



A Breath of Fresh Air: a Comparison of the Focused Update in the 2020 Asthma Management Guidelines and the 2023 GINA Guidelines Updates

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Section: Short communication

Objective:

- Identify six areas of emphasis in the 2020 National Asthma Education and Prevention Program (NAEPP) guideline update and coinciding recent recommendations in the 2023 Global Initiative for Asthma (GINA) report

Introduction

The National Asthma Education and Prevention Program (NAEPP) guidelines were updated in December 2020 to incorporate the significant progress made in the research and understanding of the pathophysiology and efficacious treatments for asthma since the previous version in 2007. The guideline updates were conducted by an Expert Panel that consisted of pulmonary, allergy, and general medicine specialists.¹ Six topics were the focus of the 2020 NAEPP guideline update and include fractional exhaled nitric oxide testing (FeNO), allergen mitigation, inhaled corticosteroids (ICS), long-acting muscarinic agonists (LAMA), immunotherapy, and bronchial thermoplasty (BT). These NAEPP guideline updates and understanding of evolving asthma management strategies through the annual Global Initiative for Asthma (GINA) report and primary literature are important to the realm of pharmacy because of the need for patient counseling on the updated topics and the inclusion of new aspects on asthma management.^{1,2}

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Fractional Exhaled Nitric Oxide Testing

The 2020 NAEPP guideline update includes a conditional recommendation for the use of a FeNO as an adjunctive diagnostic tool for patients who are at least five years old when the diagnosis of asthma is uncertain or a spirometry test cannot be performed appropriately. FeNO is also conditionally recommended as an additional assessment variable for monitoring of asthma and efficacy of anti-inflammatory therapy.¹ These updates were based upon a comparative effectiveness review of the utilization of FeNO which demonstrated a lack of robust evidence regarding FeNO-guided treatment.³ FeNO testing is not recommended by NAEPP as the sole indicator for future exacerbations, asthma control, nor the severity of asthma.¹ The 2023 GINA report states that the initiation of ICS treatment can be supported by FeNO measurements, but FeNO cannot be used to reject the use of ICS. The GINA report also notes that more studies are needed in order to determine the true benefit of FeNO-guided treatment of asthma and states that FeNO is not an established method for asthma diagnosis.²

Inhaled Corticosteroids

ICS are an important group of medications for the treatment and management of chronic asthma. The 2020 NAEPP guideline update addresses utilization of intermittent ICS courses in the treatment and management of asthma (Table 1). A new perspective has come to light from the 2023 GINA report, where terminology and approach for use of intermittent ICS are further elucidated. The term AIR (anti-inflammatory reliever) was designated for therapies that include ICS-formoterol or ICS-SABA (short-acting beta-agonist). In this most recent GINA report, AIR only therapy is indicated as the preferred reliever for steps 1-2 (over SABA alone) and in steps 3-5 where ICS-formoterol are preferred as MART (maintenance and reliever therapy).² This use of ICS-SABA is based upon a pivotal clinical trial, the MANDALA trial, that evaluated the utilization of a fixed dose albuterol-budesonide inhaler in over 3000 patients 4 years of age and older as reliever therapy. The study found a statistically significant reduction of 26% in the risk of severe asthma exacerbations between the high-dose ICS with albuterol group compared to albuterol alone (HR 0.74, 95% CI, 0.62-0.89, p = 0.001).⁴ In January 2023, the Food and Drug Administration (FDA)

approved the first ICS-SABA (albuterol and budesonide) combination product in the United States, Airsupra[®]. Notably, this combination product is only FDA approved for patients 18 years of age and older.⁵

Long-Acting Muscarinic Agonists

As use of LAMA in asthma management was not included in the previous guideline version, the 2020 NAEPP guideline update incorporated recommendations for LAMA use based upon several contemporary trials. Recommendations include patients at least 12 years of age with uncontrolled-persistent asthma receiving a long-acting beta-agonist (LABA) in addition to their ICS before a LAMA. If a LABA cannot be used in addition to the ICS, adding a LAMA is conditionally recommended instead of keeping the ICS alone. The 2020 NAEPP guideline update also recommends the addition of a LAMA in this same patient population who are already on an ICS and LABA and do not have their symptoms controlled, which is consistent with the 2023 GINA report. Both resources emphasize avoiding the use of LAMA alone in asthma to due to increased risk of severe exacerbations.^{1,2}

Immunotherapy

Immunotherapy for allergic asthma includes administration of an allergen either subcutaneously (SCIT) or sublingually (SLIT) to establish exposure to decrease the allergic response mediated by IgE in individuals when they are exposed to an allergen to which they are sensitive. The 2020 NAEPP guideline update conditionally recommends SCIT as an adjunctive treatment in individuals five years of age and older who have mild to moderate allergic asthma and evidence of worsening symptoms after exposure to a specific antigen, while SLIT is recommended against.¹ The 2023 GINA report advises that risk-benefit consideration of SCIT be made for each patient by weighing benefit of clinical improvement with risk of adverse effects, cost and inconvenience. From more recent literature, the 2023 GINA report recommends use of SLIT in adults with allergic rhinitis, sensitized to dust mites, with persisting symptoms despite low or medium dose ICS, as long as FEV₁ is >70% predicted. More evidence regarding both SCIT and SLIT are under review and are anticipated to be addressed in future GINA reports.²

Table 1: Summary of 2020 NAEPP update recommendations for intermittent ICS¹

Recommendation	Strong or Conditional	Quality of Evidence
0-4 years old with recurrent wheezing due to respiratory tract infection: start short course daily ICS along with short-acting beta-agonist (SABA)	Conditional	High
> 12 years old with mild persistent asthma: low dose daily ICS with as needed SABA or as needed ICS and SABA concomitantly	Conditional	Moderate
> 4 years old with moderate to severe persistent asthma: ICS-formoterol single inhaler for daily controller and as needed reliever therapy, referred to as MART (maintenance and reliever therapy)	Strong	Moderate-High

Bronchial Thermoplasty

The 2020 NAEPP guideline update included BT for the first time and advised against the use of BT, specifically looking at individuals 18 years and older with moderate-to-severe, persistent asthma, even if they were uncontrolled on the multicomponent medical therapy. This recommendation is on the basis that there are small benefits of BT with moderate risks and uncertainty regarding long-term outcomes and a need for further research to be conducted to collect long-term data on BT use in asthma.¹ Interestingly the 2023 GINA report includes bronchial thermoplasty as a potential treatment option in patients with severe uncontrolled asthma despite optimized therapy and care at an asthma specialty center.²

Conclusion

Exciting new developments in asthma diagnosis and therapy have occurred over the last decade resulting in six areas of emphasis in the 2020 NAEPP guideline update and even more up-to-date incorporation in the GINA reports, which are reviewed and updated annually based on continuously evolving literature on asthma. Fortunately, both resources provide additional “Implementation Guidance” and “Advice” sections for each recommendation that can be utilized by healthcare providers further seeking to apply recommendations to patients with asthma. Pharmacists and all healthcare providers can work to utilize these resources along with evaluation of emerging literature and product approval to help ensure patients with asthma receive optimal care.

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Fenfluramine: An Old Drug with New Tricks

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Section: Short Communication

Objectives:

- Discuss the current place in therapy for fenfluramine use with Dravet syndrome and Lennox-Gastaut syndrome.
- Explain the safety profile for fenfluramine use in pediatric seizure disorders, including (REMS).

Introduction and History of Use

Considerable recent attention with regards to pediatric pharmacotherapy has been directed toward the resurgence of fenfluramine for use in Dravet syndrome and Lennox-Gastaut syndrome. Fenfluramine was previously used as an appetite suppressant and antidepressant in adults in the 1960s in France and gained approval for the former indication in the United States in 1973.¹ As a selective serotonin reuptake inhibitor as well as an amphetamine derivative, its active metabolite (norfenfluramine) may affect 5-HT_{2B} receptors on cardiac tissues due to proliferative and fibrotic processes.² Heart valvopathies and pulmonary arterial hypertension led to its discontinuation both as a single-agent product and in combination with phentermine in 1997.

Recent History

In June 2020, fenfluramine, under the brand name Fintepla®, (UCB/Zogenix), resurfaced by gaining FDA approval for two new pediatric epileptic indications for patients at least 2 years of age: Dravet syndrome and Lennox-Gastaut syndrome.³ The former condition is also known as SMEI, or Severe Myoclonic Epilepsy of Infancy. Dravet syndrome is typically caused by mutations in the SCN1A gene, which is responsible for encoding a subunit of a sodium channel. This leads to frequent and prolonged seizures, typically triggered by internal (febrile) or external (environmental) hyperthermia. The clinical course of Dravet syndrome is complicated by neurologic and developmental dysfunction, as well as recalcitrance to antiepileptic medications. Lennox-Gastaut syndrome is another example of a pediatric

epileptic syndrome which demonstrates treatment resistance and developmental impairments. The exact cause of Lennox-Gastaut syndrome remains unclear. Adult patients with these two diseases suffer additive comorbidities in addition to persistent seizures, including cognitive disabilities, behavioral changes, decreased mobility, sleep issues, and gastrointestinal symptoms.^{4,5}

As with all epileptic conditions, treatment goals include reduction in the number and duration of seizures, prevention of status epilepticus, minimization of adverse drug reactions, promotion of neurocognitive development, and improvement of quality of life. Combination antiepileptic drug (AED) therapy is often used to achieve these goals due to limited efficacy of single agents for some patients. Valproic acid is considered a first line drug for both syndromes. Second line agents include clobazam and stiripentol, which are often given together with first line AEDs to achieve improved symptom control. Other drugs historically used to control these types of seizures include topiramate, felbamate, cannabidiol, and lamotrigine.^{3,4,5} As such, fenfluramine is generally considered a second-line drug. These various anticonvulsant agents have many drug interactions for which patients should be screened when the AED regimen is modified.⁵

Dosage, Supply, and Administration Considerations

Fenfluramine (as Fintepla) is formulated as a cherry-flavored oral solution in a concentration of 2.2 mg/mL and is available in sizes of 30 mL and 360 mL bottles. The starting and maintenance dosages for both seizure conditions are 0.1 mg/kg twice daily and may be increased weekly based on clinical response and

tolerance. For patients not taking stiripentol, the dose can be increased to 0.2 mg/kg twice daily after one week, and to 0.35 mg/kg twice daily after two weeks. If needed, the dose can be increased every four days, up to a maximum of 26 mg/day.⁶ Stiripentol and clobazam each are involved with major drug interactions with fenfluramine, increasing fenfluramine systemic exposure. Therefore, for patients taking both stiripentol and clobazam, recommendations are to increase the fenfluramine dose up to 0.2 mg/kg twice daily to a maximum of only 17 mg/day. Dosing adjustment is recommended in patients taking strong CYP1A2 or CYP2D6 inhibitors. A lower dose of the drug is generally recommended in hepatic impairment and severe renal impairment.⁶ When discontinuing, general recommendations with AEDs are to taper the dosage over several weeks to several months, as possible, to avoid precipitating seizures and status epilepticus. If withdrawal of the AED is needed due to a serious adverse drug reaction, then more rapid discontinuation can be considered.⁶

Clinical Trial Summary

For Dravet syndrome, two randomized controlled clinical trials were instrumental in the approval of fenfluramine. In the trial published by Lagae et al., patients were assigned 1:1:1 to receive placebo versus fenfluramine 0.2 mg/kg/day or 0.7 mg/kg/day.⁷ The mean age was 9 years old (age range 2 to 19). Approximately 46% of patients were female and 74% were white, and all patients were receiving at least one other AED. The primary endpoint was the change from baseline in the frequency of convulsive seizures per 28 days, or mean monthly convulsive seizures (MCSF). Fenfluramine 0.7 mg/kg/day showed a 70% reduction in MCSF compared with placebo ($p < 0.001$) while fenfluramine 0.2 mg/kg/day showed a 31.7% reduction in MCSF compared with placebo ($p = 0.043$). For both dosages, the change in MCSF was statistically significant. Another stiripentol-inclusive study that involved a 1:1 design with fenfluramine 0.4 mg/kg/day versus placebo also demonstrated efficacy with the same primary endpoint (59.5% reduction, $p < 0.001$). Neurologic adverse effects occurred in both trials, while cardiovascular effects included increased blood pressure from baseline.⁸

In the randomized, double-blind, placebo-controlled trial of patients with Lennox-Gastaut syndrome taking concomitant standard of care AEDs, 176 patients were treated with fenfluramine at either a dose of 0.7 mg/kg/day or 0.2 mg/kg/day, and 87 patients received placebo. The mean age was 13.7 years (range 2 to 35 years) and 29% of patients were at least 18 years old, 45% of patients were female, and 79% patients were white. All patients received at least one other AED. The median percent change from baseline in the frequency of drop seizures per 28 days was greater for the 0.7 mg/kg/day dose group compared to placebo (-23.7% versus -8.7%, $p = 0.037$). A reduction in drop seizures was observed within 2 weeks of initiating treatment with fenfluramine, and the effect remained generally consistent over the 14-week treatment period. Notably, the median reduction from baseline in drop seizure frequency per 28 days for the 0.2 mg/kg/day dose group did not reach statistical significance compared to placebo (-13.2% versus -8.7%, $p = 0.1917$).⁹

Drug Safety and Patient Access

Fenfluramine (as Fintepla) is normally supplied by the manufacturer to Risk Evaluation and Mitigation Strategies (REMS) certified specialty pharmacy programs, which dispense the drug directly to the patient as a patient specific prescription. For fenfluramine to be legitimately dispensed for patient use, the patient, pharmacy, and prescriber must be enrolled in the REMS program, which is available at www.finteplarems.com. The REMS is intended to address the historical risk of valvular heart disease and pulmonary arterial hypertension with this drug class. This REMS program requires that the patient receive an echocardiogram upon initiation, every six months during the treatment course, and a final echocardiogram three to six months after drug discontinuation. In safety studies involving over 600 patients on fenfluramine for these two disorders for up to three years, no patients were identified as having evidence of valvular structural changes or pulmonary arterial hypertension.^{6,10} While cardiac valvulopathies garner the most attention with regards to safety concerns, its previous therapeutic indication still is significant, and its appetite suppressant effects may result in significant weight loss in pediatric patients (studies report a weight loss incidence of up to 13%).

Related to its central effects as an antidepressant are risks of somnolence and sedation (one study reported an incidence of 26% versus 11% for placebo), increased blood pressure (occurrence of up to 13% in studies), and, to a lesser extent, suicidality and serotonin syndrome. Other adverse effects associated with fenfluramine and occurrence rates include fatigue (10-30%), ataxia (10%), pyrexia (5-21%), diarrhea (up to 31%), and increased salivation (up to 13%).⁶

Community, chain, and hospital pharmacies would not normally have a separate stock of this drug for filling prescriptions or orders. The cost of a 30-day supply of fenfluramine can range from approximately \$5,000 for a 10 kg patient to about \$18,542 for a 37 kg patient. For patients with commercial insurance, the Onward™ Support Program can provide copays for as little as \$0 out of pocket costs for fenfluramine and associated echocardiograms. For uninsured patients, the Onward™ Patient Support Program provides a clinical nurse educator who assists families to obtain access to fenfluramine.^{11,12}

Conclusion

Fenfluramine has emerged as a promising treatment option for Dravet syndrome and Lennox Gastaut syndrome. Recent updates and clinical trials have demonstrated efficacy in improving seizure control, revealing, perhaps, a useful agent in the treatment of these conditions. The long-term safety data has been encouraging, with no major concerns observed currently, and the drug will be monitored through REMS. The approval of fenfluramine by regulatory authorities may provide much needed therapy for patients who are unresponsive to other treatments. Ongoing research will further enhance our understanding of its efficacy and safety profile. It remains to be determined how much hope fenfluramine offers for individuals with severe juvenile epilepsy syndromes.

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Tramadol's Current Role in the New Opioid Guidelines

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Section: Review

Objectives:

- Describe the dual mechanism of action associated with tramadol.
- Identify challenges associated with tramadol dosage in special populations.
- Discuss challenges and risk associated with treatment of tramadol overdose with naloxone.
- Recognize tramadol's inclusion in the CDC Clinical Practice Guideline for Prescribing Opioids for Pain—United States, 2022 and its conversion factor for the morphine milligram equivalent.

Introduction

Tramadol, an atypical opioid, is indicated for treatment of chronic pain and as an alternative to strong opioid therapies. Tramadol was awarded approval in 1995 as a non-scheduled medication with a post-marketing surveillance program to monitor abuse potential in the United States.¹ Based on the early years (1994-2001) of the surveillance program, rates of tramadol abuse and diversion were considered low at one half to one case per 100,000 patients prescribed pain medication.² In comparison to common opioids, in 2002 tramadol accounted for one and a half percent of reported prescription diversions as compared to 40% with hydrocodone.² However, as the use of tramadol increased by 48%, non-medical emergency visits related to misuse of tramadol increased from approximately 4,000 to 16,000 visits per year between 2004 and 2010 along with increased tramadol-associated deaths.³ Tramadol was rescheduled as a controlled substance, schedule IV (C-IV) in 2014.³

The Centers of Disease Control (CDC) 2016 Guidelines for Prescribing Opioids mentioned many adjunct therapies for pain, but not specifically tramadol.⁴ As literature continued to highlight the role of tramadol in the management of pain and increase risk of opioid abuse potential, the new updated 2022 CDC guidelines added some suggestions related to tramadol.⁵ This article outlines an overview of tramadol along with its role outlined in CDC's 2022 Clinical Practice for Prescribing Opioids for Pain.

Overview of Tramadol

Tramadol is a synthetic opioid agonist with inhibitory properties of norepinephrine and serotonin re-uptake. Tramadol's parent compound is associated with norepinephrine and serotonin inhibitory effect with little binding of mu-opioid receptor. Tramadol's metabolite is mostly responsible for its opioid pain relief. Its O-demethylated metabolite (M1) has a higher affinity for the mu-opioid receptors compared to the parent compound. The M1 metabolite is 200 times more potent than tramadol in binding to the mu-opioid receptors in animal studies and was six times more potent in producing an analgesic effect. This dual mechanism of action leads to tramadol's unique analgesic activity.^{1,6,7}

Pharmacokinetics

Tramadol's mean peak concentration occurs two hours after administration and has a half-life of 6.3 ± 1.4 hours. The M1 metabolite has a mean peak concentration occurring three hours after administration and a half-life of 7.4 ± 1.4 hours. Tramadol is excreted through the urine with about 30% of the dose being unchanged and 60% of the dose being metabolites.¹

Metabolism and Drug Interactions

Seventy percent of tramadol is metabolized in the liver by cytochrome P450 (CYP) enzymes 2D6 and 3A4.¹ The enzyme CYP2D6 is responsible for the M1 metabolite concentration, associated with the affinity for the mu-opioid receptors. As tramadol metabolism occurs

to produce the M1 metabolite, the norepinephrine and serotonin analgesic effects decrease since these effects are associated with the parent compound.^{1,6}

Due to the unique metabolism and the active metabolite responsible for the opioid effect, drug interactions may play a significant role in analgesic effect and prevention of toxicity. The use of CYP2D6 inhibitors (e.g., fluoxetine) in combination with tramadol may increase the plasma concentration of the tramadol parent compound resulting in less analgesic effect and more serotonin and norepinephrine re-uptake inhibition effects. In contrast, the use of CYP3A4 inhibitors (e.g., ketoconazole), may increase plasma levels of the parent compound and available drug for metabolism via CYP2D6 enzymes, therefore resulting in an increased level of the M1 metabolite. This scenario poses a potential increased risk for opioid toxicity given increased M1 metabolite concentration. Patients with polymorphism at CYP2D6 such as poor, rapid, or ultra-rapid metabolizers at CYP2D6 should avoid tramadol.^{1,6,7}

Common and Serious Adverse Events

The most common adverse events associated with tramadol noted during clinical trials were dizziness (10-23%), vertigo (10%), nausea (15-26%), vomiting (5-10%), constipation (9-21%), headache (12-23%), pruritus (9-11%), and somnolence (7-16%). Central nervous stimulation consisting of nervousness, anxiety, agitation, tremor, euphoria, emotional lability, and hallucinations has also been reported in trials and post-surveillance marketing. Tramadol has some rare but serious adverse effects which include seizures, suicidal tendencies, and serotonin syndrome.¹

Adult Dosing

The recommended dose of tramadol for adults is 50-100 mg every four to six hours for immediate-release formulations and 100-200 mg every 12 hours for extended-release dosage forms, with a maximum dose of 400 mg daily.⁸ Renal function must always be considered as patients with renal impairment have an increase in elimination half-life.⁶ Extended release (ER) tramadol formulations should be avoided in the setting of renal impairment. Manufacturer dosing recommends that for eGFR between 10-30 mL/min, immediate release (IR) tramadol can be used at doses not to exceed 200 mg per day.⁹ Use caution in patients with hepatic

dysfunction due to decreased exposure of the M1 metabolite.¹

Older Adult Population Considerations

Inadequate pain treatment among persons aged ≥65 years has been documented. Pain management for older patients can be challenging given increased risks of both non-opioid pharmacologic therapies and opioid therapies in this population. Given possibility of reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to the accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose.⁴ Healthy patients who were between the age of 65 to 75 years of age had tramadol plasma concentrations and elimination half-lives similar to healthy patients under 65 years of age. However, in patients 75 years of age and older the elimination half-life was prolonged by about an hour and the recommended maximum daily dose is decreased to 300 mg.^{1,7} In addition, older adults experienced more side effects (constipation, fatigue, hypotension, and dyspepsia) with the extended-release formulation of tramadol compared to younger adults.¹ The extended-release formulation should be used with caution or preferably avoided in the older adult population.

Clinicians must use extra caution on prescribing opioids to minimize risk of overdose to older patients with renal and hepatic insufficiency given the diminished capacity to process and eliminate drugs. They should also implement interventions to mitigate common adverse risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

Special considerations on treatment of tramadol overdose

The guidelines recommend administering an opiate antagonist (e.g., naloxone) if clinically important respiratory or circulatory depression is present during a tramadol overdose.⁵ Opioid antagonists only partially reverse tramadol; however, healthcare professionals need to be mindful of the combination of tramadol and naloxone may increase the risk of seizures. In addition, hemodialysis may be an unlikely helpful resource due to

low removal of less than 7% of administered tramadol in a 4-hour dialysis period.¹

Practices should educate patients on overdose prevention and naloxone use along with an offer to provide education to members of their households. It is recommended that clinicians offer naloxone when prescribing opioids, particularly to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients with sleep-disordered breathing, patients taking higher dosages of opioids (e.g., ≥ 50 MME/day), patients taking benzodiazepines with opioids, and patients at risk for returning to a high dose to which they have lost tolerance.⁵

Guideline Update

The 2022 guidelines expanded their evidence and included tramadol as an opioid intervention and added to the morphine milligram equivalent conversion table for opioids. Tramadol is approved for the treatment of moderate to severe acute or chronic pain for patients in which non-opioid analgesics are unable to control their pain.⁵ For naive patients with acute or chronic pain, immediate-release formulations should be prescribed at the lowest effective dose for the shortest period. Also, guidelines established that all individuals should be evaluated individually for benefits and risks before increasing dosage or continuing pain medication therapy.^{5,7} All patients should be monitored closely for respiratory depression at initiating therapy. For acute (less than one month) severe post-operative pain in adult patients (18-75 years old), tramadol IR formulation can be initiated at a dose of 25 mg daily, then increase by 25 mg in separate doses every three days when not requiring immediate analgesic effect, or 50 mg every four to six hours as needed for rapid onset without exceeding 400 mg per day. For older adults (greater than 75 years old) the maximum dose is 300 mg daily.¹

There have been clinical studies showing that tramadol analgesic efficacy in postoperative pain is comparable to morphine and non-steroidal anti-inflammatory drugs (NSAIDs).⁸ Tramadol is also considered appropriate when NSAIDs are contraindicated for common side effects such as bleeding or gastrointestinal issues.⁸ For moderate to severe chronic pain (greater than three months), more specifically in musculoskeletal and cancer related pain in opioid naive adult patients, tramadol IR 25 to 50 mg

every six hours as needed would be appropriate. If the patient tolerates it, this dose could be titrated to 50 to 100 mg every six hours. The ER formulation dose is 100 mg daily and could be increased by 100 mg every five days with a maximum dose of 300 mg per day, and ER forms should not be used in naive patients.¹

The previous 2016 guidelines did not specifically mention tramadol and categorized in the group of non-opioids or adjunct therapies for pain management.⁴ However, the new 2022 guidelines mentioned tramadol specifically and re-grouped it as part of the opioid therapies for pain management along with a morphine conversion factor. This shift outlines the benefits and adverse issues with tramadol.⁵ With tramadol considered in the family of opioids, its role becomes more of a factor in evaluating pain control in patients. It is essential to address that tramadol is not the preferred therapy for chronic pain management, especially in musculoskeletal pain or cancer pain, due to the lack of quality studies.^{4,5} Additionally, there have been studies showing that morphine is more effective than tramadol for cancer pain. Tramadol has some off-label use for the treatment of moderate to severe osteoarthritis pain in the hand, knee or hip,¹⁰ diabetic neuropathy,¹¹ and post-therapeutic neuralgia.¹² The role of tramadol in pain management continues to be limited and patient specific due to the mixed analgesic effects.

Conversion of Tramadol to Morphine Equivalents

According to the 2022 Prescribing Opioids Guideline oral tramadol has a morphine milligram equivalent (MME) of two tenths, meaning five mg of tramadol is equivalent to one mg of morphine.⁵ An article comparing tramadol to tapentadol found the same MME of two tenths for oral tramadol and an MME of one tenth for intravenous formulation tramadol, although the intravenous formulation is not available in the United States.⁷ MME is based on the degree of μ -opioid receptor agonist activity, and tramadol has other mechanisms of action in addition to being a μ -opioid receptor agonist. Thus, it is not known if tramadol is associated with the same dose-dependent mechanism of overdose as a medication that is solely a μ -opioid receptor agonist. With the 2022 guidelines, the CDC updated the oral MME conversion factor table used for opioid dosing equivalents.⁵ The new source for the new morphine milligram equivalent doses is available at <https://www.cdc.gov/opioids/data-resources/>.

Conclusion

Tramadol may be useful in the treatment of mild to moderate acute pain; however, tramadol does pose risks similar to other opioids. Thus, the 2022 guidelines added tramadol as part of the opioid table for calculation of morphine equivalent dosing. Considering tramadol's mixed picture of action, caution should be used.

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Continuous Glucose Monitoring in the Inpatient Setting

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Section: Short communication

Objective:

- Describe the recommendations, clinical-evidence, and limitations for use of continuing glucose monitoring (CGM) in the inpatient setting.

have demonstrated the

Over the past several years, diabetes technology has rapidly evolved to assist with personal and professional glycemic management.¹⁻³ Two broad categories of diabetes technology are subcutaneous insulin infusion devices and blood glucose monitoring (BGM) devices.¹ Included in the latter category, continuous glucose monitoring (CGM) measures interstitial glucose levels via a small sensor inserted under the skin, typically in the back of the upper arm, lower abdomen, or upper buttock.^{1,2} Measured glucose levels are displayed along with graphical information depicting the patient's current blood glucose and projected trends utilizing arrows to indicate whether glucose is trending upward or downward.¹⁻³

Currently, in the United States, there are 9 CGM devices produced by 4 manufacturers. These CGM devices differ by device type (intermittently scanned or real-time), are approved for different age ranges of patients, have different medications known to interfere with their accuracy, integrate with unique insulin pump systems, have individual calibration requirements, and range in sensor wear period from 10 days to 90 days.¹⁻³ The purpose of this article is to discuss current CGM device use and future opportunities for patient care particularly in the inpatient setting.

Over time, persistent glycemic variation is associated with negative outcomes, including "more frequent and more severe hypoglycemia" which may contribute to development of both micro- and macrovascular diabetes-related complications.³⁻⁵ Glycemic variability is one of the driving factors behind widespread CGM device use.³ Visualization of glycemic trends enables proactive response to glucose changes and informs the treatment decision process when glucose fluctuations occur.^{3,6} In addition to reducing glycemic variability, several randomized control trials

effectiveness of CGM devices in the following areas: decreased hemoglobin A1C (HbA1C), increased time in range (TIR), decreased time in hypoglycemia, and reduced hypoglycemic events.^{3,7-11}

Notably, a three-year follow-up to the COMISAIR study demonstrated the superiority of CGM to fingerstick BGM in "reduction of HbA1c, hypoglycemia, and other endpoints" in 94 patients with type 1 diabetes regardless of insulin administration via multiple daily injections or continuous insulin infusions.^{3,12,13} Reduction of glycemic variability and fingerstick glucose testing has encouraged CGM device use for patients with type 1 and type 2 diabetes in the outpatient setting, particularly patients with "inconsistent or confounding glycemic control."^{3,14} These patients include individuals whose treatment increases their risk of hypoglycemia or hypoglycemic unawareness, such as those receiving multiple daily subcutaneous injections or continuous insulin infusion.^{3,14}

Despite the potential benefits for both patients and providers, point-of-care (POC) fingerstick BGM remains the gold standard for glycemic management in hospitalized patients.¹⁵ In recent years, the unprecedented challenges of the COVID-19 pandemic prompted healthcare leaders to seek alternative care methods to conserve personal protective equipment (PPE) and reduce contact time between nurses and patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{15,16} On April 1, 2020, the Food and Drug Administration (FDA) expanded availability of non-invasive remote monitoring devices, such as CGM, due to the global state of emergency.^{17,18} As hospitals began to integrate CGM use into their workflow, preliminary data has proven these efforts to be beneficial for both patient and healthcare staff safety.¹⁹⁻²⁶ Nearly two years later in March 2022, the FDA

granted Dexcom G6 CGM breakthrough device designation for inpatient use, permitting this device to be utilized for glycemic management of hospitalized patients with diabetes in conjunction with standard POC BGM.¹⁸

Patients with diabetes have an increased risk for hospitalization, often requiring insulin to maintain glycemic control during hospitalization and to decrease length of stay.²⁷ Attainment of glycemic control in hospitalized patients is often difficult, necessitating nursing staff to frequently perform POC blood glucose fingerstick tests and administer insulin. Hospitalized patients with diabetes who are receiving insulin are more prone to hypoglycemia which subsequently increases their risk for morbidity and mortality.²⁷ CGM use among hospitalized patients has been shown to limit glycemic excursions, improve nursing efficiency, and decrease the frequency of fingerstick POC testing.^{15,19-26} Table 1 provides further information on key studies of inpatient CGM studies. Further, real-time CGM (rtCGM) devices, such as Dexcom G6, have an alarm feature that has been shown to improve hypoglycemic detection, particularly nocturnal hypoglycemia.²⁸⁻³⁰

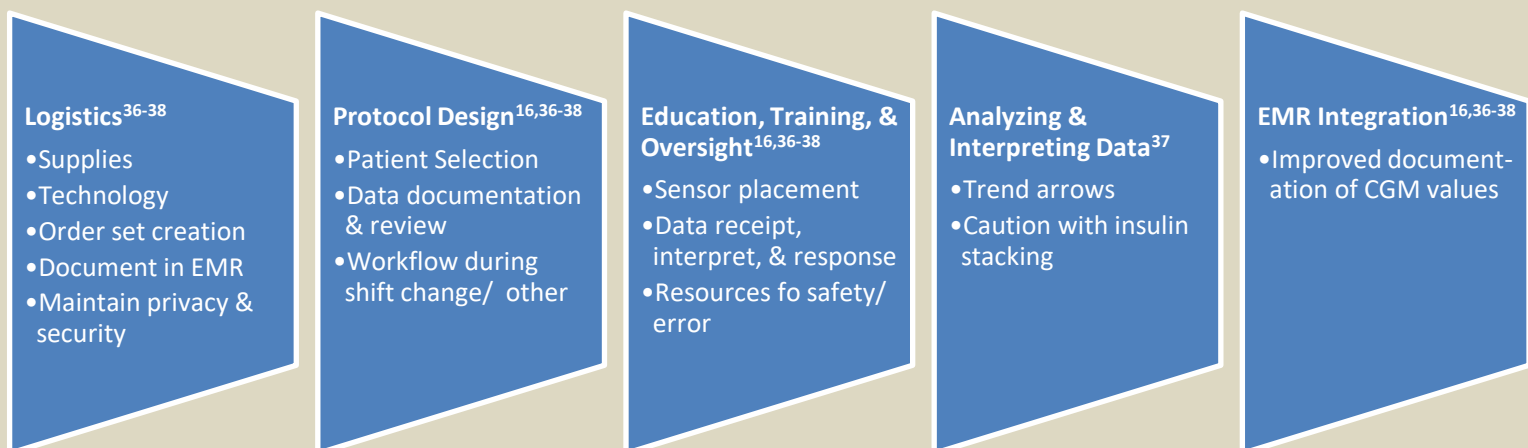
Limited, preliminary data suggests use of CGM is safe and effective as an alternative or adjunctive therapy to standard POC testing in hospitalized patients; however, several factors have created clinical controversy surrounding CGM use in the inpatient setting, particularly for those in the ICU.^{14-16,23,35-37} One major barrier to inpatient CGM device use is concern for unreliable data. Since blood glucose is measured from interstitial fluid, reading accuracy is thought to be impacted by conditions resulting in changes in volume

status.¹⁴ Patients who are “dehydrated, hypotensive, in shock, or in a hyperglycemic-hyperosmolar state with or without ketosis” are commonly ICU patients who are deemed “ineligible” for CGM use due to concerns for reading accuracy.¹⁴ Another confounding factor to accuracy of CGM use includes device, drug, and drug dose specific interferences with medications such as acetaminophen, alcohol, ascorbic acid, hydroxyurea, mannitol, and tetracycline.¹

Despite these perceived obstacles to use of CGM as a standard of care, there are future opportunities for CGM use in the inpatient setting with proper integration into workflow, logistics, and protocol design by a multidisciplinary team.^{14-16,37-39} Figure 1 provides an overview of inpatient CGM use recommendations. Continued education of both patients and staff is vital to the successful integration of CGM use in clinical practice.³⁷⁻³⁹ Resources suggest that a dedicated diabetes service, if available, should oversee the staff education and training process.^{1,15} For hospitals without a dedicated diabetes service, further educational resources should be acquired from the device manufacturer or other source.³⁹

CGM device improvement has established device accuracy; however, more data pertaining to clinical outcomes associated with CGM device use is needed for CGM to be integrated into standard workflow for hospitalized patients. Overall, use of CGM devices has proven to be a unique strategy to improve glycemic control, increase healthcare efficiency, and promote the safety of both patients and staff.^{16,36-38} Pharmacists should strive to stay abreast of emerging CGM technology and evidence for use its optimal use among hospitalized patients.

Figure 1. Summary of Inpatient CGM Use Recommendations



EMR = electronic medical record

Table 1: Summary of Key Studies Evaluating CGM Use in the Inpatient Setting

Author, Year	Population	Study Design	CGM vs. Comparator	Primary Endpoint	Key Conclusion(s)
Galindo et al, 2020²⁹	General Ward Patients (n = 97)	Prospective Pilot Study	Freestyle Libre Pro vs. POC glucose testing	Glycemic metrics (TIR, glucose average, BG < 70 mg/dL)	CGM detected a higher number of hypoglycemic events
Singh et al, 2020³⁰	General Ward Patients (n = 72)	Prospective RCT	Dexcom G6 vs. POC glucose testing	Inpatient hypoglycemia	CGM use was shown to decrease hypoglycemia via alarm feature
Spanakis et al, 2022³¹	General Ward and Surgery Patients (n = 185)	Prospective RCT	Dexcom G6 vs. POC guided insulin adjustment	TIR of 70–180 mg/dL and hypoglycemia	CGM use resulted in a reduction of recurrent hypoglycemic events
Longo RR et al, 2022³²	General Ward (n=18) and ICU Patients (n=10)	Observational Study	Accuracy of Dexcom G6 vs POC and Lab BGM vs Dexcom G6	Accuracy	CGM use is a reasonable alternative to POC and/or lab BGM to reduce healthcare worker exposure to infection
Davis GM, et al, 2021³³	General Ward and Surgery Patients (n=218)	Retrospective	Accuracy of Dexcom G6 vs POC glucose data	Accuracy	CGM use proved to be a reliable tool to monitor non-critically ill hospitalized patients with diabetes.
Schierenbeck et al, 2017³⁴	Cardiac ICU Patients (n = 26)	Observational	Freestyle Libre SC-CGM and Eirus MD-CGM	Accuracy	MD-CGM has superior accuracy. SC-CGM system, repeatedly measured BG lower than the reference
Boeder et al, 2023³⁵	ICU Patients with COVID-19 (n = 24)	Retrospective	Dexcom G6 vs. POC glucose	Accuracy and efficacy	CGM data was concordant with POC glucose levels. CGM use improved glycemic control during IV insulin.
Agarwal et al, 2021³⁶	ICU Patients with COVID-19 (n = 11)	Retrospective	Dexcom G6 vs. POC glucose data	Accuracy	CGM use was accurate, feasible, and reduced POC glucose testing frequency

RCT = randomized control trial; CGM = continuous glucose monitoring; SC = subcutaneous; MD = microdialysis; POC = point of care; ICU = intensive care unit; TIR = time in range; IV = intravenous

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New FDA-Approved RSV Vaccines for Older Adults: Arexvy® and Abrysvo®

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Section: Short Communication

Objective:

- Discuss the efficacy and safety information for the two new RSV vaccines, Arexvy and Abrysvo.

Introduction

Respiratory syncytial virus (RSV) causes approximately 60,000-160,000 hospitalizations per year and approximately 6,000-10,000 deaths per year among older adults.¹ In May 2023, the Food and Drug Administration (FDA) approved two new RSV vaccines for older adults. Glaxo Smith Kline's (GSK's) vaccine, Arexvy®, was the first to be approved, followed by Pfizer's vaccine, Abrysvo®. Both vaccines became available in September 2023 as single-dose intramuscular injections. Arexvy, a monovalent vaccine, contains the recombinant subunit RSVPreF3 (pre-fusion RSV glycoprotein antigen) and the GSK's AS01E adjuvant to help boost the immune system's response to protect against both A and B strains.² Whereas Abrysvo, a bivalent vaccine, induces an immune response against RSVPreF (prefusion F) which provides protection against preF A and preF B components.³ The use of both should be based on shared clinical decision making, for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals 60 years of age and older.^{1,4} The Centers for Disease Control and Prevention (CDC) has further clarified that RSV vaccines be considered for individuals at increased risk for severe RSV illness, including older adults with chronic underlying medical conditions such as chronic heart or lung disease, weakened immune systems, diabetes mellitus, neurologic conditions, kidney or liver disorders, and hematologic disorders.¹ Other factors that may increase the risk of severe RSV illness include advanced age, frailty, and residing in nursing homes or long-term care facilities.¹ It is currently unclear how frequently either of these two vaccines will need to be administered to the geriatric population.

Safety

Adverse Events

Table 1 displays noted adverse events of both RSV vaccines. In separate clinical studies, Arexvy and Abrysvo have demonstrated similar adverse events, but with different occurrence rates. Both manufacturers have stated that the adverse event rates observed in clinical trials may not reflect the rates observed in clinical practice.^{2,3} Serious adverse events have been found in clinical trials for both vaccines. With Abrysvo, one case of Guillain-Barre syndrome, one case of Miller Fisher syndrome, and one case of non-anaphylaxis hypersensitivity have been identified.^{3,5} With Arexvy, a single report of Guillain-Barre syndrome was reported.² The FDA is requiring both companies to perform a post-marketing study to further evaluate the risk of Guillain-Barre syndrome.^{6,7} While rare, the onset of atrial fibrillation (AF) has been a concern with these two vaccines. AF symptoms occurred within 30 days post-vaccination with limited information to determine a causal relationship between AF and these vaccines.^{2,3}

Drug Interactions

While no common drug interactions are mentioned by either manufacturer, taking concomitant immunosuppressant agents at the time of vaccination may diminish the therapeutic effect of the vaccines.^{2,3} Of note, a non-placebo controlled, open label, phase 3 study in 885 participants 60 years of age and older who received one dose of both Arexvy and Fluarix Quadrivalent either concomitantly or sequentially demonstrated no evidence of immune response interference.²

Precautions and Contraindications

Precautions are similar between both vaccines and include allergic reactions, risk of syncope, and diminished response to the vaccine in those with altered immunocompetence.^{2,3} Arexvy and Abrysvo are contraindicated in patients with a known allergy to the vaccine or any component of the formulation.^{2,3}

Efficacy from Clinical Trials

Arexvy's FDA approval status was based on data from the phase 3, placebo-controlled clinical trial (NCT04886596) involving 24,966 participants 60 years of age and older with a mean duration of 6.7 months.² The primary objective included the prevention of the first episode of confirmed RSV-A and/or RSV-B associated LRTD during the first season. Confirmed RSV cases were determined by PCR nasal swab test during all acute respiratory illness (ARI) episodes.^{2,8} Vaccine efficacy was defined as a modified exposed set that included those 60 years of age and older receiving one dose of Arexvy or placebo with no confirmed RSV-ARI within 15 days after vaccination.^{2,8} The results of preventing the first episode of confirmed RSV were found to be statistically significant (see table 1).

Abrysvo obtained FDA approval after published results from an interim analysis of an ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial (NCT05035212) involving 34,383 participants 60 years of age and older with stable chronic diseases at the time of the analysis cut-off (analysis cut-off date was July 14, 2022, when 44 study participants showed at least two RSV symptoms).^{3,9} The primary objectives included prevention of RSV-LRTD with two or more symptoms and prevention of RSV-LRTD with three or more symptoms. Participants were monitored for onset of ARI symptoms (i.e., new or increased congestion, nasal discharge, cough, wheezing, sputum production, or shortness of breath). Vaccine efficacy was determined by the relative risk reduction of the first episode of RSV-LRTD in the Abrysvo versus placebo groups during the first RSV season.^{3,9} Interim study results are provided in table 1. This clinical trial is ongoing and designed to follow participants for two RSV seasons for a total of approximately 25 months.³

Place in Therapy

Due to the variability in trial design with these two vaccines and no comparative trials available, relative safety and efficacy is uncertain; however, data

demonstrates both vaccines to be safe and effective in adults 60 years of age and older in preventing LRTD caused by RSV. These vaccines will most likely be used in older adults who are at an increased risk for severe RSV illness. There is little data comparing concomitant administration of the two RSV vaccines with other vaccines, but a study of concomitant administration with Arexvy and influenza vaccine showed sustained efficacy results. Usage should be based on shared clinical decision making, where cost and insurance coverage will be important factors in this process. Due to inpatient issues with some vaccines, such as reimbursement patterns and problems with obtaining an accurate outpatient vaccine history for inpatients, these two vaccines will likely be administered most often in the outpatient setting. Vaccine costs are presented in table 1.

In August 2023, Abrysvo obtained a second FDA-approved indication for use in pregnant individuals who are between 32- and 36-weeks gestation. This indication would help prevent RSV in infants from birth through 6 months of age through passive immunity. In a placebo controlled trial with approximately 3,500 pregnant patients in each group, Abrysvo showed a 81.8% reduction in the occurrence of severe LRTD within 90 days after birth, and a 69.4% reduction within 180 days after birth.^{10,11} While efficacy results suggest Abrysvo's benefit in this population and adverse events reported are generally mild, the FDA has required that Pfizer conduct post marketing studies to assess hypertensive disorders, including pre-eclampsia and preterm births which were observed during the trial. More data is needed to establish whether these adverse effects were associated with vaccine use.¹⁰

Conclusion

Arexvy and Abrysvo are the first vaccines approved for prevention of RSV in older adults. The CDC recommends they be administered to patients 60 years of age and older, especially those with high risk for RSV infection, and use should be based on shared decision making. Clinical trials for both vaccines are ongoing, and future recommendations may become available as those trials conclude and the annual CDC immunization recommendations become available for 2024.

Table 1. RSV Vaccine Comparison

Vaccine Comparison	Arexvy	Abrysvo
Type	Monovalent/Adjuvanted	Bivalent
Dosing	0.5 mL after reconstitution	
Efficacy	<p>First episode of RSV-LRTD occurring 15 days post-vaccination:</p> <ul style="list-style-type: none"> - <i>Overall (≥60 years):</i> 7 cases in vaccine group vs. 40 cases in placebo group with a vaccine efficacy of 82.6% (95% CI 57.9, 94.1) - <i>60 to 69 years:</i> 4 cases in vaccine group vs. 21 cases in placebo group with a vaccine efficacy of 81.0% (95% CI 43.6, 95.3) - <i>70 to 79 years:</i> 1 case in vaccine group vs. 16 cases in placebo group with a vaccine efficacy of 93.8% (95% CI 60.2, 99.9) - <i>80 years of age and older:</i> inconclusive due to limited cases 	<p>60 years of age and older:</p> <ul style="list-style-type: none"> - <i>First episode of RSV- LRTD with ≥2 symptoms:</i> 11 cases in vaccine group vs. 22 cases in placebo group with a vaccine efficacy of 66.7% (95% CI 28.8, 85.8) - <i>First episode of RSV- LRTD with ≥3 symptoms:</i> 2 cases in vaccine group vs 14 cases in placebo group with a vaccine efficacy of 85.7% (95% CI 32.0, 987)
Most Common Adverse Drug Reactions (≥10%)	<ul style="list-style-type: none"> - <i>Injection site pain:</i> 60.9% in vaccine group vs 9.3% in placebo group - <i>Fatigue:</i> 33.6% in vaccine group vs 16.1% in placebo group - <i>Myalgia:</i> 28.9% in vaccine group vs 8.2% in placebo group - <i>Headache:</i> 27.2% in vaccine group vs 12.6% in placebo group - <i>Arthralgia:</i> 18.1% in vaccine group vs 6.4% in placebo group 	<ul style="list-style-type: none"> - <i>Injection site pain:</i> 10.5% in vaccine group vs 6.0% in placebo group - <i>Fatigue:</i> 15.5% in vaccine group vs 14.4% in placebo group - <i>Headache:</i> 12.8% in vaccine group vs 11.7% in placebo group - <i>Muscle pain:</i> 10.1% in vaccine group vs 8.4% in placebo group
Pregnancy	Not FDA-approved for use in patients <60 years of age.	FDA-approved in weeks 32 to 36 of gestation to prevent RSV in infants.
Cost Per Dose*	\$238	\$273

*Average wholesale price from McKesson Drug Wholesale, McCalla, AL (November 2023)

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The Alabama Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. This program is approved for **1.5 hour(s)** (0.15 CEUs) of continuing pharmacy education credit. Participants must complete the online course evaluation and learning assessment with a minimum score of 70% before the stated deadline of (05/01/2024) to receive continuing pharmacy education credit. Proof of participation will be posted to your NABP CPE profile within 60 days. There is no fee for ALSHP members to participate in this activity; your membership must be current to receive credit. Contact mail@alshp.org for questions about this CPE activity.

This knowledge-based activity is intended for pharmacists.

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Assessment Questions

In order to receive non-live CE credit, please click on the following link or scan the QR code to submit your answers to the following assessment questions.

Link to submit answers: https://samford.qualtrics.com/jfe/form/SV_41Rcd5AVShJQoRg



A Breath of Fresh Air: a Comparison of the Focused Update in the 2020 Asthma Management Guidelines and the 2023 GINA Guidelines Updates

1. According to the 2020 National Asthma Education and Prevention Program (NAEPP) guideline update and the 2023 Global Asthma Initiative (GINA) report which adult patients should receive a long-acting muscarinic antagonist (LAMA) as part of their asthma management?
 - a. Patients with uncontrolled-persistent asthma already receiving ICS (inhaled corticosteroids) + LABA (long-acting beta-agonist)
 - b. Patients newly diagnosed with asthma experiencing symptoms less than twice a month
 - c. Patients with mild to moderate allergic asthma with evidence of worsening symptoms after exposure to a specific antigen
2. Which describes the correct use of intermittent inhaled corticosteroids (ICS) in asthma management?
 - a. Inhaled corticosteroids (ICS) monotherapy for controller therapy should be avoided in all patients
 - b. Short-acting beta-agonist (SABA) is preferred over ICS-SABA for reliever therapy
 - c. ICS-formoterol can be utilized as daily controller and as needed reliever therapy in patients > 4 years old with moderate-severe persistent asthma

Fenfluramine: An Old Drug with New Tricks

3. The Fintepla Risk Evaluation and Mitigation Strategies (REMS) is focused on which safety concern?
 - a. Aplastic anemia and neutropenia
 - b. Valvular heart disease and pulmonary arterial hypertension
 - c. Tubulointestinal nephritis and nephrotic syndrome
4. Fenfluramine use in the treatment of Dravet syndrome and Lennox-Gastaut syndrome is considered as:
 - a. Only a last-resort drug when all options have failed or cannot be used
 - b. Initial monotherapy
 - c. An option for second line adjunctive therapy

Tramadol's Current Role in the New Opioid Guidelines

5. Which of the following compound is responsible for tramadol's opioid effects?
 - a. Parent compound of tramadol
 - b. O-demethylated metabolite (M1)
 - c. Pro-drug parent compound of tramadol
 - d. O-methylated tramadol (M4)

6. According to the CDC Clinical Practice Guideline for Prescribing Opioids for Pain—United States, 2022, tramadol's oral morphine milligram equivalent (MME) is_____.
- 0.2
 - 0.5
 - 2
 - 50
7. Naloxone changes the risk of what side effect when used during a tramadol overdose?
- Increase risk of seizures
 - Decrease risk of bleeding
 - Increase risk of nausea and vomiting
 - Decrease risk of seizures

Continuous Glucose Monitoring in the Inpatient Setting

8. Which outcome has been identified in studies evaluating general ward patients monitored with a continuous glucose monitoring (CGM) device compared with point of care fingerstick glucose testing?
- Reduction of hypoglycemic events
 - Negative impact on nursing efficiency
 - Increase in total daily doses of insulin
 - Increase in mortality
9. Which is an established limitation of CGM use in the inpatient setting?
- Drug-device interference in patients receiving medications such as acetaminophen or hydroxyurea
 - Lack of an FDA-approved CGM device for inpatient use
 - Inability of CGM's to detect nocturnal hypoglycemia

New FDA-Approved RSV Vaccines for Older Adults: Arexvy® and Abrysvo®

10. Which of the following statements is false regarding Arexvy and Abrysvo?
- Direct comparative trials demonstrate that Arexvy and Abrysvo have similar efficacy and safety profiles.
 - The most common adverse drug reactions with Arexvy and Abrysvo include fatigue, injection site reactions, and headaches.
 - Abrysvo is a bivalent vaccine, while Arexvy is monovalent.
11. Select the MOST appropriate patient to receive the vaccine:
- A 9-month-old infant – Abrysvo
 - A 32-year-old pregnant person who is 34 weeks gestation – Arexvy
 - A 40-year-old health care worker with no other comorbidities -Arexvy
 - A 66-year-old person with a history of COPD - Abrysvo

Submission Guidelines for ALSHP's *InPharmative* Quarterly Clinical e-Journal Publication

InPharmative Quarterly Clinical e-Journal publication provides a forum for communication of relevant information for the practice of pharmacy. The publication encourages manuscripts from pharmacists, non-pharmacist in a pharmacy setting or academia, residents, and students. Types of contributions including original research papers, reviews, program descriptions, and short descriptions of clinical controversies or patient cases. The journal encourages new authors to submit manuscripts, and foster engagement in sharing of expertise.

To ensure that only accurate and substantive articles are included, all manuscripts undergo editorial peer-review and require editorial approval prior to acceptance. Submission of a paper to *InPharmative Quarterly* clinical e-Journal publication will be taken to imply that it represents original work not previously published, that it is not being considered elsewhere for publication, and that if accepted for publication it will not be published elsewhere in the same form without the consent of the editors. Manuscripts should be submitted electronically to inpharmative@alshp.org.

Please use these guidelines as a checklist when preparing a manuscript for submission to *InPharmative Quarterly*.

Types of Contributions

The journal will publish the following types of communications:

Research papers

Research articles describe experimental or observational investigations that used formal methods for data collection and reporting of results of studies related to pharmacy practice (1500-2500 words excluding references/table). If applicable, a statement that the research protocol was approved by relevant institutional review boards or ethics committees and that all human participants gave written informed consent if required.

Reviews

Reviews are comprehensive, well-referenced descriptive papers on topics directly related to the practice of pharmacy such as new drug updates, disease state reviews or change in practice (1500-2500 words excluding references/table).

Program descriptions and legislative updates

Program descriptions are descriptive papers outlining specific programs or service descriptions, upgrades and software changes, administrative items, and medication safety issues. To help promote practice development and progress, practice site descriptions and successful strategies implemented are very valuable as the role of pharmacy continues to grow in our state. Legislative updates are also welcomed to help keep members informed of changes affecting pharmacy practice. (maximum 1000 words excluding references/table).

Short descriptions of clinical controversies or patient cases (Short Communications)

Short descriptions of controversies or clinical pearls related to pharmacy practice. In addition, authors may submit patient cases with a concise review section about the problem and solution. (maximum 1000 words excluding references/table)

Preceptor Development (Short Communications)

Preceptor development submissions may describe any range of issues related to teaching activities in the experiential setting. (maximum 1000 words excluding references/table)

Manuscript Organization

Manuscripts should include title of the article, name of author or authors with credentials, title and institution followed by the body of the manuscript, references, tables and/or figures. References should be cited according to the AMA 11th edition. A valid e-mail of all authors should be included with an indication of the corresponding author who will check proofs and receive correspondence.

_____ Title: is concise and informative of manuscript content

_____ Authors: All authors and credentials included. If an author is a student, please designate as “PharmD Candidate 20XX”, where XX should be replaced by the anticipated graduation year. **Student authors must submit with a pharmacist co-author. Resident authors must submit with a preceptor co-author.**

_____ Author affiliation and contact information: All authors should submit their work/school related affiliations and a valid e-mail address that will be used during the peer review process.

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_____ Article category: Specify the article category under which the manuscript is being submitted.

_____ Date of submission: Include the date the manuscript is being submitted.

_____ Body of the Manuscript. The body of the manuscript must include section headings. For research articles introduction, methods, results, discussion, conclusion. For review articles, introduction, methods (literature search methods including search terms and criteria for selection of included references), clinical evidence, discussion, conclusion. Other section headings maybe granted by the editorial board based on the content of the manuscript. If submitting other section headings for reviews or research articles, please contact the editorial board.

_____ References are cited within the body of the manuscript with superscript numbers in the order they are cited. The reference section should follow the text body. The journal follows AMA style (11th edition) for all references. See examples of reference formatting below.

_____ Tables. No more than **one** table may be included per manuscript. The table should be limited to one page with text single spaced and 1 inch margins. The table should include information that is difficult to describe as text and add, rather than restate information within the text. If copyright permission is required for the table, the corresponding author must submit approval from the referenced source along with submission of the manuscript.

_____ Figures. No more than **one** figure may be included per manuscript. The figure should be limited to one page. If copyright permission is required for the figure, the corresponding author must submit approval from the referenced source along with submission of the manuscript.

_____ Font is Calibri, 12-point font, text, including references, is double spaced, margins are 1 inch.

_____ Submitted as a Microsoft Word file

Reference Formatting

Below are referencing tips and examples of the most common types of citations based on the *AMA Manual of Style*, 11th edition.

- If there are more than 6 authors, list first 3, then “et al”.
- Only the first word in the title is capitalized.
- Journal names are abbreviated and *italicized*. Find the NLM abbreviated titles at <https://www.ncbi.nlm.nih.gov/nlmcatalog/journals>.
- If there is no volume or issue number, use the issue date.
- For books, publisher name only (publisher location not needed).
- Page numbers should not be shortened (list complete number before/after dash)
- List the doi (direct object identifier) number after the page numbers. There is no period after the doi number. If no doi, list access date and URL.
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- Tichy EM, Hoffman JM, Suda KJ, et al. National trends in prescription drug expenditures and projections for 2021. *Am J Health Syst Pharm*. 2021;78(14):1294-1308. doi:10.1093/ajhp/zxab160

_____ **Book chapter** citations should be in the following format. Chapter author(s) Chapter title. In: Book author(s) or editor(s). Book title. Volume number and title. Edition number. Publisher; Year: Page number(s) if chapter of book. If e-book, delete info after delimiter in URL (after institution name, delete info beyond “/”). Add Accessed date before URL.

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_____ **Websites** should be in the following format. Author(s). Title of item cited. Name of website. [date published]. Updated date (if available). Accessed date. URL

- Centers for Disease Control and Prevention. Diabetes Fast Facts. Updated December 17, 2021. Accessed October 12, 2021. <https://www.cdc.gov/diabetes/basics/quick-facts.html>

_____ **Databases** should be in the following format. Author(s), if provided. Monograph title. Database [specific database used]. Publisher. Year of publication or version number. Updated [date]. Accessed [date]. URL.

- Metformin. Micromedex [DrugDex]. Truven Health Analytics. Updated June 29, 2022. Accessed July 18, 2022. <https://www.micromedexsolutions.com>
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_____ **Electronic package insert or prescribing information** use the following format. Drug. Prescribing information. Company; year of publication. Accessed date. URL

- Wegovy. Prescribing information. Novo Nordisk Pharmaceuticals, Inc.; 2021. Accessed May, 17, 2021. Available at <https://www.novo-pi.com/wegovy.pdf>

_____ **Other electronic media (audio or e-book, app, news)** should include the following: authors or name of the group; chapter title; In: Editor(s); book title; edition number; book medium; publisher’s name; copyright year or publication date; chapter number or inclusive pages; accessed [date]; and URL (verify that the link works).

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Authors should submit the following paperwork.

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_____ ALSHP Financial Disclosure form (for **all** authors)

_____ Curriculum vitae (for **all** authors)

Additional details about these requirements and paperwork can be found on the ALSHP website.

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Manuscripts and CE materials should be submitted as Microsoft Word documents electronically to inpharmative@alshp.org

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