Opioid Therapy For Pain: An Evidence Review

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Educational Objectives

At the conclusion of this activity participants should be able to:

- Review evidence on use of opioid therapy for chronic pain
- Assess risks and benefits of long-term opioid therapy for chronic pain and factors associated with prescription opioid overdose and misuse

**Note:** Best practices to reduce risks related to prescription opioids are discussed in a different lecture
Case

- 53-year old female transferring care because her PCP is leaving practice
  - Shoulder and hip pain secondary to avascular necrosis, s/p shoulder replacements, hip decompression, hip replacement
  - Fibromyalgia, non-radicular low back pain, chronic headache
  - Depression, fatigue
  - Gastroparesis, irritable bowel syndrome
  - Morphine IR 30 mg 5 tabs (150 mg) every 8 hrs + oxycodone 5 mg 8 tabs (40 mg) every 6 hrs
    - Morphine equivalent dose/day: 690 mg
  - Modafinil 20 mg po daily
  - Pain 6/10 on average, with day to day fluctuation
  - Can carry out activities of daily living with pain, limited exercise, no aberrant behaviors
Background

- Chronic non-cancer pain highly prevalent, with substantial burdens
  - Estimates vary, up to 1/3 of adults report some CNCP
- Opioids are increasingly prescribed for chronic non-cancer pain
  - About 5% of U.S. adults report use of long-term opioid therapy (LOT)\textsuperscript{a}
    - The U.S. is ~5% of the world’s population, but accounts for 80% of the world’s supply of opioids (99% of hydrocodone)
- Opioids are associated with potential harms, both to patients and to society
- Large practice variations in use of LOT

\textsuperscript{a}Boudreau et al Pharmacoepidemiol Drug Saf 2009
CDC: Parallel increases in opioid sales, deaths and substance abuse

US opioid sales quadrupled 2000-2010

Since 2008, 15,000 deaths per year. This exceeds MVA deaths in 30 states.

Prescription Opioid Overdose

National Overdose Deaths
Number of Deaths from Prescription Opioid Pain Relievers
(excluding non-methadone synthetics)

Source: National Center for Health Statistics, CDC Wonder

Rates are per 100,000 population age-adjusted to 2008 U.S. standard population
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm
Opioid Overdose Trends, 2000-2013

Source: CDC/NCHS National Vital Statistics System NCHS Data Brief, No. 190, March 2015
Nonmedical pain medication use among adolescents and young adults

SAMSHA 2010 National Survey on Drug Use and Health
First Opioid of Abuse in Those Using Heroin

Cicero TJ et al. JAMA Psychiatry 2014
Prescribing Trends

- Since ~2010, opioid use for chronic pain increased from 8% to 16%
  - Use of more potent opioids increased from 2 to 9%
  - Increases observed across age groups and in men and women
  - Increased use of schedule II opioids; greatest increase in daily doses occurred in prescriptions of schedule II opioids

How did we get here?

- Perceived undertreatment of chronic pain
  - Laws or regulations passed in >20 states to allow use of opioids for chronic pain
- Low risk of abuse observed with use of opioids in palliative care settings
  - “…patients rarely demonstrate euphoric responses to opioid drugs, and neither analgesic tolerance nor physical dependence is a significant clinical problem.” — Portenoy RK. J Law Medicine Ethics 1996;24:296
- Case series describing benefits of long-term opioid therapy for chronic pain, with low rates of abuse, addiction, or other serious AE’s
  - Most prescribed low doses (<20 mg MED/day)
- No ceiling dose used in palliative care settings
  - “Escalation of the opioid dose until either adequate analgesia occurs or intolerable and unmanageable side effects supervene is standard practice in cancer pain management.” — Portenoy RK. J Pain Symptom Management 1996;11:203
- Emphasis on round-the-clock dosing using sustained-release formulations
Evidence on Effectiveness of Opioid Therapy for Chronic Non-cancer Pain

• Short-term follow-up:
  ▪ Versus placebo
    – Pain intensity (71 trials): Mean difference -0.79 point (95% CI -0.93 to -0.67) on a 0 to 10 point pain scale
    – Pain response (44 trials): RR 1.35 (95% CI 1.24 to 1.48)
    – Function (44 trials): Standardized mean difference -0.22, (95% CI -0.28 to -0.16)
    – Little incremental benefit with increased doses
  ▪ Versus nonopioids
    – No difference in pain intensity (14 trials), likelihood of pain response (12 trials), or function (11 trials)
• Intermediate and long-term follow-up:
  ▪ No placebo-controlled trials
  ▪ Versus non-opioids
    – One trial (SPACE) found no difference between stepped therapy with opioids vs. non-opioids in function, opioid therapy associated with higher (worse) pain intensity (4.0 vs. 3.5 on 0 to 10 scale)
Limitations of Evidence on Effectiveness of LOT

• High loss to follow-up
• Trials typically excluded patients at higher risk for addiction or overdose, psychological comorbidities, and serious medical comorbidities
• Limited evidence on commonly treated conditions
  ▪ Fibromyalgia, headache, others
• No trial compared LOT vs. cognitive behavioral-based exercise therapy or interdisciplinary rehabilitation
Opioids vs. Non-opioid Pharmacological Therapy

SPACE RCT of stepped therapy starting with opioid therapy vs. initial non-opioid therapy for chronic LBP and OA pain

- One year VA trial in primary care, n=240
- Open-label for patients and clinicians, assessment masked
- All patients received individualized medication management using collaborative telecare pain management model
- Average opioid dose 26 vs. 1 mg MED/day
- At 12 mos, no difference in function, pain slightly worse in opioid group
- Opioids associated with more adverse symptoms; no deaths or OUD

Krebs E. JAMA 2018;319:872-82
SPACE Trial

Pain intensity

Mean BPI Severity (n=238)

- Opioid
- Non-opioid

Month

0 3 6 9 12

0 1 2 3 4 5 6

5.4 5.4 4.0 3.5

p = 0.034

Krebs E. JAMA 2018;319:872-82
Pain interference with function

Mean BPI Interference (n=238)

- Opioid
- Non-opioid

p = 0.584

Krebs E. JAMA 2018;319:872-82
### Evidence on Short-term Harms of Opioid Therapy vs. Placebo for Chronic Non-cancer Pain

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of trials</th>
<th>RR (95% CI)</th>
<th>Absolute risk difference</th>
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<tbody>
<tr>
<td>Discontinuation due to adverse events</td>
<td>61</td>
<td>2.25 (1.86 to 2.73)</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>60</td>
<td>2.46 (2.17 to 2.80)</td>
<td>17%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>49</td>
<td>3.57 (2.98 to 4.34)</td>
<td>7%</td>
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<tr>
<td>Constipation</td>
<td>58</td>
<td>3.38 (2.96 to 3.92)</td>
<td>14%</td>
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<tr>
<td>Somnolence</td>
<td>52</td>
<td>2.97 (2.44 to 3.66)</td>
<td>9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>53</td>
<td>2.66 (2.37 to 2.99)</td>
<td>8%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>30</td>
<td>3.51 (2.47 to 5.16)</td>
<td>7%</td>
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</table>
Addiction and Misuse

Trials not designed to assess risk of addiction and misuse

• In observational studies:
  ▪ Rates of misuse averaged between 21% to 29%
  ▪ Rates of addiction averaged between 8% to 12%
  ▪ Definitions inconsistent across studies and behaviors vary in seriousness
  ▪ Poorly standardized methods to detect these outcomes

• One study (n=801) based on detailed, standardized interviews
  ▪ 26% purposeful oversedation
  ▪ 39% increased dose without prescription
  ▪ 8% obtained extra opioids from other doctors
  ▪ 18% used for purposes other than pain
  ▪ 12% hoarded pain medications

\*Fleming et al. J Pain 2007
Vowles et al. Pain 2015
Factors associated with increased risk of overdose, or observed in high proportions of overdoses

• Misuse behaviors
  ▪ Obtaining opioid prescriptions from multiple providers
  ▪ Running out early, losing prescriptions
  ▪ Unauthorized dose escalations
• Recent initiation of opioids
• Methadone
• Concomitant use of benzodiazepines
• Substance use
• Psychological comorbidities
• Higher doses of opioids
Overdose: Dose-response Relationship

- Observational studies consistently show an association between opioid dose and risk of overdose or death in patients with chronic pain.
- Risk starts to increase at relatively low doses and continues to increase.
- Studies matched or adjusted for potential confounders available in administrative databases:
  - Potential for residual confounding by indication.
- Difficult to determine whether patients had chronic pain and duration of therapy.
Association Between Opioid Dose and Overdose Risk

- **Cohort study (n=9940, 51 opioid overdoses, 6 fatal)**
  - Risk of opioid overdose (vs. 1 to <20 mg/day)
    - ≥100 mg/d: HR 8.9 (4.0-20)
    - 50-<100 mg/d: HR 3.7 (1.5-9.5)
    - 20-<50 mg/d: HR 1.4 (0.57-3.6)

- **Case-control study (VA, 750 cases)**
  - Risk of opioid overdose-related death (vs. 1 to <20 mg/day)
    - >=100 mg/d: HR 7.2 (4.8-11)
    - 50-<100 mg/d: HR 4.6 (3.2-6.7)
    - 20-<50 mg/d: HR 1.9 (1.3-2.7)

- **Nested case-control study (Ontario, 498 cases)**
  - Risk of opioid-related mortality (vs. 1 to <20 mg/day)
    - ≥200 mg/d: OR 2.9 (1.8-4.6)
    - 100-199 mg/d: OR 2.0 (1.3-3.2)
    - 50-99 mg/d: OR 1.9 (1.3-2.8)
    - 20-49 mg/d: OR 1.3 (0.94-1.8)

Other Harms of Opioids

• Hyperalgesia
  ▪ Paradoxical increased sensitivity to pain
  ▪ Prevalence, risk factors and clinical significance not well understood

• Hypogonadism
  ▪ Primarily based on cross-sectional studies
  ▪ One study showing association with increased use of testosterone and ED meds

• Falls/fracture risk

• Myocardial infarction

• Poorer functional outcomes
Initiation and Titration of Opioids

- Opioids are not first-line therapy for chronic pain
- In appropriately selected patients who do not respond to non-opioid therapy, view an initial course of opioids as a short-term, therapeutic trial
  - Do not continue long-term opioid therapy in patients who are not benefitting
  - Re-assess within 1-4 weeks
- Start at low doses and titrate cautiously
- Insufficient evidence to recommend short- vs. long-acting opioids, round-the-clock versus PRN
  - Potential benefits of long-acting, round-the-clock dosing unproven
  - Potential harms of long-acting, round-the-clock dosing include increased risk of hyperalgesia, tolerance, endocrinologic adverse effects
  - Initiation with long-acting opioids associated with increased risk of overdose
  - Methadone and fentanyl not recommended as first line options due to less predictable/more complicated dosing/pharmacokinetics
  - Buprenorphine for chronic pain in higher risk patients; evidence lacking to show improved safety but theoretically lower respiratory risk
    - Higher dose buprenorphine formulations approved for treatment of opioid use disorder (off-label for pain)

Methadone

- Synthetic opioid used for treatment of addiction and pain
- Increased methadone deaths nationwide
  - 1999: 800 deaths; 2008: 4900 deaths
  - Methadone accounted for 1.7% of opioid rx’s in 2009 and 9.0% of morphine equivalents in 2010\textsuperscript{a}
  - Involved in 31% of opioid-related deaths, and 40% of single-drug deaths\textsuperscript{a}
- Half-life 15 to 60 hours, up to 120 hours
  - 60 hour half-life=12 days to steady-state
  - Start at 2.5 mg q8 hrs, increase slowly
- Higher doses of methadone associated with greater QTc interval prolongation
  - High proportion of reported cases of torsades de pointes occurred in patients prescribed >200 mg/day
  - ECG monitoring at baseline and at higher doses\textsuperscript{b}
- Morphine to methadone conversion ratio increases at higher doses
  - Incomplete cross-tolerance

\textsuperscript{a}MMWR 2012;61:493-7
\textsuperscript{b}Chou R J Pain 2014;15:321-37
Time to Reach Steady State

Steady State
- Attained after approximately four half-times
- Time to steady state independent of dosage

http://www.rxkinetics.com/pktutorial/1_6.html
Prolonged QTc and Torsades de Pointes

Figure 1 – Admitting ECG shows normal sinus rhythm with atrial bigeminy, nonspecific T-wave abnormality, and QTc prolongation (626 msec).

Figure 2 – Rhythm strip shows TdP.
# Morphine to Methadone Conversion

<table>
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<tr>
<th>24 hour total oral morphine</th>
<th>Oral morphine to methadone conversion ratio</th>
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</thead>
<tbody>
<tr>
<td>&lt;30 mg</td>
<td>2:1</td>
</tr>
<tr>
<td>31-99 mg</td>
<td>4:1</td>
</tr>
<tr>
<td>100-299 mg</td>
<td>8:1</td>
</tr>
<tr>
<td>300-499 mg</td>
<td>12:1</td>
</tr>
<tr>
<td>500-999 mg</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1000 mg</td>
<td>20:1</td>
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</tbody>
</table>

Note: Proposed morphine to methadone conversion ratios vary
Fentanyl

- Absorption and pharmacodynamics of transdermal fentanyl are complex
- Gradually increasing serum concentration during the first part of the 72-hour dosing interval
- Variable absorption based on factors such as external heat
- Dosing in mcg/hr instead of mg
- Should be prescribed with clinicians familiar with its use and complexities
Dosing

- No theoretical ceiling with opioids
  - But, little evidence to guide prescribing at higher doses
  - Additional risks (hyperlgesia, endocrine), unclear benefit, and can be a marker for abuse, addiction, or diversion
  - Higher doses associated with increased risk of overdose
  - Unclear if persons who don’t respond at relatively low doses will respond at higher doses (may be opioid non-responders)

- Definitions of “higher dose” have varied and continue to evolve; trend towards lower dose thresholds based on new evidence on dose-dependent overdose risks
  - 2009 APS/AAPM guideline defined >200 MME/day of as “higher dose”
  - 2016 CDC guideline recommends caution at 50-90 MME/day and to avoid doses >90 MME/day

- Mitigating risks of higher doses
  - Counsel patients on risks and provide opportunity to taper
  - More frequent or intense monitoring
  - Consider tapering off medication if not achieving therapeutic goals
  - Provide naloxone in conjunction with overdose education
  - Avoid co-prescribing of benzodiazepines and other medications (e.g., other sedatives, gabapentinoids) that may increase risk
High-dose Opioid Therapy Prescribing Patterns

- Small proportion of patients account for the majority of opioids prescribed
  - In one study, 5% of opioid users accounted for 48% to 70% of total use
- Factors associated with high dose therapy include:
  - Presence of substance use disorders
  - Presence of mental health disorders
  - Use of sedative-hypnotics and multiple opioids
  - Higher health service utilization
  - Multiple pain problems and high levels of medical and psychiatric comorbidity
- “Adverse selection”— persons at highest risk are more likely to receive high dose opioids
  - Address psychosocial risk factors or high distress when possible, rather than increasing dose

Mitigating Risks Associated with Opioids

- Avoid higher doses
- Monitoring, including urine drug testing
  - Reassess at least every 3 months, more frequently for higher-risk persons, after initiation and dose increases
- Review prescription drug monitoring data
- Avoid sedative-hypnotics (particularly benzodiazepines)
- More frequent follow-up
- Addiction, pain, or psychiatric consultation
- More frequent refills with smaller quantities
- Naloxone co-prescription
- Abuse-deterrent formulations
Urine Drug Tests

Recommended to help identify risky behaviors that would otherwise be undisclosed:

- Non-invasive, objective documentation of compliance with treatment plan, including use or absence of prescribed drugs, non-prescribed drugs, and illicit substances
- Longer window or detection compared to blood

When to perform urine drug testing:

- At baseline and periodically, interval may be guided in part by assessed risk
  - Test if suspected aberrant behaviors and after major changes in treatment
- Optimal frequency and usefulness of individualized or random vs. routine testing uncertain
  - 1-2 times/year may be appropriate for low-risk patients; 3-4 or more times per year for higher risk
  - Individualized or random testing may miss some abnormal tests, but higher yield and reduced costs
  - Patients may have more opportunity to tamper or alter behavior if testing expected
Cannabis Use and Opioids

- High prevalence of cannabis use in patients with chronic pain, with or without opioids

- Some evidence that states with medical cannabis laws experience slower rates of increase in opioid analgesic overdose death rates compared to states without such laws. (Bachhuber, 2014)
  - But, other evidence that states with medical cannabis laws experienced an opioid overdose death rate 22.7% higher than expected (Shover, 2019)

- Evidence limited, but cannabis may have analgesic effects, particularly for neuropathic pain
  - Effects of cannabis vary depending on THC vs. cannabidiol (CBD) content
    - THC associated with psychoactive/intoxicating effects
    - CBD associated with medicinal effects

- Little evidence on psychomotor and other effects in patients using cannabis and opioids. (Nugent, 2017).

- Association between cannabis use and opioid and other substance misuse uncertain

- Increased risk of MVA with cannabis use

- Caution in patients unable to decrease cannabis use
  - May indicate cannabis use disorder
Opioid-deterrent Formulations

- Opioid-deterrent formulations recently approved by FDA or undergoing FDA approval process
  - Designed to be tamper-resistant or co-formulated with medications that reverse opioid effects or produce noxious side effects when tampered with
  - Effectiveness for reducing misuse/substance abuse and improving clinical outcomes difficult to study
  - Likely to be primarily effective in patients who crush or inject opioids
  - Some patients switched to opioid-deterrent formulations may seek other prescription or illicit opioids

*Cicero et al. NEJM 2012*
High-risk Patients

- High-risk patients are more vulnerable to opioid abuse, misuse, addiction
- Clinicians prescribing opioids in high-risk patients must be able to implement additional measures to manage these risks
  - More frequent monitoring
  - Limited prescription fills
  - Consultation with addiction specialists and mental health professionals
    - Medications for opioid use disorder (methadone, buprenorphine, or naltrexone in conjunction with psychological therapies) recommended for most patients with opioid use disorder
  - If opioids utilized for pain, opioid-deterrent formulations may be helpful
  - Provide naloxone
Aberrant drug-related behaviors must be evaluated

- Behaviors vary in seriousness
- Need to judge seriousness, the cause or causes, likelihood of recurrence, and clinical context
  - Predictors of high likelihood of future aberrant behaviors include 3 or more episodes of aberrant behaviors and sense of “losing control”
  - Serious behaviors include diversion, injecting oral drugs
- Responses range from patient education and enhanced monitoring to referral to addiction specialist and discontinuation of therapy
Discontinuation of Opioid Therapy

- Taper or wean patients off of long-term opioid therapy when they:
  - Engage in intractable aberrant drug-related behaviors or drug misuse/diversion
  - Experience no progress towards meeting therapeutic goals
  - Experience intolerable adverse effects
- Continue to manage pain using non-opioid therapies
- Have an exit strategy when initiating a trial of long-term opioid therapy
  - Indications for stopping opioid therapy
  - Plans for tapering or discontinuing
    - Slow tapers over months or years may be required
  - Provide psychosocial support
  - Know resources for managing addiction and mental health issues

Driving and Work Safety

- Opioids may cause somnolence, incoordination, clouded mentation, or slower reflexes
- Counsel patients not to drive or perform dangerous activities when impaired
  - Impairment more likely when starting therapy, when increasing doses, and when using other drugs with psychoactive effects
  - No evidence that patients on opioids should be restricted from driving in the absence of signs of impairment
  - State laws vary on reporting requirements
Use of Opioids for Acute Pain

• Opioids generally considered the most effective medication for acute pain
  ▪ But, recent data indicates that opioids may be no more effective than an NSAID alone for some types of acute pain
    o In LBP adding oxycodone/acetaminophen to an NSAID did not improve pain or function at 1 week (Friedman BW. JAMA 2015;314:1572)
    o Opioids no more effective than NSAIDs for third molar extraction

• Use of opioids for “minor” pain associated with increased risk of long-term use
  ▪ Versus no opioid use, opioid within 7 days of minor surgery associated with 44% increased risk of use at 1 year (Alam A. Arch Intern Med 2012;172:425)

• Prescribing excessive quantities of opioids for acute pain results in leftover opioids
  ▪ Source of diversion and unprescribed use

• More judicious use of opioids for acute pain
  ▪ If used, usually limit opioids to a 3-5 day supply for most acute pain (Chou et al. Treatments for Acute Pain, Comparative Effectiveness Review AHRQ 2020)
Conclusions: What is the evidence?

• Opioids associated with modest short-term benefits and increased risk of various opioid-related side effects
• Evidence on long-term benefits limited but indicates no clear benefit versus non-opioid therapy
• Accumulating evidence on serious harms of long-term opioid therapy (including overdose) that appear to be dose-dependent
• Altogether, evidence suggests at best a close balance of benefits to harm
• For chronic pain, reserve opioids for appropriately selected patients with persistent pain despite non-opioid therapies
• If long-term opioid therapy prescribed, monitor patients and utilize risk mitigation strategies
• Patients on high doses warrant re-evaluation, additional monitoring, and follow-up
• Decrease dose or discontinue opioids in patients who are not improving or in whom benefits do not outweigh harms
• Judicious, time-limited use of opioids for acute pain with re-evaluation for persistent pain
Case

- Unclear if benefitting from very high doses of long-term opioid therapy, ?worsening of GI symptoms
- No signs of aberrant behaviors
- Slow taper initiated, over ~2 years
  - Morphine 450 mg/day reduced to 120 mg/day
  - Oxycodone 160 mg/day reduced to 5 mg bid prn
    - 690 mg/MED/day reduced to 135 mg/day
- Added non-opioid medications
  - Duloxetine 30 mg qD
  - Buspirone 30 mg bid
- Pain and function no worse than when on high doses, no serious withdrawal
  - Some periods of acute pain with temporary increases in opioids
  - Goal is to get down to <100 to 120 mg MED/day
Evidence-informed Approach to Appropriate Use of Opioids

- Preference for non-opioid therapies
  - Opioids alone do not address the psychosocial contributors to chronic pain
- Not all patients are appropriate for opioid therapy
- Use risk assessment to inform decisions
- Initiate at low doses and titrate slowly
- View initial treatment as a therapeutic trial
- Routine monitoring and risk mitigation
- Titration should be based on responsiveness of patients to initial, low doses
  - Patients who do not respond to low doses probably will not respond to higher doses—“opioid non-responders”
  - Taper in patients not responding or experiencing adverse effects
- Caution when reaching threshold doses
  - Little incremental benefit with dose escalation but increased harms
  - Much easier to titrate up doses than to titrate down
References

References

PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder.

- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medications for opioid use disorder (MOUD).

- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.

- No cost.

For more information visit: https://pcssNOW.org/mentoring/
PCSS Discussion Forum

Have a clinical question?

Ask a Colleague

A simple and direct way to receive an answer related to medications for opioid use disorder. Designed to provide a prompt response to simple practice-related questions.

http://pcss.invisionzone.com/register
PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

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<td>Association for Multidisciplinary Education and Research in Substance use and Addiction</td>
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<tr>
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