Chapter 15
Opioid Use in the Critically Ill Geriatric Patient

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Epidemiology

Older Adults in Intensive Care Unit (ICU)

Most epidemiological studies show, with some variability, an increase in the proportion of older patients (65 years and older) in the ICU population [1]. A clinical review states that older adults represent 42–52% of all United-States' ICU admissions and almost 60% of ICU-bed days [2]. The overall ICU admission rate is 0.72% for male and 0.47% for female patients and the highest peak in admission is seen for those between age 75 and 90 years (between 2.1 and 2.2%) [3].

Older Adults and Pre-ICU Opioid Exposure

Pre-ICU opioid use in geriatric ICU patients is prevalent and of great clinical importance. Clinic visits leading to opioid prescriptions for adults age 65 and older have more than doubled between 1999 and 2010 (from 4.1% to 9.0% ($p < 0.001$)) [4]. Opioids are among the most commonly used drugs in Canadian adults age 65 and

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older (15.7% in 2016 and 16% in 2014) [5, 6]. The incidence of new opioid use in this population is also quite significant. In a study performed by the Canadian Institute for Health Information on all opioids dispensed from community pharmacies in three major provinces in Canada, 8.1% of the studied population filled a new opioid prescription, with the highest incidence in 65 years and older individuals (12.2%) [7]. Accordingly, once on opioids, older patients consume them more regularly and for a much longer period [7]. Among opioid users, older adults have the highest proportion of chronic opioid use (prescribed for a duration of 90 days out of 100 days), approximately 24.8% for patients 65 years and older compared to 21.7% for those between 45 and 64 years old and 8.7% for those between 25 and 44 years old [7].

The prevalence of pre-ICU opioids exposure in older adults admitted to ICU is not as well studied. In a retrospective population-based study in Ontario on 711,312 patients older than 65 years, 35% of older adults admitted to ICU were opioid users. Of those, 48,363 (6.8%) were chronic users and 200,149 (28.1%) were intermittent users [8]. Furthermore, between 2002 and 2014, the prevalence of pre-ICU chronic opioid use increased significantly from 5.3% to 8.1% [8]. Another Canadian study on chronic opioid use in older adults before ICU admission showed that 11.2% of all chronic users had at least two or more opioid prescriptions filled concomitantly before hospital admission and their median morphine equivalent (MEQ) daily dosing before hospital admission was 32.1 mg (IQR, 17.5–75.0 mg MEQ) [9].

Pre-ICU opioid use is not without consequences. In the United States, between 2009 and 2015, an average of 52.4/10,000 ICU admissions were related to opioid overdoses, of which older adults (70 years and older) represented approximately 29% of all admissions [10]. The ICU proportion is comparable to overall hospital admissions related to opioid overdoses, which increases with age (12% were 30–39 years, 13% were 40–49 years, 19% were 50–59 years, 19% were 60–69 years, and 25% of patients were 70 years or older) [10]. Older adults seem more vulnerable to overdoses than their younger counterparts. Furthermore, irrespective of overdose, pre-ICU opioid exposure is associated with increased mortality in geriatric patients. Between 2001 and 2016, the largest relative increases of mortality related to opioids in the United States occurred among adults aged 55 to 64 years (754% increase) and those aged 65 years and older (635% increase) [11]. According to the previous Ontario ICU study, chronic opioid users and intermittent users had higher in-hospital mortality compared to non-users (adjusted odds ratio (aOR): 1.12, 95% Confidence interval (CI), 1.09–1.15, $p < 0.0001$ for chronic users; aOR: 1.09, 95% CI, 1.07–1.11, $p < 0.0001$ for intermittent users) [8].

Older Adults and Opiate Use During and After ICU Stay

Opioid use is ubiquitous in the ICU setting. Most ICU patients receive some form of opioids as part of analgesia and sedation regimens. A Korean cross-sectional study on opioid use in ventilated ICU patients, between 2012 and 2016 showed an increase in median daily MEQ over time (21.6 in 2012 vs 30.0 mg in 2016, $p < 0.01$) [12]. The

annual increase in daily MEDs paralleled the reduction of benzodiazepine use [12]. This might reflect compliance to new analgesia-sedation guidelines prioritizing optimal pain management through both opioids and other co-analgesics [13]. Just like pre-ICU opioid exposure in older patients, opioid use during an ICU stay is associated with adverse outcomes. Studies have reported a higher risk of longer delirium duration and respiratory depression [14, 15]. Adults aged between 71 and 80 had 5.4 times the risk of respiratory depression (95% CI, 2.4–11.8) and those 80 years and above had 8.7 times (95% CI, 3.8–20.0) when compared to younger adults (45 years and less) [15].

Opioid use after ICU discharge has not been extensively studied in older adults. The previous Canadian study revealed that among chronic opioid users who survived their ICU stay, 22.0% had filled prescriptions for a higher daily MEQ compared with prehospitalization at 6 months after hospital discharge, 19.8% were unchanged, 21.5% had a lower dose, and 36.7% had no prescriptions filled at all [9]. Being a medical patient (compared to a surgical one), having fentanyl as the primary opioid on hospital admission and a concurrent consumption of benzodiazepine on hospital admission were independently associated with an increased odd of continuing opioids at 6 months after discharge [9]. Interestingly, the overall median MEQ increased from 32.1 mg (IQR, 17.5–75.0 MEQ) to 39.8 mg (IQR, 20.0–93.1), $p < 0.0001$) for those who filled at least one opioid prescription at 6 months after discharge. This might reflect a change in opioid prescription patterns where higher potency medications are increasingly being prescribed. In the Ontario population study, the proportion of codeine prescriptions dropped from 42.8% before admission to 32.5% on 180-day after discharge, while hydromorphone and fentanyl prescriptions rose from 13.9% and 11.6% to 18.1% and 15.5%, respectively (Fig. 15.1) [9]. Similarly, the previous Korean study showed that during the 2012 and 2016 period, morphine use decreased, while fentanyl use increased [12].

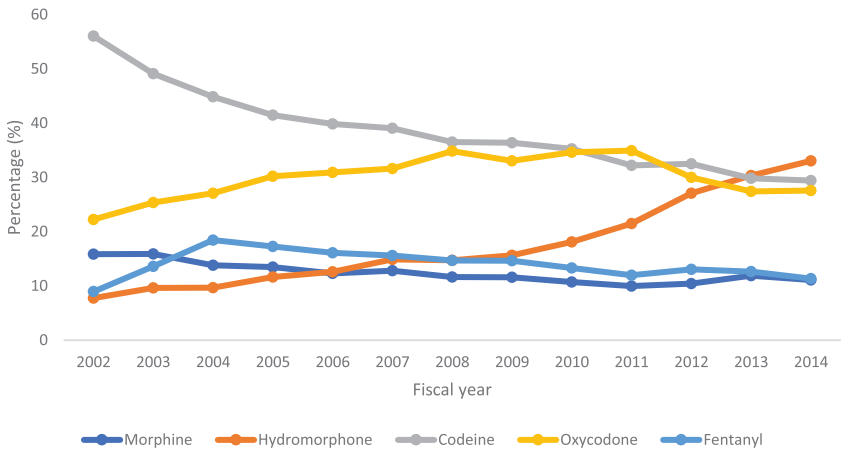

Fig. 15.1 Trends in opioid use before critical illness among 65 years and older patients in Ontario (2002–2015). (From Wang et al. [8]. With the authorization (pending) of Elsevier Inc.)

Judicious use of opioids in the ICU setting is critical considering the adverse effects they can cause. Higher opioids doses (64.6 ± 91.9 vs 32.9 ± 60.2 mg of morphine equivalents), independently of age, were associated with physical restraint use, in a retrospective study of 711 ICU mechanically ventilated patients with a mean age of 61 ± 16.7. Every 10 mg of morphine equivalents dose raised the risk of being physically restrained by 4% [16]. For reason, some authors have deemed opioid use as a potentially inappropriate medication when prescribed during ICU stay [17, 18]. Indeed, leaving a prescription active on ICU discharge when pain is no longer an issue might lead to overprescribing and inappropriate use. This does not mean opioids should be completely absent in ICU care but better, that adequate and regular pain assessment is instrumental for optimal patient management.

Pain Experience in Older Adults in Intensive Care Units

Managing pain and prescribing opioids in older ICU patients are challenging. There is a paucity of evidence and no trials specifically addressing this subgroup of patients. Nonetheless, clinical objectives are:

1. Titrating analgesia and lowering opioid doses
2. Improving analgesia quality by taking into consideration nociceptive and neuropathic pain
3. Reducing side effects

Pain in the ICU and Pain in Older Adults: Need for Monitoring

Guidelines for prevention and management of pain in ICU recommend routine pain assessment and treatment before considering sedative agents [13]. Treating older adults should not be any different. To that extent, adjunct medication to opioids for pain management has to also be considered in older ICU populations [19]. Individualizing treatment is a must since painful experiences seem to differ for the older adults compared to their younger counterparts.

Nociceptive and Neuropathic Pain in ICU

Nociceptive and neuropathic pain can coexist for ICU patients. Nociceptive pain is associated with nociceptor activation consequently to non-neural tissue damage. Neuropathic pain is due to central or peripheral somatosensory nervous system abnormalities or both. Normal aging is not associated with either nociceptive or neuropathic pain (e.g., diabetes-related neuropathic pain, chronic pain associated with osteoarthritis), but related comorbidities are more prevalent in older age [20]. For ICU patients, surgery, trauma, and invasive procedures induce additional pain.

Procedural pain (endotracheal suctioning or wound care pain) refers mostly to nociceptive pain, as long as neural tissue is not damaged. A prospective study on 3851 patients (median age of 62 (IQR 50–73)) undergoing 4812 procedures looked at pain intensity associated with 12 common ICU procedures [21]. Pain intensity during the procedure increased significantly from baseline ($p = 0.001$). Chest tube removal (pain evaluation of 5/10 (3–7) on the numeric rating scale), wound dressing removal (4.5 (2–7)), and arterial line insertion (4 (2–6)) were the three most painful procedures. A pre-intervention painful state and scheduled pre-intervention opioid exposure (preemptive analgesia) were associated with higher pain intensity [21]. Those results suggest the importance of basal pain evaluation and treatment *before* an ICU procedure. They highlight the concept of central sensitization. In either intense or repeated noxious stimuli, the subsequent stimuli can become amplified by sensitization of the nociceptive system [22, 23]. A review of the age effects on pain sensitivity supports that dorsal horn nociceptive neurons become sensitized with advancing age [22]. This enhances the theoretical pain vulnerability of older adults. The unexpected association with opioid use could be explained by an insufficient opioid dose or a lack of adequacy between time to peak effect and time of the procedure [21]. This leads to the important concept of preemptive analgesia, which aims to prevent central sensitization. Animal experiments demonstrated preemptive analgesia efficacy on initial and subsequent pain when analgesia was administered before the onset of the noxious stimulus [22]. Opioid-induced hyperalgesia, a phenomenon of increased sensitivity to painful and nonpainful stimuli secondary to high dose and high potency opioids, is another potential explanation [24]. This has been linked to opioid metabolites (morphine-3-glucuronide (M3G) or hydromorphone-3-glucuronide (H3G)) and activation of central nervous system N-methyl-D-aspartate (NMDA) receptors [25]. To our knowledge, it has not been studied in older adults.

Neuropathic pain can also be seen in some subgroups of ICU patients such as following cerebral ischemic stroke or post-surgery [26]. A cross-sectional survey of 2043 postsurgical patients (mean age 57 ± 12.37) reported a prevalence of persistent pain of 40.4% with an association between self-reported hypoesthesia or hyperesthesia (sensory abnormalities commonly seen in neuropathic pain) symptoms and the presence and intensity of persistent post-operative pain [26]. Neuropathic pain can occur after nerve damage secondary to procedural or surgical interventions. Age does not appear to be associated with an increase incidence of postsurgical neuropathic pain, although older age is associated with prolonged and increased thermal sensitivity, hyperalgesia, and allodynia [27]. Those results highlight the importance of evaluating and treating neuropathic pain, especially in older ICU patients.

Aging Pain Physiology and Homeostenosis

Emerging evidence suggests that efficient response to pain in older adults might be affected by homeostenosis, in opposition to homeostasis. Homeostasis is an adaptive response to internal and external variations, such as glucose levels or ambient

temperature. With complex and dynamic physiologic mechanisms, such as insulin response and vasoconstriction, the organism tries to maintain normal physiologic constancy. Homeostenosis, the diminished capacity to face those challenges, is a well-known concept in geriatrics. It explains the vulnerability of many older adults in acute illness when compared to younger counterparts. An example of homeostenosis is the normal insulin resistance rise and longer time taken to reach a euglycemic state after hyperglycemia in older adults [28, 29]. Vulnerability in older adults comes from inherently diminished biological, psychological, and social reserve. A limited activation and feedback of the neuroendocrine, immune, and autonomic nervous system, altered opioid receptors, and modified pharmacokinetics diminish some older adult capacity to cope with pain [30]. Animal models have demonstrated a decrease in pain inhibition neurons in the dorsal horn region with aging. The loss of those inhibitory serotonin and noradrenaline neurons has been related to the increased nociceptive activity [31, 32]. Experimental studies have explored *offset analgesia*, defined as a disproportional pain reduction between older and younger adults caused by the slight pain of thermal stimulus. Older subjects demonstrated reduced offset which might reflect an age-related endogenous inhibitory system reduction, therefore adding complexity in the management of older patients [33, 34].

Variability in Pain Experience

Besides the possible change in pain physiology, the pain might be experienced differently for older adults. Atypical presentation of medical conditions is well described in geriatrics. The absence of pain, fever, or leucocytosis where one would expect, makes it harder to investigate and diagnose older adults [35]. For example, absence or difference in typical localization of pain in myocardial infarction has been associated with worst outcomes in older patients [36, 37]. In another retrospective study (15,670 charts), pain severity in the emergency department (on a scale of 1–10) was compared between older and younger adults. Reported pain was lower in older age patients for a diagnosis like appendicitis, migraine/headaches, and renal colic [38]. This variability can partly be explained by sex, education, or racial differences [39]. It also underlines the difficulty in pain assessment in the intensive care setting.

Pain Evaluation in Older Adults Able to Communicate and Unable to Communicate

There are no pain evaluation scales designed specifically for older ICU patients. Existing scales (Visual Analogue scale (VAS), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS)) are used for all adult ICU patients, independent of their

age. Few studies have looked at the reliability and validity of these scales in older patients. A psychometric study compared those three scales and other commonly used scales in 338 chronic pain patients, evenly distributed across different age brackets (<35, 35–44, 45–54, 55–64, 65–74, and 75 years and older). Difficulty in scoring pain (differentiation between weak, moderate, and strong pain scores) was associated with increasing age. Difficulty in scoring pain was mostly seen with VAS, with all scales deemed valid but the VRS preferred by the 75 years and older patients (VDS preference: 42.9%, NRS: 28.6%, horizontal VAS: 11.4%, and vertical VAS 17.1%) [40]. In a validity study of 75 chronic pain patients (mean age 49.8), difficulty in scoring pain with VAS was also related to increasing age ($r = 0.31$, $p < 0.01$) [41]. Those results favor the VRS scale for pain evaluation in older age ICU patients able to communicate.

For patients unable to communicate, it is even more challenging. Most tools are scales that take into account body movement, facial expressions, and ventilator compliance if applicable. The Behavioral Pain Scale (BPS) and Critical Care Pain Observation Tool (CPOT) are scales recommended and most frequently employed [42–44]. One must be careful when interpreting body movements for pain assessment, even in lightly sedated patients. Restlessness has been recognized as a significant pain sign in cognitively impaired older adults [45]. Moreover, the absence of movement can be a sign of undertreated pain. In a cohort of cognitively impaired older adults (mean age 83.2, SD7.7) who underwent surgical repair of a hip fracture, movement was found to correlate with a pain-free state [46]. Experiencing pain made patients more reluctant to move. Age, comorbidities, medication, critical illness, and pain itself might induce delirium [47–50], which brings even more complexity in pain recognition and evaluation.

Pain scales (BPS, VAS, and NRS) were compared in an ICU study of 113 critically ill patients (mean age 66 ± 15). In responsive patients, a high correlation between NRS and VAS was found ($r = 0.84$, $P < 0.001$). In ventilated patients, a moderate correlation was found between the NRS and the BPS ($r = 0.55$, $P < 0.001$) [51]. This suggests pain underestimation may occur in an observer-based evaluation. New pain assessment modalities integrating multiple physiological parameters are being developed and have shown efficacy and usefulness in monitoring pain in the perioperative setting [52]. But until it is validated for ICU patients, physicians must familiarize themselves with the existing scales and understand the potential pitfalls of their application in older ICU patients.

Pain Outcome for Elderly Adults in ICU

Undertreating pain is a risk factor for delirium. Among adults with a hip fracture, patients who received less than 10 mg of IV morphine equivalents per day had an increased risk of delirium, compared to patients who received a higher

dose (RR 5.4, 95%CI 1.3–4.5) [53]. In another prospective study of 820 ICU patients, delirium incidence was higher in those who used a lower mean daily opioid dose (8.9 ± 24.3 mg morphine equivalents) compared to those using a higher mean of daily opioid dose (17–79 mg morphine equivalents) [54]. A systematic review of six observational studies in surgical settings concluded that meperidine was associated with an increased risk of delirium when compared to non-opioids. On the other hand, morphine, fentanyl, oxycodone, and codeine were not associated with delirium when compared to non-opioid and hydromorphone had the lowest association with delirium [55]. While the task is difficult, bedside providers must not underestimate the importance of pain in older ICU patients, have an adequate pharmacokinetic and dynamics of opioid medication, and use a personalized approach in managing each patient.

Opioid Analgesics, Non-opioid Analgesics, and Analgesic Alternatives

Age-Related Opioid Pharmacokinetics and Pharmacodynamics

Pharmacokinetics, which refers to absorption, distribution, metabolism, and drug elimination, and pharmacodynamics, which refer to the drug's effects, are subject to change in older adults. Generally speaking, opioids have a greater potency with age even after adjusting for age-related pharmacokinetic changes [56]. Therefore, starting with a lower dose is always a good rule of thumb [56]. More specifically, age, genetic polymorphisms, comorbidities, and concurrent medications contribute, independently and interdependently, to pharmacokinetics variability [57–59]. Some of those age-related modifications are well established while others report conflicting evidence. Therefore, predicting opioids effects and side effects in one individual is a daily reality for ICU providers. An acute illness or medical instability brings further complexity in the care of older adults. There is not one opioid that perfectly fits the wide variety of clinical situations. A network meta-analysis of 32 randomized controlled trials compared ten opioids in chronic pain analgesia. Patient satisfaction was similar with hydromorphone, oxycodone, and morphine [60].

Moreover, the vulnerability of older patients to the adverse effects of opioids strongly supports an individualized approach to care. Generating guidelines for clinical practice would be difficult and hazardous. In the following section, the most often seen and used opioids in the ICU setting will be discussed with some key concepts in pharmacokinetics and dynamics related to the older adult population (Table 15.1).

Table 15.1 Age-related opioid pharmacokinetics particularities and recommendations

Opioid	Distribution	Metabolism	Excretion	Recommendation
Fentanyl	Expected to ↗ [1, 2] ↗ intercompartmental clearance (faster redistribution between plasma and fat [3] compartment)	Phase I hepatic metabolism (CYP3A4) expected to be ↘ [4, 5]	Renal excretion ↘ [4] no active metabolite ↗ risk of tissue accumulation [6]	Use ↘ dose adequate to relieve pain or as intermittent boluses [6]
Hydromorphone	Expected to ↗ [1, 2]	Phase II hepatic metabolization glucuronidation [7], which is preserved through aging [5]	Renal excretion ↘ [4] Mostly excreted in active metabolite: H3G [8] ↗ risk of accumulation	Use ↘ dose and ↘ dose frequency adequate to relieve pain
Morphine	Expected to ↘ [9, 10]	Phase II hepatic metabolization glucuronidation [11], which is preserved through aging [5]	Renal excretion ↘ [11, 12] Mostly excreted in active metabolites: M3G and M6G [8, 13, 14] ↗ risk of accumulation	Use ↘ dose and ↘ dose frequency adequate to relieve pain Theoretical risk of higher clinical neurotoxicity: morphine is less potent than hydromorphone. requested higher dose raise active metabolites level

Refs. [59, 61–63, 65, 72–79, 81]
CYP3A4 cytochrome P450 3A4, *HG3* hydromorphone-3-glucuronide, *M3G* morphine-3-glucuronide, *M6G* morphine-6-glucuronide

Fentanyl

Intravenous fentanyl is often used to achieve analgesia in the critically ill. It is a highly lipophilic molecule [61, 62]. Age-associated reduced lean body mass and total body water leads to a proportionally higher fat mass percentage. Consequently, fentanyl is expected to have a higher volume of distribution in older adults [61, 62]. Also, fentanyl has a higher intercompartmental clearance

(faster redistribution between plasma and fat compartment) in older adults when compared to younger ones. One study on 337 adults 57 years (± 15 (range 19 to 87)) reported an approximately four- to fivefold faster distribution in tissues (14.59 ± 5.64 L/kg/h vs. 3.18 ± 4.93 L/kg/h, $p < 0.05$) [63], which could suggest a faster nervous system penetration. Nonetheless, in a prospective study of 337 ICU patients, age was not associated with volume of distribution or intercompartmental clearance. Weight, the occurrence of severe liver disease, and heart failure accounted for much more interindividual variability than age in this study, suggesting that the effects of chronic and acute organ dysfunction may have a much larger effect than age [64]. Fentanyl is metabolized by the liver through the cytochrome P450 (CYP) 3A4 and has no active metabolites [59]. The P450 pathway is part of phase I hepatic metabolism and is known to be attenuated by aging [65] in opposition to phase II hepatic metabolism, which is not significantly affected by age [66]. One of the hypotheses for this phase I change is a lower hepatic blood flow (1015 ± 163 ml/min for 75 years and older vs. 1514 ± 250 ml/min for the 45 years and less group, $p = 0.00223$ [67]) and liver volume reduction with age [68–70]. Moreover, drug interactions are to be taken into consideration with all other medications dependent on CYP3A4 due to potential drug-drug interactions [59]. For example, most anticonvulsant agents (carbamazepine, phenytoin) [71] are CYP3A4 inducers, and fluoxetine, haloperidol, nortriptyline, and sertraline are inhibitors. Ultimately, fentanyl is eliminated almost exclusively by the kidney. Renal elimination is involved in all types of opioid pharmacokinetics [59]. Aging is associated with a reduced renal excretion, hence prolongation of elimination half-life due to a reduced renal mass and renal blood flow [58]. Therefore, fentanyl does offer the advantage of no active metabolite, but physicians need to take into consideration the risk of tissue accumulation and use the lowest perfusion dose adequate to relieve pain or as intermittent boluses [72].

Hydromorphone

Hydromorphone is another highly lipophilic opioid. It can be administered intravenously, as subcutaneous injections or it can be given orally. It is extensively metabolized by glucuronidation (hepatic phase II) [73], which is preserved through aging [65]. It does not use the CYP3A4, as fentanyl does, and therefore has a low risk of interactions. The main active metabolite is hydromorphone-3-glucuronide (H3G). H3G intracerebral infusion in rats induces neuroexcitatory side effects (allodynia, myoclonus, and seizure) [74] but no human studies have reported clinical safety issues [73]. No data on adverse effects in ICU patients were found, but some were reported in the context of chronic pain management. In the previously cited network meta-analysis of 32 non-ICU randomized controlled trials, there was no significant difference in adverse events or study withdrawal when hydromorphone was

compared to other opioids [60]. Most of the hydromorphone is renally excreted in H3G. Because of its pharmacokinetic properties, hydromorphone might be a safer opioid for intermittent use. Due to its distribution in fat tissues and because of its renal clearance, HG3 can still accumulate and requires vigilance, especially in those suffering from acute kidney failure.

Morphine

Unlike the above two drugs, morphine is a hydrophilic molecule [75]. Therefore, a lower volume distribution is expected because of the lean body mass reduction in older age. Studies on healthy participants comparing older to younger adults showed either no difference or a trend to a smaller volume of distribution for morphine [76, 77]. Morphine's hepatic metabolism depends on a glucuronidation reaction (phase II) and is age-independent [75]. Morphine is metabolized into two active metabolites: Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G has no analgesic activity but is assumed to have a dose-dependent excitatory behavior (allodynia, hyperalgesia, myoclonus, and seizures) [74, 78, 79]. These effects have been suggested in animal models but have not been well elucidated in humans [79]. The other metabolite, M6G, is responsible for the analgesic effect [80]. Morphine and its active metabolites are excreted by the kidneys [75] and are at higher risk of accumulation because of reduced renal function with age [81]. Morphine clearance is lower in older than in younger adults (1.33 ± 0.12 vs 2.05 ± 0.08 ml/kg/min, $p = 0.01$). Some studies support an increased opioid pharmacodynamic effect with morphine and increased receptor affinity [66, 82, 83]. Glomerular filtration rate decreases and raises the risk for opioids or opioid metabolite toxicity. All considered, morphine is a safe choice among older ICU patients without renal failure. With renal impairment, studies have shown a level of H3G approximately 100 times that of normal plasma concentrations, although without showing clinical neurotoxicity [84]. Because morphine is less potent than hydromorphone, the neurotoxic effects might occur more frequently than with hydromorphone, although this remains speculative.

Codeine

Codeine, a pro-drug of morphine, is mostly known in its oral formulation and is not often used in the ICU setting. Codeine is metabolized by phase I hepatic enzymes, CYP2D6 [85]. CYP2D6 polymorphism produces unpredictable effects [57] in older as in younger adults. With morphine as the active metabolite and because of the known polymorphisms, there is little use of codeine in the adult ICU setting.

Oxycodone

Oxycodone has a low lipophilic profile that resembles that of morphine [86]. It has a low "first-pass" metabolism [87] and is only accessible for the enteral route in Canada and in the United States. CYP 3A4 (and partly CYP2D6) metabolizes oxycodone in oxymorphone and noroxycodone [59] and is thus affected with reduced hepatic flow associated with advancing age [65]. Oxymorphone is responsible for the analgesic activity and as with fentanyl, drug interactions are to be considered with all other drugs that are CYP3A4 inhibitors and inducers. Oxycodone's phase I metabolites have to undergo phase II glucuronidation [59]. Oxycodone and its metabolites are excreted by the kidney [73] and their use in the ICU is limited due to its formulations (tablets and suppositories) and the risk of interactions with other drugs (if intolerance or allergy).

Non-opioid Analgesics and Analgesic Alternatives

Nonpharmacological adjuncts, including optimizing sleep, limiting catheters, tubes, and IV access, thermal therapy (cold and heat), are important to opioid-based pain management. Listening to music and sounds, simple massage, distraction, passive exercises, and emotional support are other types of nonpharmacological interventions. There is a need for more studies on the effect of those interventions in the ICU, but their simplicity and limited evidence support their use [88, 89]. Similarly, non-opioid analgesics and nonchemical approaches can lower opioid requirements and improve overall pain control. The most common ones will be described below.

Paracetamol/Acetaminophen

Paracetamol, or acetaminophen as it is known in the United States, is widely used as the first-line treatment of mild to moderate pain. Its hydrophilic properties provide a decreased distribution volume in older adults. Hepatic metabolism is mainly achieved by conjugation reactions (Phase II preserved through aging) with 5–10% metabolized by CYP450 2E1 to a toxic metabolite [90]. Because of the lower proportion of lean mass in older adults, weight-based paracetamol should be prescribed based on lean weight (15 mg/kg every 6 hours) to prevent hepatotoxicity [91]. More recently, in a randomized controlled study on 120 cardiac surgery patients, 60 years and older, IV acetaminophen (1 g/h every 6 hours for 8 doses) was compared to placebo and combined with dexmedetomidine or propofol. There were significant differences favoring acetaminophen vs. placebo

in delirium duration (median, 1 vs. 2 days; difference, −1 [95% CI, −2 to 0]), ICU length of stay (median, 29.5 vs. 46.7 hours; difference, −16.7 [95% CI, −20.3 to −0.8]), and breakthrough analgesia requirement (median, 322.5 vs. 405.3 μg morphine equivalents; difference, −83 [95% CI, −154 to −14]) [92]. This study clearly demonstrates the beneficial effect of non-opioid analgesics as adjunctive therapy in an acute care setting.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are often not recommended in critical illness because of bleeding risk, renal impairment risk, or vulnerability to renal failure in older adults. NSAIDs are also highly protein-bound drugs [93] which raises the risk of drug-drug interaction. Guidelines usually are cautious and do not suggest routine use of COX-1 selective NSAIDs [13]. This rationale is even more pertinent in older adults. Nonetheless, NSAID COX-1 selective can be an option for some older adults, with caution for the potential renal or bleeding risk mentioned. For example, it could have an adjunctive pain managing benefit in post-surgical pain. Some clinicians will add proton-pump inhibitors to reduce upper-gastrointestinal events [18]. Selective COX2 inhibitors are more effective in preventing gastrointestinal events but are associated with cardiovascular events in older adults [94]. If NSAID is chosen as a non-opioid analgesic, a limited and definite time of trial is recommended.

Sodium Channel Blocker/Gabapentinoids

Sodium channel blockers are recommended for lowering the required opioid dose and for improving analgesia, especially in the setting of neuropathic pain [13]. Pregabalin has been associated with reduced total oxycodone consumption and with significantly lower postoperative pain incidence at 3 months in the cardiovascular surgery population (mean age 79.5 (75–91)) [95]. Pregabalin and gabapentin are the preferred agents for older adults. Caution on potential side effects is necessary. Dizziness, somnolence, and fatigue are common (>10%) [96, 97]. The 2019 American Geriatric Society Beers Criteria for older adults recommend avoiding the combination of pregabalin or gabapentin with opioids because of an increased risk of sedation-related adverse events [18]. However, when the combination aims to reduce the opioid dose, caution remains but the rationale supports the intervention. Carbamazepine, another sodium channel blocker, is a strong hepatic inducer CYP2C9 and CYP3A4 (auto-induction) and is implicated in numerous drug-drug interactions and therefore is less ideal [98].

Alpha 2 Agonists

Dexmedetomidine and clonidine have analgesic, anxiolytic, and sedative effects [99]. The pharmacokinetics and dynamics of dexmedetomidine in older adults have not been well documented. Dexmedetomidine, a highly protein-bound drug, is metabolized by the liver via glucuronidation (hepatic phase II) to inactive metabolites and is not influenced by renal impairment [100, 101]. In a cohort study of older post-abdominal surgery adults, use of dexmedetomidine reduced morphine consumption in the 72 hours following surgery (median difference – 9.0 mg [95% CI –10.0, −6.0], $P < 0.001$), lowered the perception of pain on the NRS scale (the median difference between −1 and −2 at time 4, 24, 48, and 72 hours after surgery, $p < 0.01$) and subjective quality of sleep was improved for the first night after surgery ($p = 0.031$) and for the night after, $p < 0.001$) [102]. Although the associated side effects, bradycardia, and hypotension [101] are to be considered before use [103], dexmedetomidine requires a continuous IV infusion which limits its clinical application.

Conclusion

Individualizing pain management approaches for the older adult ICU patient is key. Older adults' presence in the ICU and their generous exposure to opioids is rising, emphasizing the importance of a rationale for safe opioid use in that population. Individualizing opioid utilization is particularly necessary in elder individuals due to important differences between young and older adults and because of growing interindividual variability with aging. While opioid medication can definitely lead to adverse effects in ICU patients, judicious choices based on pharmacokinetics and dynamics can make them safe for older adults in ICU.

References

1. Flaatten H, et al. The status of intensive care medicine research and a future agenda for very old patients in the ICU. Intensive Care Med. 2017;43(9):1319–28.
2. Marik PE. Management of the critically ill geriatric patient. Crit Care Med. 2006;34 (9 Suppl):S176–82.
3. Garland A, et al. Epidemiology of critically ill patients in intensive care units: a population-based observational study. Crit Care. 2013;17(5):R212.
4. Steinman MA, et al. Use of opioids and other analgesics by older adults in the United States, 1999–2010. Pain Med. 2015;16(2):319–27.
5. Canadian Institute For Health Information. Drug use among seniors on public drug programs in Canada. Ottawa: Cihi; 2014.
6. Canadian Institute For Health Information. Drug use among seniors in Canada, 2016. Ottawa: Cihi; 2018.

7. Canadian Institute For Health Information. Opioid prescribing in Canada: how are practices changing? Ottawa: Cihi; 2019., Canadian Institute For Health Information.
8. Wang HT, et al. Trends in opioid use before critical illness among elderly patients in Ontario. J Crit Care. 2020;55:128–33.
9. Wang HT, et al. Opioid use after ICU admission among elderly chronic opioid users in Ontario: a population-based cohort study. Crit Care Med. 2018;46(12):1934–42.
10. Stevens JP, et al. The critical care crisis of opioid overdoses in the United States. Ann Am Thorac Soc. 2017;14(12):1803–9.
11. Gomes T, et al. The burden of opioid-related mortality in the United States. JAMA Netw Open. 2018;1(2):E180217.
12. Jung SY, Lee HJ. Utilisation of medications among elderly patients in intensive care units: a cross-sectional study using a nationwide claims database. BMJ Open. 2019;9(7):E026605.
13. Devlin JW, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):E825–73.
14. Pisani MA, et al. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. Crit Care Med. 2009;37(1):177–83.
15. Cepeda MS, et al. Side effects of opioids during short-term administration: effect of age, gender, and race. Clin Pharmacol Ther. 2003;74(2):102–12.
16. Luk E, et al. Predictors of physical restraint use in Canadian intensive care units. Crit Care. 2014;18(2):R46.
17. Morandi A, et al. Inappropriate medication prescriptions in elderly adults surviving an intensive care unit hospitalization. J Am Geriatr Soc. 2013;61(7):1128–34.
18. American Geriatrics Society. Beers Criteria Update Expert Panel, American Geriatrics Society 2019 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674–94.
19. Erstad BL. Implications of the opioid epidemic for critical care practice. J Am Coll Clin Pharm. 2019;2:161–6.
20. Reid MC, Eccleston C, Pillemer K, Management of chronic pain in older adults. BMJ. 2015;350:H532.
21. Puntillo KA, et al. Determinants of procedural pain intensity in the intensive care unit. The Europain(R) study. Am J Respir Crit Care Med. 2014;189(1):39–47.
22. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2–15.
23. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10(9):895–926.
24. Rivat C, Ballantyne J. The dark side of opioids in pain management: basic science explains clinical observation. Pain Rep. 2016;1(2):E570.
25. Chau DL, et al. Opiates and elderly: use and side effects. Clin Interv Aging. 2008;3(2):273–8.
26. Johansen A, et al. Persistent postsurgical pain in a general population: prevalence and predictors in the Tromso study. Pain. 2012;153(7):1390–6.
27. Yezierski RP. The effects of age on pain sensitivity: preclinical studies. Pain Med. 2012;13 Suppl 2:S27–36.
28. Defronzo RA. Glucose intolerance and aging: evidence for tissue insensitivity to insulin. Diabetes. 1979;28(12):1095–101.
29. Kalyani RR, Egan JM. Diabetes and altered glucose metabolism with aging. Endocrinol Metab Clin North Am. 2013;42(2):333–47.
30. Karp JF, et al. Advances in understanding the mechanisms and management of persistent pain in older adults. Br J Anaesth. 2008;101(1):111–20.
31. Ko ML, et al. The effects of aging on spinal neurochemistry in the rat. Brain Res Bull. 1997;42(2):95–8.
32. Iwata K, et al. Plastic changes in nociceptive transmission of the rat spinal cord with advancing age. J Neurophysiol. 2002;87(2):1086–93.

33. Naugle KM, et al. Offset analgesia is reduced in older adults. Pain. 2013;154(11):2381–7.
34. Naugle KM, et al. Loss of temporal inhibition of nociceptive information is associated with aging and bodily pain. J Pain. 2017;18(12):1496–504.
35. Limpawattana P, et al. Atypical presentations of older adults at the emergency department and associated factors. Arch Gerontol Geriatr. 2016;62:97–102.
36. Grosmaitre P, et al. Significance of atypical symptoms for the diagnosis and management of myocardial infarction in elderly patients admitted to emergency departments. Arch Cardiovasc Dis. 2013;106(11):586–92.
37. Breining A, et al. Determinants of clinical presentation on outcomes in older patients with myocardial infarction. Geriatr Gerontol Int. 2018;18(12):1591–6.
38. Daoust R, et al. Impact of age on pain perception for typical painful diagnoses in the emergency department. J Emerg Med. 2016;50(1):14–20.
39. Crimmins EM, Saito Y. Trends in healthy life expectancy in the United States, 1970–1990: gender, racial, and educational differences. Soc Sci Med. 2001;52(11):1629–41.
40. Peters ML, Patijn J, Lame I. Pain assessment in younger and older pain patients: psychometric properties and patient preference of five commonly used measures of pain intensity. Pain Med. 2007;8(7):601–10.
41. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain. 1986;27(1):117–26.
42. Young J, et al. Use of a behavioural pain scale to assess pain in ventilated, unconscious and/or sedated patients. Intensive Crit Care Nurs. 2006;22(1):32–9.
43. Gelinas C, et al. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420–7.
44. Dale CM, et al. Validation of the critical-care pain observation tool (Cpot) for the detection of oral-pharyngeal pain in critically ill adults. J Crit Care. 2018;48:334–8.
45. Nygaard HA, Jarland M. The checklist of nonverbal pain indicators (CNPI): testing of reliability and validity in Norwegian nursing homes. Age Ageing. 2006;35(1):79–81.
46. Feldt KS. The checklist of nonverbal pain indicators (CNPI). Pain Manag Nurs. 2000;1(1):13–21.
47. Van Rompaey B, et al. Risk factors for delirium in intensive care patients: a prospective cohort study. Crit Care. 2009;13(3):R77.
48. Inouye SK, et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med. 1993;119(6):474–81.
49. Inouye SK. Delirium in hospitalized elderly patients: recognition, evaluation, and management. Conn Med. 1993;57(5):309–15.
50. Van Rompaey B, et al. Risk factors for intensive care delirium: a systematic review. Intensive Crit Care Nurs. 2008;24(2):98–107.
51. Ahlers SJ, et al. Comparison of different pain scoring systems in critically ill patients in a general ICU. Crit Care. 2008;12(1):R15.
52. Bollag L, et al. The nociception level index (Nol) response to intubation and incision in patients undergoing video-assisted thoracoscopic surgery (Vats) with and without thoracic epidural analgesia. A pilot study. F1000Res. 2018;7:875.
53. Morrison RS, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci. 2003;58(1):76–81.
54. Ouimet S, et al. Incidence, risk factors and consequences of ICU delirium. Intensive Care Med. 2007;33(1):66–73.
55. Swart LM, et al. The comparative risk of delirium with different opioids: a systematic review. Drugs Aging. 2017;34(6):437–43.
56. Gupta DK, Avram MJ. Rational opioid dosing in the elderly: dose and dosing interval when initiating opioid therapy. Clin Pharmacol Ther. 2012;91(2):339–43.
57. Somogyi AA, Coller JK, Barratt DT. Pharmacogenetics of opioid response. Clin Pharmacol Ther. 2015;97(2):125–7.

58. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev. 2009;41(2):67–76.
59. Smith HS. Opioid metabolism. Mayo Clin Proc. 2009;84(7):613–24.
60. Meng Z, et al. Tolerability of opioid analgesia for chronic pain: a network meta-analysis. Sci Rep. 2017;7(1):1995.
61. Narayanan M, Venkataraju A, Jennings J. Analgesia in intensive care: part 1. BJA Edu. 2016;16(2):72–8.
62. Mclachlan AJ, et al. Clinical pharmacology of analgesic medicines in older people: impact of frailty and cognitive impairment. Br J Clin Pharmacol. 2011;71(3):351–64.
63. Ariano RE, Duke PC, Sitar DS. Population pharmacokinetics of fentanyl in healthy volunteers. J Clin Pharmacol. 2001;41(7):757–63.
64. Choi L, et al. Population pharmacokinetics of fentanyl in the critically ill. Crit Care Med. 2016;44(1):64–72.
65. Mclachlan AJ, Pont LG. Drug metabolism in older people--a key consideration in achieving optimal outcomes with medicines. J Gerontol A Biol Sci Med Sci. 2012;67(2):175–80.
66. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57(1):6–14.
67. Zoli M, et al. Total and functional hepatic blood flow decrease in parallel with ageing. Age Ageing. 1999;28(1):29–33.
68. Wynne HA, et al. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology. 1989;9(2):297–301.
69. Schmucker DL. Aging and the liver: an update. J Gerontol A Biol Sci Med Sci. 1998;53(5):B315–20.
70. Schmucker DL. Liver function and phase I drug metabolism in the elderly: a paradox. Drugs Aging. 2001;18(11):837–51.
71. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005;352(21):2211–21.
72. Pergolizzi J, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract. 2008;8(4):287–313.
73. Lotsch J. Opioid metabolites. J Pain Symptom Manage. 2005;29(5 Suppl):S10–24.
74. Smith MT. Neuroexcitatory effects of morphine and hydromorphone: evidence implicating the 3-glucuronide metabolites. Clin Exp Pharmacol Physiol. 2000;27(7):524–8.
75. Hospira. Morphine Sulfate injection label, Solution for Intravenous Use: U.S Food & Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019916s019,019917s012lbl.pdf. Accessed Nov 2019.
76. Baillie SP, et al. Age and the pharmacokinetics of morphine. Age Ageing. 1989;18(4):258–62.
77. Villesen HH, et al. Pharmacokinetics of morphine and oxycodone following intravenous administration in elderly patients. Ther Clin Risk Manag. 2007;3(5):961–7.
78. Labella FS, Pinsky C, Havlicek V. Morphine derivatives with diminished opiate receptor potency show enhanced central excitatory activity. Brain Res. 1979;174(2):263–71.
79. Andersen G, Christrup L, Sjogren P. Relationships among morphine metabolism, pain and side effects during long-term treatment: an update. J Pain Symptom Manage. 2003;25(1):74–91.
80. Hoskin PJ, et al. The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. Br J Clin Pharmacol. 1989;27(4):499–505.
81. King S, et al. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European palliative care research collaborative opioid guidelines project. Palliat Med. 2011;25(5):525–52.
82. Aymanns C, et al. Review on pharmacokinetics and pharmacodynamics and the aging kidney. Clin J Am Soc Nephrol. 2010;5(2):314–27.
83. Wilder-Smith OH. Opioid use in the elderly. Eur J Pain. 2005;9(2):137–40.

84. Wright AW, Mather LE, Smith MT. Hydromorphone-3-glucuronide: a more potent neuroexcitant than its structural analogue, morphine-3-glucuronide. Life Sci. 2001;69(4):409–20.
85. Naples JG, Gellad WF, Hanlon JT. The role of opioid analgesics in geriatric pain management. Clin Geriatr Med. 2016;32(4):725–35.
86. Poyhia R, Seppala T. Liposolubility and protein binding of oxycodone in vitro. Pharmacol Toxicol. 1994;74(1):23–7.
87. Purdue Pharma L.P. Oxycodone hydrochloride extended-release tablets, for oral use : U.S Food & Drug Administration. 2018. https://www.fda.gov/media/131026/download. Accessed Nov 2019.
88. Sandvik RK, et al. Pain relief from nonpharmacological interventions in the intensive care unit: a scoping review. J Clin Nurs. 2020;29(9–10):1488–98.
89. Martorella G. Characteristics of nonpharmacological interventions for pain management in the ICU: a scoping review. AACN Adv Crit Care. 2019;30(4):388–97.
90. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol. 2002;40(1):3–20.
91. Mian P, et al. Paracetamol in older people: towards evidence-based dosing? Drugs Aging. 2018;35(7):603–24.
92. Subramaniam B, et al. Effect of intravenous acetaminophen vs placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery: the dexacet randomized clinical trial. JAMA. 2019;321(7):686–96.
93. Verbeeck RK, Blackburn JL, Loewen GR. Clinical pharmacokinetics of non-steroidal anti-inflammatory drugs. Clin Pharmacokinet. 1983;8(4):297–331.
94. Solomon DH, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation. 2004;109(17):2068–73.
95. Pesonen A, et al. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. Br J Anaesth. 2011;106(6):873–81.
96. Ulc UC. Product monograph: prlyrica®, pregabalin capsules. 2020.
97. Ulc UC. Product monograph: prneurontin®, gabapentin. 2020.
98. Punyawudho B, et al. Population pharmacokinetics of carbamazepine in elderly patients. Ther Drug Monit. 2012;34(2):176–81.
99. Belleville JP, et al. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. Anesthesiology. 1992;77(6):1125–33.
100. De Wolf AM, et al. The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. Anesth Analg. 2001;93(5):1205–9.
101. Weerink MAS, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893–913.
102. Li HJ, et al. Dexmedetomidine in combination with morphine improves postoperative analgesia and sleep quality in elderly patients after open abdominal surgery: a pilot randomized control trial. PLoS One. 2018;13(8):E0202008.
103. Stamenkovic DM, et al. Chronic pain and chronic opioid use after intensive care discharge - is it time to change practice? Front Pharmacol. 2019;10:23.