The American College of Critical Care Medicine and the Society of Critical Care Medicine recently published updated clinical practice guidelines for the management of pain, agitation, and delirium (PAD) in critically ill adult patients. The new guidelines were formulated using robust methods and included practice advancements that occurred since the last iteration of the guidelines in 2002. The purpose of this review is to examine the role of pharmacists in managing PAD in the ICU and to help translate best evidence into clinical practice.

**PAD Guidelines**

In 2006, a task force of experts was recruited to develop the PAD guidelines. Four subcommittees comprehensively examined the literature regarding analgesia, sedation, delirium, and outcomes in the ICU. Important clinical management questions were formulated and served as the basis for the 54 recommendations and statements that were published this year.

Recommendations and statements were developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method. The GRADE method enabled the experts to objectively, systematically, and transparently evaluate the literature and make recommendations based on the quality and strength of evidence. Consequently, the guidelines lack statements based solely on expert opinion.

Despite the rigorous methods used to develop the PAD guidelines, limited data exist suggesting that guidelines improve outcomes. This is surprising and may be due in part to incomplete or inconsistent implementation. Many practitioners, including pharmacists, think that practice guidelines define the standard of care; rather, they should be regarded as representative of best practice. Clinical decisions always should be made within the context of patient condition, local practice norms, and resource availability. These realistic and balanced expectations will facilitate the adaptation and implementation of guidelines on a local level.

Successful efforts designed to change clinical practice consistently employ a multifaceted, interdisciplinary team approach. Pharmacists have been an instrumental part of the interdisciplinary ICU team since the 1980s. The financial impact, clinical expertise, and scholarly activities they offer an ICU team are well documented. The proposed duties and responsibilities of pharmacists in the ICU, which can be categorized as fundamental, desirable, and optimal, include guideline implementation and utilization (Table 1).

It is imperative that pharmacists become familiar with all aspects of PAD management and how they can help
alleviate the burden of PAD in critically ill patients. The first step is to appreciate the utility of systematic assessments of PAD with tools that have been tested for reliability and validity. Incorporating these tools into daily clinical practice will facilitate rational preventive and treatment interventions. Recommendations regarding pharmacotherapy made in the PAD guidelines are summarized in Table 2 and will be further explored below.

**Pain and Discomfort**

**IMPORTANCE**

Despite 2 decades of focused attention, pain continues to be the most traumatic experience reported by patients after ICU stays. Approximately 50% of medical, surgical, and trauma patients experience pain at rest, and untreated procedural pain (eg, during turning, suctioning, or wound dressing) remains a common issue.16,17

In addition to our inherent promise to provide humane care for our most vulnerable patient population, we should be mindful that unrelieved pain has clinical ramifications. The stress response from pain produces unwanted physiologic consequences including sleep impairment, hyperglycemia, inadequate tissue perfusion, vasoconstriction, impaired wound healing, and an increased risk for infection.18,19 It also has been linked to post-traumatic stress disorder (PTSD) in those discharged from the ICU.20

**ASSESSMENT**

The PAD guidelines recommend that pain should be assessed 4 or more times per nursing shift, and additionally as needed. Recent data suggest that a systematic evaluation of pain can reduce the frequency of moderate to severe pain (by nearly 50%), the need for sedative-hypnotic agents, and ICU and hospital length of stay (LOS).21

The numerical rating scale (NRS) is considered the gold standard for pain assessment in communicative patients.22 For those who cannot self-report but have intact motor function, the use of the Behavioral Pain Scale (BPS) or Critical Care Pain Observation Tool (CPOT) is recommended. Both the BPS and CPOT have been tested for reliability and validity and assess facial expression, body movements or muscle tension, and compliance with the ventilator.23,24

Tachycardia and increasing blood pressure should not be used for pain assessment because fluctuations in vital signs are not specific to pain.25 They can, however, be used as a cue to conduct more formal pain evaluations with the valid and reliable pain assessment tools. This issue represents an important gap in clinical practice that pharmacists can help rectify, considering that less than 40% of nurses routinely perform such assessments.21

**MANAGEMENT**

Pharmacists should play a prominent role in the treatment and prevention of pain. Pain should be addressed pharmacologically or nonpharmacologically within 30 minutes of identification and reassessed with the NRS, CPOT, or BPS. The preemptive treatment of pain before potentially painful procedures is imperative and also should include both pharmacologic and nonpharmacologic modalities.

Nonpharmacologic options are attractive because they are analgesic-sparing, low-cost, and devoid of adverse effects. Unfortunately, nonpharmacologic treatments have been poorly studied in ICU patients.26 A recent review of nurses and patients found that music therapy, simple massage, and family presence may offer relief.27 If these measures are not effective, pharmacologic therapy is necessary.

The PAD guidelines highlight the differences in the management of non-neuropathic and neuropathic pain. For non-neuropathic pain, all IV opioids appear to be efficacious when they are titrated to a desired pain intensity score. Neuropathic pain treatment should involve the enteral administration of gabapentin or carbamazepine in addition to IV opioids. The value of adjunctive pain medications including acetaminophen should not be underestimated. Pharmacists are encouraged to review other authoritative sources for information about the practical application of analgesics in the ICU.26,28

**Analgesedation**, an analgesic-first approach for comfort and sedation, is advocated in the guidelines. Analgesedation, typically with a short-acting IV opioid, can obviate the need for sedatives, control pain that may be difficult to assess, and may improve outcomes.29,30 It also is likely that analgesedation facilitates earlier patient mobilization, which can reduce the incidence of delirium and facilitate ICU discharge.31 Pharmacists should be alert for the adverse effects of opioids (eg, respiratory depression or reduced gastrointestinal motility) when employing analgesedation and offer remedial strategies, such as patient-specific titration and effective bowel regimens.

It is not uncommon for patients to develop tolerance or hyperalgesia when treated with opioids in the ICU.32,33 During these situations, pharmacists can suggest rotating opioids (eg, switching from fentanyl to hydromorphone), which has been successful in cancer patients.34,35 Transitioning from IV fentanyl to enteral methadone also is feasible and has been shown to facilitate ventilator weaning and ICU discharge.36,37

Overall, the management of pain and analgesia should be guided by routine evaluations with valid and reliable scales. Pain medications should be used if there are indicators of pain at rest, as part of analgesedation and before all potentially painful procedures. Analgesics should be titrated to patient-specific needs to ensure the delivery of compassionate care.

**Agitation and Sedation**

**IMPORTANCE**

Prospective cohort studies have identified agitation as an independent risk factor associated with more frequent sedative and opioid administration, longer ICU LOS, greater time on a ventilator, more nosocomial infections, and unplanned medical device removal.38,39 The identification and treatment of possible underlying etiologies such as pain, delirium, hypoxia, and substance
withdrawal form the basis for ICU agitation management. Ideally, traditional sedatives should be reserved for refractory cases or when analgosedation has failed.

**ASSESSMENT**

The PAD guidelines strongly recommend that agitation and sedation be routinely assessed 4 or more times per nursing shift, and additionally as needed. Data suggest that systematically evaluating for agitation can reduce its incidence by 33%.

The PAD guidelines recommend the Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS), which have been tested for reliability and validity. A recent psychometric evaluation of these scales further demonstrated their equivalence. Despite this, the RASS and the SAS may have clinically important inherent differences related to the evaluation of wakefulness.

Wakefulness (the ability to purposefully perform 3 of the following: open eyes, maintain eye contact, squeeze hand, stick out tongue, and wiggle toes) as a sedation goal should be achieved at least once per day. Targeting wakefulness may reduce time on the ventilator, ICU LOS, and the development of delusional memories or PTSD. These improvements may be due to less accumulation of sedatives and their active metabolites, enhanced patient participation in care, and the attainment of more accurate pain and delirium assessments.

Intrinsic to the use of the SAS is an assessment of wakefulness, especially at a SAS of 3, which indicates that a patient has responded to verbal stimuli or gentle shaking and obeyed simple commands. RASS assessments for sedation depth, on the other hand, are predicated entirely on eye opening, eye contact, and body movement. The implications of these differences are most pronounced when wakefulness is the sedation goal.

**MANAGEMENT**

Provision of adequate analgesia, reorientation to the surrounding environment, and maintenance of a normal sleep-wake cycle should be optimized before sedatives are administered. When indicated, benzodiazepines, propofol, and dexmedetomidine are the most frequently used sedatives in the ICU. The PAD guidelines emphasize that the way sedatives are used is as important as the choice of agent.

Daily sedation interruption or targeted sedation strategies can promote patient wakefulness. Sedation protocols often are developed to assist providers in reaching these goals. One study confirmed that about 30% of institutions do not use sedation protocols. Another study found that daily sedation interruption was not used in 40% of ICU patients. A way to improve adherence is to use a daily, pharmacist-enforced sedation protocol. Such a protocol has been shown to reduce ICU and hospital LOS, as well as the number of days spent with mechanical ventilation.

One of the more intriguing statements made in the guidelines is that non-benzodiazepines (propofol or dexmedetomidine) may be preferred sedatives because benzodiazepines are associated with worse clinical outcomes (eg, increasing ICU LOS by 0.5 to 1.6 days and time on the ventilator by 1.9 days) when compared with propofol or dexmedetomidine.
outcomes are likely related to the sluggish pharmacodynamic profile of the benzodiazepines, which limits their ability to be easily titrated to effect.

Despite these data, it is important for pharmacists to continue to recommend the use of benzodiazepines when appropriate. Given their amnestic, anxiolytic, and anticonvulsant properties, the benzodiazepines can be used to treat alcohol and sedative withdrawal syndromes, and intractable seizures, or as a part of a sedative regimen when neuromuscular blockers are used. Interim boluses can offer an effective way of calming an acutely agitated patient or for transferring patients to different areas of the hospital for procedures.

Propofol is characterized by a rapid onset and offset, titratability, and a relatively low cost, making it an attractive agent for sedation. It is preferred over the benzodiazepines because it is associated with a shorter ICU LOS and has not been implicated in the development of delirium. When compared with patients treated with dexmedetomidine, propofol-treated patients have similar clinical outcomes with respect to duration of mechanical ventilation, ICU or hospital LOS, frequency of hypotension or bradycardia, and mortality.

Propofol may be best used when deep sedation is necessary (eg, during therapeutic hypothermia or complex mechanical ventilation), when frequent neurologic

Table 2. Recommendations in the PAD Guidelines Pertaining to Pharmacotherapy

<table>
<thead>
<tr>
<th>Guideline Section</th>
<th>Recommendation</th>
<th>Quality of Evidence And/or Strength Of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain and analgesia</td>
<td>Preemptive analgesia and/or nonpharmacologic interventions should be administered to alleviate pain during chest tube removal</td>
<td>+1C</td>
</tr>
<tr>
<td></td>
<td>For invasive and potentially harmful procedures in adult ICU patients, preemptive analgesics and/or nonpharmacologic therapy should be used</td>
<td>+2C</td>
</tr>
<tr>
<td></td>
<td>IV opioids should be considered first-line drugs for the treatment of non-neuropathic pain in adult ICU patients</td>
<td>+1C</td>
</tr>
<tr>
<td></td>
<td>All IV opioids are equally effective when titrated to similar pain scores</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Nonopioid analgesics should be considered to decrease the amount of opioids administered and to decrease opioid-induced adverse effects</td>
<td>+2C</td>
</tr>
<tr>
<td></td>
<td>Enterally administered gabapentin or carbamazepine should be considered in addition to IV opioids for neuropathic pain</td>
<td>+1A</td>
</tr>
<tr>
<td>Agitation and sedation</td>
<td>Non-benzodiazepine sedatives may be preferred over benzodiazepines to improve clinical outcomes in mechanically ventilated patients</td>
<td>+2B</td>
</tr>
<tr>
<td></td>
<td>Sedative medications should be titrated to maintain lighter rather than deeper levels of sedation, unless clinically contraindicated</td>
<td>+1B</td>
</tr>
<tr>
<td>Delirium</td>
<td>The use of haloperidol or atypical antipsychotics to prevent delirium is not recommended</td>
<td>-2C</td>
</tr>
<tr>
<td></td>
<td>No evidence has been published to show treatment with haloperidol reduces duration of delirium in the ICU</td>
<td>No evidence</td>
</tr>
<tr>
<td></td>
<td>Atypical antipsychotics (quetiapine) may reduce the duration of delirium in the ICU</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Administration of rivastigmine to reduce duration of delirium is not recommended</td>
<td>-1B</td>
</tr>
<tr>
<td></td>
<td>Use of antipsychotics in patients at significant risk for torsades de pointes is not recommended</td>
<td>-2C</td>
</tr>
<tr>
<td></td>
<td>Delirium unrelated to alcohol or benzodiazepine withdrawal should be treated with continuous IV dexmedetomidine to reduce the duration of delirium</td>
<td>+2B</td>
</tr>
<tr>
<td>Improving outcomes</td>
<td>Use of analgesia-first (analgesedation) sedation in mechanically ventilated ICU patients is recommended</td>
<td>+2B</td>
</tr>
</tbody>
</table>

* This recommendation should not supplant clinical judgment of the provider.
assessments in relation to the degree of sedation is important. Studies have shown that there is up to a 30% reduction in the number of patients labeled as “delirious” if patients are allowed to awaken before evaluation with the CAM-ICU. These data indicate that delirium screening may be confounded by sedation and that pharmacists should encourage delirium assessment with the CAM-ICU during interruptions of sedation to reduce overdiagnosis of delirium.

The clinical implications of sedation-associated confounding of delirium assessments recently were evaluated. A study found that coma or positive CAM-ICU assessments were 10 times more likely to be reported before sedation interruption than after. The investigators followed study patients for 1 year and reported that patients with delirium that resolved after sedation was interrupted had nearly identical outcomes to those patients who never had delirium. These data are intriguing and suggest that sedation-related positive CAM-ICU assessments do not portend poor clinical outcomes.

**Management**

Delirium management should begin with identification and treatment of the underlying etiology (eg, pain, central nervous system and metabolic disorders, infections, drugs, etc). Patients at risk for ICU delirium include those with dementia, a history of hypertension or alcohol abuse, or a high severity of illness. Pharmacists can evaluate for use of deliriogenic medications such as the benzodiazepines, anticholinergics, cephalosporins, macrolides, or fluoroquinolones.

Nonpharmacologic interventions can be attempted, but supportive data are limited in the ICU population. The use of environmental, acoustic, and visual stimulation (eg, wall clocks, glasses, or music) has been examined. Promoting the sleep–wake cycle by minimizing overhead pages and dimming hallway lights during the night as well as opening window blinds and preventing napping during the day may confer some benefit. Ultimately, early physical and occupational therapy (ie, early mobilization) has shown the most promising results including improved clinical outcomes. Improved outcomes may be due to lightened sedation, less delirium assessment confounding by sedatives, and avoidance of sedation-related prolonged mechanical ventilation and ICU stay.

Traditional pharmacologic treatment of delirium has focused on the use of antipsychotics. This practice is

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**Delirium**

**Importance**

Delirium may manifest in up to 80% of mechanically ventilated critically ill patients and may be responsible for up to $16 billion in annual health care costs. Delirium is associated with increases in mortality, ICU and hospital LOS, cost of care, and long-term cognitive impairment. A recent trial confirmed that a longer duration of in-hospital delirium is associated with worse cognitive and executive function scores 3 and 12 months after discharge. Despite these data, we remain in the discovery phase of understanding the pathophysiology, appropriate assessment, and management of delirium.

**Assessment**

Delirium assessment is strongly recommended in the PAD guidelines using validated scoring tools (Confusion-Assessment Method for the ICU [CAM-ICU] and the Intensive Care Delirium Screening Checklist [ICDSC]) during every nursing shift and as needed. The CAM-ICU evaluates 4 domains, requiring 3 of the 4 to be present to identify delirium. The ICDSC assesses 8 domains, with a score of 4 or more indicating the presence of delirium. It is important to emphasize that domains affected by sedative use are not counted when delirium scores are tabulated using the ICDSC but they are counted when using the CAM-ICU.

Recent data suggest that the timing of delirium assessments in relation to the degree of sedation is important. Studies have shown that there is up to a 30% reduction in the number of patients labeled as “delirious” if patients are allowed to awaken before evaluation with the CAM-ICU. These data indicate that delirium screening may be confounded by sedation and that pharmacists should encourage delirium assessment with the CAM-ICU during interruptions of sedation to reduce overdiagnosis of delirium.

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Traditional pharmacologic treatment of delirium has focused on the use of antipsychotics. This practice is
based largely on a few studies that have found modest improvements in clinical outcomes, such as number of days spent with delirium, but have failed to show improvements in mortality or long-term cognitive function. The PAD guidelines concluded that there are limited data to support the use of antipsychotics to treat delirium and offered no formal recommendation.

Pharmacologic prevention of delirium with antipsychotics has been a topic of current research. A study completed after the publication of the guidelines found that IV prophylactic haloperidol had no effect on the duration of delirium or coma or other clinical outcomes. These data support the stance within the guidelines that no recommendation could be offered for the prevention of delirium with antipsychotics, including haloperidol.

The overall approach to delirium should start with an assessment during wakefulness with a valid and reliable tool. If delirium is detected, identification and removal of the underlying cause should ensue. Early mobilization should be encouraged in all capable patients because it is the only strategy proven to improve outcomes. Medication therapy with antipsychotics or a central α-receptor agonist (dexametomidine or clonidine) should be used only when necessary. Ultimately, there are no drugs that will reverse delirium once it is present.

Best Evidence to Clinical Practice

Implementing guideline-based recommendations at the bedside is both an art and a science. The PAD guidelines leave room for variation in clinical practice and patient condition. Thus, it may be of benefit to describe how pharmacists can incorporate the PAD guidelines outside of pharmacotherapeutic recommendations.

Since the conception of the first set of guidelines in 1971, authors of guidelines have sought to improve quality of care by reducing practice variations and expediting the implementation of practice advancements. The use of guidelines depends on the quality of the evidence on which they are based, actual and perceived barriers to implementation, and strategies used for integration. Overall, the barriers to guideline incorporation are predominantly behavioral, organizational, and economical.

The literature is replete with studies that have examined implementation strategies. Recently, a plan–do–study–act design was used to describe the implementation of an early mobilization protocol at 3 medical centers. Structured approaches that focus on systems and interdisciplinary collaboration to make large-scale changes also have been used. Pharmacists are encouraged to visit the Institute for Healthcare Improvement website for additional implementation techniques.

It is important to gain insight into a health care system’s current approach to PAD before implementing the guidelines’ recommendations. A gap analysis, or a comparison of current practices with what is recommended, can assist in the development of a priority list for change. Discrepancies are likely to exist in pain and delirium assessment, the use of benzodiazepines and the declaration of goals of care during rounds.

Pharmacists can further contribute during the gap analysis by providing drug use evaluations, assessments of prescribing trends, and chart reviews.

An interdisciplinary approach to implementing the guidelines is encouraged. Practice leaders and key stakeholders should be identified. Representation should be diverse, with members from departments that are involved with direct patient care, have administrative responsibilities, and can speak on behalf of patients and their families. Pharmacists should be recognized as a crucial member of this integrated implementation team.

Finally, pharmacists can offer interdisciplinary education and continuous quality improvement (CQI) strategies. Real-time reminders, direct feedback during rounds, and guidance at the bedside are effective ways to educate other providers. Implementation of order sets, protocols, or pathways and care bundles are exemplary ways to promote CQI. With these tools in place, pharmacists will have the data necessary to evaluate their institution’s commitment to managing PAD. Established metrics include percentage of time patients are assessed for PAD, percentage of time patients are optimally sedated, and percentage of compliance with institution-specific protocols, among others. The result of combining education with CQI will be more desirable outcomes and improved quality of care.

Conclusion

The 2013 PAD guidelines represent a significant advancement in methods and presentation of recommendations compared with the previous iteration. Critical care team members should routinely evaluate PAD patients using valid and reliable scales, optimizing pain management and titrating sedatives to wakefulness except in patients who require deeper sedation. The benzodiazepines should be avoided as primary sedatives but can still be used in intermittent boluses when indicated. There are no effective pharmacologic treatments for delirium, but early mobilization appears to be beneficial.

Pharmacists are able to facilitate implementation of the PAD guidelines by developing protocols and order sets and providing real-time reminders and direct feedback to providers. As part of CQI efforts, they also can collect data to assess established metrics. Pharmacists should embrace the introduction of each new clinical practice guideline as an opportunity to help improve clinical outcomes.

References


