# SNAP! CRACKLE! POP! MEDICATION MANAGEMENT OF TMD

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## DISCLOSURES

- I, Amy Greenwood, do not have any conflict of interest related to the content of this lecture and discussion.

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## OUTCOMES/OBJECTIVES

At the end of the program, participants should be able to:

1. Identify non-pharmacologic interventions
2. List the pharmacologic options for TMD pain management and patient medial history considerations about each
3. Identify medications that predispose individuals to TMD

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## NOW THAT WE HAVE A DIAGNOSIS, WHAT DO WE DO?

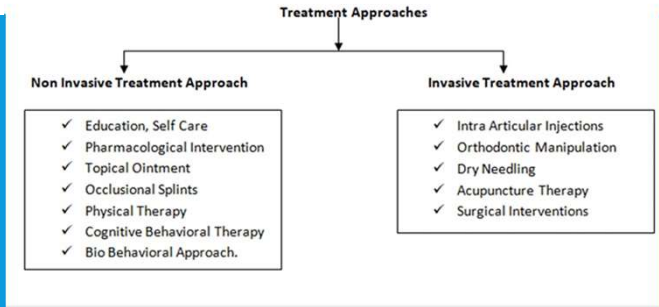


FIGURE 1: Treatment approaches

Wadhokar O C, Patil D S. Cureus. 2022

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## NON-PHARMACOLOGIC OPTIONS

- **Self Care**
  - Education is a large piece, setting expectations
  - Jaw rest
- Intra-oral appliances
- Referrals to physical and/or biomedical colleagues
- Surgical intervention

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## PHARMACOLOGIC OPTIONS- RX AND OTC

- Goal is to manage discomfort and dysfunction
- Pharmacological agents include:
  - NSAIDs
  - Skeletal muscle relaxants
  - Antidepressants
  - Anticonvulsants
  - Topical agents
  - Misc

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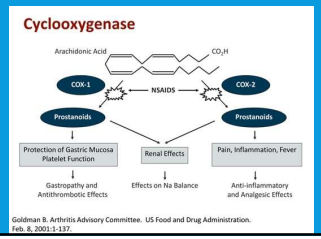
## NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

- Most common class of medications used for craniofacial pain and have evidence of efficacy in TMD pain management
- MOA: inhibit cyclo-oxygenase, resulting in decreased production of prostaglandins

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## NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

| Advantages | Disadvantages |
|---|---|
| • No sedation<br>• No constipation or respiratory depression<br>• *Anti-inflammatory effect*<br>• No psychological dependence/habituation<br>  • Analgesic rebound | • GI intolerance<br>  • Due to COX-1 activity<br>• Drug interactions<br>  • Anticoagulants/Antiplatelets<br>  • Lithium<br>  • Phenytoin<br>  • Methotrexate<br>  • Antihypertensives<br>• Disease state interactions<br>  • Cardiovascular disease<br>  • Renal disease<br>  • Diabetes |

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## RISK FACTORS FOR NSAID-INDUCED GI COMPLICATIONS

- Age >60 years
- H/O ulcer disease of GI complications
- High dose, multiple NSAIDs
- Concomitant corticosteroid therapy
- Presence of CVD, HTN, CHF
- H/O significant systemic disease
  - Rheumatoid arthritis, diabetes, CKD, etc
- Use of SSRIs

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## COMMONLY USED NSAIDS

| Non COX Selective | COX-2 Selective |
|---|---|
| **Ibuprofen** | Celecoxib (Celebrex) |
| **Naproxen** | |
| Nabumetone | |
| Meloxicam | |
| Diclofenac | |
| Ketorolac | |
| Indomethacin | |
| Etodolac | |
| Ketoprofen | |

Most common agents used
- Ibuprofen 600-800mg by mouth every 6-8 hours. Not to exceed 3200mg/day.
- Naproxen 220-440mg by mouth every 12 hours.
- Nabumetone 1000mg daily

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## WHICH NSAID TO PRESCRIBE?

- Most NSAIDS have similar efficacy
  - Patient-specific concerns will guide the choice
    - History of NSAID treatment
    - Ease of dosing regimen
    - Health history
  - If a therapeutic trial of one NSAID doesn't work, trial an agent from a different chemical class
  - If risk of GI complications
    - Use COX-2 selective agent: Celebrex
    - Use COX-1 selective agent PLUS a proton pump inhibitor

| Propionic Acids | Salicylic Acids | Naphthylalkanone |
|---|---|---|
| Fenoprofen | Asprin (OTC) | Nabumetone |
| Flurbiprofen | Oxicam | |
| Ibuprofen (OTC) | Piroxicam | COX-2 Inhibitors |
| Ketoprofen (OTC) | Meloxicam | Refecoxib |
| Naproxen (OTC) | | Celecoxib |
| Oxaprozin | Acetic Acids | Meloxicam |
| | Diclofenac | Valdecoxib |
| Anthranilic Acids | Etodolac | Etodolac |
| Meclofenamate | Indomethacin | Eloricoxib |
| Mefenamic acid | Ketorolac | Parecoxib |
| | Sulindac | Lumiracoxib |
| | Tolmetin | |

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## ROLE IN MANAGEMENT OF TMD

- Patients who see the most success
  - Often used in conjunction with other treatments
  - Prescribe regular around the clock (not PRN) during initial treatment
    - At least 2 weeks of scheduled therapy

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# RX-SKELETAL MUSCLE RELAXANTS

- **Two categories**
  - **Antispastic**
    - For treatment of conditions such as cerebral palsy, multiple sclerosis, TBI)
      - Baclofen, tizanidine, diazepam
  - **Antispasmotic (Acute musculoskeletal conditions)**
    - Cyclobenzaprine, chlorzoxazone, metaxalone, methocarbamol
      - Most studies look at cyclobenzaprine– side effects limit its use
    - Patient considerations
      - **Cardiovascular status**
      - Administration of other CNS depressants

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# CYCLOBENZAPRINE (FLEXERIL)

- Available in 5mg and 10mg tablets
  - Starting dose 5mg HS
  - For most patients 5mg as well as 10mg with much less hangover sedation
- Drug Interactions:
  - Anticholinergics, EtOH, benzodiazepines, opioids, MAOIs
- Contraindications:
  - Recent MI, arrhythmias, CHF, conduction disturbances

| Advantages | Disadvantages |
|---|---|
| Inexpensive<br>Works well for TMJ problems<br>Pain<br>Restriction of movement | Related to TCAs<br>Higher anticholinergic effects<br>Orthostatic hypertension<br>QT prolongation |

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# IOWA MEDICAID COVERAGE

- As if 10/1/2024
- If patient is willing to pay out of pocket:
- **Metaxalone is the least sedating**
  - 800mg tablets available
    - 800mg by mouth 3-4 times daily
  - Can be used in patients 13 years of age and older
  - Contraindicated in renal and hepatic impairment

**MUSCLE RELAXANTS**

| | | | |
|---|---|---|---|
| G | 11 | N | baclofen oral suspension |
| B | 11 | N | FLEQSUVY |
| G | | P | baclofen |
| G | 11 | N | baclofen oral sol |
| B | 11 | N | LYVISPAH |
| G | 11 | N | carisoprodol |
| B | 11 | N | SOMA |
| G | | P | chlorzoxazone |
| G | 11 | N | cyclobenzaprine caps |
| B | 11 | N | AMRIX |
| G | | P | cyclobenzaprine hcl |
| B | 11 | N | FEXMID |
| G | 11 | N | metaxalone |
| G | | P | methocarbamol tab |
| B | 11 | N | ROBAXIN |
| G | | P | orphenadrine citrate er tab |
| G | | P | tizanidine hcl |
| B | 11 | N | ZANAFLEX |
| B | 11 | N | DANTRIUM CAP |
| G | 11 | N | dantrolene sodium cap |

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# COMPARING SKELETAL MUSCLE RELAXANTS

**Sedation Risk:**
Metaxalone (minimally)
Chlorzoxazone (mild-moderate)
Tizanidine (dose dependent)
Methocarbamol (moderate)
Cyclobenzaprine (high)
Carisoprodol (high)

| Medication | T 1/2 Hours | Starting Dose | Special Considerations |
|---|---|---|---|
| Anti-spasticity Agents | | | |
| Baclofen | 5 | 5 mg TID | Lowers seizure threshold. Can increase Alk Phos and AST. Available intrathecal. Adult max dose 80 mg/day. Reduce dose when CrCl <80 mL/min. Also prescribed for alcohol use disorder and hiccoughs (10). FDA approved ages ≥ 12. |
| Anti-spasmodic Agents | | | |
| Cyclo-benzaprine | 18 | 5 mg TID | Structurally akin to tricyclic antidepressants; caution when cardiac issues present as patients are at risk for anticholinergic effects like orthostasis, and QTc prolongation. Adult max daily dose 30 mg. FDA approved ages 15 and above. |
| Carisoprodol | 8 | 250 mg QID | Metabolized to meprobamate which has significant abuse potential. Max adult daily dose 1400 mg. |
| Metaxalone | 9 | 800 mg TID | Caution in liver failure. Max daily adult dose 2400 mg. |
| Metho-carbamol | 1-2 | 750 mg QID | May cause brownish/green urine discoloration. Consider 1500 mg QID as a loading dose for 2-3 days. FDA approved ages 16 and above. |
| Combination Agents | | | |
| Diazepam | 48 | 2-10 mg TID | Significant abuse potential. |
| Tizanidine | 20-40 | 4 mg TID | Hypotension, asthenia, dry-mouth may result. Contra-indicated with ciprofloxaxin and other CYP A12 inhibitors. Dose reduce when CrCl <25 mL/min. Max daily dose 36 mg. |

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## ANTIDEPRESSANTS

- **Tricyclic Antidepressants**
- MOA: bind to 5-HT receptors, modulated the nociceptive system
  - amitriptyline and nortriptyline show the greatest potential
    - Amitriptyline 25mg at bedtime

| Advantages | Disadvantages |
|---|---|
| • Low doses seem to be effective | • Anticholinergic burden<br>• Cardiovascular risk<br>  • QT prolongation |

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## BENZODIAZEPINES

- MOA: enhance the effect of GABA at its receptor, slowing the signaling between neurons that result in muscle contraction

| Advantages | Disadvantages |
|---|---|
| • Some evidence to support their use along with NSAID treatment | • **CONTROLLED SUBSTANCES**<br>• **Potential for physical and psychological dependence!!!**<br>• Adverse drug reactions: sedation, confusion, amnesia, impair coordination |

- If a benzodiazepine must be used limit use to 2-4 weeks
  - Not an option for geriatric patients or individuals on other CNS depressants
- Diazepam is preferred due to its longer half-life

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## ANTICONVULSANT MEDICATIONS

- Used frequently in neuropathic pain and headache disorders
- MOA: reducing neural hyperexcitability in various ways
  - Voltage-gated and ligand-gated ion channels
  - Mimicking GABA
  - Enhance the response to GABA
- Frequently used agents
  - Gabapentin
  - Pregabalin

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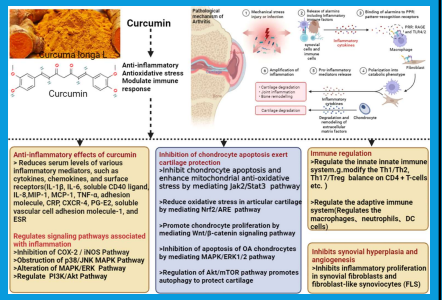
## TURMERIC CURCUMIN

- Curcumin and Curcuma longa extract may improve symptoms of inflammation in arthritis
- Use for osteoarthritis
  - Meta-analysis found curcumin and curcuma longa
  - extract may reduce pain, improve joint function and improve joint stiffness without increasing adverse events
  - When used in combination with NSAIDs improvement of function was increased without adverse effects
  - RCT are limited so clear conclusions are difficult to draw




Zeng et al. Front Immunol. 2022.

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# OPIOIDS AND CANNABIDIOL

- **Opioids**
  - Should be avoided
- **Cannabidiol (CBD)**
  - **Thought to regulate many physiologic processes, including pain sensitization and inflammation**
  - Acts on cannabinoid $CB_1$/$CB_2$ receptors
  - May reduce pain on multiple GPCR
    - Action on opioid and serotonin receptors thought to contribute to effectiveness in stress reduction, anxiety, and pain
  - Antagonizes alpha-1 adrenergic receptors and mu-opioid receptors
    - Thought to contribute to somnogenic and anti-inflammatory effects
  - Inhibit sodium and calcium channels dampening nerve excitability

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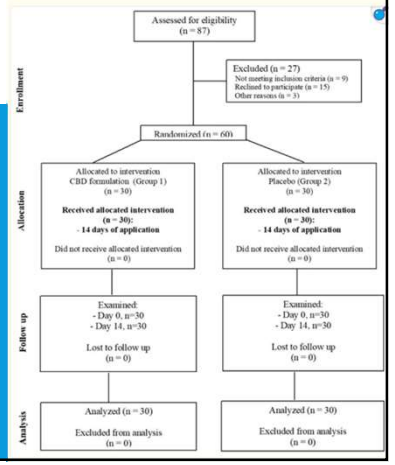
J Clin Med. 2019 Nov 6;8(11):1886. doi: 10.3390/jcm8111886

**Myorelaxant Effect of Transdermal Cannabidiol Application in Patients with TMD: A Randomized, Double-Blind Trial**

Aleksandra Nitecka-Buchta [1,*], Anna Nowak-Wachol [1], Kacper Wachol [1], Karolina Walczyńska-Dragon [1], Paweł Olczyk [2], Olgierd Batoryna [2], Wojciech Kempa [3], Stefan Baron [1]

- Double-armed, double-blind RCT
  - Dept of TMD at Medial University of Silesia, Poland
    - 1= 4% CBD formulation
    - 2= control
- 3visits total
  - Screen, Baseline, 14 days
- Gel applied externally
  - Improved SEMG activity by Group 1
  - Pain reduction was significant in Group 1
    - 70.2% reduction, compared to 9.81%

Figure 2.

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J Clin Med. 2024 Feb 29;13(5):1417. doi: 10.3390/jcm13051417

**Cannabidiol Intervention for Muscular Tension, Pain, and Sleep Bruxism Intensity—A Randomized, Double-Blind Clinical Trial**

Karolina Walczyńska-Dragon [1,*], Anna Kurek-Górecka [2], Wojciech Niemczyk [1], Zuzanna Nowak [1], Stefan Baron [1], Paweł Olczyk [2], Aleksandra Nitecka-Buchta [1], Wojciech M Kempa [3]

- Three-armed, double-blind RCT
  - Dept of TMD at Medial University of Silesia, Poland
    - 1a= 10% CBD formulation
    - 1b= 5% CBD formulation
    - 2= control
- 4 visits total
  - Screen, Baseline, 14 days, 30 days
- Gel applied internally
  - Improved SEMG activity by 11-12.6%
  - Improved sleep bruxism

Table 1.

The inclusion and exclusion criteria for patient qualification in the study.

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| 1. Patients who agreed to participate in the study. | 1. Cannabis formulation/placebo formulation allergy, hypersensitivity to substances to be used in the study. |
| 2. Patient's age within ≥18 and ≤60 years. | 2. Wounds within oral mucosa. |
| 3. Good general health. | 3. Addiction to cannabis. |
| 4. TMD positive as per the Polish version of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMDs) for group II.1.A. 1, 2, and 3. | 4. Tobacco smokers. |
| 5. Presence of all teeth (except for third molars). | 5. Patients being treated with analgesic drugs and/or drugs that affect muscle function. |
| | 6. Patients being treated with oral appliances. |
| | 7. Fixed or removable dental prosthesis. |
| | 8. Disease or autoimmune disorder associated with generalized muscular tension. |
| | 9. Patients undergoing orthodontic treatment. |
| | 10. Patients treated by a neurologist for neurological conditions. |
| | 11. Patients with psychiatric conditions. |
| | 12. Patients having undertaken radiotherapy, patients with an active neoplastic process. |
| | 13. Patients with odontogenic pain. |
| | 14. Pregnant and breastfeeding patients. |
| | 15. Use of medications that interact with CBD. |
| | 16. Use of any products containing cannabis. |

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# TOPICAL OPTIONS

| Commercially available | Compounded |
|---|---|
| • Diclofenac (Voltaren)<br>• Lidocaine (Lidoderm) | • Cyclobenzaprine<br>• Ketoprofen<br>• Lidocaine |




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# NOW THAT WE'VE TALKED ABOUT TREATMENT….ARE THERE ANY MEDICATIONS THAT CAUSE TMD??

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## MEDICATIONS ASSOCIATED WITH TMD

- **Antidepressant associated bruxism**
  - **Most common agents:** fluoxetine, sertraline venlafaxine
- Mechanism: indirectly lowering dopamine levels
  - SSRIs increase 5-HT in the mesocortical tract, which inhibits the release of dopamine
  - In this tract, dopamine acts to inhibit motor activity of jaw muscles
- Appears to be somewhat dose related
  - Mirtazapine is the only antidepressant not associated to bruxism

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REVIEW

## SSRI-associated bruxism

A systematic review of published case reports

Andrew R. Garrett, DO, MPH, MS and Jason S. Hawley, MD

*Neurology: Clinical Practice* April 2018 vol. 8 no. 2 135-141 doi:10.1212/CPJ.0000000000000433

- PubMed search of case and case series
  - "SSRI bruxism, " "SNRI bruxism," "citalopram bruxism," "escitalopram bruxism," "buspirone bruxism," and "antidepressant bruxism.
- Exclusion
  - No management of bruxism discussed
- 71 articles identified, 42 excluded, 29 included
  - 46 total patients
    - Female = 68%
    - Diagnosis of MDD or GAD (76%)
    - SSRI on board (74%), SNRI (24%)
    - Most common intervention= add on buspirone (20 cases)

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## OTHER DRUGS ASSOCIATED WITH BRUXISM

- Amphetamines and other stimulants
- Antipsychotics
  - Haloperidol
  - Quetiapine
- Other antidepressants
  - Bupropion
  - Venlafaxine

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## ADVERSE DRUG REACTION PROBABILITY SCALE

- The Naranjo ADR Probability Scale was developed to help standardize assessment of causality for all adverse drug reactions. The scale was also designed for use in controlled trials and registration studies of new medications, rather than in routine clinical practice.

| Question | Yes | No | Do Not Know | Score |
|---|---|---|---|---|
| 1. Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | |
| 2. Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 | |
| 3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 | |
| 4. Did the adverse event reappear when the drug was readministered? | +2 | -1 | 0 | |
| 5. Are there alternative causes that could on their own have caused the reaction? | -1 | +2 | 0 | |
| 6. Did the reaction reappear when a placebo was given? * | -1 | +1 | 0 | |
| 7. Was the drug detected in blood or other fluids in concentrations known to be toxic? | +1 | 0 | 0 | |
| 8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1 | 0 | 0 | |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | |
| 10. Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | |
| | | | Total Score: | |

*Question 6 refers to a typical clinical trials situation and is included here for completeness.

| Total Score | Interpretation of Scores |
|---|---|
| ≥ 9 | Definite. The reaction (1) followed a reasonable temporal sequence after drug exposure had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, (3) was confirmed by improvement on withdrawing the drug and (4) reappeared on reexposure. |
| 5 - 8 | Probable. The reaction (1) followed a reasonable temporal sequence after a drug exposure, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state. |
| 1 - 4 | Possible. The reaction (1) followed a temporal sequence after a drug exposure, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease. |
| ≤ 0 | Doubtful. The reaction was likely related to factors other than a drug. |

The Naranjo scale is a tool to help clarify how to evaluate a potential causal association. It is not intended to solve all the complex problems of identification and classification of ADRs.

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## SSRI-ASSOCIATED BRUXISM SUSPECTED

- Consult prescribing physician
  - Consider a dose decrease of the causative agent
  - Consider a change to a different SSRI
    - Mirtazapine
      - Enhances norepinephrine release by blocking 5-HT receptors, alpha-1 & -2 receptors, and H1 receptors
        - Sided effects: dry mouth, increased serum cholesterol and triglycerides, weight gain
  - Consider the addition of buspirone

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## WHY BUSPIRONE?

- MOA of buspirone:
  - Serotonin 1A (5-HTA) partial agonist at pre- and post- synaptic receptors
  - Adaptive neuronal and receptor mechanisms, instead of acute receptor mechanisms
    - Gradual effects
- Adjunct to SSRI or used alone for treatment of MMD or GAD
- Treatment
  - Buspirone 5-15mg by mouth up to three times daily
- **Interactions:**
  - $CYP_3A_4$
  - Serotonin syndrome– avoid tramadol, MAOIs

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## QUESTIONS


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