

**RULE 17, EXHIBIT 7**

**Complex Regional Pain Syndrome/  
Reflex Sympathetic Dystrophy  
Medical Treatment Guideline**

**Revised: 10/6/2017**

**Effective: 11/30/2017**

Adopted: November 4, 1996

Effective: December 30, 1996

Revised: January 8, 1998

Effective: March 15, 1998

Revised: May 27, 2003

Effective: July 30, 2003

Revised: September 29, 2005

Effective: January 1, 2006

Revised: December 27, 2011

Effective: February 14, 2012

Presented by:



**COLORADO**

Department of  
Labor and Employment

**DIVISION OF WORKERS' COMPENSATION**



## TABLE OF CONTENTS

Section	Description	Page
<b>A.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>B.</b>	<b>GENERAL GUIDELINE PRINCIPLES .....</b>	<b>2</b>
1.	APPLICATION OF GUIDELINES .....	2
2.	EDUCATION.....	2
3.	INFORMED DECISION MAKING .....	2
4.	TREATMENT PARAMETER DURATION.....	2
5.	ACTIVE INTERVENTIONS.....	2
6.	ACTIVE THERAPEUTIC EXERCISE PROGRAM.....	2
7.	POSITIVE PATIENT RESPONSE .....	2
8.	RE-EVALUATION OF TREATMENT NO LESS THAN EVERY 3 TO 4 WEEKS.....	3
9.	SURGICAL INTERVENTIONS .....	3
10.	SIX-MONTH TIME FRAME.....	3
11.	RETURN-TO-WORK.....	3
12.	DELAYED RECOVERY .....	3
13.	GUIDELINE RECOMMENDATIONS AND INCLUSION OF MEDICAL EVIDENCE .....	4
14.	TREATMENT OF PRE-EXISTING CONDITIONS.....	4
<b>C.</b>	<b>INTRODUCTION TO COMPLEX REGIONAL PAIN SYNDROME.....</b>	<b>5</b>
<b>D.</b>	<b>DEFINITIONS .....</b>	<b>6</b>
1.	AFTER SENSATION.....	6
2.	ALLODYNIA .....	6
3.	CENTRAL PAIN .....	6
4.	CENTRAL SENSITIZATION .....	6
5.	DYSTONIA.....	6
6.	HYPERALGESIA .....	6
7.	HYPEREMIA .....	6
8.	HYPERESTHESIA .....	6
9.	HYPERPATHIA.....	6
10.	HYPOESTHESIA .....	6
11.	PAIN BEHAVIOR .....	6
12.	SUDOMOTOR CHANGES .....	6
13.	SYMPATHETICALLY MAINTAINED PAIN (SMP).....	7
14.	TROPHIC CHANGES .....	7
15.	VASOMOTOR CHANGES.....	7
<b>E.</b>	<b>INITIAL EVALUATION .....</b>	<b>8</b>
1.	HISTORY TAKING AND PHYSICAL EXAMINATION (HX & PE) .....	8
a.	Medical History.....	8
b.	Pain History.....	10
c.	Medical Management History .....	10
d.	Substance Use/Abuse .....	11
e.	Other Factors Affecting Treatment Outcome.....	11
f.	Physical Examination.....	11
<b>F.</b>	<b>OVERVIEW OF CARE FOR CRPS OR SYMPATHETICALLY MEDIATED PAIN .....</b>	<b>13</b>
<b>G.</b>	<b>DIAGNOSTIC CRITERIA AND PROCEDURES .....</b>	<b>14</b>
1.	DIAGNOSIS OF CRPS .....	14

2.	DIAGNOSTIC COMPONENTS OF CLINICAL CRPS .....	17
3.	DIAGNOSTIC COMPONENTS OF CONFIRMED CRPS .....	18
4.	SYMPATHETICALLY MAINTAINED PAIN (SMP).....	18
5.	NOT CRPS OR SMP .....	18
6.	DIAGNOSTIC IMAGING .....	19
	a. Plain Film Radiography .....	19
	b. Triple Phase Bone Scan .....	19
7.	INJECTIONS – DIAGNOSTIC SYMPATHETIC .....	19
	a. Stellate Ganglion Block .....	20
	b. Lumbar Sympathetic Block .....	21
	c. Phentolamine Infusion Test .....	21
8.	THERMOGRAPHY (INFRARED STRESS THERMOGRAPHY).....	21
	a. Cold Water Stress Test (Cold Pressor Test) .....	21
	b. Warm Water Stress Test.....	21
	c. Whole Body Thermal Stress .....	22
9.	AUTONOMIC TEST BATTERY .....	22
	a. Infrared Resting Skin Temperature (RST) .....	22
	b. Resting Sweat Output (RSO).....	22
	c. Quantitative Sudomotor Axon Reflex Test (QSART).....	22
10.	OTHER DIAGNOSTIC TESTS NOT SPECIFIC FOR CRPS .....	22
	a. Electrodiagnostic Procedures .....	23
	b. Laboratory Tests .....	23
	c. Peripheral Blood Flow (Laser Doppler or Xenon Clearance Techniques).....	24
11.	PERSONALITY/ PSYCHOLOGICAL/PSYCHOSOCIAL EVALUATIONS FOR PAIN MANAGEMENT .....	24
12.	SPECIAL TESTS .....	24
<b>H.</b>	<b>THERAPEUTIC PROCEDURES – NON-OPERATIVE.....</b>	<b>25</b>
1.	ACUPUNCTURE.....	25
2.	BIOFEEDBACK.....	26
3.	COMPLEMENTARY MEDICINE.....	26
4.	DISTURBANCES OF SLEEP .....	26
5.	EDUCATION/INFORMED/SHARED DECISION MAKING.....	26
6.	INJECTIONS – THERAPEUTIC .....	28
	a. Sympathetic Injections .....	28
	b. Peripheral Nerve Blocks .....	29
	c. Other Intravenous Medications and Regional Blocks.....	30
	d. Continuous Brachial Plexus Infusions .....	30
	e. Epidural Infusions.....	30
	f. Ketamine .....	31
7.	INTERDISCIPLINARY REHABILITATION PROGRAMS .....	31
	a. Overview .....	31
	b. Formal Interdisciplinary Rehabilitation Programs .....	34
	c. Informal Interdisciplinary Rehabilitation Program .....	36
8.	MEDICATIONS AND MEDICAL MANAGEMENT .....	39
	a. General Chronic Pain Medication Management .....	39
	b. CRPS Specific Medication Management.....	42
	c. CRPS-Specific Medications .....	43
	d. Opioids .....	46
9.	OPIOID ADDICTION TREATMENT.....	72
10.	OPIOID/CHEMICAL TREATMENT PROGRAMS.....	76
11.	ORTHOTICS/PROSTHETICS/EQUIPMENT .....	78
12.	PERSONALITY/PSYCHOLOGICAL/PSYCHOSOCIAL/PSYCHIATRIC INTERVENTION .....	78

13.	RESTRICTION OF ACTIVITIES .....	78
14.	RETURN-TO-WORK.....	78
15.	THERAPY- ACTIVE .....	78
	a.    Activities of Daily Living (ADL) .....	80
	b.    Aquatic Therapy .....	81
	c.    Functional Activities .....	82
	d.    Gait Training.....	82
	e.    Mirror Therapy - Graded Motor Imagery .....	83
	f.    Neuromuscular Re-education .....	83
	g.    Stress Loading .....	84
	h.    Therapeutic Exercise .....	84
	i.    Work Conditioning.....	91
	j.    Work Simulation .....	91
16.	THERAPY—PASSIVE .....	92
	a.    Continuous Passive Motion (CPM) .....	92
	b.    Desensitization.....	93
	c.    Fluidotherapy .....	93
	d.    Paraffin Bath .....	93
	e.    Superficial Heat Therapy .....	94
<b>I.</b>	<b>THERAPEUTIC PROCEDURES – OPERATIVE .....</b>	<b>95</b>
	1.    NEUROSTIMULATION .....	95
	2.    DORSAL ROOT GANGLION STIMULATOR .....	96
	3.    PERIPHERAL NERVE STIMULATION.....	100
	4.    INTRATHECAL DRUG DELIVERY.....	100
	5.    SYMPATHECTOMY .....	100
	6.    AMPUTATION.....	101
<b>J.</b>	<b>MAINTENANCE MANAGEMENT .....</b>	<b>102</b>
	1.    FUNCTIONAL TESTS.....	102
	2.    VITAMIN C .....	102
	3.    OPIOID MEDICATION MANAGEMENT .....	103
	4.    INJECTION THERAPY .....	104
	a.    Sympathetic Blocks.....	104
	REFERENCES.....	105

# DEPARTMENT OF LABOR AND EMPLOYMENT

## Division of Workers' Compensation

CCR 1101-3

RULE 17, EXHIBIT 7

### **COMPLEX REGIONAL PAIN SYNDROME/REFLEX SYMPATHETIC DYSTROPHY MEDICAL TREATMENT GUIDELINE**

#### **A. INTRODUCTION**

This document has been prepared by the Colorado Department of Labor and Employment, Division of Workers' Compensation (Division) and should be interpreted within the context of guidelines for physicians/providers treating individuals qualifying under Colorado's Workers' Compensation Act as injured workers with Complex Regional Pain Syndrome (CRPS), formerly known as Reflex Sympathetic Dystrophy (RSD).

Although the primary purpose of this document is advisory and educational, these guidelines are enforceable under the Workers' Compensation Rules of Procedure, 7 CCR 1101-3. The Division recognizes that acceptable medical practice may include deviations from these guidelines, as individual cases dictate. Therefore, these guidelines are not relevant as evidence of a provider's legal standard of professional care.

To properly utilize this document, the reader should not skip nor overlook any sections.

## B. GENERAL GUIDELINE PRINCIPLES

The principles summarized in this section are key to the intended implementation of all Division of Workers' Compensation medical treatment guidelines and critical to the reader's application of the guidelines in this document.

- 1. APPLICATION OF GUIDELINES** The Division provides procedures to implement medical treatment guidelines and to foster communication to resolve disputes among the provider, payer and patient through the Workers' Compensation Rules of Procedure. In lieu of more costly litigation, parties may wish to seek administrative dispute resolution services through the Division or the office of administrative courts.
- 2. EDUCATION** Education of the patient and family, as well as the employer, insurer, policy makers, and the community, should be the primary emphasis in the treatment of chronic pain and disability. Currently, practitioners often think of education last, after medications, manual therapy, and surgery. Practitioners must implement strategies to educate patients, employers, insurance systems, policy makers, and the community as a whole. An education-based paradigm should always start with inexpensive communication providing reassuring and evidence-based information to the patient. More in-depth patient education is currently a component of treatment regimens which employ functional, restorative, preventive, and rehabilitative programs. No treatment plan is complete without addressing issues of individual and/or group patient education as a means of facilitating self-management of symptoms and prevention. Facilitation through language interpretation, when necessary, is a priority and part of the medical care treatment protocol.
- 3. INFORMED DECISION MAKING** Providers should implement informed decision making as a crucial element of a successful treatment plan. Patients, with the assistance of their health care practitioner, should identify their personal and professional functional goals of treatment at the first visit. Progress towards the individual's identified functional goals should be addressed by all members of the health care team at subsequent visits and throughout the established treatment plan. Nurse case managers, physical therapists, and other members of the health care team play an integral role in informed decision making and achievement of functional goals. Patient education and informed decision making should facilitate self-management of symptoms and prevention of further injury.
- 4. TREATMENT PARAMETER DURATION** Time frames for specific interventions commence once treatments have been initiated, not on the date of injury. Obviously, duration will be impacted by patient adherence, as well as availability of services. Clinical judgment may substantiate the need to accelerate or decelerate the time frames discussed in this document.
- 5. ACTIVE INTERVENTIONS** emphasizing patient responsibility, such as therapeutic exercise and/or functional treatment, are generally emphasized over passive modalities, especially as treatment progresses. Generally, passive interventions are viewed as a means to facilitate progress in an active rehabilitation program with concomitant attainment of objective functional gains.
- 6. ACTIVE THERAPEUTIC EXERCISE PROGRAM** goals should incorporate patient strength, endurance, flexibility, coordination, and education. This includes functional application in vocational or community settings.
- 7. POSITIVE PATIENT RESPONSE** Positive results are defined primarily as functional gains that can be objectively measured. Objective functional gains include, but are not

limited to: positional tolerances, range-of-motion, strength, endurance, activities of daily living, ability to function at work, cognition, psychological behavior, and efficiency/velocity measures that can be quantified. Subjective reports of pain and function should be considered and given relative weight when the pain has anatomic and physiologic correlation. Anatomic correlation must be based on objective findings. Patient completed functional questionnaires such as those recommended by the Division as part of Quality Performance and Outcomes Payments (QPOP, see Rule 18-8) and/or the Patient Specific Functional Scale can provide useful additional confirmation.

- 8. RE-EVALUATION OF TREATMENT NO LESS THAN EVERY 3 TO 4 WEEKS** If a given treatment or modality is not producing positive results within 3 to 4 weeks or within the time to produce effect in the guidelines, the treatment should be either modified or discontinued. Before discontinuing the treatment, the provider should have a detailed discussion with the patient to determine the reason for failure to produce positive results. Reconsideration of diagnosis should also occur in the event of a poor response to a seemingly rational intervention.
- 9. SURGICAL INTERVENTIONS** Surgery should be contemplated within the context of expected functional outcome and not purely for the purpose of pain relief. The concept of "cure" with respect to surgical treatment by itself is generally a misnomer. All operative interventions must be based upon positive correlation of clinical findings, clinical course, and diagnostic tests. A comprehensive assimilation of these factors must lead to a specific diagnosis with positive identification of pathologic conditions.
- 10. SIX-MONTH TIME FRAME** The prognosis drops precipitously for returning an injured worker to work once he/she has been temporarily totally disabled for more than six months. The emphasis within these guidelines is to move patients along a continuum of care and return-to-work within a six-month time frame, whenever possible. It is important to note that time frames may be less pertinent for injuries that do not involve work-time loss or are not occupationally related.
- 11. RETURN-TO-WORK** A return-to-work is therapeutic, assuming the work is not likely to aggravate the basic problem or increase long-term pain. The practitioner must provide specific physical limitations and the patient should never be released to non-specific and vague descriptions such as "sedentary" or "light duty." The following physical limitations should be considered and modified as recommended: lifting, pushing, pulling, crouching, walking, using stairs, bending at the waist, awkward and/or sustained postures, tolerance for sitting or standing, hot and cold environments, data entry and other repetitive motion tasks, sustained grip, tool usage and vibration factors. Even if there is residual chronic pain, return-to-work is not necessarily contraindicated. The practitioner should understand all of the physical demands of the patient's job position before returning the patient to full duty and should request clarification of the patient's job duties. Clarification should be obtained from the employer or, if necessary, from including, but not limited to, an occupational health nurse, occupational therapist, vocational rehabilitation specialist, an industrial hygienist, or another professional.
- 12. DELAYED RECOVERY** Strongly consider a psychological evaluation, if not previously provided, as well as initiating interdisciplinary rehabilitation treatment and vocational goal setting, for those patients who are failing to make expected progress 6 to 12 weeks after initiation of treatment of an injury. Therefore, all chronic pain patients should have a documented psychological evaluation and psychological treatment as appropriate to address issue of chronic pain. It is also appropriate to clinically reassess the patient, function goals, and differential diagnosis. The Division recognizes that 3 to 10% of all industrially injured patients will not recover within the timelines outlined in this document, despite optimal care. Such individuals may require treatments beyond the timelines discussed within this document, but such treatment requires clear documentation by the

authorized treating practitioner focusing on objective functional gains afforded by further treatment and impact upon prognosis.

**13. GUIDELINE RECOMMENDATIONS AND INCLUSION OF MEDICAL EVIDENCE** All recommendations are based on available evidence and/or consensus judgment. When possible, guideline recommendations will note the level of evidence supporting the treatment recommendation. It is generally recognized that early reports of a positive treatment effect are frequently weakened or overturned by subsequent research. When interpreting medical evidence statements in the guideline, the following apply:

- Consensus means the judgment of experienced professionals based on general medical principles. Consensus recommendations are designated in the guidelines as “generally well-accepted,” “generally accepted,” “acceptable/accepted,” or “well-established.”
- “Some evidence” means the recommendation considered at least one adequate scientific study, which reported that a treatment was effective. The Division recognizes that further research is likely to have an impact on the intervention’s effect.
- “Good evidence” means the recommendation considered the availability of multiple adequate scientific studies or at least one relevant high-quality scientific study, which reported that a treatment was effective. The Division recognizes that further research may have an impact on the intervention’s effect.
- “Strong evidence” means the recommendation considered the availability of multiple relevant and high-quality scientific studies, which arrived at similar conclusions about the effectiveness of a treatment. The Division recognizes that further research is unlikely to have an important impact on the intervention’s effect.

All recommendations in the guideline are considered to represent reasonable care in appropriately selected cases, irrespective of the level of evidence or consensus statement attached to them. Those procedures considered inappropriate, unreasonable, or unnecessary are designated in the guideline as “**not recommended**.”

Please refer to the Colorado Department of Labor and Employment’s website for evidence tables and study critiques which provide details on the studies used to develop the evidence statements.

**14. TREATMENT OF PRE-EXISTING CONDITIONS** that preexisted the work injury/disease will need to be managed under two circumstances: (a) A preexisting condition exacerbated by a work injury/disease should be treated until the patient has returned to their objectively verified prior level of functioning or Maximum Medical Improvement (MMI); and (b) A preexisting condition not directly caused by a work injury/disease but which may prevent recovery from that injury should be treated until its objectively verified negative impact has been controlled. The focus of treatment should remain on the work injury/disease.

The remainder of this document should be interpreted within the parameters of these guideline principles that may lead to more optimal medical and functional outcomes for injured workers.



## C. INTRODUCTION TO COMPLEX REGIONAL PAIN SYNDROME

Complex Regional Pain Syndrome (CRPS Types I and II) describes painful syndromes, which were formerly referred to as Reflex Sympathetic Dystrophy (RSD) and causalgia. CRPS conditions usually follow injury that appears regionally and have a distal predominance of abnormal findings, exceeding the expected clinical course of the inciting event in both magnitude and duration and often resulting in significant impairment of limb function.

CRPS I (RSD) is a syndrome that usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and appears to be disproportionate to the inciting event. It is associated at some point with evidence of edema, changes in skin, blood flow, abnormal sudomotor activity in the region of the pain, allodynia, or hyperalgesia. The site is usually in the distal aspect of an affected extremity or with a distal to proximal gradient. The peripheral nervous system and possibly the central nervous system are involved.

CRPS II (Causalgia) is the presence of burning pain, allodynia, and hyperpathia usually in the hand or foot after partial injury to a nerve or one of its major branches. Pain is within the distribution of the damaged nerve but not generally confined to a single nerve.

Historically, three stages Stage 1- Acute (Hyperemic), Stage 2- Dystrophic (Ischemic), and Stage 3 (Atrophic) were thought to occur. However, the Stages in CRPS I are not absolute and in fact, may not all be observed in any single patient. Signs and symptoms fluctuate over time and are reflective of ongoing dynamic changes in both the peripheral and central nervous systems.

Although there has been some debate regarding both the existence and pathophysiologic basis of CRPS, as with all chronic pain, psychological issues should always be addressed, but there are a number of studies identifying pathological findings.

Historically, the following studies provide further basis for the CRPS pathological model.

In animals, a mice model with tibial fracture and cast immobilization is used to create CRPS. For mice with clinical signs of CRPS, transcriptional changes in gene expression were found ([Gallagher, 2013](#)). Another study found that patients with CRPS versus those healthy controls perceive their affected hand to be larger than the unaffected hand. The finding corresponded to disease duration, decrease tactile thresholds, and a neglect score ([Peltz, 2011](#)). A functional MRI study confirmed an enlarged somatosensory cortex representation of the healthy hand ([F. S. Di Pietro, T. R.; Moseley, G. L.; Lotze, M.; McAuley, J. H., 2015](#)). Other studies have supported a difference in the primary somatosensory cortex or neuroimaging, although the quality of studies is low ([F. M. Di Pietro, J. H.; Parkitny, L.; Lotze, M.; Wand, B. M.; Moseley, G. L.; Stanton, T. R., 2013](#)).

Another small study noted an increase in blood oxygenation level in the cortical representation of the affected hand after a successful sympathetic block indicating clear central involvement for the CRPS pain ([Stude, 2014](#)).

## D. DEFINITIONS

1. **AFTER SENSATION**: refers to the abnormal persistence of a sensory perception, provoked by a stimulus even though the stimulus has ceased.
2. **ALLODYNIA**: pain due to a non-noxious stimulus that does not normally provoke pain.  
  
Mechanical Allodynia: refers to the abnormal perception of pain from usually non-painful mechanical stimulation.  
  
Static Mechanical Allodynia: refers to pain obtained by applying a single stimulus such as light pressure to a defined area.  
  
Dynamic Mechanical Allodynia: obtained by moving the stimulus such as a brush or cotton tip across the abnormal hypersensitive area.  
  
Thermal Allodynia: refers to the abnormal sensation of pain from usually non-painful thermal stimulation such as cold or warmth.
3. **CENTRAL PAIN**: pain initiated or caused by a primary lesion or dysfunction in the central nervous system (CNS).
4. **CENTRAL SENSITIZATION**: the experience of pain evoked by the excitation of non-nociceptive neurons or of nerve fibers that normally relay non-painful sensations to the spinal cord. This results when non-nociceptive afferent neurons act on a sensitized central nervous system (CNS). Experimental data suggest that pathways normally carrying pain signals themselves become overstimulated and/or fail to respond to inhibitory influences causing increased pain. An example is 'wind-up' which occurs when cells in the dorsal horn of the spinal cord increase their rate of action potential discharge in response to repeated stimulation by nociceptors ([Woolf, 2006](#); [Zhou, 2008](#)).
5. **DYSTONIA**: state of abnormal (hypo or hyper) tonicity in any of the tissues.
6. **HYPERALGESIA**: refers to an exaggerated pain response from a usually painful stimulation.
7. **HYPEREMIA**: presence of increased blood in a part or organ.
8. **HYPERESTHESIA**: (Positive Sensory Phenomenon): includes allodynia, hyperalgesia, and hyperpathia. Elicited by light touch, pin-prick, cold, warm vibration, joint position sensation, or two-point discrimination, which is perceived as increased or more.
9. **HYPERPATHIA**: a condition of altered perception such that stimuli which would normally be innocuous, if repeated or prolonged, result in severe explosive persistent pain.
10. **HYPOESTHESIA**: (also hypesthesia): diminished sensitivity to stimulation.
11. **PAIN BEHAVIOR**: the nonverbal actions (such as grimacing, groaning, limping, using visible pain relieving or support devices, and requisition of pain medications, among others) that are outward manifestations of pain and through which a person may communicate that pain is being experienced.
12. **SUDOMOTOR CHANGES**: alteration in function of sweat glands. Sweat output may increase or decrease due to changes in autonomic input to the gland.

- 13. SYMPATHETICALLY MAINTAINED PAIN (SMP):** a pain that is maintained by sympathetic efferent innervations or by circulating catecholamines and which may be a separate condition from CRPS.
- 14. TROPHIC CHANGES:** tissue alterations due to interruption of nerve or blood supply; may include changes in hair growth and texture of skin.
- 15. VASOMOTOR CHANGES:** alteration in regulation of dilation or constriction of blood vessels.

Referenced Version

## E. INITIAL EVALUATION

The Division recommends the following diagnostic procedures be considered, at least initially, the responsibility of the workers' compensation carrier to ensure that an accurate diagnosis and treatment plan can be established. Standard procedures that should be utilized when initially diagnosing a work-related chronic pain complaint are listed below. Because CRPS I is commonly associated with other injuries, it is essential that all related diagnoses are defined and treated. These disturbances are typically restricted to one extremity, usually distally, but are variable in their expression.

**1. HISTORY TAKING AND PHYSICAL EXAMINATION (HX & PE):** are generally accepted, well-established, and widely used procedures that establish the foundation/basis for and dictates subsequent stages of diagnostic and therapeutic procedures. When findings of clinical evaluations and those of other diagnostic procedures are not complementing each other, the objective clinical findings should have preference. Before the diagnosis of CRPS I or CRPS II is established, an experienced practitioner must perform a detailed neurological and musculoskeletal exam to exclude other potentially treatable pain generators or neurological lesions. The medical records should reasonably document the following:

**a. Medical History:** As in other fields of medicine, a thorough patient history is an important part of the evaluation of pain. In taking such a history, factors influencing a patient's current status can be made clear and taken into account when planning diagnostic evaluation and treatment. It may be necessary to acquire previous medical records. One efficient manner in which to obtain historical information is by using a questionnaire. The questionnaire may be sent to the patient prior to the initial visit or administered at the time of the office visit. History should ascertain the following elements:

- i.** General Information: General items requested are name, sex, age, birth date, etc.
- ii.** Level of Education: The level of patient's education may influence response to treatment.
- iii.** Work History/Occupation: to include both impact of injury on job duties and impact on ability to perform job duties, work history, job description, mechanical requirements of the job, duration of employment, and job satisfaction.
- iv.** Current employment status.
- v.** Marital status.
- vi.** Family Environment: Is the patient living in a nuclear family or with friends? Is there, or were there, any family members with chronic illness or pain problems? Responses to such questions reveal the nature of the support system or the possibility of conditioning toward chronicity.
- vii.** Ethnic Origin: Ethnicity of the patient, including any existing language barriers, may influence the patient's perception of and response to pain. Literature indicates that providers may under-treat patients of certain ethnic backgrounds due to underestimation of their pain ([Todd, 2000](#)).

viii. Belief System: Patients should be asked about their value systems, including spiritual and cultural beliefs, in order to determine how these may influence the patient's and family's response to illness and treatment recommendations.

ix. Functional Assessment: Functional ability should be assessed and documented at the beginning of treatment. Periodic assessment should be recorded throughout the course of care to follow the trajectory of recovery. Functional measures are likely to be more reliable over time than pain measures.

Patient-reported outcomes, whether of pain or function, are susceptible to a phenomenon called response shift. This refers to changes in self-evaluation, which may accompany changes in health status. Patient self-reports may not coincide with objective measures of outcome, due to reconceptualization of the impact of pain on daily function and internal recalibration of pain scales ([C. E. F. Schwartz, J. A., 2009](#)). Response shift may obscure treatment effects in clinical trials and clinical practice, and it may lead to apparent discrepancies in patient-reported outcomes following treatment interventions. While methods of measuring and accounting for response shift are not yet fully developed, understanding that the phenomenon exists can help clinicians understand what is happening when some measures of patient progress appear inconsistent with other measures of progress.

x. Activities of Daily Living: Pain has a multidimensional effect on the patient that is reflected in changes in usual daily vocational, social, recreational, and sexual activities.

xi. Past and present psychological problems.

xii. History of abuse: physical, emotional, sexual.

xiii. History of disability in the family.

xiv. Sleep disturbances: Poor sleep has been shown to increase patient's self-perceived pain scores ([Larson, 2016](#)). Pre-injury and post-injury sleep should be recorded.

xv. Causality: How did this injury occur? Was the problem initiated by a work-related injury or exposure? Patient's perception of causality (e.g., was it their fault or the fault of another).

xvi. Presenting symptoms related to CRPS:

- A) Severe, generally unremitting burning and/or aching pain and/or allodynia.
- B) Swelling of the involved area.
- C) Changes in skin color.
- D) Asymmetry in nail and/or hair growth.
- E) Abnormal sweat patterns of the involved extremity.

- F) Motor dysfunction: limited active range-of-motion, atrophy, tremors, dystonia, weakness.
- G) Subjective temperature changes of the affected area.

**b. Pain History:** Characterization of the patient's pain and of the patient's response to pain is one of the key elements for CRPS diagnosis.

- i. Site of Pain: Localization and distribution of the pain help determine the type of pain the patient has (i.e., central versus peripheral).
- ii. Pain Diagram drawing to document the distribution of pain.
- iii. Visual Analog Scale (VAS): including a discussion of the range of pain during the day and how activities, use of modalities, and other actions affect the intensity of pain.
- iv. Duration: including intermittent pain, activity related pain.
- v. Circumstances during which the pain began (e.g., an accident, an illness, a stressful incident, or spontaneous onset).
- vi. Pain characteristics: such as burning, shooting, stabbing, aching. Time of pain occurrence as well as intensity, quality, and radiation give clues to the diagnosis and potential treatment. The quality of pain can be helpful in identifying neuropathic pain which is normally present most of the day, at night, and is described as burning.
- vii. Response of pain to activity: list of activities which aggravate or exacerbate, ameliorate, or have no effect on the level of pain.
- viii. Associated Symptoms: Does the patient have numbness or paresthesia, dysesthesia, weakness, bowel or bladder dysfunction, decreased temperature, increased sweating, cyanosis or edema? Is there local tenderness, allodynia, hyperesthesia or hyperalgesia?

**c. Medical Management History:**

- i. History of diagnostic tests and results including but not limited to any response to sympathetic nerve blocks, results of general laboratory studies, EMG and nerve conduction studies, radiological examinations, for demineralization, triple phase bone scan, or thermography with autonomic stress testing, and tests of sudomotor functioning such as Quantitative Sudomotor Axon Reflex Test (QSART).
- ii. Prior Treatment: chronological review of medical records including previous medical evaluations and response to treatment interventions. In other words, what has been tried and what has been helpful?
- iii. Prior Surgery: If the patient has had prior surgery specifically for the pain, he/she may be less likely to have a positive outcome.
- iv. History of and current use of medications, including over-the-counter and herbal/dietary supplements to determine drug usage (or abuse) interactions and efficacy of treatment. Drug allergies and other side

effects experienced with previous or current medication therapy and adherence to currently prescribed medications should be documented. Ideally, this includes dosing schedules as reported by the patient or patient representative. Information should be checked against the Colorado Prescription Drug Monitoring Program, offered by the Colorado Pharmacy Board.

- v. Review of Systems Check List: Determine if there is any interaction between the pain complaint and other medical conditions.
- vi. Psychosocial Functioning: Determine if any of the following are present: current symptoms of depression or anxiety; evidence of stressors in the workplace or at home; and past history of psychological problems or other confounding psychosocial issues may be present, such as the presence of psychiatric disease. Due to the high incidence of co-morbid problems in populations that develop chronic pain, it is recommended that patients diagnosed with CRPS be referred for a full psychosocial evaluation. All patients with CRPS have chronic pain and are likely to suffer psychosocial consequences.
- vii. Pre-existing Conditions: Treatment of these conditions is appropriate when the preexisting condition affects recovery from chronic pain.
- viii. Family history pertaining to similar disorders.

**d. Substance Use/Abuse:**

- i. Alcohol use.
- ii. Smoking history and use of nicotine replacements.
- iii. History of current and prior prescription and/or illicit drug use and abuse.
- iv. The use of caffeine or caffeine-containing beverages.
- v. Substance abuse information may be only fully obtainable from multiple sources over time. Patient self-reports may be unreliable. Patient self-reports should always be checked against medical records.

**e. Other Factors Affecting Treatment Outcome:**

- i. Compensation/Disability/Litigation.
- ii. Treatment Expectations: What does the patient expect from treatment: complete relief of pain or reduction to a more tolerable level?

**f. Physical Examination:** should include examination techniques applicable to those portions of the body where the patient is experiencing subjective symptomatology. The following should be documented:

- i. Inspection: changes in appearance of the involved area, to include trophic changes, changes in hair and nail growth, muscular atrophy, changes in skin turgor, swelling and color changes.

- ii. Temperature Evaluation: Palpable temperature changes may not be detectable in early disease stages, and the examiner will generally only be able to appreciate significant temperature variations. Objective testing is preferred to demonstrate temperature asymmetries. Temperature differences of 1°C may be significant; however, these differences also occur commonly with other pain conditions ([S. P. H. Niehof, F. J.; Stronks, D. L.; Klein, J.; Zijlstra, F. J., 2007](#)).
- iii. Edema: is an important finding in CRPS. Its presence should be described in detail by the physician and when possible verified with objective testing such as volumetric testing or bilateral circumference measurements, usually performed by therapists.
- iv. Motor Evaluation: involuntary movements, dystonia, muscle weakness, atrophy, or limited range of active motion in the involved limb(s).
- v. Sensory Evaluation: A detailed sensory examination is crucial in evaluating a patient with chronic pain complaints, including the presence of allodynia and the anatomic pattern of any associated sensory abnormalities to light touch, deep touch, pain, and thermal stimulation. Quantitative sensory testing may be useful.
- vi. Musculoskeletal Evaluation: presence of associated myofascial problems, such as contractures, Range-of-Motion (ROM), or trigger points.
- vii. Evaluation of Non-physiologic Findings: Determine the presence of the following: variabilities on formal exam including variable sensory exam; inconsistent tenderness, and/or swelling secondary to extrinsic sources. Inconsistencies between formal exam and observed abilities of range-of-motion, motor strength, gait, and cognitive/emotional state; and/or observation of inconsistencies between pain behaviors, affect and verbal pain rating, and physical re-examination can provide useful information.



## F. OVERVIEW OF CARE FOR CRPS OR SYMPATHETICALLY MEDIATED PAIN

[Note: Based primarily on Washington State Guidelines ([Friedman, 2015](#)).] Once a patient has met the clinical criteria for CRPS or has disproportionate pain from the initial workers' compensation injury with additional physical findings suggestive of sympathetic involvement, directed care should begin.

Active initial treatment is the keystone to preventing disability. The date of onset of the CRPS symptoms should be documented with the physical exam findings in all of the pertinent areas: sensory, vasomotor, sudomotor and edema, and weakness or trophic changes of hair, nails, or skin.

Measurable goals should then be agreed upon with the patient. Initial treatment begins as quickly as possible ([Childs, 2015](#)) with cognitive behavior therapy desensitization, neuromuscular re-education (graded motor imagery and/or mirror box therapy), progressive active therapy, and additional activities aimed at the identified functional goals.

Sympathetic blocks are performed in order to decrease pain and encourage active therapy. Thus, progressive active therapy should take place within 24 hours of an injection.

Medication used for pain relief is primarily based on medications effective for neuropathic pain, although, bisphosphonates may be useful in some cases. Opioids are rarely useful for neuropathic pain and should be used sparingly.

As with all chronic pain patients, psychological consultation and treatment and multidisciplinary treatment is strongly recommended.

## G. DIAGNOSTIC CRITERIA AND PROCEDURES

- 1. DIAGNOSIS OF CRPS** Diagnosis of CRPS continues to be controversial. The clinical criteria used by the International Association for the Study of Pain is thought to be overly sensitive and unable to differentiate well between those patients with other pain complaints and those with actual CRPS ([R. N. B. Harden, S.; Perez, R. S.; Birklein, F.; Marinus, J.; Maihofner, C.; Lubenow, T.; Buvanendran, A.; Mackey, S.; Graciosa, J.; Mogilevski, M.; Ramsden, C.; Chont, M.; Vatine, J. J., 2010](#)). One study in which different diagnostic sets were reviewed using patient report and physician confirmed signs, the highest specificities were found for the signs of hyperesthesia, allodynia, temperature asymmetry, skin color asymmetry, and edema ([R. S. C. Perez, S.; Marinus, J.; Zuurmond, W. W.; de Lange, J. J., 2007](#)). This pattern is predominant in the other studies reporting on similar assessed physical findings. Sudomotor/sweating limb differences and atrophic changes, including nail, hair and skin changes, occur in less than half of the clinical CRPS patients; in contrast, verified temperature asymmetry, edema, and decreased motor function are frequently cited as predictive ([R. N. B. Harden, S.; Perez, R. S.; Birklein, F.; Marinus, J.; Maihofner, C.; Lubenow, T.; Buvanendran, A.; Mackey, S.; Graciosa, J.; Mogilevski, M.; Ramsden, C.; Schlereth, T.; Chont, M.; Vatine, J. J., 2010; R. S. C. Perez, S.; Marinus, J.; Zuurmond, W. W.; de Lange, J. J., 2007; R. S. K. Perez, C.; Bezemer, P. D.; Zuurmond, W. W.; de Lange, J. J., 2005](#)).

Clinical criteria alone are not dependable nor necessarily reliable and require objective testing. One study of interrater reliability for diagnosing CRPS I showed poor reliability for assessment of temperature difference and color difference between the affected limbs ([R. S. B. Perez, P. E.; Zuurmond, W. W.; Giezeman, M. J.; van Dasselaaar, N. T.; Vranken, J.; de Lange, J. J., 2002](#)). Two other studies compared physician's assessment with actual measured signs of CRPS I. The first study advocated bedside use of infrared thermometer and volume measurements. The study found a volume difference between the hands of 30.4 cc and a dorsal hand temperature difference of at least 0.78°C could be used to help establish the diagnosis. The study also noted frequent decreased mobility in the little finger. This study only included patients known to have CRPS; thus, agreement between the objective measurements and the physicians' observations was good ([Oerlemans, 1999](#)). The second study compared physicians' clinical assessments with measured objective results and found that the clinical establishment of temperature and volume asymmetry was inadequate. It also noted poor to moderate correspondence between patient reported severity of symptoms and the physicians' clinical judgment and actual measurements ([R. S. B. Perez, P. E.; Zuurmond, W. W.; Bezemer, P. D.; Brink, H. E.; de Lange, J. J., 2005](#)).

A separate study used skin surface temperature to differentiate between CRPS in patients after a fracture and control patients with other complaints following a fracture. This study also incorporated a control group of healthy patients without complaints. Notably there was significantly more asymmetry between the temperature findings in the CRPS group than in both the control groups, with and without complaints. However, the control group with complaints had greater temperature differences than the otherwise healthy group. The study concluded that the ability of skin surface temperatures under resting conditions to discriminate between CRPS patients and other patients is limited ([S. P. B. Niehof, A.; Huygen, F. J.; Zijlstra, F. J., 2008](#)). Historically some authors have used 2°C as a limit for temperature differences and others have used lower cutoffs ([R. S. Z. Perez, W. W.; Bezemer, P. D.; Kuik, D. J.; van Loenen, A. C.; de Lange, J. J.; Zuidhof, A. J., 2003](#)). This study also applied various temperature asymmetry cut offs and could identify no specific combination resulting in sufficient predictive power. However, the negative predictive power was 84% for resting temperature asymmetry less than 0.7°C. This would seem to suggest that it is unlikely a patient has CRPS if they do not have resting temperature asymmetry; however, resting temperature asymmetry differences may be due to a variety of reasons other than CRPS ([S. P. B. Niehof, A.; Huygen, F. J.;](#)

[Zijlstra, F. J., 2008](#)).

Several studies have assessed skin temperature changes in variable settings. In one study skin temperature measurements were recorded over 5-8 hours and the instruments were able to compare the difference between the limbs with every day activities. Twenty-two patients with CRPS, 18 with limb pain of other origin, and 22 of healthy controls were compared. Examining the asymmetry throughout the time period, a difference of 2°C could differentiate CRPS from patients with other painful disease with specificity of 67% and 79% versus healthy controls. It was noted many patients in all groups had a 2°C difference between the limbs at one time or another. However, the persistence of the difference and the asymmetry was important in the diagnosis. The difference between the limbs could occur in either direction, warmer or cooler, than the unaffected side ([S. B. Krumova et al., 2008](#)).

Thermographic imaging has been done in two studies using whole body warming and cooling. The initial study established the fact that in CRPS patients the temperature difference between hands increases significantly when the sympathetic system is provoked with whole body temperature changes ([S. P. H. Niehof, F. J.; van der Weerd, R. W.; Westra, M.; Zijlstra, F. J., 2006](#)). A separate more detailed study induced whole body warming and cooling and compared temperature and blood flow in three sets of patients, one with CRPS, one with patients of extremity pain of other origins, and a third group of healthy volunteers. None of the participants were on medications affecting vascular functions. Three patterns of temperature change were noted for CRPS patients. In some patients with “warm” CRPS, the temperature continually exceeded the temperature of the unaffected limb during the cooling and warming period. In others, where the affected limb was cooler than the unaffected limb, the affected limb may have remained cooler throughout the cooling and warming period. Finally, in a few patients, there was an unusual crossover where initially the patient had a warm or cooler limb compared to the unaffected side and later the affected limb showed temperature differences in the opposite direction. All of these patterns demonstrate an autonomic asymmetry that was not found in healthy volunteers whose limbs temperatures adjust in a symmetrical manner. Previous tests comparing Laser Doppler flow of extremities in healthy controls and patients with distal radius fracture to CRPS I patients showed significant sympathetic changes after contralateral cold exposure ([Schurmann, 1999](#)). Another study of patients with radius fractures found that non-stress thermography had a sensitivity of 58% and specificity of 66% ([Gradl, 2003](#)). Thus, the asymmetry of limb temperature under stress appears to be the most important factor. In this study, the temperature differences needed to exceed 2.2°C to distinguish between the groups ([G. S. Wasner, J.; Heckmann, K.; Maier, C.; Baron, R., 2001](#)).

Another study reviewed skin temperature from thermography, thermoregulatory sweat tests (TST), and quantitative sudomotor axon reflex test (QSART), early and late in patients with clinically diagnosed CRPS. In this study, the differences identified with TST persisted during later testing while QSART differences did not. Skin temperature was asymmetrical between the limbs early and late, although generally in opposite directions. This study describes the dynamic nature of CRPS ([Birklein, 1998](#)).

These studies appear to confirm the fact that causing an objectively measured, sympathetically evoked response is likely to be more predictive of CRPS than merely resting temperature differences or resting sudomotor/sweating differences. Temperature testing at any one point in time is probably not sensitive and able to distinguish between patients with pain complaints and those with CRPS. Other review articles have made similar observations regarding the need for dynamic testing ([G. Wasner, 2010](#)).

There is good evidence that CRPS is characterized by inhibition of sympathetic cutaneous responses on the affected side and by blunted sympathetic response to

physiologic stimuli ([E. K. F. Krumova, J.; Klauenberg, S.; Richter, H.; Wasner, G.; Maier, C., 2008](#); [G. S. Wasner, J.; Heckmann, K.; Maier, C.; Baron, R., 2001](#)). Based on the relatively common finding of temperature discrepancy in non-CRPS patients with chronic pain, a stress test thermogram should be used ([E. K. F. Krumova, J.; Klauenberg, S.; Richter, H.; Wasner, G.; Maier, C., 2008](#); [G. S. Wasner, J.; Heckmann, K.; Maier, C.; Baron, R., 2001](#)). Unfortunately, only two studies have been published in this area and neither used a blinded control for comparison. The most commonly reported stress tests consist of contralateral extremity cooling or whole body suit ([Conwell, 2010](#); [Cooke, 1993](#); [Gulevich, 1997](#); [S. P. H. Niehof, F. J.; van der Weerd, R. W.; Westra, M.; Zijlstra, F. J., 2006](#); [Schurmann, 1999](#); [Vogel, 2010](#); [G. Wasner, 2010](#); [G. S. Wasner, J.; Baron, R., 2002](#); [G. S. Wasner, J.; Heckmann, K.; Maier, C.; Baron, R., 2001](#)). However, the physiology behind the stress thermography testing is convincing given the prior studies ([Conwell, 2010](#); [Gulevich, 1997](#)).

In a similar manner, the QSART provides an autonomic stress that is measurable. Perhaps the main issue with the sudomotor test in isolation is that it appears some CRPS patients do not have an abnormal sweat test. To verify the diagnosis, all of these test results need to be compared to other test results, physical exam findings, and symptoms.

Thermal quantitative sensory testing has been used to study neuropathic conditions and CRPS. Components of the test include identification of light touch, warmth, cold, and pain with pressure, cold or heat. The testing relies on patient response to various recordable levels of testing in these areas. Generally, CRPS patients appear to demonstrate hypoalgesia in both the affected and unaffected limbs when compared to normals; hyperalgesia to thermal pain generators and hyperalgesia to blunt pressure ([V. L. Huge, M.; Forderreuther, S.; Kaufhold, W.; Valet, M.; Azad, S. C.; Beyer, A.; Magerl, W., 2008](#); [V. L. Huge, M.; Magerl, W.; Beyer, A.; Moehle, P.; Kaufhold, W.; Schelling, G.; Azad, S. C., 2011](#)). Findings on the specific TST test components differ according to the CRPS classification of warm or cold ([Eberle, 2009](#)). There is also some overlap of findings with other neuropathic conditions ([Maier, 2010](#)). In addition, patient response testing can be problematic in a medical legal setting. Thus, more objective tests are used for confirmation of CRPS. Routine clinical exam techniques should be used to evaluate the patient for hyper- and hypoalgesia and allodynia.

Significant harm can be done to individuals by over-diagnosing CRPS and subjecting patients to the side effects and potential morbidity of multiple sympathetic blocks, invasive procedures, or chronic medications, as well as psychological effects from the diagnosis. In order to safe guard against such harmful outcomes, patients should have objective testing to verify their diagnosis before such procedures are considered and/or are continued after the initial diagnosis. Several reviews on the subject have identified the need for more objective measurements ([R. N. B. Harden, S.; Perez, R. S.; Birklein, F.; Marinus, J.; Maihofner, C.; Lubenow, T.; Buvanendran, A.; Mackey, S.; Graciosa, J.; Mogilevski, M.; Ramsden, C.; Schlereth, T.; Chont, M.; Vatine, J. J., 2010](#); [G. Wasner, 2010](#)). Therefore, individuals must have a confirmed diagnosis of CRPS to receive these procedures.

Evidence Statements Regarding Diagnosis of CRPS			
Good Evidence	Evidence Statement	Citation	Design
	CRPS is characterized by inhibition of sympathetic cutaneous responses on the affected side and by blunted sympathetic response to physiologic stimuli.	( <a href="#">E. K. F. Krumova, J.; Klauenberg, S.; Richter, H.; Wasner, G.; Maier, C., 2008</a> )	Physiology experiment
		( <a href="#">G. S. Wasner, J.; Heckmann, K.; Maier, C.; Baron, R., 2001</a> )	Basic science (physiologic) study

- 2. DIAGNOSTIC COMPONENTS OF CLINICAL CRPS** Patients who meet the following criteria for clinical CRPS, consistent with the Budapest criteria, may begin initial treatment with oral steroids and/or tricyclics, physical therapy, a diagnostic sympathetic block, and other treatments found in the Division's Chronic Pain Disorder Medical Treatment Guideline. All treatment should be periodically evaluated with validated functional measures. Patient completed functional questionnaires such as those recommended by the Division as part of Quality Performance and Outcomes Payments (QPOP, see Rule 18-8) and/or the Patient Specific Functional Scale can provide useful additional confirmation. Further invasive or complex treatment will require a confirmed diagnosis.

Patient must meet the criteria below.

- a.** Continuing pain, which is disproportionate to any inciting event; and
- b.** At least one symptom in 3 of the 4 following categories:
- *Sensory*: reports of hyperesthesia and/or allodynia;
  - *Vasomotor*: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry;
  - *Sudomotor/edema*: reports of edema and/or sweating changes and/or sweating asymmetry; or
  - *Motor/trophic*: reports of decreased range-of-motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
- c.** At least one sign at time of evaluation in 2 or more of the following categories:
- *Sensory*: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement);
  - *Vasomotor*: evidence of temperature asymmetry and/or skin color changes and/or asymmetry. Temperature asymmetry should ideally be established by infrared thermometer measurements showing at least a 1°C difference between the affected and unaffected extremities;
  - *Sudomotor/edema*: evidence of edema and/or sweating changes and/or sweating asymmetry. Upper extremity volumetrics may be performed by therapists that have been trained in the technique to assess edema; or

- *Motor/trophic*: evidence of decreased range-of-motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

- d.** No other diagnosis that better explains the signs and symptoms ([R. N. B. Harden, S.](#); [Perez, R. S.](#); [Birklein, F.](#); [Marinus, J.](#); [Maihofner, C.](#); [Lubenow, T.](#); [Buvanendran, A.](#); [Mackey, S.](#); [Graciosa, J.](#); [Mogilevski, M.](#); [Ramsden, C.](#); [Chont, M.](#); [Vatine, J. J.](#), 2010). It is essential that other diagnoses which may require more urgent treatment, such as infection, allergy to implants, or other neurologic conditions, are diagnosed expediently before defaulting to CRPS.
- e.** Psychological evaluation should always be performed as this is necessary for all chronic pain conditions.

**3. DIAGNOSTIC COMPONENTS OF CONFIRMED CRPS** Patients should have a confirmed diagnosis of CRPS to proceed to other treatment measures in this guideline.

Both CRPS I and II confirmed diagnoses require the same elements. CRPS II is distinguished from CRPS I by the history of a specific peripheral nerve injury as the inciting event.

Patient must meet the below criteria:

- a.** A clinical diagnosis meeting the above criteria in 2, and
- b.** At least 2 positive tests from the following categories of diagnostic tests:
  - i.** Trophic tests
    - Comparative x-rays of both extremities including the distal phalanges.
    - Triple phase bone scan.
  - ii.** Vasomotor/Temperature test: Infrared stress thermography.
  - iii.** Sudomotor test: Autonomic test battery with an emphasis on QSART.
  - iv.** Sensory/ Sympathetic nerve test: Sympathetic blocks.

**4. SYMPATHETICALLY MAINTAINED PAIN (SMP)** Patients who do not qualify as confirmed CRPS may have SMP. Patients with SMP may use sympathetic blocks and active and passive therapy from this guideline. For all other treatment, refer to the Division's Chronic Pain Disorder Medical Treatment Guideline. Characteristics of SMP are a patient who:

- a.** Complains of pain;
- b.** Usually does not have clinically detectable vasomotor or sudomotor signs; and
- c.** Has significant pain relief with sympathetic blocks.

**5. NOT CRPS OR SMP** Criteria listed below. Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for treatment.

- a.** Patient complains of pain;

- b.** May or may not have vasomotor or sudomotor signs;
- c.** No relief with sympathetic blocks; and
- d.** No more than one other diagnostic test procedure is positive.

**6. DIAGNOSTIC IMAGING** is a generally accepted diagnostic procedure for CRPS. Results must be interpreted within the context of a full medical evaluation.

**a. Plain Film Radiography:**

Description: A radiological finding in CRPS may be unilateral osteoporosis; however, osteoporosis may be absent in many cases. In CRPS I, the osteoporosis may be rapid in progression. The disorder typically affects the distal part of an extremity such as a phalanges, hand or foot; however, intermediate joints such as the knee or elbow may be involved. Contralateral x-rays should be taken for comparison and should include the distal phalanges.

Results: The radiological appearance of osteoporosis has been characterized as spotty or patchy. CRPS I may exist in the absence of osteoporosis; the diagnosis of CRPS I cannot be made solely on the basis of radiographic appearance or the osteoporosis alone.

**b. Triple Phase Bone Scan:**

Description: Radionuclide imaging scintigraphy employing radio-pharmaceutical technetium coupled to a phosphate complex has been used to help facilitate the diagnosis of CRPS I. Unfortunately, there are many different types of conditions that also produce osteoporosis, and a triple-phase bone scan does not distinguish between the causes of bone demineralization.

Results: Clinical information may be derived from each of the three phases of the bone scan following injection. In the early course of CRPS I, there is usually an increased uptake seen during Phase 1. However, in the late course of the disease process, there can actually be decreased uptake. In Phase 2, which reflects the soft tissue vascularity, an increased diffuse uptake may be appreciated during the early course of CRPS I. During Phase 3, one may see a diffuse uptake of multiple bone involvement of the involved limb, reflecting the bone turnover secondary to osteoporosis. Negative bone scans may be found in up to 40% of patients clinically diagnosed with CRPS I; however, it may help to confirm the diagnosis of CRPS I when positive.

The physician should consider the risks of medical radiation and whether the diagnostic benefit of a bone scan will outweigh the risk.

**7. INJECTIONS – DIAGNOSTIC SYMPATHETIC**

Description: Diagnostic sympathetic injections are generally accepted procedures to aid in the diagnosis of CRPS I & II and SMP. Sympathetic blocks lack specificity for CRPS I & II. Each diagnostic injection has inherent risk and risk versus benefit should always be evaluated when considering injection therapy. Since these procedures are invasive, less invasive or non-invasive procedures should be considered first. Selection of patients, choice of procedure, and localization of the level for injection should be determined by clinical information.

Special Considerations: Injections with local anesthetics of differing duration are required

to confirm a diagnosis. In some cases, injections at multiple levels may be required to accurately diagnose pain. Refer to Section H.6, Therapeutic Procedures, Non-Operative, Injections – Therapeutic, for information on specific injections.

Since fluoroscopic and/or CT guidance during procedures is recommended to document technique and needle placement, an experienced physician should perform the procedure (Fiore, 2008). In addition, physicians should obtain fluoroscopy training and must also have the appropriate training in radiation safety, usually overseen by a radiation safety officer.

Complications: Complications may include transient neurapraxia, nerve injury, inadvertent spinal injection, infection, venous or arterial vertebral puncture, laryngeal paralysis, respiratory arrest, vasovagal effects, as well as permanent neurological damage.

Contraindications: Absolute contraindications of diagnostic injections include: (a) bacterial infection – systemic or localized to region of injection, (b) bleeding diatheses, (c) hematological conditions, and (d) possible pregnancy.

Relative Contraindications: Relative contraindications of these injections may include: (a) allergy to contrast or shellfish, (b) poorly controlled diabetes mellitus and/or hypertension.

Drugs affecting coagulation, such as aspirin, NSAIDs and other anti-platelets or anti-coagulants require restriction from use. Decisions regarding the number of restricted days should be made in consultation with the prescribing physician and other knowledgeable experts.

Test Results: To confirm the accuracy of the block, there should be a documented temperature difference between the affected and unaffected extremities of at least 1°C. The interpretation of the test result is primarily based upon pain relief of 50% or greater and evidence of functional improvement, for at least the duration of the local anesthetic used. A pain diary must be recorded as part of the medical record that documents response hourly for a minimum requirement of the first 8 hours post injection or until the block has clearly worn off and preferably for the week following an injection. The patient must have minimal sedation from opioids or other medication in order to be conscious and responsive during the procedure. The diagnostic significance of the test result should be evaluated in conjunction with clinical information and further information should be obtained from functional and physical reassessment performed by physical and/or occupational therapy the same day of the block.

Local anesthetics of different durations of action should be considered and could take the place of doing a "placebo" block (i.e., procaine, lidocaine, bupivacaine). Pain relief should be at least 50% or greater for the duration of the local anesthetic accompanied by functional improvement. It should be noted that with CRPS I, it is not unusual for the relief to last longer than the duration of the local anesthetic. If a placebo block is done, the needle should not be placed down to the sympathetic chain nor should an injection of saline be done around the sympathetic chain. A "sham block" would be preferable to see if the patient is a placebo responder. Contact with the sympathetic nerves by a needle or pressure on the chain by saline can cause a temporary sympathetic block and give a false positive placebo test. Additionally, patients with definite CRPS I can also be placebo responders. The fact that the patient responds positively to a placebo does not mean that he/she does not have CRPS I. It merely means that the patient is a placebo responder. This increases the value of doing another confirmatory test.

- a. **Stellate Ganglion Block:** for diagnosis and treatment of sympathetic pain involving the face, head, neck, and upper extremities secondary to CRPS I and



II. This block is commonly used for differential diagnosis and is one of the treatments for CRPS I pain involving the upper extremity. For diagnostic testing, use two blocks over a 3-14 day period. For a positive response, pain relief should be 50% or greater for the duration of the local anesthetic and pain relief should be associated with demonstrated functional improvement.

**b. Lumbar Sympathetic Block:** useful for diagnosis and treatment of pain of the pelvis and lower extremity secondary to CRPS I and II. This block is commonly used for differential diagnosis and is the preferred treatment of sympathetic pain involving the lower extremity. For diagnostic testing, use two blocks over a 3-14 day period. For a positive response, pain relief should be 50% or greater for the duration of the local anesthetic and pain relief should be associated with demonstrated functional improvement.

**c. Phentolamine Infusion Test:** are ***not recommended*** for diagnosis or treatment due to lack of effect on sudomotor testing, pain, regional blood flow, or hyperalgesia ([Verdugo, 1994](#)).

## **8. THERMOGRAPHY (INFRARED STRESS THERMOGRAPHY)**

Description: There is good evidence that CRPS is characterized by inhibition of sympathetic cutaneous responses on the affected side and by blunted sympathetic response to physiologic stimuli ([E. K. F. Krumova, J.; Klauenberg, S.; Richter, H.; Wasner, G.; Maier, C., 2008](#); [G. S. Wasner, J.; Heckmann, K.; Maier, C.; Baron, R., 2001](#)). Based on the relatively common finding of temperature discrepancy in non-CRPS patients with chronic pain, a stress test thermogram should be used ([E. K. F. Krumova, J.; Klauenberg, S.; Richter, H.; Wasner, G.; Maier, C., 2008](#); [G. S. Wasner, J.; Heckmann, K.; Maier, C.; Baron, R., 2001](#)). Infrared thermography may be useful for patients with suspected CRPS I and II and SMP. Thermography can distinguish abnormal thermal asymmetry of 1.0°C which is not distinguishable upon physical examination. It may also be useful in cases, to differentiate, of suspected small caliber fiber neuropathy and to evaluate patient response to sympatholytic interventions.

Special Considerations: The practitioner who supervises and interprets the thermographic evaluation shall follow recognized protocols and be board certified by one of the examining boards of the American Academy of Medical Infrared Imaging, American Academy of Thermology, or American Chiropractic College of Thermology, or have equivalent documented training.

Medications with anticholinergic activity (tricyclics, cyclobenzaprine, antiemetics, antipsychotics) may interfere with autonomic testing. The pre-testing protocol which includes cessation of specific medication therapy must be followed for accurate test results. Results of autonomic testing may be affected by peripheral polyneuropathy, radiculopathy or peripheral nerve injury, peripheral vascular disease, generalized autonomic failure, or by Shy-Drager syndrome.

Thermographic Tests: Functional autonomic stress testing may include the following methods:

**a. Cold Water Stress Test (Cold Pressor Test):** Paroxysmal response in the affected upper extremity is strongly suggestive of vasomotor instability.

**b. Warm Water Stress Test:** Paroxysmal response in the affected upper extremity is strongly suggestive of vasomotor instability.

- c. Whole Body Thermal Stress:** Analysis of persistent non-dermal temperature anomalies in response to whole body thermal stress from a cooling and/or warming suit.

## **9. AUTONOMIC TEST BATTERY**

Description: Resting skin temperature (RST), resting sweat output (RSO), and quantitative sudomotor axon reflex test (QSART) are a generally accepted test battery. There is good evidence that CRPS is characterized by inhibition of sympathetic cutaneous responses on the affected side and by blunted sympathetic response to physiologic stimuli ([E. K. F. Krumova, J.; Klauenberg, S.; Richter, H.; Wasner, G.; Maier, C., 2008](#); [G. S. Wasner, J.; Heckmann, K.; Maier, C.; Baron, R., 2001](#)). The tests can provide additional information regarding malfunction of the sympathetic system and the diagnosis of CRPS ([Chelimsky, 1995](#); [Sandroni, 1998](#)). Prior authorization is required. As with all diagnostic testing, the results must be interpreted in relationship to the patient's signs and symptoms.

Special Considerations: Medications with anticholinergic activity (tricyclics, cyclobenzaprine, antiemetics, anti-psychotics) may interfere with autonomic testing. Results of autonomic testing may be affected by peripheral polyneuropathy, radiculopathy or peripheral nerve injury, peripheral vascular disease, generalized autonomic failure, or by Shy-Drager syndrome.

Test Battery: These tests measure asymmetries in physiologic manifestations of autonomic activity between an affected limb and an unaffected contralateral limb. Skin temperature reflects vasomotor activity and sweat output measures sudomotor activity. The results of the three test components must be combined and scored. The battery of tests must include a measurement of each component (RST, RSO, and QSART).

- a. Infrared Resting Skin Temperature (RST):** provides thermographic measurements between the affected and unaffected limb. Generally, a 1° Celsius difference is significant. Given the previous discussion regarding differences in resting temperature between the affected and unaffected limbs in non-CRPS patients, the temperature findings may need to be interpreted cautiously as they do not reflect a stress on the sympathetic system.
- b. Resting Sweat Output (RSO):** measures an increase or reduction of 50% between the affected and unaffected limb.
- c. Quantitative Sudomotor Axon Reflex Test (QSART):** measures the sweat output elicited by iontophoretic application of acetylcholine. An increase or reduction of 50% between the affected and unaffected limb is significant.

The results of these tests should be recorded separately as abnormal or within the normal range.

A further assessment can then be done by the clinician when this information is collaborated with clinical findings. However clinical analysis is separate from the strict interpretation of each of the above three tests.

- 10. OTHER DIAGNOSTIC TESTS NOT SPECIFIC FOR CRPS** The following tests and procedures are not used to establish the diagnosis of CRPS but may provide additional information. The following are listed in alphabetical order.

**a. Electrodiagnostic Procedures:** Electromyography (EMG) and Nerve Conduction Studies (NCS) are generally accepted, well-established, and widely used for localizing the source of the neurological symptoms and establishing the diagnosis of focal nerve entrapments, such as carpal tunnel syndrome or radiculopathy, which may contribute to or coexist with CRPS II (causalgia). Traditional electrodiagnosis includes nerve conduction studies, late responses (F-Wave, H-reflex), and electromyographic assessment of muscles with needle electrode examination. As CRPS II occurs after partial injury to a nerve, the diagnosis of the initial nerve injury can be made by electrodiagnostic studies. However, the later development of sympathetically mediated symptomatology has no pathognomonic pattern of abnormality on EMG/NCS. When issues of diagnosis are in doubt, a referral or consultation with a physiatrist or neurologist trained in electrodiagnosis is appropriate.

**b. Laboratory Tests:** Laboratory tests are generally accepted, well-established, and widely used procedures. Patients should be carefully screened at the initial exam for signs or symptoms of diabetes, hypothyroidism, arthritis, and related inflammatory diseases. The presence of concurrent disease does not refute work-relatedness of any specific case. This frequently requires laboratory testing. When a patient's history and physical examination suggest infection, metabolic or endocrinologic disorders, tumorous conditions, systemic musculoskeletal disorders (e.g., rheumatoid arthritis or ankylosing spondylitis), or problems potentially related to medication (e.g., renal disease and NSAIDs), then laboratory tests, including, but not limited to the following can provide useful diagnostic information:

- i. Thyroid stimulating hormone (TSH) for hypothyroidism;
- ii. Diabetic screening: recommended for men and women with a BMI over 30, patients with a family history of diabetes, those from high risk ethnic groups, and patients with a previous history of impaired glucose tolerance. There is some evidence that diabetic patients with upper extremity disorders have sub-optimal control of their diabetes ([Ramchurn, 2009](#));
- iii. Serum protein electrophoresis;
- iv. Sedimentation rate and C-reactive protein (CRP) are nonspecific but elevated in infection, neoplastic conditions, and rheumatoid arthritis. Other screening tests to rule out inflammatory or autoimmune disease may be added when appropriate;
- v. Serum calcium, phosphorus, uric acid, alkaline, and acid phosphatase for metabolic, endocrine and neo-plastic conditions;
- vi. Complete blood count (CBC), liver, and kidney function profiles for metabolic or endocrine disorders or for adverse effects of various medications; and/or
- vii. Bacteriological (microorganism) work-up for wound, blood, and tissue.

The Division recommends that the workers' compensation carrier cover initial lab diagnostic procedures to ensure that an accurate diagnosis and treatment plan is established. When an authorized treating provider has justification for the test,

insurers should cover the costs. Laboratory testing may be required periodically to monitor patients on chronic medications.

- c. Peripheral Blood Flow (Laser Doppler or Xenon Clearance Techniques):**  
This is currently being evaluated as a diagnostic procedure in CRPS I and is ***not recommended*** at this time.

- 11. PERSONALITY/ PSYCHOLOGICAL/PSYCHOSOCIAL EVALUATIONS FOR PAIN MANAGEMENT** are generally accepted, well-established, and widely used diagnostic procedures not only with selected use in acute pain problems but also with more widespread use in subacute and chronic pain populations. Diagnostic evaluations should distinguish between conditions that are pre-existing, aggravated by the current injury, or work related.

Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for more information on clinical evaluation, a list and description of psychological functioning tests, and evidence.

- 12. SPECIAL TESTS** are generally well-accepted tests and are performed as part of a skilled assessment of the patient's capacity to return to work, his/her strength capacities, and/or physical work demand classifications and tolerance.

Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for indications, evidence, and time frames for the following procedures: computer-enhanced evaluations, functional capacity evaluations, jobsite evaluations and alterations, vocational assessment, and work tolerance screening (fitness for duty).

## H. THERAPEUTIC PROCEDURES – NON-OPERATIVE

Non-operative therapeutic rehabilitation is applied to patients with Complex Regional Pain Syndrome (CRPS) or Sympathetically Mediated Pain (SMP) who experience chronic and complex problems of de-conditioning and functional disability. Treatment modalities may be utilized sequentially or concomitantly depending on chronicity and complexity of the problem, and treatment plans should always be based on a diagnosis utilizing appropriate diagnostic procedures.

Before initiation of any therapeutic procedure, the authorized treating physician, employer, and insurer must consider these important issues in the care of the injured worker:

- Patients undergoing therapeutic procedure(s) should be released or returned to modified or restricted duty during their rehabilitation at the earliest appropriate time. Refer to Section H.14, Therapeutic Procedures, Non-operative, Return-to-Work, for detailed information.
- Reassessment of the patient's status in terms of functional improvement should be documented after each treatment. If patients are not responding within the recommended time periods, alternative treatment interventions, further diagnostic studies, or consultations should be pursued. Continued treatment should be monitored using objective measures such as:
  - Return to work or maintaining work status;
  - Fewer restrictions at work or performing activities of daily living (ADLs);
  - Decrease in usage of medications related to the work injury; and
  - Measurable functional gains, such as increased range-of-motion or documented increase in strength.
- Clinicians should provide and document education to the patient. No treatment plan is complete without addressing issues of individual and/or group patient education as a means of facilitating self-management of symptoms.
- Psychological or psychosocial screening should be performed on all chronic pain patients.

The following procedures are listed in alphabetical order:

### **1. ACUPUNCTURE**

Acupuncture for the treatment of CRPS is thought to work by promoting relaxation and allowing chemicals and blood within the body to flow properly. Acupuncture may not be well tolerated by CRPS patients, but some have reported relief of pain that is immediate, but temporary, lasting only 1 or 2 hours. Acupuncture is recommended for subacute or chronic pain patients who are trying to increase function and/or decrease medication usage and have an expressed interest in this modality. It is also recommended for subacute or acute pain for patients who cannot tolerate NSAIDs or other medications, and it should generally be used in conjunction with manipulative and physical therapy/rehabilitation. Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for indications, evidence, and time frames.

## **2. BIOFEEDBACK**

Biofeedback is a form of behavioral medicine that helps patients learn self-awareness and self-regulation skills for the purpose of gaining greater control of their physiology, such as muscle activity, brain waves, and measures of autonomic nervous system activity. Stress-related psycho-physiological reactions may arise as a reaction to organic pain and in some cases may cause pain. Electronic instrumentation is used to monitor the targeted physiology and then displayed or fed back to the patient visually, auditorily, or tactilely, with coaching by a biofeedback specialist.

Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for indications, evidence, and time frames.

## **3. COMPLEMENTARY MEDICINE**

Complementary Medicine, termed Complementary Alternative Medicine (CAM) in some systems, is a term used to describe a broad range of treatment modalities, a number of which are generally accepted and supported by some scientific literature and others which still remain outside the generally accepted practice of conventional Western Medicine. In many of these approaches, there is attention given to the relationship between physical, emotional, and spiritual well-being. While CAM may be performed by a myriad of both licensed and non-licensed health practitioners with training in one or more forms of therapy, credentialed practitioners should be used when available or applicable.

All CAM treatments require prior authorization and must include agreed upon number of visits for time to produce functional effects.

Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for indications, evidence, and time frames.

## **4. DISTURBANCES OF SLEEP**

Disturbances of sleep are common in chronic pain. An essential element of chronic pain treatment is restoration of normal sleep cycles. Although primary insomnia may accompany pain as an independent co-morbid condition, it more commonly occurs secondary to the pain condition itself. Exacerbations of pain often are accompanied by exacerbations of insomnia; the reverse can also occur. Sleep laboratory studies have shown disturbances of sleep architecture in pain patients. Loss of deep slow-wave sleep and an increase in light sleep occur. Sleep efficiency, the proportion of time in bed spent asleep, is also decreased. These changes are associated with patient reports of non-restorative sleep. Sleep apnea may also occur as a primary diagnosis or be caused or exacerbated by opioid and hypnotic use.

Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for more information on behavioral modifications to address sleep disturbances.

## **5. EDUCATION/INFORMED/SHARED DECISION MAKING** of the patient and family, as well as the employer, insurer, policy makers, and the community should be the primary emphasis to prevent disability. Unfortunately, practitioners often think of education and informed decision making last, after medications, manual therapy, and surgery.

Informed decision making is the hallmark of a successful treatment plan. In most cases, the continuum of treatment from the least invasive to the most invasive (e.g., surgery) should be discussed. The intention is to find the treatment along this continuum which most completely addresses the condition. Patients should identify their personal values and functional goals of treatment at the first visit. It is recommended that specific

individual goals are articulated at the beginning of treatment as this is likely to lead to increased patient satisfaction above that achieved from improvement in pain or other physical function ([Hazard, 2009](#)). Progress toward the individual functional goals identified should be addressed at follow-up visits and throughout treatment by other members of the health care team as well as an authorized physician.

Documentation of the informed decision process should occur whenever diagnostic tests or referrals from an authorized treating physician are contemplated. The informed decision making process asks the patients to set their personal functional goals of treatment and describe their current health status and any concerns they have regarding adhering to the diagnostic or treatment plan proposed. The provider should clearly describe the following:

- a.** The expected functional outcomes from the proposed treatment or the expected results and plan of action if diagnostic tests are involved.
- b.** Expected course of illness/injury without the proposed intervention.
- c.** Any side effects and risks to the patient.
- d.** Required post-treatment rehabilitation time and impact on work, if any.
- e.** Alternative therapies or diagnostic testing.

Before diagnostic tests or referrals for invasive treatment take place, the patient should be able to clearly articulate the goals of the intervention, the general side effects and risks associated with it, and his/her decision regarding compliance with the suggested plan. There is some evidence that information provided only by video is not sufficient education ([Newcomer, 2008](#)).

Practitioners must develop and implement an effective strategy and skills to educate patients, employers, insurance systems, policy makers, and the community as a whole. An education-based paradigm should always start with providing reassuring information to the patient and informed decision making. More in-depth education currently exists within a treatment regimen employing functional restoration, prevention, and cognitive behavioral techniques. Patient education and informed decision making should facilitate self-management of symptoms and prevention.

Evidence Statements Regarding Education / Informed Decision Making			
Some Evidence	Evidence Statement	Citation	Design
	Information provided only by video is not sufficient education.	<a href="#">(Newcomer, 2008)</a>	Prospective randomized controlled trial

Time Frames for Education / Informed Decision Making	
Time to Produce Effect	Varies with individual patient
Frequency	Should occur at every visit.

**6. INJECTIONS – THERAPEUTIC** When considering the use of injections in CRPS management, the treating physician must carefully consider the inherent risks and benefits. First, it is understood that these injections are seldom meant to be “curative” and when used for therapeutic purposes they are employed in conjunction with other treatment modalities for maximum benefit.

Second, education of the patient should include the proposed goals of the injections, expected gains, risks or complications, and alternative treatment.

Lastly, reassessment of the patient’s status in terms of functional improvement should be documented after each injection and/or series of injections. Any continued use of injections should be monitored using objective measures such as:

- Return to work or maintaining work status.
- Fewer restrictions at work or when performing activities of daily living (ADLs).
- Decrease in usage of medications related to the work injury.
- Measurable functional gains, such as increased range-of-motion or documented increase in strength.

Visual analog scales (VAS) provide important subjective data but cannot be used to measure function.

The physician must be aware of the possible placebo effect as well as the long-term effects of injections related to the patient’s physical and mental status. Strict adherence to contraindications, both absolute and relative, may prevent potential complications. Subjecting the patient to potential risks (i.e., needle trauma, infection, nerve injury, or systemic effects of local anesthetics and corticosteroids) must be considered before the patient consents to such procedures.

For post-MMI care, refer to Section J.8, Maintenance Management, Injection Therapy, in this guideline.

**a. Sympathetic Injections:**

Description: Sympathetic injections are generally accepted, well-established procedures. They include stellate ganglion blocks and lumbar sympathetic blocks. Unfortunately, there are no high quality randomized controlled trials in this area. It is recommended that all patients receiving therapeutic blocks participate in an appropriate exercise program that may include a functionally directed rehabilitation program. However, a recent Cochrane review did not find intravenous regional blockade with guanethidine effective in CRPS, and the procedure appears to be associated with the risk of significant adverse events ([N. E. W. O’Connell, B. M.; McAuley, J.; Marston, L.; Moseley, G. L., 2013](#)).

Indications: greater than 50% pain relief and demonstrated functional improvement from previous diagnostic or therapeutic blocks. Range-of-motion or increased strength are examples of objective gains that can be documented for most CRPS patients.

Special Considerations: Except for Bier blocks, fluoroscopic and/or CT guidance during procedures is recommended to document technique and needle placement; an experienced physician should perform the procedure. The



physician should participate in ongoing injection training workshops provided by organizations such as the Spine Intervention Society (SIS), formerly known as the International Spine Intervention Society. Physicians should obtain fluoroscopy training and must also have the appropriate training in radiation safety, usually overseen by a radiation safety officer.

**Complications:** Complications may include transient neurapraxia, nerve injury, inadvertent spinal injection, infection, venous or arterial vertebral puncture, laryngeal paralysis, respiratory arrest, vasovagal effects, as well as permanent neurologic damage.

**Contraindications:** Absolute contraindications of therapeutic injections include: (a) bacterial infection – systemic or localized to region of injection, (b) bleeding diatheses, (c) hematological conditions, and (d) possible pregnancy.

**Relative Contraindications:** Relative contraindications of these injections may include: (a) allergy to contrast or shellfish, (b) poorly controlled diabetes mellitus and/or hypertension.

Drugs affecting coagulation, such as aspirin, NSAIDs, and other anti-platelets or anti-coagulants require restriction from use. Decisions regarding the number of restricted days should be made in consultation with the prescribing physician and other knowledgeable experts.

**Treatment Parameters:** To be effective as a treatment modality, the patient should be making measurable progress in their rehabilitation program and should be achieving an increasing or sustained duration of relief between blocks. If appropriate outcomes are not achieved, changes in treatment should be undertaken.

Time Frames for Sympathetic Injections	
Time to Produce Effect	1 to 2 blocks. Demonstrated greater than 50% pain relief and objective/functional gains as noted under treatment parameters.
Frequency	Variable, depending upon duration of pain relief and functional gains. During the first 2 weeks of treatment, blocks may be provided every 3 to 5 days, based on patient response meeting above criteria. The blocks must be combined with active therapy. After the first 2 weeks, blocks may be given weekly with tapering for a maximum of 7 -10.
Optimum Duration	10 over a period of 6 months with documentation of progressive functional gain verified by therapist or increased work capability after each injection.
Maximum Duration	If sympathetic and functional benefits are documented with the blocks, refer to Section J, Maintenance Management, for information on further blocks.

- b. Peripheral Nerve Blocks:** These are diagnostic injections that may be used for specific nerve injury or entrapment syndromes. Not all peripheral nerve blocks require fluoroscopy. On occasion they are used for treatment in chronic pain or CRPS. Repeat injection for treatment should be based on functional changes. These injections are usually limited to 3 injections per site per year.

**c. Other Intravenous Medications and Regional Blocks:** Only low quality evidence is available regarding the use of local anesthetic blockade for treating complex regional pain syndrome ([N. E. W. O'Connell, B. M.; Gibson, W.; Carr, D. B.; Birklein, F.; Stanton, T. R., 2016](#)). There is some evidence that there is little advantage of IV regional block with guanethidine over saline blocks with respect to the resolution of tenderness in the affected hand, but the resolution of vasomotor instability may be delayed by guanethidine ([Livingstone, 2002](#)). It is possible that it assists with rehabilitative therapy.

In addition, regional blocks given by the Bier block method have the potential of aggravating CRPS due to the constriction of the extremity required for the procedure. Another inadequately powered study found no advantage from Bier blocks of lidocaine and methylprednisolone ([Taskaynatan, 2004](#)).

It is unlikely that either type of block provides a significant clinical advantage to the patient; therefore, they are **not recommended**. Intravenous blocks with guanethidine, ketanserin, beryllium phentolamin, reserpine, droperidol and atropine are also **not recommended** due to lack of effect in small studies ([N. E. W. O'Connell, B. M.; McAuley, J.; Marston, L.; Moseley, G. L., 2013](#); [R. S. Z. Perez, P. E.; Dijkstra, P. U.; Thomassen-Hilgersom, I. L.; Zuurmond, W. W.; Rosenbrand, K. C.; Geertzen, J. H.; Crps I. task force, 2010](#)).

In rare cases where repeat sympathetic blocks are contraindicated or ineffective, Bier blocks (usually alpha sympathetic blocking agent with lidocaine) may be useful when the patient has peripheral findings (CRPS II) and demonstrates functional gains. The number of blocks should not exceed those done for sympathetic blocks and active therapy must be done at the same time.

Evidence Statements Regarding Other Intravenous Medications and Regional Blocks			
Some Evidence	Evidence Statement	Citation	Design
	There is little advantage of IV regional block with guanethidine over saline blocks with respect to the resolution of tenderness in the affected hand, but the resolution of vasomotor instability may be delayed by guanethidine.	<a href="#">(Livingstone, 2002)</a>	Randomized clinical trial

**d. Continuous Brachial Plexus Infusions:** are **not recommended** due to possible complications of bleeding, infection, pneumothoracic, phrenic nerve paralysis, lack of literature documenting effectiveness and cost.

**e. Epidural Infusions:** These are **not recommended**. Literature on epidural clonidine treatment is not adequate to support their long term benefit ([R. L. Rauck, Eisenach, Jackson, Young, & Southern, 1993](#)). There is some evidence of a high rate of infection (33%), which can include meningitis ([R. L. Rauck et al., 1993](#)).

Evidence Statements Regarding Epidural Infusions			
Some Evidence	Evidence Statement	Citation	Design
	There is high rate of infection (33%), which can include meningitis.	( <a href="#">R. L. Rauck et al., 1993</a> )	Crossover randomized clinical trial

- f. **Ketamine:** is referenced in this guideline in Section G, Therapeutic Procedures, Non-Operative, CRPS-Specific Medications.

## **7. INTERDISCIPLINARY REHABILITATION PROGRAMS**

### **a. Overview:**

Interdisciplinary Rehabilitation Programs are the gold standard of treatment for individuals who have not responded to less intensive modes of treatment. There is good evidence that interdisciplinary programs that include screening for psychological issues, identification of fear-avoidance beliefs and treatment barriers, and establishment of individual functional and work goals will improve function and decrease disability ([Dobscha, 2009](#); [Lambeek, 2010](#)). There is good evidence that multidisciplinary rehabilitation (physical therapy and either psychological, social, or occupational therapy) shows small effects in reducing pain and improving disability compared to usual care and that multidisciplinary biopsychosocial rehabilitation is more effective than physical treatment for disability improvement after 12 months of treatment in patients with chronic low back pain. Patients with a significant psychosocial impact are most likely to benefit ([\[Cochrane\] Kamper, 2014](#)). The Agency for Healthcare Research and Quality (AHRQ) supports multidisciplinary rehabilitation as effective for chronic low back pain ([\[AHRQ\] R. D. Chou, R.; Friedly, J.; Skelly, A.; Hashimoto, R.; Weimer, M.; Fu, R.; Dana, T.; Kraegel, P.; Griffin, J.; Grusing, S.; Brodt, E., 2016](#)). These programs should assess the impact of pain and suffering on the patient's medical, physical, psychological, social, and/or vocational functioning.

The International Classification of Functioning, Disability and Health (ICF) model should be considered in patient program planning. The following factors should be addressed: body function and structures, activity expectations, participation barriers, and environmental and personal factors. In general, interdisciplinary programs evaluate and treat multiple and sometimes irreversible conditions, including but not limited to: painful musculoskeletal, neurological, and other chronic pain conditions and psychological issues; drug dependence, abuse, or addiction; high levels of stress and anxiety; failed surgery; and pre-existing or latent psychopathology. The number of professions involved on the team in a chronic pain program may vary due to the complexity of the needs of the person served. The Division recommends consideration of referral to an interdisciplinary program within 6 months post-injury in patients with delayed recovery, unless successful surgical interventions or other medical and/or psychological treatment complications intervene.

Chronic pain patients need to be treated as outpatients within a continuum of treatment intensity. Outpatient chronic pain programs are available with services provided by a coordinated interdisciplinary team within the same facility (formal) or as coordinated among practices by an authorized treating physician (informal). Formal programs are able to provide a coordinated, high-intensity level of

services and are recommended for most chronic pain patients who have received multiple therapies during acute management.

Patients with addiction problems, high-dose opioid use, or abuse of other drugs may require inpatient and/or outpatient chemical dependency treatment programs before or in conjunction with other interdisciplinary rehabilitation. Guidelines from the American Society of Addiction Medicine are available and may be consulted relating to the intensity of services required for different classes of patients in order to achieve successful treatment.

There is some evidence that a telephone-delivered collaborative care management intervention for primary care veteran patients produced clinically meaningful improvements in pain at 12-month follow-up compared with usual care by increasing non-opioid analgesic medications and without changing opioid usage for the management of chronic musculoskeletal pain. The management was directed by nurse case managers. Because the control group was usual care rather than an attention control, the non-specific effects of attention received in the intervention group could have contributed to the effectiveness of the intervention. If an attention control had been used as the control group, the effect size observed for improvement in pain in the intervention group may have been smaller. It is unknown how successful this would be with injured workers ([Kroenke, 2014](#)).

Informal interdisciplinary pain programs may be considered for patients who are currently employed, those who cannot attend all-day programs, those with language barriers, or those living in areas not offering formal programs. Before treatment has been initiated, the patient, physician, and insurer should agree on treatment approach, methods, and goals. Generally, the type of outpatient program needed will depend on the degree of impact the pain has had on the patient's medical, physical, psychological, social, and/or vocational functioning.

When referring a patient for formal outpatient interdisciplinary pain rehabilitation, an occupational rehabilitation program, or an opioid treatment program, the Division recommends the program meets the criteria of the Commission on Accreditation of Rehabilitation Facilities (CARF).

Inpatient pain rehabilitation programs are rarely needed but may be necessary for patients with any of the following conditions: (a) high risk for medical instability, (b) moderate-to-severe impairment of physical/functional status, (c) moderate-to-severe pain behaviors, (d) moderate impairment of cognitive and/or emotional status, (e) dependence on medications from which he/she needs to be withdrawn, and (f) the need for 24-hour supervised nursing. Whether formal or informal programs, they should be comprised of the following dimensions ([CARF, 2010-2011](#)):

- i. **Communication:** To ensure positive functional outcomes, communication between the patient, insurer, and all professionals involved must be coordinated and consistent. Any exchange of information must be provided to all parties, including the patient. Care decisions should be communicated to all parties and should include the family and/or support system.
- ii. **Documentation:** Thorough documentation by all professionals involved and/or discussions with the patient. It should be clear that functional goals are being actively pursued and measured on a regular basis to

determine their achievement or need for modification. It is advisable to have the patient undergo objective functional measures.

- iii. Risk assessments: The following should be incorporated into the overall assessment process, individual program planning, and discharge planning: aberrant medication related behavior, addiction, suicide, and other maladaptive behavior.
- iv. Treatment Modalities: Use of modalities may be necessary early in the process to facilitate compliance with and tolerance to therapeutic exercise, physical conditioning, and increasing functional activities. Active treatments should be emphasized over passive treatments. Active and self-monitored passive treatments should encourage self-coping skills and management of pain, which can be continued independently at home or at work. Treatments that can foster a sense of dependency by the patient on the caregiver should be avoided. Treatment length should be decided based upon observed functional improvement. For a complete list of active and passive therapies, refer to Section G.18, Therapy – Active, and Section G.19, Therapy – Passive. All treatment time frames may be extended based on the patient’s positive functional improvement.
- v. Therapeutic Exercise Programs: A therapeutic exercise program should be initiated at the start of any treatment rehabilitation. Such programs should emphasize education, independence, and the importance of an on-going exercise regimen. There is good evidence that exercise alone or as part of a multi-disciplinary program results in decreased disability for workers with non-acute low back pain ([Oesch, 2010](#)). There is not sufficient evidence to support the recommendation of any particular exercise regimen over another exercise regimen.
- vi. Return-to-Work: An authorized treating physician should continually evaluate the patients for their potential to return to work. For patients who are currently employed, efforts should be aimed at keeping them employed. Formal rehabilitation programs should provide assistance in creating work profiles. For more specific information regarding return to work, refer to Section G.17, Return-to-Work.
- vii. Patient Education: Patients with pain need to re-establish a healthy balance in lifestyle. All providers should educate patients on how to overcome barriers to resuming daily activity, including pain management, decreased energy levels, financial constraints, decreased physical ability, and change in family dynamics.
- viii. Psychosocial Evaluation and Treatment: Psychosocial evaluation should be initiated, if not previously done. Providers should have a thorough understanding of the patient’s personality profile, especially if dependency issues are involved. Psychosocial treatment may enhance the patient’s ability to participate in pain treatment rehabilitation, manage stress, and increase their problem-solving and self-management skills.
- ix. Family/Support System Services as appropriate: The following should be considered in the initial assessment and program planning for the individual: ability and willingness to participate in the plan, coping, expectations, educational needs, insight, interpersonal dynamics, learning style, problem solving, responsibilities, and cultural and financial

factors. Support would include counseling, education, assistive technology, and ongoing communication.

- x. Vocational Assistance: Vocational assistance can define future employment opportunities or assist patients in obtaining future employment. Refer to Section G.17, Return-to-Work, for detailed information.
- xi. Discharge Planning: Follow-up visits will be necessary to assure adherence to treatment plan. Programs should have community and/or patient support networks available to patients on discharge.
- xii. Interdisciplinary Teams: Interdisciplinary programs are characterized by a variety of disciplines that participate in the assessment, planning, and/or implementation of the treatment program. These programs are for patients with greater levels of perceived disability, dysfunction, deconditioning, and psychological involvement. Programs should have sufficient personnel to work with the individual in the following areas: behavioral, functional, medical, cognitive, communication, pain management, physical, psychological, social, spiritual, recreation and leisure, and vocational. Services should address impairments, activity limitations, participation restrictions, environmental needs, and personal preferences of the worker.

**b. Formal Interdisciplinary Rehabilitation Programs:**

- i. Interdisciplinary Pain Rehabilitation: An Interdisciplinary Pain Rehabilitation Program provides outcome-focused, coordinated, goal-oriented interdisciplinary team services to measure and improve the functioning of persons with pain and encourage their appropriate use of health care system and services. The program can benefit persons who have limitations that interfere with their physical, psychological, social, and/or vocational functioning. The program shares information about the scope of the services and the outcomes achieved with patients, authorized providers, and insurers.

The interdisciplinary team maintains consistent integration and communication to ensure that all interdisciplinary team members are aware of the plan of care for the patient, are exchanging information, and are implementing the plan of care. The team members make interdisciplinary team decisions with the patient and then ensure that decisions are communicated to the entire care team.

Teams that assist in the accomplishment of functional, physical, psychological, social, and vocational goals must include: a medical director, pain team physician(s) who should preferably be board certified in an appropriate specialty, and a pain team psychologist. The Medical Director of the pain program and each pain team physician should be board certified in pain management or be board certified in his/her specialty area and have one of the following: 1) completed a one-year fellowship in interdisciplinary pain medicine or palliative care recognized by a national board, 2) two years of experience in an interdisciplinary pain rehabilitation program, or 3) if less than 2 years of experience, participate in a mentorship program with an experienced pain team physician. The pain team psychologist should have 1) one year's full-time experience in an interdisciplinary pain program, or 2) if less than 2

years of experience, participate in a mentorship program with an experienced pain team psychologist. Professionals from other disciplines on the team may include but are not limited to: a biofeedback therapist, an occupational therapist, a physical therapist, a registered nurse (RN), a case manager, an exercise physiologist, a psychologist, a psychiatrist, and/or a nutritionist. A recent French interdisciplinary functional spine restoration program demonstrated increased return to work at 12 months ([Tavares Figueiredo, 2016](#)).

Time Frames for Interdisciplinary Pain Rehabilitation	
Time to Produce Effect	3 to 4 weeks.
Frequency	Full time programs – No less than 5 hours per day, 5 days per week; part-time programs – 4 hours per day, 2–3 days per week.
Optimum Duration	3 to 12 weeks at least 2–3 times a week. Follow-up visits weekly or every other week during the first 1 to 2 months after the initial program is completed.
Maximum Duration	4 months for full-time programs and up to 6 months for part-time programs. Periodic review and monitoring thereafter for 1 year, and additional follow-up based on the documented maintenance of functional gains.

- ii. Occupational Rehabilitation: This is a formal interdisciplinary program addressing a patient’s employability and return to work. It includes a progressive increase in the number of hours per day in which a patient completes work simulation tasks until the patient can tolerate a full work day. A full work day is case specific and is defined by the previous employment of the patient. Safe workplace practices and education of the employer and family and/or social support system regarding the person’s status should be included. This is accomplished by addressing the medical, psychological, behavioral, physical, functional, and vocational components of employability and return to work.

The following are best practice recommendations for an occupational rehabilitation program:

- A) Work assessments including a work-site evaluation when possible (Refer to Section G.17, Return-To-Work).
- B) Practice of component tasks with modifications as needed.
- C) Development of strength and endurance for work tasks.
- D) Education on safe work practices.
- E) Education of the employer regarding functional implications of the worker when possible.

- F) Involvement of family members and/or support system for the worker.
- G) Promotion of responsibility and self-management.
- H) Assessment of the worker in relationship to productivity, safety, and worker behaviors.
- I) Identification of transferable skills of the worker.
- J) Development of behaviors to improve the ability of the worker to return to work or benefit from other rehabilitation.
- K) Discharge includes functional/work status, functional abilities as related to available jobs in the community, and a progressive plan for return to work if needed ([CARF, 2016a](#)).

There is some evidence that an integrated care program, consisting of workplace interventions and graded activity teaching that pain need not limit activity, is effective in returning patients with chronic low back pain to work, even with minimal reported reduction of pain ([Lambeek, 2010](#)). The occupational medicine rehabilitation interdisciplinary team should, at a minimum, be comprised of a qualified medical director who is board certified with documented training in occupational rehabilitation, team physicians having experience in occupational rehabilitation, an occupational therapist, and a physical therapist. As appropriate, the team may also include any of the following: a chiropractor, an RN, a case manager, a psychologist, a vocational specialist, or a certified biofeedback therapist.

Time Frames for Occupational Rehabilitation	
Time to Produce Effect	2 weeks.
Frequency	2 to 5 visits per week, up to 8 hours per day.
Optimum Duration	2 to 4 weeks.
Maximum Duration	6 weeks. Participation in a program beyond 6 weeks must be documented with respect to need and the ability to facilitate positive symptomatic and functional gains.

iii. Opioid/Chemical Treatment Programs: Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline. Recent programs which incorporate both weaning from opioids and interdisciplinary therapy appear to demonstrate positive long-term results ([Huffman, 2017](#)).

**c. Informal Interdisciplinary Rehabilitation Program:**

A coordinated interdisciplinary pain rehabilitation program is one in which an



authorized treating physician coordinates all aspects of care. This type of program is similar to the formal programs in that it is goal-oriented and provides interdisciplinary rehabilitation services to manage the needs of the patient in the following areas: (a) functional, (b) medical, (c) physical, (d) psychological, (e) social, and (f) vocational.

This program is different from a formal program in that it involves lower frequency and intensity of services/treatment. Informal rehabilitation is geared toward those patients who do not need the intensity of service offered in a formal program or who cannot attend an all-day program due to employment, daycare, language, or other barriers.

Patients should be referred to professionals experienced in outpatient treatment of chronic pain. The Division recommends an authorized treating physician consult with physicians experienced in the treatment of chronic pain to develop the plan of care. Communication among care providers regarding clear objective goals and progress toward the goals is essential. Employers should be involved in return to work and work restrictions, and the family and/or social support system should be included in the treatment plan. Professionals from other disciplines likely to be involved include: a biofeedback therapist, an occupational therapist, a physical therapist, an RN, a psychologist, a case manager, an exercise physiologist, a psychiatrist, and/or a nutritionist.

Time Frames for Informal Interdisciplinary Rehabilitation Program	
Time to Produce Effect	3 to 4 weeks.
Frequency	Full-time programs – No less than 5 hours per day, 5 days per week; Part-time programs – 4 hours per day for 2–3 days per week.
Optimum Duration	3 to 12 weeks at least 2–3 times a week. Follow-up visits weekly or every other week during the first 1 to 2 months after the initial program is completed.
Maximum Duration	4 months for full-time programs and up to 6 months for part-time programs. Periodic review and monitoring thereafter for 1 year, and additional follow-up based upon the documented maintenance of functional gains.

Evidence Statements Regarding Interdisciplinary Rehabilitation Programs			
Good Evidence	Evidence Statement	Citation	Design
	Interdisciplinary programs that include screening for psychological issues, identification of fear-avoidance beliefs and treatment barriers, and establishment of individual functional and work goals will improve function and decrease disability.	<a href="#">(Dobscha, 2009)</a>	Cluster randomized trial
		<a href="#">(Lambeek, 2010)</a>	Randomized clinical trial
	Multidisciplinary rehabilitation (physical therapy and either psychological, social, or occupational therapy) shows small effects in reducing pain and improving disability compared to usual care, and multidisciplinary biopsychosocial rehabilitation is more effective than physical treatment for disability improvement after 12 months of treatment in patients with chronic low back pain. Patients with a significant psychosocial impact are most likely to benefit.	<a href="#">([Cochrane] Kamper, 2014)</a>	Meta-analyses of randomized clinical trials
	Exercise alone or as part of a multi-disciplinary program results in decreased disability for workers with non-acute low back pain.	<a href="#">(Oesch, 2010)</a>	Meta-analysis of randomized clinical trials

Evidence Statements Regarding Interdisciplinary Rehabilitation Programs			
Some Evidence	Evidence Statement	Citation	Design
	Telephone-delivered collaborative care management intervention for primary care veteran patients produced clinically meaningful improvements in pain at 12-month follow-up compared with usual care by increasing non-opioid analgesic medications and without changing opioid usage for the management of chronic musculoskeletal pain. The management was directed by nurse case managers. Because the control group was usual care rather than an attention control, the non-specific effects of attention received in the intervention group could have contributed to the effectiveness of the intervention. If an attention control had been used as the control group, the effect size observed for improvement in pain in the intervention group may have been smaller. It is unknown how successful this would be with injured workers.	<a href="#">(Kroenke, 2014)</a>	Single-blind randomized clinical trial
	An integrated care program, consisting of workplace interventions and graded activity teaching that pain need not limit activity, is effective in returning patients with chronic low back pain to work, even with minimal reported reduction of pain.	<a href="#">(Lambeek, 2010)</a>	Randomized clinical trial

**8. MEDICATIONS AND MEDICAL MANAGEMENT**

**a. General Chronic Pain Medication Management:**

There is no single formula for pharmacological treatment of patients with chronic nonmalignant pain. A thorough medication history, including use of alternative

and over-the-counter medications, should be performed at the time of the initial visit and updated periodically. The medication history may consist of evaluating patient refill records through pharmacies and the Physician Drug Monitoring Program (PDMP) to determine if the patient is receiving their prescribed regimen. Appropriate application of pharmacological agents depends on the patient's age, past history (including history of substance abuse), drug allergies, and the nature of all medical problems. It is incumbent upon the healthcare provider to thoroughly understand pharmacological principles when dealing with the different drug families, their respective side effects, drug interactions, and primary reason for each medication's usage. Patients should be aware that medications alone are unlikely to provide complete pain relief. In addition to pain relief, a primary goal of drug treatment is to improve the patient's function as measured behaviorally. Besides taking medications, continuing participation in exercise programs and using self-management techniques such as biofeedback, cognitive behavioral therapy, and other individualized physical and psychological practices are required elements for successful chronic pain management. Management must begin with establishing goals and expectations, including shared decision making about risks and benefits of medications.

Medication reconciliation is the process of comparing the medications that the patient is currently taking with those for which the patient has orders. This needs to include drug name, dosage, frequency, and route. The reconciliation can assist in avoiding medications errors such as omissions, duplications, dosing errors, or drug interactions. The results can also be used to assist discussion with the patient regarding prescribing or changing medications and the likelihood of side effects, drug interactions, and achieving expected goals. At a minimum, medication reconciliation should be performed for all patients upon the initial visit and whenever refilling or prescribing new medications.

Control of chronic non-malignant pain is expected to frequently involve the use of medication. Strategies for pharmacological control of pain cannot be precisely specified in advance. Rather, drug treatment requires close monitoring of the patient's response to therapy, flexibility on the part of the prescriber, and a willingness to change treatment when circumstances change. Many of the drugs discussed in the medication section were originally licensed for indications other than analgesia but are effective in the control of some types of chronic pain.

It is generally wise to begin management with lower cost non-opioid medications whose efficacy equals higher cost medications and medications with a greater safety profile. Decisions to progress to more expensive, non-generic, and/or riskier products are made based on the drug profile, patient feedback, and improvement in function ([Vargas-Schaffer, 2010](#)). The provider must carefully balance the untoward side effects of the different drugs with therapeutic benefits, as well as monitor for any drug interactions.

All medications should be given an appropriate trial in order to test for therapeutic effect. The length of an appropriate trial varies widely depending on the individual drug. Certain medications may take several months to determine the efficacy, while others require only a few doses. It is recommended that patients with chronic nonmalignant pain be maintained on drugs that have the least serious side effects. For example, patients need to be tried or continued on acetaminophen and/or low dose generic antidepressant medications whenever feasible, as part of their overall treatment for chronic pain. Patients with renal or hepatic disease may need increased dosing intervals with chronic acetaminophen use. Chronic use of NSAIDs is generally **not recommended** due to increased risk of cardiovascular events and GI bleeding.

Opioid analgesics and other drugs of potential abuse such as sedative hypnotics or benzodiazepines may be used in properly selected cases ([Gourlay, 2009](#)) for CRPS patients, with total elimination desirable whenever clinically feasible. It is strongly recommended that such pharmacological management be monitored or managed by an experienced pain medicine physician. Multimodal therapy is the preferred mode of treatment for chronic pain patients whether or not these drugs were used acutely or sub-acutely.

Pharmaceutical neuropathic pain studies are limited. Diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN) are the two most frequently studied noncancer neuropathic pain conditions in randomized clinical trials of drug treatment. Some studies enroll only DPN or PHN patients, while other studies may enroll both kinds of patients. There appear to be consistent differences between DPN and PHN with respect to placebo responses, with DPN showing greater placebo response than PHN. Thus, there is an increased likelihood of a “positive” trial result for clinical trials of drug treatment for PHN than for DPN ([M. S. B. Cepeda, J. A.; Gao, C. Y.; Wiegand, F.; Wada, D. R., 2012](#); [Dworkin, Malone, Panarites, Armstrong, & Pham, 2010](#)).

Although many studies focus on mean change in pain, this may not be the most reliable result. It does not necessarily allow for subgroups that may have improved significantly. Furthermore, the DPN and PHN studies do not represent the type of neurologic pain usually seen in workers’ compensation.

For these reasons, few pharmaceutical agents listed in this Guideline are supported by high levels of evidence, but the paucity of evidence statements should not be construed as meaning that medication is not to be encouraged in managing chronic pain patients.

### General Order for Trial of Neuropathic Pain Medications

Treating physician are encouraged to follow this sequence taking into consideration the patient’s individual tolerance for types of medications, their side effects, and their other medical conditions will guide pharmaceutical choices.

1. Tricyclic anti-depressants.
2. Gabapentin or pregabalin and/or serotonin norepinephrine reuptake inhibitors.
3. Other anticonvulsants as listed.
4. Opioids low dose including, tramadol, tapentadol.

It is advisable to begin with the lowest effective dose proven to be useful for neuropathic pain in the literature. If the patient is tolerating the medication and clinical benefit is appreciated, maximize the dose for that medication or add another second line medication with another mechanism of action. If a medication is not effective, taper off the medication and start another agent. Maintain goal dosing for up to 8 weeks before determining its effectiveness. Many patients will utilize several medications from different classes to achieve maximum benefit.

It is also useful to remember that there is some evidence that in the setting of uncomplicated low back pain lasting longer than 3 months, patients who were

willing to participate in a trial of capsules clearly labelled as placebo experienced short-term reductions in pain and disability after the principles of the placebo effect had been explained to them ([Carvalho, 2016](#)).

The preceding principles do not apply to chronic headache or trigeminal neuralgia patients. These patients should be referred to a physician specializing in the diagnosis and treatment of headache and facial pain (refer to the Division's Traumatic Brain Injury Medical Treatment Guideline).

For the clinician to interpret the following material, it should be noted that: (1) drug profiles listed are not complete; (2) dosing of drugs will depend upon the specific drug, especially for off-label use; and (3) not all drugs within each class are listed, and other drugs within the class may be appropriate for individual cases. Clinicians should refer to informational texts or consult a pharmacist before prescribing unfamiliar medications or when there is a concern for drug interactions.

Evidence Statements Regarding Medication Management			
Some Evidence	Evidence Statement	Citation	Design
	In the setting of uncomplicated low back pain lasting longer than 3 months, patients who were willing to participate in a trial of capsules clearly labelled as placebo experienced short-term reductions in pain and disability after the principles of the placebo effect had been explained to them.	<a href="#">(Carvalho, 2016)</a>	Randomized clinical trial

**b. CRPS Specific Medication Management:**

For CRPS management, a burst of oral steroids is usually prescribed initially followed by tricyclics. Bisphosphonates are used when osteotrophic changes are present. Neuropathic pain can be treated with a variety of medications; however, all have specific side effects and other interactions that clinicians must be mindful of. It is suggested that patients with significant peripheral neuropathic pain be trialed with a tricyclic medication initially, as low dose medication in this category frequently is tolerated and performs sufficiently to decrease pain 30 to 50% ([P. J. Wiffen, McQuay, Edwards, & Moore, 2005](#)). When these fail, side effects are not tolerated, or a patient has medical issues precluding the use of this class of drugs, other appropriate medications can be tried. Second-line drugs include the anti-convulsants gabapentin (Fanatrex, Gabarone, Gralise, Horizant, Neurontin) and pregabalin (Lyrica). Comparison studies of amitriptyline (Elavil, Endep, Vanatrip) and gabapentin or carbamazepine (Carbatrol, Epitol, Equetro, Tegretol) have shown no appreciable difference between the drugs; thus, there is good evidence that there is little clinical outcome difference between the medications, although gabapentin may be better tolerated ([Rintala, 2007](#); [Rowbotham, 2004](#); [Saarto, 2007](#)). Third line drugs are the SNRIs, which have demonstrated some effectiveness for treating neuropathic pain, and topical lidocaine ([Moulin, 2007](#); [O'Connor, 2009](#)). The SNRI duloxetine (Cymbalta) has not been shown to be

superior to the tricyclic amitriptyline ([Kaur, 2011](#)), and there is no reason to prefer duloxetine in patients who have not been treated with a tricyclic. However, it may be preferable when the patient requires concomitant treatment of CRPS and depression as tricyclics are not well tolerated at doses therapeutic for depression. Fourth line drugs are opioids and tramadol (Rybix, Ryzolt, Ultram). Other medications have few clinical trials to support them but may be helpful in some patients.

For the clinician to interpret the following material, it should be noted that: (1) drug profiles listed are not complete; (2) dosing of drugs will depend upon the specific drug, especially for off-label use; and (3) not all drugs within each class are listed, and other drugs within the class may be appropriate for individual cases. Clinicians should refer to informational texts or consult a pharmacist before prescribing unfamiliar medications or when there is a concern for drug interactions.

Evidence Statements Regarding CRPS Specific Medication Management			
Good Evidence	Evidence Statement	Citation	Design
	There is little clinical outcome difference between amitriptyline (Elavil, Endep, Vanatrip) and gabapentin or carbamazepine (Carbatrol, Eptol, Equetro, Tegretol), although gabapentin may be better tolerated.	( <a href="#">Rintala, 2007</a> )	Randomized crossover trial
		( <a href="#">Rowbotham, 2004</a> )	Randomized clinical trial
		( <a href="#">Saarto, 2007</a> )	Meta-analysis of randomized trials

The following drug classes are outlined for CRPS specific neuropathic pain:

**c. CRPS-Specific Medications:**

**i. Oral Steroids:**

Inflammation is thought to be one of the first physiological changes in CRPS; therefore, strong anti-inflammatories should provide some relief especially if provided early. There is good evidence to support oral steroid use early in the course of CRPS ([Christensen, 1982](#); [Harden, 2013](#); [Kalita, 2006](#)). The strongest study was performed on patients with CRPS of the shoulder and hand following a stroke. Forty milligrams of prednisone (Deltasone, Liquid Pred, Medicorten, Orasone, Prednicen-M, Prednicot, Sterapred, Sterapred DS) were given for 14 days and then tapered by 10 mg per week while physical therapy was provided ([Kalita, 2006](#)).

This early treatment may be trialed on patients who meet the clinical diagnostic criteria for CRPS and do not have contraindications to steroid use. Side effects in some patients include mood changes, fluid retention, hyperglycemia, gastric irritation and ulcers, aseptic necrosis, and others.

ii. Bisphosphonates: are potent inhibitors of bone resorption. There is good evidence that their use effectively decreases pain ([Varena, 2000](#)) and some evidence it increases joint motion in patients with CRPS ([Manicourt, 2004](#)). One study used alendronate (Fosamax) 40 mg orally for 8 weeks and another used IV clodronate 300 mg daily for 10 days. Several other studies that did not meet evidence criteria used different medications and dosages. It should not be used in those with severe renal dysfunction. Osteonecrosis of the jaw has been reported and there may be an association with atypical subtrochanter femoral fractures especially with long term use. The FDA recently approved Neridronate for use in the CRPS population. It may be used for qualified patients.

iii. Vitamin C: There is some evidence that Vitamin C 500mg to 2 grams taken for 50 days after a wrist fracture may help to prevent CRPS ([R. S. Z. Perez, P. E.; Dijkstra, P. U.; Thomassen-Hilgersom, I. L.; Zuurmond, W. W.; Rosenbrand, K. C.; Geertzen, J. H.; Crps I. task force, 2010; Zollinger, 2007](#)). It may be useful to prescribe Vitamin C to patients who historically have had or currently have CRPS if they suffer a fracture in order to prevent exacerbation of CRPS.

iv. Ketamine Hydrochloride:

Description: An N-methyl-D-aspartate (NMDA) receptor antagonist. Proponents of using NMDA receptor antagonists in CRPS suspect that prolonged and high intensity pain induces the NMDA receptors which trigger inflammation and central sensitization of pain leading to abnormal pain manifestations such as allodynia and hyperalgesia.

Indications: As of the time of this guideline writing, formulations of ketamine hydrochloride have been FDA approved for injection as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. There is some evidence that in CRPS I patients, low dose daily infusions of ketamine can provide pain relief compared to placebo. The relief, however, faded within a few weeks ([Sigtermans, 2009](#)). Studies have not shown any functional improvements in patients with CRPS treated with ketamine infusions ([Schwartzman, 2009; Sigtermans, 2009](#)). Because their potential harm, as described below, outweighs evidence of limited short-term benefit in patients with CRPS, NMDA receptor antagonists are not recommended. Less harmful therapies with longer term effects are available.

Contraindications: can cause significant elevations in blood pressure.

Side Effects: known to cause emergence reactions in anesthetic doses in 12% of patients. These reactions range from pleasant dream-like states to delirium accompanied by irrational behavior. Ketamine is reported to cause cognitive impairment and cystitis ([Sanacora, 2017](#)). Repeated prolonged injections have resulted in drug-induced liver damage that resolved when treatment was stopped ([Noppers, 2011](#)). Respiratory depression, apnea, and laryngospasm have occurred in anesthetic doses. Patients treated for CRPS with ketamine infusions up to 18% have had hallucinations ([Correll, 2004](#)). Ketamine is also an abused drug ([Harden, 2013](#)).

Drug interactions: When given with barbiturates or opioids, patients may have a prolonged recovery time.



Due to the potential harm and limited short-term benefit in patients with CRPS, ketamine NMDA receptor antagonists are **not recommended** since less harmful therapies are available ([Harden, 2013](#); [Persson, 2013](#)).

If ketamine is being considered for a CRPS patient who has been refractory to other treatments, there must be a complete discussion with the patient regarding lack of evidence for treatment, the possible side effects and the unknown long term side effects of repeat treatment.

- v. Calcitonin: has been described in two low quality studies and was not shown to benefit CRPS patients ([Gobelet, 1992](#); [Sahin, 2006](#)). It was thought to provide analgesic properties through release of b-endorphin and the inhibition of bone resorption. It is not approved by the FDA for use with CRPS. Some patients have GI side effects and hyperglycemia has been reported. Rare cases of neurological side effects have been reported. It is not recommended.

Evidence Statements Regarding CRPS-Specific Medications: Oral Steroids			
Good Evidence	Evidence Statement	Citation	Design
	There is good evidence to support oral steroid use early in the course of CRPS.	<a href="#">(Christensen, 1982)</a>	Randomized clinical trial
		<a href="#">(Kalita, 2006)</a>	Randomized clinical trial

Evidence Statements Regarding CRPS-Specific Medications: Bisphosphonates			
Good Evidence	Evidence Statement	Citation	Design
	Use of bisphosphonates effectively decreases pain.	<a href="#">(Varena, 2000)</a>	Randomized clinical trial
Some Evidence	Evidence Statement	Citation	Design
	Use of bisphosphonates increases joint motion in patients with CRPS.	<a href="#">(Manicourt, 2004)</a>	Randomized clinical trial

Evidence Statements Regarding CRPS-Specific Medications: Vitamin C			
Some Evidence	Evidence Statement	Citation	Design
	Vitamin C 500mg to 2 grams taken for 50 days after a wrist fracture may help to prevent CRPS.	( <a href="#">R. S. Z. Perez, P. E.;</a> <a href="#">Dijkstra, P. U.;</a> <a href="#">Thomassen-Hilgersom, I. L.;</a> <a href="#">Zuurmond, W. W.;</a> <a href="#">Rosenbrand, K. C.;</a> <a href="#">Geertzen, J. H.;</a> Crps I. task force, 2010)	Randomized clinical trial

Evidence Statements Regarding CRPS-Specific Medications: Ketamine Hydrochloride			
Some Evidence	Evidence Statement	Citation	Design
	In CRPS I patients, low dose daily infusions of ketamine can provide pain relief compared to placebo. The relief, however, faded within a few weeks.	( <a href="#">Sigtermans, 2009</a> )	Randomized clinical trial

Refer to the Division’s Chronic Pain Disorder Medical Treatment Guideline for a list of drug classes to address neuropathic pain, including evidence and time frames for alpha-acting agents, anticonvulsants, antidepressants, cannabinoid products, hypnotics and sedatives, NSAIDs, post-operative pain management, skeletal muscle relaxants, smoking cessation medications and treatment, topical drug delivery, and other agents.

**d. Opioids:** Opioids are the most powerful analgesics. Their use in acute pain and moderate-to-severe cancer pain is well accepted. Their use in chronic nonmalignant pain, however, is fraught with controversy and lack of scientific research. Deaths in the United States from opioids have escalated in the last 15 years. The CDC states the following in their 2016 guideline for prescribing opioids: Opioid pain medication use presents serious risk, including overdose and opioid use disorder. From 1999 to 2014, more than 165,000 persons died from overdose related to opioid pain medication in the United States. In the past decade, while the death rates for the top leading causes of death such as heart disease and cancer have decreased substantially, the death rate associated with opioid pain medication has increased markedly. Sales of opioid pain medication have increased in parallel with opioid-related overdose deaths. The Drug Abuse Warning Network estimated that >420,000 emergency department visits were related to the misuse or abuse of narcotic pain relievers in 2011, the most recent year for which data are available ([\[CDC Guideline\] Dowell, 2016](#)). Opioid poisoning has also been identified in work-related populations ([Fulton-Kehoe, 2013](#)).

**Effectiveness and Side Effects:** Opioids include some of the oldest and most effective drugs used in the control of severe pain. The discovery of opioid receptors and their endogenous peptide ligands has led to an understanding of effects at the binding sites of these naturally occurring substances. Most of their

analgesic effects have been attributed to their modification of activity in pain pathways within the central nervous system; however, it has become evident that they also are active in the peripheral nervous system. Activation of receptors on the peripheral terminals of primary afferent nerves can mediate anti-nociceptive effects, including inhibition of neuronal excitability and release of inflammatory peptides. Some of their undesirable effects on inhibiting GI motility are peripherally mediated by receptors in the bowel wall.

Most studies show that only around 50% of patients tolerate opioid side effects and receive an acceptable level of pain relief. Depending on the diagnosis and other agents available for treatment, the incremental benefit can be small ([Abdel Shaheed, 2016](#); [M. S. C. Cepeda, F.; Zea, C.; Valencia, L., 2007](#); [Landau, 2007](#); [Naliboff, 2011](#)).

There is strong evidence that in the setting of chronic nonspecific low back pain, the short and intermediate term reduction in pain intensity of opioids, compared with placebo, falls short of a clinically important level of effectiveness ([Abdel Shaheed, 2016](#)). There is an absence of evidence that opioids have any beneficial effects on function or reduction of disability in the setting of chronic nonspecific low back pain ([Abdel Shaheed, 2016](#)). AHRQ found that opioids are effective for treating chronic low back pain. However, the report noted no evidence regarding the long-term effectiveness or safety for chronic opioids ([\[AHRQ\] R. D. Chou, R.; Friedly, J.; Skelly, A.; Hashimoto, R.; Weimer, M.; Fu, R.; Dana, T.; Kraegel, P.; Griffin, J.; Grusing, S.; Brodt, E., 2016](#)).

There is good evidence that opioids are more efficient than placebo in reducing neuropathic pain by clinically significant amounts ([\[Cochrane\] McNicol, 2013](#)). There is a lack of evidence that opioids improve function and quality of life more effectively than placebo. There is good evidence that opioids produce significantly more adverse effects than placebo such as constipation, drowsiness, dizziness, nausea, and vomiting. There is a lack of evidence that they are superior to gabapentin or nortriptyline for neuropathic pain reduction ([\[Cochrane\] McNicol, 2013](#)).

Patients should have a thorough understanding of the need to pursue many other pain management techniques in addition to medication use in order to function with chronic pain. They should also be thoroughly aware of the side effects and how to manage them. There is strong evidence that adverse events such as constipation, dizziness, and drowsiness are more frequent with opioids than with placebo ([Abdel Shaheed, 2016](#)). Common side effects are drowsiness, constipation, nausea, and possible testosterone decrease with longer term use.

There is some evidence that in the setting of chronic low back pain with disc pathology, a high degree of anxiety or depressive symptomatology is associated with relatively less pain relief in spite of higher opioid dosage than when these symptoms are absent ([Wasan, 2015](#)). A study comparing Arkansas Medicaid and a national commercial insurance population found that the top 5% of opioid users accounted for 48-70% of total opioid use. Utilization was increased among those with mental health and substance use disorders and those with multiple pain conditions ([M. J. M. Edlund, B. C.; Fan, M. Y.; Braden, J. B.; Devries, A.; Sullivan, M. D., 2010](#)). Psychological issues should always be screened for and treated in chronic pain patients. Therefore, for the majority of chronic pain patients, chronic opioids are unlikely to provide meaningful increase in function in daily activities. However, a subpopulation of patients may benefit from chronic opioids when properly prescribed and all requirements from medical management are followed.

Hyperalgesia: Administration of opioid analgesics leads not only to analgesia, but may also lead to a paradoxical sensitization to noxious stimuli ([Liang, 2006](#)). Opioid induced hyperalgesia has been demonstrated in animals and humans using electrical or mechanical pain stimuli ([Grace, 2016](#); [Yi, 2015](#)). This increased sensitivity to mildly painful stimuli does not occur in all patients and appears to be less likely in those with cancer, clear inflammatory pathology, or clear neuropathic pain ([M. C. W. Lee, V.; Tracey, I., 2014](#)). When hyperalgesia is suspected, opioid tapering is appropriate.

Opioid Induced Constipation (OIC): Some level of constipation is likely ubiquitous among chronic opioid users. An observational study of chronic opioid users who also used some type of laxative at least 4 times per week noted that approximately 50% of the patients were dissatisfied and they continue to report stool symptoms. 71% used a combination of natural and dietary treatment, 64.3% used over-the-counter laxatives, and 30% used prescription laxatives ([LoCasale, 2015](#)). Other studies report similar percentages ([Coyne, 2016](#)). There are insufficient quality studies to recommend one specific type of laxative over others.

The easiest method for identifying constipation, which is also recommended by a consensus, multidisciplinary group, is the Bowel Function Index. It assesses the patient's impression over the last 7 days for ease of defecation, feeling of incomplete bowel evacuation, and personal judgment re-constipation ([Argoff, 2015](#)).

Stepwise treatment for OIC is recommended, and all patients on chronic opioids should receive information on treatment for constipation. Dietary changes increasing soluble fibers are less likely to decrease OIC and may cause further problems if GI motility is decreased. Stool softeners may be tried, but stimulant and osmotic laxatives are likely to be more successful. Osmotic laxatives include lactulose and polyethylene glycol. Stimulants include bisacodyl, sennosides, and sodium picosulfate, although there may be some concern regarding use of stimulants on a regular basis.

Opioid rotation or change in opioids may be helpful for some patients. It is possible that sustained release opioid products cause more constipation than short acting agents due to their prolonged effect on the bowel opioid receptors. Tapentadol is a  $\mu$ -opioid agonist and norepinephrine reuptake inhibitor. It is expected to cause less bowel impairment than oxycodone or other traditional opioids ([Dorn, 2014](#); [Poulsen, 2015](#)). Tapentadol may be the preferred opioid choice for patients with OIC.

Other prescription medications may be used if constipation cannot adequately be controlled with the previous measures. Naloxegol is a pegylated naloxone molecule that does not pass the blood brain barrier and thus can be given with opioid therapy. There is good evidence that it can alleviate OIC and that 12.5 mg starting dose has an acceptable side effect profile ([Chey, 2014](#)).

Methylnaltrexone does not cross the blood brain barrier and can be given subcutaneously or orally. It is specifically recommended for opioid induced constipation for patients with chronic non-cancer pain.

Misoprostol is a synthetic prostaglandin E1 agonist and has the side effect of diarrhea in some patients. It also has been tried for opioid induced constipation, although it is not FDA approved for this use ([Dorn, 2014](#)).

Lubiprostone is a prostaglandin E1 approved for use in opioid constipation.

Most patients will require some therapeutic control for their constipation. The stepwise treatment discussed should be followed initially. If that has failed and the patient continues to have recurrent problems with experiencing severe straining, hard or lumpy stool with incomplete evacuation, or infrequent stools for 25% of the time despite the more conservative measures, it may be appropriate to use a pharmaceutical agent.

Evidence Statements Regarding Effectiveness and Side Effects of Opioids			
Strong Evidence	Evidence Statement	Citation	Design
	In the setting of chronic nonspecific low back pain, the short and intermediate term reduction in pain intensity of opioids, compared with placebo, falls short of a clinically important level of effectiveness.	<a href="#">(Abdel Shaheed, 2016)</a>	Systematic review and meta-analysis
	Adverse events such as constipation, dizziness, and drowsiness are more frequent with opioids than with placebo.		
Good Evidence	Evidence Statement	Citation	Design
	Opioids are more efficient than placebo in reducing neuropathic pain by clinically significant amounts.	<a href="#">([Cochrane] McNicol, 2013)</a>	Systematic review and meta-analysis of randomized clinical trials
	Opioids produce significantly more adverse effects than placebo such as constipation, drowsiness, dizziness, nausea, and vomiting.		
	Naloxegol can alleviate opioid induced constipation and 12.5 mg starting dose has an acceptable side effect profile.	<a href="#">(Chey, 2014)</a>	Two identical and simultaneous multicenter randomized double-blind studies

Evidence Statements Regarding Effectiveness and Side Effects of Opioids			
Some Evidence	Evidence Statement	Citation	Design
	In the setting of chronic low back pain with disc pathology, a high degree of anxiety or depressive symptomatology is associated with relatively less pain relief in spite of higher opioid dosage than when these symptoms are absent.	<a href="#">(Wasan, 2015)</a>	Prospective cohort study

Physiologic Responses to Opioids: Physiologic responses to opioids are influenced by variations in genes which code for opiate receptors, cytochrome P450 enzymes, and catecholamine metabolism. Interactions between these gene products significantly affect opiate absorption, distribution, and excretion. Hydromorphone, oxycodone, and morphine are metabolized through the glucuronide system. Other opioids generally use the cytochrome P450 system ([Smith, 2009](#)). Allelic variants in the mu opiate receptor may cause increased analgesic responsiveness to lower drug doses in some patients. The genetic type can predict either lower or higher needs for opioids. For example, at least 10% of Caucasians lack the CYP450 2D6 enzyme that converts codeine to morphine ([Kosarac, 2009](#)). In some cases genetic testing for cytochrome P450 type may be helpful. When switching patients from codeine to other medications, assume the patient has little or no tolerance to opioids. Many gene-drug associations are poorly understood and of uncertain clinical significance. The treating physician needs to be aware of the fact that the patient's genetic makeup may influence both the therapeutic response to drugs and the occurrence of adverse effects.

Adverse Events: Physicians should be aware that deaths from unintentional drug overdoses exceed the number of deaths from motor vehicle accidents in the US. Most of these deaths are due to the use of opioids, usually in combination with other respiratory depressants such as alcohol or benzodiazepines. The risk for out of hospital deaths not involving suicide was also high ([Okie, 2010](#); [Ray, 2016](#)). The prevalence of drug abuse in the population of patients undergoing pain management varies according to region and other issues. One study indicated that ¼ of patients being monitored for chronic opioid use have abused drugs occasionally, and ½ of those have frequent episodes of drug abuse ([L. G. Manchikanti, J.; Boswell, M. V.; Fellows, B.; Manchukonda, R.; Pampati, V., 2007](#); [L. P. Manchikanti, V.; Damron, K. S.; Fellows, B.; Barnhill, R. C.; Beyer, C. D., 2001](#)). 80% of patients admitted to a large addiction program reported that their first use of opioids was from prescribed medication ([T. J. L. Cicero, M.; Todorov, A.; Inciardi, J. A.; Surratt, H. L., 2008](#)).

There is good evidence that in generally healthy patients with chronic musculoskeletal pain, treatment with long-acting opioids, compared to treatments with anticonvulsants or antidepressants, is associated with an increased risk of death of approximately 69%, most of which arises from non-overdose causes, principally cardiovascular in nature. The excess cardiovascular mortality principally occurs in the first 180 days from starting opioid treatment ([Ray, 2016](#)).

There is some evidence that compared to an opioid dose under 20 MME per day, a dose of 20-50 mg nearly doubles the risk of death, a dose of 50 to 100 mg may increase the risk more than fourfold, and a dose greater than 100 mg per day

may increase the risk as much as sevenfold. However, the absolute risk of fatal overdose in chronic pain patients is fairly low and may be as low as 0.04% ([Bohnert, 2011](#)). There is good evidence that prescription opioids in excess of 200 MME average daily doses are associated with a near tripling of the risk of opioid-related death, compared to average daily doses of 20 MME. Average daily doses of 100-200 mg and doses of 50-99 mg per day may be associated with a doubling of mortality risk, but these risk estimates need to be replicated with larger studies ([Gomes, 2011](#)).

Doses of opioids in excess of 120 MME have been observed to be associated with increased duration of disability, even when adjusted for injury severity in injured workers with acute low back pain ([Franklin, 2008](#); [B. S. V. Webster, S. K.; Gatchel, R. J., 2007](#)). Higher doses are more likely to be associated with hypogonadism, and the patient should be informed of this risk ([National Opioid Use Guideline Group, 2010](#)). Higher doses of opioids also appear to contribute to the euphoric effect. The CDC recommends limiting to 90 MME per day to avoid increasing risk of overdose ([\[CDC Guideline\] Dowell, 2016](#)).

In summary, there is strong evidence that any dose above 50 MME per day is associated with a higher risk of death and 100 mg or greater appears to significantly increase the risk.

Workers who eventually are diagnosed with opioid abuse after an injury are also more likely to have higher claims cost. A retrospective observational cohort study of workers' compensation and short-term disability cases found that those with at least one diagnosis of opioid abuse cost significantly more in days lost from work for both groups and in overall healthcare costs for the short-term disability groups. About 0.5% of eligible workers were diagnosed with opioid abuse ([Johnston, 2016](#)).

Evidence Statements Regarding Opioids and Adverse Events			
Good Evidence	Evidence Statement	Citation	Design
	In generally healthy patients with chronic musculoskeletal pain, treatment with long-acting opioids, compared to treatments with anticonvulsants or antidepressants, is associated with an increased risk of death of approximately 69%, most of which arises from non-overdose causes, principally cardiovascular in nature. The excess cardiovascular mortality principally occurs in the first 180 days from starting opioid treatment.	<a href="#">(Ray, 2016)</a>	Retrospective matched cohort study

Evidence Statements Regarding Opioids and Adverse Events			
Good Evidence, Continued	Prescription opioids in excess of 200 MME average daily doses are associated with a near tripling of the risk of opioid-related death, compared to average daily doses of 20 MME. Average daily doses of 100-200 mg and doses of 50-99 mg per day may be associated with a doubling of mortality risk, but these risk estimates need to be replicated with larger studies.	<a href="#">(Gomes, 2011)</a>	Nested case-control study with incidence density sampling
Some Evidence	Evidence Statement	Citation	Design
	Compared to an opioid dose under 20 MME per day, a dose of 20-50 mg nearly doubles the risk of death, a dose of 50 to 100 mg may increase the risk more than fourfold, and a dose greater than 100 mg per day may increase the risk as much as sevenfold. However, the absolute risk of fatal overdose of in chronic pain patients is fairly low, and may be as low as 0.04%.	<a href="#">(Bohnert, 2011)</a>	Case-cohort study
Summary of Evidence Regarding Opioids and Adverse Events			
Based on the studies with good evidence and some evidence listed above, there is strong evidence that any dose above 50 MME per day is associated with a higher risk of death and 100 mg or greater appears to significantly increase the risk.			

Dependence versus Addiction: The central nervous system actions of these drugs account for much of their analgesic effect and for many of their other actions, such as respiratory depression, drowsiness, mental clouding, reward effects, and habit formation. With respect to the latter, it is crucial to distinguish between two distinct phenomena: dependence and addiction.

- Dependence is a physiological tolerance and refers to a set of disturbances in body homeostasis that leads to withdrawal symptoms, which can be produced with abrupt discontinuation, rapid reduction, decreasing blood levels, and/or by administration of an antagonist.
- Addiction is a primary, chronic, neurobiological disease, with genetic, psychological, and environmental factors influencing its development and manifestations. It is a behavioral pattern of drug craving and seeking which leads to a preoccupation with drug procurement and an aberrant pattern of use. The drug use is frequently associated with negative



consequences.

Dependence is a physiological phenomenon, which is expected with the continued administration of opioids, and need not deter physicians from their appropriate use. Before increasing the opioid dose, the physician should review other possible causes for the decline in analgesic effect. Increasing the dose may not result in improved function or decreased pain. Remember that it is recommended for total morphine milligram equivalents (MME) per day to remain at 50 or below. Consideration should be given to possible new psychological stressors or an increase in the activity of the nociceptive pathways. Other possibilities include new pathology, low testosterone level that impedes delivery of opioids to the central nervous system, drug diversion, hyperalgesia, or abusive use of the medication.

Choice of Opioids: No long-term studies establish the efficacy of opioids over one year of use or superior performance by one type ([Agency for Healthcare Research and Quality, 2016](#)). There is no evidence that one long-acting opioid is more effective than another, or more effective than other types of medications, in improving function or pain ([Canadian Agency for Drugs and Technologies in Health, 2015](#); [R. C. Chou, S., 2008](#)). There is some evidence that long-acting oxycodone (Dazidox, Endocodone, ETH-oxycodone, Oxycontin, Oxyfast, OxyLR, Percolone, Roxicodone) and oxymorphone have equal analgesic effects and side effects, although the milligram dose of oxymorphone (Opana) is ½ that of oxycodone ([Hale, Dvergsten, & Gimbel, 2005](#); [Pedersen, 2014](#)). There is no evidence that long-acting opioids are superior to short-acting opioids for improving function or pain or causing less addiction ([R. C. Chou, S., 2008](#)). A number of studies have been done assessing relief of pain in cancer patients. A recent systematic review concludes that oxycodone does not result in better pain relief than other strong opioids including morphine and oxymorphone. It also found no difference between controlled release and immediate release oxycodone ([M. B. Schmidt-Hansen, M. I.; Hilgart, J., 2015](#)). There is some evidence that extended release hydrocodone has a small and clinically unimportant advantage over placebo for relief of chronic low back pain among patients who are able to tolerate the drug and that 40% of patients who begin taking the drug do not attain a dose which provides pain relief without unacceptable adverse effects. Hydrocodone ER does not appear to improve function in comparison with placebo ([Hale, Zimmerman, Eyal, & Malamut, 2015](#)). A Cochrane review of oxycodone in cancer pain also found no evidence in favor of the longer acting opioid ([\[Cochrane\] M. B. Schmidt-Hansen, M. I.; Arnold, S.; Bromham, N.; Hilgart, J. S., 2015](#)). There does not appear to be any significant difference in efficacy between once daily hydromorphone and sustained release oxycodone. Nausea and constipation are common for both medications between 26-32% ([Binsfeld, 2010](#)).

There is some evidence that in the setting of neuropathic pain, a combination of morphine plus nortriptyline produces better pain relief than either monotherapy alone, but morphine monotherapy is not superior to nortriptyline monotherapy, and it is possible that it is actually less effective than nortriptyline ([Gilron, 2015](#)).

Long-acting opioids should not be used for the treatment of acute, sub-acute, or post-operative pain, as this is likely to lead to drug dependence and difficulty tapering the medication. Additionally, there is a potential for respiratory depression to occur. The FDA requires that manufacturers develop Risk Evaluation and Mitigation Strategies (REMS) for most opioids. Physicians should carefully review the plans or educational materials provided under this program. Clinical considerations should determine the need for long-acting opioids given

their lack of evidence noted above.

Addiction and abuse potentials of commonly prescribed opioid drugs may be estimated in a variety of ways, and their relative ranking may depend on the measure which is used. One systematic study of prescribed opioids estimated rates of drug misuse were estimated at 21-29% and addiction at 8-12% ([Vowles, 2015](#)). There is good evidence that in the setting of new onset chronic non-cancer pain, there is a clinically important relationship between opioid prescription and subsequent opioid use disorder. Compared to no opioid use, short-term opioid use approximately triples the risk of opioid use disorder in the next 18 months. Use of opioids for over 90 days is associated with very pronounced increased risks of the subsequent development of an opioid use disorder, which may be as much as one hundredfold when doses greater than 120 MME are taken for more than 90 days. The absolute risk of these disorders is very uncertain but is likely to be greater than 6.1% for long duration treatment with a high opioid dose ([M. J. Edlund et al., 2014](#)).

Hydrocodone is the most commonly prescribed opioid in the general population and is one of the most commonly abused opioids in the population. However, the abuse rate per 1000 prescriptions is lower than the corresponding rates for extended release oxycodone, hydromorphone (Dilaudid, Palladone), and methadone. Extended release oxycodone appears to be the most commonly abused opioid, both in the general population and in the abuse rate per 1000 prescriptions ([T. J. D. Cicero, R. C.; Inciardi, J. A.; Woody, G. E.; Schnoll, S.; Munoz, A., 2007](#)). Tramadol, by contrast, appears to have a lower abuse rate than for other opioids ([T. J. I. Cicero, J. A.; Adams, E. H.; Geller, A.; Senay, E. C.; Woody, G. E.; Munoz, A., 2005](#)). Newer drug formulations such as oxymorphone, have been assumed to be relatively abuse-resistant, but their abuse potential is unknown and safety cannot be assumed in the absence of sound data ([\[CDC Guideline\] Dowell, 2016](#)).

Types of opioids are listed below:

- i. Buprenorphine: (various formulations) is prescribed as an intravenous injection, transdermal patch, buccal film, or sublingual tablet due to lack of bioavailability of oral agents. Depending upon the formulation, buprenorphine may be indicated for the treatment of pain or for the treatment of opioid dependence (addiction).

Buprenorphine for Opioid Dependence (addiction): FDA has approved a number of buccal films including those with naloxone and a sublingual tablet to treat opioid dependence (addiction).

Buprenorphine for Pain: The FDA has approved specific forms of an intravenous and subcutaneous injectable, transdermal patch, and a buprenorphine buccal film to treat pain. However, by law, the transdermal patch and the injectable forms cannot be used to treat opioid dependence (addiction), even by DATA-2000 waived physicians authorized to prescribe buprenorphine for addiction. Transdermal forms may cause significant skin reaction. Buprenorphine is **not recommended** for most chronic pain patients due to methods of administration, reports of euphoria in some patients, and lack of proof for improved efficacy in comparison with other opioids.

There is insufficient evidence to support or refute the suggestion that buprenorphine has any efficacy in any neuropathic pain condition

[\(\[Cochrane\] P. J. D. Wiffen, S.; Moore, R. A.; Stannard, C.; Aldington, D.; Cole, P.; Knaggs, R., 2015\).](#)

There is good evidence transdermal buprenorphine is noninferior to oral tramadol in the treatment of moderate to severe musculoskeletal pain arising from conditions like osteoarthritis and low back pain. The population of patients for whom it is more appropriate than tramadol is not established but would need to be determined on an individual patient basis if there are clear reasons not to use oral tramadol ([Leng, 2015](#)).

In a well done study, 63% of those on buccal buprenorphine achieved a 30% or more decrease in pain at 12 weeks compared to a 47% placebo response. Approximately 40% of the initial groups eligible for the study dropped out during the initial phase when all patients received the drug to test for incompatibility ([R. L. P. Rauck, J.; Xiang, Q.; Tzanis, E.; Finn, A., 2016](#)).

There is strong evidence that in patients being treated with opioid agonists for heroin addiction, methadone is more successful than buprenorphine at retaining patients in treatment. The rates of opiate use, as evidenced by positive urines, are equivalent between methadone and buprenorphine ([Mattick, 2014](#)). There is strong evidence that buprenorphine is superior to placebo with respect to retention in treatment, and good evidence that buprenorphine is superior to placebo with respect to positive urine testing for opiates ([Mattick, 2014](#)).

There is an adequate meta-analysis supporting good evidence that transdermal fentanyl and transdermal buprenorphine are similar with respect to analgesia and sleep quality, and they are similar with respect to some common adverse effects such as constipation and discontinuation due to lack of effect. However, buprenorphine probably causes significantly less nausea than fentanyl, and it probably carries a lower risk of treatment discontinuation due to adverse events. It is also likely that both transdermal medications cause less constipation than oral morphine ([Wolff, 2012](#)).

Overall, due to cost and lack of superiority, buprenorphine is not a front line opioid choice. However, it may be used in those with a history of addiction or at high risk for addiction who otherwise qualify for chronic opioid use. It is also appropriate to consider buprenorphine products for tapering strategies and those on high dose morphine 90 MME

- ii. Codeine with Acetaminophen: Some patients cannot genetically metabolize codeine and therefore have no response. Codeine is not generally used on a daily basis for chronic pain. Acetaminophen dose per day should be limited to 2 grams.
- iii. Fentanyl (Actiq, Duragesic, Fentora, Sublimaze): is **not recommended** for use with musculoskeletal chronic pain patients. It has been associated with a number of deaths and has high addiction potential. Fentanyl should never be used transbuccally in this population. If it is being considered for a very specific patient population, it requires support from a pain specialist.
- iv. Meperidine (Demerol): is **not recommended** for chronic pain. It and its active metabolite, normeperidine, present a serious risk of seizure and

hallucinations. It is not a preferred medication for acute pain as its analgesic effect is similar to codeine.

- v. Methadone: requires special precautions given its unpredictably long half-life and non-linear conversion from other opioids such as morphine. It may also cause cardiac arrhythmias due to QT prolongation and has been linked with a greater number of deaths due to its prolonged half-life ([R. F. Chou, G. J.; Fine, P. G.; Adler, J. A.; Ballantyne, J. C.; Davies, P.; Donovan, M. I.; Fishbain, D. A.; Foley, K. M.; Fudin, J.; Gilson, A. M.; Kelter, A.; Mauskop, A.; O'Connor, P. G.; Passik, S. D.; Pasternak, G. W.; Portenoy, R. K.; Rich, B. A.; Roberts, R. G.; Todd, K. H.; Miaskowski, C.; American Pain Society-American Academy of Pain Medicine Opioids Guidelines, Panel, 2009](#)). No conclusions can be made regarding differences in efficacy or safety between methadone and placebo, other opioids, or other treatments ([\[Cochrane\] Haroutiunian, 2012](#)). There is strong evidence that in patients being treated with opioid agonists for heroin addiction, methadone is more successful than buprenorphine at retaining patients in treatment. The rates of opiate use, as evidenced by positive urines, are equivalent between methadone and buprenorphine ([\[Mattick, 2014\]](#)). Methadone should only be prescribed by those with experience in managing this medication. Conversion from another opioid to methadone (or the other way around) can be very challenging, and dosing titration must be done very slowly (no more than every 7 days). Unlike many other opioids, it should not be used on an “as needed” basis, as decreased respiratory drive may occur before the full analgesic effect of methadone is appreciated. If methadone is being considered, genetic screening is appropriate. CYP2B6 polymorphism appears to metabolize methadone more slowly than the usual population and may cause more frequent deaths ([\[Bunten, 2011; Dennis, 2014\]](#)).
- vi. Morphine: may be used in the non-cancer pain population. A study in chronic low back pain suggested that individuals with a greater amount of endogenous opioids will have a lower pain relief response to morphine ([\[S. B. Bruehl, J. W.; Gupta, R.; Buvanendran, A.; Chont, M.; Schuster, E.; France, C. R., 2014\]](#)).
- vii. Oxycodone and Hydromorphone: There is no evidence that oxycodone (as oxycodone CR) is of value in treating people with painful diabetic neuropathy, postherpetic neuralgia, or other neuropathic conditions ([\[Cochrane\] Gaskell, 2014](#)). There was insufficient evidence to support or refute the suggestion that hydromorphone has any efficacy in any neuropathic pain condition ([\[Cochrane\] Stannard, 2016](#)). Oxycodone was not associated with greater pain relief in cancer patients when compared to morphine or oxymorphone ([\[M. B. Schmidt-Hansen, M. I.; Hilgart, J., 2015\]](#)).
- viii. Propoxyphene (Darvon, Davon-N, PP-Cap): has been withdrawn from the market due to cardiac effects including arrhythmias.
- ix. Tapentadol (Nucynta): is a mu opioid agonist which also inhibits serotonin and norepinephrine reuptake activity. It is currently available in an intermediate release formulation and may be available as extended release if FDA approved. Due to its dual activity, it can cause seizures or serotonin syndrome, particularly when taken with other SSRIs, SNRIs, tricyclics, or MAO inhibitors. It has not been tested in patients with severe renal or hepatic damage. It has similar opioid abuse issues as

other opioid medication; however, it is promoted as having fewer GI side effects, such as constipation. There is good evidence that extended release tapentadol is more effective than placebo and comparable to oxycodone ([Buynak, 2010](#)). In that study, the percent of patients who achieved 50% or greater pain relief was: placebo, 18.9%, tapentadol, 27.0%, and oxycodone, 23.3%. There is some evidence that tapentadol can reduce pain to a moderate degree in diabetic neuropathy, average difference 1.4/10 pain scale, with tolerable adverse effects ([S. E. Schwartz, M.; Shapiro, D. Y.; Okamoto, A.; Lange, R.; Haeussler, J.; Rauschkolb, C., 2011](#)). However, a high quality systematic review found inadequate evidence to support tapentadol to treat chronic pain ([\[Cochrane\] Santos, 2015](#)). Tapentadol is **not recommended** as a first line opioid for chronic, subacute, or acute pain due to the cost and lack of superiority over other analgesics. There is some evidence that tapentadol causes less constipation than oxycodone ([\[Cochrane\] Santos, 2015](#)). Therefore, it may be appropriate for patients who cannot tolerate other opioids due to GI side effects.

x. Tramadol (Rybix, Ryzolt, Ultram):

- A) Description: an opioid partial agonist that does not cause GI ulceration or exacerbate hypertension or congestive heart failure. It also inhibits the reuptake of norepinephrine and serotonin which may contribute to its pain relief mechanism. There are side effects similar to opioid side effects and may limit its use. They include nausea, sedation, and dry mouth.
- B) Indications: mild to moderate pain relief. As of the time of this guideline writing, formulations of tramadol has been FDA approved for management of moderate to moderately severe pain in adults. This drug has been shown to provide pain relief equivalent to that of commonly prescribed NSAIDs ([\[Cochrane\] Duhmke, 2006](#)). Unlike other pure opioids agonists, there is a ceiling dose to tramadol due to its serotonin activity (usually 300-400 mg per day). There is some evidence that it alleviates neuropathic pain following spinal cord injury ([Norrbrink, 2009](#)). There is inadequate evidence that extended-release tramadol/acetaminophen in a fixed-dose combination of 75mg/650 mg is more effective than placebo in relieving chronic low back pain; it is not more effective in improving function compared to placebo ([J. H. L. Lee, C. S., 2013](#)). There is some evidence that tramadol yields a short-term analgesic response of little clinical importance relative to placebo in post-herpetic neuralgia which has been symptomatic for approximately 6 months ([Boureau, 2003](#)). However, given the effectiveness of other drug classes for neuropathic pain, tramadol should not be considered a first line medication. It may be useful for patients who cannot tolerate tricyclic antidepressants or other medications.
- C) Contraindications: use cautiously in patients who have a history of seizures, who are taking medication that may lower the seizure threshold, or taking medications that impact serotonin reuptake and could increase the risk for serotonin syndrome, such as monoamine oxidase inhibitors (MAO) inhibitors, SSRIs, TCAs, and alcohol. Use with caution in patients taking other

potential QT prolonging agents. Not recommended in those with prior opioid addiction. Has been associated with deaths in those with an emotional disturbance or concurrent use of alcohol or other opioids. Significant renal and hepatic dysfunction requires dosage adjustment.

- D) Side Effects: may cause impaired alertness or nausea. This medication has physically addictive properties, and withdrawal may follow abrupt discontinuation.
- E) Drug Interactions: opioids, sedating medications, any drug that affects serotonin and/or norepinephrine (e.g., SNRIs, SSRIs, MAOs, and TCAs).
- F) Laboratory Monitoring: renal and hepatic function.

Health care professionals and their patients must be particularly conscientious regarding the potential dangers of combining over-the-counter acetaminophen with prescription medications that also contain acetaminophen. Opioid and acetaminophen combination medication are limited due to the acetaminophen component. Total acetaminophen dose per day should not exceed 4 grams per any 24-hour period and is preferably limited to 2 grams per day to avoid possible liver damage.

Indications: The use of opioids is well accepted in treating cancer pain, where nociceptive mechanisms are generally present due to ongoing tissue destruction, expected survival may be short, and symptomatic relief is emphasized more than functional outcomes. In chronic non-malignant pain, by contrast, tissue destruction has generally ceased, meaning that central and neuropathic mechanisms frequently overshadow nociceptive processes. Expected survival in chronic pain is relatively long, and return to a high-level of function is a major goal of treatment. Therefore, approaches to pain developed in the context of malignant pain may not be transferable to chronic non-malignant pain. Opioids are generally not the best choice of medication for controlling neuropathic pain. Tricyclics, SNRIs, and anticonvulsants should be tried before considering opioids for neuropathic pain.

In most cases, analgesic treatment should begin with acetaminophen, aspirin, and NSAIDs. While maximum efficacy is modest, they may reduce pain sufficiently to permit adequate function ([\[CDC Guideline\] Dowell, 2016](#)). When these drugs do not satisfactorily reduce pain, medications specific to the diagnosis should be used (e.g., neuropathic pain medications as outlined in Section G.10, Medications).

There is good evidence from a prospective cohort study that in the setting of common low back injuries, when baseline pain and injury severity are taken into account, a prescription for more than 7 days of opioids in the first 6 weeks is associated with an approximate doubling of disability one year after the injury ([Franklin, 2008](#)). Therefore, prescribing after 2 weeks in a non-surgical case requires a risk assessment ([\[ACOEM Guideline\] Hegmann, 2014b](#)). If prescribing beyond 4 weeks, a full opioid trial is suggested including toxicology screen. **Best practice suggests that whenever there is use of opioids for more than 7 days, providers should follow all recommendations for screening and follow-ups of chronic pain use.**

Consultation or referral to a pain specialist behavioral therapist should be

considered when the pain persists but the underlying tissue pathology is minimal or absent and correlation between the original injury and the severity of impairment is not clear. Consider consultation if suffering and pain behaviors are present and the patient manifests risk behaviors described below, or when standard treatment measures have not been successful or are not indicated.

A psychological consultation including psychological testing (with validity measures) is indicated for all chronic pain patients as these patients are at high risk for unnecessary procedures and treatment and prolonged recovery.

Many behaviors have been found related to prescription-drug abuse patients. None of these are predictive alone, and some can be seen in patients whose pain is not under reasonable control; however, the behaviors should be considered warning signs for higher risk of abuse or addiction by physicians prescribing chronic opioids ([L. R. F. Webster, P. G., 2010](#)). Refer to the High Risk Behavior subsection xv. below.

Recommendations for Opioid Use: When considering opioid use for moderate to moderately severe chronic pain, a trial of opioids must be accomplished as described below and the patient must have failed other chronic pain management regimes. Physicians should complete the education recommended by the FDA, risk evaluation and mitigation strategies (REMS) provided by drug manufacturing companies.

i. General Indications: There must be a clear understanding that opioids are to be used for a limited term as a trial (see trial indications below). The patient should have a thorough understanding of all of the expectations for opioid use. The level of pain relief is expected to be relatively small, 2 to 3 points on a VAS pain scale, although in some individual patients it may be higher. For patients with a high response to opioid use, care should be taken to assure that there is no abuse or diversion occurring. The physician and patient must agree upon defined functional goals as well as pain goals. If functional goals are not being met, the opioid trial should be reassessed. The full spectrum of side effects should be reviewed. The shared decision making agreement signed by the patient must clarify under what term the opioids will be tapered. Refer to section C.D, on the shared decision making agreement, below.

ii. Therapeutic Trial Indications: A therapeutic trial of opioids should not be employed unless the patient has begun multi-disciplinary pain management. The trial shall last one month. If there is no functional effect, the drug should be tapered.

Chronic use of opioids should not be prescribed until the following have been met:

- A) The failure of pain management alternatives by a motivated patient including active therapies, cognitive behavioral therapy, pain self-management techniques, and other appropriate medical techniques.
- B) Physical and psychological and/or psychiatric assessment including a full evaluation for alcohol or drug addiction, dependence or abuse, performed by two specialists including the authorized treating physician and a physician or psychologist

specialist with expertise in chronic pain. The patient should be stratified as to low, medium, or high risk for abuse based on behaviors and prior history of abuse. High risk patients are those with active substance abuse of any type or a history of opioid abuse. These patients should generally not be placed on chronic opioids. If it is deemed appropriate to do so, physician addiction specialists should be monitoring the care. Moderate risk factors include a history of non-opioid substance abuse disorder, prior trauma particularly sexual abuse, tobacco use, widespread pain, poor pain coping, depression, and dysfunctional cognitions about pain and analgesic medications (see below). Pre-existing respiratory or memory problems should also be considered. Patients with a past history of substance abuse or other psychosocial risk factors should be co-managed with a physician addiction specialist ([L. R. F. Webster, P. G., 2010](#)).

Risk Factors to Consider:

History of severe post-operative pain
Opioid analgesic tolerance (daily use for months)
Current mixed opioid agonist/antagonist treatment (e.g., buprenorphine, naltrexone)
Chronic pain (either related or unrelated to the surgical site)
Psychological comorbidities (e.g., depression, anxiety, catastrophizing)
History of substance use disorder
History of “all over body pain”
History of significant opioid sensitivities (e.g., nausea, sedation)
History of intrathecal pump use or nerve stimulator implanted for pain control

([Washington State Agency Medical Directors Group, 2015](#))

- C) Employment requirements are outlined. The patient’s employment requirements should also be discussed as well as the need to drive. It is generally not recommended to allow workers in safety sensitive positions to take opioids ([Hegmann, 2014a](#)). Opioid naïve patients or those changing doses are likely to have decreased driving ability. Some patients on chronic opioids may have nominal interference with driving ability; however, effects are specific to individuals ([Strand, 2013](#)). Providers may choose to order certified driver rehabilitation assessment.
- D) Urine drug screening for substances of abuse and substances currently prescribed. Clinicians should keep in mind that there



are an increasing number of deaths due to the toxic misuse of opioids with other medications and alcohol. Drug screening is a mandatory component of chronic opioid management. It is appropriate to screen for alcohol and marijuana use and have a contractual policy regarding both alcohol and marijuana use during chronic opioid management. Alcohol use in combination with opioids is likely to contribute to death.

- E) Review of the Physician Prescription Drug Monitoring Program.
- F) Informed, written, witnessed consent by the patient including the aspects noted above. Patients should also be counseled on safe storage and disposal of opioids.

The trial, with a short-acting agent, should document sustained improvement of pain control, at least a 30% reduction, and of functional status, including return-to-work and/or increase in activities of daily living ([J. T. B. Farrar, Jesse A.; Strom, Brian L., 2003](#); [J. T. P. Farrar, R. K.; Berlin, J. A.; Kinman, J. L.; Strom, B. L., 2000](#)). It is necessary to establish goals which are specific, measurable, achievable, and relevant prior to opioid trial or adjustment to measure changes in activity/function. Measurement of functional goals may include patient completed validated functional tools such as those recommended by the Division as part of Quality Performance and Outcomes Payments (QPOP, see Rule 18-8) and/or the Patient Specific Functional Scale can provide useful additional confirmation. Frequent follow-up at least every 2 to 4 weeks may be necessary to titrate dosage and assess clinical efficacy.

iii. On-Going, Long-Term Management after a successful trial should include:

- A) Prescriptions from a single practitioner;
- B) Ongoing review and documentation of pain relief, functional status, appropriate medication use, and side effects; full review at least every 3 months ([\[CDC Guideline\] Dowell, 2016](#));
- C) Ongoing effort to gain improvement of social and physical function as a result of pain relief;
- D) Review of the Physician Drug Monitoring Program (PDMP);
- E) Shared decision making agreement detailing the following:
  - Side effects anticipated from the medication;
  - Requirement to continue active therapy;
  - Need to achieve functional goals including return to work for most cases;
  - Reasons for termination of opioid management, referral to addiction treatment ([Rofls, 2010](#)), or for tapering

opioids (tapering is usually for use longer than 30 days). Examples to be included in the contract include, but are not limited to:

- Diversion of medication
- Lack of functional effect at higher doses
- Non-compliance with other drug use
- Drug screening showing use of drugs outside of the prescribed treatment or evidence of non-compliant use of prescribed medication
- Requests for prescriptions outside of the defined time frames
- Lack of adherence identified by pill count, excessive sedation, or lack of functional gains
- Excessive dose escalation with no decrease in use of short-term medications ([R. F. Chou, G. J.; Fine, P. G.; Adler, J. A.; Ballantyne, J. C.; Davies, P.; Donovan, M. I.; Fishbain, D. A.; Foley, K. M.; Fudin, J.; Gilson, A. M.; Kelter, A.; Mauskop, A.; O'Connor, P. G.; Passik, S. D.; Pasternak, G. W.; Portenoy, R. K.; Rich, B. A.; Roberts, R. G.; Todd, K. H.; Miaskowski, C.; American Pain Society-American Academy of Pain Medicine Opioids Guidelines, Panel, 2009; National Opioid Use Guideline Group, 2010](#))
- Apparent hyperalgesia
- Shows signs of substance use disorder (including but not limited to work or family problems related to opioid use, difficulty controlling use, craving)
- Experiences overdose or other serious adverse event
- Shows warning signs for overdose risk such as confusion, sedation, or slurred speech

Patient Agreements should be written at a 6<sup>th</sup> grade reading level to accommodate the majority of patients ([Roskos, 2007](#)).

- F) Use of drug screening initially, randomly at least once a year and as deemed appropriate by the prescribing physician ([R. F. Chou, G. J.; Fine, P. G.; Adler, J. A.; Ballantyne, J. C.; Davies, P.; Donovan, M. I.; Fishbain, D. A.; Foley, K. M.; Fudin, J.; Gilson, A. M.; Kelter, A.; Mauskop, A.; O'Connor, P. G.; Passik, S. D.; Pasternak, G. W.; Portenoy, R. K.; Rich, B. A.; Roberts, R. G.; Todd, K. H.; Miaskowski, C.; American Pain Society-American](#)

[Academy of Pain Medicine Opioids Guidelines, Panel, 2009](#); [National Opioid Use Guideline Group, 2010](#); [Rofls, 2010](#); [Washington State Agency Medical Directors Group, 2010](#)). Drug screening is suggested for any patients who have been receiving opioids for 8 to 90 days. A discussion regarding how screens positive for marijuana or alcohol will be handled should be included in the opioid contract. The concept of opioid misuse encompasses a variety of problems distinct from the development of addiction, such as nonmedical use, diversion, consultation with multiple prescribers, and unintentional overdose. In office only drug screening is insufficient as it does not identify metabolites of drugs prescribed.

Urine testing, when included as one part of a structured program for pain management, has been observed to reduce abuse behaviors in patients with a history of drug misuse ([Starrels, 2010](#); [Wiedemer, 2007](#)). Clinicians should keep in mind that there are an increasing number of deaths due to the toxic misuse of opioids with other medications and alcohol. Drug screening is a mandatory component of chronic opioid management. Clinicians should determine before drug screening how they will use knowledge of marijuana use. It is appropriate to screen for alcohol and marijuana use and have a contractual policy regarding both alcohol and marijuana use during chronic opioid management. Alcohol use in combination with opioids is likely to contribute to death. From a safety standpoint, it is more important to screen for alcohol use than marijuana use as alcohol is more likely to contribute to unintended overdose.

Physicians should recognize that occasionally patients may use non-prescribed substances because they have not obtained sufficient relief on the prescribed regime.

Although drug screens done for chronic pain management should not be routinely available to employers, as screens are part of the treatment record to which employers have limited access, patients should be aware that employers might obtain the records through attorneys or the insurer.

- G) Chronic use limited to 2 oral opioids.
- H) Transdermal medication use, other than buprenorphine, is generally not recommended.
- I) Use of acetaminophen-containing medications in patients with liver disease should be limited, including over-the-counter medications. Acetaminophen dose should not exceed 4 grams per day for short-term use or 2-3 grams/day for long-term use in healthy patients ([Washington State Agency Medical Directors Group, 2015](#)). A safer chronic dose may be 1800mg/day.
- J) Continuing review of overall therapy plan with regard to non-opioid means of pain control and functional status.
- K) Tapering of opioids may be necessary for many reasons including the development of hyperalgesia, decreased effects

from an opioid, lack of compliance with the opioid contract, or intolerance of side effects. Some patients appear to experience allodynia or hyperalgesia on chronic opioids. This premise is supported by a study of normal volunteers who received opioid infusions and demonstrated an increase in secondary hyperalgesia ([National Opioid Use Guideline Group, 2010](#)). Options for treating hyperalgesia include withdrawing the patient from opioids and reassessing their condition. In some cases, the patient will improve when off of the opioid. In other cases, another opioid may be substituted ([R. F. Chou, G. J.; Fine, P. G.; Adler, J. A.; Ballantyne, J. C.; Davies, P.; Donovan, M. I.; Fishbain, D. A.; Foley, K. M.; Fudin, J.; Gilson, A. M.; Kelter, A.; Mauskop, A.; O'Connor, P. G.; Passik, S. D.; Pasternak, G. W.; Portenoy, R. K.; Rich, B. A.; Roberts, R. G.; Todd, K. H.; Miaskowski, C.; American Pain Society-American Academy of Pain Medicine Opioids Guidelines, Panel, 2009; Fishbain, 2009; Quigley, 2004](#)).

Tapering may also be appropriate by patient choice, to accommodate “fit-for-duty” demands, prior to major surgery to assist with post-operative pain control, to alleviate the effects of chronic use including hypogonadism, medication side effects, or in the instance of a breach of drug agreement, overdose, other drug use aberrancies, or lack of functional benefit. It is also appropriate for any of the tapering criteria listed in section E above.

Generally tapering can be accomplished by decreasing the dose 10% per week. This will generally take 6 to 12 weeks and may need to be done one drug class at a time. Behavioral support is required during this service. Tapering may occur prior to MMI or in some cases during maintenance treatment.

- L) Medication assisted treatment with buprenorphine or methadone may be considered for opioid abuse disorder, in addition to behavioral therapy ([\[CDC Guideline\] Dowell, 2016](#)). Refer to abuse Section G.12. Opioid Addiction Treatment.
- M) Inpatient treatment may be required for addiction or opioid tapering in complex cases. Refer to Section G.9, Interdisciplinary Rehabilitation Programs, for detailed information on inpatient criteria.

iv. Relative Contraindications: Extreme caution should be used in prescribing controlled substances for workers with one or more “relative contraindications.” Consultation with a pain or addiction specialist may be useful in these cases.

- A) History of alcohol or other substance abuse, or a history of chronic, benzodiazepine use.
- B) Sleep apnea: If patient has symptoms of sleep apnea, diagnostic tests should be pursued prior to chronic opioid use.
- C) Off work for more than 6 months with minimal improvement in function from other active therapy.

- D) Severe personality disorder or other known severe psychiatric disease per psychiatrist or psychologist.
- E) Monitoring of behavior for signs of possible substance abuse indicating an increased risk for addiction and possible need for consultation with an addiction specialist.

v. High Risk Behavior: The following are high risk warning signs for possible drug abuse or addiction. Patients with these findings may need a consultation by a physician experienced in pain management and/or addiction. Behaviors in the left hand column are warning signs, not automatic grounds for dismissal, and should be followed up by a reevaluation with the provider. Repeated behaviors in the left hand column may be more indicative of addiction. Behaviors in the right hand column should be followed by a substance abuse evaluation.

Less suggestive for addiction but are increased in depressed patients	More suggestive of addiction and are more prevalent in patients with substance use disorder
<ul style="list-style-type: none"> <li>• Frequent requests for early refills; claiming lost or stolen prescriptions</li> <li>• Opioid(s) used more frequently, or at higher doses than prescribed</li> <li>• Using opioids to treat non-pain symptoms</li> <li>• Borrowing or hoarding opioids</li> <li>• Using alcohol or tobacco to relieve pain</li> <li>• Requesting more or specific opioids</li> <li>• Recurring emergency room visits for pain</li> <li>• Concerns expressed by family member(s)</li> <li>• Unexpected drug test results</li> <li>• Inconsistencies in the patient's history</li> </ul>	<ul style="list-style-type: none"> <li>• Buying opioids on the street; stealing or selling drugs</li> <li>• Multiple prescribers ("doctor shopping")</li> <li>• Trading sex for opioids</li> <li>• Using illicit drugs, + urine drug tests for illicit drugs</li> <li>• Forging prescriptions</li> <li>• Aggressive demands for opioids</li> <li>• Injecting oral/topical opioids</li> <li>• Signs of intoxication (ETOH odor, sedation, slurred speech, motor instability, etc.)</li> </ul>

---

Adapted from ([Washington State Agency Medical Directors Group, 2015](#))

Both daily and monthly users of nicotine were at least 3 times more likely to report non-medical use of opioid in the prior year ([Zale, 2015](#)). At least one study has demonstrated a prevalence of smokers and former smokers among those using opioids and at higher doses compared to the general population. It also appeared that smokers and former smokers used opioids more frequently and in higher doses than never smokers. Thus, tobacco use history may be a helpful prognosticator ([Plesner, 2016](#)).

In one study, four specific behaviors appeared to identify patients at risk for current substance abuse: increasing doses on their own, feeling intoxicated, early refills, and oversedating oneself. A positive test for cocaine also appeared to be related ([Fleming, 2008](#)).

One study found that half of patients receiving 90 days of continuous opioids remained on opioids several years later and that factors associated with continual use included daily opioid greater than 120 MME prior opioid exposure, and likely opioid misuse ([Martin, 2011](#)).

One study suggested that those scoring at higher risk on the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), also had greater reductions in sensory low back pain and a greater desire to take morphine. It is unclear how this should be viewed in practice ([S. B. Bruehl, J. W.; Passik, S. D.; Gupta, R.; Buvanendran, A.; Chont, M.; Schuster, E.; Orłowska, D.; France, C. R., 2015](#)).

- vi. Dosing and Time to Therapeutic Effect: Oral route is the preferred route of analgesic administration because it is the most convenient and cost-effective method of administration. Transbuccal administration should be avoided other than for buprenorphine. A daily dosage above 50 MME may be appropriate for certain patients. However, when the patient's dosage exceeds 50 MME per day and/or the patient is sedentary with minimal function, consideration should be given to lowering the dosage. Some patients may require dosages above 90 MME per day. However, if the patient reaches a dosage above 90 MME per day, it is appropriate to taper or refer to a pain or addiction specialist. The provider should also adhere to all requirements in this guideline and closely monitor the patient as this is considered a high risk dosage. In some cases buprenorphine may be a preferred medication for pain control in those patients. Consultation may be necessary.
- vii. Major Side Effects: There is great individual variation in susceptibility to opioid-induced side effects and clinicians should monitor for these potential side effects. Common initial side-effects include nausea, vomiting, drowsiness, unsteadiness, and confusion. Occasional side-effects include dry mouth, sweating, pruritus, hallucinations, and myoclonus. Rare side effects include respiratory depression and psychological dependence. Constipation and nausea/vomiting are common problems associated with long-term opioid administration and should be anticipated, treated prophylactically, and monitored constantly. Stool softeners, laxatives, and increased dietary fluid may be prescribed. Refer to Section G.10.g, Opioid Induced Constipation. Chronic sustained release opioid use is associated with decreased testosterone in males

and females and estradiol in pre-menopausal females. Patients should be asked about changes in libido, sexual function, and fatigue ([R. F. Chou, G. J.; Fine, P. G.; Adler, J. A.; Ballantyne, J. C.; Davies, P.; Donovan, M. I.; Fishbain, D. A.; Foley, K. M.; Fudin, J.; Gilson, A. M.; Kelter, A.; Mauskop, A.; O'Connor, P. G.; Passik, S. D.; Pasternak, G. W.; Portenoy, R. K.; Rich, B. A.; Roberts, R. G.; Todd, K. H.; Miaskowski, C.; American Pain Society-American Academy of Pain Medicine Opioids Guidelines, Panel, 2009; Rhodin, 2010](#)).

- viii. Naloxone: may be prescribed when any risk factors are present ([\[CDC Guideline\] Dowell, 2016](#)). The correct use of Naloxone should be discussed with the patient and family.
- ix. Benzodiazepines: should not be prescribed when opioids are used. Refer to Section G.10.f, Hypnotics and Sedatives, for more information.
- x. Sedation: driving and other tasks – Although some studies have shown that patients on chronic opioids do not function worse than patients not on medication, caution should be exerted, and patients should be counseled never to mix opioids with the use of alcohol or other sedating medication. When medication is increased or trials are begun, patients should not drive for at least 5 days ([R. F. Chou, G. J.; Fine, P. G.; Adler, J. A.; Ballantyne, J. C.; Davies, P.; Donovan, M. I.; Fishbain, D. A.; Foley, K. M.; Fudin, J.; Gilson, A. M.; Kelter, A.; Mauskop, A.; O'Connor, P. G.; Passik, S. D.; Pasternak, G. W.; Portenoy, R. K.; Rich, B. A.; Roberts, R. G.; Todd, K. H.; Miaskowski, C.; American Pain Society-American Academy of Pain Medicine Opioids Guidelines, Panel, 2009; National Opioid Use Guideline Group, 2010; Zacharoff, 2010](#)). Chronic untreated pain and disordered sleep can also impair driving abilities.
- xi. Drug Interactions: Patients receiving opioid agonists should not be given a mixed agonist-antagonist such as pentazocine (Talacen, Talwin) or butorphanol (Stadol) because doing so may precipitate a withdrawal syndrome and increase pain.
- All sedating medication, especially benzodiazepines, should be avoided or limited to very low doses. Over-the-counter medications such as antihistamines, diphenhydramine, and prescription medications such as hydroxyzine (Anx, Atarax, Atazine, Hypam, Rezine, Vistaril) should be avoided except when being used to manage withdrawal during tapering of opioids. Alcohol should not be used.
- xii. Recommended Laboratory Monitoring: Primary laboratory monitoring is recommended for acetaminophen/aspirin/NSAIDs combinations (renal and liver function, blood dyscrasia), although combination opioids are **not recommended** for long-term use. Morphine and other medication may require renal testing and other screening.
- xiii. Sleep Apnea Testing: Both obstructive and central sleep apnea are likely to be exaggerated by opioid use or may occur secondary to higher dose chronic opioid use and combination medication use, especially benzodiazepines and sedative hypnotics. Patients should be questioned about sleep disturbance and family members or sleeping partners questioned about loud snoring or gasping during sleep. If present, qualified sleep studies and sleep medicine consultation should be obtained. Portable sleep monitoring units are generally not acceptable

for diagnosing primary central sleep apnea. Type 3 portable units with 2 airflow samples and an O<sup>2</sup> saturation device may be useful for monitoring respiratory depression secondary to opioids, although there are no studies on this topic ([Mason, 2010](#)).

- xiv. Regular consultation of the Prescription Drug Monitoring Program (PDMP): Physicians should review their patients on the system whenever drug screens are done. This information should be used in combination with the drug screening results, functional status of the patient, and other laboratory findings to review the need for treatment and level of treatment appropriate for the patient. There is a separate billing code created by the DOWC to cover this service. Refer to Rule 18, Medical Fee Schedule.
- xv. Addiction: If addiction occurs, patients will require treatment. Refer to Section G.12, Opioid Addiction Treatment. After detoxification, they may need long-term treatment with naltrexone (Depade, ReVia), an antagonist which can be administered in a long-acting form or buprenorphine which requires specific education per the Drug Enforcement Agency (DEA).
- xvi. Potentiating Agents: There is some evidence that dextromethorphan does not potentiate the effect of morphine opioids and therefore is **not recommended** to be used with opioids ([Galer, 2005](#)).

Evidence Statements Regarding Choice of Opioids, Indications, and Recommendations for Use			
Strong Evidence	Evidence Statement	Citation	Design
	In patients being treated with opioid agonists for heroin addiction, methadone is more successful than buprenorphine at retaining patients in treatment. The rates of opiate use, as evidenced by positive urines, are equivalent between methadone and buprenorphine.	<a href="#">(Mattick, 2014)</a>	Meta-analysis of randomized clinical trials
	Buprenorphine is superior to placebo with respect to retention in treatment.		



Evidence Statements Regarding Choice of Opioids, Indications, and Recommendations for Use			
Good Evidence	Evidence Statement	Citation	Design
	Buprenorphine is superior to placebo with respect to positive urine testing for opiates.	<a href="#">(Mattick, 2014)</a>	Meta-analysis of randomized clinical trials
	In the setting of new onset chronic noncancer pain, there is a clinically important relationship between opioid prescription and subsequent opioid use disorder. Compared to no opioid use, short-term opioid use approximately triples the risk of opioid use disorder in the next 18 months. Use of opioids for over 90 days is associated with very pronounced increased risks of the subsequent development of an opioid use disorder, which may be as much as one hundredfold when doses greater than 120 MME are taken for more than 90 days. The absolute risk of these disorders is very uncertain but is likely to be greater than 6.1% for long duration treatment with a high opioid dose.	<a href="#">(M. J. Edlund et al., 2014)</a>	Retrospective cohort study using claims data from a large health care database
	Extended release tapentadol is more effective than placebo and comparable to oxycodone. The percent of patients who achieved 50% or greater pain relief was: placebo, 18.9%, tapentadol, 27.0%, and oxycodone, 23.3%.	<a href="#">(Buynak, 2010)</a>	Randomized clinical trial

Evidence Statements Regarding Choice of Opioids, Indications, and Recommendations for Use			
Good Evidence, Continued	Transdermal buprenorphine is noninferior to oral tramadol in the treatment of moderate to severe musculoskeletal pain arising from conditions like osteoarthritis and low back pain. The population of patients for whom it is more appropriate than tramadol is not established but would need to be determined on an individual patient basis if there are clear reasons not to use oral tramadol.	<a href="#">(Leng, 2015)</a>	Phase III noninferiority trial
	Transdermal fentanyl and transdermal buprenorphine are similar with respect to analgesia and sleep quality, and they are similar with respect to some common adverse effects such as constipation and discontinuation due to lack of effect. However, buprenorphine probably causes significantly less nausea than fentanyl, and it probably carries a lower risk of treatment discontinuation due to adverse events. It is also likely that both transdermal medications cause less constipation than oral morphine.	<a href="#">(Wolff, 2012)</a>	Network meta-analysis of randomized clinical trials
	In the setting of common low back injuries, when baseline pain and injury severity are taken into account, a prescription for more than seven days of opioids in the first 6 weeks is associated with an approximate doubling of disability one year after the injury.	<a href="#">(Franklin, 2008)</a>	Prospective cohort study

Evidence Statements Regarding Choice of Opioids, Indications, and Recommendations for Use			
Some Evidence	Evidence Statement	Citation	Design
	Long-acting oxycodone (Dazidox, Endocodone, ETH-oxydose, Oxycontin, Oxyfast, OxyIR, Percolone, Roxicodone) and oxymorphone have equal analgesic effects and side effects, although the milligram dose of oxymorphone (Opana) is ½ that of oxycodone.	<a href="#">(Hale et al., 2005)</a>	Randomized clinical trial
	Extended release hydrocodone has a small and clinically unimportant advantage over placebo for relief of chronic low back pain among patients who are able to tolerate the drug and that 40% of patients who begin taking the drug do not attain a dose which provides pain relief without unacceptable adverse effects. Hydrocodone ER does not appear to improve function in comparison with placebo.	<a href="#">(Hale et al., 2015)</a>	Randomized trial with a screening period of 7-14 days followed by an open-label titration period of up to 6 weeks followed by a double blind treatment period of up to 12 weeks
	In the setting of neuropathic pain, a combination of morphine plus nortriptyline produces better pain relief than either monotherapy alone, but morphine monotherapy is not superior to nortriptyline monotherapy, and it is possible that it is actually less effective than nortriptyline.	<a href="#">(Gilron, 2015)</a>	Crossover randomized trial
	Tapentadol can reduce pain to a moderate degree in diabetic neuropathy, average difference 1.4/10 pain scale, with tolerable adverse effects.	<a href="#">(S. E. Schwartz, M.; Shapiro, D. Y.; Okamoto, A.; Lange, R.; Haeussler, J.; Rauschkolb, C., 2011)</a>	Randomized clinical trial
	Tapentadol causes less constipation than oxycodone.	<a href="#">([Cochrane] Santos, 2015)</a>	Meta-analysis of randomized clinical trials

Evidence Statements Regarding Choice of Opioids, Indications, and Recommendations for Use			
Some Evidence, Continued	Dextromethorphan does not potentiate the effect of morphine opioids and therefore is <b>not recommended</b> to be used with opioids.	( <a href="#">Galer, 2005</a> )	Three randomized clinical trials
	Tramadol alleviates neuropathic pain following spinal cord injury.	( <a href="#">Norrbrink, 2009</a> )	Randomized clinical trial
	Tramadol yields a short-term analgesic response of little clinical importance relative to placebo in postherpetic neuralgia which has been symptomatic for approximately 6 months.	( <a href="#">Boureau, 2003</a> )	Randomized clinical trial

## 9. OPIOID ADDICTION TREATMENT

The DSM-V renames opioid addiction as substance use disorder (SUD) and classifies opioid use disorder according to categories defined as mild (2 – 3 features of stated criteria), moderate (4 – 5 features of stated criteria), or severe (6 – 7 features of stated criteria).

Definitions:

- Opioid physical dependence: opioid withdrawal symptoms (withdrawals) which occur as a result of abrupt discontinuation of an opioid in an individual who became habituated to the medication or through administration of an antagonist. Opioid physical dependency is not in and of itself consistent with the diagnosis of addiction/substance use disorder.
- Tolerance: a physiologic state caused by the regular use of an opioid in which increasing doses are needed to maintain the same affect. In patients with "analgesic tolerance," increased doses of the opioid may be needed to maintain pain relief.
- Opioid misuse: the utilization of opioid medications outside of the prescribing instructions for which it was originally prescribed. Misuse may be as innocuous as taking slightly more or less medications than prescribed to crushing or snorting an opioid.
- Opioid abuse: the use of any substance for a non-therapeutic purpose or the use of a medication for purposes other than those for which the agent is prescribed. Abuse includes intentional use for altering a state of consciousness. Abuse frequently affects the individual's ability to fulfill normal societal roles, resulting in difficulty with employment, or legal, or interpersonal problems.
- Pseudo-addiction: addiction-like behaviors consistent with overutilization of medications outside of the prescribing provider's instructions and recommendations for the express purpose of improved pain management. This occurs when a patient believes there is insufficient pain relief. Once pain is

adequately managed with a higher dose of medications than initially prescribed or with improved therapy, the behaviors consistent with addiction are discontinued.

- Addiction: a primary chronic neurobiological disease influenced by genetic, psychosocial, and/or environmental factors. It is characterized by impaired control over drug use, compulsive drug use, and continued drug use despite harm and because of craving.

Substance use disorder/addiction in the workers' compensation system can be encountered in three ways. First, the individual has an active substance use disorder at the time of injury. The party responsible for treatment of the substance use disorder may be outside of the workers' compensation system. However, if there is no other paying party and the treatment is necessary in order to recover from the current workers' compensation injury, treatment may be covered by the workers' compensation payor. The second possibility is that a patient with a substance use disorder, who is currently in recovery at the time of the workers' compensation injury, relapses as a result of the medications which are prescribed by the treating provider. This patient may become re-addicted and will manifest substance use disorder characteristics and symptoms consistent with the diagnosis. The third possibility is an individual with no history of substance use disorder who is injured as a result of an occupational accident. This particular individual becomes "addicted" to the medications as a result of the medications being prescribed. This is most likely to occur with the use of opioids but could possibly occur with use of other medications such as benzodiazepines or specific muscle relaxants such as carisoprodol.

If the treating provider is suspicious of a patient exhibiting opioid misuse, abuse, or addiction, the patient should preferably be evaluated by a specialist in the field of addiction medicine. It would be the responsibility of the specialist to identify medication misuse, abuse, addiction, or pseudo-addiction and to determine what additional treatment, if any, needs to be implemented.

During the initial injury evaluation, an authorized treating provider should obtain an addiction history as part of a complete history and physical. If it is determined at the time of the initial evaluation by the treating provider that there is the pre-existing condition of active SUD or history of opioid addiction/SUD, then it is prudent to consider an evaluation with an addiction medicine physician prior to issuing opioid treatments if possible. The addiction medicine specialist will be able to counsel the patient accordingly, determine medication needs, and determine the appropriate follow-up to hopefully avoid aggravation or relapse of substance abuse disorders which will complicate the recovery process. Many patients exhibit opioid misuse, opioid abuse, and pseudo-addictive behaviors. These issues can be managed once the problem is identified and a discussion is carried out with the patient regarding these abnormal behaviors.

Once the diagnosis of SUD is confirmed, an addiction medicine specialist familiar with addiction treatment should assist in co-managing the patient's care and the problematic drug prescriptions. This co-management technique is critical for the injured worker with a SUD diagnosis during the initial injury phase, recovery, and stabilization phase until he/she has reached MMI. If it is determined during the active treatment and recovery phase that there is no longer a need for opioids, then the addiction medicine specialist will be in charge of the transition from use of opioids to safe taper/discontinuation of the opioids while monitoring for relapse of addiction.

Co-management is equally important for managing the chronic pain patient that has a concomitant opioid addiction/SUD with a legitimate need for analgesic medications. The addiction medicine specialist in all likelihood will monitor the patient more closely

including judicious prescribing, PDMP reviews, urine drug testing, drug counts, and clarifying functional improvement as a result of the medications prescribed and frequent follow-ups which may initially seem excessive.

All abstinence addiction treatment begins with a discontinuation of the addicting substance; this is referred to as the detox phase of the treatment and can be performed in a number of ways. However, detoxification alone is not considered adequate addiction treatment. Detoxification is simply a method of discontinuing the medications in an effort to stabilize the patient prior to more extensive treatment.

#### Phase 1:

The methods of detoxification can include 1) abrupt discontinuation – **not recommended** due to high rate of relapse due to craving and withdrawal symptoms, 2) slow but progressive taper – 10% of total dosage per week as an outpatient treatment, 3) conversion to a different medication opioid (buprenorphine/naloxone) to enable a more stable and comfortable taper occasionally done as an outpatient but commonly done as part of a more comprehensive treatment program, and 4) rapid detox under anesthesia – **not recommended** due to relatively high incidence of complications and high expense. The methodology chosen for phase 1 detoxification is left up to the specialist and is simply the initial phase of stabilization prior to considering the need for a phase 2 of addiction treatment program.

#### Phase 2:

Once a patient is safely through the detoxification phase and the condition is stabilized regardless of the method chosen, then successful addiction treatment begins generally utilizing a number of techniques to prevent the return to active substance use and addiction. This phase of treatment generally involves teaching the patient to develop control over the compulsions, psychosocial factors, and associated mental health issues which are critical to maintain abstinence. This phase of treatment is generally managed in a 30 – 90 day non-hospital residential treatment program. The treatment prescribed in a residential treatment program generally includes individual and group therapy with certified addiction counselors and psychologists. Phase 2 of treatment may or may not be combined with opioid substitution therapy with medications such as buprenorphine/naloxone (partial agonist of the opioid receptor), methadone, or naltrexone. Injectable depot naltrexone may be used.

Buprenorphine/naloxone therapy utilizes a sublingual partial opioid receptor agonist which binds to the opioid receptor, reducing craving and resulting in analgesia when necessary. Due to its high affinity to the opioid receptor, it blocks the effect of non-approved additional opioid use. The buprenorphine is administered either sublingually or, when FDA approved, as a subcutaneous implant. Naloxone was added to the sublingual drug formulation to discourage using this medication intravenously. With intravenous administration of buprenorphine/naloxone, the naloxone becomes absorbed neutralizing the effects of opioids. Buprenorphine/naloxone can be an excellent option in patients requiring analgesic medications with a prior history of opioid addiction because buprenorphine results in less sedation and euphoria than the other standard schedule II opioid medications. Prescribing Suboxone film (buprenorphine/naloxone) for addiction purposes can only be done by a physician and requires special training and certification. Once special training is completed, an application is filed with the DEA to obtain a special DEA license referred to as an X-DEA number. This X-DEA number needs to accompany all prescription for Suboxone when delivered to the pharmacy and identifies the prescription is being issued specifically for the treatment of addiction/SUD.

Methadone may be an option if the patient is admitted to a federally licensed methadone

treatment facility where a daily dose of medication is administered and the patient continues to utilize therapeutic treatments/cognitive behavioral therapies as noted above. There is strong evidence that in patients being treated with opioid agonists for heroin addiction, methadone is more successful than buprenorphine at retaining patients in treatment. The rates of opiate use, as evidenced by positive urines, are equivalent between methadone and buprenorphine ([\[Cochrane\] Mattick, 2014](#)). The methodology and rationale for methadone treatment is to saturate the opioid receptors with methadone (a slow onset and prolonged duration opioid), reducing the opioid craving. The majority of the opioid receptors are bound by the methadone leaving very few unbound opioid receptors available in the event additional opioids are utilized in an attempt to achieve the euphoric effect. When the patient is stabilized on a methadone dose determined by the federally licensed methadone clinic and their associated physicians, the patient's drug-seeking, craving, legal issues, and attempts to utilize non-approved medications is reduced. Patients will frequently return to more productive lives free of the compulsions, cravings, and legal issues and are usually able to maintain jobs and improve family dynamics.

Other medications which may be useful and can be utilized during the phase 2 and 3 treatment include opioid receptor antagonists such as naltrexone (ReVia, Vivitrol) which produces no euphoria. The purpose of naltrexone therapy is to add an additional layer of protection and treatment for the patients by allowing them to receive a daily oral dose of naltrexone (ReVia) or a monthly injection of naltrexone (Vivitrol). Administration of naltrexone will bind with very high affinity to the opioid receptor resulting in the opioid receptors being non-responsive to other opioid utilization thereby preventing any euphoric response or reinforcement with unsanctioned opioid use. This treatment method can be problematic in an individual receiving intramuscular naltrexone therapy especially if that individual requires surgery and post-operative pain management because the analgesics needed for post-operative pain management will be significantly less effective because of the prolonged opioid antagonist properties of the naltrexone.

In Summary:

Medication assisted treatment for patients addicted to opioids is the treatment recommended by most experts. A Canadian evidence-based guideline recommends long-term treatment with buprenorphine/naloxone, or methadone for some patients, based on the high relapse rate without medication assistance ([Dunlap, 2016](#)). The likelihood of relapse in the workers' compensation population for individuals who have become addicted through prescription drug use is unknown. Buprenorphine implants are likely equally effective as sublingual buprenorphine for preventing illicit opioid use ([Rosenthal, 2016](#)). Implants are significantly more costly. Naltrexone treatment, an opioid agonist, has also been used to maintain abstinence. It can be provided in monthly injections or orally 3 times per week ([Schuckit, 2016](#)). Choice of these medications should be made by the addiction specialist.

Phase 3:

Aftercare begins after discharge from the non-hospital residential treatment program and is designed for long-term management of addiction. This phase is potentially the time when relapse is most likely to occur if the patient has not developed significant skills necessary to deal with the compulsions, cravings, and associated psychosocial factors contributing to SUD. Long-term strategies include 1) intense outpatient programs (IOP), 2) group therapy/meetings such as Narcotics Anonymous, and 3) residential communities (RC) which are groups of patients living together in a community for up to 6 months for the express purpose of maintaining abstinence from their drug of choice but at the same time transitioning and learning how to live in the general community. Residential communities are extremely useful to give patients an opportunity to be reintroduced to

employment and psychosocial interactions with family and friends while maintaining contact with the community supporting their addiction recovery. In addition, phase 3 medication treatment may include utilization of opioid substitution therapy (buprenorphine/naloxone) or opioid receptor antagonist therapy as noted above.

It must be noted that relapse is common despite the utilization of intense cognitive behavioral therapy, addiction treatment strategies, and long-term phase 3 treatment and medication. Risk monitoring should be continued, including checking for behavioral aberrancies, checking the PDMP, and drug testing,. Additional treatment or readmission for repeat treatment is not uncommon.

Evidence Statements Regarding Opioid Addiction Treatment			
Strong Evidence	Evidence Statement	Citation	Design
	In patients being treated with opioid agonists for heroin addiction, methadone is more successful than buprenorphine at retaining patients in treatment. The rates of opiate use, as evidenced by positive urines, are equivalent between methadone and buprenorphine.	<a href="#">([Cochrane] Mattick, 2014)</a>	Meta-analysis of randomized clinical trials

**10. OPIOID/CHEMICAL TREATMENT PROGRAMS**

Chemical dependency for workers’ compensation issues will usually be related to opioids, anxiolytics, or hypnotics as prescribed for the original workers’ compensation injury. Chemical dependency should be treated with specific programs providing medical and psychological assessment, treatment planning, and individual as well as group counseling and education. Established functional goals which are measurable, achievable, and time specific are required ([CARF, 2016b](#)).

Inpatient or outpatient programs may be used, depending upon the level of intensity of services required. Formal inpatient treatment programs are appropriate for patients who have more intense (e.g., use extraordinarily excessive doses of prescription drugs to which they have developed tolerance) or multiple drug abuse issues (e.g., benzodiazepines and/or alcohol) and those with complex medical conditions or psychiatric issues related to drug misuse. A medical physician with appropriate training and preferably board certified in addiction medicine should provide the initial evaluation and oversee the program. Full primary assessment should include behavioral health assessment; medical history; physical examination; mental status; current level of functioning; employment history; legal history; history of abuse, violence, and risk taking behavior; education level; use of alcohol, tobacco and other drugs; and social support system. The initial medical exam should include appropriate laboratory testing such as liver function, screening for sexual diseases, etc.

Addiction specialists, alcohol and drug counselors, psychologists, psychiatrists, and other trained health care providers as needed, are involved in the program. Peer and group support is an integral part of the program and families are encouraged to attend. Peer support specialists should receive competency based training. A designated individual is assigned to each worker to assist in coordinating care. There should be good



communication between the program and other external services, external health care providers, Al-Anon, Alcoholics Anonymous (AA), and pain medicine providers. Drug screening should be performed as appropriate for the individual, at least weekly during the initial detoxification and intensive treatment phases. At least 8 random drug screens per year should be completed for those on medication assisted treatment and drug diversion control methods should be in place ([CARF, 2016b](#)).

Clear withdrawal procedures are delineated for voluntary, against medical advice, and involuntary withdrawal. Withdrawal programs must have a clear treatment plan and include description of symptoms of medical and emotional distress, significant signs of opioid withdrawal, and actions taken. All programs should have clear direction on how to deal with violence in order to assure safety for all participants. Transition and discharge should be carefully planned with full communication to outside resources ([CARF, 2016b](#)). Duration of inpatient programs are usually 4 weeks while outpatient programs may take 12 weeks.

Drug detoxification may be performed on an outpatient or inpatient basis. Detoxification is unlikely to succeed in isolation when not followed by prolonged chemical dependency treatment. Isolated detoxification is usually doomed to failure with very high recidivism rates.

Both ultra-rapid and rapid-detoxification are **not recommended** due to possible respiratory depression and death and the lack of evidence for long range treatment success. Refer to Section G.12, Opioid Addiction Treatment, for more specific details on treatment plans.

Tapering opioids on an outpatient basis requires a highly motivated patient and diligent treatment team and may be accomplished by decreasing the current dose 10% per day or per week. Tapering programs under the supervision of physicians with pain expertise may proceed more aggressively. Tapering should be accompanied by addiction counseling. Failing a trial of tapering, a patient should be sent to a formal addiction program. When the dose has reached 1/3 of the original dose, the taper should proceed at half or less of the initial rate. Doses should be held or possibly increased if severe withdrawal symptoms, pain, or reduced treatment failure otherwise occurs. This method is tedious, time consuming, and more likely to fail than more rapid and formalized treatment programs.

Time Frames for Opioid / Chemical Treatment Programs	
Time to Produce Effect	3 to 4 weeks
Frequency	Full time programs - no less than 5 hours/day, 5 days/week; part time programs - 4 hours/day for 2-3 days per week.
Optimum Duration	2 to 12 weeks at least 2-3 times a week. With follow-up visits weekly or every other week during the first 1 to 2 months after the initial program is completed.
Maximum Duration	4 months for full time programs and up to 6 months for part-time programs. Periodic review and monitoring thereafter for 1 year, additional follow-up based upon the documented maintenance of functional gains.

**11. ORTHOTICS/PROSTHETICS/EQUIPMENT** Devices and adaptive equipment are rarely necessary for CRPS patients as motion is to be encouraged. Specific devices may be useful in rare cases to aid in return to work duties.

**12. PERSONALITY/PSYCHOLOGICAL/PSYCHOSOCIAL/PSYCHIATRIC INTERVENTION**

Psychosocial treatment is a well-established therapeutic and diagnostic intervention with selected use in acute pain problems and more widespread use in sub-acute and chronic pain populations. Psychosocial treatment is recommended as an important component in the total management of a patient with chronic pain and should be implemented as soon as the problem is identified.

Refer the Division's Chronic Pain Disorder Medical Treatment Guideline for indications, evidence, and time frames.

**13. RESTRICTION OF ACTIVITIES** Continuation of normal daily activities is the recommendation for most patients since immobility will negatively affect rehabilitation. Prolonged immobility results in a wide range of deleterious effects, such as a reduction in aerobic capacity and conditioning, loss of muscle strength and flexibility, increased segmental stiffness, promotion of bone demineralization, impaired disc nutrition, and the facilitation of the illness role.

Some level of immobility may occasionally be appropriate which could include splinting/casting or as part of a structured schedule that includes energy conservation or intentional rest breaks between activities. While these interventions may occasionally have been ordered in the acute phase, the provider should be aware of their impact on the patient's ability to adequately comply with and successfully complete rehabilitation. Activity should be increased based on the improvement of core strengthening.

Patients should be educated regarding the detrimental effects of immobility versus the efficacious use of limited rest periods. Adequate rest allows the patient to comply with active treatment and benefit from the rehabilitation program. In addition, complete work cessation should be avoided, if possible, since it often further aggravates the pain presentation and promotes disability. Modified return to work is almost always more efficacious and rarely contraindicated in the vast majority of injured workers.

**14. RETURN-TO-WORK** Return-to-work and/or work-related activities whenever possible is one of the major components in treatment and rehabilitation. Return-to-work is a subject that should be addressed by each workers' compensation provider at the first meeting with the injured employee and updated at each additional visit. A return-to-work format should be part of a company's health plan, knowing that return to work can decrease anxiety, reduce the possibility of depression, and reconnect the worker with society.

A prolonged time off work is likely to lead to chronic disability. In complex cases, experienced nurse case managers may be required to assist in return to work. Other services, including psychological evaluation and/or treatment, jobsite analysis, and vocational assistance, may be employed.

Refer the Division's Chronic Pain Disorder Medical Treatment Guideline for considerations and recommendations.

**15. THERAPY- ACTIVE** The following active therapies are widely used and accepted methods of care for a variety of work-related injuries. Active therapy is based on the philosophy that therapeutic exercise and/or activity can alleviate discomfort and are beneficial for restoring flexibility, strength, endurance, function, and range-of-motion. All active therapy plans should be made directly with patients in the interest of achieving

long-term individualized goals.

Active therapy requires an internal effort by the individual to complete a specific exercise or task. This form of therapy requires supervision from a therapist or medical provider such as verbal, visual, and/or tactile instruction(s). Active therapy is intended to promote independence and self-reliance in managing the physical pain as well as to improve functional status in regard to the specific diagnosis, general conditioning, and well-being. At times, a provider may help stabilize the patient or guide the movement pattern but the energy required to complete the task is predominately executed by the patient. Therapy in this section should not be merely a repeat of previous therapy but should focus specifically on the individual goals and abilities of the patient with CRPS.

The goal of active therapy is to teach the patient exercises that they can perform regularly on their own. Patients should be instructed to continue active therapies at home as an extension of the treatment process in order to maintain improvement levels. Follow-up visits to reinforce and monitor progress and proper technique are recommended. Home exercise can include exercise with or without mechanical assistance or resistance and functional activities with assistive devices.

On occasion, specific diagnoses and post-surgical conditions may warrant durations of treatment beyond those listed as "maximum." Factors such as exacerbation of symptoms, re-injury, interrupted continuity of care, need for post-operative therapy, and co-morbidities may also extend durations of care. Specific goals with objectively measured functional improvement during treatment must be cited to justify extended durations of care. It is recommended that, if no functional gain is observed after the number of treatments under "time to produce effect" has been completed, then alternative treatment interventions, further diagnostic studies, or further consultations should be pursued.

**Pain Neuroscience Education (PNE)**: PNE is an educational strategy used by physical therapists and other practitioners that focuses on teaching people in pain more about the neurobiological and neurophysiological processes involved in their pain experience, versus a focus on anatomical and pathoanatomical education. PNE helps patients develop an understanding of various pain processes including central sensitization, peripheral sensitization, inhibition, facilitation, the brain's processing of threat appraisal, and various biological systems involved in a pain experience. This reconceptualization of pain via PNE is then combined with various behavioral strategies including aerobic exercise, pacing, graded exposure, graded activity, and goal setting. PNE is likely to positively influence pain ratings, disability, fear-avoidance behaviors, pain catastrophization, limitations in movement, pain knowledge, and healthcare utilization. PNE is recommended with active therapy for chronic pain patients ([Louw, 2016](#)).

Evidence Statements Regarding Patient Education			
Good Evidence	Evidence Statement	Citation	Design
	Pain neuroscience education combined with a physical intervention is more effective in reducing pain, improving disability, and reducing healthcare utilization compared with either usual care, exercise, other education or another control group for the treatment of patients with chronic musculoskeletal pain.	( <a href="#">Louw, 2016</a> )	Narrative systematic review of randomized clinical trials
Some Evidence	Evidence Statement	Citation	Design
	A cognitive intervention consisting of 2 consultations lasting 1 hour each with a physical medicine specialist and a physical therapist covering coping strategies and patient education on motion produces short-term reductions in sub-acute back disability.	( <a href="#">Storheim, 2003</a> )	Randomized clinical trial
	In the setting of non-specific chronic low back pain, patient-centered cognitive functional therapy from physical therapists produced superior outcomes for pain reduction and functional improvement compared with traditional manual therapy and exercise at post-intervention and at 12-month follow-up.	( <a href="#">Vibe Fersum, 2013</a> )	Single-blind randomized clinical trial

Since CRPS and SMP patients frequently have additional myofascial pain generators, other active therapies not listed may be used in treatment. Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for therapies and timeframe parameters not listed.

The following active therapies are listed in alphabetical order:

- a. **Activities of Daily Living (ADL):** instruction, active-assisted training, and/or adaptation of activities or equipment to improve a person's capacity in normal daily activities such as self-care, work re-integration training, homemaking, and driving.

Time Frames for Activities of Daily Living	
Time to Produce Effect	4 to 5 treatments.
Frequency	1 to 5 times per week.
Optimum Duration	4 to 6 weeks.
Maximum Duration	6 weeks.

**b. Aquatic Therapy:** is a well-accepted treatment which consists of the therapeutic use of aquatic immersion for therapeutic exercise to promote strengthening, core stabilization, endurance, range-of-motion, flexibility, body mechanics, and pain management. Aquatic therapy is the implementation of active therapeutic procedures (individual or group) in a swimming or therapeutic pool heated to 88 to 92°F. The pool should be large enough to allow full extremity range-of-motion and fully erect posture. Aquatic vests, belts, and other devices can be used to provide stability, balance, buoyancy, and resistance. The water provides a buoyancy force that lessens the amount of force of gravity applied to the body. The decreased gravity effect allows the patient to have a mechanical advantage and more likely have a successful trial of therapeutic exercise. In addition, the compression of the water against the affected extremity and ability to move easier with decreased gravity allow for resulting muscular compression against vessels improving lymphatic drainage resulting in decreased edema. Aquatic therapy may also provide an additional stimulus to assist with desensitization.

There is good evidence that aquatic exercise and land-based exercise show comparable outcomes for function and mobility among people with symptomatic osteoarthritis of the knee or hip ([Batterham, 2011](#)).

Indications: The therapy may be indicated for individuals who:

- Cannot tolerate active land-based or full-weight bearing therapeutic procedures;
- Require increased support in the presence of proprioceptive deficit;
- Are at risk of compression fracture due to decreased bone density;
- Have symptoms that are exacerbated in a dry environment;
- Have a higher probability of meeting active therapeutic goals than in a dry environment.

After the supervised aquatics program has been established, either a self-directed aquatic program or a transition to a self-directed dry environment exercise program is recommended.

Evidence Statements Regarding Aquatic Therapy			
Good Evidence	Evidence Statement	Citation	Design
	Aquatic exercise and land-based exercise show comparable outcomes for function and mobility among people with symptomatic osteoarthritis of the knee or hip.	( <a href="#">Batterham, 2011</a> )	Systematic Review and meta-analysis of randomized clinical trials

Time Frames for Aquatic Therapy	
Time to Produce Effect	4 to 5 treatments.
Frequency	3 to 5 times per week.
Optimum Duration	4 to 6 weeks.
Maximum Duration	6 weeks.

- c. Functional Activities:** are well-established interventions which involve the use of therapeutic activity to enhance mobility, body mechanics, employability, coordination, and sensory motor integration.

Time Frames for Functional Activities	
Time to Produce Effect	4 to 5 treatments.
Frequency	1 to 5 times per week.
Optimum Duration	4 to 6 weeks.
Maximum Duration	8 weeks.

- d. Gait Training:** indications include the need to promote normal gait pattern with assistive devices and/or to reduce risk of fall or loss of balance. This may include instruction in safety and proper use of assistive devices and gait instruction on uneven surfaces and steps (with or without railings).

Time Frames for Gait Training	
Time to Produce Effect	1 to 6 sessions.
Frequency	1 to 3 times per week.
Optimum Duration	2 weeks. Could be needed intermittently as

Time Frames for Gait Training	
	changes in functional status occur.
Maximum Duration	1 month.

- e. Mirror Therapy - Graded Motor Imagery:** is a several week program that is accomplished through patient participation. It usually begins with limb laterality recognition, imagined motion, and mirror movements. Each phase gradually increases the number of repetitions. Therapy visits are once a week in the last phases, and the treatment is performed at home at least 30 minutes per day. There is some evidence that mirror box therapy 30 minutes per day for 4 weeks is likely to reduce pain in CRPS ([Cacchio, 2009](#); [Smart, 2016](#)). Therapy usually lasts 4-6 weeks for training and oversight. Most of the program is accomplished through patient participation at home. Time to produce effect is not known.

Evidence Statements Regarding Mirror Therapy - Graded Motor Imagery			
Some Evidence	Evidence Statement	Citation	Design
	Mirror box therapy 30 minutes per day for 4 weeks is likely to reduce pain in CRPS.	<a href="#">(Cacchio, 2009)</a>	Randomized clinical trial
		<a href="#">(Smart, 2016)</a>	Systematic Review and Meta-Analysis

Time Frames for Mirror Therapy – Graded Motor Imagery	
Training period	4 to 8 lessons.
Optimum Duration	4-6 weeks with 2 follow-up visits.

- f. Neuromuscular Re-education:** is a generally accepted treatment. It is the skilled application of exercise with manual, mechanical, or electrical facilitation to enhance strength; movement patterns, neuromuscular response, proprioception, kinesthetic sense, coordination; education of movement, balance, and posture.

There is some evidence that there is a modest benefit from adding a back school to other treatments such as NSAIDs, massage, transcutaneous electrical nerve stimulation (TENS), and other physical therapy modalities ([\[Cochrane\] Heymans, 2004](#)). However, a recent adequate quality systematic review found no evidence for the effectiveness of back schools for treating chronic low back pain ([S. H. Straube, M.; Schroder, H.; Arendacka, B.; Fan, X.; Moore, R. A.; Friede, T., 2016](#)).

Indications include the need to promote neuromuscular responses through carefully timed proprioceptive stimuli, to elicit and improve motor activity in patterns similar to normal neurologically developed sequences, and to improve neuromotor response with independent control.

Evidence Statements Regarding Neuromuscular Re-education			
Some Evidence	Evidence Statement	Citation	Design
	There is a modest benefit from adding a back school to other treatments such as NSAIDs, massage, transcutaneous electrical nerve stimulation (TENS), and other physical therapy modalities.	( <a href="#">Cochrane</a> ) Heymans, 2004)	Systematic review of randomized clinical trials

Time Frames for Neuromuscular Re-education	
Time to Produce Effect	2 to 6 treatments.
Frequency	1 to 3 times per week.
Optimum Duration	4 to 8 weeks.
Maximum Duration	8 weeks.

- g. Stress Loading:** is a generally accepted reflex and sensory integration technique involving the application of a compressive load and a carry load. It is carried out in a consistent, progressive manner and integrated as part of a home program. Use of this technique may increase symptoms initially, but symptoms generally subside with program consistency. This technique is used for upper as well as lower extremities

Time Frames for Stress Loading	
Time to Produce Effect	3 weeks.
Frequency	2 to 3 times per week.
Optimum Duration	4 to 6 weeks and concurrent with an active daily home exercise program
Maximum Duration	6 to 10 weeks.

- h. Therapeutic Exercise:** with or without mechanical assistance or resistance, may include isoinertial, isotonic, isometric, and isokinetic types of exercises. May also include alternative/complementary exercise movement therapy (with oversight of a physician or appropriate healthcare professional).

Indications include the need for cardiovascular fitness, reduced edema, improved muscle strength; improved connective tissue strength and integrity, increased bone density, promotion of circulation to enhance soft tissue healing,



improvement of muscle recruitment, improved proprioception, and coordination, and increased range-of-motion are used to promote normal movement patterns.

Yoga may be an option for motivated patients with appropriate diagnoses.

Therapeutic exercise programs should be tissue specific to the injury and address general functional deficits as identified in the diagnosis and clinical assessment. Patients should be instructed in and receive a home exercise program that is progressed as their functional status improves. Upon discharge, the patient would be independent in the performance of the home exercise program and would have been educated in the importance of continuing such a program. Educational goals would be to maintain or further improve function and to minimize the risk for aggravation of symptoms in the future.

Available evidence supporting therapy mainly exists in the chronic low back literature.

Evidence Statements Regarding Therapeutic Exercise			
Strong Evidence	Evidence Statement	Citation	Design
	In the short, intermediate, and long-term, motor control exercises that emphasize the transversus abdominis and multifidi are at least as effective as other forms of exercise and manual therapy. They are possibly more effective than other minimal interventions in reducing pain and improving disability in patients for the treatment of chronic non-specific low back pain.	<a href="#">(Bystrom, 2013)</a>	Meta-analysis of randomized clinical trials
		<a href="#">(Saragiotto, 2016)</a>	Meta-analysis of randomized clinical trials

Evidence Statements Regarding Therapeutic Exercise			
Good Evidence	Evidence Statement	Citation	Design
	A 12 week course of treatment in the McKenzie method is at most modestly more effective than spinal manipulation of similar duration in reducing disability in patients with persistent (more than 6 weeks duration, mean = 95 weeks) nonspecific low back pain, although a clinically relevant difference was not apparent. The McKenzie method should not be utilized if there is severe nerve root involvement with motor, sensory, or reflex abnormality.	<a href="#">(Petersen, 2011)</a>	Randomized clinical trial
	Pilates is more effective in reducing pain and improving disability compared with a minimal intervention at intermediate term follow-up, but Pilates is equally as effective as other forms of exercise in improving disability at short- or intermediate-term follow-up for the treatment of patients with chronic non-specific low back pain.	<a href="#">([Cochrane] Yamato, 2015)</a>	Meta-analyses of randomized clinical trials
	Exercise alone or part of a multi-disciplinary program results in decreased disability for workers with non-acute low back pain.	<a href="#">(Oesch, 2010)</a>	Meta-analysis of randomized clinical trials

Evidence Statements Regarding Therapeutic Exercise			
Some Evidence	Evidence Statement	Citation	Design
	An unsupervised 12-week, periodized musculoskeletal rehabilitation program of weight training conducted 2, 3, or 4 days a week is effective at improving musculoskeletal strength and quality of life and at reducing pain and disability in untrained persons with chronic low back pain. The 4 days a week training volume is most effective. The volume (total number of reps) of PMR exercise prescribed is important.	<a href="#">(Kell, 2011)</a>	Randomized clinical trial
	Trunk balance exercises combined with flexibility exercises are more effective than a combination of strength and flexibility exercises in reducing disability and improving physical function in patients with chronic low back pain.	<a href="#">(Gatti, 2011)</a>	Single-blind randomized clinical trial
	<p>An exercise program which includes resistance training of the cervical and scapulothoracic muscles, combined with stretching of the same muscles, is likely to be beneficial for mechanical neck pain.</p> <p>Cervicolscapular endurance exercises are beneficial for chronic cervicogenic headache.</p> <p>General fitness exercises and upper extremity exercises are unlikely by themselves to be beneficial for mechanical neck pain and are therefore <b>not recommended</b>.</p>	<a href="#">(Kay, 2012)</a>	Meta-analysis of randomized clinical trials

Evidence Statements Regarding Therapeutic Exercise			
Some Evidence, Continued	There is no significant difference in the effectiveness of an 12-week, 20 session comprehensive supervised exercise program and an unsupervised simple exercise program with advice for improvement in average pain intensity in the preceding week in people with a mild chronic whiplash-associated disorder even though both interventions resulted in small reductions of pain over 12 months.	<a href="#">(Michaleff, 2014)</a>	Assessor single-blind randomized clinical trial
	A 4-month intervention for chronic neck pain patients containing pain education, specific exercises and graded activity training shows a significant effect, although clinically small, on improved physical and mental health related quality of life compared with controls receiving pain education alone. Good adherence increased the effect in favor of the exercise group.	<a href="#">(Ris, 2016)</a>	Assessor single-blind randomized controlled superiority multicenter clinical trial
	12 weeks of supervised high-dose exercise, spinal manipulative therapy, or low-dose home exercise with advice are all equally effective for reducing pain in the short- and long-term (one year) in those who have chronic low back pain.	<a href="#">(Bronfort, 2011)</a>	Assessor single-blinded randomized controlled trial
	Intensive exercise coupled with cognitive behavioral therapy is as effective for chronic un-operated low back pain as posterolateral fusion.	<a href="#">(Brox, 2010)</a>	Randomized clinical trial

Evidence Statements Regarding Therapeutic Exercise			
Some Evidence, Continued	In the setting of non-specific chronic low back pain, patient-centered cognitive functional therapy from physical therapists produced superior outcomes for pain reduction and functional improvement compared with traditional manual therapy and exercise at post-intervention and at 12-month follow-up.	( <a href="#">Vibe Fersum, 2013</a> )	Single-blind randomized clinical trial
	There is no significant difference in the effectiveness of an 8-week supervised walking program, an evidence-based group exercise class, and usual physiotherapy for improvement in functional disability after 6 months for people with chronic low back pain even though all 3 interventions resulted in small, significant improvements in physical function, reduction of pain, quality of life, and fear avoidance over time.	( <a href="#">Hurley, 2015</a> )	Assessor single-blind randomized clinical trial

Evidence Statements Regarding Yoga			
Strong Evidence	Evidence Statement	Citation	Design
	Yoga has small to moderate advantages over providing only a booklet in reducing low back pain and back-specific disability, but there is no evidence that yoga is superior to stretching and strengthening classes led by a licensed physical therapist.	( <a href="#">Cramer, 2013</a> )	Meta-analysis of randomized clinical trials

Good Evidence	Evidence Statement	Citation	Design
	In the setting of chronic low back pain, 8 weeks of 2 hour weekly group sessions of either mindfulness based stress reduction meditation program with yoga or Cognitive Behavioral Therapy results in small, significant improvements in physical function and reduction in pain compared to usual care at 26 weeks with no significant differences in outcomes between the 2 treatments.	<a href="#">(Cherkin, 2016)</a>	Single-blind randomized clinical trial
Some Evidence	Evidence Statement	Citation	Design
	Iyengar yoga, which avoids back bending, results in improved function and decreased chronic mechanical low back pain for up to 6 months. Instruction occurred 2 times per week for 24 weeks and was coupled with home exercise. One quarter of the participants dropped out.	<a href="#">(Williams, 2009)</a>	Randomized clinical trial
	In the setting of chronic pain, both an 8-week mindfulness based stress reduction meditation program with yoga and an 8-week multidisciplinary pain intervention program with exercise resulted in small, significant reductions in pain intensity and pain-related distress post intervention but with no significant differences in outcomes between the 2 programs.	<a href="#">(Wong, 2011)</a>	Single-blind randomized clinical trial

Time Frames for Therapeutic Exercise	
Time to Produce Effect	2 to 6 treatments.
Frequency	2 to 5 times per week.

Time Frames for Therapeutic Exercise	
Optimum Duration	4 to 8 weeks and concurrent with an active daily home exercise program.
Maximum Duration	8 to 12 weeks of therapist oversight. Home exercise should continue indefinitely. Additional sessions may be warranted during periods of exacerbation of symptoms

Yoga may be an option for motivated patients.

Time Frames for Yoga	
Time to Produce Effect	8 sessions
Maximum Duration	48 sessions is the maximum expected duration

- i. **Work Conditioning:** This program is a work-related, outcome-focused, individualized treatment program. Objectives of the program include, but are not limited to, improvement of cardiopulmonary and neuromusculoskeletal functions (strength, endurance, movement, flexibility, postural control, and motor control functions), patient education, and symptom relief. The goal is for patients to gain full- or optimal-function and return-to-work. The service may include the time-limited use of modalities, both active and passive, in conjunction with therapeutic exercise, functional activities, general conditioning body mechanics, and lifting techniques re-training.

This program is usually initiated once re-conditioning has been completed but may be offered at any time throughout the recovery phase. It should be initiated when imminent return of a patient to modified- or full-duty is not an option, but the prognosis for returning the patient to work at completion of the program is at least fair to good.

Time Frames for Work Conditioning	
Time to Produce Effect	1 to 2 hours per day.
Frequency	2 to 5 visits per week.
Optimum Duration	2 to 4 weeks.
Maximum Duration	6 weeks. Participation in a program beyond 6 weeks must be documented with respect to need and the ability to facilitate positive symptomatic and functional gains.

- i. **Work Simulation:** is a program where an individual completes specific work-related tasks for a particular job and return to work. Use of this program is appropriate when modified duty can only be partially accommodated in the work

place, when modified duty in the work place is unavailable, or when the patient requires more structured supervision. The need for work place simulation should be based upon the results of a functional capacity evaluation and/or jobsite analysis.

Time Frames for Work Simulation	
Time to Produce Effect	2 to 6 hours per day.
Frequency	2 to 5 visits per week.
Optimum Duration	2 to 4 weeks.
Maximum Duration	6 weeks. Participation in a program beyond 6 weeks must be documented with respect to need and the ability to facilitate positive symptomatic and functional gains.

- 16. THERAPY—PASSIVE** Most of the following passive therapies and modalities are generally accepted methods (unless otherwise noted) of care for a variety of work-related injuries. Passive therapy includes those treatment modalities that do not require energy expenditure on the part of the patient. They are principally effective during the early phases of treatment and are directed at controlling symptoms such as pain, inflammation and swelling and to improve the rate of healing soft tissue injuries. They should be used adjunctively with active therapies such as postural stabilization and exercise programs to help control swelling, pain, and inflammation during the active rehabilitation process. Please refer to Section B.5, General Guideline Principles, Active Interventions. Passive therapies may be used intermittently as a practitioner deems appropriate or regularly if there are specific goals with objectively measured functional improvements during treatment; or if there are episodes of acute pain superimposed upon a chronic pain problem.

On occasion, specific diagnoses and post-surgical conditions may warrant durations of treatment beyond those listed as "maximum". Factors such as exacerbation of symptoms, re-injury, interrupted continuity of care and co-morbidities may extend durations of care. Having specific goals with objectively measured functional improvement during treatment can support extended durations of care. It is recommended that if after 6 to 8 visits no treatment effect is observed, alternative treatment interventions, further diagnostic studies or further consultations should be pursued.

The following passive therapies are listed in alphabetical order:

- a. Continuous Passive Motion (CPM):** is rarely indicated in CRPS but may occasionally be warranted if the patient shows signs of contracture despite active therapy.

Time Frames for Continuous Passive Motion	
Time to Produce Effect	4 to 6 treatments.



Time Frames for Continuous Passive Motion	
Frequency	Varies, between 2 to 3 times per day and 1 time per week.
Optimum Duration	4 treatments.
Maximum Duration	6 treatments. Provide home unit with improvement.

- b. Desensitization:** is accomplished through sensory integration techniques. Concurrent desensitization techniques are generally accepted as a treatment for CRPS. Home techniques using soft cloths of various textures, massage, and vibrators may be beneficial in reducing allodynia and similar sensory abnormalities.

Time Frames for Desensitization	
Time to Produce Effect	6 treatments.
Frequency	3 times per week and concurrent with home exercise program.
Optimum Duration	3 weeks with reinforcement of home program.
Maximum Duration	1 month.

- c. Fluidotherapy:** used primarily for desensitization and to facilitate increased active range-of-motion. Thermal heat conduction and convection is advantageous for vasodilation, muscle relaxation, and preparation for stress and activity (exercise).

Time Frames for Fluidotherapy	
Time to Produce Effect	3 treatments.
Frequency	3 times per week.
Optimum Duration	2 months.
Maximum Duration	2 months as a primary therapy or intermittently as an adjunct therapy to other procedures.

- d. Paraffin Bath:** Indications include the need to enhance collagen extensibility before stretching, reduce muscle guarding, and to prepare for functional restoration activities.

Time Frames for Paraffin Bath	
Time to Produce Effect	1 to 2 treatments.
Frequency	1 to 3 times per week as an adjunct treatment to other procedures. May use daily if available at home.
Optimum Duration	2 weeks.
Maximum Duration	3 to 4 weeks. If effective, purchase a home unit.

- e. **Superficial Heat Therapy:** Superficial heat is a thermal agent applied to raise the body tissue temperature. It is indicated before exercise to elevate the pain threshold, alleviate muscle spasm, and promote increased movement. Heat packs can be used at home as an extension of therapy in the clinic setting.

Time Frames for Superficial Heat Therapy	
Time to Produce Effect	Immediate.
Frequency	1 to 3 times per week.
Optimum Duration	2 weeks as primary or intermittently as an adjunct to other therapeutic procedures.
Maximum Duration	2 weeks. Home use as a primary modality may continue at the providers' discretion.

## I. THERAPEUTIC PROCEDURES – OPERATIVE

When considering operative intervention in CRPS management, the treating physician must carefully consider the inherent risk and benefit of the procedure. All operative intervention should be based on a positive correlation with clinical findings, the clinical course, and diagnostic tests. A comprehensive assessment of these factors should have led to a specific diagnosis of confirmed CRPS with positive identification of the pathologic condition. Operative treatment is indicated when the natural history of surgically treated lesions is better than the natural history for non-operatively treated lesions.

Surgical procedures are seldom meant to be curative and should be employed in conjunction with other treatment modalities for maximum functional benefit. Functional benefit should be objectively measured and includes the following:

- Return-to-work or maintaining work status.
- Fewer restrictions at work or performing activities of daily living.
- Decrease in usage of medications prescribed for the work-related injury.
- Measurable functional gains, such as increased range-of-motion or a documented increase in strength.

Education of the patient should include the proposed goals of the surgery, expected gains, risks or complications, and alternative treatment.

Smoking may affect soft tissue healing through tissue hypoxia. Patients should be strongly encouraged to stop smoking and be provided with appropriate counseling by the physician. If a treating physician recommends a specific smoking cessation program peri-operatively, this should be covered by the insurer. Physicians may monitor smoking cessation with laboratory tests such as cotinine levels. The surgeon will make the final determination as to whether smoking cessation is required prior to surgery. Similarly, patients with uncontrolled diabetes are at increased risk of post-operative infection and poor wound healing. It is recommended that routine lab work prior to any surgical intervention include a hemoglobin A1c. If it is higher than the recommended range, the surgery should be postponed until optimization of blood sugars has been achieved.

Prior to surgical intervention, the patient and treating physician should identify functional operative goals and the likelihood of achieving improved ability to perform activities of daily living or work activities, and the patient should agree to comply with the pre- and post-operative treatment plan including home exercise. The provider should be especially careful to make sure the patient understands the amount of post-operative therapy required and the length of partial- and full-disability expected post-operatively.

### **1. NEUROSTIMULATION**

Spinal cord stimulation (SCS) is the delivery of low-voltage electrical stimulation to the spinal cord or peripheral nerves to inhibit or block the sensation of pain. The system uses implanted electrical leads and a battery powered implanted pulse generator (IPG).

Refer the Division's Chronic Pain Disorder Medical Treatment Guideline for indications and evidence.

## **2. DORSAL ROOT GANGLION STIMULATOR**

Description: neurostimulator device implanted in the epidural space near to dorsal root ganglion – up to 4 leads may be placed. It is used for lower extremity CRPS pain.

There is good evidence that dorsal root ganglion (DRG) stimulation is non-inferior to conventional SCS with respect to pain relief for CRPS patients with lower extremity pain. There is some evidence that DRG stimulation is superior to SCS with respect to pain relief for up to 12 months after implantation. Neurological deficits related to stimulation with either device appear to be rare. 46% of the DRG patients had more serious complications compared to 26% for SCS ([Deer et al., 2016](#)).

Particular technical expertise is required to perform this procedure and is available in some neurosurgical, rehabilitation, and anesthesiology training programs and fellowships. Physicians performing this procedure must be trained in neurostimulation implantation and participate in ongoing training workshops on this subject, such as those sponsored by the Spine Intervention Society (SIS), North American Neuromodulation Society (NANS), or as sponsored by implant manufacturers.

Complications: Serious, extremely rare complications include spinal cord compression, paraplegia, epidural hematoma, and epidural hemorrhage. Other less serious complications / undesirable side effects include undesirable change in stimulation, seroma, CSF leakage, infection, erosion, allergic response, accidental dural puncture, hardware malfunction or equipment migration, pain at implantation site, loss of pain relief, chest wall stimulation, and other surgical risks. Neurological deficits related to stimulation with either device appear to be rare. 46% of the DRG patients had complications (mostly technical issues) compared to 26% for SCS.

Surgical Indications: Patients with established CRPS I or II with persistent, functionally limiting lower extremity pain. Candidates must have failed full conservative therapy including active therapy, medical management with at least 2 medications, and therapeutic injections. They must also have completed psychological treatment and evaluation and have a successful stimulator trial. Prior authorization is required. Habituation to opioid analgesics in the absence of a history of addictive behavior does not preclude the use of SCS. Patients with severe psychiatric disorders and issues of secondary gain or one or more primary risk factors are not candidates for the procedure, and the prognosis worsens as the number of secondary risk factors increases ([D. D. Bruns, J. M., 2009, 2013](#); [M. A. B. Kemler, G. A.; van Kleef, M.; de Vet, H. C.; Rijks, C. P.; Furnee, C. A.; van den Wildenberg, F. A., 2000](#)). Approximately, one third to one half of patients who qualify for SCS can expect a substantial reduction in pain relief; however, it may not influence allodynia and hypesthesia ([G. K. Barolat, B.; He, J., 1998](#); [G. O. Barolat, J. C.; Law, J. D.; North, R. B.; Ketcik, B.; Sharan, A., 2001](#); [Frey, 2009](#); [M. A. d. V. Kemler, H. C.; Barendse, G. A.; van den Wildenberg, F. A.; van Kleef, M., 2008](#); [North, 2005](#)). Patients' expectations need to be realistic, and therefore, patients should understand that the intervention is not a cure for their pain but rather a masking of their symptomatology which might regress over time. Historically, there appears to be a likely benefit of up to 3 years with spinal cord stimulator. It may be similar with the DRG ([M. A. d. V. Kemler, H. C.; Barendse, G. A.; van den Wildenberg, F. A.; van Kleef, M., 2008](#)).

Prior to surgical intervention, the patient and treating physician should identify functional operative goals and the likelihood of achieving improved ability to perform activities of daily living or work, as well as possible complications. The patient should agree to comply with the pre- and post-operative treatment plan including home exercise. The provider should be especially careful to make sure the patient understands the amount of post-operative therapy required and the length of partial- and full-disability expected post-operatively.

Informed decision making should be documented for all invasive procedures. This must include a thorough discussion of the pros and cons of the procedure and the possible complications as well as the natural history of the identified diagnosis. Since many patients with the most common conditions will improve significantly over time, without invasive interventions, patients must be able to make well-informed decisions regarding their treatment.

Smoking may affect soft tissue healing through tissue hypoxia. Patients should be strongly encouraged to stop smoking and be provided with appropriate counseling by the physician. If a treating physician recommends a specific smoking cessation program peri-operatively, this should be covered by the insurer. Typically, the patient should show some progress toward cessation at about 6 weeks. Physicians may monitor smoking cessation with laboratory tests such as cotinine levels. The surgeon will make the final determination as to whether smoking cessation is required prior to surgery. Patients with demonstrated success may continue the program up to 3 months or longer if needed based on the operative procedure. Refer to Section H.8.m, Smoking Cessation Medications and Treatment, for further details.

DRG may be indicated in a subset of patients who have confirmed CRPS, have burning pain in a distribution amenable to stimulation coverage, and have pain at night not relieved by position. The extremity pain should account for at least 50% or greater of the overall leg and back pain experienced by the patient.

*Prior* to the stimulator trial, a comprehensive psychiatric or psychological evaluation, for a chronic pain evaluation ([D. Bruns, 2014, 2015](#); [D. D. Bruns, J. M., 2013](#); [Deer et al., 2014](#)). Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for more information. This evaluation should include a standardized detailed personality inventory with validity scales (e.g., MMPI-2, MMPI-2-RF, or PAI); pain inventory with validity measures (e.g., BHI 2, MBMD); clinical interview and complete review of the medical records. The psychologist or psychiatrist performing these evaluations should not be an employee of the physician performing the implantation. This evaluation must be completed, with favorable findings, before the screening trial is scheduled. Before proceeding to a spinal stimulator trial, the evaluation should find the following:

- No indication of falsifying information;
- No indication of invalid results on testing;
- No primary psychiatric risk factors or "red flags" (e.g., psychosis, active suicidality, severe depression, or addiction) ([D. D. Bruns, J. M., 2009](#); [M. A. B. Kemler, G. A.; van Kleef, M.; de Vet, H. C.; Rijks, C. P.; Furnee, C. A.; van den Wildenberg, F. A., 2000](#)). (Note that tolerance and dependence to opioid analgesics are not addictive behaviors and do not preclude implantation);
- A level of secondary risk actors or "yellow flags" (e.g., moderate depression, job dissatisfaction, dysfunctional pain conditions) judged to be below the threshold for compromising the patient's ability to benefit from neurostimulation ([Block, 2001](#); [D. Bruns, 2014](#); [D. D. Bruns, J. M., 2009, 2013](#); [Celestin, 2009](#); [den Boer, 2006](#); [Rosenberger, 2006](#)).
- The patient is cognitively capable of understanding and operating the neurostimulation control device;
- The patient is cognitively capable of understanding and appreciating the risks

and benefits of the procedure;

- The patient is familiar with the implications of having an implant, can accept the complications, potential disfigurement, and effort it takes to maintain the device;
- The patient is cognitively capable of understanding the course of injury both with and without neurostimulation;
- The patient has demonstrated a history of motivation in and adherence to prescribed treatments;
- The patient understands the work related restrictions that may occur with placement of the stimulator. All reasonable surgical and non-surgical treatment has been exhausted;
- The topography of pain and its underlying pathophysiology are amenable to stimulation coverage (the entire painful area has been covered); and
- A successful neurostimulation screening test of at least 5 to 7 days ([M. A. B. Kemler, G. A.; van Kleef, M.; de Vet, H. C.; Rijks, C. P.; Furnee, C. A.; van den Wildenberg, F. A., 2000](#); [M. A. d. V. Kemler, H. C.; Barendse, G. A.; van den Wildenberg, F. A.; van Kleef, M., 2008](#); [North, 2005](#)).

For a neurostimulation screening test, a temporary lead is implanted at the level of pain and attached to an external source to validate therapy effectiveness. A screening test is considered successful if the patient meets both of the following criteria: (a) experiences a 50% decrease radicular or CRPS in pain, which may be confirmed by visual analogue scale (VAS) or Numerical Rating Scale (NRS) ([M. A. B. Kemler, G. A.; van Kleef, M.; de Vet, H. C.; Rijks, C. P.; Furnee, C. A.; van den Wildenberg, F. A., 2000](#); [Kumar, 2007](#); [North, 2005](#)), and (b) demonstrates objective functional gains or decreased utilization of pain medications ([M. A. B. Kemler, G. A.; van Kleef, M.; de Vet, H. C.; Rijks, C. P.; Furnee, C. A.; van den Wildenberg, F. A., 2000](#); [Kumar, 2007](#); [North, 2005](#)).

Objective, measurable, functional gains must be evaluated by an independent occupational therapist, not affiliated with the physician performing the screening or the implant of the stimulator, and/or physical therapist and the primary treating physician prior to and before discontinuation of the trial. Functional gains may include: standing, walking, positional tolerance, upper extremity activities, increased social participation, or decreased medication use.

Contraindications:

- Unsuccessful trial: inability to obtain objective, documented, functional improvement, or reduction of pain.
- Those with cardiac pacemakers should be evaluated on an individual basis as some may qualify for surgery ([Ooi, 2011](#)).
- Patients who are unable to properly operate the system.
- Patients who are anti-coagulated and cannot be without anticoagulation for a few days (e.g., patients with artificial heart valves).
- Patients with frequent severe infections.

- Patients for whom a future MRI is likely.

Operative Treatment: Implantation of stimulating leads connected by extensions to either an implanted neurostimulator or an implanted receiver powered by an external transmitter. The procedure may be performed either as an open or a percutaneous procedure, depending on the presence of epidural fibrosis and the anatomical placement required for optimal efficacy. During the final procedure, the patient must be awakened to establish full coverage from the placement of the lead. One of the most common failures is misplaced leads. Functional improvement is anticipated for up to 3 years or longer when objective functional improvement has been observed during the time of neurostimulation screening exam based on spinal cord stimulator studies ([M. A. d. V. Kemler, H. C.; Barendse, G. A.; van den Wildenberg, F. A.; van Kleef, M., 2008](#)).

Post-operative Considerations: MRI may be contraindicated depending on the model and implant location.

Work restrictions postplacement include no driving when active paresthesias are present. Thus, use of potentially dangerous or heavy equipment while the simulator is active is prohibited. The physician may also limit heavy physical labor.

Post-operative Therapy: Active and/or passive therapy should be employed to improve function. Implantable stimulators will require frequent monitoring such as adjustment of the unit and replacement of batteries. Estimated battery life of SCS implantable devices is usually 3 years; however, newer systems may last longer. For the DRG system, expected duration of the implanted batter is about 5 years.

Evidence Statements Regarding Dorsal Root Ganglion Stimulator			
Good Evidence	Evidence Statement	Citation	Design
	Dorsal root ganglion stimulation is non-inferior to conventional spinal cord stimulation with respect to pain relief for CRPS patients with lower extremity pain.	( <a href="#">Deer et al., 2016</a> )	Randomized non-inferiority clinical trial
Some Evidence	Evidence Statement	Citation	Design
	Dorsal root ganglion stimulation is superior to spinal cord stimulation with respect to pain relief for up to 12 months after implantation. Neurological deficits related to stimulation with either device appear to be rare. 46% of the DRG patients had more serious complications compared to 26% for SCS.	( <a href="#">Deer et al., 2016</a> )	Randomized non-inferiority clinical trial

### **3. PERIPHERAL NERVE STIMULATION**

There are no randomized controlled studies for this treatment. This modality should only be employed with a clear nerve injury or when the majority of pain is clearly in a nerve distribution in patients who have completed 6 months of other appropriate therapy including the same pre-trial psychosocial evaluation and treatment as are recommended for spinal cord stimulation ([D. Bruns, 2014](#); [D. D. Bruns, J. M., 2009, 2013](#); [Deer et al., 2014](#)). A screening trial should take place over 3 to 7 days and is considered successful if the patient meets both of the following criteria: (a) experiences a 50% decrease in pain, which may be confirmed by Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) and (b) demonstrates objective functional gains or decreased utilization of pain medications. Objective, measurable, functional gains must be evaluated by an independent occupational therapist and/or physical therapist and the primary treating physician (who did not place the nerve stimulator) prior to and before discontinuation of the trial. It may be used for proven occipital, ulnar, median, and other isolated nerve injuries ([Crucchi, 2007](#); [Frey, 2009](#); [Mekhail, 2010](#); [Van Calenbergh, 2009](#)).

### **4. INTRATHECAL DRUG DELIVERY**

***Not generally recommended.*** Requires prior authorization. Due to conflicting studies in this population and complication rate for long-term use, it may be considered only in very rare occasions when dystonia and spasticity are dominant features or when pain is not able to be managed using any other non-operative treatment.

Refer the Division's Chronic Pain Disorder Medical Treatment Guideline for indications.

### **5. SYMPATHECTOMY** including use of phenol or radiofrequency.

Description: destruction of part of the sympathetic nervous system, which is not generally accepted or widely used. Long-term success with this pain relief treatment is poor. Expected duration of pain relief is 3 to 5 months. There is currently a lack of evidence supporting long-term pain relief, and increased pain can result ([\[Cochrane\] S. D. Straube, S.; Moore, R. A.; McQuay, H. J., 2010](#)). This procedure is generally ***not recommended*** and requires prior authorization. It may be considered for patients who are unable to return to normal activities of daily living when using the other non-operative treatments (as listed in Section G, Non-operative Procedures) and who meet the strict indications below.

The practice of surgical and chemical sympathectomy for neuropathic pain and CRPS is based on very little high quality evidence. Sympathectomy should be used cautiously in clinical practice, in carefully selected patients, and probably only after failure of other treatment options. In these circumstances, establishing a clinical register of sympathectomy may help to inform treatment options on an individual patient basis ([\[Cochrane\] S. D. Straube, S.; Moore, R. A.; Cole, P., 2013](#)).

Indications: single extremity CRPS I with a significant amount of sympathetically mediated ischemia and distal pain only. The procedure should not be done if the proximal extremity is involved. Local anesthetic stellate ganglion block or lumbar sympathetic block consistently gives 90 to 100% relief each time a technically good block is performed and results in a temperature difference between the affected and the unaffected extremity of at least 1°C. The procedure may be considered for individuals who have limited duration of relief from blocks. Permanent neurological complications are common.



**6. AMPUTATION**

Amputation is ***not recommended*** in CRPS except in cases of gangrene or frequent/recurrent limb infections with the risk for osteomyelitis or systemic sepsis.

Referenced Version

## J. MAINTENANCE MANAGEMENT

Successful management of chronic pain conditions results in fewer relapses requiring intense medical care. Failure to address long-term management as part of the overall treatment program may lead to higher costs and greater dependence on the health care system. Management of CRPS continues after the patient has met the definition of maximum medical improvement (MMI). MMI is declared when a patient's condition has plateaued and an authorized treating physician believes no further medical intervention is likely to result in improved function. Patients with either clinical or confirmed CRPS may qualify for an impairment when functional deficits exist related to CRPS physiology which are distinct from any other related conditions. When the patient has reached MMI, a physician must describe in detail the maintenance treatment.

Maintenance care in CRPS requires a close working relationship between the carrier, the providers, and the patient. Providers and patients have an obligation to design a cost-effective, medically appropriate program that is predictable and allows the carrier to set aside appropriate reserves. Carriers and adjusters have an obligation to assure that medical providers can design medically appropriate programs. Designating a primary physician for maintenance management is strongly recommended.

Maintenance care will be based on principles of patient self-management. When developing a maintenance plan of care, the patient, physician, and insurer should attempt to meet the following goals:

- Maximal independence will be achieved through the use of home exercise programs or exercise programs requiring special facilities (e.g., pool, health club) and educational programs;
- Modalities will emphasize self-management and self-applied treatment;
- Management of pain or injury exacerbations will emphasize initiation of active therapy techniques and may occasionally require anesthetic injection blocks;
- Dependence on treatment provided by practitioners other than an authorized treating physician will be minimized;
- Reassessment of the patient's function must occur regularly to maintain daily living activities and work function; and
- Patients will understand that failure to comply with the elements of the self-management program or therapeutic plan of care may affect consideration of other interventions.

**1. FUNCTIONAL TESTS:** It is recommended that valid functional tests are used with treatments to track efficacy. Refer to the Division's Chronic Pain Disorder Medical Treatment Guideline for Specific Maintenance Interventions and Parameters, including home exercise programs and exercise equipment, exercise programs requiring special facilities, patient education management, psychological management, non-opioid medication management, therapy management, and purchase or rental of durable medical equipment.

**2. VITAMIN C:** There is some evidence that Vitamin C 500mg taken for 50 days after a wrist fracture may help to prevent CRPS ([Zollinger, 2007](#)). It may be useful to prescribe vitamin C to patients who historically have had or currently have CRPS if they suffer a fracture in order to prevent exacerbation of CRPS.

Evidence Statements Regarding Vitamin C			
Some Evidence	Evidence Statement	Citation	Design
	Vitamin C 500mg taken for 50 days after a wrist fracture may help to prevent CRPS.	<a href="#">(Zollinger, 2007)</a>	Randomized clinical trial

**3. OPIOID MEDICATION MANAGEMENT:** In very selective cases, scheduled opioids may prove to be the most cost effective means of ensuring the highest function and quality of life; however, inappropriate selection of these patients may result in a high degree of iatrogenic illness including addiction and drug overdose. A patient should have met the criteria in the opioids section of this guideline before beginning maintenance opioids. Laboratory or other testing may be appropriate to monitor medication effects on organ function. The following management is suggested for maintenance opioids:

- The medications should be clearly linked to improvement of function, not just pain control. All follow-up visits should document the patient's ability to perform routine functions satisfactorily. Examples include the abilities to perform: work tasks, drive safely, pay bills or perform basic math operations, remain alert and upright for 10 hours per day, or participate in normal family and social activities. If the patient is not maintaining reasonable levels of activity the patient should usually be tapered from the opioid and tried on a different long-acting opioid.
- A lower risk opioid medication regimen is defined as less than 50 MME per day ([Bohnert, 2011](#)). This may minimally increase or decrease over time. Dosages will need to be adjusted based on side effects of the medication and objective function of the patient. A patient may frequently be maintained on non-opioid medications to control side effects, treat mood disorders, or control neuropathic pain; however, only one long-acting opioid and one short-acting opioid for rescue use should be prescribed. Buccally absorbed opioids other than buprenorphine are not appropriate for these non-malignant pain patients. Transdermal opioid medications are **not recommended**, other than buprenorphine.
- All patients on chronic opioid medication dosages need to sign an appropriate opioid contract with their physician for prescribing the opioids.
- The patient must understand that continuation of the medication is contingent on their cooperation with the maintenance program. Use of non-prescribed drugs may result in tapering of the medication. The clinician should order random drug testing at least annually and when deemed appropriate to monitor medication compliance.
- Patients on chronic opioid medication dosages must receive them through one prescribing physician.

Time Frames for Opioid Medication Management	
Maintenance Duration	12 visits within a 12 month period to review the opioid plan. Laboratory and other monitoring, as appropriate.

**4. INJECTION THERAPY:**

- a. Sympathetic Blocks:** These injections are considered appropriate if they increase function for a minimum of 4 to 8 weeks. Maintenance blocks are combined with and are enhanced by the appropriate neuro-pharmacological medication(s) and an active self-management exercise program. It is anticipated that the frequency of the maintenance blocks may increase in the cold winter months or with stress.

Time Frames for Sympathetic Blocks	
Maintenance Duration	Not to exceed 4 to 6 blocks in a 12 month period for a single extremity and to be separated by no less than 4 week intervals. Increased frequency may need to be considered for multiple extremity involvement or for acute recurrences of pain and symptoms. For treatment of acute exacerbations, consider 2 to 6 blocks with a short time interval between blocks. A positive result would include a return to baseline function as established at MMI, return to increased work duties, and measurable improvement in physical activity goals including return to baseline after an exacerbation. Injections may only be repeated when these functional and time goals are met and verified by the designated primary physician. Patient completed functional questionnaires such as those recommended by the Division as part of Quality Performance and Outcomes Payments (QPOP, see Rule 18-8) and/or the Patient Specific Functional Scale can provide useful additional confirmation.

## REFERENCES

- Abdel Shaheed, C. M., C. G.; Williams, K. A.; Day, R.; McLachlan, A. J. (2016). Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis. *JAMA Intern Med*, 176(7), 958-968. doi:10.1001/jamainternmed.2016.1251
- Agency for Healthcare Research and Quality. (2016). The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain - Executive Summary. Retrieved from <https://www.ahrq.gov/research/findings/evidence-based-reports/opoidstp.html>
- Argoff, C. A., P.; Stanos, S.; Robinson, C. Y.; Galer, B. S.; Gould, E.; Gammaitoni, A. (2015). Relationship between change in pain intensity and functional outcomes in patients with chronic pain receiving twice daily extended-release hydrocodone bitartrate. *J Opioid Manag*, 11(5), 417-424. doi:10.5055/jom.2015.0291
- Barolat, G. K., B.; He, J. (1998). Long-term outcome of spinal cord stimulation for chronic pain management. *Neuromodulation*, 1(1), 19-29. doi:10.1111/j.1525-1403.1998.tb00027.x
- Barolat, G. O., J. C.; Law, J. D.; North, R. B.; Ketcik, B.; Sharan, A. (2001). Epidural spinal cord stimulation with a multiple electrode paddle lead is effective in treating intractable low back pain. *Neuromodulation*, 4(2), 59-66. doi:10.1046/j.1525-1403.2001.00059.x
- Batterham, S. I. H., S.; Keating, J. L. (2011). Systematic review and meta-analysis comparing land and aquatic exercise for people with hip or knee arthritis on function, mobility and other health outcomes. *BMC Musculoskelet Disord*, 12, 123. doi:10.1186/1471-2474-12-123
- Binsfeld, H. S., L.; Waechter, S.; Richarz, U.; Sabatowski, R. (2010). A randomized study to demonstrate noninferiority of once-daily OROS((R)) hydromorphone with twice-daily sustained-release oxycodone for moderate to severe chronic noncancer pain. *Pain Pract*, 10(5), 404-415. doi:10.1111/j.1533-2500.2009.00342.x
- Birklein, F. R., B.; Claus, D.; Neundorfer, B. (1998). Pattern of autonomic dysfunction in time course of complex regional pain syndrome. *Clin Auton Res*, 8(2), 79-85.
- Block, A. R. O., D. D.; Guyer, R. D.; Rashbaum, R. F.; Hochschuler, S. H. (2001). The use of presurgical psychological screening to predict the outcome of spine surgery. *Spine J*, 1(4), 274-282.
- Bohnert, A. S. V., M.; Bair, M. J.; Ganoczy, D.; McCarthy, J. F.; Ilgen, M. A.; Blow, F. C. (2011). Association between opioid prescribing patterns and opioid overdose-related deaths. *Jama*, 305(13), 1315-1321. doi:10.1001/jama.2011.370
- Boureau, F. L., P.; Kabir-Ahmadi, M. (2003). Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Pain*, 104(1-2), 323-331.
- Bronfort, G. M., M. J.; Evans, R. L.; Schulz, C. A.; Bracha, Y.; Svendsen, K. H.; Grimm, R. H., Jr.; Owens, E. F., Jr.; Garvey, T. A.; Transfeldt, E. E. (2011). Supervised exercise, spinal manipulation, and home exercise for chronic low back pain: a randomized clinical trial. *Spine J*, 11(7), 585-598. doi:10.1016/j.spinee.2011.01.036
- Brox, J. I. N., O. P.; Holm, I.; Keller, A.; Ingebrigtsen, T.; Reikeras, O. (2010). Four-year follow-up of surgical versus non-surgical therapy for chronic low back pain. *Ann Rheum Dis*, 69(9), 1643-1648. doi:10.1136/ard.2009.108902
- Buehl, S. B., J. W.; Gupta, R.; Buvanendran, A.; Chont, M.; Schuster, E.; France, C. R. (2014). Endogenous opioid inhibition of chronic low-back pain influences degree of back pain relief after morphine administration. *Reg Anesth Pain Med*, 39(2), 120-125. doi:10.1097/aap.000000000000058
- Buehl, S. B., J. W.; Passik, S. D.; Gupta, R.; Buvanendran, A.; Chont, M.; Schuster, E.; Orłowska, D.; France, C. R. (2015). The Contribution of Differential Opioid Responsiveness to Identification of Opioid Risk in Chronic Pain Patients. *J Pain*, 16(7), 666-675. doi:10.1016/j.jpain.2015.04.001
- Bruns, D. (2014). Clinical and forensic standards for the psychological assessment of patients with chronic pain. *Psychological Injury and Law*, 7(4), 297-316. doi:<http://link.springer.com/article/10.1007/s12207-014-9211-1>
- Bruns, D. (2015). *Psychological Tests Commonly Used in the Assessment of Chronic Pain*. Colorado Department of Labor and Employment: Division of Worker Compensation Retrieved from <http://www.healthpsych.com/testing/psychtests.pdf>.
- Bruns, D. D., J. M. (2009). Assessment of biopsychosocial risk factors for medical treatment: a collaborative approach. *J Clin Psychol Med Settings*, 16(2), 127-147. doi:10.1007/s10880-009-9148-9

- Bruns, D. D., J. M. (2013). The Psychological Assessment of Patients with Chronic Pain. In T. R. Deer (Ed.), *Comprehensive Treatment of Chronic Pain: Medical, Interventional, and Behavioral Approaches* (pp. 805-826). New York: Springer.
- Bunten, H. L., W. J.; Pounder, D.; Seneviratne, C.; Osselton, M. D. (2011). CYP2B6 and OPRM1 gene variations predict methadone-related deaths. *Addict Biol*, 16(1), 142-144.
- Buynak, R. S., D. Y.; Okamoto, A.; Van Hove, I.; Rauschkolb, C.; Steup, A.; Lange, B.; Lange, C.; Etropolski, M. (2010). Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother*, 11(11), 1787-1804. doi:10.1517/14656566.2010.497720
- Bystrom, M. G. R.-B., E.; Grooten, W. J. (2013). Motor control exercises reduces pain and disability in chronic and recurrent low back pain: a meta-analysis. *Spine (Phila Pa 1976)*, 38(6), E350-358. doi:10.1097/BRS.0b013e31828435fb
- Cacchio, A. D. B., E.; De Blasis, V.; Santilli, V.; Spacca, G. (2009). Mirror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. *Neurorehabil Neural Repair*, 23(8), 792-799. doi:10.1177/1545968309335977
- Canadian Agency for Drugs and Technologies in Health. (2015) *Long-acting Opioids for Chronic Non-cancer Pain: A Review of the Clinical Efficacy and Safety*. Ottawa (ON).
- CARF. (2010-2011). *Medical Rehabilitation Standards Manual*. United States of America: Commission on Accreditation of Rehabilitation Facilities.
- CARF. (2016a). *Medical Rehabilitation Standards Manual*. United States of America: Commission on Accreditation of Rehabilitation Facilities.
- CARF. (2016b). *Opioid Treatment Program Standards Manual*. United States of America.
- Carvalho, C. C., J. M.; Cunha, L.; Rebouta, P.; Kaptchuk, T. J.; Kirsch, I. (2016). Open-label placebo treatment in chronic low back pain: a randomized controlled trial. *Pain*, 157(12), 2766-2772. doi:10.1097/j.pain.0000000000000700
- Celestin, J. E., R. R.; Jamison, R. N. (2009). Pretreatment psychosocial variables as predictors of outcomes following lumbar surgery and spinal cord stimulation: a systematic review and literature synthesis. *Pain Medicine*, 10(4), 639-653. doi:10.1111/j.1526-4637.2009.00632.x
- Cepeda, M. S. B., J. A.; Gao, C. Y.; Wiegand, F.; Wada, D. R. (2012). Placebo response changes depending on the neuropathic pain syndrome: results of a systematic review and meta-analysis. *Pain Med*, 13(4), 575-595. doi:10.1111/j.1526-4637.2012.01340.x
- Cepeda, M. S. C., F.; Zea, C.; Valencia, L. (2007). Tramadol for osteoarthritis: a systematic review and metaanalysis. *J Rheumatol*, 34(3), 543-555.
- Chelimsky, T. C. L., P. A.; Naessens, J. M.; Wilson, P. R.; Amadio, P. C.; O'Brien, P. C. (1995). Value of autonomic testing in reflex sympathetic dystrophy. *Mayo Clin Proc*, 70(11), 1029-1040. doi:10.1016/S0025-6196(11)64438-8
- Cherkin, D. C. S., K. J.; Balderson, B. H.; Cook, A. J.; Anderson, M. L.; Hawkes, R. J.; Hansen, K. E.; Turner, J. A. (2016). Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain: A Randomized Clinical Trial. *Jama*, 315(12), 1240-1249. doi:10.1001/jama.2016.2323
- Chey, W. D. W., L.; Sostek, M.; Lappalainen, J.; Barker, P. N.; Tack, J. (2014). Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med*, 370(25), 2387-2396. doi:10.1056/NEJMoa1310246
- Childs, J. D. F., J. M.; Wu, S. S.; Flynn, T. W.; Wainner, R. S.; Robertson, E. K.; Kim, F. S.; George, S. Z. (2015). Implications of early and guideline adherent physical therapy for low back pain on utilization and costs. *BMC Health Serv Res*, 15, 150. doi:10.1186/s12913-015-0830-3
- Chou, R. C., S. (2008) *Drug Class Review: Long-Acting Opioid Analgesics: Final Report Update 5*. Portland (OR).
- Chou, R. D., R.; Friedly, J.; Skelly, A.; Hashimoto, R.; Weimer, M.; Fu, R.; Dana, T.; Kraegel, P.; Griffin, J.; Grusing, S.; Brodt, E. (2016). *Noninvasive treatments for low back pain Comparative effectiveness review number 169. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 16-EHC004-EF. Rockville, MD: Agency for Healthcare Research and Quality; Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK350276/>*

- Chou, R. F., G. J.; Fine, P. G.; Adler, J. A.; Ballantyne, J. C.; Davies, P.; Donovan, M. I.; Fishbain, D. A.; Foley, K. M.; Fudin, J.; Gilson, A. M.; Kelter, A.; Mausek, A.; O'Connor, P. G.; Passik, S. D.; Pasternak, G. W.; Portenoy, R. K.; Rich, B. A.; Roberts, R. G.; Todd, K. H.; Miaskowski, C.; American Pain Society-American Academy of Pain Medicine Opioids Guidelines, Panel. (2009). Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*, 10(2), 113-130. doi:10.1016/j.jpain.2008.10.008
- Christensen, K. J., E. M.; Noer, I. (1982). The reflex dystrophy syndrome response to treatment with systemic corticosteroids. *Acta Chir Scand*, 148(8), 653-655.
- Cicero, T. J. D., R. C.; Inciardi, J. A.; Woody, G. E.; Schnoll, S.; Munoz, A. (2007). The development of a comprehensive risk-management program for prescription opioid analgesics: researched abuse, diversion and addiction-related surveillance (RADARS). *Pain Med*, 8(2), 157-170. doi:10.1111/j.1526-4637.2006.00259.x
- Cicero, T. J. I., J. A.; Adams, E. H.; Geller, A.; Senay, E. C.; Woody, G. E.; Munoz, A. (2005). Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: results of an abuse monitoring system, 1994-2004. *Pharmacoepidemiol Drug Saf*, 14(12), 851-859. doi:10.1002/pds.1113
- Cicero, T. J. L., M.; Todorov, A.; Inciardi, J. A.; Surratt, H. L. (2008). Co-morbid pain and psychopathology in males and females admitted to treatment for opioid analgesic abuse. *Pain*, 139(1), 127-135. doi:10.1016/j.pain.2008.03.021
- Conwell, T. D. H., W. B.; Giordano, J. (2010). Sensitivity, Specificity and Predictive Value of Infrared Cold Water Autonomic Functional Stress Testing As Compared with Modified IASP Criteria for CRPS. *Thermology interanational*, 20(2).
- Cooke, E. D. S., M. D.; Pearson, R. M.; Fleming, C. E.; Toms, S. L.; Elusade, J. A. (1993). Reflex sympathetic dystrophy and repetitive strain injury: temperature and microcirculatory changes following mild cold stress. *J R Soc Med*, 86(12), 690-693.
- Correll, G. E. M., J.; Gracely, E. J.; Muir, J. J.; Harbut, R. E. (2004). Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Med*, 5(3), 263-275. doi:10.1111/j.1526-4637.2004.04043.x
- Coyne, K. S. S., C.; LoCasale, R. J.; King, F. R.; Margolis, M. K.; Ahmedzai, S. H. (2016). Opioid-Induced Constipation among a Convenience Sample of Patients with Cancer Pain. *Front Oncol*, 6, 131. doi:10.3389/fonc.2016.00131
- Cramer, H. L., R.; Haller, H.; Dobos, G. (2013). A systematic review and meta-analysis of yoga for low back pain. *Clin J Pain*, 29(5), 450-460. doi:10.1097/AJP.0b013e31825e1492
- Cruccu, G. A., T. Z.; Garcia-Larrea, L.; Hansson, P.; Jensen, T. S.; Lefaucheur, J. P.; Simpson, B. A.; Taylor, R. S. (2007). EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol*, 14(9), 952-970. doi:10.1111/j.1468-1331.2007.01916.x
- Deer, T. R., Levy, R. M., Kramer, J., Poree, L., Amirdelfan, K., Grigsby, E., . . . Mekhail, N. (2016). Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain*. doi:10.1097/j.pain.0000000000000814
- Deer, T. R., Mekhail, N., Provenzano, D., Pope, J., Krames, E., Leong, M., . . . North, R. (2014). The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. *Neuromodulation*, 17(6), 515-550. doi:10.1111/ner.12208
- den Boer, J. J. O., R. A.; Beems, T.; Munneke, M.; Oerlemans, M.; Evers, A. W. (2006). A systematic review of bio-psychosocial risk factors for an unfavourable outcome after lumbar disc surgery. *Eur Spine J*, 15(5), 527-536. doi:10.1007/s00586-005-0910-x
- Dennis, B. B. B., M.; Thabane, L.; Sohani, Z.; Samaan, Z. (2014). Impact of ABCB1 and CYP2B6 genetic polymorphisms on methadone metabolism, dose and treatment response in patients with opioid addiction: a systematic review and meta-analysis. *PLoS One*, 9(1), e86114. doi:10.1371/journal.pone.0086114
- Di Pietro, F. M., J. H.; Parkitny, L.; Lotze, M.; Wand, B. M.; Moseley, G. L.; Stanton, T. R. (2013). Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. *J Pain*, 14(10), 1001-1018. doi:10.1016/j.jpain.2013.04.001

- Di Pietro, F. S., T. R.; Moseley, G. L.; Lotze, M.; McAuley, J. H. (2015). Interhemispheric somatosensory differences in chronic pain reflect abnormality of the healthy side. *Hum Brain Mapp*, 36(2), 508-518. doi:10.1002/hbm.22643
- Dobscha, S. K. C., K.; Perrin, N. A.; Hanson, G. C.; Leibowitz, R. Q.; Doak, M. N.; Dickinson, K. C.; Sullivan, M. D.; Gerrity, M. S. (2009). Collaborative care for chronic pain in primary care: a cluster randomized trial. *Jama*, 301(12), 1242-1252. doi:10.1001/jama.2009.377
- Dorn, S. L., A.; Cremonini, F. (2014). Opioid-induced bowel dysfunction: epidemiology, pathophysiology, diagnosis, and initial therapeutic approach. *Am J Gastroenterol Suppl*, 2(1), 31-37. doi:10.1038/ajgsup.2014.7
- Dowell, D. H., T. M.; Chou, R. (2016). CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *Jama*, 315(15), 1624-1645. doi:10.1001/jama.2016.1464
- Duhmke, R. M. H., J.; Cornblath, D. R. (2006). Tramadol for neuropathic pain. *Cochrane Database Syst Rev*(3), CD003726. doi:10.1002/14651858.CD003726.pub3
- Dunlap, B. C., A. S. (2016). Clinical Management of Opioid Use Disorder. *Jama*, 316(3), 338-339. doi:10.1001/jama.2016.9795
- Dworkin, R. H., Malone, D. C., Panarites, C. J., Armstrong, E. P., & Pham, S. V. (2010). Impact of postherpetic neuralgia and painful diabetic peripheral neuropathy on health care costs. *J Pain*, 11(4), 360-368. doi:10.1016/j.jpain.2009.08.005
- Eberle, T. D., B.; Kramer, H. H.; Geber, C.; Fechir, M.; Magerl, W.; Birklein, F. (2009). Warm and cold complex regional pain syndromes: differences beyond skin temperature? *Neurology*, 72(6), 505-512. doi:10.1212/01.wnl.0000341930.35494.66
- Edlund, M. J., Martin, B. C., Russo, J. E., DeVries, A., Braden, J. B., & Sullivan, M. D. (2014). The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain*, 30(7), 557-564. doi:10.1097/AJP.0000000000000021
- Edlund, M. J. M., B. C.; Fan, M. Y.; Braden, J. B.; Devries, A.; Sullivan, M. D. (2010). An analysis of heavy utilizers of opioids for chronic noncancer pain in the TROUP study. *J Pain Symptom Manage*, 40(2), 279-289. doi:10.1016/j.jpainsymman.2010.01.012
- Farrar, J. T. B., Jesse A.; Strom, Brian L. (2003). Clinically Important Changes in Acute Pain Outcome Measures. *J Pain Symptom Manage*, 25(5), 406-411. doi:10.1016/s0885-3924(03)00162-3
- Farrar, J. T. P., R. K.; Berlin, J. A.; Kinman, J. L.; Strom, B. L. (2000). Defining the clinically important difference in pain outcome measures. *Pain*, 88(3), 287-294.
- Fiore, M. C. J., Carlos Roberto; Baker, Timothy B.; Bailey, William C.; Benowitz, Neal L.; Curry, Susan J.; Dorfman, Sally Faith; Froelicher, Erika S.; Goldstein, Michael G.; Heaton, Cheryl G.; Henderson, Patricia Nez; Heyman, Richard B.; Koh, Howard K.; Kottke, Thomas E.; Lando, Harry A.; Mecklenburg, Robert E.; Mermelstein, Robin J.; Mullen, Patricia Dolan; Orleans, C. Tracy; Robinson, Lawrence; Stitzer, Maxine L.; Tommasello, Anthony C.; Villejo, Louise; Wewers, Mary Ellen. (2008). *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline* (2008 update ed.). Rockville, Md.: U.S. Dept. of Health and Human Services, Public Health Service.
- Fishbain, D. A. C., B.; Lewis, J. E.; Gao, J.; Rosomoff, R. S. (2009). Do opioids induce hyperalgesia in humans? An evidence-based structured review. *Pain Med*, 10(5), 829-839. doi:10.1111/j.1526-4637.2009.00653.x
- Fleming, M. F. D., J.; Passik, S. D. (2008). Reported lifetime aberrant drug-taking behaviors are predictive of current substance use and mental health problems in primary care patients. *Pain Med*, 9(8), 1098-1106. doi:10.1111/j.1526-4637.2008.00491.x
- Franklin, G. M. S., B. D.; Turner, J. A.; Fulton-Kehoe, D.; Wickizer, T. M.; Disability Risk Identification Study, Cohort. (2008). Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine (Phila Pa 1976)*, 33(2), 199-204. doi:10.1097/BRS.0b013e318160455c
- Frey, M. E. M., L.; Benyamin, R. M.; Schultz, D. M.; Smith, H. S.; Cohen, S. P. (2009). Spinal cord stimulation for patients with failed back surgery syndrome: a systematic review. *Pain Physician*, 12(2), 379-397.
- Friedman, A. (2015). Work-Related Complex Regional Pain Syndrome: Diagnosis and Treatment. *Phys Med Rehabil Clin N Am*, 26(3), 563-572. doi:10.1016/j.pmr.2015.04.006



- Fulton-Kehoe, D. G., R. K.; Turner, J. A.; Bauer, A. M.; Sullivan, M. D.; Wickizer, T. M.; Franklin, G. M. (2013). Opioid poisonings and opioid adverse effects in workers in Washington state. *Am J Ind Med*, 56(12), 1452-1462. doi:10.1002/ajim.22266
- Galer, B. S. L., D.; Ma, T.; Nagle, B.; Schlagheck, T. G. (2005). Morphidex (morphine sulfate/dextromethorphan hydrobromide combination) in the treatment of chronic pain: three multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or reduction in tolerance. *Pain*, 115(3), 284-295. doi:10.1016/j.pain.2005.03.004
- Gallagher, J. J. T., M.; Guo, T.; Shi, X.; Li, W.; Zheng, M.; Peltz, G.; Kingery, W. S.; Clark, J. D. (2013). Acute and chronic phases of complex regional pain syndrome in mice are accompanied by distinct transcriptional changes in the spinal cord. *Mol Pain*, 9, 40. doi:10.1186/1744-8069-9-40
- Gaskell, H. M., R. A.; Derry, S.; Stannard, C. (2014). Oxycodone for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*(6), Cd010692. doi:10.1002/14651858.CD010692.pub2
- Gatti, R. F., S.; Tettamanti, A.; Barbero, M.; Balestri, A.; Calori, G. (2011). Efficacy of trunk balance exercises for individuals with chronic low back pain: a randomized clinical trial. *J Orthop Sports Phys Ther*, 41(8), 542-552. doi:10.2519/jospt.2011.3413
- Gilron, I. T., D.; Holden, R. R.; Jackson, A. C.; DuMerton-Shore, D. (2015). Combination of morphine with nortriptyline for neuropathic pain. *Pain*, 156(8), 1440-1448. doi:10.1097/j.pain.000000000000149
- Gobelet, C. W., M.; Meier, J. L. (1992). The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. *Pain*, 48(2), 171-175.
- Gomes, T. M., M. M.; Dhalla, I. A.; Paterson, J. M.; Juurlink, D. N. (2011). Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*, 171(7), 686-691. doi:10.1001/archinternmed.2011.117
- Gourlay, D. L. H., H. A. (2009). Universal precautions revisited: managing the inherited pain patient. *Pain Med*, 10 Suppl 2, S115-123. doi:10.1111/j.1526-4637.2009.00671.x
- Grace, P. M. S., K. A.; Galer, E. L.; Urban, D. J.; Wang, X.; Baratta, M. V.; Fabisiak, T. J.; Anderson, N. D.; Cheng, K.; Greene, L. I.; Berkelhammer, D.; Zhang, Y.; Ellis, A. L.; Yin, H. H.; Campeau, S.; Rice, K. C.; Roth, B. L.; Maier, S. F.; Watkins, L. R. (2016). Morphine paradoxically prolongs neuropathic pain in rats by amplifying spinal NLRP3 inflammasome activation. *Proc Natl Acad Sci U S A*, 113(24), E3441-3450. doi:10.1073/pnas.1602070113
- Gradl, G. S., M.; Witzgall, I.; Mittlmeier, T.; Schurmann, M. (2003). [Acute CRPS I (morbus sudeck) following distal radial fractures--methods for early diagnosis]. *Zentralbl Chir*, 128(12), 1020-1026. doi:10.1055/s-2003-44851
- Gulevich, S. J. C., T. D.; Lane, J.; Lockwood, B.; Schwettmann, R. S.; Rosenberg, N.; Goldman, L. B. (1997). Stress infrared telethermography is useful in the diagnosis of complex regional pain syndrome, type I (formerly reflex sympathetic dystrophy). *Clin J Pain*, 13(1), 50-59.
- Hale, M. E., Dvergsten, C., & Gimbel, J. (2005). Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain*, 6(1), 21-28. doi:10.1016/j.jpain.2004.09.005
- Hale, M. E., Zimmerman, T. R., Eyal, E., & Malamut, R. (2015). Efficacy and safety of a hydrocodone extended-release tablet formulated with abuse-deterrence technology in patients with moderate-to-severe chronic low back pain. *J Opioid Manag*, 11(6), 507-518. doi:10.5055/jom.2015.0304
- Harden, R. N. B., S.; Perez, R. S.; Birklein, F.; Marinus, J.; Maihofner, C.; Lubenow, T.; Buvanendran, A.; Mackey, S.; Graciosa, J.; Mogilevski, M.; Ramsden, C.; Chont, M.; Vatine, J. J. (2010). Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. *Pain*, 150(2), 268-274. doi:10.1016/j.pain.2010.04.030
- Harden, R. N. B., S.; Perez, R. S.; Birklein, F.; Marinus, J.; Maihofner, C.; Lubenow, T.; Buvanendran, A.; Mackey, S.; Graciosa, J.; Mogilevski, M.; Ramsden, C.; Schlereth, T.; Chont, M.; Vatine, J. J. (2010). Development of a severity score for CRPS. *Pain*, 151(3), 870-876. doi:10.1016/j.pain.2010.09.031
- Harden, R. N. O., A. L.; Burton, A. W.; Perez, R. S.; Richardson, K.; Swan, M.; Barthel, J.; Costa, B.; Graciosa, J. R.; Bruehl, S. (2013). Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. *Pain Med*, 14(2), 180-229. doi:10.1111/pme.12033
- Haroutiunian, S. M., E. D.; Lipman, A. G. (2012). Methadone for chronic non-cancer pain in adults. *Cochrane Database Syst Rev*, 11, Cd008025. doi:10.1002/14651858.CD008025.pub2

- Hazard, R. G. S., K. F.; McDonough, C. M.; Carayannopoulos, A. G.; Olson, C. M.; Reeves, V.; Sperry, M. L.; Ossen, E. S. (2009). The impact of personal functional goal achievement on patient satisfaction with progress one year following completion of a functional restoration program for chronic disabling spinal disorders. *Spine (Phila Pa 1976)*, 34(25), 2797-2802. doi:10.1097/BRS.0b013e3181a9e640
- Hegmann, K. T. W., M. S.; Bowden, K.; Branco, F.; DuBrueler, K.; Els, C.; Mandel, S.; McKinney, D. W.; Miguel, R.; Mueller, K. L.; Nadig, R. J.; Schaffer, M. I.; Studt, L.; Talmage, J. B.; Travis, R. L.; Winters, T.; Thiese, M. S.; Harris, J. S. (2014a). ACOEM practice guidelines: opioids and safety-sensitive work. *J Occup Environ Med*, 56(7), e46-53. doi:10.1097/jom.0000000000000237
- Hegmann, K. T. W., M. S.; Bowden, K.; Branco, F.; DuBrueler, K.; Els, C.; Mandel, S.; McKinney, D. W.; Miguel, R.; Mueller, K. L.; Nadig, R. J.; Schaffer, M. I.; Studt, L.; Talmage, J. B.; Travis, R. L.; Winters, T.; Thiese, M. S.; Harris, J. S. (2014b). ACOEM practice guidelines: opioids for treatment of acute, subacute, chronic, and postoperative pain. *J Occup Environ Med*, 56(12), e143-159. doi:10.1097/jom.0000000000000352
- Heymans, M. W. v. T., M. W.; Esmail, R.; Bombardier, C.; Koes, B. W. (2004). Back schools for non-specific low-back pain. *Cochrane Database Syst Rev*(4), CD000261. doi:10.1002/14651858.CD000261.pub2
- Huffman, K. L. R., T. E.; Fan, Y.; Sweis, G. W.; Vij, B.; Covington, E. C.; Scheman, J.; Mathews, M. (2017). Sustained improvements in pain, mood, function and opioid use post interdisciplinary pain rehabilitation in patients weaned from high and low dose chronic opioid therapy. *Pain*. doi:10.1097/j.pain.0000000000000907
- Huge, V. L., M.; Forderreuther, S.; Kaufhold, W.; Valet, M.; Azad, S. C.; Beyer, A.; Magerl, W. (2008). Interaction of hyperalgesia and sensory loss in complex regional pain syndrome type I (CRPS I). *PLoS One*, 3(7), e2742. doi:10.1371/journal.pone.0002742
- Huge, V. L., M.; Magerl, W.; Beyer, A.; Moehle, P.; Kaufhold, W.; Schelling, G.; Azad, S. C. (2011). Complex interaction of sensory and motor signs and symptoms in chronic CRPS. *PLoS One*, 6(4), e18775. doi:10.1371/journal.pone.0018775
- Hurley, D. A. T., M. A.; Lonsdale, C.; Boreham, C. A.; van Mechelen, W.; Daly, L.; Tynan, A.; McDonough, S. M. (2015). Supervised walking in comparison with fitness training for chronic back pain in physiotherapy: results of the SWIFT single-blinded randomized controlled trial (ISRCTN17592092). *Pain*, 156(1), 131-147. doi:10.1016/j.pain.0000000000000013
- Johnston, S. S. A., A. H.; Masters, E. T.; Mardekian, J.; Semel, D.; Malangone-Monaco, E.; Riehle, E.; Wilson, K.; Sadosky, A. (2016). Costs and Work Loss Burden of Diagnosed Opioid Abuse Among Employees on Workers Compensation or Short-term Disability. *J Occup Environ Med*, 58(11), 1087-1097. doi:10.1097/JOM.0000000000000865
- Kalita, J. V., A.; Misra, U. K. (2006). Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: a randomized controlled trial. *QJM*, 99(2), 89-95. doi:10.1093/qjmed/hcl004
- Kamper, S. J. A., A. T.; Chiarotto, A.; Smeets, R. J.; Ostelo, R. W.; Guzman, J.; van Tulder, M. W. (2014). Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. *Cochrane Database Syst Rev*(9), Cd000963. doi:10.1002/14651858.CD000963.pub3
- Kaur, H. H., D.; Bhansali, A.; Dutta, P.; Bansal, D.; Chakrabarti, A. (2011). A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial. *Diabetes Care*, 34(4), 818-822. doi:10.2337/dc10-1793
- Kay, T. M. G., A.; Goldsmith, C. H.; Rutherford, S.; Voth, S.; Hoving, J. L.; Bronfort, G.; Santaguida, P. L. (2012). Exercises for mechanical neck disorders. *Cochrane Database Syst Rev*(8), Cd004250. doi:10.1002/14651858.CD004250.pub4
- Kell, R. T. R., A. D.; Barden, J. M. (2011). The response of persons with chronic nonspecific low back pain to three different volumes of periodized musculoskeletal rehabilitation. *J Strength Cond Res*, 25(4), 1052-1064. doi:10.1519/JSC.0b013e3181d09df7
- Kemler, M. A. B., G. A.; van Kleef, M.; de Vet, H. C.; Rijks, C. P.; Furnee, C. A.; van den Wildenberg, F. A. (2000). Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med*, 343(9), 618-624. doi:10.1056/NEJM200008313430904
- Kemler, M. A. d. V., H. C.; Barendse, G. A.; van den Wildenberg, F. A.; van Kleef, M. (2008). Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-

- up of patients in a randomized controlled trial. *J Neurosurg*, 108(2), 292-298.  
doi:10.3171/JNS/2008/108/2/0292
- Kosarac, B. F., A. A.; Collard, C. D. (2009). Effect of genetic factors on opioid action. *Curr Opin Anaesthesiol*, 22(4), 476-482. doi:10.1097/ACO.0b013e32832e34c9
- Kroenke, K. K., E. E.; Wu, J.; Yu, Z.; Chumbler, N. R.; Bair, M. J. (2014). Telecare collaborative management of chronic pain in primary care: a randomized clinical trial. *Jama*, 312(3), 240-248. doi:10.1001/jama.2014.7689
- Krumova, E. K. F., J.; Klauenberg, S.; Richter, H.; Wasner, G.; Maier, C. (2008). Long-term skin temperature measurements - a practical diagnostic tool in complex regional pain syndrome. *Pain*, 140(1), 8-22. doi:10.1016/j.pain.2008.07.003
- Krumova, S. B., Koehorst, R. B., Bota, A., Pali, T., van Hoek, A., Garab, G., & van Amerongen, H. (2008). Temperature dependence of the lipid packing in thylakoid membranes studied by time- and spectrally resolved fluorescence of Merocyanine 540. *Biochim Biophys Acta*, 1778(12), 2823-2833. doi:10.1016/j.bbamem.2008.09.007
- Kumar, K. T., R. S.; Jacques, L.; Eldabe, S.; Meglio, M.; Molet, J.; Thomson, S.; O'Callaghan, J.; Eisenberg, E.; Milbouw, G.; Buchser, E.; Fortini, G.; Richardson, J.; North, R. B. (2007). Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain*, 132(1-2), 179-188. doi:10.1016/j.pain.2007.07.028
- Lambeek, L. C. v. M., W.; Knol, D. L.; Loisel, P.; Anema, J. R. (2010). Randomised controlled trial of integrated care to reduce disability from chronic low back pain in working and private life. *Bmj*, 340, c1035. doi:10.1136/bmj.c1035
- Landau, C. J. C., W. D.; Razzetti, A. J.; Sessler, N. E.; Munera, C.; Ripa, S. R. (2007). Buprenorphine transdermal delivery system in adults with persistent noncancer-related pain syndromes who require opioid therapy: a multicenter, 5-week run-in and randomized, double-blind maintenance-of-analgesia study. *Clin Ther*, 29(10), 2179-2193. doi:10.1016/j.clinthera.2007.10.010
- Larson, R. A. C., J. R. (2016). Total Sleep Deprivation and Pain Perception during Cold Noxious Stimuli in Humans. *Scand J Pain*, 13, 12-16. doi:10.1016/j.sjpain.2016.05.037
- Lee, J. H. L., C. S. (2013). A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the extended-release tramadol hydrochloride/acetaminophen fixed-dose combination tablet for the treatment of chronic low back pain. *Clin Ther*, 35(11), 1830-1840. doi:10.1016/j.clinthera.2013.09.017
- Lee, M. C. W., V.; Tracey, I. (2014). Imaging opioid analgesia in the human brain and its potential relevance for understanding opioid use in chronic pain. *Neuropharmacology*, 84, 123-130. doi:10.1016/j.neuropharm.2013.06.035
- Leng, X. L., Z.; Lv, H.; Zheng, Y.; Liu, Y.; Dai, K.; Yao, C.; Yan, X.; Zeng, X. (2015). Effectiveness and Safety of Transdermal Buprenorphine Versus Sustained-release Tramadol in Patients With Moderate to Severe Musculoskeletal Pain: An 8-Week, Randomized, Double-Blind, Double-Dummy, Multicenter, Active-controlled, Noninferiority Study. *Clin J Pain*, 31(7), 612-620. doi:10.1097/ajp.000000000000144
- Liang, D. Y. L., G.; Wang, J.; Usuka, J.; Guo, Y.; Peltz, G.; Clark, J. D. (2006). A genetic analysis of opioid-induced hyperalgesia in mice. *Anesthesiology*, 104(5), 1054-1062.
- Livingstone, J. A. A., R. M. (2002). Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. *J Bone Joint Surg Br*, 84(3), 380-386.
- LoCasale, R. J. D., C. J.; Margolis, M. K.; Tack, J.; Coyne, K. S. (2015). The impact of opioid-induced constipation among chronic pain patients with sufficient laxative use. *Int J Clin Pract*, 69(12), 1448-1456. doi:10.1111/ijcp.12718
- Louw, A. Z., K.; Puenteadura, E. J.; Diener, I. (2016). The efficacy of pain neuroscience education on musculoskeletal pain: A systematic review of the literature. *Physiother Theory Pract*, 32(5), 332-355. doi:10.1080/09593985.2016.1194646
- Maier, C. B., R.; Tolle, T. R.; Binder, A.; Birbaumer, N.; Birklein, F.; Gierthmuhlen, J.; Flor, H.; Geber, C.; Hugel, V.; Krumova, E. K.; Landwehrmeyer, G. B.; Magerl, W.; Maihofner, C.; Richter, H.; Rolke, R.; Scherens, A.; Schwarz, A.; Sommer, C.; Tronnier, V.; Uceyler, N.; Valet, M.; Wasner, G.; Treede, R. D. (2010). Quantitative sensory testing in the German Research Network on

- Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain*, 150(3), 439-450. doi:10.1016/j.pain.2010.05.002
- Manchikanti, L. G., J.; Boswell, M. V.; Fellows, B.; Manchukonda, R.; Pampati, V. (2007). Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients. *J Opioid Manag*, 3(2), 89-100.
- Manchikanti, L. P., V.; Damron, K. S.; Fellows, B.; Barnhill, R. C.; Beyer, C. D. (2001). Prevalence of opioid abuse in interventional pain medicine practice settings: a randomized clinical evaluation. *Pain Physician*, 4(4), 358-365.
- Manicourt, D. H. B., J. P.; Boutsen, Y.; Depreux, G.; Devogelaer, J. P. (2004). Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. *Arthritis Rheum*, 50(11), 3690-3697. doi:10.1002/art.20591
- Martin, B. C. F., M. Y.; Edlund, M. J.; Devries, A.; Braden, J. B.; Sullivan, M. D. (2011). Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med*, 26(12), 1450-1457. doi:10.1007/s11606-011-1771-0
- Mason. (2010). Diagnosis of Obstructive Sleep Apnea *Murray and Nadel's Textbook of Respiratory Medicine* (5th ed.).
- Mattick, R. P. B., C.; Kimber, J.; Davoli, M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*(2), CD002207. doi:10.1002/14651858.CD002207.pub4
- McNicol, E. D. M., A.; Eisenberg, E. (2013). Opioids for neuropathic pain. *Cochrane Database Syst Rev*(8), Cd006146. doi:10.1002/14651858.CD006146.pub2
- Mekhail, N. A. C., J.; Narouze, S.; Kapural, L.; Mekhail, M. N.; Deer, T. (2010). Clinical applications of neurostimulation: forty years later. *Pain Pract*, 10(2), 103-112. doi:10.1111/j.1533-2500.2009.00341.x
- Michaleff, Z. A. M., C. G.; Lin, C. W.; Rebbeck, T.; Jull, G.; Latimer, J.; Connelly, L.; Sterling, M. (2014). Comprehensive physiotherapy exercise programme or advice for chronic whiplash (PROMISE): a pragmatic randomised controlled trial. *Lancet*, 384(9938), 133-141. doi:10.1016/s0140-6736(14)60457-8
- Moulin, D. E. C., A. J.; Gilron, I.; Ware, M. A.; Watson, C. P.; Sessle, B. J.; Coderre, T.; Morley-Forster, P. K.; Stinson, J.; Boulanger, A.; Peng, P.; Finley, G. A.; Taenzer, P.; Squire, P.; Dion, D.; Cholkan, A.; Gilani, A.; Gordon, A.; Henry, J.; Jovey, R.; Lynch, M.; Mailis-Gagnon, A.; Panju, A.; Rollman, G. B.; Velly, A.; Canadian Pain, Society. (2007). Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag*, 12(1), 13-21.
- Naliboff, B. D. W., S. M.; Schieffer, B.; Bolus, R.; Pham, Q.; Baria, A.; Aragaki, D.; Van Vort, W.; Davis, F.; Shekelle, P. (2011). A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain*, 12(2), 288-296. doi:10.1016/j.jpain.2010.09.003
- National Opioid Use Guideline Group. (2010). Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain - Part B: Recommendations for Practice.
- Newcomer, K. L. V. D., K. S.; Shelerud, R. A.; Long, K. H.; Crawford, B. (2008). Is a videotape to change beliefs and behaviors superior to a standard videotape in acute low back pain? A randomized controlled trial. *Spine J*, 8(6), 940-947. doi:10.1016/j.spinee.2007.08.007
- Niehof, S. P. B., A.; Huygen, F. J.; Zijlstra, F. J. (2008). Using skin surface temperature to differentiate between complex regional pain syndrome type 1 patients after a fracture and control patients with various complaints after a fracture. *Anesth Analg*, 106(1), 270-277, table of contents. doi:10.1213/01.ane.0000289635.95869.70
- Niehof, S. P. H., F. J.; Stronks, D. L.; Klein, J.; Zijlstra, F. J. (2007). Reliability of observer assessment of thermographic images in complex regional pain syndrome type 1. *Acta Orthop Belg*, 73(1), 31-37.
- Niehof, S. P. H., F. J.; van der Weerd, R. W.; Westra, M.; Zijlstra, F. J. (2006). Thermography imaging during static and controlled thermoregulation in complex regional pain syndrome type 1: diagnostic value and involvement of the central sympathetic system. *Biomed Eng Online*, 5, 30. doi:10.1186/1475-925X-5-30
- Noppers, I. O., E.; Niesters, M.; Aarts, L.; Mooren, R.; Dahan, A.; Kharasch, E.; Sarton, E. (2011). Effect of rifampicin on S-ketamine and S-norketamine plasma concentrations in healthy volunteers after intravenous S-ketamine administration. *Anesthesiology*, 114(6), 1435-1445. doi:10.1097/ALN.0b013e318218a881

- Norrbrink, C. L., T. (2009). Tramadol in neuropathic pain after spinal cord injury: a randomized, double-blind, placebo-controlled trial. *Clin J Pain*, 25(3), 177-184. doi:10.1097/AJP.0b013e31818a744d
- North, R. B. K., David H.; Farrokhi, Farrokh; Piantadosi, Steven A. (2005). Spinal Cord Stimulation versus Repeated Lumbosacral Spine Surgery for Chronic Pain: A Randomized, Controlled Trial. *Neurosurgery*, 56(1), 98-107. doi:10.1227/01.neu.0000144839.65524.e0
- O'Connell, N. E. W., B. M.; Gibson, W.; Carr, D. B.; Birklein, F.; Stanton, T. R. (2016). Local anaesthetic sympathetic blockade for complex regional pain syndrome. *Cochrane Database Syst Rev*, 7, CD004598. doi:10.1002/14651858.CD004598.pub4
- O'Connell, N. E. W., B. M.; McAuley, J.; Marston, L.; Moseley, G. L. (2013). Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database Syst Rev*(4), Cd009416. doi:10.1002/14651858.CD009416.pub2
- O'Connor, A. B. D., R. H. (2009). Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med*, 122(10 Suppl), S22-32. doi:10.1016/j.amjmed.2009.04.007
- Oerlemans, H. M. O., R. A.; de Boo, T.; Perez, R. S.; Goris, R. J. (1999). Signs and symptoms in complex regional pain syndrome type I/reflex sympathetic dystrophy: judgment of the physician versus objective measurement. *Clin J Pain*, 15(3), 224-232.
- Oesch, P. K., J.; Hagen, K. B.; Bachmann, S. (2010). Effectiveness of exercise on work disability in patients with non-acute non-specific low back pain: Systematic review and meta-analysis of randomised controlled trials. *J Rehabil Med*, 42(3), 193-205. doi:10.2340/16501977-0524
- Okie, S. (2010). A flood of opioids, a rising tide of deaths. *N Engl J Med*, 363(21), 1981-1985. doi:10.1056/NEJMp1011512
- Ooi, Y. C. F., S.; Wang, D.; Jallo, J.; Ho, R. T.; Sharan, A. (2011). Simultaneous use of neurostimulators in patients with a preexisting cardiovascular implantable electronic device. *Neuromodulation*, 14(1), 20-25; discussion 25-26. doi:10.1111/j.1525-1403.2010.00314.x
- Pedersen, L. B., P. C.; Riphagen, II; Fredheim, O. M. (2014). Long- or short-acting opioids for chronic non-malignant pain? A qualitative systematic review. *Acta Anaesthesiol Scand*, 58(4), 390-401. doi:10.1111/aas.12279
- Peltz, E. S., F.; Lanz, S.; Muller, R.; Maihofner, C. (2011). Impaired hand size estimation in CRPS. *J Pain*, 12(10), 1095-1101. doi:10.1016/j.jpain.2011.05.001
- Perez, R. S. B., P. E.; Zuurmond, W. W.; Bezemer, P. D.; Brink, H. E.; de Lange, J. J. (2005). Physicians' assessments versus measured symptoms of complex regional pain syndrome type 1: presence and severity. *Clin J Pain*, 21(3), 272-276.
- Perez, R. S. B., P. E.; Zuurmond, W. W.; Giezeman, M. J.; van Dasselaar, N. T.; Vranken, J.; de Lange, J. J. (2002). Interrater reliability of diagnosing complex regional pain syndrome type I. *Acta Anaesthesiol Scand*, 46(4), 447-450.
- Perez, R. S. C., S.; Marinus, J.; Zuurmond, W. W.; de Lange, J. J. (2007). Diagnostic criteria for CRPS I: differences between patient profiles using three different diagnostic sets. *Eur J Pain*, 11(8), 895-902. doi:10.1016/j.ejpain.2007.02.006
- Perez, R. S. K., C.; Bezemer, P. D.; Zuurmond, W. W.; de Lange, J. J. (2005). Predictive value of symptom level measurements for complex regional pain syndrome type I. *Eur J Pain*, 9(1), 49-56. doi:10.1016/j.ejpain.2004.04.003
- Perez, R. S. Z., P. E.; Dijkstra, P. U.; Thomassen-Hilgersom, I. L.; Zuurmond, W. W.; Rosenbrand, K. C.; Geertzen, J. H.; Crps I. task force. (2010). Evidence based guidelines for complex regional pain syndrome type 1. *BMC Neurol*, 10, 20. doi:10.1186/1471-2377-10-20
- Perez, R. S. Z., W. W.; Bezemer, P. D.; Kuik, D. J.; van Loenen, A. C.; de Lange, J. J.; Zuidhof, A. J. (2003). The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. *Pain*, 102(3), 297-307.
- Persson, J. (2013). Ketamine in pain management. *CNS Neurosci Ther*, 19(6), 396-402. doi:10.1111/cns.12111
- Petersen, T. L., K.; Nordsteen, J.; Olsen, S.; Fournier, G.; Jacobsen, S. (2011). The McKenzie method compared with manipulation when used adjunctive to information and advice in low back pain patients presenting with centralization or peripheralization: a randomized controlled trial. *Spine (Phila Pa 1976)*, 36(24), 1999-2010. doi:10.1097/BRS.0b013e318201ee8e
- Plesner, K. J., H. I.; Hojsted, J. (2016). Smoking history, nicotine dependence and opioid use in patients with chronic non-malignant pain. *Acta Anaesthesiol Scand*, 60(7), 988-994. doi:10.1111/aas.12741

- Poulsen, J. L. B., C.; Olesen, A. E.; Nilsson, M.; Drewes, A. M. (2015). Evolving paradigms in the treatment of opioid-induced bowel dysfunction. *Therap Adv Gastroenterol*, 8(6), 360-372. doi:10.1177/1756283x15589526
- Quigley, C. (2004). Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev*(3), CD004847. doi:10.1002/14651858.CD004847
- Ramchurn, N. M., C.; Leitch, E.; Arutchelvam, V.; Narayanan, K.; Weaver, J.; Hamilton, J.; Heycock, C.; Saravanan, V.; Kelly, C. (2009). Upper limb musculoskeletal abnormalities and poor metabolic control in diabetes. *Eur J Intern Med*, 20(7), 718-721. doi:10.1016/j.ejim.2009.08.001
- Rauck, R. L., Eisenach, J. C., Jackson, K., Young, L. D., & Southern, J. (1993). Epidural clonidine treatment for refractory reflex sympathetic dystrophy. *Anesthesiology*, 79(6), 1163-1169; discussion 1127A.
- Rauck, R. L. P., J.; Xiang, Q.; Tzanis, E.; Finn, A. (2016). Efficacy and tolerability of buccal buprenorphine in opioid-naive patients with moderate to severe chronic low back pain. *Postgrad Med*, 128(1), 1-11. doi:10.1080/00325481.2016.1128307
- Ray, W. A. C., C. P.; Murray, K. T.; Hall, K.; Stein, C. M. (2016). Prescription of Long-Acting Opioids and Mortality in Patients With Chronic Noncancer Pain. *Jama*, 315(22), 2415-2423. doi:10.1001/jama.2016.7789
- Rhodin, A. S., M.; Gordh, T. (2010). Opioid endocrinopathy: a clinical problem in patients with chronic pain and long-term oral opioid treatment. *Clin J Pain*, 26(5), 374-380. doi:10.1097/AJP.0b013e3181d1059d
- Rintala, D. H. H., S. A.; Courtade, D.; Fiess, R. N.; Tastard, L. V.; Loubser, P. G. (2007). Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Arch Phys Med Rehabil*, 88(12), 1547-1560. doi:10.1016/j.apmr.2007.07.038
- Ris, I. S., K.; Gram, B.; Agerbo, K.; Boyle, E.; Juul-Kristensen, B. (2016). Does a combination of physical training, specific exercises and pain education improve health-related quality of life in patients with chronic neck pain? A randomised control trial with a 4-month follow up. *Man Ther*, 26, 132-140. doi:10.1016/j.math.2016.08.004
- Rolfs, R. T. J., E.; Williams, N. J.; Sundwall, D. N.; Utah Department of, Health. (2010). Utah clinical guidelines on prescribing opioids for treatment of pain. *J Pain Palliat Care Pharmacother*, 24(3), 219-235. doi:10.3109/15360288.2010.503265
- Rosenberger, P. H. J., P.; Ickovics, J. (2006). Psychosocial factors and surgical outcomes: an evidence-based literature review. *J Am Acad Orthop Surg*, 14(7), 397-405.
- Rosenthal, R. N. L., M. R.; Kim, S.; Chen, M.; Beebe, K. L.; Vocci, F. J. (2016). Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial. *Jama*, 316(3), 282-290. doi:10.1001/jama.2016.9382
- Roskos, S. E. K., A. J.; Newman, L. M.; Wallace, L. S. (2007). Literacy demands and formatting characteristics of opioid contracts in chronic nonmalignant pain management. *J Pain*, 8(10), 753-758. doi:10.1016/j.jpain.2007.01.005
- Rowbotham, M. C. G., V.; Kunz, N. R.; Lei, D. (2004). Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain*, 110(3), 697-706. doi:10.1016/j.pain.2004.05.010
- Saarto, T. W., P. J. (2007). Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*(4), CD005454. doi:10.1002/14651858.CD005454.pub2
- Sahin, F. Y., F.; Kotevoglou, N.; Kuran, B. (2006). Efficacy of salmon calcitonin in complex regional pain syndrome (type 1) in addition to physical therapy. *Clin Rheumatol*, 25(2), 143-148. doi:10.1007/s10067-005-1153-2
- Sanacora, G. F., M. A.; McDonald, W.; Mathew, S. J.; Turner, M. S.; Schatzberg, A. F.; Summergrad, P.; Nemeroff, C. B.; American Psychiatric Association Council of Research Task Force on Novel Biomarkers; Treatments,. (2017). A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry*, 74(4), 399-405. doi:10.1001/jamapsychiatry.2017.0080
- Sandroni, P. L., P. A.; Ferrer, T.; Opfer-Gehrking, T. L.; Willner, C. L.; Wilson, P. R. (1998). Complex regional pain syndrome I (CRPS I): prospective study and laboratory evaluation. *Clin J Pain*, 14(4), 282-289.

- Santos, J. A., J.; Fareleira, F.; Vaz-Carneiro, A.; Costa, J. (2015). Tapentadol for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev*(5), Cd009923. doi:10.1002/14651858.CD009923.pub2
- Saragiotto, B. T. M., C. G.; Yamato, T. P.; Costa, L. O.; Menezes Costa, L. C.; Ostelo, R. W.; Macedo, L. G. (2016). Motor control exercise for chronic non-specific low-back pain. *Cochrane Database Syst Rev*(1), Cd012004. doi:10.1002/14651858.cd012004
- Schmidt-Hansen, M. B., M. I.; Arnold, S.; Bromham, N.; Hilgart, J. S. (2015). Oxycodone for cancer-related pain. *Cochrane Database Syst Rev*(2), CD003870. doi:10.1002/14651858.CD003870.pub5
- Schmidt-Hansen, M. B., M. I.; Hilgart, J. (2015). Oxycodone for Cancer Pain in Adult Patients. *Jama*, 314(12), 1282-1283. doi:10.1001/jama.2015.8556
- Schuckit, M. A. (2016). Treatment of Opioid-Use Disorders. *N Engl J Med*, 375(4), 357-368. doi:10.1056/NEJMra1604339
- Schurmann, M. G., G.; Andress, H. J.; Furst, H.; Schildberg, F. W. (1999). Assessment of peripheral sympathetic nervous function for diagnosing early post-traumatic complex regional pain syndrome type I. *Pain*, 80(1-2), 149-159.
- Schwartz, C. E. F., J. A. (2009). Understanding inconsistencies in patient-reported outcomes after spine treatment: response shift phenomena. *Spine J*, 9(12), 1039-1045. doi:10.1016/j.spinee.2009.05.010
- Schwartz, S. E., M.; Shapiro, D. Y.; Okamoto, A.; Lange, R.; Haeussler, J.; Rauschkolb, C. (2011). Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin*, 27(1), 151-162. doi:10.1185/03007995.2010.537589
- Schwartzman, R. J. A., G. M.; Grothusen, J. R.; Paylor, T.; Reichenberger, E.; Perreault, M. (2009). Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain*, 147(1-3), 107-115. doi:10.1016/j.pain.2009.08.015
- Sigtermans, M. J. v. H., J. J.; Bauer, M. C.; Arbous, M. S.; Marinus, J.; Sarton, E. Y.; Dahan, A. (2009). Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain*, 145(3), 304-311. doi:10.1016/j.pain.2009.06.023
- Smart, K. M. W., B. M.; O'Connell, N. E. (2016). Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. *Cochrane Database Syst Rev*, 2, Cd010853. doi:10.1002/14651858.CD010853.pub2
- Smith, H. S. (2009). Opioid metabolism. *Mayo Clin Proc*, 84(7), 613-624. doi:10.1016/S0025-6196(11)60750-7
- Stannard, C. G., H.; Derry, S.; Aldington, D.; Cole, P.; Cooper, T. E.; Knaggs, R.; Wiffen, P. J.; Moore, R. A. (2016). Hydromorphone for neuropathic pain in adults. *Cochrane Database Syst Rev*(5), CD011604. doi:10.1002/14651858.CD011604.pub2
- Starrels, J. L. B., W. C.; Alford, D. P.; Kapoor, A.; Williams, A. R.; Turner, B. J. (2010). Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med*, 152(11), 712-720. doi:10.7326/0003-4819-152-11-201006010-00004
- Storheim, K. B., J. I.; Holm, I.; Koller, A. K.; Bo, K. (2003). Intensive group training versus cognitive intervention in sub-acute low back pain: short-term results of a single-blind randomized controlled trial. *J Rehabil Med*, 35(3), 132-140.
- Strand, M. C. F., B.; Arnestad, M.; Morland, J. (2013). Can patients receiving opioid maintenance therapy safely drive? A systematic review of epidemiological and experimental studies on driving ability with a focus on concomitant methadone or buprenorphine administration. *Traffic Inj Prev*, 14(1), 26-38. doi:10.1080/15389588.2012.689451
- Straube, S. D., S.; Moore, R. A.; Cole, P. (2013). Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. *Cochrane Database Syst Rev*(9), CD002918. doi:10.1002/14651858.CD002918.pub3
- Straube, S. D., S.; Moore, R. A.; McQuay, H. J. (2010). Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. *Cochrane Database Syst Rev*(7), CD002918. doi:10.1002/14651858.CD002918.pub2
- Straube, S. H., M.; Schroder, H.; Arendacka, B.; Fan, X.; Moore, R. A.; Friede, T. (2016). Back schools for the treatment of chronic low back pain: possibility of benefit but no convincing evidence after 47

- years of research-systematic review and meta-analysis. *Pain*, 157(10), 2160-2172. doi:10.1097/j.pain.0000000000000640
- Stude, P. E.-K., E. K.; Lenz, M.; Lissek, S.; Nicolas, V.; Peters, S.; Westermann, A.; Tegenthoff, M.; Maier, C. (2014). Local anesthetic sympathectomy restores fMRI cortical maps in CRPS I after upper extremity stellate blockade: a prospective case study. *Pain Physician*, 17(5), E637-644.
- Taskaynatan, M. A. O., A.; Tan, A. K.; Dincer, K.; Kalyon, T. A. (2004). Bier block with methylprednisolone and lidocaine in CRPS type I: a randomized, double-blinded, placebo-controlled study. *Reg Anesth Pain Med*, 29(5), 408-412.
- Tavares Figueiredo, I. D., A.; Tran, B.; Duflos, C.; Julia, M.; Herisson, C.; Coudeyre, E. (2016). Educational self-care objectives within a functional spine restoration program. Retrospective study of 104 patients. *Ann Phys Rehabil Med*, 59(5-6), 289-293. doi:10.1016/j.rehab.2016.03.006
- Todd, K. H. D., C.; D'Adamo, A. P.; Goe, L. (2000). Ethnicity and analgesic practice. *Ann Emerg Med*, 35(1), 11-16.
- Van Calenbergh, F. G., J.; Van Laere, K.; Dupont, P.; Plaghki, L.; Depreitere, B.; Kupers, R. (2009). Long term clinical outcome of peripheral nerve stimulation in patients with chronic peripheral neuropathic pain. *Surg Neurol*, 72(4), 330-335; discussion 335. doi:10.1016/j.surneu.2009.03.006
- Varenna, M. Z., F.; Ghiringhelli, D.; Binelli, L.; Bevilacqua, M.; Bettica, P.; Sinigaglia, L. (2000). Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. *J Rheumatol*, 27(6), 1477-1483.
- Vargas-Schaffer, G. (2010). Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician*, 56(6), 514-517, e202-515.
- Verdugo, R. J. O., J. L. (1994). 'Sympathetically maintained pain.' I. Phentolamine block questions the concept. *Neurology*, 44(6), 1003-1010.
- Vibe Fersum, K. O. S., P.; Skouen, J. S.; Smith, A.; Kvale, A. (2013). Efficacy of classification-based cognitive functional therapy in patients with non-specific chronic low back pain: a randomized controlled trial. *Eur J Pain*, 17(6), 916-928. doi:10.1002/j.1532-2149.2012.00252.x
- Vogel, T. G., G.; Ockert, B.; Pellengahr, C. S.; Schurmann, M. (2010). Sympathetic dysfunction in long-term complex regional pain syndrome. *Clin J Pain*, 26(2), 128-131. doi:10.1097/AJP.0b013e3181b5effc
- Vowles, K. E. M., M. L.; Julnes, P. S.; Frohe, T.; Ney, J. P.; van der Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*, 156(4), 569-576. doi:10.1097/01.j.pain.0000460357.01998.f1
- Wasan, A. D. M., E.; Edwards, R. R.; Katz, J. N.; Nedeljkovic, S. S.; Dolman, A. J.; Janfaza, D.; Isaac, Z.; Jamison, R. N. (2015). Psychiatric Comorbidity Is Associated Prospectively with Diminished Opioid Analgesia and Increased Opioid Misuse in Patients with Chronic Low Back Pain. *Anesthesiology*, 123(4), 861-872. doi:10.1097/aln.0000000000000768
- Washington State Agency Medical Directors Group. (2010). Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain: An Educational Aid to Improve Care and Safety with Opioid Therapy.
- Washington State Agency Medical Directors Group. (2015). Interagency Guideline on Prescribing Opioids for Pain. In W. S. A. M. D. G. (AMDG) (Ed.), (3rd Edition ed., Vol. 3rd Edition). Washington State.
- Wasner, G. (2010). Vasomotor disturbances in complex regional pain syndrome--a review. *Pain Med*, 11(8), 1267-1273. doi:10.1111/j.1526-4637.2010.00914.x
- Wasner, G. S., J.; Baron, R. (2002). Skin temperature side differences--a diagnostic tool for CRPS? *Pain*, 98(1-2), 19-26.
- Wasner, G. S., J.; Heckmann, K.; Maier, C.; Baron, R. (2001). Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. *Brain*, 124(Pt 3), 587-599.
- Webster, B. S. V., S. K.; Gatchel, R. J. (2007). Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. *Spine (Phila Pa 1976)*, 32(19), 2127-2132. doi:10.1097/BRS.0b013e318145a731
- Webster, L. R. F., P. G. (2010). Approaches to improve pain relief while minimizing opioid abuse liability. *J Pain*, 11(7), 602-611. doi:10.1016/j.jpain.2010.02.008
- Wiedemer, N. L. H., P. S.; Arndt, I. O.; Gallagher, R. M. (2007). The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med*, 8(7), 573-584. doi:10.1111/j.1526-4637.2006.00254.x
- Wiffen, P. J., McQuay, H. J., Edwards, J. E., & Moore, R. A. (2005). Gabapentin for acute and chronic pain. *Cochrane Database Syst Rev*(3), CD005452. doi:10.1002/14651858.CD005452



- Wiffen, P. J. D., S.; Moore, R. A.; Stannard, C.; Aldington, D.; Cole, P.; Knaggs, R. (2015). Buprenorphine for neuropathic pain in adults. *Cochrane Database Syst Rev*(9), Cd011603. doi:10.1002/14651858.CD011603.pub2
- Williams, K. A., C.; Steinberg, L.; Doyle, E.; Epstein, B.; Smith, D.; Hobbs, G.; Gross, R.; Kelley, G.; Cooper, L. (2009). Evaluation of the effectiveness and efficacy of Iyengar yoga therapy on chronic low back pain. *Spine (Phila Pa 1976)*, 34(19), 2066-2076. doi:10.1097/BRS.0b013e3181b315cc
- Wolff, R. F. A., D.; Truysers, C.; Hernandez, A. V.; Misso, K.; Riemsma, R.; Kleijnen, J. (2012). Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. *Curr Med Res Opin*, 28(5), 833-845. doi:10.1185/03007995.2012.678938
- Wong, S. Y. C., F. W.; Wong, R. L.; Chu, M. C.; Kitty Lam, Y. Y.; Mercer, S. W.; Ma, S. H. (2011). Comparing the effectiveness of mindfulness-based stress reduction and multidisciplinary intervention programs for chronic pain: a randomized comparative trial. *Clin J Pain*, 27(8), 724-734. doi:10.1097/AJP.0b013e3182183c6e
- Woolf, C. (2006). Wall & Melzacks text book of pain. 5th ed. Ch 5 pg 91,95. - 2006.pdf>
- Yamato, T. P. M., C. G.; Saragiotto, B. T.; Hancock, M. J.; Ostelo, R. W.; Cabral, C. M.; Menezes Costa, L. C.; Costa, L. O. (2015). Pilates for low back pain. *Cochrane Database Syst Rev*(7), CD010265. doi:10.1002/14651858.CD010265.pub2
- Yi, P. P., P. (2015). Opioid Induced Hyperalgesia. *Pain Med*, 16 Suppl 1, S32-36. doi:10.1111/pme.12914
- Zacharoff, K. L. (2010). Chronic Opioid Therapy: Driving and Work Safety. Retrieved from [https://www.painedu.org/articles\\_timely.asp?ArticleNumber=31](https://www.painedu.org/articles_timely.asp?ArticleNumber=31)
- Zale, E. L. D., M. L.; Hooten, W. M.; Warner, D. O.; Zvolensky, M. J.; Ditte, J. W. (2015). Tobacco Smoking, Nicotine Dependence, and Patterns of Prescription Opioid Misuse: Results From a Nationally Representative Sample. *Nicotine Tob Res*, 17(9), 1096-1103. doi:10.1093/ntr/ntu227
- Zhou, Y. L. (2008). Principles of Pain Management *Bradley: Neurology in Clinical Practice* (5th ed.): MD Consult.
- Zollinger, P. E. T., W. E.; Breederveld, R. S.; Kreis, R. W. (2007). Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study. *J Bone Joint Surg Am*, 89(7), 1424-1431. doi:10.2106/JBJS.F.01147