Opioid Treatment Guidelines for Chronic Pain Part 2

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VIII. Discussion of Recommendations

A. Initiation and Continuation of Opioids

Recommendation

1. a) We recommend against initiation of long-term opioid therapy for chronic pain. **(Strong against)**
   b) We recommend alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments. **(Strong for)**
   c) When pharmacologic therapies are used, we recommend non-opioids over opioids. **(Strong for)**
   (Reviewed, New-replaced)

Discussion

As outlined in this CPG, there is a rapidly growing understanding of the significant harms of LOT even at doses lower than 50 mg oral morphine equivalent daily dose [MEDD], including but not limited to overdose and OUD. At the same time there is a lack of high quality evidence that LOT improves pain, function, and/or quality of life. The literature review conducted for this CPG identified no studies evaluating the effectiveness of LOT for outcomes lasting longer than 16 weeks. Given the lack of evidence showing sustained functional benefit of LOT and moderate evidence outlining harms, non-opioid treatments are preferred for chronic pain. Patient values, goals, concerns, and preferences must be factored into clinical decision making on a case-by-case basis. When considering the initiation or continuation of LOT, it is important to consider whether LOT will result in clinically meaningful improvements in function such as readiness to return to work/duty and/or measurable improvement in other areas of function, such that the benefits outweigh the potential harms.

While there is currently no evidence in the literature documenting the benefit of LOT that demonstrates improvement in pain and function, we recognize that in a rare subset of individuals a decision to initiate LOT may be considered (e.g., for intermittent severe exacerbations of chronic painful conditions). If a decision is made to initiate LOT, a careful assessment of benefits and risks should be made to ensure that the benefits are expected to outweigh the well-documented risks. In addition, prior to this consideration, a multimodal treatment plan should be integrated into the patient's care. Once opioid therapy is initiated, all opioid risk mitigation strategies outlined in this guideline (see Recommendation 7) should be put into place.

In 2011, in response to the recognition of pain and its management as a public health problem, the National Academy of Medicine investigated and reported on the state of pain research, treatment, and education in the U.S. The report called for a cultural transformation in the way pain is viewed and treated.[3] Accordingly, the U.S. Department of Health and Human Services (HHS) National Pain Strategy (March 2016) recommends a biopsychosocial approach to pain care that is multimodal and interdisciplinary.[26] The underlying concepts of the biopsychosocial model of pain include the idea that pain perception and its effects on the patient's function is mediated by multiple factors (e.g., mood, social support, prior experience, biomechanical factors), not just biology alone. With this overall change in construct, a biopsychosocial assessment and treatment plan should be tailored accordingly.

Psychological therapies (e.g., cognitive behavioral interventions such as Cognitive Behavioral Therapy [CBT], biofeedback) have been found to be effective for pain reduction in multiple pain conditions.[80-82]

Exercise treatments, including yoga, also have evidence of benefit for reducing pain intensity and disability when compared to usual care in the treatment of chronic pain conditions.[83-85] Exercise and psychological therapies may each exert their influence through multiple mechanisms including but not limited to the reduction in fear-avoidance, reduction in catastrophizing, and/or enhancing mood.[80] Similarly, multidisciplinary biopsychosocial rehabilitation (described as a combination of a physical intervention such as graded exercise and a psychological, social, or occupational intervention) has been shown to be more effective than usual care in improving pain and disability.[81] These interventions are safe and have not been shown to increase morbidity or mortality.

In light of the low harms associated with exercise and psychological therapies when compared with LOT these treatments are preferred over LOT, and should be offered to all patients with chronic pain including those currently receiving LOT. There is insufficient evidence to recommend psychological over physical therapies or vice versa; the choice of which to try first should be individualized based on patient assessment and a shared decision making process (see Patient Focus Group Methods and Findings).[80]

In addition to non-pharmacological therapies (e.g., exercise, CBT), appropriate mechanism and condition-specific non-opioid pharmacologic agents should be tried and optimized before consideration of opioid medications (e.g., gabapentin in neuropathic pain states).[83] Potential contraindications and long-term risks of use should be considered for non-opioid pharmacologic agents as well, as these also can carry risk of harm, depending on the specific patient and chosen medication.

Patient access to physical, psychological, and pain rehabilitation modalities should be considered. In some cases access to care may be limited; all VA and DoD clinics may not have access to multidisciplinary pain services. Still, all avenues for obtaining these treatments (e.g. Internet based CBT) and all appropriate non-opioid medications should be exhausted before consideration of LOT.[82]

Further studies may help determine earlier in the course of treatment which patients are most likely to benefit from a specific non-pharmacologic therapy (physical, psychological, and pain rehabilitation) or non-opioid pharmacologic therapies alone or as part of a multimodal approach.

Recommendations

2. If prescribing opioid therapy for patients with chronic pain, we recommend a short duration.
   (Strong for| Reviewed, New-replaced)

   Note: Consideration of opioid therapy beyond 90 days requires re-evaluation and discussion with patient of risks and benefits.

3. For patients currently on long-term opioid therapy, we recommend ongoing risk mitigation strategies (see Recommendations 7-9), assessment for opioid use disorder, and consideration for tapering when risks exceed benefits (see Recommendation 14).
   (Strong for| Reviewed, New-replaced)

Discussion

The support for these recommendations is two-fold: a paucity of research showing benefit for LOT and the strength of the evidence demonstrating the potential for life-threatening harm. Of utmost concern is the

heightened risk for developing OUD in patients who receive OT beyond 90 days (see Appendix C for Diagnostic and Statistical Manual of Mental Disorders [DSM] 5 diagnostic criteria for OUD).

Similar to other risk factors, continuing OT beyond 90 days' duration should be weighed heavily in the risk-benefit calculus for LOT. Continuing OT for longer than 90 days is not an absolute contraindication to LOT. There may be some situations where the benefits of LOT clearly outweigh the risks. That must be determined through individual clinical assessment.

Moderate quality evidence demonstrates that the prevalence of OUD in patients with CNCP is related to duration of opioid use as well as dose (see Recommendations 7-9).[86-88] There are two studies of patients with CNCP which support the current recommendations. Edlund et al. (2014) conducted a large retrospective cohort study where they examined claims data from a health insurance database between 2000 and 2005 to examine factors predictive of developing OUD.[86] Days' supply of opioids was categorized as none, acute duration (1-90 days), or chronic duration (91+ days). Average daily dose was defined as none, low (1-36 mg MEDD), medium (36-120 mg MEDD), or high (>120 mg MEDD). The OR of developing OUD ranged based on dose and duration (OR: 3.03, 95% CI: 2.32-3.95 for low dose, acute opioid prescription; OR: 14.92, 95% CI: 10.38-21.46 for low dose, chronic opioids prescriptions; OR: 3.10, 95% CI: 1.67-5.77 for high dose, acute opioid prescriptions; OR: 122.45, 95% CI: 72.79-205.99 for high dose, chronic opioid prescriptions). They found that even greater than opioid dose, duration of OT was the strongest predictor of developing OUD. Additionally, a study by Boscarino et al. (2011) examined medical records from a large healthcare system.[89] Through interviews with a random sample of patients on LOT, they examined factors associated with and the prevalence of OUD (using DSM IV and 5 criteria). These results showed that the prevalence of lifetime OUD for patients on LOT was 34.9% (based on DSM-5 criteria) and 35.5% (based on DSM-IV criteria).

The relationship between OUD and duration of therapy is magnified when patients have a history of previous opioid or non-opioid SUD. A cross-sectional cohort study found that provision of LOT (four prescriptions within a 12 month period) to CNCP patients who had a history of severe OUD resulted in increased odds of developing OUD (OR: 56.36, 95% CI: 32.49-97.76).[88]

Patients should be informed that progression from acute to long-term OT is associated with little evidence for sustained analgesic efficacy but a substantial increase in risk for OUD. Providers should discuss this information with patients at initiation of OT and continuously thereafter to ensure that the patient understands the associated risks and benefits of LOT. Fully informed, some patients may desire continuation of OT while others may decline its continued provision.

Research is necessary to more accurately determine how long it takes for OUD to occur and whether the nature of the pain is one of the factors that can influence either of this phenomena.

Recommendation

4. a) We recommend against long-term opioid therapy for pain in patients with untreated substance use disorder. **(Strong against)**
   b) For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, we recommend close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering (see Recommendation 14 and Recommendation 17). **(Strong for)**
   (Reviewed, Amended)

Discussion

Opioids carry a significant risk for OUD, overdose, and death, especially among patients with untreated SUD. The recommendation against LOT for patients with SUD is supported by five large studies (four retrospective case cohort studies and one case cohort study).[59,61,66,86,87] Individually, these studies are of moderate strength; however, the combined weight of their results is strongly supportive of this recommendation. Clinicians should note that this recommendation does not refer to patients whose sole SUD relates to tobacco misuse.

The Edlund et al. (2014) study of 568,640 commercial health plan patients (see Recommendation 2 and 3) found that those diagnosed with CNCP and an alcohol use or non-opioid drug use disorder had higher rates of OUD (OR: 3.22, 95% CI: 1.79-5.80 for patients with pre-index alcohol use disorder compared to no alcohol use disorder; OR: 8.26, 95% CI: 4.74-14.39 for patients with pre-index non-opioid drug use disorders compared to no non-opioid drug use disorders).[86] Moreover, Huffman et al. (2015) found that the presence of a lifetime history of SUD for patients with CNCP was associated with 28 times increased odds of therapeutic opioid addiction compared to patients with CNCP without a lifetime history of SUD (OR: 28.58, 95% CI: 10.86-75.27).[87]

The following three studies concern the serious risks of overdose and death. A study of 206,869 health maintenance organization patients who received opioid prescriptions and who had a diagnosis of an alcohol or drug use disorder were also found to have a significantly higher risk of overdose.[66] The VHA's National Patient Care Database case cohort study of 154,684 patients also found that patients diagnosed with SUD and CNCP had a significantly elevated risk of overdose death (hazard ratio [HR]: 2.53, 95% CI: 1.99-3.22) compared to patients with no SUD diagnosis.[59] The third study used a VHA database to review the outcomes of patients who had been prescribed chronic short-acting or long-acting opioids.[61] This study found that patients who received chronic short-acting or long-acting opioids and who were diagnosed with SUD had an increased risk of suicide attempts compared to those without an SUD diagnosis (OR: 2.42, standard error [SE]: 0.035 for chronic short-acting for patients with drug use disorder; OR: 2.83, SE: 0.057 for chronic long-acting for patients with drug use disorder; OR: 1.99, SE: 0.033 for chronic short-acting for patients with alcohol use disorder; OR: 1.87, SE: 0.056 for chronic long-acting for patients with alcohol use disorder).

Some patients with SUD may disagree with the recommendation to use non-opioid modalities in lieu of LOT to treat their pain. However, the lack of evidence of efficacy of LOT and considerable evidence of significant harms of overdose, death from overdose, and increased risk of suicide outweigh any potential modest benefit of prescribing LOT in this population. See Recommendation 7 for additional information

regarding UDT and risk mitigation. See the VA/DoD SUD CPG for guidance on management of SUD.[7]

Given the increasing use of cannabis among patients with chronic pain and the lack of RCTs comparing outcomes of prescribing LOT versus other therapies for patients with and without cannabis use and cannabis use disorder, future research is needed to optimize care for these patients. Research is also needed to determine which subpopulations of patients with active SUD are at greatest risk of OUD, overdose, and death. Finally, further research is needed on the efficacy of alternative treatments for pain and ways to mitigate risks of opioid-related adverse events in patients with SUD and pain.

Recommendation

5. We recommend against the concurrent use of benzodiazepines and opioids.
   (Strong against | Reviewed, New-added)

   Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate (see Recommendation 14 and the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders).

Discussion

Harms may outweigh benefits for the concurrent use of benzodiazepines and LOT. There is moderate quality evidence that concurrent use of benzodiazepines with prescription opioids increases the risk of overdose and overdose death.[66] In a retrospective cohort study, the adjusted odds ratio (AOR) for drug overdose was highest for individuals on LOT for chronic pain (without anxiety or PTSD) who also received concurrent long-term benzodiazepine therapy.[66] In another retrospective study that involved over 200,000 participants (not included in the evidence review), Veterans receiving both opioids and benzodiazepines were at an increased risk of death from drug overdose.[90] Furthermore, there is a lack of evidence in favor of long-term therapy with benzodiazepines and opioids for chronic pain.[91]

There is a large variation in patient preference regarding the concurrent use of benzodiazepines and LOT. This is especially true for patients who are already accustomed to receiving both medications (see Patient Focus Group Methods and Findings). Concurrent benzodiazepine and LOT use is a serious risk factor for unintentional overdose death and should be weighed heavily in the risk-benefit evaluation for tapering versus continuing one or both agents. Once initiated, benzodiazepines can be challenging to discontinue due to symptoms related to benzodiazepine dependence, exacerbations of PTSD, and/or anxiety.[91] Moreover, abrupt discontinuation of benzodiazepines should be avoided, as it can lead to serious adverse effects including seizures and death. Tapering benzodiazepines should be performed with caution and within a team environment when possible (see Recommendation 26 in the VA/DoD SUD CPG).[7] Due to the difficulty of tapering or discontinuing benzodiazepines, particular caution should be used when considering

[7] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

initiating benzodiazepines for Veterans with PTSD who have co-occurring chronic pain. The VA/DoD PTSD CPG[8] recommends against benzodiazepines for the prevention of PTSD and cautions against their use in treatment of PTSD. Benzodiazepines to treat acute anxiety symptoms after trauma are associated with a higher incidence of PTSD symptoms. For treatment of PTSD, there is evidence of lack of efficacy from small clinical trials and evidence of harm from observational studies of benzodiazepines for PTSD. Although anxiety may initially improve with benzodiazepines, the improvement is short-lived and may result in tolerance to increasing doses and eventual failure of the treatment. Even gradual benzodiazepine taper may result in exacerbation of severe PTSD symptoms. Concomitant use of benzodiazepines is considered a contraindication to initiation of OT.

In addition to benzodiazepines, the addition of other psychoactive medications to LOT must be made with caution. While the evidence for harm associated with the combination of opioids and Z-drugs (e.g., zolpidem, eszopiclone) is not as strong as the evidence for harm associated with the combination of opioids and benzodiazepines, we suggest not prescribing Z-drugs to patients who are on LOT, as moderate quality evidence demonstrates that the combination of zolpidem and opioids increases the AOR of overdose.[66] The evidence reviewed also identifies potential adverse outcomes (e.g., risk of overdose) with the combined use of antidepressants and opioids in patients who do not have depression.[66] This particular study did not differentiate between classes of antidepressants, limiting the ability of the Work Group to recommend for or against prescribing opioids and a specific class of antidepressants. As such, there is no recommendation in this guideline with respect to using specific classes of antidepressants and LOT.

Recommendation

6. a) We recommend against long-term opioid therapy for patients less than 30 years of age secondary to higher risk of opioid use disorder and overdose. **(Strong against)**
   b) For patients less than 30 years of age currently on long-term opioid therapy, we recommend close monitoring and consideration for tapering when risks exceed benefits (see Recommendation 14 and Recommendation 17). **(Strong for)**
   (Reviewed, New-replaced)

Discussion

All patients who take opioids chronically are at risk for OUD and overdose, but especially those who are younger than 30 years of age. Seven studies were identified that examined age as a predictor of OUD, respiratory/CNS depression, and/or overdose. Four of the seven studies were rated as fair quality evidence,[59,86,88,92] while three were rated as poor quality evidence.[58,62,87] Six of the seven studies demonstrated that age was inversely associated with the risk of OUD and overdose.[59,62,86-88,92] One

[8] See the VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Available at: http://www.healthquality.va.gov/guidelines/MH/ptsd/

of the three low quality studies showed that older subjects had a higher HR of overdose.[58] The Work Group's overall confidence in the quality of the evidence was moderate.

Similar to other risk factors, age <30 years should be weighed heavily in the risk-benefit determination for initiating LOT. Age <30 years is not an absolute contraindication to LOT. There may be some situations where the benefits of LOT clearly outweigh the risks of OUD and overdose. Hospitalized patients recovering from battlefield injuries, for example, are known to have less chronic pain, depression, and PTSD when their pain is aggressively managed starting soon after injury.[93] In those cases, LOT may be appropriate only if risk mitigation strategies are employed and patients are titrated off LOT as soon as it is appropriate (see Recommendations 14 and 15).

The added risk that younger patients using opioids face for OUD and overdose is great. Edlund et al. (2014) found that, compared to patients ≥65 years old, patients 18-30 years old carried 11 times the odds of OUD and overdose. Patients 31-40 years old carried 5 times the odds of OUD and overdose compared to those ≥65 years old.[86] Bohnert et al. (2011) found that, compared to subjects 18-29 years old, patients 30-39 years old had roughly half the risk of developing OUD or overdose (HR: 0.56, 95% CI: 0.27-1.17). Compared to the subjects 18-29 years old, patients ≥70 years old had a far less risk (nearly 1/17) of developing OUD or overdose (HR: 0.06, 95% CI: 0.02, 0.18).[59]

Younger patients are also at a higher risk of opioid misuse (as suggested by a UDT indicating high-risk medication-related behavior). Turner et al. (2014) showed that patients in the 45-64 year age group were significantly less likely to have an aberrant UDT (detection of a non-prescribed opioid, non-prescribed benzodiazepine, illicit drug, or tetrahydrocannabinol [THC]) in comparison to patients in the 20-44 age group.[94] Patients in the 45-64 and ≥65 age groups were significantly less likely than 20-44 year olds to have non-detection of a prescribed opioid as well (indicating possible diversion).[94]

An age of 30 years was chosen based on how age was categorized in the six studies that showed an inverse relationship between age and OUD or overdose. One of those six studies found that patients with OUD were younger than patients without OUD, but did not find a statistically significant relationship.[87] Two of those six studies examined age as a continuous predictor, and neither reported a specific age where the risk of OUD or overdose changed markedly.[62,92] One study examined age as a dichotomous (<65 and ≥65) predictor.[88] In the two remaining studies, the highest risk included ages ranging from 18 to 30 years.[59,86] As such, the Work Group chose 30 years of age as a clinically reasonable threshold.

Some may interpret the recommendation to limit opioid use by age as arbitrary and potentially discriminatory when taken out of context; however, there is good neurophysiologic rationale explaining the relationship between age and OUD and overdose. Studies in other areas (e.g., use of different substances) indicate that developing brains (age <30 years) are at increased risk of abnormalities and addiction when exposed to substance use early in life.[95-98]

Toward augmenting this evidence base, we recommend that future observational research examine age as a continuous predictor of adverse outcomes. Additionally, we recommend that future trials examine which risk mitigation strategies can reduce the additional risk of OUD and overdose in younger patients on LOT. Lastly, a deeper understanding of the mechanisms for addiction to opioids in young brains is needed.

B. Risk Mitigation

Recommendation

7. We recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include:
   - Ongoing, random urine drug testing (including appropriate confirmatory testing)
   - Checking state prescription drug monitoring programs
   - Monitoring for overdose potential and suicidality
   - Providing overdose education
   - Prescribing of naloxone rescue and accompanying education

   (Strong for | Reviewed, New-replaced)

Discussion

Risk mitigation for LOT should begin before the opioids are prescribed, through an informed consent discussion, reviewing the patient's history, checking state PDMPs, or instructing patients about using drug take back programs to dispose of unused medication. It should also occur concurrently with the therapy (e.g., ongoing UDT, OEND) and in response to adverse events (e.g., needle exchange programs for those who develop an intravenous drug use disorder). The 2010 OT CPG recommended use of an opioid pain care agreement, monitoring for appropriate opioid use, and, with patients' consent, obtaining a UDT. A literature search was conducted dating back to the original 2010 recommendation to identify studies comparing the effectiveness of different risk mitigation strategies for patients on or being considered for LOT. One identified study was a systematic review of 11 studies looking at opioid treatment agreements (OTAs) and UDT strategies utilizing opioid misuse risk reduction as the main outcome measure.[99] The study revealed weak evidence to support the use of OTAs and UDT. A second study, a retrospective database study, demonstrated decreased risk of suicide attempts in various cohorts with frequent UDT, regular follow-up (including follow-up within four weeks for patients with new opioid prescription), and rehabilitative services are offered.[61] The confidence in the quality of the evidence was moderate for the outcome of attempted suicide risk. The third study was a retrospective cohort study that looked at the intervention of a clinical pharmacist guidance team versus control.[100] Outcome measures included adverse events, pain management, and quality of life. Details of the actual intervention were vague and did not necessarily include OTAs or UDT. Thus, the confidence in the quality of the evidence was very low.

The confidence in the quality of the evidence was moderate for UDT and frequent follow-up and was low for OTAs. The frequency of follow-up and monitoring should be based on patient level of risk as determined by an individual risk assessment.

There may be some variation in patient values and preferences. Certain patients may appreciate the use of risk mitigation strategies and others may not. Participants in the patient focus group expressed an understanding of why various risk mitigation strategies were used (see Patient Focus Group Methods and Findings).

Implementing more extensive risk mitigation strategies entails an investment of resources. Primary care providers may require more time with patients to allow for shared decision making and treatment

planning. More frequent follow-up of patients on LOT can affect access to care for all empaneled patients. VHA providers must also follow VHA policy regarding education and signature informed consent when providing LOT for patients with non-cancer pain.[101]

Written Informed Consent and Opioid Treatment Agreements

There is a paradigm shift occurring in approaches to ensuring and documenting patient and provider understanding and expectations regarding the risks and benefits of LOT. The 2010 OT CPG reflected prior practice of using opioid treatment (or pain care) agreements. OTAs have been described as coercive rather than therapeutic, lack respect for individual autonomy, can be a barrier to pain care, and may be harmful to the patient-provider relationship.[102-105]

Given the recognized risks of opioid therapy, an optimal approach to care should include a robust, signature informed consent process that is patient-centered and provides patients with information about known benefits and harms of OT and treatment alternatives. In 2014, VA established a requirement for signature informed consent, consistent with VA policy for other treatments or procedures with a significant risk of complications or morbidity. See Appendix A, *Taking Opioids Responsibly for Your Safety and the Safety of Others: Patient Information Guide on Long-term Opioid Therapy for Chronic Pain* (found at http://www.healthquality.va.gov/guidelines/Pain/cot/OpiodTheraphyforChronicPainPatientTool20May2013print.pdf), and 38 C.F.R. §17.32 (2012).

Patients may decline offered treatments (e.g., OT) and may also decline risk mitigation strategies (e.g., UDT, pill counts) that are recommended in the course of clinical care. However, providers should discuss this decision with the patient, including the likelihood that their decision may result in the risks of LOT outweighing its potential benefits. This would require a consideration of patient's safety, and a clinical decision may be made not to initiate OT or to discontinue ongoing OT through tapering (see Recommendation 14 and Recommendation 17).

State Prescription Drug Monitoring Programs

State database queries for detection of multi-sourcing of controlled substances are used throughout the country. Data comparing states with an implemented state database program to states without one showed 1.55 fewer deaths per 100,000 people.[106] The CDC currently recommends at least quarterly checks of the state database system.[33]

Urine Drug Testing and Confirmatory Testing

As substance misuse in patients on LOT is more than 30% in some series,[107] UDT and confirmatory testing is used as an additional method of examining for patient substance misuse and adherence to the prescribed regimen. UDTs, used in the appropriate way, help to address safety, fairness, and trust with OT.

Availability of accurate and timely confirmatory testing (e.g., gas chromatography-mass spectrometry [GCMS]) is critical due to the false positive and negative rates associated with UDTs.[53] Interpretation of a UDT and confirmatory results requires education and knowledge of the local procedures and clinical scenario. Local education and access to expert interpretation is necessary.

UDT results are helpful and can help identify active SUD or possible diversion. Accordingly, clinicians should

obtain UDT prior to initiating or continuing LOT and periodically thereafter. When a patient is referred for SUD treatment or is engaged in on-going treatment there should be close communication between the SUD and pain management providers. The ideal approach is an interdisciplinary format (see Recommendation 16).

For more information, see Appendix B on UDT and confirmatory testing.

Prescribing of Naloxone Rescue and Accompanying Education

Naloxone administration has been identified as a life saving measure following opioid overdose. A systematic review of 22 observational studies provided moderate quality evidence that take home naloxone programs are effective in improving overdose survival and decreasing mortality, with a low rate of adverse events.[108] One meta-analysis of nine studies determined that take home naloxone kits were used approximately nine times within the first three months of follow-up for every 100 individuals trained.[109] Further, studies have shown that naloxone administration has been efficacious whether given by medical personnel or lay people, with more than 26,000 reversals documented by the CDC from 1996-2014.[110,111] In addition, prescription of naloxone rescue and accompanying education has also been found to reduce opioid-related emergency department visits.[112] Distribution of naloxone for reversal is supported by SAMHSA, the American Medical Association (AMA), and other medical societies, and is facilitated through the VA via Pharmacy Benefits Management. Clinical efficacy has been established for its use on short-acting opioids, but not for its use on long-acting opioids such as methadone or exceptionally potent opioids.[108]

Synthetic opioids such as fentanyl analogs, potent opioid receptor agonists, are responsible for a recent rise in death rates. Fentanyl analogs that may be used to create counterfeit opioid analgesic pills can cause a toxidrome characterized by significant CNS and profound respiratory depression requiring multiple naloxone doses for reversal.[113]

Patients at High Risk for Opioid Use Disorder

Those patients receiving opioid analgesics who do not meet DSM-5 criteria for OUD may benefit from an alternative management strategy: close follow-up and CBT. Jamison et al. (2010) randomized patients at high-risk for OUD (as measured by standard rating scales) to receive either standard pain management or close follow-up with CBT for pain.[114] Both of these groups were compared to a low-risk, chronic pain control group receiving standard management. The authors report that, compared to a matched high-risk group receiving standard care, patients receiving additional monitoring and CBT exhibited significantly reduced illicit substance use over six months (percentage of patients with positive drug misuse index scores: 73.7% versus 26.3% versus 25.0%; $p<0.01$). At six months, there was no difference between the high-risk group receiving close follow-up and the low-risk group receiving standard therapy. Authors also reported that pain perception was less in the high-risk group receiving additional monitoring and behavior therapy; however, analysis of activity interference reporting reflected no significant difference between study groups.

Other Risk Mitigation Strategies

Take Back Programs

Returning unused opioid medications has been explored as a strategy to reduce the amount of opioids in the community, as it has been estimated that 70% of opioid prescriptions are left unused.[115] Accordingly, the National Drug Control Strategy advocates take back programs as an effective tool.[24] For example, in a 2013 medication take back event in a Michigan community, 3,633 containers containing 345 different prescription medications were collected in four hours. The top five most common medications collected were pain relievers.[116] System-wide efficacy of a nationwide program is unknown.[117]

Community-based Needle Exchange Programs or Syringe Service Programs

Nearly 80% of new users of injectable opioids had previously used prescription oral opioid pain medication.[118,119] Illicit use of injectable opioids is accompanied by an increased rate of human immunodeficiency virus (HIV) and hepatitis infection. Community-based needle exchange programs have been shown to be an effective risk mitigation strategy for reducing high-risk behaviors (e.g., sharing needles) and infectious disease transmission among injection drug users.[120] For those patients who develop OUD and progress to intravenous drug use, the first recommendation should be for medication-assisted treatment (MAT) for OUD (see Recommendation 17). For patients who decline MAT for OUD, clinicians should consider educating the patient regarding sterile injection techniques and community-based needle exchange programs, if programs are available. The 2015 outbreak of HIV/hepatitis in rural Indiana and subsequent successful implementation of a needle exchange program is an example of the threat to rural communities from non-prescription opioid use and the potential benefits of needle exchange programs for use as a risk mitigation strategy.[121,122]

Recommendation

8. We recommend assessing suicide risk when considering initiating or continuing long-term opioid therapy and intervening when necessary.
   (Strong for | Reviewed, Amended)

Discussion

Opioid medications are potentially lethal and an assessment of current suicide risk should be made at every phase of treatment. The VA/DoD Suicide CPG[9] recommends restricting the availability of lethal means for patients considered to be at intermediate or high acute risk of suicide (determined by presence and severity of suicidal ideation, level of intention to act, existence of risk factors, limited or absent protective factors, etc.). Accordingly, suicidality is considered to be an important risk factor for OT (see Risk Factors for Adverse Outcomes of Opioid Therapy).

[9] See the VA/DoD Clinical Practice Guideline for Assessment and Management of Patients at Risk of Suicide. Available at: http://www.healthquality.va.gov/guidelines/MH/srb/

A number of studies suggest certain chronic pain conditions represent an independent risk factor for suicide.[123-130] A recent large retrospective cohort study also suggests an association with prescribed opioid dose and suicide risk among Veterans receiving OT for CNCP.[131] Suicide risk is not static, and many factors influence an individual's risk of suicide at any given point in time, as noted in the VA/DoD Suicide CPG.[10] Thus, ongoing assessment of suicide risk is important whether one is initiating, maintaining, or terminating LOT.

There is moderate quality evidence that intensification of monitoring helps mitigate the risk of suicide among patients on LOT. Im et al. (2015) found moderate quality evidence that, at the facility level, patients on LOT within facilities ordering more drug screens than the comparison group were associated with decreased risk of suicide attempt (chronic short-acting opioid group: OR: 0.2, 95% CI: 0.1-0.3; chronic long-acting opioid group: OR: 0.3, 95% CI: 0.2-0.6). In addition, patients on long-acting opioids within the facilities providing more follow-up after new prescriptions were associated with decreased risk of suicide attempt (OR: 0.2, 95% CI: 0.0-0.7).[61]

Some patients on LOT who suffer from chronic pain and co-occurring OUD, depression, and/or personality disorders may threaten suicide when providers recommend discontinuation of opioids. However, continuing LOT to "prevent suicide" in someone with chronic pain is not recommended as an appropriate response if suicide risk is high or increases. In such cases, it is essential to involve behavioral health to assess, monitor, and treat a patient who becomes destabilized as a result of a medically appropriate decision to taper or cease LOT.

Further research is needed to identify strategies for safely managing patients at elevated risk of suicide who demand opioid medications or become further destabilized during tapering.

Recommendation

9. We recommend evaluating benefits of continued opioid therapy and risk for opioid-related adverse events at least every three months.
   (Strong for | Reviewed, New-replaced)

Discussion

Prior to initiating OT, an individualized assessment of potential opioid-related harms relative to realistic treatment goals must be completed. After initiating OT, frequent visits contribute to the appropriate use and adjustment of the planned therapy.

The Work Group recommends follow-up at least every three months or more frequently (see Recommendation 7 and Recommendation 11) due to the balance of benefits and harms associated with this recommendation. Although the 2010 OT CPG recommended follow-up every six months, this

[10] See the VA/DoD Clinical Practice Guideline for Assessment and Management of Patients at Risk of Suicide. Available at: http://www.healthquality.va.gov/guidelines/MH/srb/

recommended interval for follow-up and reassessment has not been sufficient to reduce the potential harm associated with LOT or adequately implement comprehensive, biopsychosocial pain care. More frequent follow-up is needed in order to increase the impact of risk mitigation strategies and enhance the delivery of comprehensive, biopsychosocial pain care. Frequency of visits should thereafter be based on risk stratification. Similarly, the CDC guideline for OT recommends re-evaluating harms versus benefits within one to four weeks of starting OT or at any dose change, and at least every three months or more frequently if needed.[132]

At follow-up visits, a clinician should re-examine the rationale for continuing the patient on OT. Clinicians should take into account changes in co-occurring conditions, diagnoses/medications, and functional status when conducting the risk/benefit analysis for LOT. Alcohol use, pregnancy, nursing of infants, and lab abnormalities may change the risk/benefit calculus for LOT. Ongoing OT prescribing practice may include pharmacy review, informed consent, UDTs, and checking state PDMPs. A clinician should also be mindful of signs of diversion during follow-up (see Risk Factors for Adverse Outcomes of Opioid Therapy). The longer the patient is on opioids, the greater the potential for change in patient status and development of opioid-related harms.

C. Type, Dose, Duration, Follow-up, and Taper of Opioids

Recommendations

10. If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits.
    (Strong for | Reviewed, New-replaced)

    Note: There is no absolutely safe dose of opioids.

11. As opioid dosage and risk increase, we recommend more frequent monitoring for adverse events including opioid use disorder and overdose.
    - Risks for opioid use disorder start at any dose and increase in a dose dependent manner.
    - Risks for overdose and death significantly increase at a range of 20-50 mg morphine equivalent daily dose.

    (Strong for | Reviewed, New- replaced)

12. We recommend against opioid doses over 90 mg morphine equivalent daily dose for treating chronic pain.
    (Strong against | Reviewed, New-replaced)

    Note: For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate for tapering to reduced dose or to discontinuation (see Recommendations 14 and 15).

Discussion

There is moderate quality evidence from retrospective cohort and retrospective case control studies indicating that risk of prescription opioid overdose and overdose death exists even at low opioid dosage levels and increases with increasing doses. Significant risk (approximately 1.5 times) exists at a daily dosage range of 20 to <50 mg MEDD and further increases (approximately 2.6 times) at a range of 50 to <100 mg

MEDD compared to risk at <20 mg MEDD. Risk continues to increase at higher dosage ranges (≥100 mg MEDD) (Table 2).[58,59,66,133]

Table 2. Risks of Prescription Opioid Overdose and Overdose Death at Selected Morphine Equivalent Daily Dose Intervals [58,59,66,133]

Study	Expression of risk	MEDD (mg)				
		0	1 to 19	20 to <50	50 to <100	≥100
Turner and Liang (2015)[1] [66]	AOR (95% CI)	1	0.80 (0.50-1.27)	1.54 (1.23-1.94)	2.08 (1.61-2.69)	4.34 (3.37-5.57)
Zedler et al. (2014)[1,2,3] [58]	OR (95% CI)	-	1	1.5 (1.1-1.9)	2.2 (1.5-3.2)	4.1 (2.6-6.5)
Dunn et al. (2010)[1] [133]	HR (95% CI)	0.19 (0.05-0.68)	1	1.19 (0.40-3.60)	3.11 (1.01-9.51)	11.18 (4.80-26.03)
Bohnert et al. (2011)[1,3] [59]	HR (95% CI)	-	1	1.88 (1.33-2.67)	4.63 (3.18-6.74)	7.18 (4.85-10.65)
Bohnert et al. (2011)[2,3] [59]	HR (95% CI)	-	1	1.74 (0.69-4.35)	6.01 (2.29-15.78)	11.99 (4.42-32.56)

[1]Chronic non-cancer pain; [2]Chronic cancer pain; [3]Study conducted in U.S. Veterans
Abbreviations: AOR: adjusted odds ratio; 95% CI: 95% confidence interval; HR: hazard ratio; MEDD: morphine equivalent daily dose; OR: odds ratio

In a nested case-control study of U.S. Veterans (not included in our evidence review as it was published after the end of the search date range), Bohnert et al. (2016) examined the association between prescribed opioid dose as a continuous measure (in 10 mg MEDD increments) and overdose.[134] Prescribed opioid dosage was a moderately good predictor of overdose death, but the study did not reveal a specific dosage cut point or threshold above which risk of overdose increased dramatically. Lower prescribed opioid dosages were associated with reduced risk for overdose, but risk was not completely eliminated at lower doses; approximately 40% of overdoses were observed in patients who were prescribed <50 mg MEDD.

In a prospective cohort study (not included in the evidence review as it did not include information on acute versus chronic pain in the patient population), Dasgupta et al. (2015) compared residents of North Carolina who had received an opioid prescription in the last year to residents who had not. The study examined the outcome of population-based rates of opioid overdose mortality by opioid dose, without use of a presupposed threshold (Table 3).[135] There was no safe dose of opioid. Among the over nine million individuals followed for one year, 629 died from opioid overdose. Of these 629 individuals, 151 had no record of having been dispensed an opioid. It is possible these opioids were obtained through illicit channels or social sharing/diversion. Of the 478 patients who died from an opioid overdose who were prescribed opioids, 235 (49%) had been prescribed <80 mg MEDD. Overdose incidence rate ratios (IRRs) doubled each time the MEDD ranges increase from 60.0-79.9 mg to 80.0-99.9 mg (IRR 2.9 to 6.2), then to 120-139.9 mg (IRR 14.1), 160-179.9 mg (IRR 29.5), and 350-399.9 mg (IRR 63.2).

Table 3. Incidence Rate Ratios for Opioid Overdose Deaths, by Average Milligrams Morphine Equivalent Daily Dose[135]

MEDD (mg)	Deaths	Person-Years	Sample Size	IRR	95% CI
Unexposed	151	3,554,850	7,377,860	0.57	0.44-0.73
>0 - 39.9	98	1,305,835	1,305,969	1	
40 - 59.9	90	457,227	457,322	2.6	2.0-3.5
60 - 79.9	47	213,816	213,868	2.9	2.1-4.1
80 - 99.9	34	72,448	72,483	6.2	4.2-9.2
100 - 119.9	23	45,536	45,559	6.7	4.3-10.6
120 - 139.9	22	20,699	20,721	14.1	8.9-22.5
140 - 159.9	14	14,586	14,599	12.8	7.3-22.4
160 - 179.9	15	6,769	6,784	29.5	17.1-50.7
180 – 199.9	11	9,604	9,615	15.2	8.2-28.4
200 – 249.9	24	11,653	11,678	27.4	17.5-42.8
250 – 299.9	20	7,406	7,425	35.9	22.2-58.0
300 – 349.9	17	4,495	4,512	50.2	30.0-84.0
350 – 399.9	17	3,563	3,580	63.2	37.8-105.7
400 – 499.9	14	3,527	3,541	52.7	30.1-92.2
500 – 5000	32	4,684	4,718	90.4	60.7-134.6
Total	**629**	**5,736,696**	**9,560,234**	--	--

Abbreviations: 95% CI: 95% confidence interval, IRR: incidence rate ratios; MEDD: morphine equivalent daily dose; mg: milligram(s)

Achieving an improved understanding of the factors contributing to prescription opioid-related overdose is an essential step toward addressing this epidemic problem. Although it is widely accepted that progressively higher doses of prescribed opioids result in correspondingly higher risks of opioid overdose, patients using any dose of opioids can still experience life-threatening respiratory or CNS depression, especially when opioid-naïve. This risk begins to increase with MEDD as low as 20-50 mg. Risk is further increased when certain concomitant demographic factors, co-occurring medical or psychiatric conditions, or interacting medications or substances exist.

Recognizing the lack of evidence of long-term benefit associated with LOT used alone and the risks of harms with use of opioids without risk mitigation, dosing determinations should be individualized based upon patient characteristics and preferences, with the goal of using the lowest dose of opioids for the shortest period of time to achieve well-defined functional treatment goals. Understandably, there will be greater mortality, co-occurring medical conditions, and other adverse events in patients who require higher doses of opioids, even in those who benefit from such therapy. When closer follow-up is needed, healthcare resources and patient adherence should be considered.

Subgroups at higher risk

Risk of prescription opioid overdose is elevated across MEDD dosage levels in patients with co-occurring depression (moderate quality evidence).[66,133] Following an elevated baseline adjusted risk ratio (ARR) of 3.96, depressed patients taking 1-19 mg, 20 to <50 mg, 50 to <100 mg, and ≥100 mg MEDD had

respective odds of overdose of 4.75, 5.47, 6.44, and 7.06, compared to those taking an opioid at the same dosage level without a diagnosis of depression.[66]

Similarly, a history of or active SUD increases risk for serious prescription opioid-related toxicity or overdose across opioid dosages (moderate quality evidence).[58,87,133] A retrospective cohort review of patients with CNCP receiving LOT at least five days per week for 90 days determined that those with a history of non-opioid SUD had 28 times the odds of developing OUD.[87] Each 50 mg increase in MEDD nearly doubled the odds while each 100 mg MEDD increase tripled the risk for OUD. Concurrent prescribing of sedative-hypnotics and benzodiazepines increases risk of fatal or non-fatal opioid overdose 2-10 fold across opioid dose ranges.[66,133,135]

There is moderate quality evidence to support that opioids taken PRN (as needed) for chronic cancer pain versus regularly scheduled doses, or simultaneous PRN plus regularly scheduled, places patients at elevated risk for opioid overdose (HR: 2.75, 95% CI: 1.31-5.78 for as needed; HR: 1.00 for regularly scheduled; HR: 1.84, 95% CI: 0.83-4.05 for simultaneous PRN plus regularly scheduled).[59]

In patients receiving LOT, moderate quality evidence indicated that men are 50% more likely (HR: 1.44, 95% CI: 1.21-1.70) to escalate to high-dose opioids (defined as >200 mg MEDD) and twice as likely to experience an opioid-related death (adjusted HR: 2.04, 95% CI: 1.18-3.53) compared to women.[136] Risk of opioid overdose morbidity or mortality is also increased in non-Hispanic white versus non-Hispanic black patients (moderate quality evidence).[59,136]

Future Research

Future research is needed to better determine the impact of systematic reductions in MEDD in terms of pain relief, specific pain and medical conditions, overdose morbidity and mortality as well as potential adverse outcomes (e.g., the incidence of associated OUD, infectious diseases related to intravenous drug use disorder, and drug-related crime and diversion) and to determine whether/which conditions may be appropriately treated with LOT. Research is also needed to determine how frequency of monitoring should be impacted by dose.

Recommendation

13. We recommend against prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy.
    (Strong against| Reviewed, New- replaced)

Discussion

Long-acting opioids, as further discussed below, should not be used for treatment of acute pain, on an as-needed basis, or during initiation of LOT (see Short-acting versus Long-acting Opioids). In general, however, no single opioid or opioid formulation is preferred over the others. However, individuals may have a better response, degree of safety, or tolerability depending on their individual characteristics and preferences. Additional information for use when deciding on appropriate pharmacological treatment of pain for a specific patient can be found in Appendix D.

There was insufficient evidence to recommend for or against any specific opioid or opioid formulation, specifically the following:

- Short-acting versus long-acting opioids (for LOT for chronic pain)
- Route of administration/delivery among alternatives such as transdermal, buccal, sublingual, or pumps
- Abuse deterrent formulations of opioids compared to non-abuse deterrent formulations
- Tramadol and other dual-mechanism opioids
- Buprenorphine for pain (compared to other opioids)
- Methadone (with QT monitoring)

Short-acting versus Long-acting Opioids

Avoid use of long-acting agents for acute pain (with exception of oxycodone/acetaminophen extended-release [ER] tablets), on an as-needed basis, or for initiation of OT.[10,137-139] There is very low quality evidence to recommend for or against short-acting versus long-acting opioids for maintenance of OT.

There were two RCTs included in the evidence review that looked at safety and efficacy. One RCT comparing long-acting to short-acting dihydrocodeine found no statistically or clinically significant differences in stability of pain intensity between the two groups, as well as no difference in adverse events. Although study results may be inconclusive due to poor study design, the authors state that they do not support the use of long-acting agents for chronic non-malignant pain.[140]

A second non-inferiority RCT compared once-daily hydromorphone ER to twice-daily oxycodone controlled-release in patients with moderate-to-severe cancer pain. The primary efficacy endpoint was patient assessment of "Brief Pain Inventory (BPI) worst pain in the past 24 hr." Results demonstrated similar improvements in BPI and that the once-daily hydromorphone formulation was non-inferior to the twice-daily oxycodone formulation. Treatment-emergent adverse events were comparable between the groups as well.[141] The efficacy of long-acting opioids used once-daily is non-inferior to twice-daily use. There was a lack of statistical analysis of the outcomes and a lack of statistical power in both studies, and a small sample size in one study.

There is concern for additional overdose risk associated with long-acting versus short-acting opioids. A study (not included in the evidence review due to its design) suggests increased risk for non-fatal overdose in VA patients with initiation of a long-acting opioid compared with immediate-release opioids.[137] Also, recent research demonstrates that patients with CNCP on long-acting OT have a significantly increased risk of all-cause mortality compared to patients with CNCP who are taking an analgesic anticonvulsants or a low-dose antidepressant.[10]

Route of Administration/Delivery

The systematic evidence review for this CPG did not find any studies that compared alternative delivery systems (e.g., fentanyl transdermal, fentanyl buccal) to other delivery systems (e.g., oral, intravenous) (information on transdermal and sublingual buprenorphine is included in the following section on Buprenorphine for Pain). The concomitant use of oral and transdermal opioids or oral and intrathecal

pumps should be approached with extreme caution and warrants specialty consultation. Discussions of intrathecal pumps are beyond the scope of this guideline.

Although some patients may prefer either transdermal or buccal opioid delivery for opioids, there is significant potential for harm from OT with these delivery mechanisms, with no evidence of benefit over traditional opioid delivery systems in patients with chronic pain. Clinicians need to be especially aware of the risks associated with a fentanyl transdermal delivery system (or patch) (Appendix D) including its:

- Unique pharmacokinetic profile
- Continuous delivery, even after the patch is removed due to depot effect
- Increased rate of delivery
- Unpredictable variation in rate of delivery
    - Due to alterations in temperature due to external heat, skin integrity, and amount of adipose tissue
    - Among patients with fever, skin damage, or cachexia

Given the potential serious risks with starting fentanyl and challenges with tapering, clinicians intent on prescribing transdermal fentanyl for chronic pain are encouraged to consult with other clinicians (e.g., pain specialists, pharmacists) and to be familiar with the unique properties of fentanyl. Specific safety precautions that all clinicians should be aware of regarding transdermal fentanyl include:

- Transdermal fentanyl should not be used in opioid-naïve patients
- Patients need to be informed that:
    - Heat (e.g., sun exposure, heating pad, febrile condition) can increase the rate and quantity of absorption
    - Proper application includes: being sure to take old patch off; never applying damaged patch or a patch to non-intact skin; proper disposal to avoid exposure to children and pets, and precautions taken against possible diversion of remaining drug in used patch
- Adjusted dose (i.e., decreased patch size) should be used in patients with renal or hepatic insufficiency and considered in elderly patients and those with febrile illness

Abuse Deterrent Formulations of Opioids

The aim of most abuse deterrent formulations is to present a physical barrier to prevent chewing, crushing, cutting, grating, or grinding of the dosage form, or present a chemical barrier, such as a gelling agent, that will resist extraction of the opioid with use of a common solvent. Alternatively, an opioid antagonist (naloxone or naltrexone) can be added to interfere with, reduce, or defeat the euphoria associated with abuse of an agent intended for oral use when taken nasally or parenterally.[142] While these properties deter abuse they do not fully prevent abuse; no opioid formulation prevents consumption of a large number of intact capsules or tablets which continues to be the most common method of abuse.

We do not recommend for or against abuse deterrent formulations for LOT. Our searches identified two RCTs in which the benefits of co-prescribing of naloxone with opioids were examined.[143,144] However,

both RCTs were rated as low to very low quality with short-term follow-up. One open-label RCT enrolling 453 patients with chronic low back pain considered the safety and tolerability of an abuse deterrent formulation of oxycodone/naloxone relative to oxycodone or morphine at 12-week follow-up.[143] Another RCT considered the safety and efficacy of oxycodone/naloxone prolonged-release relative to oxycodone prolonged-release in 184 patients with moderate-to-severe chronic cancer pain at four-week follow-up.[144] An observational study (not included in the evidence review) suggested that the introduction of abuse deterrent opioid formulations did not help reduce abuse of opioids as a class and that patients may switch from one opioid to another based on the availability or the lack of availability of abuse deterrent formulations.[145]

Future research is needed to ascertain whether abuse deterrent formulations actually reduce OUD when used for chronic pain, and whether said formulations differ across clinical outcomes such as pain, function, and adverse events.

Dual-Mechanism Opioids

Dual-mechanism opioids include formulations of an opioid medication with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI). Two common examples are tramadol and tapentadol. While both are dual-mechanism opioids, they differ in their affinity for the mu opioid receptor, resulting in partial versus full agonist effects, and as such are discussed separately.

Tramadol

There is low quality evidence that tramadol may be more effective than placebo for pain relief. In one short-term study, compared to placebo, tramadol was more effective for pain.[146] There is no long-term evidence of the comparative efficacy of tramadol versus another opioid or a non-opioid comparison such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. Due to tramadol's partial mu agonist activity and demonstrated safety profile when used in conjunction with acetaminophen in elderly patients, it may be a preferred agent in that patient group.[147,148]

Tapentadol

In long-term studies, compared to placebo, low quality evidence indicates that tapentadol is more effective for pain-related primary and secondary outcomes, but results were mixed for several different self-reported quality of life measures in these studies.[149-151] Compared to oxycodone, moderate quality evidence suggests that tapentadol might be more effective for pain relief. Low quality evidence suggests there is no difference in serious adverse events. Moderate quality evidence suggests tapentadol might be superior for avoiding non-serious adverse events or discontinuation of treatment due to adverse events; however, the clinical implications of these findings are unclear.[149]

Safety and Risk Mitigation

All recommendations in this CPG apply to dual-mechanism opioid products, including the recommendations regarding safety measures and risk mitigation strategies (e.g., to monitor for suicidality, accidental overdose, and OUD).

Dual-mechanism opioid medications have additional considerations as a result of their dual action. They include a lowering of seizure threshold in susceptible patients and the risk of serotonin syndrome.

Evidence related to safety of dual-mechanism opioids versus placebo was reviewed. No evidence on the safety of tramadol met our inclusion criteria, and no new evidence was reviewed. Tramadol may be considered lower-risk than tapentadol due to its mechanism of action and existing safety profile as noted above. Evidence on the safety of tapentadol was reviewed for this guideline update. In long-term studies, there is low quality evidence that, when compared to placebo, patients experience more adverse events when taking tapentadol. Some severe adverse events experienced by a small portion of patients receiving tapentadol included chest pain,[150,151] coronary artery disease,[151] and severe upper abdominal pain possibly related to the study drug.[150] There was one death due to myocardial ischemia but this was not likely related to tapentadol. In one study comparing tapentadol versus placebo, minor adverse events observed in patients treated with tapentadol included nausea and vomiting in 21.1% and 12.7% of patients, respectively.[151] In short-term studies, there is overall low to very low quality evidence that, when compared to placebo, patients receiving tapentadol experience more adverse events (e.g., vomiting, tiredness, dry mouth, dizziness, sweating, constipation, nausea) and drop out of treatment more often than the placebo groups.[146,152-154]

Buprenorphine for Pain

There is insufficient evidence to recommend buprenorphine over other opioids for the treatment of chronic pain. Transdermal buprenorphine was found to be efficacious and well-tolerated for the short-term treatment of chronic, moderate-to-severe low back pain.[155] In patients with chronic, moderate-to-severe osteoarthritis (OA) pain of the hip and/or knee, short-term use of seven-day low-dose buprenorphine patches were an effective and well-tolerated analgesic.[156] Furthermore, during a 28-day assessment period, seven-day low-dose transdermal buprenorphine patches were as effective as sublingual (SL) buprenorphine, with a better tolerability profile.[157] In terms of dosing, transdermal buprenorphine provides effective analgesia with an acceptable tolerability profile when initiated at 10 micrograms (mcg)/hour (hr) and titrated upward to a maximum of 40 mcg/hr.[158] One study suggested efficacy for two-thirds of elderly OA patients (whose pain responds to opioids) at a seven-day low-dose buprenorphine patch at 5-20 mcg/hr when surgery was not possible and when NSAIDs were not recommended. Focus on and management of side effects is necessary.[159]

Buprenorphine has several properties that make it a potentially desirable as an analgesic. It is a synthetic opioid analgesic with partial mu opioid agonist and kappa opioid antagonist properties.[157] It has high affinity to the opiate receptor and a long duration of action (24-72 hr). Buprenorphine is a partial agonist agent and as such may be associated with less euphoria and easier withdrawal. Buprenorphine should not be added to patients that are on a full mu agonist as it will precipitate withdrawal. In addition, caution should be exercised when adding full mu agonists to patients on buprenorphine as the efficacy and side effect profiles may vary.

Pregnancy and liver disease require consideration of monotherapy (buprenorphine without naloxone). Other considerations for buprenorphine may be found in the VA/DoD SUD CPG.[11] Consideration should be given to specialty consultation when patients on buprenorphine have acute or post-operative pain conditions. Practitioners who prescribe SL buprenorphine or SL buprenorphine/naloxone for pain are not required to have an X Drug Enforcement Administration (DEA) number. However, practitioners do not need an X DEA license to prescribe buprenorphine patches labeled for pain. When buprenorphine is used for pain, higher doses should be used with caution in opioid-naïve patients. Split dosing is often preferred as the duration of pain relief may be 8-12 hr. All safety measures discussed in this guideline apply to buprenorphine products. For additional information, see Table 4 and Table 5 below.

Buprenorphine for Opioid Use Disorder

Patients on LOT may meet DSM-5 criteria for OUD. In addition, patients on LOT may have undiagnosed OUD that may manifest at the time of taper. The lifetime prevalence of any prescription OUD in patients on LOT may be as high as 41.3%.[160] In these cases, abrupt changes or discontinuation of the prescription opioid may result in increased risk of adverse events. Provision of SL buprenorphine may assist the provider and patient in meeting therapeutic goals for both pain and management of OUD. Specialty consultation is suggested in cases where pain and OUD are being treated concurrently. Further research is needed for managing patients with OUD and pain. There is substantial evidence for improved outcomes with MAT, which includes frequent drug use monitoring and counseling/psychotherapy at initiation of treatment in addition to medication (see Recommendation 17). Use of buprenorphine products for OUD is detailed in the VA/DoD SUD CPG.[11] Under the Drug Addiction Treatment Act of 2000 (DATA 2000), in order to prescribe buprenorphine for OUD, physicians must qualify for a physician waiver, which includes completing eight hours of required training and an application to SAMHSA.[161] Waivered physicians are provided with an X DEA number and there are limits regarding the number of patients that one provider can treat with buprenorphine for OUD.

[11] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

Table 4. Buprenorphine Formulations [162]

Route	Dosage Form	Strengths	Brand Name	Use
Topical	Transdermal System	5 mcg/hr 7.5 mcg/hr 10 mcg/hr 15 mcg/hr 20 mcg/hr	Butrans®	Management of pain severe enough to require around-the-clock, long-term, opioid treatment and for which alternative treatment options are inadequate
Buccal	Film	75 mcg 150 mcg 300 mcg 450 mcg 600 mcg 750 mcg 900 mcg	Belbuca®	Management of pain severe enough to require around-the-clock, long-term, opioid treatment and for which alternative treatment options are inadequate
Parenteral	Injection	0.3 mg/mL	Buprenex®	Management of moderate-to-severe pain
Sublingual	Tablets	2 mg 8 mg	Subutex®	Treatment of opioid dependence

Abbreviations: hr: hour(s); mcg: microgram(s); mg: milligram(s); mL: milliliter(s)

Table 5. Buprenorphine/Naloxone Formulations [162]

Route	Dosage Form	Strengths (listed as buprenorphine/naloxone)	Brand Name	Use
Buccal	Film	2.1 mg/0.3 mg 4.2 mg/0.7 mg 6.3 mg/1.0 mg	Bunavail®	Treatment of opioid dependence
Sublingual	Film	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	Suboxone®	Treatment of opioid dependence
Sublingual	Tablets	2 mg/0.5 mg 8 mg/2 mg	generic	Treatment of opioid dependence
Sublingual	Tablets	1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg 8.6 mg/2.1 mg 11.4 mg/2.9 mg	Zubsolv®	Treatment of opioid dependence

Abbreviations: hr: hour(s); mg: milligram(s)

Methadone

There is insufficient evidence to recommend methadone over other opioids for the treatment of chronic pain.[163] The only study included in the evidence review was limited to patients with cancer pain and suggested greater adverse effects with methadone than with other opioids.[166] An epidemiologic study suggests that the use of methadone contributes disproportionately to opioid overdose deaths relative to the frequency with which methadone has been prescribed.[164]

An analysis of opioid prescriptions by VA from 2010 to 2012 concluded that the prescribing of any long-acting/ER opioid medication, including methadone, was predictive of overdose or serious opioid-induced respiratory depression.[165] Studies comparing treatment of pain with methadone to treatment with other opioids describe inconsistent results and indicate that the risks associated with use of methadone vary greatly with treatment settings and management, monitoring, and risk mitigation strategies. A retrospective study of Tennessee Medicaid records (for years 1997 to 2007), documented an increased risk for overdose for non-institutionalized patients with non-cancer pain receiving methadone, including at low dosages.[166] A retrospective cohort study among Oregon Medicaid recipients (for years 2000 to 2004) found no statistically significant differences between methadone and long-acting morphine in risk for death. However, for the subgroup of patients with non-cancer pain, methadone was associated with greater risk of overdose symptoms, but not mortality or hospitalization.[167] A retrospective observational study of a large cohort drawn from VA healthcare databases (for years 2000 to 2007) documents that propensity-adjusted mortality was lower for methadone than for morphine. The study found no evidence of excess all-cause mortality among VA patients who received methadone compared with those who received long-acting morphine.[168]

Yet the unique pharmacologic properties of methadone make it particularly risky to prescribe. Methadone carries a risk of cardiac arrhythmia, and risk assessment for QT prolongation and electrocardiographic monitoring is essential. Methadone has a variable half-life with peak respiratory depressant effect occurring later and lasting longer than peak analgesic effect. Dose escalation to improve pain relief may lead to unintentional intoxication and corresponding respiratory depression or arrest.[166] Additionally, the metabolism of methadone varies by dose and individual, making dosing unpredictable. Plus, there are medications that interact with methadone and should not be prescribed concurrently (see Table D-2).

Only clinicians who are experienced with methadone and who are prepared to implement appropriate precautions, risk mitigation strategies, and patient/caregiver education should initiate, titrate, or taper methadone for chronic pain. Prescribers and patients should be familiar with these unique characteristics and institute appropriate safety precautions.

Specific guidance for clinicians about the risks of methadone is summarized below and detailed in Appendix D:

- Monitoring for cardiotoxicity [169]
  - Inform patients of the arrhythmia risk
  - Ask patients about heart disease, arrhythmia, and syncope
  - Obtain baseline ECG and regularly thereafter in intervals appropriate to risk/dosage
  - If the QTc interval is greater than 450 ms, but less than 500 ms, reevaluate and discuss with the patient the potential risks and benefits of therapy and the need for monitoring the QTc more frequently
  - If the QTc interval exceeds 500 ms, discontinue or taper the methadone dose and consider using an alternative therapy; other contributing factors, such as drugs that cause hypokalemia or QT prolongation, should be eliminated whenever possible

    - Be aware of interactions between methadone and other drugs that may prolong QTc interval or slow the elimination of methadone, and educate patients about potential drug interactions
- Conservative dosing
    - Methadone should not be initiated in opioid-naïve patients in the outpatient setting
    - Primary care clinicians should never rotate from another opioid to methadone without guidance from an experienced clinician regarding the starting dose of methadone
    - When initiating or increasing dosage, close follow-up is recommended (e.g., within five to seven days) to assess signs of methadone toxicity, such as excess sedation or delirium
    - Wait at least one week on a particular dose of methadone before increasing dosage of methadone to make sure that the full effects of the previous dosage are evident

Recommendations

14. We recommend tapering to reduced dose or to discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits.
    (Strong for | Reviewed, New-added)

    Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns.

15. We recommend individualizing opioid tapering based on risk assessment and patient needs and characteristics.
    (Strong for | Reviewed, New-added)

    Note: There is insufficient evidence to recommend for or against specific tapering strategies and schedules.

Discussion

Clinicians should reassess the use of LOT in all patients currently receiving the therapy and consider tapering or discontinuing opioids in all patients on LOT when the risks exceed the benefits of therapy. Treatment of chronic pain with LOT in general is associated with considerable risk and must be justified by attainment of benefit that outweighs those risks in any individual patient. Non-pharmacologic therapies and non-opioid pharmacologic therapies are preferred and should be optimized. See Recommendation 1 for additional information on recommended treatments for chronic pain.

Observational studies (not included in the evidence review) suggest that when opioids are tapered or discontinued within the context of a multi-modal pain rehabilitation care plan, patients can experience an improvement in their pain, function, and mood.[170,171] Although the confidence in the quality of the evidence was low, the Work Group's determination that the benefits of individualized tapering of OT (when risks of LOT outweigh benefits) greatly outweigh the harms of tapering, as well as their consideration of individual patients' values and preferences, supported strong recommendations.

Indications for Tapering

If risks of OT outweigh benefits, OT should be tapered to a reduced dose or tapered to discontinuation. In the context of shared decision making, patient-specific goals, values, and preferences, the following should

be taken into consideration when determining the balance of risks and benefits of OT, recognizing that multiple risk factors increase cumulative risk:[172,173]

- Concomitant use of medications that increase risk of overdose
- Co-occurring medical or mental health conditions that increase risk
- Concerns about OUD or other SUD
- Patient adherence with opioid safety measures and opioid risk mitigation strategies
- Patient non-participation in a comprehensive pain care plan
- Prescribed dose higher than the maximal recommended dose (which increases risk of adverse events) (see Recommendations 10-12)
- Pain condition not effectively treated with opioids (e.g., back pain with normal magnetic resonance imaging [MRI]; fibromyalgia)
- Improvement in the underlying pain condition being treated
- Lack of clinically meaningful improvement in function
- Unmanageable side effects

When there is strong concern for diversion, opioids should be discontinued. For all patients, the prescribing clinician should regularly inquire about the patient's preference to taper OT to a reduced dose or discontinuation and explore ambivalence. OT should be tapered when patients voice their preference to reduce dosage and/or discontinue LOT.

There is large variation in patient preferences regarding continuing versus tapering OT and regarding the various processes that can be used when tapering opioids. Participants in the patient focus group expressed concern that when patients are receiving LOT, they may experience impaired judgement regarding decisions about opioid discontinuation due to the reinforcing nature of OT. Patients, therefore, may benefit from the outside perspective of their family members and healthcare providers. Such involvement should occur in accord with patient's preferences and within applicable privacy requirements (see Patient Focus Group Methods and Findings).

Low frequency of follow-up in primary care and limited access to comprehensive interdisciplinary specialty pain, rehabilitation, mental health, and addiction services may be barriers to tapering LOT that may need to be addressed.

Assessment/Follow-up

A biopsychosocial assessment including evaluation of medical, psychiatric, and co-occurring substance use conditions, as well as the patient's social support system, should be completed prior to the initiation of an opioid taper. The risks and benefits of the current opioid regimen should be weighed with the risks and benefits associated with a reduction in opioid dose. Periodic re-evaluation of risks and benefits coupled with a biopsychosocial assessment should occur when implementing an opioid taper and on follow-up. The frequency and type of follow-up is determined by risk assessment performed by the healthcare team. Follow-up should occur within a range of one week to one month after any opioid dosage change. Each follow-up interaction with the patient is an opportunity to provide education about self-management

strategies and the risks associated with OT while optimizing whole person approaches to pain care and treatment of co-occurring medical and mental health conditions. Following discontinuation of opioids, consider continuing risk mitigation strategies. Tapering may unmask underlying OUD. Therefore, frequent assessment for OUD is recommended (for more information on diagnosis and treatment of OUD see the VA/DoD SUD CPG).[12]

Referral

Clinicians should consider using an interdisciplinary, team-based approach that may include primary care, mental health, pain specialty/rehabilitation, pharmacy, physical therapy, and/or SUD services during the opioid tapering process. The treatment setting should be selected based on safety and the availability of services while also incorporating patient preferences.

It is important to recognize that some patients who are undergoing an opioid taper may experience symptoms of OUD that were not present or had not been previously identified prior to the taper. Opioid prescribers and the treatment team should remain vigilant for signs and symptoms of OUD for patients receiving LOT; particular attention is warranted during the tapering process. When there is concern for OUD or other SUD in a patient undergoing opioid tapering, clinicians should recommend SUD assessment and treatment to the patient in a setting that corresponds to the patient's level of risk and availability of services, while considering patient preferences (see the VA/DoD SUD CPG).[12] The possibility exists that some patients may be able to be seen in the primary care setting while others may be more appropriate for specialty care.

Patients on LOT with OUD are at increased risk of overdose when opioids are either continued or discontinued without appropriate treatment for OUD. We recommend MAT for OUD (e.g., MAT using methadone, buprenorphine/naloxone, or ER injectable naltrexone) (see the VA/DoD SUD CPG[12] and Recommendation 17). Treatment of OUD with MAT can occur in SUD programs as well as in primary care, specialty pain care, and mental health settings when the necessary resources are available. In patients with OUD, the opioid prescriber should ensure that OEND has been offered. The opioid prescriber may consider slowing the taper until a smooth hand-off to OUD treatment can be accomplished; however, close monitoring must occur for all patients during this transition process. Expediting the taper process and continuing to offer OUD treatment may be appropriate in some situations (e.g., if patient is not adherent to opioid taper and declines OUD treatment).

Additionally, underlying mental health disorders may be exacerbated by opioid use and/or opioid tapering and may require ongoing interdisciplinary care that includes mental health services.

The care team should take great efforts to ensure that the patient does not feel abandoned during the opioid tapering process. This includes clear communication with the patient that the care team will

[12] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

maintain frequent contact with the patient during the opioid taper and emphasizing that the care team will continue to pursue non-opioid pain care options during and after opioid tapering.

Clinicians should also educate the patient/family about acute and protracted opioid withdrawal symptoms and provide treatment strategies to mitigate these symptoms as appropriate.[174] To foster patient engagement with the taper plan, clear written and verbal instructions should be given to the patient/family regarding the tapering protocol, strategies to mitigate withdrawal symptoms, and additional non-opioid treatments for the patient's pain condition.

> Strongly caution patients that it takes as little as a week to lose tolerance to their prior opioid dose and that they are at risk of an overdose if they resume their prior dose.

Regardless of the initial speed of taper, the rate of taper may need to be adjusted during the course of lowering the opioid dose. The pace of taper should be reevaluated after each dose change.

If patients are receiving both long-acting and short-acting opioids, the decision regarding which formulation to be tapered first needs to be individualized based on safety, medical history, mental health diagnoses, and patient preference. However, it should be kept in mind when making this decision that long-acting opioids may be associated with higher overdose, overdose death, and all-cause mortality rates when compared to short-acting opioids, which may suggest tapering long-acting opioids first.[10,137] There may also be times when tapering both formulations simultaneously is appropriate.

If an opioid dose reduction is the initial treatment goal, ongoing assessment of the balance of risks and clinically meaningful benefits should be performed once the original treatment goal is achieved. If this assessment determines that the benefits of continuing OT do not outweigh risks, additional dose reduction and/or tapering to discontinuation should be pursued.

Tapering Process

The goal of opioid tapering is to improve the balance of risks and clinically meaningful benefits for patients on LOT. The risks and benefits of the current opioid regimen should be weighed with the risks and benefits associated with a reduction in opioid dose. If the provider determines a patient to be at significant risk of adverse outcomes due to the use of LOT, and if either the patient or the clinician is concerned about potential destabilizing effects of opioid tapering, referral to, or consultation with, specialty services including mental health, SUD, pain medicine, and rehabilitation should be strongly considered.

Abrupt discontinuation of opioids may be justified in certain high-risk circumstances. When there is evidence for diversion, the clinician may need to discontinue OT, frequently assess for withdrawal symptoms, and offer necessary support for withdrawal symptoms and treatment of SUD, if present. When a patient exhibits dangerous behaviors (e.g., threatening behaviors, persistent and serious disruptive behavior, suicidal ideation or behaviors), the clinician may consider abruptly discontinuing OT while providing urgent or emergent psychiatric referral and medical care for the management of opioid withdrawal. When relevant, dangerous or illegal behavior should be documented accurately and completely in the EMR to guide future care. When ongoing pain is suspected, non-opioid treatment for pain should be implemented.[175]

The characteristics that will determine the speed of tapering include opioid dose, duration of therapy, type of opioid formulation, and co-occurring psychiatric, medical, and substance use conditions. The tapering treatment plan should be individualized and should address the pace of tapering, setting of care, and frequency of follow-up. When determining the pace of opioid tapering, factors that would suggest a more gradual taper include higher opioid dose and longer duration of OT; factors that would suggest a more rapid taper include non-adherence to the treatment plan and escalating high-risk medication-related behaviors. When safety permits, gradual tapers are often better tolerated. In addition, for some patients, pauses in the taper for weeks or months may allow the patient time to acquire new skills for management of pain and emotional distress while also allowing time for neurobiological equilibration.

The rate of taper takes into account many factors that include initial dose, formulations available, and risk factors that increase harm. A gradual taper over months or even years for patients starting on very high opioid doses involves reducing by 5-20% every four weeks. In some patients, a faster taper may be needed when risks are too high to consider a gradual taper; consider tapering the dose by 5-20% per week in this patient population.

When it is determined that patient risks are significantly high to warrant a rapid taper over a period of days or weeks, then specialty consultation should be obtained to determine the rate of taper and resources needed. These patients will need frequent follow-up and reevaluation of SUD, mental health, and/or co-occurring medical conditions with every dose change.

Patients Receiving Very High Dose Opioid Therapy

For patients currently prescribed ≥90 mg MEDD, a comprehensive assessment that recognizes the increased risk of high dose OT should be performed. Tapering to a reduced dose or tapering to discontinuation should be pursued when clinically meaningful functional benefit is not demonstrated or when significant risk factors in addition to the prescribed opioid dose are present. It should be recognized that elevated dose alone poses increased risk of overdose, overdose death, adverse effects, and the development of OUD. Assessing clinically meaningful functional benefit should be individualized and incorporate the use of SMART goals and considered in the context of patient-specific goals, values, and preferences (see table Guide in Setting SMART Goals).

Mental health and SUD comorbidities that were previously unrecognized or that may worsen should be assessed and addressed with an interdisciplinary approach. Interdisciplinary care including mental health, rehabilitation, and SUD treatment services may be necessary to support the tapering process. Use of MAT, which includes behavioral approaches, should be offered for patients in whom a diagnosis of OUD is made (see the VA/DoD SUD CPG).[13]

[13] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

Naloxone

Overdose education should be provided and naloxone should be offered as an antidote to all patients at risk for an opioid overdose including those who are in the process of tapering. During and following an opioid taper, patients may still be using opioids from other sources such as saved opioids, other prescribers, friends and family, as well as illicit sources. Continued surveillance for OUD and assessment for naloxone is suggested in patients who are no longer on opioids but who remain at risk for opioid use from unknown sources. For more information, see Recommendations 7-9.

Future Research

Additional research is needed to identify the opioid tapering processes that are associated with the best patient outcomes among a broad range of domains including general functioning, psychosocial functioning, mood, pain related disability, and adverse outcomes assessed in the short, medium, and long-term.

Recommendation

16. We recommend interdisciplinary care that addresses pain, substance use disorders, and/or mental health problems for patients presenting with high risk and/or aberrant behavior. **(Strong for| Reviewed, New-replaced)**

Discussion

A variety of high-risk medication-related behaviors (e.g., early refills, lost or stolen medications, problematic findings on urine tests) may suggest the presence of SUD (also known as opioid addiction, abuse, or dependence). Non-adherence to treatment plans or repeated failure to show for clinic appointments can add to the challenge of safely providing LOT in the primary care setting. The presence of co-occurring SUD or psychiatric conditions in some patients can make prescribing LOT an overwhelming problem for primary care providers. Chronic pain is a complex human experience influenced by physical, psychological, and social factors. Multidisciplinary care that addresses these influences is helpful for all patients, but is absolutely essential when pain is accompanied by co-occurring conditions, impaired function, or psychological problems.

Low quality evidence supports the benefits of providing brief behavioral interventions and close monitoring to patients at high risk for prescription opioid misuse.[114] Some evidence suggests that patients referred to highly structured opioid-renewal programs that provide patients with frequent UDT monitoring, frequent clinic visits, smaller quantities of medications, and ongoing counseling/education is helpful for patients and primary care providers. Meghani et al. (2009) found that high-risk medication-related behaviors resolved in 45.6% of patients managed in a pharmacist-run opioid renewal clinic.[176] Although the confidence in the quality of the evidence was low, the Work Group's determination that the benefits of interdisciplinary care for patients with pain and other comorbidities (e.g., SUD, mental health problems) contributed to a strong recommendation.

Consider referring patients with co-occurring substance use or psychiatric conditions to addiction medicine/psychiatry or other behavioral health specialists. Coordination of care between pain care and other specialty care, including SUD clinicians, is advised. If structured comprehensive programs are not available, coordination among individual healthcare providers is essential to address the full range of high-

risk behaviors. Chronic pain in general, and LOT in particular, requires consideration of all of the patient's life problems. If resources do not exist to address co-occurring SUD and psychiatric conditions or if the patient declines to participate, treatment with LOT should be reconsidered.

Research is needed to identify the efficacy and feasibility of providing multidisciplinary care to patients demonstrating significant high-risk medication-related behaviors when prescribed LOT in primary care settings.

Recommendation

17. We recommend offering medication assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder.
    (Strong for | Reviewed, New-replaced)

    Note: See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.

Discussion

OUD (also known as opioid addiction, abuse, or dependence) is a chronic brain disease that impairs one's ability to control opioid use. Opioids disrupt the functioning of brain circuits that mediate a complex array of functions involved in obtaining natural rewards such as food and water that are essential for survival. Because opioids activate these circuits more powerfully than natural rewards, the primitive brain learns to prioritize attention to and motivation for opioids over other natural rewards.[177] Repeated opioid use over time can lead to OUD. While there are some risk factors such as other substance use or co-occurring mental illness that can increase the risk of developing an OUD among those taking opioid analgesics, by far the most powerful risk factor for developing OUD is long-term opioid analgesics use. All persons using opioid analgesics are at-risk for developing an OUD. Persons who become addicted to opioids gradually become more and more preoccupied with opioid use and spend more of their time seeking the drug, using it, or recovering from its effects. They may continue to use opioids even though they:

- Know that opioid use is harmful
- Often use more than they intended
- Engage in risky behaviors such as driving while intoxicated or combining opioids with alcohol or other sedatives
- Have multiple unsuccessful attempts to cut down or control opioid use
- Report strong craving or urges to use opioids in response to withdrawal symptoms, stress, negative emotions, or simply cues that the drug is available

OUD is associated with premature death from opioid overdose and other medical complications such as acquired immunodeficiency syndrome (AIDS), hepatitis C, and sepsis. On average, OUD carries a 40-60% 20-year mortality rate.[178] Persons with OUD are at high-risk for premature death, not only from opioid

overdose, but from other consequences. Thus, providing first-line treatment is important to save lives as well as to improve the quality of life of patients.

Strong evidence supports the use of opioid agonist therapy (e.g., methadone, buprenorphine/naloxone) as first-line treatment for moderate-to-severe OUD (see VA/DoD SUD CPG).[14] However, because this research has been conducted primarily on persons addicted to heroin, the populations studied have had a higher prevalence of co-occurring SUD and lower prevalence of chronic pain. Patients and their treating clinicians may be concerned that treatments proven effective in different OUD populations may not be effective for patients with chronic pain, or may not be necessary for patients who have become addicted to prescription opioid analgesics. This concern has been unfounded and was addressed by Weiss and colleagues in the Prescription Opioid Abuse Treatment Study (POATS).[179]

Early research suggested that patients with prescription OUD may have a better prognosis than those who are primarily addicted to heroin, implying that those with prescription OUD may not need MAT.[180,181] However, in studies with patients with DSM-IV opioid dependence (which were conducted prior to use of DSM-5), buprenorphine maintenance therapy is more effective than a four-week taper. One multicenter RCT tested the hypothesis that patients with prescription OUD would respond well to a four-week tapering of buprenorphine/naloxone to discontinuation plus two regimens of outpatient counseling.[179] Those who did not achieve successful outcomes after buprenorphine taper in phase one were invited to participate in phase two consisting of 12-weeks treatment using buprenorphine/naloxone followed by taper to discontinuation. During both phases, patients were randomized to receive a manualized, physician-delivered psychosocial intervention known as Standard Medical Management or Standard Medical Management plus manually-driven opioid drug counseling delivered by a trained therapist. Only 6.6% of these patients achieved a successful outcome after tapering in phase one with no difference between the groups. In phase two, while taking buprenorphine/naloxone, 49% of patients achieved a successful outcome again with no difference between the counseling groups. Eight weeks after tapering again, only 8.6% of patients achieved a successful outcome. This suggests that MAT with moderate dose buprenorphine/naloxone and brief, structured counseling by the prescribing physician can be successful for about half of selected patients with prescription OUD, whereas withdrawal management alone, even with close weekly follow-up and counseling is successful for less than 10% of patients.

Furthermore, the presence of chronic pain does not seem to interfere with the success of MAT. The RCT by Weiss et al. (2011) and a meta-analysis by Dennis et al. (2015) reached the same conclusion that the presence of chronic pain did not influence response to opioid agonist therapy.[179,182] Given the high mortality associated with OUD and the safety and efficacy of MAT for OUD in multiple clinical trials and meta-analyses, we recommend MAT for those chronic pain patients who meet DSM-5 criteria for OUD. Those who do not respond to minimal counseling may benefit from a comprehensive assessment and more intensive treatment of OUD and any co-occurring conditions in SUD specialty care settings.

[14] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

D. Opioid Therapy for Acute Pain

Recommendation

18. a) We recommend alternatives to opioids for mild-to-moderate acute pain. **(Strong for)**
    b) We suggest use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain. **(Weak for)**
    c) If take-home opioids are prescribed, we recommend that immediate-release opioids are used at the lowest effective dose with opioid therapy reassessment no later than 3-5 days to determine if adjustments or continuing opioid therapy is indicated. **(Strong for)**
    (Reviewed, New-added)

    Note: Patient education about opioid risks and alternatives to opioid therapy should be offered.

Discussion

As this guideline is related to LOT, the use of opioids for acute pain is not reviewed in detail. However, because acute OT can be a gateway to LOT, it is part of this CPG. A review of the literature indicates that LOT can result from acute opioid use initially intended for short-term therapy. Further, there is a risk of opioid-related overdose even during acute OT. While it is understood that acute OT for severe pain due to injuries or surgery is the most effective option for many patients, the risks associated with acute therapy must be addressed when opioids are prescribed or considered.

The risks of acute OT extending into LOT are increased in patients with mood disorders, those who refill the initial prescription, higher prescribed dose (greater than 120 mg MEDD), and initiation using long-acting opioids.[183-185] The risk of acute post-operative OT progressing into LOT is increased with a history of depression, SUD, catastrophizing, higher preoperative total body pain, history of back pain, and preoperative use of sedative-hypnotics or antidepressants.[186,187]

In addition, the risk of overdose includes the use of opioids for acute pain. Factors that increase overdose risk when opioids are used for acute pain include high prescribed dose, history of SUD, and history of mental health concerns. While the risk of overdose increases at doses above 20 mg MEDD or greater, this risk increases even further as doses increase to over 50 or 100 mg MEDD.[58,59,188]

There are situations in which opioids may be necessary therapy for acute pain, even when substantial risk factors exist. It is important to incorporate opioid risk mitigation strategies into opioid prescribing for acute pain. These strategies should include patient education, use of non-opioid adjunctive therapy, and structured reassessment of opioid risks and benefits for all on acute OT. Also, consider checking the PDMP and performing a UDT.

For those at higher risk of adverse events related to opioid therapy, the following strategies may help to decrease opioid-related overdose events and unintended long-term use: checking the PDMP, performing a UDT, placement in an inpatient setting or monitored environment, and/or providing OEND.

Monitoring standards with administration of OT for acute pain vary depending on a number of factors including the setting, specifics of the painful insult, patient medical factors, and selected medication potency/dose/route of administration/adjunct selection.

The Opioid Therapy for Chronic Pain Work Group.
(2017, February).
VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain.
Department of Veterans Affairs, Department of Defense.