IV. Alternatives to Opioids for the Treatment of Pain

"We cannot solve our problems with the same thinking we used when we created them."

—Albert Einstein

Using nonopioids to address pain management is a novel strategy called Alternatives to Opioids (ALTO). The first Colorado ALTO program was implemented in 2016 at Swedish Medical Center in Englewood, a busy level-1 trauma center. The press has inaccurately branded such emergency departments as "opioid-free EDs," an exclusionary term that misrepresents the care provided. ALTO simply recommends using opioids infrequently, primarily as second-line treatments and only after effective nonopioid alternatives have been trialed.

Such programs should be studied by all ED providers and uniformly adopted by hospitals. Through education, the implementation of novel concepts, and partnerships within the community, an ALTO-based multidisciplinary approach can transform pain management practice in Colorado.

Treatment Goals

- Utilize nonopioid approaches as the first-line therapy.
- Utilize opioids as a second-line treatment.
- Opioids can be given as rescue medication.
- Discuss realistic pain management goals with patients.
- Discuss addiction potential and side effects with those using opioids.

The ALTO program utilizes the CERTA concept: **c**hannels, **e**nzymes, **r**eceptors, **t**argeted, **a**nalgesia. The CERTA concept optimizes the following medication classes in place of opioids: Cox-1, 2, 3 inhibitors, NMDA receptor antagonists, sodium channel blockers, nitrous oxide, inflammatory cytokine inhibitors, and GABA agonists/modulators. Specific agents include NSAIDs and acetaminophen, ketamine, lidocaine, nitrous oxide, corticosteroids, benzodiazepines, and gabapentin.

The protocol targets multiple pain receptors, making use of nonopioid medications, trigger-point injections, nitrous oxide, and ultrasound-guided nerve blocks to tailor a patient's pain management needs and substantially decrease opioid use. Examples of this approach include:

- Treating renal colic with intravenous lidocaine;
- Managing acute lower back pain with a combination of oral nonopioids and topical pain medications with directed trigger-point injections;
- Treating extremity fractures with ultrasound-guided nerve blocks; and
- Using an algorithm to manage acute headache/migraine pain with a variety of nonopioid medications.

Only if patients' pain is not adequately managed using ALTO techniques are opioids used as a rescue medication.

Alternative Medications

Ketamine

Ketamine has been used extensively in the emergency department for procedural sedation and rapid-sequence intubation. Recent research has demonstrated that a low (subdissociative) dose (0.1-0.3 mg/kg IV) is safe and effective for pain management.[78-81] Due to the relatively short-lived analgesic effects of the drug, the initial bolus can be followed by an infusion (9-30 mg/hour) for sustained effect.[92-95] Caution should be used in any patient with a significant psychiatric history, and use should be avoided in anyonet with a history of post-traumatic stress disorder.

Lidocaine

Lidocaine is an ideal agent for treating visceral and central pain, and also may be useful when narcotics are inefficient or lead to undesirable side effects. Intravenous or topical (4% or 5% transdermal patch) doses are effective for controlling renal colic and neuropathic pain associated with conditions such as diabetic neuropathy, postoperative or post-herpetic pain, headaches, and neurological malignancies.[82-83] Topical lidocaine also is an appropriate treatment for low-back pain.[84-88] Intravenous lidocaine should be used with caution in any patient with a significant cardiac history. Side effects of the drug are minimal when used sparingly.

Trigger-Point Injections

A focal area of spasm and inflammation (eg, trapezius, rhomboid, low back) can be associated with chronic myofascial pain syndrome. Palpation of the trigger point should fully reproduce pain, which may be referred to other areas (eg, nodule or taut band of spasm). Dry needling will cause a disruption of the spastic feedback loop by interrupting abnormal activity in the sensory and motor nerve endings and muscle fibers. Using local anesthetics such as marcaine or lidocaine for this procedure often resolves pain and decreases soreness. Indications for this approach include a palpable, taut band or nodule, reproducible pain with palpitation, or a chronic painful condition.[89-92] Trigger-point injection has also been found to be a successful treatment strategy for migraines.[93-95]

Nitrous Oxide

Nitrous oxide is a tasteless, colorless gas administered in combination with oxygen via mask or nasal hood at a maximum concentration of 70%. The gas is absorbed via pulmonary vasculature and does not combine with hemoglobin or other body tissues. Featuring a rapid onset and elimination (<60 sec), the agent contains both analgesic and anxiolytic properties. It typically is used in combination with a local anesthetic or other pain medications. Pulse oximetry is the only patient monitoring required. There are no fasting requirements; patients can drive after administration; and no IV line is needed. There is solid evidence to support its role in the management of pediatric pain and sedation, prehospital pain relief, colonoscopy, and bronchoscopy.[96-99] Additional indications for the use of nitrous oxide include laceration repair, incision and drainage, wound care, foreign body removal, central venous access, peripheral venous access, fecal disimpaction, and as an adjunct for dislocations and splinting.

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to manage most painful conditions, particularly musculoskeletal pain, migraine, and renal colic.[100] These agents can be administered intravenously, intramuscularly, orally, and topically. For ketorolac, literature supports using a maximum intravenous dose of 15 mg, as higher doses do not increase efficacy and may introduce unnecessary harm.[101,102] Caution should be used in patients with renal dysfunction or heart failure, or when there is a concern for bleeding.[103] For these subpopulations, consider topical choices such as diclofenac gel or a patch. Topical agents have significantly lower systemic absorption and lower rates of adverse drug events.

Haloperidol

Haloperidol is a "typical" or first-generation antipsychotic agent. It can be administered intravenously, intramuscularly, and orally and often is used for the treatment of psychiatric emergencies. The drug also can be used in low doses as an adjunct treatment for pain and nausea. At doses of 2.5 to 5 mg, haloperidol is effective for the management of abdominal pain and migraine-associated headaches.[104,105] Anecdotally there has been a rise in the number of haldol "allergies." If a patient's reaction is suspected to stem from a true allergy rather than an extrapyramidal side effect of the drug, olanzepine is a reasonable alternative.

Dicyclomine

Dicyclomine is an antispasmodic and anticholinergic agent that acts to alleviate smooth muscle spasms in the gastrointestinal tract. It is effective for treating abdominal pain, particularly caused by cramping.[106-108] The drug can be administered either orally or intramuscularly, but should NOT be administered intravenously. Due to its anticholinergic action, dicyclomine should be avoided in the geriatric population.[109]

Special Populations

Not all patients are appropriate candidates for each agent suggested in the ALTO treatment protocol. All medications should be administered with thoughtful consideration of patient-specific factors such as age, organ function, comorbidities, and other medications being taken.

Geriatric Patients

Great care should be taken when treating elderly patients. Some of the therapies suggested may be inappropriate for use in this vulnerable population, including dicyclomine, haloperidol, diphenhydramine, and muscle relaxants. The Beers Criteria list is a well-established resource that should be consulted when making treatment decisions for patients older than 65 years.[109] When possible, consider prescribing topical agents instead of oral or intravenous drugs. Also consider recommending heat, massage, and physical therapy on discharge for musculoskeletal pain.

Renal Dysfunction

Not all ALTO agents are safe for patients with renal dysfunction, particularly NSAIDs. In patients who cannot receive systemic NSAIDs, consider prescribing topical agents such as diclofenac gel or patches.

Heart Failure

Not all ALTO agents are recommended for use in patients with heart failure, particularly steroids and NSAIDs. For patients in whom these medications should be avoided, consider prescribing topical alternatives.

Pregnant Patients

Pregnant women should be excluded from the ALTO protocol. Many of these agents are contraindicated in pregnancy, including haloperidol, NSAIDs, and valproic acid.

Pediatric Patients

Do not use the ALTO protocol when managing children younger than 15 years or less than 40 kg. Although ALTO principles are applicable to the pediatric population, precautions should be considered and agents must be dosed appropriately.

PRACTICE RECOMMENDATIONS

Note: Many of the recommendations in the following section are based on the ALTO clinical model. A full discussion of each drug and procedure is beyond the scope of these guidelines. Appropriate references are listed, however. (See *Figure 5* for specific treatment pathways by indication.)

1. **All emergency departments should implement ALTO programs and provide opioid-free pain treatment pathways for the following conditions *(see Appendix 1)*:**
    a. Acute on chronic opioid-tolerant radicular lower back pain
    b. Opioid-naive musculoskeletal pain
    c. Migraine or recurrent primary headache
    d. Extremity fracture or joint dislocation
    e. Gastroparesis-associated or chronic functional abdominal pain
    f. Renal colic
2. **Emergency departments should integrate ALTO into their computerized physician order entry systems to facilitate a seamless adoption by clinicians.**
3. **For musculoskeletal pain, consider a multimodal treatment approach using acetaminophen, NSAIDs, steroids, topical medications, trigger-point injections, and (for severe pain) ketamine.**
4. **For headache and migraine, consider a multimodal treatment approach that includes the administration of antiemetic agents, NSAIDs, steroids, valproic acid, magnesium, and triptans. Strongly consider cervical trigger-point injection.**

5. **For pain with a neuropathic component, consider gabapentin.**
6. **For pain with a tension component, consider a muscle relaxant.**
7. **For pain caused by renal colic, consider an NSAID, lidocaine infusion, and desmopressin nasal spray.**
8. **For chronic abdominal pain, consider low doses of haloperidol, diphenhydramine, and lidocaine infusion.**
9. **For extremity fracture or joint dislocation, consider the immediate use of nitrous oxide and low-dose ketamine while setting up for ultrasound-guided regional anesthesia.**
10. **For arthritic or tendinitis pain, consider an intra-articular steroid/anesthetic injection.**
11. **Outpatient prescribing patterns should follow ALTO principles by minimizing opioids and utilizing a multimodal approach to adequately control pain. (See *Appendix 2* for discharge prescribing guidelines.)**

FIGURE 5. PAIN PATHWAYS BY INDICATION

POLICY RECOMMENDATIONS

1. **Hospitals should update institutional guidelines and put policies in place that enable clinicians to order and nurses to administer dose-dependent ketamine and IV lidocaine in non-ICU areas. (For more information, download the Denver Health policy on Ketamine for Acute Pain in the ED.)**
2. **Emergency departments are encouraged to assemble an interdisciplinary pain management team that includes clinicians, nurses, pharmacists, physical therapists, social workers, and case managers.**
3. **Reimbursement should be available for any service directly correlated to pain management, the reduction of opioid use, and treatment of drug-addicted patients.**

Marijuana Use in Chronic Pain

Patients frequently inquire about the use of medical marijuana for the treatment of painful conditions. Although a number of studies have been conducted on the drug's potential role in the treatment of chronic pain, results are limited. Most of the trials have been short, and many have focused on neuropathic pain resulting from a narrow range of etiologies; fewer than 3,000 patients have been studied.

Marijuana plants are comprised of more than 65 cannabinoids, including tetrahydrocannabinols (THC) and cannabidiols (CBD). It is important to note that while studies have shown the effectiveness of treating pain with a combination of these two chemicals, more research is needed to identify the positive and negative attributes of the remaining active ingredients.[110-112]

The current scheduling nature of the drug presents several roadblocks for researchers.[113,114] While previous studies have focused on the use of medical marijuana for alleviating chronic pain, there are interesting links between recently enacted state laws and an overall decline in opioid-linked overdoses and deaths. According to a study that examined medical marijuana laws and opioid analgesic overdose rates from 1999 to 2010, "States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws."[115]

At this time COACEP takes no position on the use of medical marijuana for the control of chronic pain, and recommends that emergency physicians refrain from prescribing or advocating its use until definitive studies have been conducted.

Appendix 1. ALTO Protocols and References

Musculoskeletal Pain

Note: This includes sprains, strains, or opioid-naïve lower back pain, acute neck, joint and soft tissue pain; rotator cuff tendonitis, arthritis of knee, lateral epicondylitis, greater trochanteric bursitis, biceps tendonitis, etc. Acute on chronic radicular lower back pain (opioid tolerant) can be approached in a similar manner.

NON-IV TREATMENT OPTIONS

- Acetaminophen 1,000 mg PO
- NSAID: ibuprofen 600 mg PO ***OR*** ketorolac 15 mg IV/30 mg IM
- Muscle relaxant: cyclobenzaprine 5 mg PO ***OR*** diazepam 5 mg PO
- Intranasal ketamine 50 mg
- Trigger-point injection with 1-2 mL of lidocaine 1%
- Gabapentin 300-600 mg (neuropathic component of pain)
- Lidocaine 5% patch to most painful area (max 3 patches); instruct patient to remove after 12 hours

IV TREATMENT OPTIONS

- Dexamethasone 8 mg IV
- Diazepam 5 mg IV
- Ketamine 0.1-0.3 mg/kg IV infusion over 10 min (0.1 mg/kg/hr drip)

Headache/Migraine

Note: The American Academy of Neurology and the American Headache Society do not recommend opioids except in extraordinary cases in which other agents are contraindicated (eg, pregnancy, etc.) Numerous studies reveal that opioids are not as effective as standard treatments for the management of headaches, and can render acute migraine medications less efficacious (eg, triptans). Opioid use can, in fact, promote chronic migraine and medication overuse headaches, and increase anxiety, disability, and depression in patients who suffer from migraine pain.

IMMEDIATE/FIRST-LINE THERAPY

- 1 L 0.9% NS bolus ***PLUS*** high-flow oxygen
- Dexamethasone 8 mg IV
- Ketorolac 15 mg IV
- Metoclopramide 10 mg IV
- Cervical or trapezius trigger-point injection with 1-2 mL lidocaine 1%

ALTERNATIVES

- Acetaminophen 1,000 mg PO ***PLUS*** ibuprofen 600 mg PO
- Promethazine 12.5 mg PO/IV ***OR*** prochlorperazine 10 mg PO/IV
- Sumatriptan 6 mg subcutaneous injection
- Magnesium 1 gm IV over 60 min
- Valproic acid 500 mg/50 mL normal saline over 30 min

- Haloperidol 2.5-5 mg IV over 5 min
- If tension component:
  - Cyclobenzaprine 5 mg ***OR*** diazepam 5 mg PO/IV
  - Trigger-point injection (see above)
  - Lidocaine 5% patch
- If <50% pain relief is achieved, consider placing patient in the observation unit and consulting neurology.

Renal Colic

IMMEDIATE/FIRST-LINE THERAPY

- Ketorolac 15 mg IV
- Acetaminophen 1,000 mg PO
- 1 L 0.9% normal saline bolus

SECOND-LINE IV THERAPY

- Lidocaine 1.5 mg/kg IV in 100 mL normal saline over 10 min (max 200 mg)

ALTERNATIVES

- Desmopressin acetate (DDAVP) 40 mcg IN
- Ketamine 50 mg IN

Extremity Fracture or Joint Dislocation

Note: The following strategies present an opportunity to address pain quickly and without the need for IV access.

- Focused nonsedating pain control
- Long-lasting relief for fracture pain
- Short-acting relief for joint reduction
- Proximal blocks (eg, brachial plexus)
- Distal blocks (eg, ulnar nerve)
- Immediate therapy (while setting up for block):
  - Ketamine intranasal 0.5 mg/kg (concentration 100 mg/mL); (max dose 50 mg; max volume per nare 1 mL)
  - Nitrous oxide titrated up to 70%
  - Acetaminophen 1,000 mg PO
- Followed by ultrasound-guided regional anesthesia:
  - Joint dislocation: lidocaine 0.5% perineural infiltration (max 5 mg/kg)
  - Extremity fracture: lidocaine 0.5% perineural infiltration (max 5 mg/kg)
- Discharge medications:
  - Acetaminophen 1,000 mg PO every 4-6 hrs ***PLUS*** naprosyn 500 mg PO every 12 hrs

Gastroparesis-Associated/Chronic Abdominal Pain

IMMEDIATE/FIRST-LINE THERAPY

- Metoclopramide 10 mg IV
- Prochlorperazine 10 mg IV
- Diphenhydramine 25 mg IV
- Dicyclomine 20 mg PO/IM

ALTERNATIVE OPTIONS

- Haloperidol 2.5 mg IV
- Lidocaine 1.5 mg/kg in 100 mL normal saline over 10 min (max 200 mg)
- Ketamine 0.1-0.3 mg/kg IV infusion over 10 min (0.1 mg/kg/hr until pain is tolerable)

Appendix 2. ALTO Prescribing Guide for Discharge

Headache[139,140]

FOR ACUTE ATTACKS

- Sumatriptan 100 mg PO
- Acetaminophen/aspirin/caffeine (Excedrin Migraine) PO every 6 hours ***OR*** acetaminophen 1,000 mg every 6 hours
- Dihydroergotamine mesylate 2 mg nasal spray
- Naproxen 500-550 mg 2x/day ***OR*** ibuprofen 600 mg PO every 6 hours
- Metoclopramide 10 mg PO every 6 hours

FOR PREVENTION

- Propranolol 40 mg PO 2x/day
- Divalproex DR 250 mg PO 2x/day ***OR*** extended release 500 mg PO daily
- Topiramate 25 mg PO at bedtime
- Magnesium supplementation 600 mg PO daily

Sore Throat

- Ibuprofen 600 mg PO every 6 hours
- Acetaminophen 1,000 mg PO every 6 hours
- Dexamethasone 10 mg PO once
- Viscous lidocaine

Fibromyalgia[141,142]

- Cardiovascular exercise
- Strength training
- Massage therapy
- Amitriptyline 10 mg PO at bedtime
- Cyclobenzaprine 10 mg PO every 8 hours
- Pregabalin 75 mg PO 2x/day

Uncomplicated Neck Pain[143]

- Acetaminophen 1,000 mg PO every 6 hours
- Ibuprofen 600 mg PO every 6 hours
- Cyclobenzaprine 5 mg PO every 8 hours
- Physical therapy
- Lidocaine 5% transdermal patch every 24 hours (remove after 12 hours)

Uncomplicated Back Pain[144,145]

- Acetaminophen 1,000 mg PO every 6 hours
- Ibuprofen 600 mg PO every 6 hours

- Lidocaine 5% transdermal patch every 24 hours (remove after 12 hours)
- Diclofenac 1.3% transdermal patch 2x/day ***OR*** diclofenac 1% gel 4 g 4x/day as needed
- Cyclobenzaprine 5 mg PO 3x/day
- Heat
- Physical therapy
- Exercise program

Simple Sprains[146]

- Immobilization
- Ice
- Ibuprofen 600 mg PO every 6 hours
- Acetaminophen 1,000 mg PO every 6 hours
- Diclofenac 1.3% transdermal patch 2x/day ***OR*** diclofenac 1% gel 4 g 4x/day as needed

Contusions[147]

- Compression
- Ice
- Ibuprofen 600 mg PO every 6 hours
- Acetaminophen 1,000 mg PO every 6 hours
- Lidoderm 5% patch transdermal patch every 24 hours (remove after 12 hours)

Nontraumatic Tooth Pain[148]

- Ibuprofen 600 mg PO every 6 hours ***PLUS*** acetaminophen 1,000 mg PO every 6 hours

Osteoarthritis[149]

- Diclofenac 50 mg PO every 8 hours ***OR*** naproxen 500 mg PO 2x/day ***OR*** ***c***elecoxib 200 mg daily
- Diclofenac 1.3% transdermal patch 2x/day ***OR*** diclofenac 1% gel 4 g 4x/day as needed

Undifferentiated Abdominal Pain

- Dicyclomine 20 mg PO every 6 hours
- Ibuprofen 600 mg PO every 6 hours
- Acetaminophen 1,000 mg PO every 6 hours
- Metoclopramide 10 mg PO every 6 hours
- Prochlorperazine 10 mg PO every 6 hours

Neuropathic Pain

- Gabapentin 300 mg PO at bedtime
- Amitriptyline 25 mg PO at bedtime
- Pregabalin 75 mg PO 2x/day

REFERENCES

1. Stack SJ. Confronting a crisis: An open letter to America's physicians on the opioid epidemic. *The Huffington Post*. http://www.huffingtonpost.com/steven-j-stack/confronting-a-crisis-an-o_b_9911530.html. Accessed July 7, 2016.
2. Joranson DE, Ryan KM, Gilson AM. Trends in medical use and abuse of opioid analgesics. *JAMA*. 2000; 283(13):1710-1714.
3. Wide-ranging online data for epidemiologic research (WONDER). Centers for Disease Control and Prevention WONDER online database. http://wonder.cdc.gov/. Updated December 22, 2016. Accessed December 26, 2016.
4. International Narcotics Control Board Report 2008. United Nations Pubns. 2009. p. 20
5. Substance Abuse and Mental Health Services Administration, *Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits*. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.
6. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. *Treatment Episode Data Set (TEDS): 2003-2013*. National Admissions to Substance Abuse Treatment Services. BHSIS Series X-XX, HHS Publication No. (SMA) XX-XXXX. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015.
7. Coalition Against Insurance Fraud. Prescription for peril: how insurance fraud finances theft and abuse of addictive prescription drugs. Washington, DC: Coalition Against Insurance Fraud; 2007.
8. Florence CS, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Medical Care*. 2016;54(10):901-906.
9. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR*. 2017;66:265–269.
10. Personal communication, Kirk Bol, Colorado Department of Public Health and Environment, June 8, 2016.
11. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. *National Survey on Drug Use and Health: Comparison of 2011-2012 and 2012-2013.* www.samhsa.gov/data/sites/default/files/NSDUHStateEst2012-2013-p1/ChangeTabs/NSDUHsaeShortTermCHG2013.pdf. Accessed July 7, 2016.
12. 2014 Statewide Survey, Dec. 2014, by National Research Center, Boulder, for Public Awareness Work Group, Colorado Consortium for Prescription Drug Abuse Prevention.
13. Personal communication, Kevin Wong, Colorado High Intensity Drug Trafficking Area Program (HIDTA), June 22, 2016.
14. Portenoy RK, Foley KM. Chronic use of opioid analgesics in nonmalignant pain: report of 38 cases. *Pain*. 1986;25:171-186.
15. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain*. 1997;13:6-8.
16. Pizzo PA, Clark NM. Alleviating suffering 101—pain relief in the United States. *N Engl J Med*. 2012;366:197-199.
17. Lanser P, Gesell S. Pain management: the fifth vital sign. *Healthcare Benchmarks*. 2001;8:62, 68-70.
18. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* Washington, DC: National Academies Press; 2011.
19. Lembke A. Why doctors prescribe opioids to known opioid abusers. *N Engl J Med*. 2012;367:1580-1581.
20. Bhakta HC, Marco CA. Pain management: association with patient satisfaction among emergency department patients. *J Emerg Med*. 2014;46:456-464.
21. Catan T, Perez E. A Pain-Drug Champion Has Second Thoughts. The Wall Street Journal. http://www.wsj.com/articles/SB10001424127887324478304578173342657044604. Published 2012. Accessed July 30, 2016.
22. Von Korff M, Kolodny A, Deyo RA, et al. Long-term opioid therapy reconsidered. *Ann Intern Med*. 2011;155:325-328.
23. Grady D, Berkowitz SA, Katz MH. Opioids for chronic pain. *Arch Intern Med*. 2011;171:1426-1427.
24. Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. *BMJ*. 2011;343:5142.
25. Volkow ND, McLellan TA, Cotto JH. Characteristics of opioid prescriptions in 2009. *JAMA*. 2011;305:1299-1301.
26. Gunderson M. Prehospital pain management. *EMS Insider*. 2011. http://www.jems.com/ems-insider/articles/2011/01/prehospital-pain-management.html. Accessed July 7, 2016.
27. Bitterman, RA. Is "severe pain" considered an emergency medical condition under EMTALA? *ACEP News*. 2013;34(4). http://www.acepnow.com/article/severe-pain-considered-emergency-medical-condition-emtala/. Accessed July 30, 2015.
28. Mazer-Amirshahi M, Nelson L, Pines J. West Virginia Supreme Court ruling allows physician liability for patient addiction. *Emergency Physicians Monthly*. 2015. http://www.epmonthly.com/www.epmonthly.com/departments/subspecialties/medico-legal/you-re-suing-me-for-what/?utm_source=July+30th+Ezine&utm_campaign=EPM+August+27+2014&utm_medium=email. Accessed July 24, 2015.
29. Centers for Disease Control and Prevention. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999—2008. *MMWR*. 2011; 60(43);1487-1492.
30. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014;71(7):821-826
31. Williams, J. Regulation of mu-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol Rev.* 2013;65(1):223-54.
32. Moller LF, Matic S, van den Bergh BJ, et al. Acute drug-related mortality of people recently released from prisons. *Public Health*. 2010;124(11):637-9.
33. Buster M, et al. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Ansterdam. *Addiction*. 2002;97(8):993-1001.
34. Leon-Casasola OAD. Opioids for chronic pain: new evidence, new strategies, safe prescribing. *Am J Med*. 2013;126(3).
35. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005;6(6):432-42.
36. Stakely T. Colorado DORA. Colorado Prescription Monitoring program open forum presentation. http://www.ichpcolorado.com/docs/RCCO-Opioid-Forum-Presentation.pdf. Accessed December 26, 2016.

37. Baehren DF, Marco DA, Droz DE, et al. A statewide prescription monitoring program affects emergency department prescribing behaviors. *Ann Emerg Med*. 2010;56:19-23.
38. Cantrill, et al. ACEP Clinical Policy: Critical Issues in the Prescribing of Opioids for Adult Patients in the Emergency Department. *Ann Emerg Med*. 2012;60:499-525.
39. Smulowitz PB, Cary C, Boyle KL, et al. Variation in opioid prescribing patterns between ED providers. *Intern Emerg Med*. 2016 Dec; 11(8):1121-1124.
40. Barnett ML, Olenski AR, Jena AB. Opioid-Prescribing Patterns of Emergency Physicians and Risk of Long-Term Use. *N Engl J Med*. 2017 Feb 16;376(7):663-673.
41. Burton JH, Hoppe JA, Echternach JM, et al. Quality improvement initiative to decrease emergency physician opioid analgesic prescribing. *WJEM*. 2016 May; 17(3):258-263
42. Roelofs PDDM, Deyo RA, Koes BW, et al. Non-steroidal anti inflammatory drugs for low back pain. *Cochrane Database Syst Rev*. 2008;(1):CD000396
43. Franklin GM, Stover BD, Turner JA, et al. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine*. 2008;33(2):199-204.
44. Ashworth J, Green DJ, Dunn KM, Jordan KP. Opioid use among low back pain patients in primary care: Is opioid prescription associated with disability at 6-month follow-up? *Pain*. 2013;154(7):1038-1044.
45. Dowell D, Haegerich,T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recomm Rep*. 2016;65. http://www.cdc.gov/media/dpk/2016/dpk-opioid-prescription-guidelines.html. Accessed December 26, 2016.
46. Dasgupta N, Funk MJ, Proescholdbell S, et al. Cohort Study of the Impact of High-dose Opioid Analgesics on Overdose Mortality. *Pain Medicine*. 2015. http://onlinelibrary.wiley.com/doi/10.1111/pme.12907/abstract. Accessed December 26, 2016.
47. Jena AB, Goldman D, Weaver L, et al. Opioid prescribing by multiple providers in Medicare: retrospective observational study of insurance claims. *BMJ*. 2014;348:1393.
48. Open Letter to the General Public on the Quad-Regulator Joint Policy for Prescribing and Dispensing Opioids, 2014. Colorado Department of Regulatory Agencies. http://www.ucdenver.edu/academics/colleges/PublicHealth/research/centers/CHWE/Documents/DORA%20Opioid%20Policy%20Revised%2010.15.14.pdf. Accessed July 26, 2016.
49. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. *J Pain Symptom Manage*. 2003;26:1026-1048.
50. New York City Emergency Department Discharge Opioid Prescribing Guidelines, 2013. New York City Department of Health and Mental Hygeine. https://www1.nyc.gov/assets/doh/downloads/pdf/basas/opioid-prescribing-guidelines.pdf. Accessed July 29, 2015
51. Straube ST, Lopez JJ, Baird J, et al. Prescription opioid misuse is common among emergency department patients discharged with opioids [abstract]. *Ann Emerg Med*. 2013;62(4):92.
52. Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. *CBHSQ Data Rev*. 2013. http://www.samhsa.gov/data/2
53. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system [published online ahead of print August 16, 2010] *Addiction*. 2010;105(10):1776-82.
54. Miech R, Johnston L, O'Malley PM, et al. Prescription opioids in adolescence and future opioid misuse. *Pediatrics*. 2015;136(5):1169-77
55. Cazacu I, Mogosan C, Loghin F. Safety issues of current analgesics: an update [published online ahead of print April 15, 2015]. *Clujul Med*. 2015;88(2):128-36.
56. Kuryshev YA, Bruening-Wright A, Brown AM, Kirsch GE. Increased cardiac risk in concomitant methadone and diazepam treatment: pharmacodynamic interactions in cardiac ion channels. *J Cardiovasc Pharmacol*. 2010;56:420-430.
57. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350:1013-1022.
58. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. *J Pain*. 2002;3:377-384.
59. Abs R, Verhelst J, Maeyaert J, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab*. 2000;85:2215-2222.
60. Tennant F. A 10-year evaluation of chronic pain patients treated with opioids. *Heroin Addict Relat Clin Probl*. 2009;11:31-34.
61. Wei G, Moss J, Yuan CS. Opioid-induced immunosuppression: is it centrally mediated or peripherally mediated? *Biochem Pharmacol*. 2003;65:1761-1766.
62. Welters ID. Is immunomodulation by opioid drugs of clinical relevance? *Curr Opin Anaesthesiol*. 2003;16: 509-513
63. Lee M, Silverman S, Hansen H, et al. A Comprehensive Review of Opioid-Induced Hyperalgesia. *Pain Physician*. 2011;14:145-161.
64. Dimsdale JE, Norman D, Dejardin D, Wallace MS. The effect of opioids on sleep architecture, *J Clin Sleep Med*. 2007;3:33-36.
65. Khansari MR, Sohrabi MR, Zamani Farhad. The Useage of Opioids and their Adverse Effects in Gastrointestinal Practice: A Review. *Middle East J Dig Dis*. 2013;5:5-16.
66. Passik PS, Webster ML. Opioid analgesics: Does potency matter? *J Opioid Manag*. 2014;10(4):263-275.
67. Bohnert AS. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315.
68. Paulozzi LJ, Kilbourne EM, Shah NG, et al. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Med*. 2012;13(1):87-95.
69. Dunn KM. Opioid Prescriptions for Chronic Pain and Overdose. *Ann Intern Med*. 2010;152(2):85.
70. Becker W. Prescription drug misuse: Epidemiology, prevention, identification, and management. http://www.uptodate.com.hsl-ezproxy.ucdenver.edu/contents/prescription-drug-misuse-epidemiology-prevention-identification-and-management?source=search_result&search=opioid prescribing&selectedTitle=2~150. Accessed June 31, 2016.
71. National Survey Shows Friends and Family Are Primary Sources of Abused Painkillers. The White House. https://www.whitehouse.gov/ondcp/news-releases-remarks/national-survey-shows-friends-and-family-are-primary-sources-of-abused-painkillers. Published 2012. Accessed August 18, 2016.

72. Enhancing Access to Prescription Drug Monitoring Programs Using Health Information Technology: Integrating Health IT and PDMPs to Improve Patient Care. 2012. The MITRE Corportation. https://www.healthit.gov/sites/default/files/connecting_for_impact-final-508.pdf. Accessed December 26, 2016
73. Enhancing Access to Prescription Drug Monitoring Programs Using Health Information Technology: Connecting Prescribers and Dispensers to PDMPs through Health IT: Six Pilot Studies and Their Impact. 2012. The MITRE Corporation. https://www.healthit.gov/sites/default/files/pdmp_pilot_studies_summary_0.pdf. Accessed December 26, 2016
74. Fallon E, Fung S, Rubal-Peace G, Patanwala AE. Predictors of patient satisfaction with pain management in the emergency department. *Adv Emerg Nurs J.*. 2016;38(2):115-22.
75. Kelly S, Johnson GT, Harbison RD. "Pressure to prescribe" The impact of economic and regulatory factors on South-Eastern ED physicians managing the drug seeking patient. *J Emerg Trauma Shock*. 2016;9(2):58-63
76. Gunderman, Richard. "When Physicians' Careers Suffer Because They Refuse to Prescribe Narcotics," *The Atlantic* 2014, http://www.theatlantic.com/health/archive/2013/10/when- physicians-careers-suffer-because-they-refuse-to-prescribe-narcotics/280995/
77. Pomerleau AC, Nelson LS, Hoppe JA, et al. The impact of prescription drug monitoring programs and prescribing guidelines on emergency department prescribing: a multi-center survey [published online ahead of print March 19, 2016]. *Pain*.
78. Ahern TL, Herring AA, Miller S, Frazee BW. Low-dose ketamine infusion for emergency department patients with severe pain. *Pain Medicine.* 2015;16:1402-1409.
79. Sin B, Ternas T, Motov SM. The use of subdissociative ketamine for acute pain in the emergency department. *Acad Emerg Med.* 2015;22:251-257.
80. Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: a randomized, controlled trial. *Acad Emerg Med.* 2015;33:402-408.
81. Motov S, Rockoff B, Cohen V, et al. Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: A randomized, controlled trial. *Ann Emerg Med.* 2015; 66(3):222-229.
82. Ferrini RA, Paice J. How to initiate and monitor infusional lidocaine for severe and/or neuropathic pain. *J Support Oncol.* 2004;2:90-94.
83. Afhami MR, Salmasi PH. Studying analgesic effect of preincisional infiltration of lidocaine as a local anesthetic with different concentrations on postoperative pain. *Pak J Med Sci.* 2009;25(5):821-824.
84. Soleimanpour H, Hassanzadeh K, Vaezi H, et al. Effectiveness of intravenous lidocaine versus intravenous morphine for patients with renal colic in the emergency department. *BMC Urol.* 2012;12(13):1-5.
85. Gammaitoni AR, Galer BS, Onawola R, et al. Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: results of a pilot 2-week, open-label study using the Neuropathic Pain Scale. *Curr Med Res Opin.* 2004;20(suppl 2):13-9.
86. Galer BS, Gammaitoni AR, Oleka N, et al. Use of the lidocaine patch 5% in reducing intensity of various pain qualities reported by patients with low-back pain. *Curr Med Res Opin.* 2004;20(suppl 2):5-12.
87. Davies PS, Galer BS. Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. *Drugs.* 2004;64(9):937-47.
88. Argoff CE, Galer BS, et al. Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: assessment with the neuropathic pain scale. *Curr Med Res Opin.* 2004;20(suppl 2):21-8.
89. Alvarez DJ, Rockwell PG. Trigger points: diagnosis and management. *Am Fam Physician.* 2002;65(4):653-60.
90. Rachlin ES. Myofascial Pain and Fibromyalgia: Trigger Point Management. *St Louis: Mosby.* 1994;1:145-157.
91. Tough EA, White AR, Cummings TM, et al. Acupuncture and dry needling in the management of myofascial trigger point pain: a systematic review and meta-analysis of randomised controlled trials. *Eur J Pain.* 2009;13(1):3-10.
92. Kietrys DM, Palombaro KM, Azzaretto E, et al. Effectiveness of dry needling for upper-quarter myofascial pain: a systematic review and meta-analysis. *J Orthop Sports Phys Ther.* 2013;43(9):620-34.
93. Mellick L, Verma M. Headache management with occipital nerve blocks, cervical injections, and trigger point injections. *Open Emer Med J.* 2010;3:32-5.
94. Mellick LB, McIlrath ST, Mellick GA. Treatment of headaches in the ED with lower cervical intramuscular bupivacaine injections: a 1-year retrospective review of 417 patients. *Headache.* 2006;46(9):1441-9.
95. Mellick LB, Mellick GA. Treatment of acute orofacial pain with lower cervical intramuscular bupivacaine injections: a 1-year retrospective review of 114 patients. *J Orofac Pain.* 2008;22(1):57-64.
96. Herres J, Chudnofsky CR, Manur R, Damiron K, et al. The use of inhaled nitrous oxide for analgesia in adult ED patients: a pilot study. *Am J Emerg Med.* 2016;34(2):269-73.
97. Furuya A, Ito M, Fukao T, et al. The effective time and concentration of nitrous oxide to reduce venipuncture pain in children. *J Clin Anesth.* 2009;21(3):190-3.
98. Ducassé JL, Siksik G, Durand-Béchu M, et al. Nitrous oxide for early analgesia in the emergency setting: a randomized, double-blind multicenter prehospital trial. *Acad Emerg Med.* 2013;20(2):178-84.
99. Aboumarzouk OM, Agarwal T, Syed Nong Chek SA, et al. Nitrous oxide for colonoscopy. *Cochrane Database Syst Rev.* 2011;(8):CD008506.
100. Catapano MS. The analgesic efficacy of ketorolac for acute pain. *J Emerg Med.* 1996;14(1):67-75.
101. Motov S, Yasavolian M, et al. Comparison of intravenous ketorolac at three single-dose regimens for treating acute pain in the emergency department: A randomized controlled trial. *Ann Emerg Med.* 2016
102. Soleyman-Zomalan E, Motov S, et al. Patterns of ketorolac dosing by emergency physicians. *World J Emerg Med.* 2017;8(1):43-46.
103. Garcia Rodriguez LA, Cattaruzzi C, et al. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med.* 1998;158(1):33-39.
104. Benevides ML, Oliveira SS, Aguilar-Nascimento JE. Combination of haloperidol, dexamethasone, and ondansetron reduces nausea and pain intensity and morphine consumption after laparoscopic sleeve gastrectomy. *Braz J Anesthesiol.* 2013 Sep-Oct;63(5):404-9.
105. Honkaniemi J, Liimatainen S, Rainesalo S, et al. Haloperidol in the acute treatment of migraine: a randomized, double-blind, placebo-controlled study. *Headache.* 2006;46(5):781-787.
106. Grillage MG, Nankani JN, Atkinson SN, et al. A randomised, double-blind, study of mebeverine versus dicyclomine in the treatment of functional abdominal pain in young adults. *Br J Clin Pract.* 1990;44(5):176-0.

107. Rosen JM, Alioto A, Saps M. Advances in pain-predominant functional gastrointestinal disorders in the adolescent. *Adolesc Med State Art Rev.* 2016; 27(1): 34-56.
108. Chiou E, Nurko S. Management of functional abdominal pain and irritable bowel syndrome in children and adolescents. Expert Rev Gastroenterol Hepatol 2010; 4(3): 293-304.
109. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Amer Geriatrics Soc.* 2015;63(11):2227-46.
110. Noyes RJ et al. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther* 1975; 18: 84–9.
111. Pertwee RG. Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol.* 2006; 147 suppl 1: S163–71.
112. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symp Manag* 2010; 39(2):167–79.
113. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ* 2010; 182(14): E694-E701.
114. Eisenberg E, Miri O, Shlomo A. The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: A phase 1A study. *J Pain Palliat Care Pharmacother.* 2014;28(3):216-225.
115. Bachhuber MA, Saloner B, Chinazo O, et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med.* 2014; 174 (10):1668-1673.
116. Centers for Disease Control and Prevention. HIV Surveillance Report, 2012; vol. 24. http://www.cdc.gov/hiv/library/reports/surveillance/. Published November 2014. Accessed December 26, 2016.
117. Centers for Disease Control and Prevention. Surveillance for Acute Viral Hepatitis – United States, 2007. *MMWR Surveillance Summary* 2009;58:1-27. http://www.cdc.gov/mmwr/PDF/ss/ss5803.pdf. Accessed December 26, 2016.
118. Van Boekel LC, Brouwers EP, van Weeghel J, et al. Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: systematic review. *Drug Alcohol Depend.* 2013;131(1-2):23–35. .
119. Courtwright DT. The NIDA brain disease paradigm: History, resistance and spinoffs. *History Faculty Publications*. 2010 Paper 2 Retrieved from http://digitalcommons.unf.edu/ahis_facpub/2.
120. Wheeler E, Jones S, Gilbert MK, Davidson PJ. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons — United States, 2014. Centers for Disease Control and Prevention. *MMWR*. 2015;64(23):631-635. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a2.htm. Published 2015. Accessed November 27, 2016.
121. Palmateer N, Kimber J, Hickman M, et al. Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews. *Addiction.* 2010;105(5):844-859.
122. Wodak A, Cooney A. (2004). Effectiveness of Sterile Needle and Syringe Programming in Reducing HIV/AIDS Among Injecting Drug Users. World Health Organization. Retrieved 18 July 2013.
123. Yoast R, Williams MA, Deitchman SD, Champion HC. Report of the Council on Scientific Affairs. *J Addict Dis.* 2001;20(2):15–40.
124. Szalavitz M, Szalavitz M. Preventing Overdose: Obama Administration Drug Czar Calls For Wider Access to Overdose Antidote. *Time*. http://healthland.time.com/2012/08/22/preventing-overdose-obama-administration-drug-czar-calls-for-wider-access-to-overdose-antidote. Accessed October 20, 2015.
125. Attorney General Holder Announces Plans for Federal Law Enforcement Personnel to Begin Carrying Naloxone | OPA | Department of Justice. 2014. http://www.justice.gov/opa/pr/attorney-general-holder-announces-plans-federal-law-enforcement-personnel-begin-carrying. Accessed October 20, 2015.
126. Mufson S, Zezima K. Obama announces new steps to combat heroin, prescription drug abuse. *The Washington Post.* https://www.washingtonpost.com/politics/white-house-announces-newsteps-to-combat-heroin-prescriptiondrug-abuse/2015/10/21/e454f8fa-7800-11e5-a958-d889faf561dc_story.html. Accessed October 23, 2015.
127. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: Interrupted time series analysis. *BMJ*. 2013;346:174.
128. Albert S, Brason FW, Sanford CK, et al. Project Lazarus: Community-based overdose prevention in rural North Carolina. *Pain Med*. 2011;12(suppl 2):77-85.
129. Davis CS, Ruiz S, Glynn P, et al. Expanded access to naloxone among firefighters, police officers, and emergency medical technicians in Massachusetts. *Am J Public Health*. 2014;104:7-9.
130. Kim D, Irwin K, Khoshnood K. Expanded Access to Naloxone: Options for Critical Response to the Epidemicof Opioid Overdose Mortality. *Am J Public Health*. 2009;99(3):402-407.
131. Attorney General Holder, Calling Rise in Heroin Overdoses 'Urgent Public Health Crisis,' Vows Mix of Enforcement, Treatment | OPA | Department of Justice. https://www.justice.gov/opa/pr/attorney-general-holder-calling-rise-heroin-overdoses-urgent-public-health-crisis-vows-mix. Accessed April 1, 2015.
132. Dwyer K, Walley AY, Langlois BK, et al. Opioid education and nasal naloxone rescue kits in the emergency department. *West J Emerg Med*. 2015;16:381-384.
133. Samuels E. Emergency department naloxone distribution: A Rhode Island department of health, recovery community, and emergency department partnership to reduce opioid overdose deaths. *R I Med J*. 2014;97:38-39.
134. Disposal of unused medicines: what you should know. U.S. Food and Drug Administration. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186187.htm. Updated November 15, 2016. Accessed December 26, 2016.
135. D'Onofrio G, et al. Development and implementation of an emergency department practitioner-performed brief intervention for hazardous and harmful drinkers in the emergency department. *Acad Emerg Med.* 2005;12(3):249- 256.
136. Saitz RM. Screening and brief intervention enter their 5th decade. *Subst Abuse*. 2007;28(3):3-6.
137. Madras BK, Compton WM, Avula D, et al. Screening, brief interventions, referral to treatment (SBIRT) for illicit drug and alcohol use at multiple health care sites: Comparison at intake and 6 months later. *Drug Alcohol Depend*. 2009;99(1-3):280-295.

138. Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev.* 2016, Issue 5. Art. No.: CD002024.doi: 10.1002/14651858.CD002024.pub5.
139. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. *Headache.* 2015 Jan;55(1):3-20.
140. Matchar DB, Young WB, Rosenberg JH, et. al. Evidence-based guidelines for migraine headaches in the primary care setting: pharmacological management of acute attacks. Available from the American Academy of Neurology [online]. http://www.aan.com.
141. Chinn S, Caldwell W, Gritsenko K. Fibromyalgia pathogenesis and treatment options update. *Curr Pain Headache Rep.* 2016; 20-25.
142. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA*. 2004 Nov 17;292(19):2388-95.
143. Schnitzer, TJ. Update on guidelines for the treatment of chronic musculoskeletal pain. 25 (Suppl 1), *Clin Rheumatol*. 2006;25 Suppl 1:S22-9
144. McIntosh G, Hall H. Low back pain (acute). *Clin Evid (Online)*. 2011;05:1102.
145. Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. *Cochrane Database Syst Rev.* 2005;(3).
146. Derry S, Moore RA, Gaskell H, et al. Topical NSAIDs for acute musculoskeletal pain in adults. *Cochrane Database Syst Rev.* 2015.
147. Jones P, Dalziel SR, Lamdin R, et al. Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury. *Cochrane Database Syst Rev*. 2015 Jul 1.
148. Moore PA, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions. *JADA*. 2013; 898-908.
149. da Costa, Bruno R et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis *The Lancet*. 2016. 2093-2105.