American College of Clinical Pharmacy

Adult Medicine PRN
Spring Newsletter

Edited by Andrew Miesner, PharmD, BCPS & Beth Resman-Targoff, PharmD, FCCP

Inside this issue...

A Message From The Chair

Kurt Wargo, PharmD, FCCP, BCPS (AQ-ID)

Mother Teresa once said *"You can do what I cannot do. I can do what you cannot do. Together we can do great things."* As I read this quote, I could only think about the many talented members we have in our Adult Medicine PRN, and how many of you have come together to accomplish great things.

This year we restructured our committees, and developed several new committees, in an effort to increase involvement and engage more members in the work our PRN is doing. While the work ALL our committees have been doing is exceptional, I wanted to take this time to highlight a few of them. The Programming Committee is our PRN's largest, composed of 29 members, chaired by the Adult Medicine PRN Chair-Elect, **Leigh Anne Gravatt**, along with vice-chair **Antoine Jenkins**. Having chaired this committee last year, I personally know how difficult it can be to develop the programming for our Annual Meeting. Therefore, I would like to personally thank the committee for working so diligently to develop programming for the 2017 Annual Meeting in Phoenix, October 7-10.

I am also personally VERY proud of the work being done by the newly formed External Affairs Committee, chaired by **Ryan Owens** and vice-chaired by **Ryan D'Angelo**, along with their 13 members. This committee has been charged with engaging a broader base of our members through the social media sites of the Adult Medicine PRN. They have done a wonderful job of staying abreast of current topics in health care and sharing those with you via the Facebook and Twitter pages. In addition, this committee has initiated a mentoring program that pairs new practitioners with seasoned mentors in an effort to provide guidance and career advice. They have also initiated a monthly resident journal club, where a resident teams up with a mentor to review a current piece of literature and present their findings via webinar. This committee is starting to reach out to new members, as well as recently dropped members through emails that have included flyers advertising benefits/new initiatives of the PRN. They also developed a survey for

2016 Annual Meeting Award Winners

AMED PRN Outstanding Paper of the Year: Kurt Wargo, PharmD, BCPS AQ-ID (Wingate University)

Wargo KA, McCreary EK, English TM. Vancomycin combined with clindamycin for the treatment of acute bacterial skin and skin-structure infections. Clin Infect Dis 2015;61(7):1148-54.

AMED PRN Mentoring Award: Asha Tata, PharmD (University of Maryland School of Pharmacy)

Service Appreciation Award: Jacky Olin, MS, PharmD, BCPS (Wingate University)

Practitioner Registration Award: Jamielynn Sebaaly, PharmD (Wingate University)

Pictured above:

Resident Travel Award: Ryan Owens, PharmD, BCPS (University of Oklahoma)

Student Travel Award: Emily Shor, PharmD candidate (St. Louis College of Pharmacy)

dropped members to determine if there was anything we as a PRN could have done differently to better serve them. One final thing this committee is working on is planning a social event for our members at the Annual Meeting and an event geared towards our students and residents in conjunction with our PRN business meeting. More details to come on this initiative!

The Travel & Training Committee, under the direction of the chair **Jennifer Twilla**, vice-chair **Lindsay Arnold**, and immediate past-chair **Jessica Wallace,** and their 22 members, will be issuing calls for award nominations. The award criteria are posted on the PRN website, and some awards include funding to attend the Annual Meeting. Additionally, the Nominations Committee, chaired by **Sarah Anderson** and vice-chair **Andy Woods** and their 15 members will be soliciting a call for nominations for Adult Medicine PRN awards, as well as a call for individuals to run for the Adult Medicine PRN offices of Chair-Elect and Secretary/Treasurer. I would encourage you to consider running for one of these offices if this is something you have been considering. It is a great way to serve the Adult Medicine PRN, and in the process, contribute to our success and achieve your own career goals. Please reach out to any of your Adult Medicine PRN officers and committee chairs if you have questions and want to become more involved.

The Research Committee, chaired by **Branden Nemecek** with vice-chair **Rachel Flurie** and their 13 members has also been doing some wonderful things. This committee has developed a document of research ideas that can be found on the PRN's website in order to foster collaboration amongst members who would like to conduct research with multiple sites. I can't say enough how very valuable the idea of collaboration and teamwork is to our overall success, and so I am excited to see what comes out of this group.

Finally, the Internal Affairs committee, chaired by the Adult Medicine PRN Secretary/Treasurer **Andrew Miesner** and vice-chair **Beth Resman-Targoff** has worked diligently with their committee of 23 members to develop this wonderful newsletter with a theme that we are all facing in our practices, dependence upon opioid medications. We certainly hope you all enjoy!

In summary, I wish to thank the Adult Medicine PRN officers, committee chairs, vice-chairs, and members who have provided their time and enthusiasm towards making our goals possible. Remember, you have great talents, and when you combine those talents with others to form a team, wonderful things can be accomplished! And while I was unable to get to our Walk Rounds and Research Committees, you can be sure the work they are doing is indeed helping the PRN reach our goals. All the officers will continue to encourage your involvement in shaping the PRN to help us best serve you, our patients, and society.

Recent Accomplishments from our PRN Members

Promotions:

Michael D. Novario: Regional Director of Pharmacy Operations for OSF Healthcare

Mate M. Soric: Vice Chair, Practice-Based Research Northeast Ohio Medical University College of Pharmacy

Grants:

Sarah L. Anderson: Qualitative and Quantitative Assessment of Electronic Examination Implementation. Funding Agency: University of Colorado Skaggs School of Pharmacy & Pharmaceutical Sciences. Direct costs: $2,175.00

Awards:

Mate M. Soric: ACCP New Clinical Practitioner Award

Alexandra Vance: Navy Pharmacy's Civilian Pharmacist of the Year - Oct 2016

Alexandra Vance: Naval Hospital Jacksonville Senior Civilian Employee of the Year (for 2016) - Feb 2017

Other Notable Achievements:

Sarah L. Anderson: Most accessed paper in *Pharmacotherapy* in 2016: "The effect of medical marijuana on migraine headache frequency in an adult population"

Kelly Covert: Accepted Assistant Professor of Pharmacy Practice position at East Tennessee State University Bill Gatton College of Pharmacy

Jason Lancaster: National Presentation: Conley M, DiVall M, Gonyeau M, and **Lancaster JW**. "Curricular Integration and Evaluation of the Joint Commission of Pharmacy Practitioners (JCPP) Pharmacist Patient Care Process". Presented at: American Association of Colleges of Pharmacy Annual Meeting; July 27, 2016.

Beth Resman-Targoff: Invited Presentation: "Rheumatoid Arthritis in the Geriatric Patient, Secondary Prevention, Polypharmacy and Challenges" and "Interprofessional Case Discussion", Clinical Focus Course, Association of Rheumatology Health Professionals, Washington, DC, November 12, 2016

Jon Wietholter: Facilitator's Workshop: Clinical Pharmacy in South Africa. Presented at the University of the Western Cape in Cape Town, South Africa; July 2016

Congratulations to the 2016 ACCP Fellows from the AMED PRN!

Amy Donihi, PharmD, BCPS, FCCP
University of Pittsburgh School of Pharmacy, Bethel Park, PA

Rima Mohammad, PharmD, BCPS, FCCP
University of Michigan Health System Pharmacy Services, Ann Arbor, MI

Sarah A. Nisly, PharmD, BCPS, FCCP
Wingate University School of Pharmacy, Wingate, NC

Linda Spooner, PharmD, BCPS, FCCP
Massachusetts College of Pharmacy & Health Sciences, Worcester, Sturbridge, MA

Kurt Wargo, PharmD, BCPS(AQ-ID), FCCP
Wingate University School of Pharmacy, Hendersonville, NC

Abigail M. Yancey, PharmD, BCPS, FCCP
St. Louis College of Pharmacy, St. Louis, MO

Pictured above:

ACCP's New Fellow Inductees at the 2016 Annual Meeting in Hollywood, FL

Recent Publications from Our PRN Members

Sarah L. Anderson

Anderson SL, Kattappuram R, Marrs JC, Joseph NM. Intentional brodifacoum ingestion. *Am J Med* 2017;130(1):e27-28.

Kelly Covert

Covert K, Mardis C, Fleming J, Pilch N, et al. Development of a predictive model for drug-related problems in kidney transplant recipients. *Pharmacotherapy*. 2017;37(2):159-169.

Ryan D'Angelo

D'Angelo RG, Rincavage M, Tata AL, Millstein LS, Gulati MS, Flurie RW, Gonzales JP. Impact of an Antipsychotic Discontinuation Bundle During Transitions of Care in Critically Ill Patients. *J Intensive Care Med*. 2016 Jan 1:[Epub ahead of print].

Jason Lancaster

McAuliffe L, O'Gara E, Balaguera H, Lei Y, Mitchell L, and Lancaster JW. Evaluation of Antibiotic Management in the Reduction of Recurrent Chronic Obstructive Pulmonary Disease (COPD) Exacerbations. *Journal of Academic Hospital Medicine*. 2016;8(2).

Set J, O'Gara E, Grgurich P, Lancaster, JW, Lei Y, and Craven D. Evaluation of Initial Antimicrobial Management in Patients with Community-Acquired and Healthcare-Associated Pneumonia at a Tertiary, Teaching Hospital. *Journal of Academic Hospital Medicine*. 2016;8(1).

Kelsey Lyon

Lyon K, Martello J, Likar E, Regier M. Retrospective cross-sectional pilot study of rifaximin dosing for the prevention of recurrent hepatic encephalopathy. *J Gastroenterol Hepatol*. 2017. doi: 10.1111/jgh.13759. [Epub ahead of print]

Joel Marrs

Anderson SL, Kattappuram R, Marrs JC, Joseph NM. Intentional brodifacoum ingestion. *Am J Med* 2017;130(1):e27-28.

Tressa McMorris

McMorris TE, Smith WJ, Kupiec K, Salvaggio M, Skrepnek GH, Abraham L, Resendez S. Micafungin therapy for symptomatic candiduria in hospitalized patients: a review of 14 cases. *Infect Dis Clin Pract*. 2017;25(2):88-93.

Andrew Miesner

Miesner AR, Lyons W, and McLoughlin A. Educating medical residents through podcasts created by PharmD students. *Curr Pharm Teach Learn*. [Accepted, In Press]

Sarah Nisly

Dy-Boarman E, Martin D, Nisly SA. Use of a health screening and education event to change student attitudes towards the elderly. *Curr Pharm Teach Learn* 2017;9(1):101-107.

Nisly SA, Janzen KM, Steuber TD, Trujillo TN. Alumni survey as a quality improvement tool for defining residency success. *Am J Health Syst Pharm* 2016;73(21)1722-1725.

Nisly SA, Isaacs AN, White C, Chamberlin SM. 24-month pharmacotherapy residency: the what and how behind these programs. *Curr Pharm Teach Learn* 2016;8(6):796-803.

Recent Publications continued

Alvin Oung

Oung AB, Saseen J. Do statins reduce the effectiveness of the influenza vaccine? *Evidence-Based Practice*. 2017; 20 (3): 9.

Ryan Owens

Oliphant CS, Owens RE, Bolorunduro OB, Jha SK. Ivabradine: A review of labeled and off-label uses. *Am J Cardiovasc Drugs*. 2016;16(5):337-47.

Owens RE, Snyder HS, Twilla JD, Satapathy SK. Pharmacologic treatment of alcoholic hepatitis: examining outcomes based on disease severity stratification. *J Clin Exp Hepatol*. 2016;6(4):275-281.

Mate M. Soric

Ulbrich TR, Rogers J, Soric MM. "Top 10 residency application mistakes." *Student Pharmacist* 2016; 13(2):14-15.

Soric MM, Moorman JM, Boyle JA, Dengler-Crish CM. Prevalence and predictors of metformin prescribing in adults with type 2 diabetes mellitus: a national cross sectional study. *Pharmacotherapy* 2016; 36 (7):715-22.

Kurt Wargo

Wargo KA. Transitioning from Pharmacy Practice into Administration. *Curr Pharm Teach Learn*. 2017.

ACCP Educational Affairs Committee (Schwinghammer TL, Crannage AJ, Boyce EG, Bradley B, Christensen A, Dunnenberger HM, Fravel M, Gurgle H, Hammond DA, Kwon J, Slain D, Wargo KA). The 2016 ACCP Pharmacotherapy Didactic Curriculum Toolkit (ACCP Commentary). *Pharmacotherapy*. 2016;36(11):e189-94.

Mospan GA, Wargo KA. Researchers' Experience with Clinical Data Sharing. *J Am Board Fam Med*. 2016;29(6):805-7.

Mospan GA, Wargo KA. Evaluation of an outpatient 5-day course of levofloxacin in males with a urinary tract infection: A subgroup analysis of a previously published trial. *J Am Board Fam Med*. 2016;29(6):654-62.

Jon Wietholter

Wietholter JP, Ponte CD, Long DM. The perceived value of clinical pharmacy service provision by pharmacists and physicians: an initial assessment of family medicine and internal medicine providers. *Int J Pharm Pract*. 2016; doi: 10.1111/ijpp.12322.

Wietholter JP. Chapter 66: Glaucoma. In: Pharmacotherapy Principles & Practice Study Guide: A Case-Based Care Plan Approach, 4th ed. New York: McGraw-Hill, 2016: 261-263.

Wietholter JP, Coetzee R, Nardella B, Kincaid SE, Slain D. Chapter 19: International Healthcare Experiences: Caring While Learning and Learning While Caring. In: Handbook of Research on Study Abroad Programs and Outbound Mobility. 1st ed. Hershey: IGI Global, 2016: 470-496

A Review of the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain

Jennifer Austin Szwak, PharmD, BCPS and Lida Thimothy, PharmD, BCPS

Although there are varying definitions, chronic pain is typically defined as pain lasting greater than three months or longer than normal tissue healing.[1,2] The 2012 National Health Interview Survey (NHIS) found that most American adults experience some level of pain and 25.5 million adults (11.2%) had pain every day for the three months preceding the survey with nearly 40 million adults (17.6 %) experiencing severe pain. [1,3]

The use of opioids for the treatment of pain has been increasing drastically over the past decade. An estimated 259 million prescriptions were written by health care providers for opioid pain medications in 2012. There are no studies comparing opioid therapy to placebo or non-opioid therapy for effectiveness of managing chronic pain in the long-term (≥1 year). However, long-term opioid use has been found to be associated with an increased risk of opioid abuse or dependence, dose-dependent risk for fatal overdose, increased fracture risk, as well as increased risk for cardiovascular events. [1]

The new CDC guideline for prescribing opioids is intended to assist primary care providers treating patients with chronic pain in the outpatient setting. The guidelines excluded patients undergoing active cancer treatment, palliative care, or end-of-life care as these patients often have different goals of therapy.[1] The three key principles of chronic pain management and recommendations from the guidelines are summarized in Table 1.

Although the guidelines address an important and timely issue in patient management, there are several limitations to the recommendations. First, the level of evidence is low and by only considering studies of 1 year duration or longer, those investigating opioid use over 3-12 months are excluded. In the setting of limited data, excluding such a large time period may compromise the quality of evidence and recommendations made by the CDC guidelines. There is also concern that the guidelines may inadvertently discourage treatment of pain in people who may need opioids and lead to over characterization of opioid abuse or addiction. Additionally, drug-testing recommendations may add additional costs and stigmata for patients seeking management of chronic pain. The American Medical Association has raised concern that these guidelines may have unintended consequences such as limiting access and insurance coverage.[4] While the CDC recommends that clinicians be equipped to manage the sequelae of their prescribing by providing resources and management strategies for patients who meet the DSM-5 criteria for opioid use disorder, there are no requirements for clinicians who prescribe opioids to provide the behavioral and pharmacologic treatment strategies to their patients.[5.] While the new CDC guidelines bring to light some important concepts in managing chronic pain, it is evident that more studies are needed to examine the efficacy and safety of opioid use in chronic pain.

Table 1: CDC Recommendations and Key Points for Managing Chronic Pain[1]

Evidence rating uses the GRADE methodology (www.gradeworkinggroup.org)

When to Initiate or Continue Opioids for Chronic Pain	
Recommendation 1 Nonpharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patients. If opioids are used, they should be combined with non-pharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. *Category A, Evidence 3*	- Include nonpharmacologic therapies as core components of pain management (physical therapy, weight loss, etc) - Coordinate medical, psychological, and social aspects of health care in integrated pain management programs - Ensure accurate diagnosis and mechanism of pain to treat with corresponding agents - Evaluate patient-specific factors before starting any alternative agents

Recommendation 2 Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is a clinically meaningful improvement in pain and function that outweighs risks to patient safety. *Category A, Evidence 4*	- Address treatment goals before prescribing opioids for chronic pain - Consider an "exit strategy" to enact if opioids are not successful in managing chronic pain - Use validated instruments to track outcomes, such as the PEG Assessment Scale (pain average, interference with enjoyment of life, and interference with general activity) - If opioid therapy is not providing meaningful improvements in both pain and function, consider tapering and discontinuing opioids and focusing on nonpharmacologic and non-opioid aspects of pain management
Recommendation 3 Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy. *Category A, Evidence 3*	- Patient education and discussion is a critical component of starting opioid therapy - Include patient preferences and values in discussion of opioid use to allow for informed clinical decisions - Communicate potential benefits, potential harms, and alternative options before starting or continuing opioid therapy
Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation	
Recommendation 4 When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids, instead of extended-release/ long-acting opioids. *Category A , Evidence 4*	- Continuous, scheduled long-acting opioids have not been found to be more effective or safer than use of immediate-release formulations administered on an as needed basis - Long-acting agents should be reserved for severe pain when alternative options are ineffective, not tolerated, or provide inadequate pain management in accordance with FDA labeling - Long-acting agents should not be prescribed to patients who have not already receiving at least one week of immediate-release opioids - In general, avoid the use of immediate-release and long-acting agents in combination for chronic pain to mitigate risk

Recommendation 5 When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to >50 morphine milligram equivalents (MME) dosage, and should avoid increasing dosage to >90 MME/day or carefully justify a decision to titrate dosage to >90 MME/day. *Category A, Evidence 3*	- Higher opioid doses are associated with increased risks of overdose, opioid use disorder and motor vehicle injuries - Start at the lowest possible effective dose and use the smallest practical dose increases when using opioids - Maintain opioid doses of <50 MME/day for most patients and limit patients receiving ≥90 MME/day without individual assessment and justification - Collaborate with patients to develop opioid tapering plans
Recommendation 6 Long-acting opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate- release opioid and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed. *Category A, Evidence 4*	- Acute pain can be often managed without opioids - Evaluate causes for pain and underlying etiologies and treat appropriately - Opioid use should be limited to less than 3-7 days - Re-evaluate patients who experience severe pain lasting longer than expected to reassess diagnosis and adjust the management - Do not use long-acting opioids for treatment of acute pain
Recommendation 7 Clinicians should evaluate benefits and harms with patient within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harm of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patient to taper opioids to a lower dosage or to taper and discontinue opioids. *Category A, Evidence 4*	- Patients who continue therapy for 3 months are at the greatest risk for developing opioid abuse disorder. - Overdoses are most common in the first 3-7 days after initiation of opioids or dose increases - If patients aren't experiencing pain relief within 1 month with opioids, they are unlikely to experience pain relief at later stages and discontinuation may be appropriate - Patients who use opioids longer than 3 months are at greatest risk for developing opioid use disorder and should be targeted for reevaluation - Frequent reassessments (every 3 months) should address if opioids are meeting treatment goals, adverse side effects are occurring, or signs of opioid use disorder are present - If risks outweigh benefits, patients request it, or an overdose occurs, tapering or discontinuation should be a goal - A decrease of 10% or less of the original dose per week is a reasonable starting point unless more rapid tapering is warranted based on serious adverse events

Assessing Risk and Addressing Harms of Opioid Use	
Recommendation 8 Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plans strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosage (>50 MME/day) or concurrent benzodiazepine use are present. *Category A, Evidence 4*	- Evaluate risk factors for opioid related harms frequently - Consider offering naloxone to high risk opioid users (history of overdose, substance abuse, opioid dosage [>50 MME/day] or concurrent benzodiazepine use) - Special populations - avoid or limit opioid use when possible: ○ Patients with moderate to severe sleep-disordered breathing ○ Pregnant or breastfeeding women ○ Hepatic or renal insufficiency ○ Age ≥65 years ○ Patients with mental health issues especially during acute psychiatric instability or with uncontrolled suicide risk ○ Patients with substance abuse disorder or history of overdose - Buprenorphine or methadone should be offered to pregnant women to prevent complications during pregnancy and in newborns - Implement interventions to mitigate common risks of opioid therapy in all patients, especially patients ≥65 years of age (exercise, bowel regimen, fall risk assessment, and monitoring for cognitive impairment)
Recommendation 9 Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosage or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy and periodically during therapy for chronic pain, ranging from every prescription to every 3 months. *Category A, Evidence 4*	- Check PDMP data for multiple prescribers. - Discuss findings from PDMP and safety concerns with patients - PDMP information should not be used to dismiss patients from a clinic as this can lead to further undesired outcomes and miss an opportunity to have a positive impact on the patient's care
Recommendation 10 When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider using drug testing at least annually to assess for prescribed medication as well as other controlled prescription drugs and illicit drugs. *Category B , Evidence 4*	- The effectiveness of urine drug testing has not been demonstrated in studies - Establishing a routine frequency or randomly performing urine tests can decrease stigmatization that is associated with testing - Practitioners should be familiar with urine drug testing panels and the substances that will be tested at their site - Unexpected results should be discussed with the patient and used to improve patient safety

Recommendation 11 Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. *Category A, Evidence 3*	- The combination of opioid pain medication and benzodiazepines can lead to central nervous system depression and decreased respiratory drive - Patients receiving opioids and benzodiazepines are at a much high risk of overdose-related death - Benzodiazepines should be tapered gradually to avoid withdrawal symptoms including anxiety, hallucinations, seizures, delirium tremens, and death
Recommendation 12 Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder. *Category A, Evidence 2*	- Identify treatment resources in the community - Naltrexone can be considered for highly motivated patients - Any clinician prescribing opioids should consider receiving a Substance Abuse and Mental Health Services Administration waiver to treat opioid use disorder with buprenorphine

References:

1. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1-49.
2. Washington State Agency Medical Directors' Group. AMDG 2015 interagency guideline on prescribing opioids for pain. Olympia, WA: Washington State Agency Medical Directors' Group; 2015. http://www.agencymeddirectors.wa.gov/guidelines.asp
3. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. J Pain 2015; 16;769-80.
4. Ciccone TG, Kean N. Responses and criticisms over new CDC opioid prescribing guidelines. Practical Pain Management March 17, 2016. https://www.practicalpainmanagement.com/resources/news-and-research/responses-criticisms-over-new-cdc-opioid-prescribing-guidelines. Accessed 27 February 2017.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.

New Agents for Treatment of Opioid Dependence: Vivitrol® and Probuphine®

Alvin B. Oung, PharmD and Melissa J. Ruble, PharmD, BCPS

Opioid dependence is of national concern as the number of opioid-associated deaths continues to rise. From 1999-2014 the rate of overdose deaths involving opioids nearly quadrupled, amounting to over 165,000 deaths.[1] In March 2015, the U.S. Department of Health and Human Services proposed an initiative that targets three priority areas: improving prescribing practices, expanding the use of naloxone, and expanding the use of medication-assisted treatment (MAT).

MAT, along with reducing morbidity, mortality, and the spread of infectious diseases, has been seen to decrease illicit opioid use at a greater rate than abstinence-based therapy or psychosocial intervention alone.[2] Treatment options include methadone, buprenorphine ± naloxone, and naltrexone. However, as these medications are traditionally dosed daily, poor adherence can result in cravings, withdrawal symptoms, and ultimately relapse. Thus, there is a growing need for innovative delivery methods. This article describes two newly approved agents for the treatment of opioid dependence: Vivitrol® and Probuphine®.

Vivitrol® is a once-monthly injectable formulation of naltrexone, an opioid antagonist, that was first

approved April 13, 2006 for the treatment of alcohol dependence.[3] On October 13, 2010 the FDA approved Vivitrol® in combination with psychosocial support for the prevention of relapse in patients with opioid dependence.[3] Psychological support was defined as bi-weekly counseling sessions that focused on opioid dependence and individual drug counseling. This extended release intramuscular injection is administered by a healthcare provider into the gluteal muscle every 4 weeks. Before initiating treatment, patients should be opioid-free for at least 7 to 10 days to avoid precipitating withdrawal symptoms. Each injection contains 380 mg/4.2 mL of naltrexone and is dispensed in cartons containing the medication as well as supplies to reconstitute and administer. This product should be stored in the refrigerator and warmed to room temperature prior to preparing.

The safety and efficacy of Vivitrol® was demonstrated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of patients who were opioid dependent. All patients were receiving treatment or recently received detoxification treatment in the inpatient setting prior to initiating the medication.[4] The specific detoxification treatment was not defined but patients were required to be opioid-free (including buprenorphine and methadone) for at least 7 days prior to initiating the first dose.[3] Patients were randomized to receive treatment every 4 weeks with either Vivitrol® 380 mg or placebo along with psychosocial support biweekly to all patients as mentioned above. The primary outcome was complete abstinence (the percentage of opioid-free weeks) during weeks 5 through 24 and was confirmed with a negative urine drug test and no self-reported use. Secondary outcomes included self-reported opioid free days, cravings, treatment retention, and relapse to physiologic opioid dependence. Patients receiving Vivitrol® had a statistically significant increase in confirmed abstinence compared with placebo (36% vs. 23% p=0.0224). The median proportion of weeks in the evaluation period with confirmed abstinence was 90% for patients receiving Vivitrol® compared to 35% for those receiving placebo (p=0.0002). All secondary endpoints favored the use of Vivitrol® over placebo with statistical significance. Discontinuation rates due to adverse events were similar in both groups.[4]

The most common side effects of Vivitrol® include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Patients should be made aware that if they miss a dose or discontinue this medication that they are more sensitive to lower doses of opioids which may lead to an accidental overdose if opioids are restarted. Signs and symptoms of opioid overdose include altered mental status, decreased respiratory rate, pin-point pupils, and hypotension. Vivitrol® is only approved for intramuscular injection and should never be used intravenously or subcutaneously. A medication guide must be given to all patients due to the increased risk for opioid withdrawal and overdose as well as other serious side effects listed above.[3]

Probuphine®, approved on May 26, 2016, is an implantable formulation of buprenorphine, a partial opioid agonist. It consists of 4 single-rod implants inserted subdermally into the inner side of the upper arm as an outpatient office procedure. Each rod is an ethylene vinyl acetate implant, 26 mm in length and 2.5 mm in diameter, containing 74.2 mg of buprenorphine.[5] Buprenorphine is released as an initial pulse followed by a constant and low level release over 6 months before its removal. It is indicated for the maintenance treatment of opioid dependence in persons between the ages of 16 and 65 who have achieved and sustained clinical stability on buprenorphine. This is defined as doses ≤ 8 mg/day of Subutex® or Suboxone® sublingual tablets or its transmucosal buprenorphine product equivalent for ≥3 months without any need for supplemental dosing or adjustments.[5] Probuphine® should be used in conjunction with counseling and psychosocial support.

The safety and efficacy of Probuphine® was demonstrated in PRO-814, a randomized, active-controlled, double-blind, double dummy clinical trial evaluating whether 6-month buprenorphine implants (BI) were noninferior to daily sublingual buprenorphine (SL BPN) as maintenance treatment for opioid-dependent patients with stable abstinence.[6] The primary endpoint was the difference in proportion of responders - those with at least 4 of 6 months without illicit opioid use, confirmed with a negative urine drug test and no self-reported use. Eighty-one of 84 patients (96.4%) receiving BI and 78 of 89 (87.6%) receiving SL BPN were

responders, an 8.8% difference (1-sided 97.5% CI, 0.009 to ∞; P<0.001 for noninferiority). As a secondary endpoint, over 6 months, 85.7% receiving BI and 71.9% receiving SL BPN maintained opioid abstinence, HR 13.8; 95% CI, 0.018-0.258; P=0.03.[6] There were no statistically significant differences in craving or withdrawal scores.

The most common side effects of Probuphine® are implant-site pain, pruritus, and erythema, as well as headache, depression, constipation, nausea, vomiting, back pain, toothache, and oropharyngeal pain.[5] Insertion sites should be examined within one week for any abnormalities. Finally, due to the potential of implant migration, protrusion, expulsion, and nerve damage, all healthcare providers who intend to prescribe or perform insertions of Probuphine® implants must first complete a live training program and become certified in the Probuphine® Risk Evaluation and Mitigation Strategy (REMS) program.

Opioid dependence and relapse are serious concerns affecting patients across the country. Use of MAT helps decrease this burden but compliance with these medications remains low. Newer agents including Vivitrol® and Probuphine® may help to decrease the number of relapses and help patients gain control of their addiction. It is important to emphasize the need for psychosocial support in addition to these medications for optimal outcomes. Pharmacists play a key role in identifying patients who may benefit from these medications and ensuring proper dosing and administration. Pharmacists can also help with educating patients on the importance of adherence and the benefits of treatment. As the opioid epidemic continues, practitioners will be relying on treatment modalities to help their patients overcome their addiction. Current literature focuses on the immediate treatment of opioid overdose and the need for programs to help educate the public on access to care and administering these life-saving medications. Future studies will build upon these innovative routes of administration and new roles of therapy for prescription opioid vaccines to help decrease overdose mortality.[7] As healthcare practitioners, it is important to work together to ensure we meet the initiative and address the opioid epidemic.

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Management of Pain for Patients on Opioid Dependence Maintenance Therapies

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From 2007 to 2012, opioid prescriptions in the United States increased 7.3% per capita.[1] Also, in 2013, approximately 2 million people abused or were dependent on prescription opioids.[2] These statistics highlight the lack of consensus among prescribers regarding appropriate pain management. This may result in opioid dependence. Opioid dependence therapy, also known as opioid agonist therapy (OAT), is used to treat opioid dependence to control drug use and limit the incidence of adverse events. This involves prescribing controlled amounts of longer-acting but less euphoric opioids to reduce cravings and prevent withdrawal symptoms.[2] This article will review several challenges for healthcare professionals in treating both acute and chronic pain as well as provide considerations for treatment options in patients receiving opioid dependence therapy.

Acute Pain

In patients with opioid dependence, opioids should be utilized as medically indicated for the treatment of acute pain, along with nonpharmacologic and non-opioid therapies. For most patients, analgesics should be scheduled instead of administered on an as needed basis to alleviate pain and anxiety between doses.[3] Due to tolerance, patients on OAT may require higher doses and shorter dosing intervals than the general population. Mixed agonists/antagonists such as nalbuphine, pentazocine, and butorphanol should be avoided as they may displace the maintenance opioid from the mu receptor and exacerbate withdrawal.[4]

There is lack of data concerning specific methods of treating acute pain in patients receiving OAT. A variety of methods have been used and varies depending on the type of OAT. In order to treat acute pain in patients receiving OAT, the patients' daily opioid requirement must first be met, either through continuation of opioid maintenance therapy or conversion to another opioid. For patients receiving methadone, methadone is continued at the maintenance dose and a different short-acting opioid analgesic is given to treat pain. Methadone is not preferred for treatment of acute pain due to slow onset and long half-life. Methadone maintenance therapy should not be converted to another opioid as dose conversions from methadone to other opioids are variable due to cross tolerance.[3-4]

Buprenorphine has a high affinity for mu and kappa receptors. High opioid doses may be required if buprenorphine is continued during treatment of acute pain.[3] Reinitiating buprenorphine while opioids are present may precipitate withdrawal. Four main strategies have been used for the acute treatment of pain in patients receiving buprenorphine maintenance therapy:

1. The first is to continue buprenorphine and titrate another short-acting opioid for pain management. This is useful for pain of short duration.
2. Alternatively, buprenorphine can be utilized as an analgesic. The maintenance dose is divided and administered every 6-8 hours, then titrated to provide adequate analgesia. Some patients may require additional opioid therapy for pain control.
3. Most patients with severe pain will require discontinuation of buprenorphine. Buprenorphine can be discontinued and long and short acting opioid agents can be used to control pain. Once the patient no longer requires opioids for pain management, buprenorphine can be reinitiated. This strategy may work well in patients with anticipated pain (e.g. surgery) when the buprenorphine can be discontinued at least 24 hours in advance of the surgery.
4. Finally, buprenorphine may be discontinued and replaced with methadone for OAT given its lower affinity for the mu receptor. Methadone should be slowly titrated to alleviate withdrawal symptoms, while short acting opioids are used for pain management. Once the patient no longer requires pain management with opioids, methadone can be discontinued and the patient can be restarted on buprenorphine.[3]

Chronic Pain

Patients with chronic pain and substance abuse disorders can be treated alternatively with non-opioid agents, and typically, a multidisciplinary approach is recommended.[5] Non-pharmacologic therapies including cognitive-behavioral therapy, exercise, and complementary medicine, such as yoga, acupuncture, and meditation, are being utilized for the management of chronic pain. Use of non-opioid analgesics is also recommended in multiple guidelines including acetaminophen, nonselective nonsteroidal anti-inflammatory drugs (NSAIDS) and cyclooxygenase-2 inhibitors. Particularly for osteoarthritis and lower back pain, NSAIDs should primarily be used. Additionally, prescribers may find opioids in various routes of administration (i.e., topical or sublingual) helpful in the management of chronic pain with less concern for withdrawal symptoms and euphoria. Current literature recommends the use of antidepressants (TCAs, SSRIs, and SNRIs) and anticonvulsants (gabapentin and pregabalin) as first- or second-line treatment for neuropathic pain. Finally, interventional neural-stimulation therapies, electromyography, and neurofeedback with the use of functional magnetic resonance imaging are being used as supplemental approaches for chronic pain management. Varying efficacy data is available for these strategies, and research is ongoing to continue to assess their value in the management of chronic pain with opioid dependence.[5] In conclusion, the management of pain in patients receiving opioid dependence therapy is complex. Due to tolerance and hyperalgesia, which alters the patient's pain experience, analgesics may be less effective or require alternative dosing strategies.[3] Ultimately, clinical decision making for pain management in patients with opioid dependence should be based on a direct prescriber-patient relationship and a full understanding of the patient's clinical situation.

Misconceptions

Common misconceptions of healthcare providers interfere with proper prescribing and monitoring of opioids for pain management in patients with substance use disorders receiving opioid dependence therapy.[4] The first misconception is that OAT provides analgesia. Hyperalgesia and opioid tolerance counteract the analgesic effects of maintenance opioids (i.e., methadone or buprenorphine) despite their benefits in opioid dependence. Second, a common concern of healthcare providers is addiction relapse resulting from the use of opioids for analgesia in patients receiving OAT. However, no evidence indicates that exposure to opioids for acute pain increases relapse rates. Furthermore, evidence does suggest stress caused by unrelieved pain can trigger relapse. Third, physicians note concern that respiratory and central nervous system (CNS) depression are more likely in patients receiving OAT and opioid analgesics for pain, though this risk has not been demonstrated clinically. Finally, providers remain apprehensive in prescribing opioids to patients with substance use disorders because the complaint of pain may actually be drug-seeking behavior. While this concern is substantial, difficult to quantify, and oftentimes, emotional, careful clinical assessment for evidence of pain and a full understanding of the patient's request and/or behavior will decrease this risk.[4]

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