peripheral mechanisms are needed. Otherwise, if there is no inflammation, APAP, which acts on central mechanisms, can replace the NSAIDs.

The action mechanism of NSAIDs is usually explained by cyclo-oxygenase (COX). The COX is traditionally divided into the constitutive COX-1 isoform in the normal condition and the inducible COX-2 isoform in the inflammatory condition. However, controversially, the COX-1 and -2 isoforms are widely found in the human body, such as the central nervous system, peripheral nervous system, cardiovascular system, gastrointestinal system, endocrine system, and reproductive system under normal conditions. In addition, the COX-2 is especially found in the brain, kidney, and female reproductive system [12].

All currently available NSAIDs have 3 common representative therapeutic effects, namely, an analgesic, anti-inflammatory, and antipyretic effect, and also have 3 common representative ADRs, specifically gastric damage, renal damage, and an antiplatelet function. Therefore, it is better to choose and prescribe a familiar NSAID only for a short period of inflammation, while considering its half-life.

Common ADRs of NSAIDs in detail are (1) gastrointestinal problems related to gastrointestinal mucosa damage, due to decreased prostaglandin (PG) E₂ resulting from COX-1 inhibition, such as dyspepsia, and gastric erosion, ulceration, perforation, and bleeding, (2) renal problems related to sodium and water retention, hypertension, and hemodynamic acute renal injury due to decreased PG E₂ and PGI₂, resulting from COX-1 and COX-2 inhibition, and

(3) cardiovascular and platelet aggregation problems, such as stroke and myocardial infarction due to decreased PGI₂, resulting from greater COX-2 and lesser COX-1 inhibition, and increased bleeding tendency due to decreased thromboxane (TX) A₂, resulting from COX-1 inhibition.

Relative COX-1 and COX-2 selectivity (COX-1/COX-2 half maximal inhibitory concentration [IC₅₀] value) for commonly used NSAIDs and ASA in order of value would be ketorolac, ketoprofen, indomethacin, ASA, naproxen, ibuprofen, piroxicam, meloxicam, diclofenac, celecoxib, valdecoxib, etoricoxib, rofecoxib, and lumiracoxib [13].

NSAIDs, APAP, and ASA have a ceiling effect, in which the fixed maximal therapeutic effect is achieved, but ADRs continue to worsen, as their doses increase. Finally, they increase the risk to benefit ratio, developing a ceiling effect.

② ASA

ASA has been commercially available from 1899 under the name Aspirin[®] (Bayer AG, Leverkusen, Germany). In addition to the 4 representative therapeutic effects already mentioned, a low dose of ASA has been used for reducing the risk of heart attack and stroke [14]. Long-term medication for at least 10-20 years may be effective in cancer prevention, especially with colorectal cancer [15], but also with endometrial [16], breast [17], and prostate cancer [18].

After Vane's discovery of COX in 1971, the mechanisms of action of non-opioid analgesics, including ASA, NSAIDs, and steroids, have been apparent [19,20]. However, ASA, unlike other NSAIDs, is known to produce a unique, irreversible inactivation of COX, since it covalently modifies both COX-1 and COX-2 by acetylating serine residue within the COX active sites. This irreversible inactivation of COX-1 results in a representative ADR, gastrotoxicity, ranging from gastritis to peptic ulcers and gastrointestinal bleeding [21-23].

In addition, COX-1 is the main form in the mature platelets in the blood, where it transforms arachnoid acid via the intermediates PG G/H to TX A₂ (vasoconstrictor and platelet activator). This inhibition of TX A₂ explains the antithrombotic properties of ASA [14,21-23].

There is a theory related to a clinical benefit in which ASA turns off COX-2's production of PGs, but switches on COX-2's ability to produce novel protective lipid mediators (ASA-triggered lipoxins). In other words, ASA, in a different way from NSAIDs, converts COX-2 into a protective mediator-generating system with anti-inflammatory and pro-resolving properties [23].

③ APAP

APAP is used to treat pain and fever (but not inflammation or itching) after being synthesized in 1877 and being marketed as Tylenol® or Panadol® in 1955 [24,25]. Its weak anti-inflammatory property is probably due to its poor effectiveness in high peroxide concentrations at the inflammatory site [26,27].

As with ASA, which has a history of more than 100 years, the mechanism of action of APAP is still unclear. Potential analgesic mechanisms of APAP are (1) positive effects on the serotonergic descending inhibitory pain pathway, and (2) interactions with opioid systems, eicosanoid systems, and nitric oxide containing pathways [27,28].

(2) Steroids

Steroids have the ability to inhibit both COX and lipoxygenase, resulting in a reduction of PGs and leukotrienes (LTs).

LTs are inflammatory mediators, and include the dihydroxy acid LT (LTB₄) and the cysteinyl LTs (CysLTs; LTC₄, LTD₄, LTE₄). The high-affinity LTB₄ receptors are known as BLT₁, the LTC₄, and LTD₄ receptors as CysLT₁ and CysLT₂, and the LTE₄ receptors as GPR99. BLT₁ signaling stimulates the degranulation, chemotaxis, and phagocytosis of neutrophils, and CysLT₁ and CysLT₂ signaling induces airway inflammation by bronchial smooth muscle contraction and increasing vascular permeability. Therefore, these LTs are involved in chronic inflammatory disorders, such as asthma, atopic dermatitis, psoriasis, atherosclerosis, arthritis, obesity, cancer, and age-related degeneration [29,30].

Steroids in palliative care are indicated for special conditions, such as spinal cord compression, increased intracranial pressure, and bowel obstruction, and for responding to general conditions, such as reducing pain, stimulating appetite, suppressing nausea, and alleviating fatigue. Generally, inhibition of PG and LT synthesis by steroids leads to reducing pain, inflammation, and vascular permeability (edema) [31].

(3) Opioids

Opioids for analgesia have been used for over 5,000 years. Opioids are substances that act on the opioid receptors, such as the mu, kappa, and delta receptors. According to the action on the opioid receptors, opioids can be divided into agonists, antagonists, and partial agonists/antagonists. Opioid agonists bind to G-protein coupled receptors, and cause cellular hyperpolarization [32].

Opioid up-titration may be needed due to cancer pro-

gression from a visceral origin. However, in cases of newly-developed invasions into other structures, non-opioid analgesics are helpful to manage the somatic pain, and anticonvulsants and antidepressants are effective to control the neuropathic pain.

Opioids are effective for both somatic and visceral nociceptive pain; however, they should only be started in patients with chronic non-malignant disorders if physicians are confident, they can taper and then discontinue them. Extra caution should be used in giving immediate-release opioids to young patients with chronic non-malignant disorders, especially chronic pancreatitis (visceral pain), complex regional pain syndrome (neuropathic pain), or bony fracture (somatic pain). Thanks to the development of the diagnosis and treatment of cancer, patients who experience complete recovery from cancer may be candidates for opioid addiction.

Methadone was approved by the U.S. Food and Drug Administration in 1972 for the treatment of opioid addiction. It has 2 enantiomers found in equal amounts in a racemic mixture; the active R enantiomer has a half-life of 36-48 hours and the inactive S enantiomer has a half-life of approximately 16 hours. Therefore, it is rapidly absorbed by the oral route with a delayed onset of action (with peak level at 2-4 hr) and with sustained levels maintained over 24 hours. It also has N-methyl-D-aspartate (NMDA) receptor antagonist properties. The initial dose starts with 20-40 mg/day, then the dose is gradually increased by 10 mg every 4-7 days [33].

Conventional opioids activate 2 intracellular signaling pathways: the G protein pathway induces analgesia, while the beta-arrestin pathway is responsible for the opioid-related ADRs. An academically ideal oliceridine (TRV130) has been studied for its role in both activation of the G protein pathway for analgesia and deactivating the beta-arrestin pathway for reducing ADRs [34]. Clinicians await the launch of this novel opioid with lesser ADRs.

2) Neuropathic pain

Pharmacologic treatment of neuropathic pain begins from the translation of symptoms and signs in patients into the underlying mechanisms, and simply classifying them as positive or negative (Table 2) [2,5].

Representative negative sensory symptoms and signs in neuropathic pain (with their underlying mechanisms) are a reduced sensation of (1) touch (A β fiber abnormalities), (2) vibration (A β fiber abnormalities), (3) pin prick (A δ fiber abnormalities), and (4) cold and heat (A δ /C fibers abnormalities).

On the other hand, positive symptoms and signs can be divided into spontaneous or evoked pain according to the

Table 2. Recognition of Neuropathic Pain: Sensory Symptoms and Signs of Neuropathic Pain, Clinical and Laboratory Tests, and Underlying Mechanisms

Sensory symptom and sign	Bedside examination	Laboratory examination	Mechanism
1. Negative sensory symptoms and signs			
1) Reduced touch	Touch skin with cotton wool	Graded von Frey hair	A β fibers
2) Reduced pin prick	Prick skin with a pin single stimulus	von Frey hair specific (e.g., 100-g)	A δ fibers
3) Reduced cold and warm	Thermal response to cold and warm objects (20°C and 45°C)	Detection of pain threshold for warm and cold objects	A δ /C fibers
4) Reduced vibration	Tuning fork on the medial malleolus	Vibrometer	A β fibers
2. Positive sensory symptoms and signs			
1) Spontaneous pain			
(1) Paresthesia	Grade (0-10)	Area in cm ² grade (0-10)	Spontaneous activity in long-term A β afferent fibers
(2) Dysesthesia	Grade (0-10)	Area in cm ² grade (0-10)	Spontaneous activity in A δ /C afferent fibers
(3) Paroxysms	Grade (0-10)	Threshold for evocation	Spontaneous activity in C nociceptors
(4) Superficial burning pain	Grade (0-10)	Area in cm ² grade (0-10)	Spontaneous activity in C nociceptors
(5) Deep pain	Grade (0-10)	Area in cm ² grade (0-10)	Spontaneous activity in joint/muscle nociceptors
2) Evoked pain			
(1) Touch evoked hyperalgesia	Stroking skin with brush	None	Central sensitization: C fiber input and loss of C fiber input
(2) Static hyperalgesia	Gentle mechanical pressure	Evoked pain to pressure	Peripheral sensitization
(3) Punctate hyperalgesia	Pricking skin with a pin	von Frey hair	Central sensitization: A δ afferent fibers input
(4) Punctate repetitive hyperalgesia (windup-like pain)	Pricking skin with a pin 60 times/30 sec	von Frey hair	Central sensitization: A δ afferent fibers input
(5) Aftersensation	Measurement of pain duration after stimulation	Measurement of pain duration after stimulation	Central sensitization
(6) Cold hyperalgesia	Stimulation skin with cool metal roller	Evoked pain to cold stimuli	Central sensitization and disinhibition
(7) Heat hyperalgesia	Stimulation skin with warm metal roller	Evoked pain to heat stimuli	Peripheral sensitization
(8) Chemical hyperalgesia	Topical capsaicin	Topical capsaicin	Peripheral sensitization
(9) Sympathetic maintained pain	Sympathetic blockade	Modulation of sympathetic outflow	Sympathetic afferent coupling

Reproduced from the article of Jensen and Baron (Pain 2003; 102: 1-8) [2].

absence or presence of stimuli. Spontaneous pain (and its underlying spontaneous activity) includes (1) paresthesia (low threshold A β afferents), (2) dysesthesia (A δ /C afferents), (3) paroxysms (C-nociceptors), (4) superficial burning pain (C-nociceptors), and (5) deep pain (joint/muscle nociceptors). Evoked pain includes (1) touch evoked hyperalgesia (central sensitization related to C fiber input), (2) static hyperalgesia (peripheral sensitization), (3) punctate hyperalgesia (central sensitization related to A δ fiber input), (4) punctate repetitive hyperalgesia (windup-like pain, central sensitization related to A δ fiber input), (5) aftersensation (central sensitization), (6) cold hyperalgesia (central sensitization and disinhibition), (7) heat hyperalgesia (peripheral sensitization), (8) chemical hyperalgesia (peripheral sensitization), and (9) sympathetic maintained pain (sympathetic afferent coupling). In summarizing positive neuropathic pain, spontaneous pain includes paresthesia, dysesthesia, paroxysms, superficial burning pain, and deep pain; evoked pain includes various kinds of hyperalgesia, aftersensation, and sympathetic maintained

pain [5].

The representative evoked positive symptoms of neuropathic pain are mechanical (dynamic, punctate, and superficial or deep static) and thermal (cold and heat) hyperalgesia and allodynia [5].

Several available clinical assessment tools for neuropathic pain have been developed for evaluation of the neuropathic pain component ratio among patients' whole pain, and for comparison of neuropathic pain scores before and after non-invasive or invasive treatment. Common screening tools for neuropathic pain are (1) the neuropathic pain questionnaire (NPQ), (2) douleur neuropathique en 4 (DN4), (3) Leeds assessment of neuropathic symptoms and signs (LANSS), (4) ID pain, (5) painDETECT (Table 3), as well as (6) the neuropathic pain symptom inventory (NPSI) questionnaire (Table 4) [4,5,35-42].

The NPQ includes 12 items scored from 0 to 100 and its coefficient: (1) burning \times 0.006, (2) overly sensitive to touch \times 0.005, (3) shooting pain \times 0.005, (4) numbness \times 0.020,

Table 3. Summary of Various Neuropathic Pain Questionnaires

NPQ [38]	DN4 [39]	LANSS [40]	ID pain [41]	painDETECT [42]
1. Burning × 0.006	Question 1 ^a	Pain questionnaires	1. Pins and needles (Yes: 1, No: 0)	1. Grading of pain (0: never, 1: hardly, 2: slightly, 3: moderately, 4: strongly, or 5: very strongly noticed)
2. Overly sensitive to touch × 0.005	1. Burning	1. Dysesthesia (Yes: 5, No: 0)	2. Hot/burning sensation (Yes: 1, No: 0)	2. The pain course pattern (0: persistent pain with slight fluctuations, -1: persistent pain with pain attacks, +1: persistent pain without pain between attacks, or +1: persistent pain with pain between attacks)
3. Shooting pain × 0.005	2. Painful cold	2. Color change of the skin in the painful area (Yes: 5, No: 0)	3. Numbness (Yes: 1, No: 0)	3. Radiating pain (+2: yes, or 0: no)
4. Numbness × 0.020	3. Electric shocks	3. Abnormal sensitivity to touch in the affected skin (Yes: 3, No: 0)	Electric shocks (Yes: 1, No: 0)	The total score varies from 0 to 8.
5. Electric pain × -0.008	Question 2 ^a	4. Abnormal skin temperature change in the painful area (Yes: 2, No: 0)	Worsening with touch (Yes: 1, No: 0)	
6. Tingling × 0.010	4. Tingling	5. Abnormal skin temperature change (Yes: 1, No: 0)	Limited to the joints (Yes: -1, No: 0)	
7. Squeezing × -0.004	5. Pins and needles	The sensory testing	The total score varies from -1 to 5.	
8. Freezing × 0.004	6. Numbness	1. Allodynia (Yes: 5, No: 0)		
9. Unpleasant × 0.006	7. Itching	2. An altered pin-prick threshold (Yes: 3, No: 0)		
10. Overwhelming × -0.003		The total score varies from 0 to 24.		
11. Tactile hyperalgesia × 0.006	Question 3 ^b	If the score < 12, neuropathic mechanisms are unlikely to be contributing to the patient's pain.		
12. Increased pain due to weather changes × -0.005	8. Hypoesthesia to touch	If the score ≥ 12, neuropathic mechanisms are likely to be contributing to the patient's pain.		
If the total score minus 1.408 is below 0, it predicts non-neuropathic pain.	9. Hypoesthesia to pinprick			
On the contrary, if the total score minus 1.408 is at or above 0, it predicts neuropathic pain.	Question 4 ^b			
	10. Pain caused by or increased by brushing Yes = 1, No = 0 Patient's score = □/10			

NPQ: neuropathic pain questionnaire, DN4: douleur neuropathique en 4, LANSS: Leeds assessment of neuropathic symptoms and signs.

^aFrom interview of the patient. ^bFrom examination of the patient.

(5) electric pain × -0.008, (6) tingling × 0.010, (7) squeezing × -0.004, (8) freezing × 0.004, (9) unpleasant × 0.006, (10) overwhelming × -0.003, (11) tactile hyperalgesia × 0.006,

and (12) increased pain due to weather changes × -0.005. If the total score minus 1.408 is below 0, it predicts non-neuropathic pain. On the contrary, if the total score minus

Table 4. Neuropathic Pain Symptom Inventory Questionnaire

Neuropathic pain symptom inventory	Interpretation of pain	Score
Q1. Burning	Superficial spontaneous pain	0-10
Q2. Squeezing	Deep spontaneous pain	0-10
Q3. Pressure		0-10
Q4. Spontaneous pain during the past 24 hr		Permanently 8-12 hr 4-7 hr 1-3 hr < 1 hr
Q5. Electric shocks	Paroxysmal pain	0-10
Q6. Stabbing		0-10
Q7. Pain attacks during the past 24 hr		> 20 times/day 11-20 times/day 6-10 times/day 1-5 times/day 0 times/day
Q8. Pain provoked by or increased by brushing on the painful area	Evoked pain	0-10
Q9. Pain provoked by or increased by pressure on the painful area		0-10
Q10. Pain provoked by or increased by contact with something cold on the painful area		0-10
Q11. Pins and needles	Paresthesia/Dysesthesia	0-10
Q12. Tingling		0-10
Results		
Total intensity score	Sub-scores	0-100
Q1 = Superficial spontaneous pain	/1 = 0-10 × 2	0-20
Q2 + Q3 = Deep spontaneous pain	/2 = 0-10 × 2	0-20
Q5 + Q6 = Paroxysmal pain	/2 = 0-10 × 2	0-20
Q8 + Q9 + Q10 = Evoked pain	/3 = 0-10 × 2	0-20
Q11 + Q12 = Paresthesia/Dysesthesia	/2 = 0-10 × 2	0-20

0 means no pain, but 10 means maximal pain imaginable.

Modified from the article of Bouhassira et al. (Pain 2004; 108: 248-57) [5].

1.408 is at or above 0, it predicts neuropathic pain [37].

The DN4 is composed of 10 question items (yes: 1, no: 0) with 2 categories. First, from the interview of the patient, question 1 includes pain characteristics: (1) burning, (2) painful cold, and (3) electric shocks. Question 2 includes the presence of these combined symptoms: (4) tingling, (5) pins and needles, (6) numbness, and (7) itching. From the examination of the patient, question 3 includes the presence of hypoesthesia: (8) hypoesthesia to touch, and (9) hypoesthesia to pinprick. Question 4 is whether (10) the pain can be caused by or increased by brushing the painful area [39].

The LANSS pain scale includes a pain questionnaire and sensory testing. The pain questionnaire includes (1) unpleasant sensations such as pricking, tingling, or pins and needles (yes: 5, no: 0), (2) different appearance of the skin in the painful area, such as mottled or a red/pink appearance (yes: 5, no: 0), (3) abnormal sensitivity to touch (yes: 3, no: 0), (4) pain appearing suddenly and in bursts for no apparent reason, such as electric shocks, jumping, and bursting (yes: 2, no: 0), and (5) abnormal skin temperature change, such as feeling hot or a burning sensation (yes: 1, no: 0). The sensory testing for the presence of allodynia and an altered pinprick threshold includes (6) allodynia (yes: 5, no: 0) and (7) an altered pinprick threshold (yes: 3,

no: 0). The total score varies from 0 to 24. If the score < 12, neuropathic mechanisms are unlikely to be contributing to the patient's pain. If the score ≥ 12, neuropathic mechanisms are likely to be contributing to the patient's pain [40].

The ID pain score includes 6 items scoring from -1 to 5: (1) pain feeling like pins and needles (1/0), (2) hot/burning sensation (1/0), (3) numbness (1/0), (4) electric shocks (1/0), (5) worsening with touch (1/0), and (6) pain limited to the joints (-1/0) [41].

The painDETECT was developed to assess the neuropathic pain component in low back pain. It includes 3 items with (1) grading of pain (0: never, 1: hardly, 2: slightly, 3: moderately, 4: strongly, or 5: very strongly noticed), (2) the pain course pattern (0: persistent pain with slight fluctuations, -1: persistent pain with pain attacks, +1: persistent pain without pain between attacks, or +1: persistent pain with pain between attacks), and (3) radiating pain (+2: yes, or 0: no). The total score varies from 0 to 8 [42].

The NPSI is recommendable for evaluating the change of intensity of neuropathic pain before and after treatment. It includes positive symptoms and signs of neuropathic pain, including spontaneous pain (superficial burning and deep pain [squeezing and pressure], paresthesia or dysesthesia [pins/needles and tingling], as well as paroxysmal pain [electric shocks and stabbing]) and evoked pain (by brush-

ing, pressure, and contact) (Table 4) [5].

(1) Carbamazepine

Carbamazepine (Tegretol[®]) is still considered the first-line drug for the treatment of trigeminal neuralgia [43,44]. According to the White and Sweet diagnostic criteria of trigeminal neuralgia, the pain should be (1) paroxysmal, (2) provoked by light touch to the face, (3) confined to the trigeminal zone, and (4) unilateral, with (5) showing a normal clinical sensory test in the painful area [45].

In addition, according to the diagnostic criteria for classical and symptomatic trigeminal neuralgia of the International Classification of Headache Disorders (second edition) by the International Headache Society, classical trigeminal neuralgia shows (1) a paroxysmal attack of facial pain which last a few seconds to less than 2 minutes, affecting one or more divisions of the trigeminal nerve, (2) intense, sharp, superficial, or stabbing pain, or pain precipitated from trigger areas or by trigger factors, (3) stereotyped attacks in the individual patient, (4) no abnormal neurologic deficit, and (5) that it is not attributed to another disorder [46].

The metabolite of carbamazepine, carbamazepine-10,11-epoxide, plays an important role for ADRs of carbamazepine. For the safer use of carbamazepine, (1) a monotherapy prescription (if possible), (2) adequate dose titration with monitoring plasma concentration, and (3) routine laboratory check-up, such as complete blood count and liver function test, are recommended [47].

(2) Oxcarbazepine

Oxcarbazepine (Trileptal[®]) has been developed from carbamazepine through structural variation to avoid metabolites causing ADRs. However, oxcarbazepine is different from carbamazepine; (1) The mode of action of both drugs consists mainly of a blockade of sodium currents. However, in comparison to calcium channel blockade, oxcarbazepine or monohydroxy derivate expresses its effect *via* N-, P-, and/or R-type calcium currents, instead of the L-type calcium currents in carbamazepine. (2) It increases neither 5-hydroxytryptamine (HT) release nor acetylcholine receptor blockade. (3) It does not inhibit the cytochrome P 450 enzymes, and it reduces the concentration of gamma-glutamyltransferase in the serum [48].

Oxcarbazepine and its metabolites are mostly excreted in the urine; an ability of renal clearance is important to determine the dose of administration. In patients with an impaired glomerular filtration rate below 30 mL/mo, (1) the daily dose should be halved to 4-5 mg/kg (almost 300 mg/day), (2) slower dose increases should be made, and (3)

the dosing interval should be prolonged [48].

There is no evidence that oxcarbazepine is more effective than other medications in the treatment of diabetic neuropathy, radiculopathy, or postherpetic neuralgia [49]. First-line therapy for trigeminal neuralgia is still considered to be carbamazepine (600-1,200 mg/day), or if not, oxcarbazepine (600-1,800 mg/day) [4].

(3) Gabapentin

When we think of neuropathic pain, except trigeminal neuralgia, gabapentin and pregabalin are the first-line medications. Pain physicians consider these drugs to be neuropathic medications rather than anticonvulsants. Most medications are effective for specific symptoms and signs, not specific disorders or diseases. Gabapentin and/or pregabalin are effective for positive symptoms of neuropathic pain in various disorders or diseases. The current consensus for pain management includes not only opioid and non-opioid analgesics, as major analgesics, but also anticonvulsants and antidepressants, as adjuvants. Chronic pain results from subacute pain followed by acute pain, due to extensive tissue damage or the presence of neuropathic pain. Therefore, evaluation of pain characteristics is essential at the beginning of pain treatment.

Gabapentinoids $\alpha_2\delta$ ligands, are derived from gamma aminobutyric acid (GABA) which blocks $\alpha_2\delta$ subunit-containing voltage-dependent calcium channels. Currently available gabapentinoids include gabapentin (Neurontin[®]), pregabalin (Lyrica[®]), mirogabalin (Tarlige[®], DS-5565) used in Japan since 2019 [50], and gabapentin enacarbil (Horizant[®], Regnite[®]) [51].

(4) Pregabalin

The next generation anticonvulsant for neuropathic pain, which followed gabapentin, is pregabalin. Pregabalin shows a stronger and longer action duration than gabapentin. However, it is necessary to change from gabapentin to pregabalin in patients with intractable neuropathic pain who are taking a high single dose of gabapentin (over 900 mg), which causes lower bioavailability (a high dose administration of oral gabapentin excretes directly into the stool). An increased frequency of oral intake with a different dose may be needed in prescriptions for both gabapentin and pregabalin for reducing pain and ADRs in initial titration (Table 5) [52].

The maximal dose recommended by the manufacture is 600 mg/day; however, many patients with intractable neuropathic pain during the period of up-titration may need a higher dose to achieve adequate pain relief with tolerable ADRs [53].

Table 5. Different Titration Methods and Conversion of Gabapentin and Pregabalin for Patients with Intractable Pain Requiring a Rapid Dose Increase

Day	Gabapentin								Pregabalin					
	TID			Total daily dose	QID				BID		Total daily dose	TID		
	7A	1P	7P		7A	1P	7P	11P	7A	7P		7A	3P	11P
1	-	-	300	300	-	-	-	300	50	50	100	25	25	50
2	300	-	300	600	100	100	100	300	75	75	150	50	50	50
3	300	300	300	900	200	200	200	300	100	100	200	50	50	100
4-6	400	400	400	1,200	300	300	300	300	150	150	300	75	75	150
7-10	500	500	500	1,500	300	300	300	600	200	200	400	100	100	200
11-14	600	600	600	1,800	400	400	400	600	250	250	500	125	125	250
15	800	800	800	2,400	600	600	600	600	300	300	600	150	150	300

TID: *ter in die*; three times a day, QID: *quarter in die*; four times in a day, BID: *bis in die*; twice in a day, -: not available.

Modified from the article of Yang et al. (Korean J Anesthesiol 2013; 65: 48-54) [52].

(5) Mirogabalin

Both gabapentin and pregabalin have been known to act non-specifically on the $\alpha_2\delta$ -1 and -2. Binding to the $\alpha_2\delta$ -1 may produce analgesic effects, whereas binding to the $\alpha_2\delta$ -2 may be related to ADRs of the central nervous system, such as somnolence. Mirogabalin has been known to show more selective binding and slower dissociation to the $\alpha_2\delta$ -1. Maximal plasma concentration after oral intake is achieved at around 1 hour. The plasma protein binding of mirogabalin is relatively low at 25%. It is largely excreted in the urine [54,55].

The equianalgesic dose of 30 mg/day mirogabalin, for achieving over 50% pain relief (when the number needed to treat is around 5) in the treatment of diabetic peripheral neuropathy, is considered to be roughly 600 mg/day of pregabalin, over 1,200 mg/day of gabapentin, and 60 mg/day of duloxetine. However, the ADRs of mirogabalin are lower than the other 3 drugs [55,56].

(6) Nefopam

Nefopam (fenazocine, Acupan[®]) is a non-opioid, non-steroidal, centrally acting analgesic drug. The mechanism of analgesic action is similar to those of the triple neurotransmitters (serotonin, dopamine, and norepinephrine), uptake inhibitors (antipsychotics or antidepressants), and anticonvulsants. Therefore, it is suitable to use for neuropathic pain intravenously (continuous infusion), intramuscularly, or orally. It should be given intravenously, slowly, over 15-20 minutes, or intramuscularly, due to preventing known ADRs, such as cold sweating, dizziness, tachycardia, and drowsiness. It is also convenient to convert from intravenous medication during hospitalization into oral medication after discharge. The recommended dose of intravenous administration is 60-120 mg/day, and oral administration for 3 to 6 times totaling 90-180 mg/day [57].

(7) Antidepressants

Antidepressants have been used for the treatment of negative neuropathic pain, based on 6 mechanisms; (1) blockade of norepinephrine and serotonin, (2) blockade of sodium channels, (3) antagonism of NMDA glutamate receptors, (4) sympathetic blockade, (5) effects on visceral nerve fibers, and (6) effects on mood [58].

Antidepressants can be divided into first generation and second generation antidepressants. Nortriptyline has been chosen among the first generation antidepressants (tricyclic antidepressants, including amitriptyline, imipramine, and desipramine), due to the same strong analgesic effect with norepinephrine and serotonin reuptake inhibition, but lesser ADRs, such as anticholinergic effects (dry mouth), postural hypotension, and sedation. On the other hand, amitriptyline may be chosen due to its strong sedative effect in cases of insomnia (Table 6) [59].

2. Emotional component of pain

In addition to the sensory component of pain originating from actual tissue damage, the emotional component of pain from potential tissue damage should also be treated. While treating all sensory components of pain, including nociceptive and neuropathic pain, patients may complain of mysterious and vague generalized pain [59].

Available medications for the emotional component of pain are antipsychotics, anxiolytics, and antidepressants. There are 3 major neurotransmitters in the human brain: serotonin, norepinephrine, and dopamine. These neurotransmitters have their own functions: (1) serotonin is charged with the control of cognitive impulse and relaxation with memory, (2) norepinephrine has a relation to alertness, concentration, socialization, and energy, and (3) dopamine is deeply engaged in pleasure, motivation, reward, pain avoidance, and reality [59].

It is difficult to quantify each emotional item and to

Table 6. Antidepressants Commonly Used to Treat Pain

Antidepressant	Analgesia	Reuptake inhibition		Adverse effects				Elimination of half-life of parent drug (hr)
		NE	SE	Anticholinergic effects	Postural hypotension	Sedation	Cardiac arrhythmia	
Nortriptyline	+++	++	++	++	+	+	+++	18-48
Amitriptyline	+++	++	++	+++	+++	+++	+++	9-46
Imipramine	+++	++	++	+++	+++	++	+++	6-28
Desipramine	++	+++	0	+	++	+	+++	12-28
Paroxetine	+	0	+++	0	0	0	0	21
Citalopram	+	0	+++	0	0	0	0	24
Venlafaxine	?	++	+++	0	0	0	0	4

NE: norepinephrine, SE: serotonin.

Modified from Max and Gilron (Antidepressants, muscle relaxants, and N-methyl-D-aspartate receptor antagonists. In: Bonica's Management of Pain. 3rd ed. Edited by Loeser JD; 2000, pp. 1710-26) [59].

supply a deficit in the clinical field. However, not only the sensory component, but also the emotional component should be considered in the treatment of pain.

1) Antipsychotics

Antipsychotics are effective in pain patients with positive psychotic symptoms (related to the mesolimbic pathway), not negative, affective, and cognitive symptoms (related to the mesocortical pathway) [59].

The antipsychotics can be divided into typical and atypical categories. The typical antipsychotics act on the D₂ receptor; however, they produce extrapyramidal symptoms (dystonia, pseudo-parkinsonism, akathisia, and tardive dyskinesia) related to the nigrostriatal pathway and produce elevated serum prolactin levels.

In order to reduce the extrapyramidal symptoms and hyperprolactinemia, atypical antipsychotics have been developed through a decreased D₂ receptor binding affinity, but an increased 5-HT_{2A} receptor binding effect. Certain atypical antipsychotics, such as risperidone, ziprasidone, sertindole, clozapine, olanzapine, zotepine, aripiprazole, and quetiapine, produce somnolence effect related to the 5-HT_{2A} receptor binding. On the contrary, sulpiride and amisulpride, like the typical antipsychotic haloperidol, do not produce somnolence. In addition, they increase the risk of metabolic syndromes, such as weight gain, diabetes, or dyslipidemia.

Antipsychotic equivalent oral doses, based on a daily oral dose of 100 mg of chlorpromazine, are similar to 2 mg (1-5 mg) of haloperidol, 100 mg (30-150 mg) of clozapine, 2 mg (0.5-3 mg) of risperidone, 75 mg of quetiapine, 5 mg of olanzapine, and 7.5 mg of aripiprazole [59].

2) Anxiolytics

If antipsychotics are called as major tranquilizers (neu-

roleptics), anxiolytics are known as minor tranquilizers. Representative anxiolytic agents are GABAergics, such as benzodiazepines, barbiturates, and etifoxine.

The GABAA receptor consists of 5 subunits, two $\alpha_{(1-6)}$, two $\beta_{(1-3)}$, and one $\gamma_{(1-3)}$. Benzodiazepines are binding at the interfaces between the α_1 and γ_2 subunit, and barbiturates bind at the interfaces between the α_1 and β_2 subunit. Etifoxine directly acts on the β_2 or β_3 subunit, and indirectly activates the 18 kDa translocator protein. It shows lesser ADRs of anterograde amnesia, sedation, impaired psychomotor performance, and withdrawal syndromes than those of benzodiazepines [58].

3. Transition from intravenous patient-controlled analgesia into oral medication inpatients with intractable pain

Patients with intractable pain need hospitalization for the investigation of the origin of the pain, the treatment of correctable causes, and the transition of analgesia from intravenous to oral medication for discharge. Available intravenous medications for analgesia are morphine, ketorolac, nefopam, dexmedetomidine, midazolam, steroids, and antiemetics (ramosetron, palonosetron, or ondansetron).

The first dose of each medication is determined by the origin and intensity of the pain. While escalating the daily dose of oral medication, the dose of intravenous medications with patient-controlled analgesia can be diluted with normal saline to half of the initial dose every 3 days.

After 4 cycles of dilution at 12 days, the transition to oral from intravenous medications is completed, using such medications as oral morphine, NSAIDs, nefopam, anxiolytics (antidepressant or antipsychotic), anticonvulsants, antidepressants, and steroids. Patients can be discharged from the hospital at 14 days after confirmation of having tolerable pain and ADRs.

CONCLUSIONS

Most analgesics, except NSAIDs, ASA, or APAP, need the process of dose-up and -down titration. In order to achieve the 3 steps including reducing (1) night pain, (2) resting pain during the day, and (3) daily activity, the initial dose at night should be larger, even though the daily total dose is the same. Simultaneously, it is emphasized that the ADRs, such as orthostatic hypotension and dizziness, may develop at night. Dose-up titration is finished when both pain and ADRs are tolerable. When down-titration for discontinuing the analgesics begins, the dose at night should be the last to be reduced or discontinued.

According to the origin of the pain, an effective analgesic drug should be chosen. 1) For an unpleasant emotional experience, an antipsychotic, antidepressant, or anxiolytic is considered. 2) Various analgesics are needed for the control of an unpleasant sensory experience. (1) An NSAID, ASA, or APAP is effective for somatic nociceptive pain. (2) An opioid is helpful to relieve visceral nociceptive pain. (3) An anticonvulsant is used to control positive neuropathic pain. (4) On the contrary, an antidepressant should be chosen to relieve negative neuropathic pain.

Chronic pain, which has 2 or more pain components, needs combined therapy using these analgesics. Chronification of pain comes from a greater intensity of tissue damage or an existence of neuropathic pain. Therefore, chronic pain may include sensory component (nociceptive and/or neuropathic pain), as well as, emotional component which has developed from the beginning and/or may develop during the chronification of pain. In summary, various combination of analgesics, such as NSAIDs for somatic pain, opioids for visceral pain, anticonvulsants and/or antidepressants for neuropathic pain, and antipsychotics and/or anti-anxiety drugs for emotional component, should be used properly and/or simultaneously. Polypharmacy is enhancing therapeutic analgesic effects while reducing ADRs. It is unreasonable to assume that opioids rather than NSAIDs are more effective or stronger for somatic pain.

When multiple analgesics are used for the treatment of pain (emotional and/or sensory components), the general and special condition of the patients and inter-analgesic medications should be considered.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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