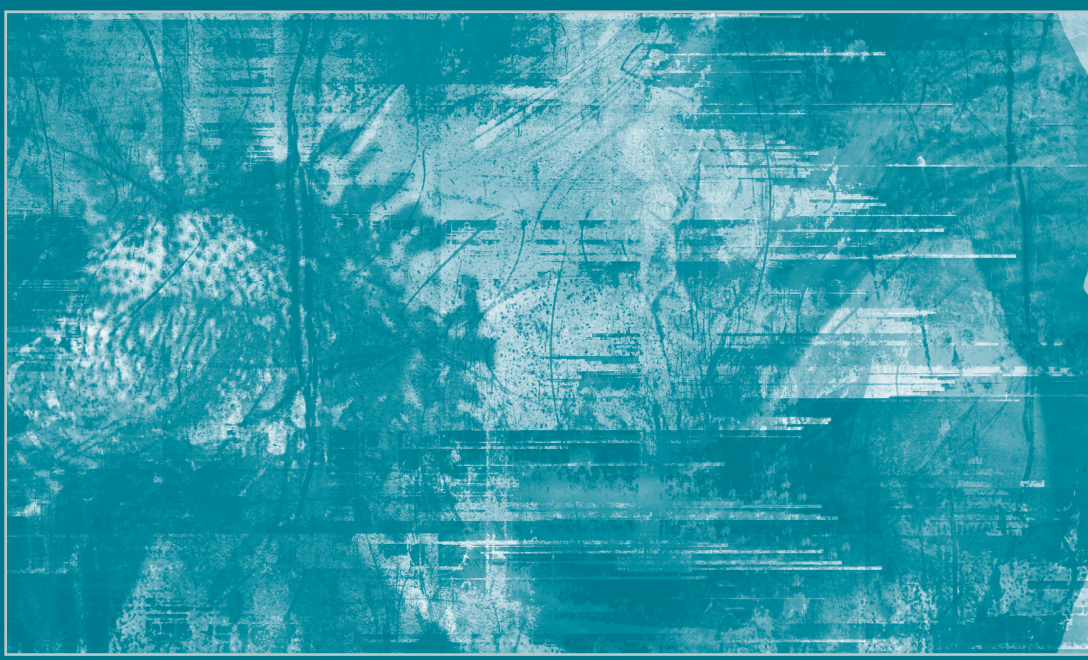
Opioid-Induced Hyperalgesia



Edited by

Jianren Mao

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Edited by
Jianren Mao
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts, USA

informa
healthcare

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Preface

Despite the extensive effort over several decades searching for new pharmacological tools for clinical pain treatment, opioid analgesics remain the mainstay of contemporary pain medicine. Opioid analgesics are extensively used for the management of both acute and chronic pain including cancer-related pain. Opioid analgesics have a number of side effects including respiratory depression, miosis, nausea, vomiting, constipation, biliary tract spasm, urinary retention, hypotension, dizziness, dysphoria, metal status change, and pruritis. However, most of these side effects are dose dependent and manageable in the clinical setting.

Other opioid-related clinical issues such as opioid tolerance, dependence, and addiction have limited the use of opioid analgesics in pain medicine, particularly for chronic pain management. More recently, both preclinical and clinical studies have shown that chronic exposure to opioid analgesics can alter the response of the central nervous system to nociceptive input leading to the increased pain sensitivity, which is often referred to as opioid-induced hyperalgesia. Both preclinical and clinical findings suggest that opioid analgesics that are intended to reduce pain may paradoxically increase pain under certain clinical conditions, calling for a new approach to managing clinical opioid therapy.

This book is intended to provide clinically oriented discussions on the diagnosis and management of opioid-induced hyperalgesia. Clinical practitioners who are currently involved or interested in pain management are intended primary readers, including such specialties as anesthesiology, pain medicine, neurology, oncology, palliative care, addiction medicine, primary care, rheumatology, and surgery.

The first chapter (by Dr Mao) provides an overview on the concept of opioid-induced hyperalgesia, followed by a focused discussion on possible

cellular mechanisms of opioid-induced hyperalgesia and its relation to opioid tolerance (by Dr Ueda). The third chapter (by Drs Angst, Chu, Clark) provides readers with a thorough discussion on the clinical features of opioid-induced hyperalgesia and their impact in pain medicine. The clinical utility of quantitative sensory testing in the diagnosis of opioid-induced hyperalgesia is the focus of chapter 4 (by Dr Edwards), which gives the detailed accounts on the history, methodology, and clinical utility of quantitative sensory testing.

The clinical interaction between addiction and opioid therapy is a vitally important issue in pain medicine and addiction medicine. Chapter 5 (by Dr Ballantyne) and chapter 6 (by Drs Ling and Compton) focus on the relationship between addiction and clinical features and management of opioid-induced hyperalgesia. These two chapters provide profound details on the neurobiology, philosophy, clinical features, and clinical management of the interaction between addiction and opioid-induced hyperalgesia.

Chapters 7 and 8 present practical guidelines on the clinical diagnosis and management of opioid-induced hyperalgesia under various clinical circumstances, including primary care settings (by Dr McCarberg) and perioperative care (by Drs Crooks and Cohen). Additional approaches to managing opioid-induced hyperalgesia in other clinical circumstances are the topics of chapters 9, 10, and 11, which include discussions on the role of ketamine (by Dr Vorobeychik), opioid rotation and tapering (by Dr Smith), and adjuvant medications (by Drs Giampetro and Vorobeychik). The final chapter (by Dr Mao) summarizes clinical differential diagnosis between opioid-induced hyperalgesia and opioid tolerance and discusses future research directions on this important clinical phenomenon.

I would like to express my deep appreciation for my colleagues in this field, who have contributed to the work of this book project and/or basic science and clinical research on this important topic.

Jianren Mao

Contents

Contributors

Martin S. Angst Stanford University School of Medicine, Stanford, California, U.S.A.

Jane C. Ballantyne Penn Pain Medicine Center, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

Larry F. Chu Stanford University School of Medicine, Stanford, California, U.S.A.

J. David Clark Stanford University School of Medicine and Palo Alto Veterans Affairs Hospital, Palo Alto, California, U.S.A.

Steven P. Cohen Pain Management Division, Johns Hopkins School of Medicine, Baltimore, Maryland and Walter Reed Army Medical Center, Washington, D.C., U.S.A.

Peggy Compton School of Nursing, University of California at Los Angeles, Los Angeles, California, U.S.A.

Matthew Crooks Department of Anesthesiology, Pain Management Division, David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.

Robert R. Edwards Department of Anesthesiology, Brigham and Women's Hospital, and Harvard School of Medicine, Boston, Massachusetts, U.S.A.

David Giampetro Department of Anesthesiology, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, Hershey, Pennsylvania, U.S.A.

Walter Ling Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California, U.S.A.

Jianren Mao Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

Bill McCarberg Kaiser Permanente, Chronic Pain Management Program, University of California, San Diego, California, U.S.A.

Howard S. Smith Department of Anesthesiology, Albany Medical College, Albany, New York, U.S.A.

Hiroshi Ueda Division of Molecular Pharmacology and Neuroscience, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Yakov Vorobeychik Department of Anesthesiology, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, Hershey, Pennsylvania, U.S.A.

1

Overview on Opioid-Induced Hyperalgesia

Jianren Mao

Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston Massachusetts, U.S.A.

INTRODUCTION

Opioids produce analgesia through a primarily inhibitory effect on the nociceptive system. To date, opioids remain the most powerful analgesics for clinical management of moderate to severe pain. Besides many known side effects of opioids such as sedation and constipation, chronic opioid exposure is associated with the development of tolerance to opioid analgesics. This process is largely due to an adaptive change of the opioid analgesic system that leads to the desensitization of opioid receptors and associated intracellular cascades.

Another consequence of chronic opioid exposure is the development of opioid dependence. A notable feature of opioid dependence is that hyperalgesia (exacerbated painful response to noxious stimulation) occurs during a precipitated opioid withdrawal. Over the past 15 years, compelling preclinical evidence has accumulated, indicating that hyperalgesia also occurs following opioid administration in the absence of overt, precipitated opioid withdrawal. A growing body of evidence suggests that the development of opioid-induced hyperalgesia is mediated through the neural mechanisms that involve changes at the cellular and neural circuit level, which interact with the mechanisms underlying the development of pathological pain such as pain induced by peripheral nerve injury. Thus, chronic

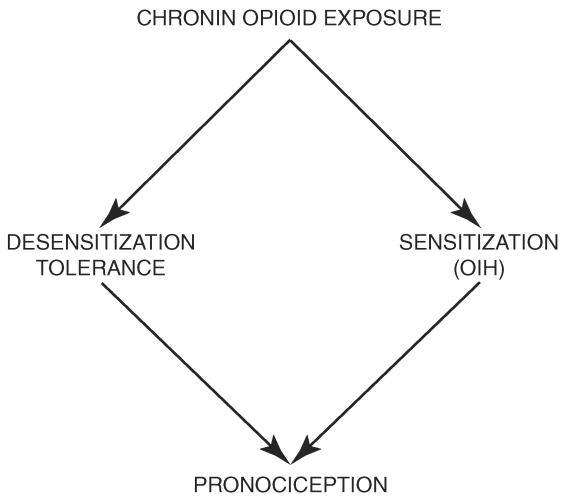

Figure 1 Schematic illustration of two interrelated outcomes of chronic opioid exposure. Both the desensitization and sensitization processes contribute to the enhanced pronociceptive process after chronic opioid exposure.

opioid exposure also leads to a sensitization process within the central nervous system that is pronociceptive even in the presence of opioid analgesics.

As illustrated in Figure 1, the desensitization process reduces the clinical efficacy of opioid analgesics, whereas the sensitization process facilitates nociception, thereby counteracting the opioid analgesic effect. Both the desensitization and sensitization processes lead to a pronociceptive outcome that contributes to apparent clinical opioid tolerance, that is, the need for opioid dose escalation to maintain the opioid analgesic effect. Since the nociceptive system is a primitive and vital defense system, the development of analgesic tolerance and hyperalgesia in response to chronic opioid exposure helps counteract the impact of analgesics on blunting the nociceptive response as an important warning signal. This chapter will focus on preclinical evidence for opioid-induced hyperalgesia and its possible cellular mechanisms. The following chapters will discuss clinical features of opioid-induced hyperalgesia and approaches to diagnosing and managing this clinical condition. The last chapter of this book will provide a brief summary on the clinical implications of opioid-induced hyperalgesia and future research directions on this important clinical issue.

PRECLINICAL EVIDENCE FOR OPIOID-INDUCED HYPERALGESIA

Preclinical studies of opioid tolerance assess changes of the antinociceptive efficacy before and after opioid boluses or continuous opioid administration. One of the most commonly used methods in preclinical studies is a tail-flick test, which is used to evaluate the antinociceptive effects of opioids. For example, the

opioid antinociceptive effect is seen as the increased baseline nociceptive threshold in a tail-flick test. Conversely, a decrease in the baseline nociceptive threshold is an indication of the hyperalgesic response. For years, differences in baseline nociceptive thresholds before and after an opioid treatment are not readily detected using the tail-flick test, because this test often uses a steep stimulation curve with a fast-rising stimulation intensity that could mask subtle changes of a baseline nociceptive threshold. By comparison, a test that utilizes a slow-rising stimulation curve such as the foot-withdrawal test (1) enables the detection of subtle changes in baseline nociceptive threshold.

As shown in Figure 2, a progressive reduction of the baseline nociceptive threshold was observed using a foot-withdrawal test in rats receiving repeated intrathecal morphine administration over a seven-day period (2–4). The reduced baseline nociceptive threshold was also observed in animals receiving subcutaneous fentanyl boluses using the Randall–Sellitto test in which a constantly increasing pressure is applied to a rat's hind paw (5,6). The decreased baseline nociceptive threshold lasted five days after the cessation of four fentanyl bolus injections (5). Moreover, the reduced baseline nociceptive threshold was detected in animals with repeated heroin administration (5). These results indicate that repeated opioid administration leads to a progressive and lasting reduction of the baseline nociceptive threshold, which is referred to as opioid-induced hyperalgesia.

Since hyperalgesia occurs during an opioid withdrawal, it is possible that the decreased baseline nociceptive threshold observed in these preclinical studies simply reflects a subliminal withdrawal in which changes in the baseline nociceptive threshold are present without other withdrawal signs such as wet-dog

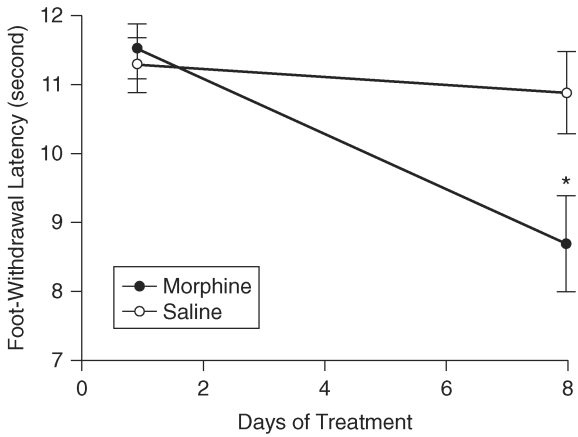

Figure 2 A preclinical model of opioid-induced hyperalgesia. Intrathecal administration of morphine (10 μg, once daily × 7 days) resulted in the decreased nociceptive threshold in rats as detected using a foot-withdrawal test. $*p < 0.05$, as compared with the saline group.

shake and jumping. However, a progressive reduction of the baseline nociceptive threshold is also present in animals receiving a course of continuous intrathecal opioid infusion via osmotic pumps (3,4,7). Collectively, these data support the notion that a prolonged opioid treatment not only results in the loss of the opioid antinociceptive effect, a negative sign of system adaptation (desensitization), but also leads to activation of a pronociceptive system manifested as the reduction of the nociceptive threshold, a positive sign of system adaptation (sensitization).

NEURAL AND CELLULAR MECHANISMS UNDERLYING OPIOID-INDUCED HYPERALGESIA

If the primary effect of opioids is inhibitory at various sites of the nociceptive pathways, how would chronic opioid exposure lead to the sensitization of the central nervous system? Both opioid tolerance and opioid-induced hyperalgesia are initiated by opioid administration. It would be difficult to differentiate between these two outcomes of opioid-induced changes, if the assessment end point is a shift of opioid antinociceptive dose response curves in animal studies or a change in opioid dose demand in clinical settings. However, these two outcomes would involve two opposing cellular mechanisms, that is, a desensitization process versus a sensitization process. Because of the involvement of two opposing cellular processes, clinical approaches to resolving opioid tolerance and hyperalgesia should be different. In this regard, it is important to understand the possible neural and cellular mechanisms underlying the development of opioid-induced hyperalgesia and their interaction with the mechanism of opioid tolerance. To date, several possibilities have been raised with regard to the mechanisms of opioid-induced hyperalgesia, as briefly summarized in the following sections.

Role of Spinal Dynorphin

It has indicated that spinal dynorphin plays an important role in the expression of both opioid tolerance and abnormal pain sensitivity (for review see Ref. 8). Of significance to note is that spinal dynorphin content increases following a period of continuous infusion with a μ-opioid receptor agonist (7). Moreover, there is an increase in the evoked release of spinal excitatory neuropeptides such as calcitonin gene-related peptide from primary afferents in morphine-treated animals, which requires the spinal dynorphin activity (9). These observations lend support to the concept that opioid administration induces a pronociceptive process, in part, by increasing the synthesis of excitatory neuropeptides and facilitating their release upon peripheral stimulation.

Role of Descending Facilitation

Additional evidence for the involvement of a sensitization process following opioid administration comes from a group of studies that indicate the influence

of descending facilitation on opioid-induced pain sensitivity. First, subsets of neurons (on- and off-cells) within the rostral ventromedial medulla (RVM) have characteristic response patterns to opioids (10,11). Their activities may contribute to the mechanisms of descending facilitation that influences spinal nociceptive processing (12). Second, on-cell activity within the RVM increases in association with the behavioral manifestation of naloxone-precipitated hyperalgesia (13). Third, bilateral lesioning of the dorsolateral funiculus, an anatomic pathway connecting the brainstem and spinal cord, blocks the increase in spinal excitatory neuropeptides in opioid-treated animals (9), suggesting that the descending facilitation may function in part through the modulation of spinal neuropeptide contents.

Role of the Central Glutamatergic System

Activation of excitatory amino acid receptors such as the *N*-methyl-D-aspartate receptor (NMDAR) has been implicated in the mechanisms of pharmacological opioid tolerance (14,15). Subsequently, the NMDAR has been shown to be critical to the cellular mechanisms of opioid-induced hyperalgesia (2,6). The current data suggests that opioid-induced desensitization (pharmacological tolerance) and sensitization (opioid-induced hyperalgesia) processes may have many common cellular elements that are linked to the activation of the glutamatergic system.

First, inhibition of NMDAR prevents the development of both pharmacological tolerance and opioid-induced hyperalgesia (2,14,15). Second, perturbation of spinal glutamate transporter activity, which regulates extracellular glutamate availability, modulates the development of both morphine tolerance and the associated pain sensitivity (3). Third, the Ca^{2+}-regulated intracellular protein kinase C (PKC) is likely to be an intracellular link between cellular mechanisms of tolerance and opioid-induced hyperalgesia (2,16,17). Fourth, cross talk between the neural mechanisms of opioid tolerance and pathological pain may exist and contribute to the exacerbated pain and reduced opioid analgesic efficacy under such circumstances (18,19). Fifth, prolonged morphine administration induces NMDAR-mediated neurotoxicity in the form of apoptotic cell death, which is, at least in part, contributory to both morphine tolerance and abnormal pain sensitivity (4). Taken together, these lines of evidence strongly indicate a critical role of the central glutamatergic system in the neural mechanisms of both opioid tolerance and opioid-induced hyperalgesia.

A Schematic Illustration of NMDAR-Mediated Cellular Mechanisms

If NMDAR were critically contributory to opioid-induced hyperalgesia, how would chronic opioid exposure result in the activation of NMDAR? Figure 3 shows the interaction between opioid receptors and NMDAR at the cellular level within the spinal cord dorsal horn, which includes a presynaptic site of primary

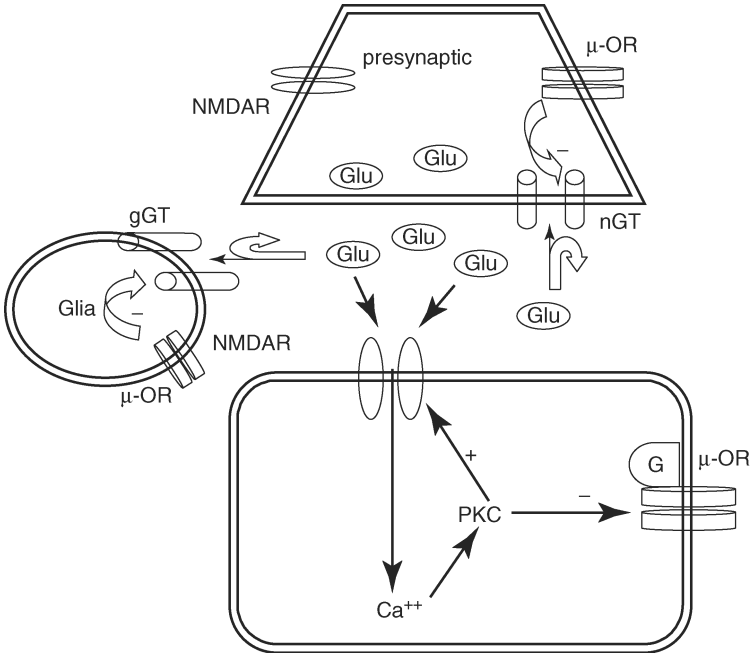

Figure 3 Schematic illustration of the NMDAR-mediated cellular mechanisms of opioid-induced hyperalgesia (see the main text for a detailed discussion). *Abbreviations*: gGT, glial glutamate transporter; nGT, neuronal glutamate transporter; Glu, glutamate; G, G-protein; NMDAR, *N*-methyl-D-aspartate receptorl; PKC, protein kinase C.

nociceptive afferents, a postsynaptic site of projection neurons (neurons that send ascending axons to the brain) or interneurons (neurons that participate in local connections), and glial cells.

Opioid receptors (e.g., μ-opioid receptors) are present, so are NMDARs, at the presynaptic site, postsynaptic site, and glial cells. The NMDAR is a unique receptor-Ca^{2+} channel complex. The activation of NMDAR leads to the opening of the Ca^{2+} channel. Seated deeply inside the channel is the Mg^{2+} block that is normally removed through partial depolarization of the cell membrane. This partial depolarization takes place through activation of other coexisting receptors such as non-NMDA glutamate receptors and neurokinin receptors (e.g., NK-1).

Since the predominant effect of opioid analgesics is the cell membrane hyperpolarization, which is opposite to the cell membrane excitation (cell depolarization), it would be difficult to envision that the deeply seated Mg^{2+} block inside the NMDAR-Ca^{2+} channel complex could be removed in the presence of the inhibitory effect of opioid analgesics. In this regard, the intracellular PKC plays a pivotal role in removing the Mg^{2+} block in the absence of partial depolarization of the cell membrane, because chronic opioid exposure increases the PKC expression (18,19). That is, the NMDAR can be primed by

PKC activation, which is in turn induced by chronic opioid exposure. PKC activation also plays a role in the desensitization of opioid receptors. Priming NMDAR contributes to the mechanisms of opioid-induced hyperalgesia, whereas desensitizing opioid receptors contributes to the mechanisms of opioid tolerance. Moreover, chronic opioid exposure also downregulates both neuronal and glial glutamate transporters and increases the glutamate (the endogenous ligand of the NMDAR) availability at the synaptic site, further enhancing the NMDAR function. As an example of possible cellular mechanisms of opioid-induced hyperalgesia, the opioid receptor-NMDAR interaction supports the notion that chronic opioid exposure could lead to a central state of pronociceptive process. Accordingly, inhibition of NMDAR or PKC has been shown to prevent the development of opioid-induced hyperalgesia in several preclinical studies (2).

SUMMARY

Several lines of evidence strongly support an active pronociceptive process within the central nervous system initiated by chronic opioid exposure. It is possible that the involvement of each of these cellular elements discussed in the preceding text may depend on the route (intrathecal vs. systemic) and the duration of opioid administration. For instance, the difference between the involvement of the central glutamatergic system and dynorphin is that opioid tolerance could be reduced acutely by a dynorphin antiserum but not by an NMDAR antagonist (2,7,14), although both systems are involved in the mechanisms of opioid-induced hyperalgesia. Another interesting issue is that since the descending facilitation is triggered by activation of opioid receptors, the development of opioid tolerance (a desensitization process) at the cellular level may, over time, diminish the impact of the descending facilitation on the maintenance of opioid-induced hyperalgesia.

Clinical features of opioid-induced hyperalgesia will be thoroughly discussed in other chapters. In the final chapter of this book, a detailed discussion on the clinical implications of opioid-induced hyperalgesia will be provided as well.

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2 Chapter 2. Cellular Mechanisms Underlying Morphine Analgesic Tolerance and Hyperalgesia

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Figure 2 Candidate molecules to inhibit opioid tolerance in the anti-opioid glutamate/

NMDA receptor hypothesis. In this hypothesis, glutamate neurotransmission and NMDA

receptor signaling are upregulated, following chronic opioid treatments. Some parts of this

hypothesized mechanism are mediated by neuron-glia interactions, as stated in the text.

Candidate molecules to inhibit opioid tolerance are indicated by the number in the figure,

as follows: (i) NMDA receptor (NR2A) antagonists; (ii) anti-BDNF antibody or TrkB

antagonists; (iii) CBP inhibitors, such as curcumin; (iv) unknown compounds to inhibit

the GLT-1 downregulation, racemase inhibitors; (v) astrocyte inactivators, such as fluo

rocitrate; (vi) microglia inactivators, such as minocycline; and (vii) nNOS inhibitors.

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3 Chapter 3. Overview on Clinical Features of Opioid-Induced Hyperalgesia

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4 Chapter 4. Clinical Assessment Tools: Quantitative Sensory Testing

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5 Chapter 5. Opioid Tolerance, Dependence, and Hyperalgesia

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6 Chapter 6. Challenging Clinical Issues on the Interaction Between Addiction and Hyperalgesia

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9 Chapter 9. Role of Ketamine in Managing Opioid-Induced Hyperalgesia

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10 Chapter 10. Role of Opioid Rotation and Tapering in Managing Opioid-Induced Hyperalgesia

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11 Chapter 11. Role of Adjuvant Medications in Managing Opioid-Induced Hyperalgesia

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