Adult Medicine PRN Spring Newsletter

Edited by Jon P. Wietholter, PharmD, BCPS and Kathleen K. Adams, PharmD, BCPS

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Message from the Chair

Ryan E. Owens, PharmD, BCPS

Submitted: March 9th, 2020

"I might happen to be at the right place at the right time to make a difference."
–Dan Schneider

The beginning of 2020 has provided some widespread exposure of the profession of pharmacy, with two vastly different stories represented in the media. If you haven't had a chance to watch *The Pharmacist* on Netflix yet, put it on your watch list as soon as possible. The story focuses on Dan Schneider, a community pharmacist in Louisiana, who not only recognized the opioid epidemic years before it made headline news, but also risked his job to intervene in order to prevent patient harm. The show has received a lot of praise for both exposing inappropriate opioid prescribing and showcasing the role pharmacists can play in combating the opioid epidemic. The second spotlight on pharmacy occurred via *The New York Times* article, "How Chaos at Chain Pharmacies is Putting Patients at Risk." The article outlines inappropriate working conditions in several chain pharmacies and medication errors that occur as a result. Most concerning are the anonymous quotes included from pharmacists commenting on the impact of the working conditions on their quality of life and patient care.

You may be thinking at this point, "what do both of those exposés have to do with our members in the Adult Medicine PRN?" The majority of our members practice in either inpatient or outpatient settings, not in community pharmacies. While we may work in different areas, we are all still pharmacists. We often get segregated into our individual specialties and may not pay attention to the issues occurring outside our practice areas. Just because the issues occurring in community pharmacy don't directly affect the

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APRIL 15TH

MAY 20TH

JUNE 17TH

JULY 15TH

majority of us, it does not mean we should turn a blind eye to it. The practitioners working in community pharmacies sat beside us in pharmacy school, were at our sites for experiential rotations prior to graduation, and are our colleagues in the profession. As shown in Dan's story, our colleagues in community pharmacy play a major role in patient care and can have a significant clinical impact. It is concerning to read of the disconnect in *The Times* article that some major corporations are not providing community pharmacists the resources or administrative support to produce similar outcomes. In the *Oath of a Pharmacist*, we all agree to "advocate changes that improve patient care." In order to bring about change, we need to stand united as the voice of a profession. While we often quickly stand behind initiatives to advance clinical pharmacy services in hospital or ambulatory care settings, we also need to be quick to stand behind initiatives that enhance patient care and working conditions in community settings. Our PRN represents a wide variety of practice areas and at the end of the day, we are all taking care of the same patients. The patient you see in the hospital is following up in the clinic and also picking up medications at the community pharmacy. The more meaningful interactions a patient can have with pharmacists across the continuum of care, the better outcomes we can produce.

Being an election year, it is the right time to make a difference for all of us. When choosing who you vote for, regardless of the position or party, research where they stand on issues that affect pharmacy and healthcare, to ensure that it aligns with our oath of improving patient care. If an initiative does not directly affect your practice area, reach out to colleagues or organizations who it may affect to get their input to ensure you are well informed. I also want to challenge all of our members to get involved with advocacy for our profession throughout the year to your state boards of pharmacy, to your local representatives, to national organizations. It could be as simple as writing to your local representative or signing a petition that comes across your inbox. Our collective voice matters. Our collective vote matters. Our collective profession matters.

Thank you all for everything you are doing to help advance our profession on a local level in your area, on a committee level within our PRN, and on a national level with ACCP.

"Presidents Row" from the Adult Medicine PRN at the 2019 ACCP Annual Meeting in New York City

From Left to Right: Andrew Miesner (2018-2019), Sharon See (2006-2007), Sarah Anderson (2015-2016), Lindsay Arnold (2010-2011), Nancy Yunker (2011-2012), Joel Marrs (2009-2010), Ryan Owens (2019-2020), Carmen Smith (2020-2021)

2019-2020 ACCP Adult Medicine PRN Officers

- Ryan E. Owens—President
- Carmen B. Smith—President-Elect
- Jon P. Wietholter—Secretary/Treasurer

2019 ADULT MEDICINE PRN STUDENT AND RESIDENT/FELLOW RESEARCH AWARD RECIPIENTS

* **Resident/Fellow Research Award**
  Eric Kinney, PharmD; PGY2 Internal Medicine Pharmacy Resident, Duquesne University School of Pharmacy & UPMC Mercy Hospital

Carvedilol versus metoprolol succinate for heart failure with reduced ejection fraction and concomitant cocaine use

"Following the submission of my research abstract, curriculum vitae, and personal statement to the Travel and Training Awards Committee, I was fortunate to receive the Resident Research Grant from the ACCP Adult Medicine PRN (AMED PRN). Like many residents, my program allocated reimbursement for one pharmacy conference during the year, but with the funds provided by the AMED PRN I was able to extend my attendance to both the 2019 ACCP Annual Meeting and 2020 ACCP Spring Forum. This support enabled me to participate in the programming at each event and therefore complete the ACCP Leadership and Management Academy. In addition, these opportunities allowed me to present my research both in a poster to the ACCP membership as well as at a podium to the AMED PRN specifically. My involvement in the organization's national meeting, made possible by this award, was an enriching experience in networking, research, and continuing education at the highest level. "

* **Student Research Award**
  Karissa Chow, 2020 PharmD Candidate from Philadelphia College of Pharmacy

Predictors of drug therapy problems and the need for interventions by internal medicine clinical pharmacists

"It was an honor to receive the ACCP AMED PRN Student Research Award. I am very thankful for the $1,000 travel scholarship to attend my first ACCP Annual Meeting and present my research titled "Predictors of Drug Therapy Problems and the Need for Interventions by Internal Medicine Clinical Pharmacists" at the AMED PRN Business Meeting. After spending 2+ years designing and executing my research project, including learning multiple statistical programs, I was deeply humbled to be recognized for my work and the experience to present nationally as a student. The meeting was a wonderful opportunity to learn from and network with practicing pharmacists so that I could develop my ability to optimize my patients' health outcomes. I was able to use the experience to help start a student chapter of ACCP at my pharmacy school. The meeting also inspired me to become involved nationally with ACCP and I subsequently joined the Internal Affairs Committee of the AMED PRN. Thank you to the scholarship committee and generous PRN members who funded the scholarship which allowed me to continue to develop as a clinical pharmacist."

ADULT MEDICINE PRN ANNOUNCEMENTS

Nominations Committee

- **CALL FOR OFFICER NOMINATIONS**
  Would you like to serve the PRN as an officer in 2020-2021? The Adult Medicine Nominations committee is now accepting self-nominations and nominations of colleagues for:
    - Chair-Elect
    - Treasurer/Secretary

  Officer roles can be found at: http://amedprn.accp.com/docs/prns/amed/AMPRN_Officer_responsibilities.pdf

  Nominations are due by Thursday, April 30th. To nominate or learn more, please contact the committee chair at andrewmiesner@gmail.com

- **AMED NAME DROPPER**
  Do you want the Nominations Committee to know about an awesome PRN member, but not sure they want to go through the nominations process? Think someone is great, but no time to write a letter of recommendation for an award? Just drop their name!

  The AMED PRN Name Dropper is an easy way to suggest a name anonymously for a PRN award, fellowship, or PRN officer. We'll take it from there! www.tinyurl.com/amednamedropper

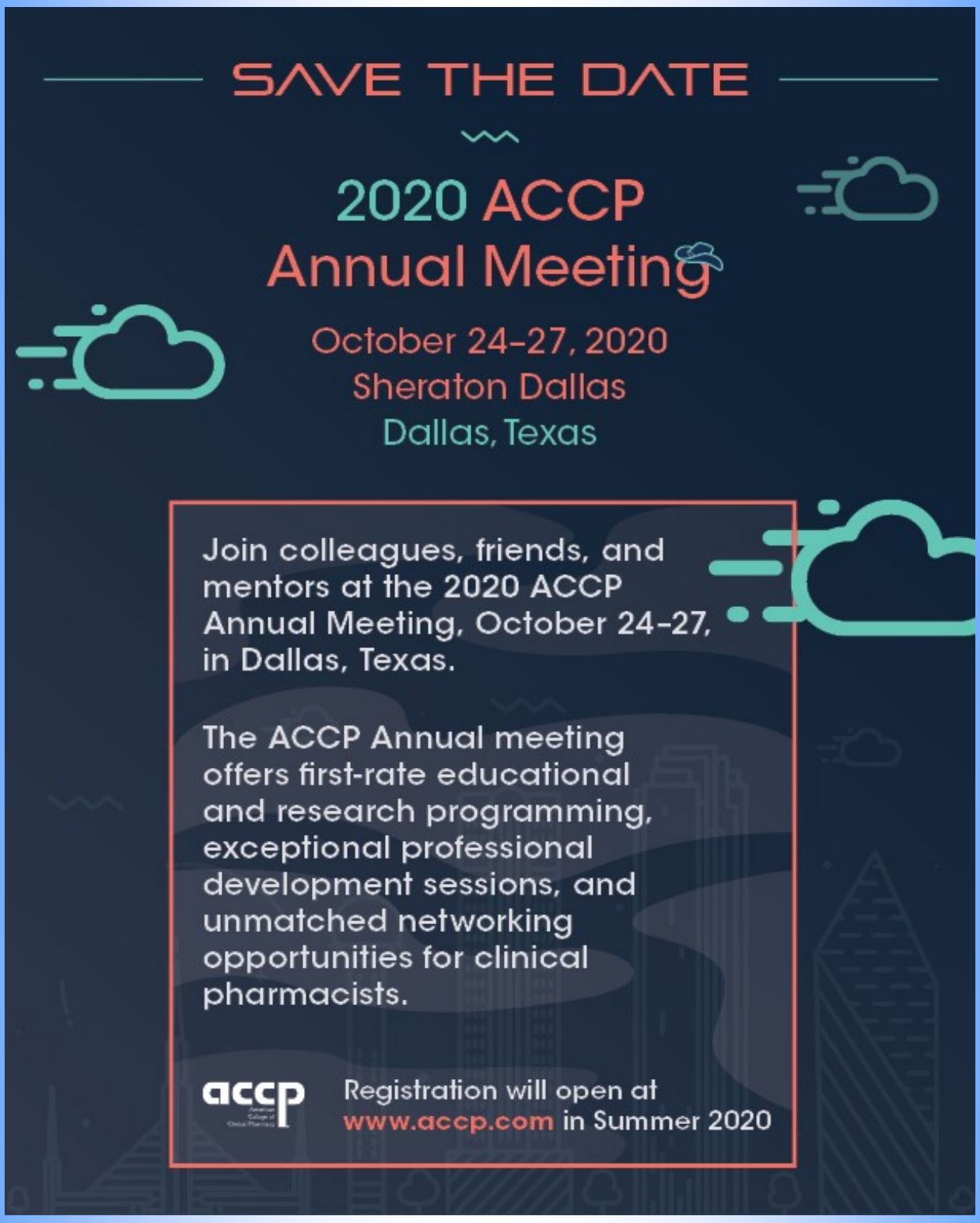
External Affairs Committee

- Consider nominating yourself or other ACCP AMED PRN members, residents, or student chapter representatives to be featured on social media pages: https://forms.gle/yFmgHo36fziESWPw9

Student/Resident Engagement Committee

- Be on the lookout to sign up to be a presenter (resident) or mentor for AMED PRN eJournal Club for the 2020-2021 year

- **AMED PRN TEACHABLE MOMENTS**
  Calling all AMED PRN preceptors! Do you have a "teachable moment" that you would like to pass along? If so, consider involving your students in presenting a patient case/clinical scenario related to that "teachable moment." Contact tran@musc.edu to participate or for more information.



Call for Abstracts

June 15, 2020 - Deadline for all abstract categories, except Research-In-Progress

July 15, 2020 - Deadline for Research-In-Progress abstracts

Member Accomplishments 08/2019-02/2020

Promotions:

Alex Ebied, Pharm.D, BCCCP, *Promoted to Director of Interprofessional Education*, High Point University Fred Wilson School of Pharmacy

Sarah A. Nisly, Pharm.D, BCPS, FCCP**,** *Promoted to Professor*, Wingate University School of Pharmacy

Jeff Sherer, Pharm.D, MPH, BCPS, BCGP, *Promoted to Clinical Professor*, University of Houston College of Pharmacy

Awards:

Erika Lambert Brechtelsbauer, Pharm.D, BCPS, *Patient Safety Award: Beyond the Call of Duty*, Emory University Hospital Midtown

Jay L. Martello, Pharm.D, BCPS, *Award of Excellence in Experiential Education*, American Association of Colleges of Pharmacy (AACP)

Charles F. Seifert, Pharm.D, FCCP, BCPS, *2019 President's Excellence in Interprofessional Teamwork Award for the Impact Clinic for the development of Lubbock County Indigent Care Clinic,* Texas Tech University Health Sciences Center

Grants:

Jennifer Austin Szwak, Pharm.D, BCPS, University of Chicago Medicine, **O**utpatient **P**rinciples **i**n **A**ddiction **T**raining and **E**ducation (OPIATE) Initiative, Association of American Medical Colleges Curricular Innovation Award, $2500

Publications:

Greene RA, **Adams KK**, Rogers RD, Berard-Collins C, Lorenzo MP. Pharmacokinetics of flucytosine in a critically ill patient on continuous venovenous hemodiafiltration. *Am J Health Syst Pharm* 2020;77(8):609-613.

Lee C, **Austin Szwak J**, Bastow S, McCarthy S. Impact of a nurse-driven diabetic ketoacidosis insulin infusion calculator on the rate of hypoglycemia. *J Patient Saf* 2019. [Epub ahead of print]. doi: 10.1097/ PTS.0000000000000647

Boylan PM, Murzello A, Parmar J, Chow NK. Integration of Latin American complementary and alternative medicine topics into a Doctor of Pharmacy curriculum and survey of student attitudes and behaviors. *J Med Educ Curric Dev* 2020;7:1-4. DOI:10.1177/2382120520904121

Boylan PM, Sedlacek J, Santibañez M, Church AF, Lounsbury N, Nguyen J. Development and implementation of interprofessional relations between a college of pharmacy and osteopathic residency programs in a community teaching hospital. *J Pharm Technol* 2020;36(1):3-9. DOI:10.1177/8755122519865540

Publications, cont.

Ebied AM, Nguyen DT, Dang T. Evaluation of Occipital Nerve Blocks for Migraines. *J Clin Pharmacol* 2020;60(3):378–383.

Ebied AM, Patel KH, Cooper-DeHoff RM. New Drugs Approved in 2019. *Am J Med* 2020 Feb 18 [Epub ahead of print].

Schwier NC, Cornelio CK, **Epperson TM**. Managing acute and recurrent idiopathic pericarditis. *JAAPA* 2020;33(1):16-22.

Engle JP, Burke JM, Ashjian EJ, Avery L, Borchert JS, Faro SJ, Harris CS, Herink MC, Jain B, MacLaughlin EJ, **Martello JL**, Moore K, Rogers E, Smith WJ, Stranges PM. ACCP clinical pharmacist competencies: Advocating alignment between student, resident, and practitioner competencies. *J Am Coll Clin Pharm* 2020:3(1):124-132.

Tran T, Arnall J, **Moore DC**, Ward L, Palkimas S, Man L. Vonicog alfa for the management of von Willebrand disease: a comprehensive review and single-center experience. *J Thromb Thrombolysis* 2020 Jan 4. [Epub ahead of print]. doi: 10.1007/s11239-019-02018-1

Moore DC, Elmes J, Shibu P, Larck C, Park SI. Mogamulizumab: an anti-CC chemokine receptor 4 antibody for T-cell lymphomas. *Ann Pharmacother* 2020;54(4):371-379.

Moore DC, Ringley JT, Nix D, Muslimani A. Impact of obesity on the incidence of bortezomib-induced peripheral neuropathy in patients with newly diagnosed multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2020;20(3):168-173. doi: 10.1016/j.clml.2019.08.012

Summers K, Davis KA, **Nisly SA**. Bleeding risk of therapeutic unfractionated heparin and low molecular weight heparin in patients with cirrhosis. *Clin Drug Inv* 2020;40:191-196.

Nisly SA, Fillius AG, McClain D, Davis KA. Oral antibiotics for the treatment of gram negative blood stream infections: a retrospective comparison of three classes. *J Glob Animicrob Resist* 2020;20:74-77.

Nisly SA, Sebaaly J, Fillius AG, Haltom WR, Dinkins MM. Changes in metacognition through self-evaluation during advanced pharmacy practice experiences. *Am J Pharm Educ* 2020;84(1):Article 7489.

Brammer KE, Brennan L, Phan D, Payne L, Ali A, Davis SM, **Nisly SA**. Evaluation of a resident-led residency preparation series for fourth year pharmacy students. *Innov Pharm* 2019;10(4):Article 12.

Steuber TD, **Nisly SA**, Gillette C. Grit in pharmacy faculty: a pilot analysis focused on productivity measures. *Curr Pharm Teach Learn* 2019;11(10):1029-1034.

Isaacs AN, Walton AM, Gonzalvo J, Howard ML, **Nisly SA**. Pharmacy educator evaluation of web-based learning. *Clin Teach* 2019;16(6):630-635.

Nguyen CT, Davis KA, **Nisly SA**, Li J. Treatment of Helicobacter pylori in special patient populations. *Pharmacotherapy* 2019;39(10):1012-1022.

Steuber TD, Howard ML, **Nisly SA**. Direct oral anticoagulants in chronic liver disease. *Ann Pharmcother* 2019;53 (10):1042-1049.

Horyna TJ, Jimenez R, McMurry L, Buscemi D, Cherry B, **Seifert CF**. An Evaluation of Interprofessional Patient Navigation Services in High Utilizers at a County Tertiary Teaching Health System. *J Healthc Manag* 2020;65(1);62-70.

Publications, cont.

Shah, S, Peng I, **Seifert CF**. A Model to Predict NAPLEX Outcomes and Identify Students Needing Additional Preparation. *Curr Pharm Teach Learn* 2019;11:810-817.

Smith SM, Invaded by Cancer, and the Patient is Me. *Innov Pharm* 2019;10(3);Article 16. 10.24926/iip.v10i3.2074

Smith SM, Coleman M, Dolder CR. Evaluation of generational influences among 4th year pharmacy students and experiential preceptors. *Curr Pharm Teach Learn* 2019;11(9):888-894. doi 10.1016/j.cptl.2019.05.012

Marler J, **Twilla JD**, Finch CK, Animalu C. Severe Ceftaroline-Induced Thrombocytopenia With Rapid Onset on Rechallenge. *Ann Pharmacoth*er 2020;54(2):187-188.

Ilcewicz HN, Coetzee R, Taylor M, Piechowski K, Martello JL, **Wietholter JP**. Evaluation of pharmacy students' perceptions of clinical pharmacy in South Africa. *J Am Coll Clin Pharm* 2020 Feb 13. [Epub ahead of print]. DOI: 10.1002/jac5.1208

Wietholter JP, Maynor LM, Clutter JL. A Correlation of Student Personality Style and First Year Academic Performance *Am J Pharm Educ* 2020 Feb 4. [Epub ahead of print]. DOI: https://doi.org/10.5688/ajpe7909

Hill JB, **Wietholter JP**. Evaluation of Risks versus Benefits with Concomitant Use of Budesonide Nebulizers and Systemic Corticosteroids in COPD Exacerbations. *Int J Med Pharm* 2019;7(2):1-5.

Other Notable Achievements:

Alex Ebied, Pharm.D, BCCCP, American College of Clinical Pharmacy (ACCP) Research and Scholarship Certificate

2020 ACCP Virtual Poster Symposium

May 25-31:

- Asynchronous viewing and comment

May 26-27 (7-9PM Central Time):

- Authors will be available for real-time online question-and-answer interactions

One-HIT wonders or mainstays of therapy? Evaluation of literature regarding direct oral anticoagulants (DOACs) in heparin-induced thrombocytopenia (HIT)

By: Leslie Wooten, PharmD, BCPS & Stanley Luc, PharmD, BCPS

"There are currently no head-to-head trials comparing the efficacy and safety of warfarin to DOACs in the long-term treatment of HIT. DOAC treatment for HIT does not demonstrate a significant risk in existing case reports. In conclusion, DOAC therapy may be an appropriate option in most clinically stable patients with HIT who are eligible for treatment with oral anticoagulation."

Introduction

Heparin-induced thrombocytopenia (HIT) is an uncommon hematologic disorder in response to exposure to heparin products characterized by low platelet count and hypercoagulability, which can lead to thrombotic events. The absolute risk of HIT is higher for unfractionated heparin (UFH) at 2.6% as compared to that of low-molecular-weight heparin (LMWH) at 0.2%.[1] Other relevant risk factors listed in the literature include: duration of heparin therapy, full anticoagulation dosing of UFH, autoimmune disease(s), hemodialysis, gout, heart failure, surgery, and trauma.[2,3] In 2018, the American Society of Hematology (ASH) published HIT management guidelines. This condition can further be chronologically categorized as: suspected HIT, acute HIT, subacute HIT A, subacute HIT B, and remote HIT (Table 1).[4]

Table 1: The 5 Phases of HIT [4]

Phase	Platelet count	Functional assay	Immunoassay
Suspected HIT	↓	unknown	unknown
Acute HIT	↓	+	+
Subacute HIT A	recovered	+	+
Subacute HIT B	recovered	-	+
Remote HIT	recovered	-	-

Information from American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia

In suspected HIT, the ASH guidelines recommend using the 4T score to assess the probability of HIT.[4] This scoring tool estimates HIT probability as low (< 0.1%), intermediate (0.1 - 1%), or high (> 1%) by assessing the **T**iming of platelet drop, degree of **T**hrombocytopenia, suspected or proven **T**hrombosis, and other causes of **T**hrombocytopenia. If there is an intermediate or high HIT probability, then an immunoassay test to detect platelet factor 4 (PF4)/heparin antibodies is recommended. A negative result rules out HIT. However, this test is less specific, and a functional assay, such as the serotonin release assay, is suggested to confirm the diagnosis of acute HIT. For patients with a high 4T score and strongly positive immunoassay test, a confirmatory functional assay is unnecessary as this combination of features is fairly specific. If there is an intermediate or high probability of HIT, the ASH guidelines recommend heparin discontinuation and initiation of non-heparin anticoagulant therapy at prophylactic or therapeutic intensity, depending on HIT probability, bleeding risk, and presence of thrombosis.[4] Non-heparin anticoagulant options include: argatroban, bivalirudin, danaparoid, fondaparinux, and direct oral anticoagulants (DOACs). Of these drugs, argatroban is the only agent that is both FDA-approved for HIT and readily available in the United States.[5] DOAC use is off-label for HIT. Selection of HIT pharmacotherapy is primarily influenced by drug factors (e.g., half-life, route of administration, safety and efficacy monitoring), patient factors, and clinician experience. Argatroban and bivalirudin are most appropriate in critically ill patients, those undergoing surgery or other invasive procedures, and/or those with life- or limb-threatening thromboembolism; whereas fondaparinux and DOACs are appropriate in clinically stable patients. Also, DOACs are appealing options compared to parenteral anticoagulants if extended non-heparin anticoagulation is required. DOACs have widespread availability and proven efficacy in treating venous thromboembolism (VTE), but published evidence with DOACs in HIT is limited.

The following tables and sections describe and summarize the associated literature detailing DOAC use in HIT. Management of HIT with DOACs is further divided into indications and sub-indications as there are multiple phases and presentations of HIT. Primary acute HIT treatment with DOAC therapy is defined when a DOAC is the first non-heparin anticoagulant used to treat HIT. Secondary HIT treatment with DOAC therapy is defined when non-DOAC therapy (e.g., argatroban, bivalirudin, fondaparinux) is the first non-heparin anticoagulant initiated for HIT and this drug is subsequently transitioned to DOAC for continuation and/or completion of therapy. Within primary and secondary HIT treatments with DOAC therapy, patients can present as HIT with thrombosis (HITT) or without thrombosis (isolated HIT). For secondary HIT treatment, DOAC therapy can be initiated during the acute or subacute HIT phases, which are differentiated by platelet recovery.[4] Of note, published literature regarding edoxaban and betrixaban usage in HIT was unable to be found at the time of this article's development.

Primary Acute HIT Treatment with DOACs

Twenty-seven case reports outline the use of DOACs in primary treatment of HIT (Tables 2A and 2B). Rivaroxaban (n=17) is the DOAC most commonly seen in the primary treatment of HIT followed by apixaban (n=6) and dabigatran (n=4). There is also a less detailed retrospective review of dabigatran (n=40) use in HIT. Primary treatment for HITT was most common with rivaroxaban (n=11) followed by apixaban (n=4) and dabigatran (n=2). Indication for anticoagulation, thrombotic complications, and DOAC regimens are outlined in Table 2A. Reported rivaroxaban dosing for the primary treatment of HITT is variable, however, the most common reported dosing is rivaroxaban 15 mg by mouth (PO) twice daily for 21 days followed by rivaroxaban 20 mg PO daily which aligns with ASH guideline recommendations and typical VTE treatment dosing.[4,6-9] Apixaban for primary treatment of HITT is described in several patients in the case series by Davis and Davis. The dosing is outlined in Table 2A.[12] Apixaban was also used as primary therapy in a case report by Bhardwaj, et al. This patient was initially started on low dose apixaban due to thrombocytopenia (platelets 16 $x10^9$/L) but was later increased to apixaban 10 mg PO twice daily for 7 days followed by apixaban 5 mg PO twice daily.[13] No complications were reported in these patients treated with apixaban for HITT.[12,13] The use of dabigatran for primary treatment of HITT is described in 3 case reports outlined in Table 2A.[14-16] The only case report of long-term treatment with dabigatran in HITT was by Mirdamadi.[16] Primary treatment of HIT without thrombotic complications or the presence of thrombosis (isolated HIT) has been described in case reports (n=9) as well. Rivaroxaban (n=6) was most commonly used for primary treatment of isolated HIT. All patients with isolated HIT were successfully treated with DOACs.[6,12,17-19] A retrospective chart review described the use of dabigatran as primary treatment for HIT. Patients were excluded for reduced renal clearance (creatinine clearance <15 mL/min), hepatic impairment (Child-Pugh B and C), mechanical heart valves, active bleeding, or weight extremes (<50 or >120 kg). Forty patients were included in the review. Thirty-three patients were started on dabigatran 110 mg PO twice daily while the remaining 7 patients were started on dabigatran 75 mg PO twice daily due to creatinine clearance (CrCl) 15-30 mL/min. One patient developed a second DVT during dabigatran therapy. Two patients had minor bleeding resulting in skin ecchymosis.[20] Most commonly reported DOAC regimens for the treatment of HITT or isolated HIT have used dosing that is indicated in the treatment of VTE. Alternative dosing was used at times and is described further in Tables 2A and 2B. Rivaroxaban and dabigatran have the most supporting literature for the primary treatment of HIT.

Secondary HIT Treatment with DOACs

Case reports for HIT treatment with DOAC therapy after initial, non-heparin parenteral therapy for HIT are summarized in Tables 3A and 3B. Of note, some case report descriptions did not clearly specify the platelet count when DOAC therapy was initiated and/or the DOAC dosing. For initial parenteral HIT therapy, fondaparinux (n=16) and argatroban (n=14) were most frequently utilized. Among HITT cases (n=23), rivaroxaban (n=13), apixaban (n=9), and dabigatran (n=1) were utilized for long term treatment after initial parenteral therapy for HIT. The most frequently described rivaroxaban dosing was 15 mg PO twice daily for 21 days then 20 mg PO daily, which matches ASH guideline remarks and typical VTE treatment dosing.[4] A large majority of the following HITT cases involved VTE, and there did not appear to be significant complications of therapy for these patients except Kunk, et al. who reported 2 episodes of significant bleeding that required cessation of anticoagulation.[6,8,12,21-24] Excluding these 2 patients who discontinued DOAC therapy due to bleeding and those who did not have follow-up beyond discharge, each HITT case that featured VTE and secondary treatment with DOAC was anticoagulated for at least 3 months total.[6,8,12,21-24] There were few cases of arterial thrombosis as well.[8,12,25,26] Historically, arterial thromboembolism is treated long-term with vitamin K antagonists, and rivaroxaban has recently proven to be inferior to warfarin in preventing arterial thromboembolism in antiphospholipid syndrome patients.[27,28] Therefore, despite acute HIT typically being only a transient hypercoagulable state, caution must be exercised before considering DOAC therapy in HITT patients with known arterial thrombosis (especially those that are inoperable) due to paucity of supporting evidence. Among isolated HIT cases (n=15),

rivaroxaban (n=10) was utilized most frequently for long-term treatment after initial parenteral therapy for HIT. Variable rivaroxaban dosing (e.g., 10 or 20 mg PO daily, 15 mg PO twice daily) during the subacute HIT A phase (after platelet recovery to ≥ 150 x10^9/L) was described. Warkentin, et al. and Davis and Davis reported no thrombotic or hemorrhagic events with rivaroxaban or apixaban, respectively, during the short follow-up period (range: 1 to 30 days).[6,12] Rivaroxaban 15 mg PO twice daily dosing regimen is mentioned within the ASH guideline remarks for acute isolated HIT with a transition to 20 mg PO daily dosing if there is platelet recovery and an ongoing indication for anticoagulation.[4] This dosing regimen is supported by Linkins, et al. as 3 patients experienced platelet recovery (defined as increase to ≥ 150 x10^9/L or return to baseline if baseline count was < 150 x10^9/L) within a week without any thrombotic or hemorrhagic complications.[4,8]

DOAC Therapy for HIT in Special Populations

Select patient populations were originally excluded or under-represented in DOAC trials. These patient populations include underweight and obese patients, patients with bioprosthetic heart valves, patients with active malignancy, and those with chronic kidney disease (CKD) including those with end stage renal disease (ESRD) on hemodialysis (HD). However, use of DOACs in these special populations is increasing and has been incorporated into guideline directed therapy.[31,32] Vavlukis, et al. described the successful use of rivaroxaban in an obese man for the treatment of HITT complicated by pulmonary embolism.[11] Patients with bioprosthetic valves were represented in 6 cases included and described previously.[6,8,19,21,30] Eleven case reports have been written to describe the successful use of DOACs for the treatment of HIT in patients with active malignancy. Primary treatment with rivaroxaban (n=6) was most common followed by secondary treatment with rivaroxaban (n=4) after primary treatment with argatroban (n=1) or fondaparinux (n=3).[5,6,8,24,34-36] One patient with active malignancy was treated with apixaban.[33] Among the treatment for HITT (n=8), one patient developed a mural thrombus and two other patients developed DVT.[6,34,36] Four case reports included patients with cancer associated VTE. Two patients reported bleeding including hemoptysis and rectal bleeding with anticoagulation. Both authors attributed these events to malignancy.[8,24] Nine case reports are published describing the treatment of HIT in patients with CKD and ESRD. The case reports (n=4) from Ong, et al. describe HITT treated with rivaroxaban 10 mg PO daily. Apixaban was used in the other case reports (n=5) both as primary therapy and as long-term therapy. Apixaban dosing was variable when reported. Both apixaban 2.5 and 5 mg PO twice daily were used. The increasing use of DOACs in these special patient populations for treatment of VTE leaves further information needed for unique clinical scenarios.

Discussion and Conclusions

Based on published case reports and series, rivaroxaban and dabigatran are the most frequently described DOACs in treating HIT both as primary and secondary therapy. Conversely, the most well-described cases providing sufficient detail for DOACs in HIT involve rivaroxaban and apixaban. For rivaroxaban, it is recommended to initiate the loading dose during primary treatment for HITT and isolated HIT. If initiated as secondary therapy, the loading dose of rivaroxaban can be omitted if platelet count is recovered during isolated HIT or if the loading dose period of 21 days has been achieved (in conjunction with platelet recovery) while on a parenteral non-heparin anticoagulant for HITT.[4,6,24] As compared to warfarin, DOAC therapy is a more practical oral option in many HIT cases as DOACs feature an earlier and more efficient transition from non-heparin parenteral anticoagulation or can be initiated without initial parenteral anticoagulation. There are currently no head-to-head trials comparing the efficacy and safety of warfarin to DOACs in the long-term treatment of HIT. DOAC treatment for HIT does not demonstrate a significant risk in existing case reports. In conclusion, DOAC therapy may be an appropriate option in most clinically stable patients with HIT who are eligible for treatment with oral anticoagulation. DOAC selection and dosing are dependent on index of suspicion for HIT, presence of thrombosis, bleeding risk, and other relevant factors, which include renal and hepatic function as well as drug-drug interactions. Refer to the ASH guidelines on HIT management for an evidence-based summary of DOAC dosing in HIT.[4] DOACs have some evidence for use in special patient populations such as CKD/ESRD and cancer for HIT treatment. Despite the perceived advantages of DOACs, these drugs have not proven to be efficacious or safe for thromboprophylaxis with mechanical prosthetic heart valves and prevention and treatment of arterial thromboembolism in antiphospholipid syndrome as warfarin has historically been the agent of choice for these indications and should still be used in these patient populations.[27,28,40]

Table 2A. Case reports: Primary acute treatment of HITT

Author	Patient	Initial indication for anticoagulation	Initial treatment of HIT	Long term treatment of HIT	HIT related complications
Ong[7]	66 M	DVT, PE	Rivaroxaban 15 mg BID		DVT
Ong[7]	38 M	PCI and IABP	Rivaroxaban 10 mg daily		DVT
Ong[7]	49 M	PE	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily		Worsening PE
Ong[7]	46 M	DVT, PE	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily		None
Ong[7]	40 F	PE	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily		None
Linkins[8]	71 F	DVT prophylaxis	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily		DVT, bilateral adrenal hemorrhage
Warkentin[6]	94 F	DVT prophylaxis	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily		LE DVT
Warkentin[6]	72 M	DVT prophylaxis	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily		PE
Samos[9]	50 F	DVT prophylaxis	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily		DVT, PE
Abouchakra[10]	53 M	CABG	Rivaroxaban 20 mg BID		Mural thrombus, graft thrombosis
Vavlukis[11]	35 M	PE	Rivaroxaban 15 mg BID		None
Davis[12]	79 M	VTE prophylaxis	Apixaban 5 mg BID		DVT
Davis[12]	66 F	AFib	Apixaban 5 mg BID		PE
Davis[12]	85 F	VTE	Apixaban 10 mg BID		None
Bhardwaj[13]	67 F	TKA	Apixaban 2.5 mg BID	Apixaban 5 mg BID, then 10 mg BID x 7 days	PE
Noel[14]	77 M	ACS, AFib	Dabigatran	Lepirudin	Cerebral infarcts
Bircan[15]	57 F	TKA	Dabigatran 150 mg BID	Warfarin	PE
Mirdamadi[16]	67 F	Orthopedic surgery	Dabigatran 110 mg BID		DVT

ACS: acute coronary syndrome, AFib: atrial fibrillation, CABG: coronary artery bypass graft, DVT: deep vein thrombosis, IABP: intra-aortic balloon pump, LE: lower extremity, PCI: percutaneous coronary intervention, PE: pulmonary embolism, TKA: total knee arthroplasty, VTE: venous thromboembolism

Table 2B. Case reports: Primary acute treatment of isolated HIT

Author	Patient	Initial indication for anticoagulation	Initial treatment of HIT	Long term treatment of HIT	HIT related complications
Linkins[8]	85 M	Bioprosthetic AVR surgery	Rivaroxaban 15 mg BID x21 days, then 20 mg daily		None
Linkins[8]	79 M	CABG, AFib	Rivaroxaban 15 mg BID x21 days, then 20 mg daily		None
Linkins[8]	65 M	TAVR, DVT prophylaxis	Rivaroxaban 15 mg BID x21 days, then 20 mg daily		None
Linkins[8]	82 F	DVT prophylaxis	Rivaroxaban 15 mg BID x21 days, then 20 mg daily		Bilateral adrenal hemorrhage
Warkentin[6]	83 F	DVT prophylaxis	Rivaroxaban 10 mg daily		Bilateral adrenal hemorrhage
Tardy- Poncet[17]	71 F	TKA	Rivaroxaban 10 mg Q8hr	Dabigatran 220 mg daily	None
Davis[12]	55 F	AFib	Apixaban 5 mg BID		None
Samos[19]	79 M	Bioprosthetic AVR MVR surgery, AFib	Apixaban 5 mg BID	Apixaban	None
Fieland[18]	70 M	CABG, AFib	Dabigatran 150 mg BID	Warfarin	None

AFib: atrial fibrillation, AVR: aortic valve replacement, CABG: coronary artery bypass graft, DVT: deep vein thrombosis, MVR: mitral valve replacement, TAVR: transcatheter aortic valve replacement, TKA: total knee arthroplasty

Table 3A. Case reports: Secondary treatment of HITT

Author	Patient	Initial indication for anticoagulation	Initial treatment of HIT	Long term treatment of HIT	HIT related complications
Casan[22]	56 F	TKA	Fondaparinux 7.5 mg SC daily	Rivaroxaban 15 mg BID x21 days, then 20 mg daily	DVT
Hantson[25]	36 M	Orthopedic surgery	Fondaparinux 2.5 mg SC daily	Rivaroxaban 15 mg BID x21 days, then 20 mg daily	Radial artery thrombus
Sartori[23]	68 M	DVT	Fondaparinux 7.5 mg SC daily	Rivaroxaban 20 mg daily	None
Kunk[24]	N/A	DVT prophylaxis	Bivalirudin	Rivaroxaban	DVT, PE
Kunk[24]	N/A	PE	Argatroban	Rivaroxaban	None
Davis[12]	73 M	DVT prophylaxis	Argatroban	Rivaroxaban 15 mg BID	Cerebral infarcts
Davis[12]	40 F	VTE	Argatroban	Rivaroxaban 15 mg BID	None
Davis[12]	65 M	DVT prophylaxis	Argatroban	Rivaroxaban 15 mg BID	Jugular vein thrombosis
Linkins[8]	80 M	VTE	Danaparoid	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily	Bilateral LE arterial ischemia, BKA
Linkins[8]	61 M	VTE	Fondaparinux	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily	DVT extension until catheter removal
Linkins[8]	85 F	CV surgery	Fondaparinux	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily	DVT, PE
Warkentin[6]	69 F	CABG	Fondaparinux	Rivaroxaban 15 mg BID x 21 days, then 20 mg daily	HIT thrombosis
Warkentin[6]	78 M	DVT prophylaxis	Argatroban, Fondaparinux	Rivaroxaban 20 mg daily	DVT
Ezekwudo[21]	66 M	Bioprosthetic AVR surgery, AFib	Argatroban	Apixaban 5 mg BID	DVT
Kunk[24]	N/A	DVT, PE	Bivalirudin	Apixaban	None
Kunk[24]	N/A	DVT prophylaxis	Bivalirudin	Apixaban	DVT, PE
Kunk[24]	N/A	CABG	Bivalirudin	Apixaban	Arterial clot, DVT
Kunk[24]	N/A	DVT	Argatroban	Apixaban	None
Kunk[24]	N/A	PE	Argatroban	Apixaban	None
Kunk[24]	N/A	DVT, PE	Argatroban	Apixaban	None
Kunk[24]	N/A	DVT prophylaxis	Argatroban	Apixaban	DVT, PE
Davis[12]	50 F	VTE	Argatroban	Apixaban 5 mg BID	None
Alcantar[26]	83 F	ACS	Argatroban	Dabigatran 110 mg BID	None

ACS: acute coronary syndrome, AFib: atrial fibrillation, AVR: aortic valve replacement, BKA: below the knee amputation, CABG: coronary artery bypass graft, CV: cardiovascular, DVT: deep vein thrombosis, LE: lower extremity, PE: pulmonary embolism, SC: subcutaneous, TKA: total knee arthroplasty, VTE: venous thromboembolism

Table 3B. Case reports: Secondary treatment of isolated HIT

Author	Patient	Initial indication for anticoagulation	Initial treatment of HIT	Long term treatment of HIT	HIT related complications
Tvito[29]	85 F	THA	Fondaparinux 2.5 mg SC daily	Rivaroxaban	None
Kopolovic[30]	67 M	Bioprosthetic AVR surgery, CABG, DVT prophylaxis	Fondaparinux 7.5 mg SC daily	Rivaroxaban	None
Linkins[8]	87 M	DVT prophylaxis	Fondaparinux	Rivaroxaban 15 mg BID x21 days, then 20 mg daily	None
Linkins[8]	74 F	CVA prophylaxis	Fondaparinux	Rivaroxaban 15 mg BID x21 days, then 20 mg daily	None
Linkins[8]	55 F	CABG	Fondaparinux	Rivaroxaban 15 mg BID x21 days, then 20 mg daily	None
Warkentin[6]	55 F	DVT prophylaxis	Fondaparinux	Rivaroxaban 10 mg daily	None
Warkentin[6]	56 F	DVT prophylaxis	Fondaparinux	Rivaroxaban 10 mg daily	None
Warkentin[6]	92 F	DVT prophylaxis	Fondaparinux	Rivaroxaban 10 mg daily	None
Warkentin[6]	72 M	CABG	Fondaparinux	Rivaroxaban 20 mg daily	None
Warkentin[6]	74 M	AVR surgery	Fondaparinux	Rivaroxaban 15 mg BID x21 days, then 20 mg daily	None
Kunk[23]	N/A	CABG, DVT prophylaxis	Bivalirudin	Apixaban	None
Kunk[23]	N/A	AFib	Bivalirudin	Apixaban	None
Kunk[23]	N/A	CABG	Argatroban	Apixaban	None
Davis[12]	70 M	DVT prophylaxis	Argatroban	Apixaban 2.5 mg BID	None
Davis[12]	77 F	DVT prophylaxis	Argatroban	Apixaban 5 mg BID	None

AFib: atrial fibrillation, AVR: aortic valve replacement, CABG: coronary artery bypass graft, CVA: cerebral vascular accident, DVT: deep vein thrombosis, SC: subcutaneous, THA: total hip arthroplasty

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Alternative Agents for Opioid and Alcohol Withdrawal

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"A multimodal approach to target specific symptoms is recommended, however the alpha-2 adrenergic agonists can be used to manage general opioid withdrawal symptoms."

"Gabapentin and phenobarbital may be two potential options in the treatment of AWS in general medicine patients, demonstrating efficacy as adjunctive treatment and monotherapy. Finally, supportive care remains a mainstay of therapy, regardless of treatment setting, with thiamine, folate, and magnesium supplementation."

Opioid Withdrawal

Background

Abrupt cessation or dose reduction of chronic opioid medications can lead to opioid withdrawal. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines opioid withdrawal as the development of symptoms following the cessation or reduction of opioid use or administration of an opioid antagonist that are not attributable to another medical condition.[1] Opioid withdrawal typically manifests in two phases: acute and chronic. The duration of acute withdrawal is dependent on the half-life and duration of the opioid medication used and lasts 5 to 14 days on average.[2]

The majority of acute opioid withdrawal symptoms can be attributed to increased activity of the autonomic nervous system. The locus coeruleus is the primary site of norepinephrine (NE) synthesis in the central nervous system (CNS). Chronic opioid use inhibits NE synthesis from the locus coeruleus. In response to this, the locus coeruleus up-regulates the production of cyclic adenosine monophosphate (cAMP), which stimulates the release of additional NE. Abrupt discontinuation of opioid medications leads to over-activation of the locus coeruleus and sympathetic output from the CNS leading to symptoms such as sweating, diarrhea, piloerection, intestinal cramps, nausea, anxiety, and irritability.[3]

Dopamine is also an important neurotransmitter in the manifestation of opioid withdrawal. Opioid use leads to high levels of dopamine release in the nucleus accumbens, one of the brain's key pleasure centers. To combat elevated levels of dopamine, the body releases gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. Chronic opioid abusers will need higher levels of opioids to combat the effects of GABA. Abrupt discontinuation of chronic opioids can lead to dopamine withdrawal, which can manifest as pain, agitation, and malaise.[3]

Several opioid withdrawal scales exist to determine the severity of opiate withdrawal including the Clinical Institute Narcotic Assessment (CINA), Clinical Opiate Withdrawal Scale (COWS), and Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop). The COWS appears to be the most widely utilized in clinical and research settings and is designed to be completed in 2 minutes by a clinician.[4] The COWS is an 11-item scale that can be administered in both the inpatient and outpatient settings to monitor symptoms of opiate withdrawal over time. A score of 5 to 12 indicates mild withdrawal, 13 to 24 moderate withdrawal, 25 to 36 moderately severe withdrawal, and over 36 severe withdrawal.[5]

A guideline endorsed by the American Society of Addiction Medicine was published in 2015 and addresses managing opioid withdrawal with alternative agents, such as alpha-2 adrenergic agonists, but acknowledges that additional studies are needed for these additional agents.[6]

Treatment

Alpha-2 adrenergic agonists

Alpha-2 adrenergic agonists result in decreased sympathetic output from the CNS. This class of medications includes clonidine, lofexidine, dexmedetomidine, guanfacine, methyldopa, and tizanidine. A review published in 2016 evaluated alpha-2 adrenergic agonists in the management of opioid withdrawal and found them to be more efficacious than placebo and with similar efficacy to tapering doses of methadone.[7]

Clonidine

Clonidine has demonstrated the ability to control symptoms of withdrawal better than placebo and has comparable efficacy to the opioid agonist methadone.[8] The review by Gowing and colleagues indicates that clonidine can be used as an alternative to tapering doses of methadone, but is

associated with more adverse effects including hypotension.[7] A similar review published in 2017 illustrated that clonidine can be used as an alternative agent to buprenorphine, but was associated with higher withdrawal scores and patients receiving clonidine were less likely to complete treatment.[9]

Lofexidine

Lofexidine was the first non-opioid medication approved for management of opioid withdrawal in May 2018. Lofexidine differs from clonidine in its high affinity for the alpha-2A receptor which results in less antihypertensive effects than clonidine. A trial published in 2017 demonstrated the efficacy of lofexidine compared to placebo in the reduction of opioid withdrawal scores (7.0 vs 8.9, p = 0.0037) and ability of patients to complete opioid detoxification (49% vs 33%, p = 0.02).[10] Lofexidine is approved for use up to 14 days with dosing guided by symptoms. The usual initial lofexidine dose is three 0.18 mg tablets (0.54 mg) four times daily at 5 to 6 hour intervals during peak withdrawal symptoms and should be tapered over 2 to 4 days once treatment is complete. Important adverse effects of lofexidine include QTc prolongation, orthostatic hypotension, bradycardia, dizziness, and sedation. Patients on concurrent methadone and buprenorphine were excluded from clinical trials with lofexidine. Electrocardiogram (ECG) monitoring is recommended for patients receiving concurrent methadone and lofexidine as they both have potential to prolong the QT interval.[11,12]

Other Alpha-2 adrenergic agonists

The 2016 review found insufficient evidence to support using tizanidine or guanfacine.[7] Dexmedetomidine, a parenteral agent primarily used for sedation has also been proposed as a possible treatment option in critically ill patients experiencing opioid withdrawal. However, there is limited data to support this recommendation.[13]

Other agents

Trazodone

Trazodone is an antidepressant that inhibits reuptake of serotonin. It also strongly inhibits alpha-1 adrenergic receptors which leads to a decreased sympathetic nervous system response. There are two reports of outpatient non-opioid detoxification protocols published that utilized trazodone in combination with other medications. In these trials, 54-61% of IV drug users were able to successfully complete their detoxification protocol. Additionally, trazodone can be used to help manage insomnia associated with opioid withdrawal.[14,15]

Hydroxyzine

Hydroxyzine is a piperazine-derivative antihistamine commonly used for anxiety. Clinical trial data supporting its use for the management of opioid withdrawal symptoms is limited. However, Hauser and colleagues proposed that hydroxyzine may be effective in managing withdrawal symptoms due to its anxiolytic, anticholinergic, and antiemetic properties.[16] Rudolf and colleagues published a retrospective chart review that reported success with a protocol for managing opioid withdrawal that included tizanidine, hydroxyzine, and gabapentin. They reported a reduction in COWS scores and successful transition to maintenance naltrexone therapy in a majority of their patients.[17]

Tramadol

Tramadol is a Schedule IV opioid agonist with low affinity for the μ, κ, and δ opioid receptors and has an active metabolite with μ agonist activity. Tramadol also inhibits the reuptake of norepinephrine and serotonin. There is evidence to suggest that tramadol may be an alternative to buprenorphine for the management of opioid withdrawal. In a small clinical trial of 103 patients, Dunn and colleagues demonstrated similar efficacy to buprenorphine in the management of opioid withdrawal symptoms assessed with the Subjective Opioid Withdrawal Scale (SOWS). Results from the study suggested better control of opioid withdrawal symptoms with tramadol compared to clonidine (7.4 vs 13.1), and similar efficacy to buprenorphine (7.4 vs 6.1).[18]

Summary

Managing opioid withdrawal in clinical situations where treatment options are limited can be challenging. A multimodal approach to target specific symptoms is recommended, however the alpha-2 adrenergic agonists can be used to manage general withdrawal symptoms. A guideline endorsed by the American Society of Addiction Medicine was published in 2015, endorsing clonidine and lofexidine to manage symptoms of opioid withdrawal. Of note, an update to that guideline is expected in Spring 2020.

Table 1. Symptomatic treatment of opioid withdrawal[19]

Symptom	Treatment
General withdrawal symptoms	Lofexidine (FDA Approved); Clonidine
Myalgias/Arthralgias	Nonsteroidal Anti-inflammatory Drugs (NSAIDs); Acetaminophen
Rhinorrhea, Lacrimation, Sweating	Diphenhydramine; Hydroxyzine
Diarrhea	Loperamide; Diphenoxylate-atropine; Dicyclomine
Nausea/Vomiting	5-HT_3 Antagonists; Phenothiazine derivatives
Insomnia	Trazodone

Alcohol Withdrawal

Background

Alcohol use disorder (AUD) is a medical disease characterized by the inability to avoid alcohol intake that interferes with one's routine responsibilities, activities, and behaviors.[1] It is estimated that AUD affects up to 14.4 million adults in the United States, with only 7.9% of affected persons receiving treatment.[20] Alcohol withdrawal syndrome (AWS) is a condition that occurs due to abrupt cessation of longstanding and/or heavy alcohol use, affecting up to 8% of hospitalized patients. Alcohol increases the effects of the inhibitory neurotransmitter γ-amino-butyric acid (GABA). Over time, this process leads to downregulation of GABA receptors and upregulation of N-methyl-D-aspartate (NMDA) excitatory receptors. Upon alcohol cessation, overstimulation of NMDA receptors results in autonomic hyperactivity, manifesting as AWS. Symptoms of AWS usually emerge 6-72 hours after the last consumed drink and are characterized by autonomic overdrive, motor abnormalities, and psychiatric disturbances. Symptoms of severe AWS include delirium tremens (DTs), hallucinations, and/or seizures. Benzodiazepines (BZDs) are recognized as the first-line treatment for AWS, either in a fixed-dose or symptom-triggered regimen. Symptom-triggered doses are determined by an objective measure of symptom severity, the Clinical Institute Withdrawal for Alcohol Scale, Revised (CIWA-Ar), with the intent of minimizing BZD doses and avoiding adverse effects (e.g., oversedation, respiratory depression).[21] Other adjunct agents demonstrating utility in critically ill patients include dexmedetomidine, propofol, and ketamine.[22-24] However, the need to administer these agents by continuous infusion limits their use to the intensive care unit (ICU). In this article, we review alternative strategies for AWS that may be used in the general medicine population either in combination with BZDs or as monotherapy.

Treatment

Gabapentin

Gabapentin, which is structurally similar to GABA, has anxiolytic and sedative properties that may be efficacious in managing symptoms related to AWS. Gabapentin is thought to exert its effects by binding to voltage-gated calcium channels to increase the synthesis and release of GABA into the synaptic cleft.[25] Gabapentin has been studied in the inpatient setting with variable dosing strategies. A prospective, observational study assessed the efficacy of gabapentin loading doses on CIWA-Ar scores in 37 patients with severe AWS (CIWA-Ar ≥ 15). All patients received an initial gabapentin 800 mg loading dose. Patients whose CIWA-Ar score fell below 15 within 2 hours, defined as "early responders," received additional gabapentin doses (total daily dose of 3200 mg on day 1, 2400 mg on day 2, 1600 mg on day 3, reducing by 400 mg each day thereafter). Non-responders were treated with usual care of either clomethiazole or clonazepam. Of the 27 "early responders," 2 patients experienced seizures and 1 patient experienced worsening AWS; these 3 patients were subsequently treated with usual care. Notably, of the 10 non-responders, the mean initial CIWA-Ar score was 20.1 ± 4.6, suggesting that patients with more severe AWS may not benefit from gabapentin treatment.[26] More recently, a retrospective cohort study observed the effects of high-dose gabapentin in patients with severe AWS, defined as a CIWA-Ar score ≥ 15. Included patients were administered gabapentin 600 mg every 8 hours in addition to a scheduled 5-day lorazepam taper with symptom-triggered lorazepam available based on CIWA-Ar scores. Fifty patients in the gabapentin group were matched to patients in a historical control group that received lorazepam only. Compared to the control group, the gabapentin group required lesser amounts of BZDs (88.5 ± 35.6 mg vs. 109.5 ± 53.4 mg lorazepam equivalents, p=0.023), without increased risk of oversedation. Additionally, patients in the gabapentin group had a shorter hospital stay (6.0 ± 2.6 days vs. 7.4 ± 4.0 days, p=0.034).[27] In comparison to benzodiazepines, the low toxicity profile of gabapentin and lack of drug interactions due to its absence of protein binding and hepatic metabolism may make it a favorable option in the management of acute alcohol withdrawal.[25]

Phenobarbital

Phenobarbital, a barbiturate historically used in the treatment of epilepsy, may be another potential treatment option for AWS. Phenobarbital enhances inhibitory effects by binding to the GABA receptor at the alpha subunit, a separate location from the binding sites of both GABA and BZDs. Additionally, phenobarbital blocks the AMPA receptor, an NMDA excitatory receptor subtype.[28] One retrospective cohort study observed phenobarbital monotherapy compared to a standard symptom-triggered BZD protocol in 120 critically ill patients. Patients in the phenobarbital group (n=60) received high, medium, or low doses of phenobarbital (initial doses: IV 260 mg, oral 97.2 mg, or oral 64.8 mg), depending on the presence of DTs, history of DTs, or no history of DTs, respectively.

Initial doses were followed by a phenobarbital taper. They also received as-needed lorazepam based on provider discretion. The patients in the standard symptom-triggered BZD group (n=60) received lorazepam based on CIWA-Ar scores. Compared with the symptom-triggered BZD group, the phenobarbital group had a significant reduction in hospital length of stay (4.3 ± 3.4 days vs. 6.9 ± 6.6 days, p=0.004) and BZD use (11.3 ± 18 mg vs. 35.2 ± 48.5 mg lorazepam equivalents, p <0.001). Although the patients in this study were in the ICU, it was noted that only 1 patient in the phenobarbital group required mechanical ventilation vs. 14 patients in the symptom-triggered BZD group.[29] A more recent retrospective study observed the effects of a fixed-dose BZD protocol vs. a phenobarbital monotherapy protocol on the risk of developing alcohol withdrawal-related complications, defined as seizures, hallucinations, delirium, or the need for ICU admission. Phenobarbital loading doses varied between 6 to 15 mg/kg and depended on an objective risk for AWS, sedation, and respiratory compromise. Although patients in the phenobarbital group were considered higher risk at baseline (i.e., increased history of AWS, alcohol withdrawal seizures, and alcohol withdrawal delirium), there were similar rates of alcohol withdrawal-related complications between the two groups.[30] While dosing strategies are variable, current data suggests a potential role for phenobarbital monotherapy as an alternative for the treatment of AWS.

Nutritional Support

Thiamine

Chronic alcohol use is associated with depletion of the body's stores of B vitamins, folate, and magnesium. Thiamine (B1) deficiency has been reported in up to 30-80% of alcoholics, which can result in compromise of multiple thiamine-dependent enzymes involved in the Krebs cycle. This disruption in enzyme function in the brain can cause Wernicke-Korsakoff Syndrome (WKS), a medical condition with significant morbidity and mortality if left untreated. WKS, interchangeably referred to as Wernicke's encephalopathy (WE), presents with acute confusion/delirium, ataxia, nystagmus, and/or ophthalmoplegia.[31] Given the presentation of WE is non-specific and potentially life-threatening, thiamine repletion is recommended for those that may be at risk of developing WE. This could include patients with AWS and malnourishment, poor self-care or living alone, or other deficiency states (e.g., malignancy, renal disease, acquired immunodeficiency syndrome). Although thiamine repletion is crucial to WE treatment, dosing regimens are variable and not well-defined. For patients at high risk of or with suspected WE, some guidelines suggest parenteral thiamine 250-500 mg daily for 3-5 days, followed by oral thiamine 300 mg daily. For patients with confirmed WE, one suggested dosing regimen is parenteral thiamine 500 mg three times daily for 2 days, followed by 250 mg daily for 5 days or until improvement. For well-nourished, otherwise low-risk patients, oral thiamine 300 mg daily is recommended.[32]

Magnesium

Magnesium deficiency is also common in patients with alcohol misuse and is a cofactor to thiamine-dependent enzymes. It has been noted that magnesium deficiency is associated with failure to respond to parenteral thiamine replacement in WE.[32,33] Furthermore, low serum magnesium has been associated with more severe AWS and increased 1-year mortality.[34] Thus, magnesium supplementation is essential throughout treatment for AWS per institution protocol.

Folate

Folate deficiency can occur in up to 60-80% of patients with alcohol misuse and is associated with complications, such as depression, confusion, and peripheral neuropathies. For patients with a diagnosed deficiency, folate repletion is recommended via oral folic acid 1 mg daily.[35]

Summary

In summary, AWS is a common medical condition in hospitalized patients that can result in multiple complications, including autonomic hyperactivity, DTs, seizures, and psychiatric disturbances. While the mainstay of treatment for AWS is either fix-dosed or symptom-triggered BZDs, alternative therapies and adjunct agents are of interest to avoid oversedation and respiratory depression. Gabapentin and phenobarbital may be two potential options in the treatment of AWS in general medicine patients, demonstrating efficacy as adjunctive treatment and monotherapy. Finally, supportive care remains a mainstay of therapy, regardless of treatment setting, with thiamine, folate, and magnesium supplementation.

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