DENTAL GUIDELINE ON PRESCRIBING OPIOIDS FOR PAIN

Developed by the Dr. Robert Bree Collaborative and Washington State Agency Medical Directors’ Group (AMDG)* in collaboration with Actively Practicing Dentists and Public Stakeholders

Written for Clinicians Who Care for Patients with Pain July 2017
Prescribing Opioids for Acute Dental Pain

Introduction

This guideline was developed in collaboration with a broad advisory group of the state’s academic leaders, pain experts, and dentists in general care and specialty areas in response to the growing epidemic of opioid-related overdoses and supplements the Agency Medical Director’s Group (AMDG) Interagency Guideline on Prescribing Opioids for Pain. The guideline is based on the best available clinical and scientific evidence from the literature and a consensus of expert opinion.

This is an easy-to-use reference to help dentists, oral surgeons, and others follow a set of clinical recommendations and access supporting evidence and resources in the appendices. We recommend revising office-prescribing practices as necessary to be consistent with this guideline, the American Dental Association (ADA) statement, and the Centers for Disease Control and Prevention (CDC) guideline. We also recommend considering the feasibility of embedding key practices from these guidelines into electronic health record systems. Lastly, we recommend educating office staff and patients about the risks and benefits of opioids, individualizing pain management strategies for each patient’s clinical situation, and avoiding “just in case” prescribing.

Dentists Play a Critical Role

The United States is experiencing a dramatic increase in prescription opioid overdose deaths, primarily among 35-55 year olds.1,2 The majority of new heroin users start out with prescribed opioids.3 While the exact number of opioids consumed postoperatively is unclear, substantial amounts are leftover to be later reused, shared among friends and family, or abused non-medically.4

Among prescribers of opioids for adolescents, dentists are proportionately the most prevalent prescribers (Fig 1).5 Dentists write approximately 31% of opioid prescriptions for patients between 10 to 19 years.6 An estimated 56 million tablets of 5 mg hydrocodone are prescribed after third molar extractions each year in the United States.6 High schoolers who receive an opioid prescription are 33% more likely to misuse opioids between the ages of 18 and 23 years.7 Data shows an upsurge in heroin-related deaths among 18 to 25 year olds.1,2 Therefore, dental providers could play a critical role in minimizing opioid exposure for vulnerable young people by reducing the number of opioid tablets prescribed for common procedures such as extractions.

In response to the release of the 2016 CDC opioid guidelines, which recommended limiting the duration of opioid prescriptions for acute pain, Dr. Paul Moore, speaking for the American Dental Association Council on Scientific Affairs, said, "For dental practitioners, the importance of these recommendations should be carefully considered . . . Every year, millions of adolescents receive their first introduction to opioids following the extraction of their third molars. Many of these young adults may have never received these centrally-acting analgesics before in their lives. We have a special responsibility to counsel them about their dangers and educate them about their safe use of opioids when taken for acute postoperative pain."8
Clinical Recommendations

Acute pain management poses many challenges to providers regarding treatment decisions, improving quality of recovery, and identifying patients at risk for poor pain management or uncontrolled pain. Assessing patients and proposing pain management plans that minimize risk while optimizing benefits is incumbent on providers. Good practice involves skilled initial patient assessment, individualized pain management strategies, effective intervention, and re-assessment as necessary. In those rare instances when opioids are prescribed for chronic orofacial pain, providers should follow the best practices in the AMDG Interagency Guideline on Prescribing Opioids for Pain.

Preoperative Period

1. Conduct a thorough evaluation including a patient interview with dental and medical history. Screen for past or current use of opioids and benzodiazepines, sedative-hypnotics, or anxiolytics. See Appendix A for list of benzodiazepines, sedative-hypnotics, and anxiolytics.
   a. Check the Prescription Monitoring Program (PMP) for every patient for whom you write a prescription for opioids to be certain there have been no prior or concurrent prescriptions of opioids or sedatives. This is especially critical for patients who report a history of chronic opioid or sedative use. Please note, in Washington, you can delegate licensed staff in your office to check the PMP (AMDG Interagency Guideline on Prescribing Opioids for Pain, Appendix C: How to use the Prescription Monitoring Program).
   b. If you find anything in the PMP of concern, screen with a validated tool. (See AMDG – Assessment Tools for free validated assessment tools.)
   c. Ask if the patient is currently being or has been previously prescribed chronic opioids. If so, coordinate with the pain management provider before prescribing opioids.

2. Unless contraindicated, prescribe non-opioid analgesics as the FIRST line of pain control in dental patients.
   a. Prescribe combinations of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen following dental procedures where post-operative pain is anticipated, unless there are contraindications:
      i. NSAIDs contraindications include, but are not limited to: known hypersensitivity to the drug, history of gastrointestinal bleeding, and aspirin sensitivity asthma.
      ii. Acetaminophen contraindications include, but are not limited to: severe liver disease, known hypersensitivity to the drug, and consumption of more than two to three alcohol-containing drinks per day.
      iii. Adjust dose or duration and monitor for patients with hepatic or renal impairment or drug-to-drug interactions.
      iv. Consider a selective cyclooxygenase-2 inhibitor (e.g., celecoxib) for patients at risk for bleeding (e.g., on anticoagulation therapy).
b. Advise patients not to take multiple acetaminophen-containing preparations concomitantly. Refer patients to the FDA’s Taking Acetaminophen Safely video.

3. Consider pre-surgical medication, such as an NSAID, one hour immediately prior to procedure, except where contraindicated.

4. If use of an opioid is warranted, follow the CDC guidelines: “clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.”

   a. Prescribe opioids IN COMBINATION with first-line therapy. Avoid multiple acetaminophen-containing preparations concomitantly.

   b. For adolescents and young adults through 24 years old who are undergoing minor surgical procedures (e.g., third molar extractions), limit opioid prescriptions to 8-12 tablets.

   c. Codeine and tramadol are contraindicated in children younger than 12 due to variability in metabolism. The use of codeine and tramadol should also be avoided in those aged 12-17. See FDA warning here.

   d. Avoid prescribing opioids in combination with benzodiazepines, sedative-hypnotics, or anxiolytics. See Appendix A for a list of benzodiazepines, sedative-hypnotics, and anxiolytics.

5. Avoid opioids when:

   a. Patient or parent specifically requests NO opioid prescriptions.

   b. Patient is in recovery from a substance use disorder but at high risk of relapse or has a significant family history of substance use disorder. See Appendix C for special considerations for patients with substance use disorder.

6. Educate the patient and family on appropriate use and duration of opioids in a language and at a level (e.g., 8th grade reading level) that they can understand.

   a. Review possible adverse effects of opioids, including the sensation of drug craving. Remind them of the dangers of prescription opioid diversion and the importance of secure storage of their medications.

   b. Share information on prompt disposal of leftover opioids through community-based drug take back programs, a DEA-approved take back program, or FDA guideline for safe disposal of medicine.

   c. Advise the patient to avoid combining opioids with benzodiazepines, sedative-hypnotics, anxiolytics, or other central nervous system depressants, including alcohol. These combinations exponentially (not just additively) increase risk for dangerous respiratory depression.
Intraoperative Period

1. Use pre-emptive analgesia where indicated. Consider long-acting local anesthetic injections (bupivacaine + epinephrine 1:200,000) unless contraindicated.

Postoperative Period

1. Unless contraindicated, prescribe non-opioid analgesics as the FIRST line of pain control in dental patients.
   a. Prescribe combinations of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen following dental procedures where post-operative pain is anticipated unless there are contraindications:
      i. NSAIDs contraindications include, but are not limited to: known hypersensitivity to the drug, history of gastrointestinal bleeding, and aspirin sensitivity asthma.
      ii. Acetaminophen contraindications include, but are not limited to: severe liver disease, known hypersensitivity to the drug, and consumption of more than two to three alcohol-containing drinks per day.
      iii. Adjust dose or duration and monitor for patients with hepatic or renal impairment or drug-to-drug interactions.
      iv. Consider a selective cyclooxygenase-2 inhibitor (e.g., celecoxib) for patients at risk for bleeding (e.g., on anticoagulation therapy).
   b. Advise patients not to take multiple acetaminophen-containing preparations concomitantly. Refer patients to FDA’s Taking Acetaminophen Safely video.

2. If use of an opioid is warranted, follow the CDC guidelines: “clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.”
   a. Prescribe opioids IN COMBINATION with first-line therapy. Avoid multiple acetaminophen-containing preparations concomitantly.
   b. For adolescents and young adults through 24 years old who are undergoing minor surgical procedures (e.g., third molar extractions), limit opioid prescriptions to 8-12 tablets.
   c. Codeine and tramadol are contraindicated in children younger than 12 due to variability in metabolism. The use of codeine and tramadol should also be avoided in those aged 12-17. See FDA warning here.
   d. Avoid prescribing opioids in combination with benzodiazepines, sedative-hypnotics, or anxiolytics. See Appendix A for a list of benzodiazepines, sedative-hypnotics, and anxiolytics.
3. Dentists should recognize multimodal pain strategies (e.g., ice) for management of acute postoperative pain as a means for sparing the need for opioid analgesics.

4. Educate the patient and family on appropriate use and duration of opioids in a language and at a level (e.g., 8th grade reading level) that they can understand.
   
   a. Review possible adverse effects of opioids, including the sensation of drug craving. Remind them of the dangers of prescription opioid diversion and the importance of secure storage of their medications.

   b. Share information on prompt disposal of leftover opioids through community-based drug take back programs, a DEA-approved take back program or FDA guideline for safe disposal of medicine.

   c. Advise the patient to avoid combining opioids with benzodiazepines, sedative-hypnotics, anxiolytics, or other central nervous system depressants, including alcohol. These combinations exponentially (not just additively) increase risk for dangerous respiratory depression.
Evidence

Opioids are efficacious analgesics for severe acute pain and are widely used for this purpose. However, opioids do not have anti-inflammatory properties, so non-opioid analgesics (e.g., NSAIDs) can be a better first choice for pain relief. In addition, opioids carry many risks, including physical tolerance, dependence, addiction, and overdose. That patients do not use or need most of the opioids prescribed for acute pain is clear. In children undergoing minor procedures (not including dental extractions), the vast majority of initially prescribed opioid doses are still leftover by day four. For example, an average of 52 opioid tablets are dispensed after tonsillectomy and an average of 44 tablets go unused. Often, these leftover opioid tablets are later misused for non-medical purposes. Even in the case of common major elective surgeries, the majority of currently prescribed post-operative opioids go unused; as few as five-15 tablets sufficed for 80% of patients after physician education led to substantial reductions in prescribed doses. Although it is not known exactly how many opioid doses taken during acute pain episodes may lead to increased risk of dependence or subsequent misuse, a recent observational study using a large commercial database suggests that even a few days of opioids can increase risk. The risk of being on opioids at one year increases about one percent for each day of opioid supplied, starting with a three days’ supply of an initial prescription.

Prudent practice encourages the prevention of pain, where possible, by administering non-opioid analgesics before pain occurs. Efficacy is seen with preemptive and concurrent use of NSAIDs and acetaminophen, around the clock for as many days as necessary. In some studies, analgesic regimens using NSAIDs and acetaminophen have demonstrated pain relief comparable to hydrocodone/acetaminophen 5/325mg. Moore and Hersh, in a systematic review of the evidence, concluded that, “the ibuprofen-APAP combination may be a more effective analgesic, with fewer untoward effects, than are many of the currently available opioid-containing formulations.” These authors also concluded that the ibuprofen-APAP combination is more effective than either drug alone. Another systematic review of analgesic efficacy to treat pain of endodontic origin recommends NSAIDs as the drug class of choice for pain of endodontic origin as long as there is no contraindication for such use. Moderate evidence supports use of pre-operative NSAIDs to reduce inflammation and post-operative analgesic requirements. Providers should be aware that NSAIDs and acetaminophen also have potential for serious adverse outcomes.

If use of an opioid for acute pain is warranted, “clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.” The specific recommendation for adolescents and young adults is based on emerging evidence that two thirds of all patients receiving opioids for third molar extractions are 14 to 24 years old, there is a three-fold variation in the amounts prescribed, and substantial proportions are left unused and available for subsequent misuse. Because the developing brain is at increased risk for addiction, limiting opioid exposure to the shortest duration is very important in this population. The ADA recommends reviewing the CDC recommendations for safe opioid prescribing (see Appendix B), and the Bree Collaborative AMDG Opioid Prescribing Guideline Implementation workgroup emphasizes its importance, given the vulnerability of this population.
Providers should be aware that the Food and Drug Administration approved tramadol and single-ingredient codeine only for use in adults. Both opioids are contraindicated in children younger than 12 years due to the risk of serious breathing problems in some children with ultra-rapid metabolism. Providers should also limit use in adolescents between 12 and 18.

Providers should check the Washington State Prescription Monitoring Program (PMP; also called the Prescription Drug Monitoring Program or PDMP in other states) for every patient before prescribing opioids to be certain there have been no prior or concurrent prescriptions of opioids or sedatives. This is strongly recommended by both the CDC Guideline for Prescribing Opioids for Chronic Pain and by the AMDG Interagency Guideline on Prescribing Opioids for Pain. Per McCauley et al, “a notable minority of dental patients had incidents of multiple preexisting opioid prescriptions, a factor implicated in patient misuse, abuse, overdose and diversion.” Recent data suggests that in New York, which has implemented a mandatory PDMP program, there have been substantial reductions in opioid prescriptions and increases in non-opioid analgesic therapy among dental prescribers. Among patients receiving pain medications in dental practice, 30.6% received an opioid prior to mandatory PMP implementation, while this number dropped to 14.1% and 9.6% in the two three-month periods following implementation. This recommendation is also consistent with the ADA February 2017 Statement on the Use of Opioids in the Treatment of Dental Pain: “Dentists should register with and utilize the prescription drug monitoring program to promote the appropriate use of controlled substances for legitimate medical purposes, while deterring the misuse, abuse and diversion of these substances.” See Appendix B for the full list of ADA recommendations.
Appendix A: Benzodiazepines, Sedative-hypnotics, and Anxiolytics

- Benzodiazepines
  - Alprazolam
  - Chlordiazepoxide
  - Clonazepam
  - Clorazepate
  - Diazepam
  - Estazolam
  - Flurazepam
  - Lorazepam
  - Midazolam
  - Oxazepam
  - Quazepam
  - Temazepam
  - Triazolam

- Barbiturates
  - Butabarbital
  - Butalbital
  - Mephobarbital
  - Phenobarbital
  - Secobarbital

- Skeletal muscle relaxants
  - Carisoprodol

- Non-benzodiazepine hypnotics
  - Chlormidal Hydrate
  - Eszopiclone
  - Meprobamate
  - Suvorexant
  - Zaleplon
  - Zolpidem
Appendix B: American Dental Association Statement on the Use of Opioids in the Treatment of Dental Pain

1. When considering prescribing opioids, dentists should conduct a medical and dental history to determine current medications, potential drug interactions and history of substance abuse.

2. Dentists should follow and continually review Centers for Disease Control and State Licensing Boards recommendations for safe opioid prescribing.

3. Dentists should register with and utilize a prescription drug monitoring program (PDMP) to promote the appropriate use of controlled substances for legitimate medical purposes, while deterring the misuse, abuse and diversion of these substances.

4. Dentists should have a discussion with patients regarding their responsibilities for preventing misuse, abuse, storage, and disposal of prescription opioids.

5. Dentists should consider treatment options that utilize best practices to prevent exacerbation of or relapse of opioid misuse.

6. Dentists should consider nonsteroidal anti-inflammatory analgesics (NSAIDs) as the first-line therapy for acute pain management.

7. Dentists should recognize multimodal pain strategies for the management of acute postoperative pain as a means of sparing the need for opioid analgesics.

8. Dentists should consider coordination with other treating doctors, including pain specialists, when prescribing opioids for management of chronic orofacial pain.

9. Dentists who are practicing in good faith and who use professional judgment regarding the prescription of opioids for the treatment of pain should not be held responsible for the willful and deceptive behavior of patients who successfully obtain opioids for non-dental purposes.

10. Dental students, residents and practicing dentists are encouraged to seek continuing education in addictive disease and pain management as related to opioid prescribing.

*ADA House of Delegates*

*Adopted: October 2016*
Appendix C: Special Considerations for Patients with Substance Use Disorder

Patients with substance use and/or psychiatric disorders are more likely to have complications from opioid use, such as misuse, abuse or overdose.\(^{30}\)

1. Support patients who have made a commitment to a drug-free lifestyle and take precautions when considering prescribing opioids.

2. Use validated instruments to assess predictors of suboptimal recovery, such as depression, fear avoidance, and catastrophizing, which can lead to persistent pain and functional limitation. Instruments are available [here](#).

3. Be knowledgeable of community resources for treatment of substance use disorders and be prepared to make referrals: [Washington Recovery Help Line](#).

4. Complete the ADA opioid continuing education (CE) webinar and review educational materials on managing dental pain:
   b. Advancing Pain Management in Oregon. Online training from the Pain Management Commission of the Oregon Health Authority: [www.oregon.gov/oha/OHPR/PMC/Pages/index.aspx](http://www.oregon.gov/oha/OHPR/PMC/Pages/index.aspx)
   c. American Dental Association statement on use of opioids in the treatment of dental pain (See [Appendix B](#)).
   d. Specialists should follow additional guidelines from their specialty associations (e.g., AAPD, AAP, AAOMS, AAE).

5. Consult with the treating addiction specialist if the patient is in active treatment for substance use disorder and coordinate before prescribing opioids.

6. Contact the Substance Abuse and Mental Health Services Administration (SAMHSA)’s [Providers’ Clinical Support System for Opioids (PCSS-O)](http://www.samhsa.gov/ providers-clinical-support-system) and [Medication Assisted Treatment (PCSS-MAT)](http://www.samhsa.gov/ providers-clinical-support-system) for treatment issues. Expert mentors are available to assist with questions or concerns about opioids and treatment of substance use disorders.

7. Support patients who are in successful long-term recovery from a previous substance use disorder of any kind (e.g., alcohol, opioids, heroin, methamphetamine) and have committed to a drug-free lifestyle.
   a. Avoid “just in case” opioid prescriptions.
   b. If severe post-operative pain is expected, take special precautions in providing opioids. For example, involve a family member, 12-step program sponsor, or addiction counselor in medication administration, and increase attendance at meetings and/or counseling sessions during the post-operative period.
Acknowledgements

The Bree Collaborative and Washington State Agency Medical Directors’ Group wish to acknowledge the many individuals and groups from both the private and public sectors who provided crucial consultation and input to this guideline. Their clinical, scientific, and technical expertise helped ensure that this guideline would be relevant, accurate, and of practical use to dental prescribers. Every effort was made to create a guideline as evidence-based as possible. Where scientific evidence was insufficient or unavailable, the best clinical opinions and consensus of the advisory group were used.

We are grateful for the time and efforts made by each of the following persons:

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carsten DDS, David</td>
<td>Dental Quality Assurance Commission, Olympia, WA</td>
</tr>
<tr>
<td>Christensen DDS, Rolf</td>
<td>UW School of Dentistry, Seattle, WA</td>
</tr>
<tr>
<td>Carbery DMD, John</td>
<td>Dental Quality Assurance Commission, Olympia, WA</td>
</tr>
<tr>
<td>Dodd DDS, Sue Ann</td>
<td>Oral and Maxillofacial Surgery</td>
</tr>
<tr>
<td>Dodson DMD, MPH, Tom</td>
<td>UW School of Dentistry, Seattle, WA</td>
</tr>
<tr>
<td>Gandara DDS, Bea</td>
<td>UW School of Dentistry, Seattle, WA</td>
</tr>
<tr>
<td>Larson DDS, PS, BJ</td>
<td>Larson Pediatric Dentistry, Mount Vernon, WA</td>
</tr>
<tr>
<td>Madden DDS, PhD, Theresa</td>
<td>Periodontics and Dental Implants, Olympia, WA</td>
</tr>
<tr>
<td>Neal DDS, MD, Craig</td>
<td>Neal, Leonard &amp; Sorenson Oral and Maxillofacial Surgery, Seattle, WA</td>
</tr>
<tr>
<td>Terman MD, PhD, Gregory</td>
<td>University of Washington, Seattle, WA</td>
</tr>
<tr>
<td>Walco PhD, Gary</td>
<td>Seattle Children’s Hospital, Seattle, WA</td>
</tr>
</tbody>
</table>

**Washington State Medical Directors, Bree Collaborative & Agency Staff**

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fliss, Mary</td>
<td>Health Care Authority, Olympia, WA</td>
</tr>
<tr>
<td>Fotinos MD, Charissa</td>
<td>Health Care Authority, Olympia, WA</td>
</tr>
<tr>
<td>Freeburg, Jim</td>
<td>Office of the Insurance Commissioner, Olympia, WA</td>
</tr>
<tr>
<td>Franklin MD, MPH, Gary</td>
<td>Labor and Industries, University of Washington, Olympia, WA</td>
</tr>
<tr>
<td>Hammond MD, PhD, G. Steven</td>
<td>Department of Corrections, Olympia, WA</td>
</tr>
<tr>
<td>Lessler MD, Dan</td>
<td>Health Care Authority, Olympia, WA</td>
</tr>
<tr>
<td>Lofy MD, Katherine</td>
<td>Department of Health, Olympia, WA</td>
</tr>
<tr>
<td>Mai PharmD, Jaymie</td>
<td>Department of Labor and Industries, Olympia, WA</td>
</tr>
<tr>
<td>Pham PharmD, MPH, Christy</td>
<td>Department of Labor and Industries, Olympia, WA</td>
</tr>
<tr>
<td>Pistoressis PharmD, Ryan</td>
<td>Health Care Authority, Olympia, WA</td>
</tr>
<tr>
<td>Sullivan PharmD, MS, Donna</td>
<td>Health Care Authority, Olympia, WA</td>
</tr>
<tr>
<td>Transue MD, Emily</td>
<td>Health Care Authority, Olympia, WA</td>
</tr>
<tr>
<td>Weir MPH, Ginny</td>
<td>Bree Collaborative, Seattle, WA</td>
</tr>
</tbody>
</table>

**Associations and Stakeholders**

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greg, Mia</td>
<td>Olympic Community of Health, Bremerton, WA</td>
</tr>
<tr>
<td>Kavanagh MPH, Laurie</td>
<td>Washington Health Alliance, Seattle, WA</td>
</tr>
<tr>
<td>Killpack MBA, Bracken</td>
<td>Washington State Dental Association, Seattle, WA</td>
</tr>
<tr>
<td>Kushner MPH, CPH, Siri</td>
<td>Olympic Community of Health, Bremerton, WA</td>
</tr>
<tr>
<td>Lay, Linda</td>
<td>Delta Dental, Seattle, WA</td>
</tr>
<tr>
<td>Lovell MPA, Emily</td>
<td>Washington State Dental Association, Seattle, WA</td>
</tr>
<tr>
<td>McAleenan JD, Mellani</td>
<td>Washington State Dental Association, Seattle, WA</td>
</tr>
<tr>
<td>Norwitz, Justine</td>
<td>BenchMarket Medical, Seattle, WA</td>
</tr>
<tr>
<td>Pawelko, Tessa</td>
<td>BenchMarket Medical, Seattle, WA</td>
</tr>
<tr>
<td>Puckett MPA, Glenn</td>
<td>Washington State Dental Foundation, Seattle, WA</td>
</tr>
<tr>
<td>Rochon PharmD, Jeff</td>
<td>Washington State Pharmacy Association, Renton, WA</td>
</tr>
<tr>
<td>Shepard, Jeb</td>
<td>Washington State Medical Association, Renton, WA</td>
</tr>
</tbody>
</table>
References

27. Tobias JD, Green TP, Cote CJ. Codeine: Time to Say "No". Pediatrics 2016;138.