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PEER REVIEW

Continuing Pharmacy Education

Combating the Opioid Epidemic: Innovative Strategies
in the Emergency Department

Clinical Pearl

Getting Started as a New Preceptor

Clinical Pearl

Aspirin's Disappearing Act – Updates on the Role of Aspirin
in Cardiovascular Disease

Original Research

Use of Pharmacy Residents to Increase Pharmacist
Involvement with Acute Cardiac Life Support

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Honoring the Past and Maintaining Relevance for the Future

Loriann De Martini, CEO of CSHP

The *California Journal of Hospital Pharmacy* (later renamed *California Journal of Health-System Pharmacy* or *CJHP*) was originally created more than thirty years ago at a time when CSHP was known as the California Society of Hospital Pharmacists. Designated at the time as the official publication of CSHP, it was introduced by then-Executive Vice President Max Ray as a replacement to previous communication vehicles including the *Voice*, *Clout* and the CSHP Newsletter. *CJHP* was originally conceived to provide members with professional practice news, organizational news, legislative and regulatory news of importance to pharmacy, and news about drugs and drug technology — all at a time when print media was a highly digested and essential medium of communication. The desire was for issues of *CJHP* to be relevant to contemporary pharmacy practice and to the CSHP member.

In the 30 years since *CJHP* was introduced, times have changed and along with it the pharmacy profession and pharmacy practice. The definition of health-system pharmacy has expanded to include a greater emphasis on population health and optimal medication use. The advent of board certification and refinement of post-graduate residency training has allowed health-system pharmacists to assume more specialized roles in the treatment and outcomes of patients and patient care teams. Technology has transformed how pharmacists can both treat and monitor patients through greater streamlined

communication and continually changing health information tools. And the California Society of Hospital Pharmacists has morphed into the California Society of Health-System Pharmacists to better reflect the changing profession and what its membership encompasses.

CSHP has worked throughout the years to support health-system pharmacists, pharmacy technicians and students and has prominently utilized e-mail and social media — current communication technologies with greater timeliness and efficiency — to help share news that was previously communicated to members through *CJHP*. To that end, CSHP and members of its Editorial Advisory Board have spent much time and consideration on how members prefer to receive and digest information and have made tireless efforts through the years to help refine *CJHP* in light of such evolving technology and need to redefine relevance. Such efforts included changing the focus of the journal to scientific/clinical articles, the introduction of the peer review process, and provisions of continuing education through reading articles in each edition (now becoming more digested via webinars that are increasing in popularity).

Similar to its purpose in the past, *CJHP*'s original purpose is now fulfilled by technologies previously unavailable during its inception — technologies that CSHP has embraced in order to meet the needs of today's members from a communications and educational

perspective. *CJHP* was an important tool for its time — for CSHP members who were reliant on the technologies available to them. However, CSHP recognizes that it must continue to evolve as an organization with what is now and continues to be modernizing pharmacy practice and today's health care practitioners. To deny such acknowledgment would mean relying on antiquated methodologies of organizational practices while ignoring the importance of staying relevant with the future.

With its mission now being carried out in other mediums, *CJHP* will cease operations as of the end of 2019. CSHP acknowledges and thanks the many members who've contributed immensely to its 30-year history including writers, peer reviewers and editorial advisory board members past and present. *CJHP*'s 30-year run is an unprecedented achievement and is embraced with immense pride and joy. CSHP will continue to identify ways of supporting members from a communications and educational perspective and remains committed to meeting the needs of its members past and present. ○



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**To Represent and Empower
Pharmacists and Pharmacy
Technicians Practicing in
Health-Systems to Promote
Wellness, Patient Safety and
Optimal Use of Medications**

CSHP vision

**Pharmacists are
Recognized as Leaders
in Wellness, Patient Safety
and the Optimal Use
of Medications**

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Peer Review

The California Journal of Health-System Pharmacy is a peer-reviewed publication!

Peer reviewed, or refereed, publications utilize an editorial process to ensure that the articles published are as scholarly as possible. From this point forward, when an article is submitted to *CJHP*, the editors will send it out to other (peer) pharmacists and clinicians in the same field to obtain their opinion as to the appropriateness of the manuscript for publication, the relevance to the field of study, and the quality of the research.

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Combating the Opioid Epidemic: Innovative Strategies in the Emergency Department

Kimberly J. Won, PharmD, BCCCP • Kevin A. Kaucher, PharmD, BCCCP

Introduction

The rate of opioid-related deaths continues to increase in the US, with the most recent data showing that about 68% of the 70,237 drug overdose deaths in 2017 involved an opioid.¹ One of the major contributors to the opioid problem is prescription opioids: when analyzing opioid prescription rates using IMS Health's National Prescription Audit, emergency medicine (EM) was the eighth leading specialty for highest opioid-prescribing rates – accounting for about 4.4% (12.5 million) of opioid prescriptions in the US – behind family medicine, general practice, internal medicine, surgery, dentistry, pain medicine, and advanced practice providers.^{2,3} Approximately 24% of all emergency department (ED) visits involve an opioid prescription and as the number of ED visits per year continues to increase, the number of opioid-related ED visits may also continue to increase.³ Since pain syndromes are the most common chief complaint for ED visits, avoiding opioid analgesics is likely not a viable solution as they are standards of care for many pain syndromes and are often required for certain conditions, such as long bone fractures and traumatic wounds. Thus, providing analgesia in the ED will need to continue but will also require alternative approaches.⁴

To face the challenges of the opioid epidemic, a multifaceted approach at national, state, hospital and organizational levels is warranted. Nationally, the Centers for Disease Control and Prevention (CDC) has created guidelines on prescribing opioids for chronic pain, and several agencies have developed opioid-related education and awareness programs.⁵ Additionally, several states have created their own opioid-prescribing guidelines including California.^{6,7} Though California is one of 22 states that actually has a drug overdose rate lower than the national average, California officials have still taken a proactive stance in implementing opioid-related legislation, including assembly bills (AB) mandating the utilization of California's prescription drug monitoring program (Controlled Substance Utilization Review and Evaluation System) (AB 528 and 1753); improving access to opioid rehabilitation and medication-assisted treatment (MAT) programs (AB 1642, 1512 and 1327); and providing a prescription for an opioid antagonist (ie, naloxone) to patients who are prescribed both an opioid and a benzodiazepine, have a total daily dose of opioids of 90 or more morphine milligram equivalents, and for any other patients who are at high risk for opioid overdose (AB 714 and 2760).^{5,6}

At the hospital level, many EDs have increased patient education on opioid abuse and access to mental health counseling. Some EDs have developed opioid reduction protocols, whereas others have strived to become “opioid-free.”^{7,8} Additionally, some EDs have started dispensing naloxone from the ED and there has been a recent increase in the number of EDs that are implementing processes to assist with induction therapy and referral to Opioid Treatment Programs (OTP) and MAT facilities

Learning Objectives:

After reading this article, the reader should be able to:

1. Identify evidence-based approaches of pharmacologic and non-pharmacologic alternatives to opioids for the treatment of pain in the emergency department.
2. Describe dosing strategies of pharmacologic alternatives to opioids that can be used in place of or in combination with opioid therapy to treat pain in the emergency department.
3. Compare the differences between FDA-approved medications used for the treatment of opioid withdrawal.
4. Identify the patient-centered outcomes that an emergency department-initiated buprenorphine program provides to patients.
5. Assess and titrate buprenorphine according to current recommended treatment practices.

Keywords

alternative to opioids, emergency department, medication-assisted treatment, opioid epidemic, pain

Requests for Information

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from the ED.^{9,10} To aid EM providers with opioid-related practices, the American Academy of Emergency Medicine (AAEM) has published evidence-based consensus guidelines for treating non-cancer-related pain in the ED. In addition, the American College of Emergency Physicians (ACEP) has developed provider resources (<https://www.acep.org/by-medical-focus/mental-health-and-substance-use-disorders/opioids/>) for prescribing opioids in the ED and managing opioid use disorder (OUD), as well as patient education handouts that EM providers can distribute to their patients.¹¹

Since pain remains one of the most frequent reasons for an ED visit, EM clinicians are uniquely faced with the challenge of limiting opioid use while still safely and effectively treating patients' pain. Failure to treat patients' pain could lead to further detrimental outcomes including psychological complications and post-traumatic stress disorder, decreased mobility, increased number of falls, and increased risk of coronary artery disease.^{4,12} The AAEM recently published a white paper to promote their opioid prescribing guidelines and to support the use of non-opioid alternatives or alternatives to opioids (ALTO) to treat pain in the ED, such as nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose ketamine (LDK), acetaminophen, anesthetics, and nitrous oxide.^{11,12}

Alternatives to Opioids (ALTO)

NSAIDs

NSAIDs are preferred non-opioid analgesics that can be used for both acute and chronic pain in the ED and are considered first-line treatments for renal colic, headache and other pain in the ED. They reduce pain by inhibiting cyclooxygenase-1 and -2 (COX-1/COX-2), which further leads to a decrease in prostaglandin synthesis. Conversely,

this decrease in prostaglandin synthesis also causes vasoconstriction of the renal afferent artery, so NSAIDs should be used with caution in patients with renal insufficiency and should not be used in patients with acute renal failure. COX-1 and COX-2 blockade with NSAIDs can affect platelets, resulting in increased risk of gastrointestinal hemorrhage and risk of a cardiovascular event (especially post-myocardial infarction). Aside from these considerations, NSAIDs are widely used for many pain-related indications in the ED. The variety of different available over-the-counter (OTC) and prescription NSAID products make this drug class an appealing option for treating pain both in the ED and in outpatient settings post-ED discharge.¹³

Diclofenac is an NSAID available in prescription-only oral and topical formulations. Diclofenac is dosed 18-35 mg orally three times a day, with peak concentrations occurring at roughly 60 minutes, for acute pain. Diclofenac is extensively metabolized by CYP2C9 and its topical solution formulation is mostly used to treat osteoarthritis of the knee. Diclofenac gel (Voltaren®) and patch formulations can provide localized pain relief with minimal systemic adverse effects, which make these products ideal for localized musculoskeletal pain. Diclofenac gel 2 g or 4 g should be applied up to four times a day to the affected area using the manufacturer-supplied dosing card. The maximum daily dose varies based on the location of the affected area. The diclofenac patch is an extended-release product that reaches peak concentrations in about 10-20 hours. The gel can be applied once or twice daily and is indicated for minor strains, sprains and contusions.¹⁴ Though these agents are ideal for localized pain, their long onset of action makes them less favorable for acute relief compared to more quicker-acting intravenous analgesics.

Ketorolac (Toradol®) is one of the commonly used NSAIDs in the ED because, in addition to its oral formulation, it is also available as an injectable solution. The recommended dose is 10-30 mg intravenously (IV) or 30-60 mg intramuscularly (IM), either as a single one-time dose or every 6 hours for pain (maximum 120 mg/day). Patients ≥65 years or who weigh <50 kg require a lower dose of 15 mg IV or 30 mg IM, either as a single dose or every 6 hours (maximum 60 mg/day). Regardless of the dose, ketorolac should not be used for >5 days.¹³ Doses <15 mg IV have also been found to provide adequate analgesic benefit compared to higher doses. A recent randomized, double-blind trial found that single doses of ketorolac 10, 15 and 30 mg IV all substantially reduced pain in 240 ED patients between 18 and 65 years of age with pain scores of ≥5 due to acute flank, abdominal musculoskeletal or headache-type pain. There were no significant differences in reported numerical rating scale (NRS) or adverse effects between the three doses. The most common adverse effects included dizziness, nausea and vomiting.¹⁴ Ketorolac is also available as a nasal spray (Sprix®) that is administered intranasally (not inhaled) for pain, including migraine-type pain.^{13,16}

Although NSAIDs are appropriate alternatives to opioids, they should be used with caution in elderly patients and patients with renal insufficiency, cardiovascular disease, heart failure, hypertension, or patients at high risk for gastrointestinal bleeding.^{12,13} As with all pain medications, NSAIDs should be used at the lowest effective dose to provide pain relief.¹² If a patient is not an appropriate candidate for NSAID therapy, acetaminophen may be another non-opioid analgesic option.

Acetaminophen

Acetaminophen has been shown to provide safe and adequate analgesia for acute pain in the ED. The AAEM recommends using acetaminophen either as monotherapy for mild pain or as adjunct for moderate-to-severe pain.¹² Acetaminophen is an ideal ALTO, especially for patients who are not appropriate candidates for NSAIDs (eg, high risk of bleeding or renal insufficiency). However, acetaminophen should not be used in patients with active hepatic disease or hepatic injury due to its risk for hepatotoxicity. Just like NSAIDs, acetaminophen is available OTC and in several different formulations (eg, oral tablets and solution). Acetaminophen is also available as a prescription-only IV formulation (Ofirmev®). The recommended dosing of IV acetaminophen for adults and adolescents weighing ≥ 50 kg is 1 g IV every 6 hours or 650 mg every 4 hours, with a maximum single dose of 1 g and a maximum total daily dose of 4 g. For children ≥ 2 years old and patients weighing < 50 kg, the recommended dose is 15 mg/kg IV every 6 hours or 12.5 mg/kg every 4 hours with a maximum single dose of 15 mg/kg (up to 750 mg) and a maximum total daily dose of 75 mg/kg (up to 3750 mg). Regardless of the dose, the minimum dosing interval between doses is 4 hours and it should be administered as a 15-minute infusion.¹³ Both the oral and IV formulations have a quick onset, between 3-5 minutes onset with the IV formulation and as quick as 11-60 minutes onset with the oral formulation.^{13,14} One main difference between the two formulations is price: a 1 g dose of the IV formulation can cost up to 40 times more than the cost of the oral equivalent.¹⁵ Since both formulations have been shown to achieve adequate analgesic relief without significant differences between the two formulations, it is hard to justify using the IV formulation unless patients cannot take oral medications. Additionally, acetaminophen is also available as a rectal suppository.¹³

Despite the expensive price, IV acetaminophen is commonly used in the ED for a variety of pain-related diagnoses including trauma, abdominal pain, migraine, renal colic, and more.¹⁶⁻²¹

A recent randomized controlled trial (RCT) compared IV acetaminophen 1 g to IV hydromorphone 1 mg in 206 adult patients presenting to the ED with acute abdominal, extremity, head/neck, back, or chest pain, with the trial looking to identify between-group differences in verbal changes to the NRS. At 5 and 30 minutes post-analgesia administration, both groups showed a decrease in verbal NRS pain scores; however, at 60 minutes post-analgesia the primary outcome favored the hydromorphone group. There was no significant difference between the number of patients requiring rescue analgesia from 0 to 60 minutes, but at 60 minutes more patients in the hydromorphone group declined additional analgesia when asked. The hydromorphone group also had a higher incidence of new-onset nausea and vomiting.¹⁷ Other studies comparing IV acetaminophen to morphine and NSAIDs have demonstrated similar results and have shown no difference in pain score reductions in the ED.¹⁸

IV acetaminophen has also been used for migraines in the ED.¹⁶ Compared to placebo, acetaminophen has not only been found to be effective in treating pain but also in improving functional viability, photophobia and phonophobia associated with migraines (with or without aura). A 2016 update by the American Headache Society (AHS) summarized RCTs evaluating acetaminophen for the treatment of migraine pain.¹⁹ One RCT involving 200 patients found no difference in pain scores between IV acetaminophen vs placebo and dexametoprolol, respectively, for treating migraine pain in the ED. Another RCT evaluated 148 patients presenting to the ED with migraine pain rated 6/10 or higher for at least

3 hours: randomized patients received either IV propacetamol 1 g (prodrug of acetaminophen) or oral rizatriptan 5 mg. Despite the IV propacetamol group having statistically higher pain relief based on visual analog scale (VAS) at 60 minutes post-analgesia administration, there was no significant difference between the two groups at 30 and 120 minutes. Based on the limited number of RCTs available and varying levels of evidence, the AHS concluded that IV acetaminophen “may be offered” (Level C recommendation) to adults who present to the ED with acute migraines. Conversely, IV metoclopramide, IV prochlorperazine, and subcutaneous sumatriptan are all pharmacologic options that should be offered (Level B recommendation) to adult patients presenting to the ED with acute migraines. There were no Level A recommendations for drugs that must be offered to patients presenting to the ED with acute migraines.¹⁶

In addition to migraine pain, IV acetaminophen has also been used for other headache pain. Meyering et al compared IV acetaminophen to placebo in 90 patients who presented to the ED with a migraine, tension headache, cluster headache, or general headache. All patients received IV diphenhydramine 50 mg and IV prochlorperazine 10 mg, and then were randomized to receive either IV acetaminophen 1 g or placebo. At 90 minutes post-study drug administration, 80% of patients in the IV acetaminophen group reported a statistically significant pain score reduction by two or more points from baseline (compared to 55% of patients in the placebo group).²⁰ This study did not differentiate patients by type of headache, but IV acetaminophen may be a reasonable option for patients who present with headache and cannot take oral medications.

A recent meta-analysis, which included the Panthan et al trial as well as four additional RCTs with <150 patients each, evaluated IV acetaminophen use for renal colic in the ED. Three of the studies found a significant VAS mean pain score reduction in patients receiving IV acetaminophen 1 g compared to IM piroxicam 20 mg and IV morphine 0.1 mg/kg, respectively. However, the two other small studies showed no significant difference in VAS pain score reduction between IV acetaminophen 1 g and IV morphine 0.1 mg/kg at 15 and 30 minutes. Overall, the weighted results of this meta-analysis concluded that there was a significant reduction in pain scores with IV acetaminophen compared to morphine, but no difference in comparison to NSAIDs.²¹

Acetaminophen is a ubiquitous analgesic agent that is considered noninferior to other analgesics, including opioids and NSAIDs. When used as adjunct therapy, acetaminophen can help to decrease the number of opioids needed to provide pain relief. Though there is a lack of studies on IV acetaminophen use in the US healthcare system, there are a limited number of RCTs from other countries. Overall, when compared to morphine for ED patients with renal colic or traumatic pain, IV acetaminophen has been shown to provide effective pain relief that is similar to or just as effective as morphine, with fewer adverse effects.^{17,21} When comparing oral to IV acetaminophen, there is no significant difference between the two formulations in terms of efficacy; however, given that IV acetaminophen is considerably more expensive than its oral formulation, the IV formulation should be reserved for those who cannot take oral medications.²²

Lidocaine

Lidocaine is an amide-linked local anesthetic that is associated with analgesic, anti-hyperalgesic and possibly anti-inflammatory properties.^{13,23} In

addition to properties such as sodium channel inhibition and nerve blockade, local anesthetics are emerging in literature as options to treat systemic acute pain in the ED, specifically IV lidocaine. Outside of the ED, IV lidocaine has been used for many years in the management of surgery- and cancer-related pain, chronic pain syndrome, postherpetic neuralgia pain, spinal cord injury pain and more.²⁴ Its use for acute pain in the ED has gained recent interest as clinicians are now using IV lidocaine for acute abdominal pain, renal colic, back pain, sickle cell crisis, and acute pain due to limb ischemia, migraine and trauma – including fractures – in the ED. The dosing for these indications have ranged from 50-100 mg along with weight-based dosing of 1-2 mg/kg (maximum dose up to 150 mg) of lidocaine 2% (without epinephrine) administered as a slow IV push over 2-5 minutes or as an infusion over 10-15 minutes for better tolerability.^{22,24} A retrospective chart review of 44 adult ED patients with nephrolithiasis, renal colic or obstructive uropathy received an average dose of 1.5 mg/kg IV lidocaine, either as a primary or rescue analgesic. IV lidocaine monotherapy, or in combination with ketorolac or morphine, demonstrated significant reductions in pain scores when used as a primary analgesic (average dose 117.2 mg; range 76-200 mg) and as a rescue analgesic (average dose 113 mg; range 60-200mg).²⁵

Lidocaine's quick onset of action makes it an ideal agent to treat acute pain with a good safety profile: some patients have reported transient vertigo, dizziness, tinnitus, perioral numbness or slurred speech with lidocaine use.²³⁻²⁵ However, lidocaine also has a short duration of effect which might not be as ideal. In addition to a solution for injection, lidocaine is also available in multiple topical preparations – including a transdermal patch, gel/jelly, cream and spray – which

may be preferred to localize pain relief and minimize systemic absorption.^{13,23} The lidocaine 5% transdermal patch has been shown to be safe and effective for both musculoskeletal (eg, acute and chronic low back pain or carpal tunnel syndrome) and neuropathic pain (eg, postherpetic neuralgia or diabetic neuropathy), but its onset of action may be a rate-limiting factor against its routine use in the ED.¹³

Ketamine

Ketamine is a phencyclidine derivative that non-competitively antagonizes the N-methyl-D-aspartate receptors in the central nervous system. Because of its rapid onset, ketamine has been used in the ED as an induction agent for rapid sequence intubation and procedural sedation at doses of 1-2 mg/kg IV – which provides about 5-10 minutes of anesthesia – and less commonly at 10 mg/kg IM to provide 12-25 minutes of anesthesia.^{13,14,26} In addition to amnestic effects, ketamine also has analgesic properties and has been used for several years to treat chronic pain in pain clinic settings and acute pain in intensive care units.²⁷ It was not until recent growing concerns for opioid misuse that ED providers found ketamine to be a favorable alternative or adjunct to opioids to manage acute pain in the ED.^{13,28,29} When used as an analgesic, the recommended off-label dosing is low-dose ketamine (LDK), also known as subdissociative-dose ketamine (≤ 0.5 mg/kg IV). A recent meta-analysis showed LDK (0.3-0.5 mg/kg IV) to be statistically noninferior to morphine as an analgesic.²⁸ Furthermore, when used as an adjunct to opioids, studies have reported lower needs for opioid morphine equivalents. At this time, ketamine is not recommended for migraine pain.^{18,19}

A recent randomized, double-dummy study evaluated the efficacy and safety between LDK 0.3 mg/kg slow 5-minute IV push vs short 15-minute infusion

in 48 adult patients presenting to the ED with an NRS >5 secondary to acute abdominal, flank, back, traumatic chest or musculoskeletal pain. There was no significant difference between the two groups with regards to changes in vital signs, reduction in pain score or the need for rescue medication. However, patients who received ketamine IV push experienced significantly greater feelings of unreality and sedation compared to patients who received ketamine infusion.²⁹ Thus, LDK administered as a quick 15-minute infusion should be considered to minimize adverse effects. While ketamine may be an appropriate ALTO, it should be used with caution in patients with a history of psychiatric disorders, including post-traumatic distress syndrome, since it can cause an emergence reaction in this patient population. However, this incidence seems to be lower with LDK compared to anesthetic doses of ketamine. Ketamine is also associated with laryngeal spasm, pulmonary edema and respiratory distress, and should be used with caution in patients who may have increased risks for these serious adverse effects.¹³

Acupuncture

In addition to pharmacologic alternatives to opioids, a novel non-pharmacologic ALTO in EM practice for the US is acupuncture. Acupuncture is recognized as a treatment modality by both the World Health Organization and National Institutes of Health and has traditionally been used to manage pain associated with chronic conditions, including musculoskeletal pain, headache, low back pain, etc. However, acupuncture's effectiveness and feasibility to treat acute pain in an emergency setting has been evaluated in Germany, South Korea, North Africa, Australia and, only recently, in the United States.^{30,31} Both traditional acupuncture and auricular acupuncture have been investigated for the treatment of spinal pain, limb fractures, migraines, and renal

colic in ED settings.³⁰⁻³² A pilot study conducted at a level I trauma center in California reported a significant decrease in pain measured via VAS immediately following acupuncture and at 30 minutes post-acupuncture in patients with acute musculoskeletal extremity pain due to a nonpenetrating injury.³¹ A more recent prospective, randomized, nonblinded study conducted in the ED of a tertiary care facility in Tunisia compared acupuncture to IV titrated morphine (0.1 mg/kg, followed by 0.05 mg/kg every 5 minutes; maximum dose 15 mg) in patients with abdominal pain, lower back pain, headache, upper or lower limb pain, or other pain. The acupuncture group had significantly more patients who achieved a 50% decrease in pain score via VAS compared to the morphine group. Though patients in the morphine group had a significantly quicker resolution time compared to the acupuncture group, those patients also experienced significantly more adverse effects (eg, dizziness, nausea/vomiting) than those in the acupuncture group.³¹

Conversely, one of the largest randomized controlled trials in acupuncture to date evaluated the effectiveness and patient satisfaction with acupuncture in 529 patients presenting to one of four Australian EDs with lower back pain, migraine, or an ankle sprain. This trial showed similar ineffectiveness between patients randomized to receive acupuncture monotherapy, pharmacotherapy alone or both acupuncture and pharmacotherapy. After one-hour post-therapy, all three treatment arms failed to decrease pain scores by ≥ 2 points on the verbal NRS in <40% of patients. Additionally, the group assigned to acupuncture monotherapy required significantly more rescue analgesia. However, the study investigators commented that it was unclear if this was due to patients in the acupuncture-assigned group feeling as if they had "missed out" on receiving standard care

with medications, or whether it was because patients assigned to pharmacotherapy initially did not want to receive rescue analgesia with parenteral opioids. Despite these findings, the majority of the patients in all three groups – including the two groups that received acupuncture – stated that they would probably or definitely repeat the same treatment.³²

Acupuncture is a unique form of complementary and alternative medicine as well as a novel ALTO that has been used to treat pain in the ED. Though acupuncture is commonly used to treat chronic pain in an ambulatory care setting, there is limited yet noteworthy literature demonstrating its utility in the ED to treat acute pain that warrants further investigation. The feasibility of offering acupuncture services in an ED will be limited to the availability of acupuncture experts, which will likely not coincide with an ED's hours of operation. Furthermore, researchers have had difficulty creating a sham-control for comparison with acupuncture in placebo-controlled studies. Thus, though acupuncture may be an option as an ALTO, the practicality of incorporating it into ED practice in the US will be challenging and possibly non-feasible.

As treatment options for pain expand with the incorporation of non-opioid alternatives, pharmacists can provide unique roles and perspectives in changing practice. With new practices come the need for streamlined institutional protocols and education to providers, a role clinical pharmacists are well-positioned to provide. Additionally, bedside medication administration and pharmacist consultation – along with identifying and understanding patient-specific variables – will be required to effectively and safely treat patient pain and to reduce overall opioid use. Though alternatives have demonstrated efficacy, this is just part of the solution to combating the opioid epidemic in the ED.

Medication-Assisted Treatment in the ED

Aside from providing novel agents as alternatives to opioids for acute or chronic pain, EDs are being asked to take on an even larger or expanded role in addressing the opioid epidemic. Historically, ED practitioners only had alternative non-opioid therapies, such as α_2 -agonists, NSAIDs, antiemetics or benzodiazepines, to offer patients suffering from acute opioid withdrawal. The successes of these interventions are marginally effective compared to opioid agonist or partial-agonist therapies, specifically methadone and buprenorphine, which have been traditionally started in the outpatient setting.^{9,33,34} The Surgeon General, the CDC, and State governments are now calling on ED practitioners to expand their approach, including induction and referral to OTP or MAT facilities.¹¹

By definition, MAT is the use of FDA-approved medications, in combination with counseling and behavioral therapies, to provide a holistic approach to the treatment of substance use disorders.³⁵ This bundle of services is most successful when each component is provided, and a lack of either component, medications or psychosocial counseling has been proven to be less successful at maintaining retention in MAT at one year. Relief of withdrawal symptoms, abstinence from other illicit drugs and opioids, reduced mortality, and even reduced rates of HIV and hepatitis C transmission are associated with MAT retention.^{9,36} Unfortunately, symptomatic treatments do not have the same efficacy outcomes as opioid agonists/partial agonists. A recent systematic review that assessed all studies comparing the outcomes between buprenorphine, methadone, and α_2 -agonists (eg, clonidine and lofexidine) showed that buprenorphine and methadone, compared to α_2 -agonists, were found to be more effective in

reducing clinical withdrawal scores and increasing lengths of stay or retention in MAT programs. Furthermore, the buprenorphine group had a significantly greater percentage of patients who successfully completed therapy in their MAT program. Limitations to this analysis include the lack of full MAT psychosocial services provided to those treated symptomatically with α_2 -agonists compared to opioid agonists/partial agonists. These results must be taken cautiously as the evidence to date has not included ED patients.³³

A 2015 landmark study by D'Onofrio et al demonstrated that ED-based buprenorphine initiation and induction, with referral to cognitive and psychosocial services, is feasible and effective in maintaining patients' long-term engagement in addiction treatment services. The study found reduced self-reported illicit opioid use and higher retention in MAT: roughly 75% of patients who were induced with buprenorphine in the ED and referred to an addiction treatment facility were still engaged at 60 days, compared to roughly 50% who were offered just information and/or referral.⁹ Another study by Kaucher et al evaluated their institution's ED-based buprenorphine induction program and found just 49% of patients were still enrolled in MAT at 30 days.⁴⁶ Such evidence is limited, however, and has not gained widespread acceptance throughout the EM community. Although buprenorphine induction is feasible and effective, challenges have prevented ED providers from adding buprenorphine induction and prescribing to their clinical practices, including lack of familiarity, need for training, and institutional infrastructure. There is also a lack of consensus on various aspects of the induction and referral process, mainly due to a lack of experience and a "trial-by-fire" approach to this ever-evolving process.

Although we know opioid withdrawal is not life-threatening itself, evidence suggests that opioid users who are recently discharged from inpatient settings or incarceration are at a higher risk of death in a short-term period, mostly due to overdose.³⁷ Therefore, we should consider opioid withdrawal as a condition like any other with potentially deadly short-term complications and provide safe and effective treatment that includes buprenorphine induction and referral to a MAT facility.

Opioid Use Disorder Management

There are currently three FDA-approved medications for opioid dependence: methadone, naltrexone, and buprenorphine. The pharmacology and roles in therapy for each of these will be discussed with the understanding that these be used in conjunction with referral to OTPs for comprehensive management of opioid use disorders.

Methadone

Methadone, a full opioid agonist, binds to the μ -opioid receptor as do heroin, morphine and oxycodone: it is a potent analgesic and is often used for refractory pain syndromes due to its long half-life (15-55 hours). Adverse effects with methadone can be considerably more pronounced, especially if patients use concomitant sedatives or opioids. Euphoria, somnolence and respiratory depression are most common while severe cardiac arrhythmias can occur due to methadone blocking delayed rectifier potassium channels in the cardiac conduction system.³⁹ Methadone administered at very low doses, either as 10 mg IM or 20 mg orally, has been shown to be as effective as buprenorphine compared to traditional symptomatic therapies and in reduced Clinical Opioid Withdrawal Scale (COWS) scores from ED patients presenting with mild-to-moderate

withdrawal.^{40,41} Without a ceiling effect and quick onset like buprenorphine, methadone dosing for rapid-opioid withdrawal in the ED is not as alluring and is not considered a preferred agent.

There is no currently available literature comparing ED-initiated methadone to buprenorphine; however, literature exists on patients already enrolled in MAT programs and their long-term outcomes. Hser et al assessed long-term outcomes including mortality and opioid use over a period of five years.⁴² There was no difference identified in mortality between groups, however those randomized to buprenorphine did have a higher rate of positive urine drug screens at various follow-ups compared to methadone. The systematic review previously described by Gowing et al also did not identify any differences in outcomes when evaluating subgroups of patients on methadone compared to those on buprenorphine for withdrawal symptom reduction or treatment success in MAT. There were, however, slight improvements in the duration of time patients stayed in their respective MAT programs.³³

Naltrexone

Naltrexone, a full opioid antagonist, blocks and prevents other opioids from binding to the μ -opioid receptor. Unlike methadone and buprenorphine, which are considered replacement therapy, naltrexone is considered avoidance therapy in which the patient experiences a reduction in cravings; if the patient attempts to relapse while on naltrexone, they will not experience any effect from the opioid. Though naltrexone's oral tablet formulation has a long duration of action (~24 hours), it is also available as a long-acting IM product that only requires dosing every four weeks.⁴³ Unlike methadone and buprenorphine, there are no regulations over prescribing naltrexone as it is not considered a controlled substance by the Controlled Substances Act. Since naltrexone is not

effective at ameliorating withdrawal symptoms, it is rarely used as an ED option as it will prevent any subsequent withdrawal symptoms from being managed by opioid agonist therapy.

Buprenorphine

Buprenorphine, a partial opioid agonist with low intrinsic activity, binds with very high affinity to the μ -opioid receptor longer and with greater affinity than most other available opioids, including heroin and hydromorphone. Therefore, co-administration of buprenorphine with other opioids can precipitate acute withdrawal symptoms if buprenorphine displaces

another opioid. It is 50 times more potent than morphine in its binding affinity to the μ -opioid receptor. Buprenorphine is highly lipophilic and very well-absorbed after sublingual administration, reaching peak plasma concentrations within 60-90 minutes.⁴⁴ Buprenorphine undergoes extensive first-pass metabolism so it should not be swallowed. Because of its low intrinsic activity, it is known to have a ceiling effect which is responsible for its very limited effects of euphoria, sedation, and respiratory depression (Figure 1). Its duration of effect is dose-dependent and at high doses (>16 mg) can last 24-72 hours. These variables make

it the most favorable option for ED use. In July 2018, the FDA approved the first generic version of buprenorphine/naloxone combination film, hoping to increase availability and expand access to those unable to afford the combination previously.^{9,44}

The foundation of buprenorphine dosing for opioid withdrawal is mostly extrapolated from office or home induction experience, but this can still be utilized for ED use. The Substance Abuse and Mental Health Services Administration (SAMHSA) Center for Substance Abuse Treatment has published treatment improvement protocol guidelines with the intent to streamline buprenorphine induction.⁴⁵ This method encompasses a slow titration of buprenorphine dosing with routine COWS score assessments. This protocol is oftentimes referred to as the TIP 40 method of dosing. Since this protocol was initially intended for office or home-based induction, its use in the ED setting is limited.

Alternative buprenorphine administration strategies that are more suitable for ED use include those with initially higher dosing and shorter intervals to ameliorate withdrawal symptoms as well as those that rely on buprenorphine's long duration of action to help bridge patients to outpatient treatment that may occur in the next 12-24 hours.^{44,46} Figure 2 illustrates a common algorithm for buprenorphine induction in the ED.⁴⁷

Figure 1. Conceptual Representation of Opioid Effect vs Dose for Opioid Agonists, Antagonists and Partial Agonists⁴⁵

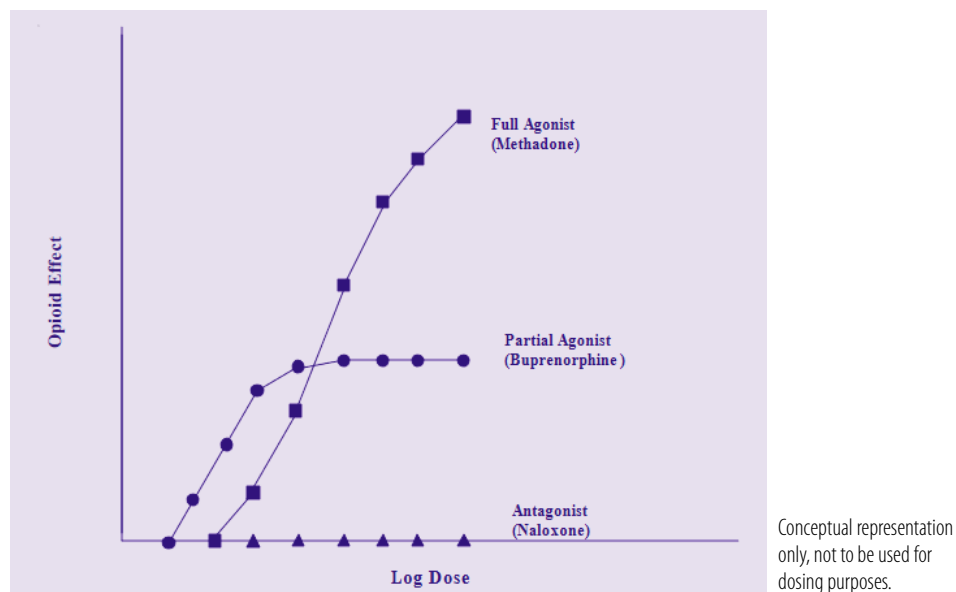


Table 1. Opioid Replacement and Opioid Avoidance Therapies^{39,43,44}

	Mechanism at μ -opioid Receptor	FDA-approved Formulations for OUD	Pharmacokinetics	Adverse Effects
Buprenorphine	Partial agonist	Sublingual tablet, buccal filmstrip, subdermal implant, ^a long acting injectable ^b	Peak: 90-120 min, Duration: 12-72 h	Sedation, respiratory depression, precipitated opioid withdrawal
Methadone	Full agonist	Liquid, tablet	Peak: 60-120 min, Duration: 24-72 h	Somnolence, respiratory depression, QTc prolongation
Naltrexone	Antagonist	Tablet, intramuscular injection ^b	Peak: 60 min, Duration: 24-36 h	Precipitated opioid withdrawal

^a 180 days.

^b 30 days.

Abbreviations: FDA, Food and Drug Administration; OUD, opioid use disorder.

Naloxone, a μ -opioid receptor antagonist, is added to oral buprenorphine products (eg, Suboxone[®], Zubsolv[®] and Bunavil[®]) in a 4:1 buprenorphine-to-naloxone ratio as an abuse deterrent only. If crushed and inhaled/injected, naloxone will displace other opioids and precipitate withdrawal. Due to naloxone's poor oral bioavailability (<5%), it is not absorbed systemically so it is safe to administer with buprenorphine in buccal or sublingual forms.³⁸

General Approach to ED-Initiated Buprenorphine Induction

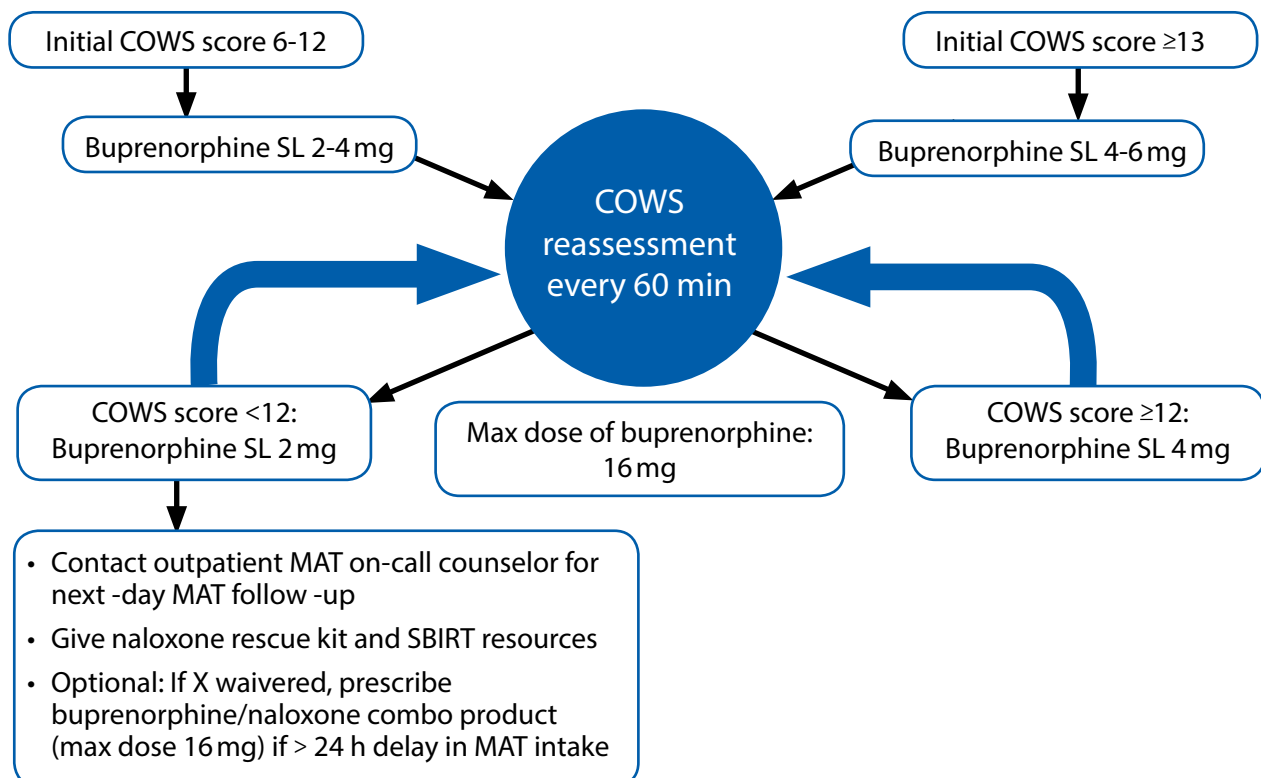
Identifying patients who may be interested or who are candidates for ED-initiated buprenorphine induction is often challenging and may rely on an individual patient requesting to be induced for clinical assessment. Utilization of triage-scoring tools, SBIRT (Screening, Brief Intervention, and Referral to Treatment) counselors,

and patient-reported histories of abuse potential are other ways to potentially identify candidates.⁴⁹ The use of DSM-5 Criteria for Opioid Use Disorder or other diagnostic tools (such as the Rapid Opioid Dependence Screening tool) can help if integrated into triage systems or electronic health records, but use is often not required after identifying a candidate.^{49,50}


Upon patient identification, routine assessments should be used to rapidly manage opioid withdrawal. The COWS scoring tool is the most widely used scale by behavioral health specialists and in ED protocols because the tool allows for objective measurement of opioid withdrawal in addition to assessment of the effects of ED-administered buprenorphine, which can aide providers with titrating buprenorphine therapy (Figure 3).⁴⁰ The COWS scoring tool consists of 11 items, with a higher score

indicating more severe opioid withdrawal. Recommendations vary on the level of withdrawal necessary before treatment should be started, but most consistently a level of mild-to-moderate withdrawal is based on COWS score >7. However, some argue that patients who score low or mild on a COWS assessment (<5) may have significant cravings and could be at risk for resorting to illicit opioids if discharged or leaving against medical advice. Prior to initiating induction therapy, providers should confirm that patients have not recently used opioids as this would precipitate withdrawal. A washout period of 12 hours is suggested for short-acting opioid agonists and up to 72 hours for long-acting opioids such as methadone. Since the highest risk of death secondary to opioid overdose tends to occur after recent discharge or release from incarceration, immediate next-day follow-up after induction is encouraged.³⁷


Figure 2. Buprenorphine Dosing Protocol for ED Induction (Adopted from Kaucher KA et al)⁴⁶



Abbreviations: COWS, Clinical Opioid Withdrawal Scale; ED, emergency department; MAT, medication-assisted treatment; SBIRT, Screening, Brief Intervention, and Referral to Treatment; SL, sublingual.



Once feasibility and workflow are established, the final factor required for any successful ED-based program is a collaboration or partnership with local OTPs or community-based providers who can provide ongoing care. As mentioned previously, behavioral and psychosocial counseling – in addition to opioid replacement therapies – are crucial for patient-centered successes.



Developing an ED Initiation and Induction Program

Many practitioners in the ED may find developing an ED-initiating program challenging. However, if provided with appropriate resources and referral capabilities, practitioners can be successful. Institutions all across the country – from Oakland to Boston – have successfully implemented programs with and without federal or state funding for assistance. Guidance documents from SAMHSA and the National Institute on Drug Abuse, relating to ED-initiated buprenorphine induction and referral to treatment, have been published to assist practitioners interested in developing programs and processes.⁴⁵ As mentioned previously, experiences from ED-initiated programs have been anecdotal but based on mounting successes and widespread implementation, these programs are proven feasible. Unfortunately, until consensus recommendations are developed, some of the current recommendations are extrapolated from office-based techniques and may not be ideal for ED settings (eg, lower dosing and slower titration methods). Complicating clinical and social factors should also be evaluated prior to buprenorphine induction in high-risk patient populations including:

1. No form of identification or inability to present to the MAT facility for initial intake
2. History of cirrhosis/hepatitis: buprenorphine has been associated with acute liver injury and necrosis – liver function tests should be evaluated if suspicion exists; methadone may be preferred
3. Chronic and/or recent long-acting opioid use: risk of precipitation of withdrawal

4. Chronic benzodiazepine use: higher risk of respiratory depression
5. Pregnancy: buprenorphine with or without naloxone is considered safe during pregnancy but fetal monitoring is recommended

Once feasibility and workflow are established, the final factor required for any successful ED-based program is a collaboration or partnership with local OTPs or community-based providers who can provide ongoing care. As mentioned previously, behavioral and psychosocial counseling – in addition to opioid replacement therapies – are crucial for patient-centered successes.

Prescribing and Regulatory issues

There are a few common misconceptions regarding administration of buprenorphine in the ED. Buprenorphine and methadone administration, or “direct administration,” is permitted for maintenance or detoxification purposes without a Drug Addiction Treatment Act of 2000 (DATA2000) X-waiver. The “three-day rule” per Title 21, Code of Federal Regulations, Part 1306.07, applies to the direct administration of these agents for any person experiencing withdrawal as a bridge to MAT or until a licensed prescriber – in the case of buprenorphine – can prescribe long-term therapy. This “three-day rule” allows a patient to be given buprenorphine or methadone in the ED, if needed, for up to three consecutive days for purposes of withdrawal. If a delay in intake at MAT is expected, an X-waiver is required to prescribe buprenorphine. The X-waiver was part of the DATA2000 mandate to ensure all prescribers completed a SAMHSA-certified training course on the risks of buprenorphine induction and administration in patients who may have recently taken concomitant opioids or benzodiazepines. Methadone cannot be prescribed for purposes of

withdrawal even if the prescriber has an X-waiver. For this indication, patients are required to receive methadone from only a SAMHSA-certified MAT facility or methadone clinic.⁴⁸

Since the X-waiver is not required for buprenorphine induction programs in the ED, EM providers may still benefit from X-waiver SAMHSA training, which provides additional knowledge and understanding of OUD that may be absent from their historical practice. Additionally, knowledge and training may potentially foster greater awareness and willingness to provide ED-based induction.

The Pharmacist's Role

All practitioners in the 'medication use system' are involved with developing ALTO protocols or ED-initiated buprenorphine induction programs. As such, pharmacists are uniquely positioned to advocate for and be an integral member of a multidisciplinary team tasked with addressing the opioid epidemic from several aspects within health systems. An understanding of the opioid crisis and its relationship to EM providers, as well as hospital policies and protocols, will allow pharmacists to identify targets for change within pain management protocols and policies while establishing areas within the ED where pharmacists can assist in MAT induction workflow improvements.

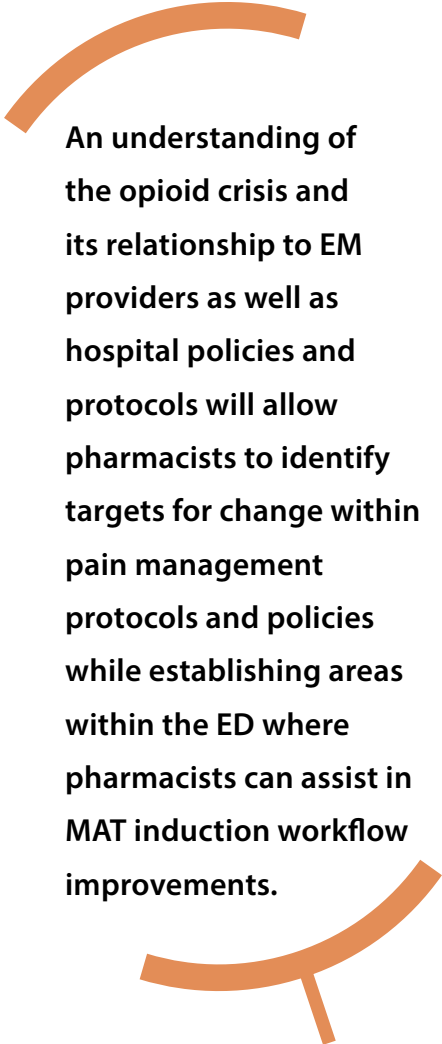
A deep knowledge of pharmacotherapy and patient variables is essential for developing ALTO-related protocols since careful considerations are needed, including indications, dosing strategies, hospital formulary management, and contraindications to ALTO medications. Assessments of previously implemented interventions and medication use evaluations should be considered and completed after program implementation to assess for proper protocol adherence and trends in opioid and ALTO use over time. These activities that are well within a pharmacist's scope

of practice may even be required by local quality initiatives and may be linked to payment and funding opportunities.

The pharmacist's involvement in MAT-induction processes can be extensive as knowledge and understanding of monitoring and assessment tools, adverse effects and the risk of precipitated withdrawal, dosing strategies, discharge counseling and naloxone distribution, and transitions of care are all essential to any effective MAT program. Due to differences between insurance formularies, understanding the prior authorization system may be crucial if outpatient prescribing is required. Nursing and provider education on the use of an assessment tool, proper sublingual administration, and evaluation of laboratory values are all areas where pharmacists can contribute. With all these potential areas to improve the medication use system involving buprenorphine induction practices, these areas provide great opportunities for pharmacy intern and resident education along with fostering pharmacy's integration into the care team.

Conclusion

The opioid crisis continues to be a top priority for government officials and health care leaders. Pharmacists and EM providers, along with affiliated organizations, have developed strategies to combat the opioid epidemic but there is still more to be accomplished. Novel approaches to combat the opioid epidemic should be a multimodal and multidisciplinary effort. Adoption of ALTO-related practices to reduce opioid use and development of a MAT program within the ED are ideal situations given the appropriate resources. Pharmacists are well-positioned members of this multidisciplinary team who can change practice and implement programs to improve patient outcomes. ○



An understanding of the opioid crisis and its relationship to EM providers as well as hospital policies and protocols will allow pharmacists to identify targets for change within pain management protocols and policies while establishing areas within the ED where pharmacists can assist in MAT induction workflow improvements.

Figure 3: Clinical Opioid Withdrawal Scale⁴⁰

<p>Resting Pulse Rate: _____ beats/minute</p> <ul style="list-style-type: none"> • <i>Measured after patient is sitting or lying for 1 minute</i> <input type="checkbox"/> 0... pulse rate 80 or below <input type="checkbox"/> 1... pulse rate 81-100 <input type="checkbox"/> 2... pulse rate 101-120 <input type="checkbox"/> 4... pulse rate greater than 120	<p>GI Upset:</p> <ul style="list-style-type: none"> • <i>Over last ½ hour</i> <input type="checkbox"/> 0...no GI symptoms <input type="checkbox"/> 1...stomach cramps <input type="checkbox"/> 2...nausea or loose stool <input type="checkbox"/> 3...vomiting or diarrhea <input type="checkbox"/> 5...multiple episodes of diarrhea or vomiting
<p>Sweating:</p> <ul style="list-style-type: none"> • <i>Over past ½ hour not accounted for by room temperature or patient activity.</i> <input type="checkbox"/> 0...no report of chills or flushing <input type="checkbox"/> 1...subjective report of chills or flushing <input type="checkbox"/> 2...flushed or observable moistness on face <input type="checkbox"/> 3...beads of sweat on brow or face <input type="checkbox"/> 4...sweat streaming off face	<p>Tremor:</p> <ul style="list-style-type: none"> • <i>Observation of outstretched hands</i> <input type="checkbox"/> 0...No tremor <input type="checkbox"/> 1...tremor can be felt, but not observed <input type="checkbox"/> 2...slight tremor observable <input type="checkbox"/> 4...gross tremor or muscle twitching
<p>Restlessness:</p> <ul style="list-style-type: none"> • <i>Observation during assessment</i> <input type="checkbox"/> 0...able to sit still <input type="checkbox"/> 1...reports difficulty sitting still, but is able to do so <input type="checkbox"/> 3...frequent shifting or extraneous movements of legs/arms <input type="checkbox"/> 5...Unable to sit still for more than a few seconds	<p>Yawning:</p> <ul style="list-style-type: none"> • <i>Observation during assessment</i> <input type="checkbox"/> 0...no yawning <input type="checkbox"/> 1...yawning once or twice during assessment <input type="checkbox"/> 2...yawning three or more times during assessment <input type="checkbox"/> 4...yawning several times/minute
<p>Pupil size:</p> <input type="checkbox"/> 0...pupils pinned or normal size for room light <input type="checkbox"/> 1...pupils possibly larger than normal for room light <input type="checkbox"/> 2...pupils moderately dilated <input type="checkbox"/> 5...pupils so dilated that only the rim of the iris is visible	<p>Anxiety or Irritability:</p> <input type="checkbox"/> 0...none <input type="checkbox"/> 1...patient reports increasing irritability or anxiousness <input type="checkbox"/> 2...patient obviously irritable anxious <input type="checkbox"/> 4...patient so irritable or anxious that participation in the assessment is difficult
<p>Bone or Joint aches:</p> <ul style="list-style-type: none"> • <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i> <input type="checkbox"/> 0...not present <input type="checkbox"/> 1...mild diffuse discomfort <input type="checkbox"/> 2...patient reports severe diffuse aching of joints/muscles <input type="checkbox"/> 4...patient is rubbing joints or muscles and is unable to sit still because of discomfort	<p>Gooseflesh skin:</p> <input type="checkbox"/> 0...skin is smooth <input type="checkbox"/> 3...piloerection of skin can be felt or hairs standing up on arms <input type="checkbox"/> 5...prominent piloerection
<p>Runny nose or tearing:</p> <ul style="list-style-type: none"> • <i>Not accounted for by cold symptoms or allergies</i> <input type="checkbox"/> 0...not present <input type="checkbox"/> 1...nasal stuffiness or unusually moist eyes <input type="checkbox"/> 2...nose running or tearing <input type="checkbox"/> 4...nose constantly running or tears streaming down cheeks	<p>• <i>The total score is the sum of all 11 items...</i></p> <p style="text-align: right;">Total Score: <input type="text"/> <input type="text"/></p>

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

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Getting Started as a New Preceptor

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Keywords

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Background

Clinical experience in the healthcare field plays a crucial role in shaping future professionals into competent and well-rounded providers. Equally important is the ability to facilitate the learning process of learners to promote self-directed, lifelong learning and critical thinking.¹⁻³ Preceptorship can vary in approach depending on the design of the learning experience: direct instruction, modeling, coaching, mentoring, and facilitation.⁴⁻⁶ In addition, there are many teaching tools available such as One-Minute Preceptor, layered teaching, providing reflections, and thinking out loud.⁷⁻⁹ To be an effective preceptor, developing skills through self-reflection and seeking out professional development to strengthen areas of weakness are important. However, despite all the precepting methods, tools, and resources available, how does one truly know they are effective and accomplishing their goals as a preceptor? Many individuals can think of what they want to achieve and how they want to be perceived as a preceptor, but few develop a plan of how to accomplish it. This article focuses on helping new preceptors get started in their role by developing a precepting philosophy, exploring preceptor roles, providing feedback, and navigating common precepting challenges.

Developing a Precepting Philosophy

Many novice preceptors may overlook formally developing a precepting philosophy, and some experienced preceptors may not realize their precepting philosophy changes over time. A precepting philosophy can provide a framework that can guide and structure learning experiences. A precepting philosophy can help you narrow down your precepting-related goals and inform the choices made about the type of precepting style you want to incorporate. Subsequently this can lead to directing the types of preceptor development to be most effective.

Questions to Consider as a Guide to Building your Framework

- What goals do you have for yourself to better align with your philosophy?
- What beliefs, theories, and methods will help you align better with your philosophy as a preceptor?
- How do you know you are being effective as a preceptor?
- How do you develop positive relationships with your students/residents?
- How do you create a supportive learning environment?
- What are you doing or not doing that you can change to better align with your framework?

Example of a Precepting Philosophy

To begin, reflect on some aspirational words or statements that drive you as a preceptor. Once you have the words, start building out your words into goals with objectives you can measure. This will become the skeleton for your philosophy of precepting. Once you have established your general philosophy, consider how your philosophy can be built into a framework that can guide you as a preceptor. This framework can then be used to evaluate all aspects of how you precept – how you develop your learning experiences, how you orient residents/students, and what preceptor development is required to reach your personal goals. This framework is your roadmap to fully embracing the preceptor you envision for yourself.

Let us explore a precepting philosophy of positivity, intention, and continuous growth. The aspirational words of positivity, intention, and growth are used to build a framework. The words reflect a personal desire to be a preceptor who establishes a positive environment, approaches each situation with intention, and strives to better oneself. In addition, these words capture what the goals are for the learners: to develop within themselves the skills needed to face situations with positivity, be self-directed, and to be life-long learners. We will break down each part of this philosophy by answering these two questions:

1. How do we implement this/ What does this look like in practice?

2. How do we evaluate the effectiveness of our precepting philosophy?

Positivity:

- One approach to implementing a positive environment is by having an optimistic attitude. We can display optimism by believing in ourselves, students, and patients. By having a “can-do” attitude, students can witness

their preceptor manage difficult situations and overcome challenging tasks. We can further create a positive environment by encouraging students and providing positive reinforcement with constructive feedback when necessary. This will enhance the student’s confidence and skills. We can evaluate our positive environment by witnessing our students’ progress, our students’ ability to take on new responsibilities, and our students’ evolving confidence when speaking with patients and making appropriate clinical recommendations.

Intention:

- Structuring all learning experiences with intention allows us to take into consideration the resident’s/student’s and the program’s goals so that no meaningless task consumes your learner’s time and efforts if a valuable outcome is not associated with it. We can implement this by creating activities and assignments that align with one or more of the following: 1) a goal for the learning experience, 2) part of the personal development plan of the learner, or 3) a need for the institution. We can assess our intention by evaluating the achievement of the end goal by the learner. If the intended goal was not met, then the activity may need to be restructured to accomplish the desired outcome.

Growth:

- Continuous improvement of oneself can be achieved by enhancing self-awareness through reflection. Utilizing self-awareness tools, discussing evaluations through self-reflection, and using monthly self-reflection journals can help strengthen our self-awareness. By taking the time to self-reflect, we can actively improve our skills and teaching strategies. We can also promote the growth of our learners by implementing reflections after presentations or activities to

encourage learners to identify their areas of improvement and better themselves. We can assess the learner’s improvement through self-reflection by witnessing their ability to evaluate their own progress without confirmation from others. Commonly utilized tools to develop self-awareness include *Strength Finders 2.0* by Tom Rath, the Myers-Briggs Type Indicator, and *Emotional Intelligence 2.0* by Travis Bradberry and Jean Greaves.¹⁰⁻¹²

This is an example of how a philosophy can be used as a guide to assess whether activities, teaching methods, and learning experiences are aligning with what you envisioned for yourself as a preceptor and the outcomes you want from your learner. A philosophy allows you to also assess for gaps in your precepting and areas needed for development.

Preceptor Roles

Once a precepting philosophy is established, preceptors should understand how to utilize four key roles to supplement their philosophy and assist with the development of students. The American Society of Health-System Pharmacists has identified these roles as direct instruction, modeling, coaching, and facilitation.⁶ The first role of direct instruction allows for the student/resident to gather the appropriate resources and gain background education before application of their knowledge. Once the preceptor believes the student/resident has the baseline knowledge of the topic, the preceptor can move onto the role of modeling. Modeling consists of “thinking out loud” and demonstration to allow the student to witness the thought process of completing the responsibility at hand. When you believe the student is ready to perform, the preceptor will progress to the role of coaching. Coaching allows for the preceptee to perform the task with direct feedback from the preceptor to guide them along the way. As soon as the preceptor feels comfortable with

the preceptee's skills, the preceptor will advance to the final role of facilitation, which allows for the student/resident to perform tasks independently with the preceptor available (if necessary). The rate of progression for roles will depend on the preceptee. If the learner struggles with the assigned tasks, they may be in the modeling or coaching phase longer before reaching facilitation. These roles allow the preceptee to improve their skills and progress to becoming independent practitioners.⁶

Providing Effective Feedback

Honest evaluations in experiential education are a part of our duty to the public, our profession, and to developing students.¹³ Our role as preceptors is essential in shaping practice-ready pharmacists who are about to step out into the world on their own. To strengthen the student's skills, preceptors must be comfortable

with providing direct feedback to allow for improvement. Typically, students are not aware of what they do not know and the gaps in their knowledge, which may lead to poor habits, behaviors, and poor clinical decision-making that may continue if the learner is not properly guided. Feedback can be delivered in a variety of ways depending on the situation. This includes positive or constructive feedback, verbal feedback (on the spot or written), and summative or formative feedback.^{13,14} All methods of feedback are necessary and useful for learners of all levels. Regardless of the approach utilized, feedback should be direct, consistent, constructive, timely, specific, and reflective to be most effective.¹³⁻¹⁵

Providing regular feedback starts to come naturally with time and experience as a preceptor. These tips are a brief introduction to the broad topic of feedback. Additional resources include *Getting*

Started as a Pharmacy Preceptor and The Preceptor's Handbook for Pharmacists.^{12,14}

Pearls to Precepting Scenarios

Experiences from other preceptors can provide valuable insight to dealing with various types of learners. With every set of new students and residents that are being precepted, we learn more about ourselves and become better preceptors. Much of what we learn comes not only from positive experiences, but challenges we face along the way. Many of us may face similar pitfalls throughout our careers as preceptors. Knowing how to navigate common precepting challenges and scenarios may be beneficial to new preceptors.

Precepting is a privilege and opportunity to give back to junior colleagues and developing students. Creating a precepting philosophy is an important step to becoming an effective preceptor. By identifying who we want to be as a preceptor, what outcomes we want for our learners, navigating common challenges, and learning from experiences of our own and others, we can adequately guide our students to success. The preceptor-preceptee relationship may flourish into a mentorship which is rewarding for both individuals involved. ○

Table 1. Characteristics of Effective Feedback

Type of Feedback	Important Clinical Pearl(s)
Direct	Be honest and straightforward with feedback given to students. They should be aware of areas and items they excel in and areas that need improvement.
Consistent	Create a habit to provide consistent feedback throughout the rotation. Providing feedback once or twice during a rotation does not promote continuous growth.
Constructive	The feedback students receive should serve the purpose of building the student up, not breaking them down. When students perform poorly, their actions should be discussed and how it can be improved moving forward. Avoid commenting on personality and other personal factors.
Timely	Feedback given immediately after an activity is most beneficial as they can immediately recall what occurred. If too much time lapses between the event and the feedback, neither you and the student may not remember the details nor is the student given the opportunity to improve.
Specific	Provide concrete details of what the learner did well on and what they need to work on. Vague feedback leaves room for misinterpretation of the situation.
Reflection	Teaching and encouraging self-reflection will lead to a better ability to receive and provide effective feedback. Reflection closes the evaluation loop by providing the opportunity for students to critique themselves and analyze the situation.
Examples of Strong Feedback	<p>Preceptor to student: "How do you think the patient encounter went? What are areas you can continue to work on?"</p> <p>Preceptor to student after response: "I was impressed by your knowledge of the agents used to control diabetes. However, when explaining the importance of adherence with the patient, make sure to stay consistent with using lay language. The patient seemed confused when you mentioned preventing microvascular complications."</p>

Table 2. Pearls for Common Precepting Scenarios

Scenario	Pearl	Explanation
Having one high-achieving student and one struggling student during the same rotation	Avoid a similar approach with both students	A high-achieving student can be given more autonomy and additional responsibilities (eg, updating a protocol, presenting an in-service, or being more independent with patient care). The struggling student may benefit from achieving the goals of the rotation with more modeling and coaching. Another strategy to consider is a paired teacher approach between the two students, where one student teaches the other and then vice-versa. However, relying heavily on the stronger student to consistently provide guidance to the struggling student may also cause unnecessary stress to the stronger student. Ensuring all stated objectives of the learning experience are met by both students and creating some individualized learning strategies will make for a more enriching experience. Approaching both students similarly may be a disservice to one of them.
Teaching activities throughout the rotation	Be creative	Experiment with adding variety to teaching activities to make the experience more enjoyable and to expose students to other styles of teaching. For example, try having the students lead a discussion at their own discretion, incorporate games such as Jeopardy!, provide complex cases to stimulate discussion, bring in other preceptors that are an expert in their field to provide real-life examples of their experience, allow students to critique journal articles, show videos, have students role play complicated scenarios, etc. These are various approaches to promote student learning and critical thinking. Creativity allows preceptors to discover a teaching style best suited to their precepting philosophy.
Students not progressing to the preceptor's rotation objectives	Identify the gap(s) in knowledge or skills and help the student progress	Certain expectations of our students can become shaped by our work with previous students. Try not to allow past experiences with students good or bad influence your beliefs to compare students with each other. Learn about your current student and understand how to help them overcome challenges to meet the desired learning objectives. Breaking down the objective into smaller achievable goals and providing more time for the student to work on the tasks may assist with improving their skills in a stepwise manner to meet the overall objective. Understanding the student's gap(s) in knowledge/skill will guide preceptors in choosing the appropriate preceptor role to better help the student progress.
Dealing with an unprofessional student	Be firm and seek additional resources	Be firm with the unprofessional student. Communicate with the school and seek advice and support. Punishing the student or retaliation should be avoided in these situations. Unprofessional conduct should be addressed at the root of the problem to avoid recurrence in the future. Problems with professionalism may stem from lack of awareness, knowledge, or the proper tools on how to deal with a certain situation. The school should be made aware of the situation and they may provide additional guidance to navigating challenges. Other seasoned colleagues may also provide an alternative perspective that may have never been considered on your own. This allows for preceptors to share and problem-solve together, which can strengthen precepting skills. Throughout this process, document what occurred and the feedback provided to the student.
Your student has difficulty with responding to questions during their presentation	Avoid providing little to no direction or feedback when preparing the student	To better prepare the student, listen to the presentation beforehand, provide specific feedback regarding presentation style and content, give examples of questions that may be asked, and have them ask themselves these three questions: 1) what are key takeaways 2) what may be unclear, and 3) what questions may be asked. This will help them get a deeper understanding of the material and better prepare.
Asking the student to participate in a task, meeting or project that does not contribute to an end goal prespecified by your philosophy or syllabus	Avoid assigning tasks that lack authenticity	This goes back to providing opportunities with intention. Ensure the student/resident is investing their time in an activity that will contribute to their development, goals or the institution's needs. If there is value in the task assigned, providing an explanation for the need and the goals of the task may help the student understand the purpose and desired outcome of the duty.
Your relationship with your preceptee	Create a positive environment for learning	All preceptors have a different approach to teaching and precepting. Regardless of the teaching style, it is important to create an environment that encourages growth and critical thinking. As preceptors, we must find a balance to avoid being too controlling, too friendly or too relaxed to allow the student to become independent with enough guidance to be on the right track. For example, we can allow a student to use their creativity when it comes to creating a presentation without telling the student exactly what to say or include. Feedback can be provided after their first draft of their presentation. If we as preceptors tell them how complete every task, it takes away from their experience and they may struggle with navigating issues, managing their time, or problem solving in the future.

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Aspirin's Disappearing Act – Updates on the Role of Aspirin in Cardiovascular Disease

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Introduction

For the past four decades, acetylsalicylic acid (commonly known as aspirin) has been a backbone in the prevention of cardiovascular (CV) events in patients with established atherosclerotic CV disease (ASCVD). However, aspirin's role in other patient populations is less well-established. In patients without clinical ASCVD, the magnitude of aspirin's absolute benefit is generally smaller than that in the secondary prevention population and may be offset by the risks of bleeding. Despite this, aspirin use is widespread. Data from the National Health Interview Survey administered to 90,558 Americans between 2012 and 2015 show that the prevalence of aspirin use for primary CV disease prevention was 22.1%.¹ The selection of appropriate antithrombotic therapy is also less clear for patients with history of atrial fibrillation (AF) and recent coronary stent placement who potentially require three antithrombotic agents (two antiplatelet agents plus an anticoagulant). In this clinical pearl, recent literature is discussed regarding aspirin therapy as well as the latest recommendations from national guidelines or guidance documents for these two populations.

Primary Prevention

Historical Data

The first trial to evaluate aspirin in a primary prevention population was published in 1988: aspirin 500 mg daily was studied in a cohort of 5,139 healthy male British physicians.² Since then, many clinical trials have been published but only a few have shown reductions in CV outcomes, such as CV death, myocardial infarction (MI) and stroke. Several review articles provide excellent overviews of aspirin clinical trials from 1988 to the present:³⁻⁵ most have shown aspirin's futility to achieve the primary efficacy outcome of interest in respective trials. In 2009, the Antithrombotic Trialists' (ATT) Collaboration published a landmark meta-analysis of clinical trials comparing low-dose aspirin with control, which included six primary prevention trials representing 95,000 individuals at low average risk and 660,000 person-years.⁶ The ATT meta-analysis found a 12% relative reduction in serious vascular events (defined as MI, stroke, or vascular death) with aspirin use compared to control (0.51% vs 0.57% per year, $P=0.0001$). This was attributed mostly to a reduction in non-fatal MI (0.18% vs 0.23% per year, $P<0.0001$) since the net effect on stroke was not significant (0.20% vs 0.21% per year, $P=0.4$). Aspirin significantly increased the risk of gastrointestinal (GI) and extracranial bleeding (0.10% vs 0.07% per year, $P<0.0001$).

Since the initial release of the ATT meta-analysis, other meta-analyses and systematic reviews have been published (see Table 1). A systematic review for the US Preventive Services Task Force (USPSTF) published in 2016 included 11 primary prevention

Keywords

aspirin, atrial fibrillation, cardiovascular diseases, percutaneous coronary intervention, primary prevention, secondary prevention, triple therapy

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studies.^{7,8} It found a 22% relative reduction of non-fatal MI with the use of aspirin (RR 0.78; 95% CI, 0.71-0.87; I²=61.9%).⁷ There was little or no benefit with aspirin for non-fatal stroke (RR 0.95; 95% CI, 0.85-1.06; I²=25.1%), all-cause mortality (RR 0.94; CI, 0.89-0.99; I²=0%), or CV mortality (RR 0.94; CI, 0.86-1.03; I²=8.8%). The USPSTF systematic review also found a significantly increased risk of major GI bleeding (OR 1.5; 95% CI 1.32-1.91; I²=22.2%) and hemorrhagic stroke (OR 1.33; CI, 1.03-1.71; I²=0%).⁸ Most recent meta-analyses, including those published within the past year, have generally shown a pattern of reductions in MI and ischemic stroke but have also shown increases in hemorrhagic stroke, major bleeding, and GI bleeding with

aspirin use. However, the statistical significance of these findings has been inconsistent from study to study.

Recent Data

In 2018, three major trials (ASPREE, ARRIVE and ASCEND) were published to provide more information regarding aspirin use in the primary prevention of ASCVD. The ASPREE trial is a randomized, placebo-controlled trial that evaluated aspirin use in a population of community-dwelling persons from Australia and the United States who were ≥70 years old and free of documented CV/cerebrovascular disease or physical disability.⁹ The study also included black and Hispanic patients in the US ≥65 years

old due to rationale that their risks of CVD or dementia are higher. The primary endpoint of the ASPREE trial was disability-free survival defined as survival free from dementia or persistent physical disability, measured through a composite of events including death, dementia and persistent physical disability. The trial also had eight pre-specified secondary endpoints including fatal and nonfatal CVD, fatal and nonfatal cancer, and major hemorrhage. A total of 19,114 participants were enrolled from 2010 to 2014 and then followed for an average of 4.7 years. The study design included an interim analysis to take place when 1,893 primary endpoints had occurred. However, event rates were lower than

Table 1. Meta-analyses of Aspirin Primary Prevention Trials Including ASPREE, ARRIVE, and ASCEND

Authors and publication date	Total pooled patients	Studies included	All-cause mortality	Ischemic stroke	Myocardial infarction	Major bleeding	Intracranial hemorrhage or hemorrhagic stroke
Mahmoud AN, et al. 2019 ¹	157,248	11	RR 0.98 (95% CI 0.93-1.02)	RR 0.94 (95% CI 0.86-1.02)	RR 0.82 (95% CI 0.71-0.94)	RR 1.47 (95% CI 1.31-1.65)	RR 1.33 (95% CI 1.13-1.58)
Zheng SL, et al. 2019 ²	164,225	13	HR 0.94 (95% CrI 0.88-1.01)	HR 0.81 (95% CrI 0.76-0.87)	HR 0.85 (95% CrI 0.73-0.99)	HR 1.43 (95% CI 1.30-1.56)	HR 1.34 (95% CI 1.14-1.57)
Abdelaziz HK, et al. 2019 ³	165,402	15	RR 0.97 (95% CI 0.93-1.01)	HR 0.87 (95% CI 0.79-0.95)	RR 0.85 (95% CI 0.76-0.95)	RR 1.50 (95% CI 1.33-1.69)	RR 1.32 (95% CI 1.12-1.55)
Xie W, et al. 2019 ⁴	139,392	16	RR 0.97 (95% CI 0.93-1.02)	RR 0.95 (95% CI 0.86-1.03)	RR 0.83 (95% CI 0.73-0.95)	RR 1.40 (95% CI 1.25-1.57)	RR 1.30 (95% CI 1.06-1.60)
Barbarawi M, et al. 2019 ⁵	164,862	17	RR 0.97 (95% CI 0.93-1.01)	N/A	RR 0.88 (95% CI 0.78-0.98)	RR 1.41 (95% CI 1.29-1.54)	RR 1.35 (95% CI 1.14-1.59)
Seidu S, et al. 2019 ⁶	34,227	12	RR 0.95 (95% CI 0.88-1.02)	RR 0.82 (95% CI 0.55-1.23)	RR 0.84 (95% CI 0.64-1.11)	RR 1.30 (95% CI 0.92-1.82)	HR 1.24 (95% CI 0.85-1.80)
Shah R, et al. 2019 ⁷	164,751	14	RR 0.96 (95% CI 0.92-1.01)	RR 0.89 (95% CI 0.82-0.97)	RR 0.84 (95% CI 0.75-0.94)	RR 1.49 (95% CI 1.32-1.69)	RR 1.25 (95% CI 1.02-1.51)

Abbreviations: CI, confidence interval; CrI, credible interval; HR, hazard ratio; N/A, not available; RR, relative risk.

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originally expected and in March 2017, the data showed similar rates between the two groups. The decision was made by the National Institute on Aging in June 2017 to stop the trial because it was unlikely for aspirin to achieve a significant treatment effect by the trial end. Aspirin did not reduce the primary composite endpoint of risk of death, dementia, or physical disability compared to placebo (HR 1.01; 95% CI, 0.92-1.11; $P=0.79$). The rates of major hemorrhagic events were higher in the aspirin group (3.8%) compared to the placebo group (2.8%; HR 1.38; 95% CI 1.18-1.62; $P<0.001$). Additionally, aspirin did not significantly reduce the risk of major adverse CV events (HR 0.89; 95% CI 0.77-1.03), fatal or non-fatal MI (HR 0.93; 0.76-1.15), or fatal or non-fatal ischemic stroke (HR 0.89; 95% CI 0.71-1.11).¹⁰ All-cause mortality was higher in the aspirin group (HR 1.14; 95% CI 1.01-1.29), with cancer being the underlying cause for the increased risk of death.¹¹ The rates of cancer-related death were 6.7 events per 1,000 person-years in the aspirin group and 5.1 events per 1,000 person-years in the placebo group (HR 1.31; 95% CI 1.10-1.56). Overall, the study concluded that aspirin did not improve disability-free survival or reduce the risks of all-cause mortality or CV events in a cohort of healthy elderly patients. However, the use of aspirin did increase the risk of major bleeding.

The ARRIVE trial is a randomized, placebo controlled trial that enrolled 12,546 individuals who had an assessed moderate level of CV risk (defined as an estimated 10-year CVD risk of 10-20%).¹² The study included men ≥ 55 years old with two to four risk factors as well as women ≥ 60 years old with three or more risk factors. Risk factors included elevated total cholesterol or low-density lipoprotein cholesterol, current cigarette smoking, low high-density lipoprotein cholesterol, high blood pressure or using a blood pressure-lowering medication, and family history of CVD. The study

excluded participants with diabetes or high risk of bleeding. The study compared enteric-coated aspirin 100 mg to placebo with a primary efficacy endpoint of time to first occurrence of MI, stroke, CV death, unstable angina, or transient ischemic attack (TIA). Notably, the study protocol was amended several times due to lower-than-expected event rates. The primary composite endpoint was expanded to include unstable angina and TIA and the study follow-up period was extended from 60 months to approximately 72 months. Aspirin did not reduce the risk of CV disease in the ARRIVE trial as there was a non-significant difference between aspirin and placebo in the rates of the primary composite endpoint (aspirin 4.29% vs placebo 4.48%, HR 0.96, 95% CI 0.81-1.13; $P=0.6038$) in the intention-to-treat population. The rates of secondary endpoints or individual endpoints also did not differ between groups. There was a significant rate of participant dropout in both groups: 29.4% in the aspirin group and 29.9% in the placebo group. When analyzing the per-protocol population, fatal and non-fatal MI were both significantly lower in the aspirin group. The risk of GI bleeding was more than doubled by aspirin (0.97% in the aspirin group vs 0.46% in placebo, HR 2.11, 95% CI 1.36-3.28, $P=0.0007$). The ARRIVE investigators concluded that since the event rate was lower than expected, the study population was more representative of a low-risk population and not the moderate-risk population that was originally intended. Despite this, aspirin increased the risk of GI bleed by two-fold but did not reduce CVD risk in a primary prevention population.

The ASCEND trial investigated the use of aspirin in a population of patients in the United Kingdom with diabetes.¹³ The study used a 2x2 factorial design to randomize 15,480 patients to receive either enteric-coated aspirin 100 mg or placebo as well as omega-3 fatty acids or placebo. The study included

Table 2. Summary of Aspirin Primary Prevention Guidelines

Organization	Year	Recommendation	Class/Strength of Recommendation
ADA/AHA/ACCF ¹	2010	Low-dose ASA 75-162 mg PO daily is reasonable for adults with diabetes and no previous history of vascular disease who are at increased CVD risk (10-year risk >10%) and who are not at increased risk of bleeding.	Class IIa, Level of Evidence B
		ASA should not be recommended for CVD prevention in adults with diabetes at low CVD risk.	Class III, Level of Evidence C
		Low-dose ASA 75-162 mg PO daily might be considered for those with diabetes at intermediate CVD risk.	Class IIb, Level of Evidence C
ACCP ²	2012	Low-dose ASA 75-100 mg PO daily is recommended for patients ≥50 years of age without symptomatic CVD.	Grade 2B
AHA/ADA ³	2015	Low-dose ASA 75-162 mg PO daily is reasonable among those with 10-year CVD risk ≥10% and without increased bleed risk.	Class IIa, Level of Evidence B
		Low-dose ASA is reasonable in adults with DM at intermediate CVD risk (10-year risk of 5-10%).	Class IIb, Level of Evidence C
ESC ⁴	2016	Antiplatelet therapy is not recommended for individuals without CVD due to increased risk of major bleeding.	Class III, Level B
USPSTF ⁵	2017	Initiate low-dose ASA for primary prevention of CVD in adults 50–59 years old and 10-year CVD ≥10% who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose ASA daily for at least 10 years.	B
		Low-dose ASA use is an individual decision for adults 60–69 years of age with 10-year CVD ≥10%. Those who are more likely to benefit from ASA include those at lower risk of bleeding, have life expectancy at least 10 years, and are willing to take ASA for at least 10 years.	C
		Insufficient evidence for recommendations in adults <50 years or ≥70 years old.	I (Insufficient evidence)
ADA ⁶	2019	ASA 75-162 mg PO daily may be considered in those with diabetes who are at increased CV risk after discussion with the patient on risk versus benefit.	C
ACC/AHA ⁷	2019	Low-dose ASA 75-100 mg PO daily might be considered for primary prevention in adults 40-70 years old at higher ASCVD risk but not at increased bleeding risk.	IIb
		Low-dose ASA 75-100 mg PO daily should not be administered on a routine basis for primary prevention among adults >70 years old	III: Harm
		Low-dose ASA should not be administered for primary prevention among adults of any age who are at increased risk of bleeding.	III: Harm
ESC/EASD ⁸	2019	ASA for primary prevention is not recommended for patients with DM at moderate CV risk.	Class III, Level B
		Primary prevention with low-dose ASA may be considered in patients with DM at very high/high risk in the absence of contraindications.	Class IIb, Level A

Abbreviations: ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; ADA, American Diabetes Association; AHA, American Heart Association; ASA, aspirin; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESC, European Society of Cardiology; ESDA, European Association for the Study of Diabetes; PO, orally; USPSTF, United States Preventative Services Task Force.

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men and women ≥ 40 years old who had diabetes of any type and did not have known CVD. The primary efficacy endpoint was the first serious vascular event defined as a composite of non-fatal MI, non-fatal stroke or TIA, or death from any vascular cause. The primary safety endpoint was the first occurrence of any major bleeding event. Of note, the estimated mean adherence rate was 70% in each group, with the use of non-trial aspirin and other antiplatelet agents increasing in the placebo group while adherence to aspirin in the treatment group decreased. After a mean follow-up period of 7.4 years, the risk of serious vascular events was significantly lower in the aspirin group compared to the placebo group (8.5% in the aspirin group vs 9.6% in placebo; rate ratio 0.88; 95% CI 0.79-0.97; $P=0.01$). There was also a significant 29% increase in the risk of major bleeding with the use of aspirin (4.1% in the aspirin group vs 3.2% in placebo; rate ratio 1.29; 95% CI 1.09-1.52; $P=0.003$). Exploratory analyses showed that the benefits of aspirin occurred mainly in the first five years with no further gains beyond that, while the bleeding effects did not decrease over time. Of the first major bleeding events, the most common types were GI bleeding (41.3%), sight-threatening bleeding of the eye (21.1%), and intracranial bleeding (17.2%). Assignment to omega-3 fatty acids or placebo in the other trial arm did not affect outcomes. The authors concluded that in a population of patients with diabetes, lower rates of serious vascular events with aspirin were largely counterbalanced by the risk of serious bleeding.

Guidelines

Following the ARRIVE, ASPREE and ASCEND trials, the American College of Cardiology (ACC) and American Heart Association (AHA) published guidelines on the primary prevention of CV disease

in 2019¹⁴ which differed from previously published guidelines (see Table 2). The ACC and AHA recognize the difficulty of balancing harm versus benefit in the primary prevention population. Because baseline risk for disease is lower in the primary prevention population, it is generally more difficult to demonstrate benefit from drug therapy in clinical trials. The guidelines recommend against the routine use of low-dose aspirin (defined as 75-100 mg daily) for the primary prevention of CVD in adults >70 years old as well as in adults of any age who have increased risk of bleeding. These were level III recommendations indicating strong recommendations for the purpose of preventing harm.

The ACC/AHA guidelines allow that low-dose aspirin may be considered for primary prevention in select patients between the ages of 40 and 70 who are at higher risk of ASCVD but not at increased risk of bleeding. This was a level IIb recommendation that allows patients and clinicians to weigh individualized risk versus benefit and tailor decisions on a case-by-case basis. The guidelines state that some clinicians may choose to focus on optimal control of other modifiable ASCVD risk factors instead of utilizing aspirin to prevent ASCVD. The guidelines also emphasize lessons learned from recent clinical trials including that “low-dose prophylactic aspirin may be best justified among persons at high ASCVD risk who cannot achieve optimal control of other ASCVD risk factors.”

Antithrombotic Therapy in Patients with Recent Coronary Stent Placement and Atrial Fibrillation

The benefit of aspirin in the secondary prevention of ASCVD is well established. After MI and percutaneous coronary intervention (PCI) with stent placement, dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor (such as clopidogrel, prasugrel or ticagrelor) is standard of therapy for at least 12 months.¹⁵ Beyond one year, the P2Y₁₂

inhibitor may be discontinued based on clinical judgment but aspirin is recommended to be continued indefinitely. However, the treatment of a patient with ASCVD is complicated if the patient also has AF with a CHA₂DS₂-VASc score that indicates a need for anticoagulation therapy to prevent ischemic stroke. The most recent ACC/AHA guidelines for AF recommend anticoagulant use in men with a CHA₂DS₂-VASc score of at least 2 and in women with a CHA₂DS₂-VASc score at least 3.¹⁶ Men with AF and a CHA₂DS₂-VASc score of 1 and women with AF and a CHA₂DS₂-VASc score of 2 may also receive anticoagulation but at a lower level of recommendation. In these patients, their annual risk of stroke necessitates preventative treatment with an anticoagulant, preferably a direct oral anticoagulant (DOAC), such as apixaban, rivaroxaban, edoxaban or and dabigatran, for eligible candidates with non-valvular AF (NVAF). However, placing patients on a triple antithrombotic regimen with aspirin, a P2Y₁₂ inhibitor and an anticoagulant significantly increases the risk of bleeding. In one study, patients on a combination of aspirin, clopidogrel, and a vitamin K antagonist (VKA) for 6 months after stent placement resulted in a 9.9% rate of major and minor bleeding based on Thrombolysis in Myocardial Infarction (TIMI) criteria.¹⁷ The rate of any bleeding based on Bleeding Academic Research Consortium criteria in this group was 40.2%, with half of the bleeding events occurring in the first six weeks. In a Danish cohort study, the adjusted hazard ratio of major bleeding was 3.73 (95% CI 3.23-4.31) for triple antithrombotic therapy with VKA and 2.28 (95% CI 1.67-3.12) for triple antithrombotic therapy with DOAC.¹⁸ Data like this have led to attempts to find treatment alternatives for these patients who potentially require triple antithrombotic therapy.

Recent Data

Recently, four studies have been published comparing triple therapy to

double therapy in patients with AF and recent acute coronary syndrome (ACS) or PCI with stent placement. The WOEST study is the only study to evaluate a VKA-based combination treatment.¹⁹ The other studies, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS, evaluated short-term DOAC-based therapy immediately after recent acute coronary syndrome (ACS) or PCI with stent placement.²⁰⁻²² A fifth study, AFIRE, evaluated antithrombotic therapies in patients with AF but with stable CAD.²³

The WOEST study was an open-label trial performed in The Netherlands and Belgium that randomized 573 patients who required anticoagulation and were undergoing PCI to clopidogrel alone or clopidogrel with aspirin.¹⁹ After PCI, the oral anticoagulant dose was titrated according to the target INR indicated for the underlying disease. Most participants (69%) had AF but 10-11% had mechanical valves and 20% had other indications for chronic anticoagulation therapy. For patients who received a bare metal stent, allocated antiplatelet treatment was continued for at least one month and up to one year at the discretion of the physician. In patients with ACS or who received a drug-eluting stent, clopidogrel was continued for at least one year. Patients were followed for one year or until time of death. For the primary endpoint of any bleeding episode, patients in the triple therapy group had significantly higher rates of bleeding (44.4%) compared to those in the double therapy group (19.4%; HR 0.36; 95% CI 0.26-0.50, $P<0.0001$). The number of patients requiring at least one blood transfusion was higher in the triple therapy group compared to the double therapy group (9.5% vs 3.9%; OR 0.39; 95% CI 0.17-0.84; $P=0.011$). For the secondary composite endpoint of death, myocardial infarction, stroke, target-vessel revascularization and stent thrombosis, there were more events in the triple therapy group (17.6%) compared to the double therapy group (11.1%; non-adjusted HR 0.60; 95% CI

0.38-0.94; $P=0.025$). Among the individual thrombotic or thromboembolic endpoints, rates of MI, revascularization, stroke, and stent thrombosis did not differ between groups. The study concluded that an antithrombotic regimen consisting of clopidogrel and VKA resulted in lower rates of bleeding and thrombotic events compared to triple therapy with those agents plus aspirin. The study did not find evidence of harm by withholding aspirin in a population undergoing PCI and requiring anticoagulation.

The first of the studies to evaluate DOAC-based double agent regimens for patients with concomitant AF and ASCVD was PIONEER AF-PCI.²⁰ The open-label study randomized 2,124 patients with NVAF who had undergone PCI with stenting to receive one of three regimens: rivaroxaban 15 mg once daily plus a P2Y₁₂ inhibitor for 12 months (group 1); rivaroxaban 2.5 mg twice daily plus DAPT for 1, 6, or 12 months (group 2); or the standard dose-adjusted VKA once daily plus DAPT for 1, 6, or 12 months (group 3). Prior to randomization, the investigator prespecified the duration of DAPT and the intended P2Y₁₂ inhibitor (either clopidogrel, ticagrelor or prasugrel). The participants were then stratified by these variables and randomized within 72 hours after sheath removal in a 1:1:1 ratio to group 1, 2 or 3. For patients who were randomized to group 2 or 3 and received either one or six months of DAPT, low-dose aspirin and the respective anticoagulant were continued for the remainder of the 12-month treatment period after the P2Y₁₂ inhibitor was discontinued. The primary safety endpoint was a composite of major and minor bleeding according to TIMI criteria and bleeding requiring medical attention. One of the secondary endpoints included the occurrence of a major adverse CV event (MACE), a composite of CV death, MI, and stroke. After 12 months, the rate of bleeding was lowest in the group that received rivaroxaban 15 mg daily and a P2Y₁₂ inhibitor.

Most patients in group 1 received clopidogrel 75 mg daily (93.1%) while the others received prasugrel (1.7%) or ticagrelor (5.2%). The primary endpoint occurred in 16.8% of participants in group 1, 18% of participants in group 2, and 26.7% of participants in group 3 (HR for group 1 vs group 3, 0.59; 95% CI 0.47-0.76; $P<0.001$; HR for group 2 vs group 3, 0.63; 95% CI 0.50-0.80; $P<0.001$). With regards to the secondary endpoint for efficacy, MACE occurred in 6.5% of group 1 participants, 5.6% of group 2 participants, and 6% in group 3 participants ($P>0.05$ for both comparisons). The authors concluded that the two rivaroxaban-based therapies were associated with lower rates of clinically significant bleeding compared to standard therapy with dose-adjusted VKA therapy. Although the study was not adequately powered to detect differences in the secondary endpoint, there were no detectable differences in the rates of MACE between groups.

RE-DUAL PCI was the second study to compare triple antithrombotic therapy to dual antithrombotic therapy in a population with AF undergoing PCI.²¹ Like PIONEER AF-PCI, this was an open-label study that randomized 2,725 patients to one of three treatment groups. The first group received dabigatran 110 mg twice daily plus either clopidogrel or ticagrelor (110 mg dual therapy group). The second group received dabigatran 150 mg twice daily plus either clopidogrel or ticagrelor (150 mg dual therapy group). The third group received triple therapy with dose-adjusted warfarin plus low-dose aspirin and either clopidogrel or ticagrelor (triple therapy group), although aspirin was discontinued after one month in patients with bare metal stents or after three months in patients with drug-eluting stents. All patients received an anticoagulant and a P2Y₁₂ inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) for at least 12 months after randomization. Patients were stratified by age and location before randomization as elderly patients outside the US were not eligible

to be assigned to the 150 mg dual therapy group due to differences in dabigatran labeling in these countries. The primary endpoint was the first major or clinically relevant nonmajor bleeding event as defined by International Society on Thrombosis and Hemostasis (ISTH) criteria. One of the main secondary endpoints was a composite of death, unplanned revascularizations and thromboembolic events (including MI, stroke and systemic embolism). When compared to the third group, the first group (110 mg dual therapy group) had a statistically significant lower bleeding rate (15.4% in group 1 vs 26.9% in corresponding group 3; HR 0.52; 95% CI 0.42-0.63; $P<0.001$ for non-inferiority). Similarly, the rate of bleeding was lower in the second group (150 mg dual therapy group) compared to the third group (20.2% in group 2 vs 25.7% in corresponding group 3; HR 0.72; 95% CI 0.58-0.88; $P<0.001$ for non-inferiority). With regards to the secondary endpoint for efficacy, the 150 mg dual therapy group had a non-significant lower rate of thromboembolic events, death or unplanned revascularization compared to the corresponding triple therapy group (11.8% vs 12.8%; HR 0.89; 95% CI 0.67-1.19; $P=0.44$). The 110 mg dual therapy group had a higher rate of the secondary endpoint compared to the corresponding triple therapy group, but this was not statistically significant (15.2% vs 13.4%; HR 1.13; 95% CI 0.90-1.43; $P=0.30$). Of note, most patients received clopidogrel and only 12% received ticagrelor. The authors concluded that dual therapy with a P2Y₁₂ inhibitor and dabigatran (either 110 mg twice daily or 150 mg twice daily) resulted in lower rates of bleeding compared to triple therapy with warfarin and two antiplatelet agents. In addition, dual therapy with dabigatran was non-inferior to triple therapy with warfarin in terms of risk for thromboembolic events, death or unplanned revascularization.

The largest of these clinical trials was the AUGUSTUS study.²² Unlike the

other studies that involved three groups, the AUGUSTUS study randomized 4,614 patients with AF in a 2x2 factorial design to receive apixaban or VKA and either low-dose aspirin or placebo for six months. The study enrolled patients with planned use of a P2Y₁₂ inhibitor (including clopidogrel, prasugrel or ticagrelor) for six months after ACS or PCI. Patients randomized to receive apixaban took 5 mg twice daily unless they met criteria for 2.5 mg twice daily dosing. Assignment to apixaban or dose-adjusted VKA was open-label but the assignment to aspirin or placebo was double-blinded. The primary outcome for both factorial comparisons was either major or clinically relevant nonmajor bleeding according to ISTH criteria. Secondary outcomes included the composite of death or hospitalizations and the composite of death or ischemic events. After six months of follow-up, the rate of major and clinically nonmajor bleeding was 10.5% in the apixaban group compared to 14.7% in the VKA group (HR 0.69; 95% CI 0.58-0.81; $P<0.001$ for non-inferiority and superiority testing). In the antiplatelet regimen comparison, bleeding occurred in 16.1% in the aspirin group and 9% in the placebo group (HR 1.89; 95% CI 1.59-2.24; $P<0.001$). The rate of primary endpoint was highest among those receiving VKA and aspirin (18.8%) and lowest among patients receiving apixaban and placebo (7.3%). With regard to secondary outcomes, the composite of death and hospitalization occurred in 23.5% of the apixaban group and 27.4% of the VKA group (HR 0.83; 95% CI 0.74-0.93; $P=0.002$). In the antiplatelet regimen comparison, death or hospitalization occurred in 26.2% of the aspirin group compared to 24.7% of the placebo group (HR 1.08; 95% CI 0.96-1.21, P -value non-significant). Death or hospitalization was most common in the group receiving VKA and aspirin (27.5%) and lowest among those receiving apixaban and placebo (22%). For the composite endpoint of death or ischemic events, the

rate was 6.7% in the apixaban group vs 7.1% in the VKA group (HR 0.93; 95% CI 0.75-1.16; *P*-value non-significant). The rate was 6.5% in the aspirin group vs 7.3% in the placebo group (HR 0.89; 95% CI 0.71-1.11; *P*-value not tested). This was the first study to test the independent effects of antiplatelet agents and anticoagulation therapy in patients with AF and recent ACS or PCI with stent placement. Apixaban was associated with a lower rate of bleeding and hospitalization compared to VKA. There was a higher rate of bleeding with aspirin compared to placebo with no difference in secondary outcomes. Therefore, authors concluded that apixaban with clopidogrel, but without aspirin, appeared to be effective and was not associated with excess adverse events in this high-risk population after ACS or PCI.

The most recent trial is the AFIRE study, an open-label, non-inferiority study conducted in Japan that randomized 2,236 patients to receive monotherapy with rivaroxaban 15 mg daily or combination therapy with rivaroxaban plus a single antiplatelet agent (either aspirin or a P2Y₁₂ inhibitor).²³ The study included patients with AF and stable coronary artery disease (CAD) defined as a history of PCI or coronary artery bypass grafting (CABG) at least one year prior to enrollment or a history of angiography-confirmed CAD not requiring revascularization. The primary efficacy endpoint was the composite of stroke, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause. The primary safety endpoint was major bleeding as defined by ISTH. The study was terminated two months early by recommendation of the independent data and safety monitoring committee due to higher risk of death from any cause in the combination therapy group. At the time of termination, the median

treatment duration was 23 months and 70% of the patients in the combination treatment group were on aspirin. For each of the primary endpoints, the rates were lower in the rivaroxaban monotherapy group. For the efficacy endpoint, the rates were 4.14% and 5.75% for the monotherapy and combination therapy groups, respectively (HR 0.72; 95% CI 0.55-0.95; *P*<0.001 for non-inferiority). Likewise, the rates of bleeding were 1.62% and 2.76% for the monotherapy and combination therapy groups, respectively (HR 0.59; 95% CI 0.39-0.89; *P*=0.01). The AFIRE study showed that rivaroxaban monotherapy was non-inferior to combination therapy with rivaroxaban and an antiplatelet agent for the composite of CV events or death from any cause in a population of patients with AF and stable CAD. The study also showed that rivaroxaban monotherapy was associated with a significantly lower rate of bleeding.

WOEST, RE-DUAL PCI, PIONEER AF-PCI, and AUGUSTUS together indicate that double therapy with a P2Y₁₂ inhibitor and an oral anticoagulant reduces the risk of bleeding in patients who have AF and recent ACS or PCI. Eliminating aspirin from the antithrombotic regimen in these patients reduces major and nonmajor bleeding. One limitation of these studies is that the follow-up periods were relatively short, generally limiting study duration to the first year after ACS or PCI. The follow-up period ranged from 6 months in AUGUSTUS to a mean of 14 months in RE-DUAL PCI. Another limitation was that the studies were powered for primary outcomes related to bleeding. Ischemic or thrombotic events were studied only as secondary endpoints and thus, the studies were not

powered to detect differences in ischemic or thrombotic events. The AFIRE study provides additional information by evaluating patients who had undergone PCI or CABG more than one year previously. Furthermore, the AFIRE study was the only one powered to assess the non-inferiority of rivaroxaban monotherapy for the primary efficacy endpoint. Therefore, the five studies collectively indicate that antithrombotic therapy without aspirin may be used safely in patients with AF and ASCVD. Additionally, single oral anticoagulation therapy without any antiplatelet agents may be preferred over combination therapy in those who are beyond the first year after PCI or ACS.

Guidelines

In 2019, the AHA and ACC updated their guidelines for the treatment of AF after the publication of WOEST, PIONEER AF-PCI, and RE-DUAL PCI.¹⁶ The 2019 guidelines update includes several recommendations for patients with AF who have undergone PCI with stenting for ACS based on clinical trial data. For these patients, there are Class IIa recommendations that double therapy is a reasonable option to reduce the risk of bleeding compared to triple therapy. Options for double therapy include:

1. A P2Y₁₂ inhibitor (clopidogrel or ticagrelor) and dose-adjusted VKA
2. A P2Y₁₂ inhibitor (clopidogrel) and low-dose rivaroxaban 15 mg daily, and
3. A P2Y₁₂ inhibitor (clopidogrel) and dabigatran 150 mg twice daily.

Considering that the AUGUSTUS study was published after the guidelines update, it is reasonable to assume that double therapy with apixaban and a P2Y₁₂ inhibitor would be similarly recommended. The guidelines further state that if triple therapy is prescribed for patients who are at higher risk for stroke, a transition to double therapy at four to six weeks may be considered as a Class IIb recommendation. Therefore, the recommendations

indicate that aspirin may not be necessary outside of the periprocedural period with stent placement unless patients are at high thrombotic risk. In concordance with the ACC/AHA AF guidelines update, expert opinion published as a white paper in 2018 states that double therapy should be the default strategy for most patients, with the preference for clopidogrel as the antiplatelet agent of choice.²⁴ If a patient is at higher risk of thrombosis and lower risk of bleeding, then ticagrelor can be considered. Expert opinion also states that elimination of aspirin from patients' antithrombotic regimens should be done as soon as possible, including upon discharge after hospitalization for ACS and PCI with stent placement. Finally, expert opinion recommends lifelong use of an oral anticoagulant agent (preferably a DOAC) and discontinuation of the single antiplatelet agent (preferably clopidogrel) after 12 months in most patients

depending on individual bleeding and thrombotic risks. Even though the AFIRE study was published after the white paper, it corroborates the recommendations based on expert opinion.

Conclusion

A growing body of evidence involving aspirin seems to indicate that aspirin may be increasing the risk of bleeding without conferring substantial antithrombotic benefit in certain populations. In the primary prevention population, the decision to utilize aspirin to prevent CV disease will be on a case-by-case basis after discussions between clinicians and patients regarding the risk-versus-benefit ratio (especially in patients with higher baseline risk). In patients with AF and ASCVD after stent placement, aspirin can be used in the periprocedural period but recent clinical trial data and expert opinion indicate that aspirin can

be discontinued soon after, with the patient remaining on an anticoagulant (preferably a DOAC agent and a P2Y₁₂ inhibitor). After one year on this combination, it may be safe to discontinue the antiplatelet agent, leaving the patient on long-term anticoagulation therapy only. As more clinical trials are concluded, additional data will help to elucidate the ideal antithrombotic therapy, either with or without aspirin to treat and prevent future CV events. ○

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Use of Pharmacy Residents to Increase Pharmacist Involvement with ACLS

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Requests for Information

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Introduction

Pharmacist participation on advanced cardiac life support (ACLS) teams has been shown to increase compliance with treatment guidelines and decrease hospital mortality.¹⁻³ Despite this finding, the overwhelming majority of institutions indicate that pharmacists do not participate on their ACLS teams.^{3,4} Reasons for lack of participation can include insufficient staffing, inadequate training, and viewing pharmacist involvement as an unnecessary pharmacy service.⁴ Pharmacy residents have been identified as providers who can expand pharmacist-specific patient care roles, and numerous pharmacy residency programs incorporate residents into the multidisciplinary response to cardiopulmonary resuscitation events.⁵⁻⁹ However, there is a lack of literature assessing if pharmacy residents can be used to increase pharmacist involvement on ACLS teams at institutions where pharmacists do not currently participate. We hypothesized that pharmacy residents could be trained to become ACLS responders at institutions unable to involve staff pharmacists in ACLS events.

Methods

This prospective, observational study was designed to assess the feasibility of utilizing pharmacy residents to increase pharmacist involvement with ACLS teams and was performed at Loma Linda University Medical Center (LLUMC) from July 2015 to June 2016. Institutional Review Board approval was obtained on April 17, 2015 (IRB# 5150091). LLUMC is a 797-bed university teaching hospital designated as a level I adult/pediatric trauma center. The pharmacy residency program includes general practice and community pharmacy practice postgraduate year 1 (PGY1) residencies. ACLS events occurring outside of intensive care units (ICU) and the Emergency Department (ED) are activated as Code Blues. Code Blues are utilized for patients experiencing cardiac arrest. Other types of medical emergencies, including myocardial infarction, stroke, and trauma, are assigned different codes (eg, Code STEMI, Stroke, and Trauma) and different code teams (eg, cardiology, neurology, and trauma). This study was only designed to promote pharmacist involvement with Code Blue events; therefore, residents only responded to Code Blues. Code Blues will be referred to as ACLS events for the remainder of this manuscript.

ACLS event teams include an attending physician, medical residents, nursing, and respiratory therapists who are notified of events via a pager system. ACLS event teams are always present and respond to all events in the hospital. Prior to this study, pharmacists were not included on these teams (ie, pharmacists did not carry pagers to be notified of ACLS events). Additionally, ACLS certification was not mandatory for staff pharmacists. However, the pharmacy department utilized a decentralized pharmacy staffing model, so staff pharmacists were regularly present in inpatient units during

daytime hours Monday through Friday. If staff pharmacists with ACLS certification were present in an inpatient unit with a patient experiencing an ACLS event, the pharmacist could assist the team.

PGY1 general practice pharmacy residents at LLUMC were recruited for this study. After obtaining informed consent, collecting demographic information (eg, age and gender), and verifying that American Heart Association Basic Life Support (BLS) and ACLS certification had been acquired, residents completed a pharmacist-specific ACLS training program that included didactic instruction and a high-fidelity simulation experience. Didactic instruction was taught by ACLS-certified pharmacists and included a review of medications typically used during ACLS, rapid sequence intubation (RSI), vasopressors, and inotropes. This review included discussion of indications, precautions, contraindications, dosing, pharmacokinetics and pharmacodynamics (ie, expected onset and duration), adverse effects, administration recommendations, and monitoring parameters. This medication-specific information was not provided by this institution's ACLS certification courses. Discussion of RSI medications was included because patients requiring ACLS often require intubation. Methods of preparing intravenous (IV) dosage forms were also reviewed during instruction. To assess baseline and acquired knowledge, residents completed a written competency before and after didactic instruction consisting of 30 multiple-choice questions and assessing information covered during didactic instruction. Residents completed the same competency before and after didactic instruction. Answers to competency questions were reviewed with all residents after completion of the post-didactic instruction competency. Didactic instruction was completed during the first month of the PGY1

residency program and was incorporated into resident orientation.

Immediately after completion of didactic instruction, residents participated in a high-fidelity simulation session designed to test ACLS and medical emergency knowledge. Mannequins used for the session were SimMan® 3G and operated with Laerdal Learning Application software (Laerdal Medical AS, Stavanger, Norway). Mannequins had palpable pulses, functional airways and voice feedback as well as the ability to display physiologic variables including heart rate, blood pressure, cardiac rhythm, and oxygen saturation. Because residents would be responding to ACLS events as members of a team, residents were divided into two teams with each team participating in one clinical scenario. Scenarios involved adult patients who developed cardiac arrest due to reversible causes (sepsis or gastrointestinal bleed) with rhythms including pulseless electrical activity (PEA), asystole, or ventricular tachycardia. Residents were required to interact with the mannequins – along with physician, nurse, and respiratory therapist actors – in order to provide pharmacotherapy-related recommendations. Residents were expected to make recommendations based on patient medical history, allergies, laboratory results, physiologic variables, and cardiac rhythms. Actors were permitted to ask residents questions and provide clinical information to offer guidance and emphasize teaching points. After each scenario, the residents were debriefed and provided feedback from scenario actors and ACLS-certified facilitators. Suggestions for improvement and review of clinical pearls relevant to the case were also provided. The process was then repeated for the second group of residents. Based on resident feedback, another optional session was offered later in the residency year with a format similar to the aforementioned session;

however, two different cases were used. Causes of cardiac arrest in those cases included sepsis or intentional overdose, with rhythms including PEA or asystole.

After completing the pharmacist-specific ACLS training and obtaining their pharmacist licensure, residents were assigned to ACLS response with the hospital's ACLS event teams. During each six-week residency rotation block, residents were assigned to two-week periods where two residents would carry ACLS event pagers from 8:00 AM to 4:00 PM Monday through Friday. Only residents physically present in the hospital for their rotations were required to carry pagers. Both residents were expected to respond to all ACLS events during their assigned response periods and provide medication-related support (eg, medication preparation, dosing recommendations, drug information, IV compatibility, order entry, etc) to ACLS event teams.

To assess the impact of training and ACLS event response on resident ACLS knowledge, confidence, comfort, and understanding of the pharmacist's role during ACLS events, residents were required to complete anonymous self-evaluations before training, after training, and periodically during the ACLS event response period (Table 1). Self-evaluations utilized a five-point Likert-type scale (1- strongly disagree, 2- disagree, 3- neither agree nor disagree, 4- agree, 5- strongly agree). Residents were also asked to include the number of ACLS event responses they had participated in at the time of evaluation completion.

Demographic data was analyzed using descriptive statistics. Ordinal and continuous variables were reported as medians with interquartile ranges (IQR) and means with standard deviations (SD), respectively. Pre- and post-didactic instruction competency scores were

Table 1. Self-Evaluation Distributed to Pharmacy Residents

Statement	Strongly Disagree				Strongly Agree
S1. I am familiar with the contents of the medication tray in the code cart	1	2	3	4	5
S2. I am familiar with the contents of the RSI box	1	2	3	4	5
S3. I am comfortable preparing medications for ACLS/medical emergencies	1	2	3	4	5
S4. I am comfortable dosing medications for ACLS/medical emergencies	1	2	3	4	5
S5. I am comfortable providing medication recommendations to other healthcare providers during ACLS/medical emergencies	1	2	3	4	5
S6. I understand the role of the pharmacist during medical emergencies	1	2	3	4	5
S7. I believe pharmacists should not be involved with ACLS/medical emergencies	1	2	3	4	5
S8. I am prepared to participate in ACLS/medical emergencies in the hospital	1	2	3	4	5
Statement					
S9. Number of medical emergencies I have participated in (eg, code blue emergency, trauma resuscitation, intubation, etc)	0	1-4	5-10	>10	

Abbreviations: ACLS, advanced cardiac life support; RSI, rapid sequence intubation; S, statement.

Table 2. Results of Self-Evaluations Prior to and Immediately After Pharmacist-Specific ACLS Training

Statement, median (IQR) ^a	Prior to training	Immediately after training	P-value
S1. I am familiar with the contents of the medication tray in the code cart	3 (2.25-3)	3.5 (3-4)	0.096
S2. I am familiar with the contents of the RSI box	2 (1.25-2.75)	3 (3-3.75)	0.02
S3. I am comfortable preparing medications for ACLS/medical emergencies	2 (2-3)	2 (2-3.75)	0.157
S4. I am comfortable dosing medications for ACLS/medical emergencies	2.5 (2-3)	3 (2.25-3)	0.083
S5. I am comfortable providing medication recommendations to other healthcare providers during ACLS/medical emergencies	2 (1.25-3)	3 (2.25-3)	0.102
S6. I understand the role of the pharmacist during medical emergencies	4 (3-4)	4 (3-4)	0.317
S7. I believe pharmacists should not be involved with ACLS/medical emergencies	1 (1-1)	1 (1-1.75)	0.317
S8. I am prepared to participate in ACLS/medical emergencies in the hospital	3 (2-3)	3 (2-3)	0.317

^a Responses based on Likert scale of which 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree.

Abbreviations: ACLS, advanced cardiac life support; IQR, interquartile range; RSI, rapid sequence intubation; S, statement.

compared using the paired t-test. Self-evaluation scores were compared using the Wilcoxon signed rank test. Statistical significance was set at $P < 0.05$ and all tests were two-tailed. Statistical analysis was completed using SPSS 23.0 (IBM, Inc., Armonk, NY).

Results

Eight PGY1 residents were included in the study. Mean age was 26.3 (SD, 1.03) and 75% of participants were female. After completion of the didactic instruction component involving pharmacist-specific ACLS training, residents achieved significantly higher competency scores compared to scores prior to training (24.88 [SD, 4.67] vs 22.75 [SD, 4.77]; $P = 0.0345$). Self-evaluations collected prior to and immediately after training demonstrated a significant increase in familiarity with RSI medications after completion of training (Table 2). There were no significant differences between any other self-evaluation statements (Table 2).

Comparison of self-evaluation scores prior to training and four months after the start of ACLS event response demonstrated significant increases in familiarity with contents of ACLS medication trays, comfort with preparation of ACLS medications, dosing of ACLS medications, and comfort with making recommendations to providers during ACLS events (Table 3). There were no significant differences in familiarity with RSI medication box contents, understanding the role of the pharmacist during medical emergencies, belief that pharmacist should not be involved with ACLS/medical emergencies, and preparedness to participate in ACLS/medical emergencies (Table 3).

Comparison of self-evaluation scores prior to training and eight months after start of ACLS event response demonstrated significant increases in familiarity with contents of ACLS medication trays and RSI trays,

preparation and dosing, ability to make recommendations, and preparedness to participate in ACLS events (Table 4). The only scores not significantly different were related to understanding the role of the pharmacist during medical emergencies and belief that pharmacists should not be involved with ACLS/medical emergencies (Table 4).

Over the course of the 8-month ACLS event response period, residents reported the number of ACLS events they attended. Prior to training, 25% of residents had attended no ACLS events (Table 5). Eight months after the start of the ACLS event response, all residents had attended at least one event (Table 5).

Discussion

This study analyzed the feasibility of utilizing PGY1 pharmacy residents to increase pharmacist response with ACLS teams. Providing pharmacist-specific ACLS training – including didactic and high-fidelity simulation components – in addition to ACLS certification increased competency scores and familiarity with RSI medications. Significant increases in familiarity with dosing and preparation of ACLS medications, understanding the role of the pharmacist during ACLS events, and preparedness to participate in ACLS events were not immediately observed but were noted at four and eight months after residents had started responding to ACLS events. These findings suggest that residents needed to respond to real-life ACLS events to solidify their knowledge.

Numerous studies with different learners demonstrate improvements in knowledge acquisition, knowledge retention, preparedness, confidence, and clinical performance when simulation training is used to supplement didactic instruction.¹⁰⁻²² Two studies employed classroom and high-fidelity simulation training to enhance pharmacy resident ACLS skills.^{10,11} Eng et al found that residents demonstrated improvement in

Table 3. Results of Self-Evaluations Prior to Pharmacist-Specific ACLS Training and 4 Months After Start of ACLS Event Response

Statement, median (IQR) ^a	Prior to training	Four months after start of code blue response	P-value
S1. I am familiar with the contents of the medication tray in the code cart	3 (2.25-3)	4 (4-4)	0.014
S2. I am familiar with the contents of the RSI box	2 (1.25-2.75)	3 (2.25-4)	0.059
S3. I am comfortable preparing medications for ACLS/medical emergencies	2 (2-3)	3.5 (2.25-4)	0.038
S4. I am comfortable dosing medications for ACLS/medical emergencies	2.5 (2-3)	3.5 (2.25-4)	0.034
S5. I am comfortable providing medication recommendations to other healthcare providers during ACLS/medical emergencies	2 (1.25-3)	3 (2-4)	0.02
S6. I understand the role of the pharmacist during medical emergencies	4 (3-4)	4 (3.25-5)	0.096
S7. I believe pharmacists should not be involved with ACLS/medical emergencies	1 (1-1)	1.5 (1-5)	0.102
S8. I am prepared to participate in ACLS/medical emergencies in the hospital	3 (2-3)	3.5 (2.25-4)	0.068

^a Responses based on Likert scale of which 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree.

Abbreviations: ACLS, advanced cardiac life support; IQR, interquartile range; RSI, rapid sequence intubation; S, statement.

Table 4. Results of Self-Evaluations Prior to Pharmacist-Specific ACLS Training and 8 Months After Start of ACLS Event Response

Statement, median (IQR) ^a	Prior to training	Eight months after start of code blue response	P-value
S1. I am familiar with the contents of the medication tray in the code cart	3 (2.25-3)	4 (4-4)	0.016
S2. I am familiar with the contents of the RSI box	2 (1.25-2.75)	4 (3-4)	0.038
S3. I am comfortable preparing medications for ACLS/medical emergencies	2 (2-3)	4 (3.25-4.75)	0.026
S4. I am comfortable dosing medications for ACLS/medical emergencies	2.5 (2-3)	4 (3.25-4)	0.015
S5. I am comfortable providing medication recommendations to other healthcare providers during ACLS/medical emergencies	2 (1.25-3)	4 (3-4)	0.016
S6. I understand the role of the pharmacist during medical emergencies	4 (3-4)	5 (4-5)	0.054
S7. I believe pharmacists should not be involved with ACLS/medical emergencies	1 (1-1)	1 (1-1.75)	0.785
S8. I am prepared to participate in ACLS/medical emergencies in the hospital	3 (2-3)	4 (3.25-4.75)	0.026

^a Responses based on Likert scale of which 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree.

Abbreviations: ACLS, advanced cardiac life support; IQR, interquartile range; RSI, rapid sequence intubation; S, statement.

knowledge, confidence, and competency with advanced resuscitation skills after completion of lectures and simulation sessions involving cardiopulmonary arrest.¹⁰ Bartel found that didactic instruction followed by simulation experience increased resident comfort and confidence and that residents felt this training prepared them to function on ACLS teams.¹¹ Although the participants, training, and self-evaluation statements were similar between our study and those of Eng et al and Bartel, these findings differed slightly. We found that only competency scores and familiarity with RSI medications significantly increased post-training. This result was surprising considering the content of our didactic instruction included similar topics (ACLS pharmacology, medication preparation); however, we did not include extensive review of ACLS algorithms or cardiac rhythm identification. It was hypothesized that the education received on these topics during ACLS certification would be adequate to perform their role during an ACLS event. The simulation component in our study was also similar to Eng et al and Bartel in that it included high-fidelity patient simulators and multiple ACLS cases. It is possible that differences between when training was completed (first month of residency in our study vs three to six months into residency in Eng et al and Bartel) could

have affected self-evaluation scores. More experienced residents may have already been familiar with ACLS and simulation training helped review the concepts they were unfamiliar with, resulting in increased confidence post-simulation.

To our knowledge this is the first study to evaluate pharmacy resident self-assessment scores as they became primary pharmacist responders on ACLS teams. The consistent improvements in comfort, preparedness, and confidence over the ACLS event response period suggest that participation in events effectively empowered residents to participate. In a survey of pharmacy residency programs (PGY1 and PGY2) throughout the United States and Puerto Rico, 30% of residency programs required resident response at CPR events while 38% made the opportunity optional.⁹ In that survey, 74% of responders stated that pharmacists were required to attend CPR events at their institutions which suggests residents responding to these events were responding with a pharmacist preceptor.⁹ In our study, residents alone were responding to ACLS events. Pharmacists at our medical center have the option of participating in ACLS events if they are ACLS-certified, but they do not carry pagers and would only be aware that an ACLS event is occurring if they were physically in the unit or if they were notified by hospital staff. Our hospital regularly staffs pharmacists in ICUs, several non-ICU inpatient units, and the ED, so it is possible that residents responding to ACLS events were given guidance by staff pharmacists. However, ACLS events are not activated in ICUs or the ED and staff pharmacists are only present in a few inpatient units, which suggests residents did not have regular interaction with staff pharmacists during ACLS events.

Several studies have evaluated utilizing pharmacy residents to expand clinical services. Services provided have included physician education and managing a

Table 5. ACLS Events Attended by PGY1 Pharmacy Residents Prior to Pharmacist-Specific Training, Four Months, and Eight Months After Start of ACLS Event Response

Number of ACLS Events, n (%)	Prior to training	Four months	Eight months
0	2 (25)	1 (12.5)	0 (0)
1-4	4 (50)	3 (37.5)	2 (25)
5-10	2 (25)	2 (25)	3 (37.5)
>10	0 (0)	2 (25)	3 (37.5)

Abbreviations: ACLS, advanced cardiac life support; PGY1, postgraduate year 1.

transition of care service.^{6,8} Agee et al reported a significant decrease in stress ulcer prophylaxis prescribing after a pharmacy resident-led education seminar.⁶ Salas et al noted a reduction in 30-day heart failure readmission rates following implementation of a pharmacy resident-led transition of care service which included counseling, ensured obtainment of prescriptions, and follow-up.⁸ These studies highlight the positive impact resident-led services can have on patient care and suggests that residents can be a useful resource to health care institutions. Draper et al observed a significant increase in compliance with ACLS guidelines when pharmacists were present during CPR events (59.3% vs 31.9%; $P=0.03$).¹ The responsibilities of the pharmacist in that study – including drug therapy recommendations, procurement, and preparation for administration – were similar to the responsibilities instilled during our pharmacist-specific training. We believe that resident involvement during ACLS response may result in safer, more appropriate care; however, studies evaluating clinical outcomes would be necessary to evaluate this hypothesis.

There were several limitations of this study. First, we did not have a control group of residents who responded to ACLS events but did not undergo pharmacist-specific training. This leaves us unable to assess if training contributed to increases observed in self-evaluation scores or if increases were due to rotation or staffing experiences. Second, residents completed the same competency before and after didactic training, so improvement in scores could have been due to factors other than increased medication knowledge (eg, memorization of responses to assessment questions). However, instructors did not review competency answers until after residents completed the post-training competency. This limits the likelihood that improvements were solely due to

memorizing answers. Third, we did not assess the clinical impact of pharmacy residents during ACLS response. Draper et al found that presence of a pharmacist on resuscitation teams increased compliance with ACLS guidelines.¹ McEvoy et al observed that adherence to ACLS guidelines had a positive correlation with return of spontaneous circulation.²³ If residents were increasing adherence to ACLS guidelines, they could have a positive impact on clinical outcomes.

Fourth, we did not use evaluators to assess resident performance during ACLS event response. Previous studies involving medical students, nurses, respiratory therapists, and pharmacy residents have employed evaluators to assess participant performance during simulation.^{10,16,19} In these studies, evaluators utilized performance checklists to ensure participants were completing important actions, such as obtaining relevant clinical information, identifying cardiac rhythms, and providing appropriate dosing recommendations.^{10,16,19} Although we did not complete formal checklists during our simulation training, facilitators took note of important interventions not completed by residents and provided feedback during debriefing. Due to staffing limitations, study investigators were unable to evaluate residents during ACLS event response and could not assess if key interventions emphasized during training were being performed. Future studies with similar staffing limitations could consider having residents self-assess after each event to determine if their performance was appropriate (eg, able to identify cardiac rhythm, appropriate dosing recommendations, closed-loop communication, etc). Fifth, we did not survey physician, nursing, and respiratory therapist members of ACLS event teams to determine the impact of pharmacy residents during ACLS events. Two surveys of ED providers and nurses reported that pharmacist participation

in codes and resuscitations was the second most-important contribution to medication safety after availability for consultations.^{24,25} This suggests that the presence of pharmacists on ACLS event teams have a positive impact on patient safety and team dynamics. Finally, our sample size was small, which may limit the generalizability of our findings. Larger studies may be needed to confirm the results of our study.

Conclusion

Completion of pharmacist-specific ACLS training followed by participation in ACLS events allowed PGY1 pharmacy residents to develop the knowledge, skills, and confidence to become independent members of ACLS teams. However, research evaluating their impact on clinical outcomes is needed. Institutions unable to involve staff pharmacists with these teams should consider utilizing pharmacy residents in this role. ○

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