Immunopharmacotherapy for Opioid-Use Disorder: Feasibility of an Education Module

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Abstract

Opioid-use disorder (OUD) has become a national crisis, killing over 100 Americans daily and costing 78 billion dollars annually. The current treatments for opioid abuse are associated with unfavorable side effects, illicit use, and costly maintenance. In contrast, opiate-specific vaccinations reduce the targeted opioid potency, brain concentration levels, and self-administration rates during pre-clinical trials, which limits over-dose induced lethality and decreases OUD. As a consequence, increasing the effective dose (ED50) of opioids would impact patient pain management by Certified Registered Nurse Anesthetists (CRNA). Increased knowledge of new treatments from interactive online-based learning allows CRNAs to provide effective, safe patient care and adequate treatment of pain for patients who may receive the opiate-specific vaccinations if they gain approval. Student Registered Nurse Anesthetists (SRNA) at AdventHealth University (AHU), however, have yet to develop an American Association of Nurse Anesthetists (AANA) approved continuing education (CE) module through the Echelon media development platform. Therefore, a feasibility study on the development of an online education module approved for CE credits by the AANA was conducted to determine the viability of digital education to CRNAs on the treatment of OUD with immunopharmacotherapy. The CE module received approval by the AANA for 1.00 Class A CE credit and 1.00 CE credit in pharmacology. A cost/benefit analysis revealed that the non-monetary benefits cause the process to be recommended for AHU, SRNAs, and healthcare professions. CE module development is projected to generate revenue for the University, increase name recognition, and offer extensive access to evidence-based knowledge at low cost and flexibility to CRNAs.

Keywords: opioid use disorder, immunopharmacotherapy, continuing education, feasibility study, module development

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More than half of drug-related deaths in the United States, including non-urban environments, involve opioids, but current treatments for opioid-use disorder (OUD), like non-selective opioid antagonists, have limited success (Banks, Olson, & Janda, 2018; Griffis et al., 2017; Olson & Janda 2018). This epidemic has led to the declaration of a state of emergency by the President of the United States and increased research on pain and addiction management. Newly developed pre-clinical, immunopharmacotherapy vaccinations have shown to effectively elicit antibodies against target opioids, which prevent the drug from acting on specific central receptors (Banks et al., 2018; Bremer et al., 2016; Nguyen et al., 2017; Raleigh, Pentel, & LeSage, 2014). If the anti-opioid vaccinations are not fully understood by Certified Registered Nurse Anesthetists (CRNAs), the patient's pain will be inefficiently treated. When pain is undertreated, it can lead to negative health effects and a decreased quality of life (AANA, 2018).

CRNAs, who are considered experts in pain management by the American Association of Nurse Anesthetists (AANA), have prescriptive authority and extensive education in the concepts of pain and its pharmacological management. However, after a review of the literature, it was found that there is a lack of CRNA-directed educational resources regarding OUD and pre-clinical treatment with immunopharmacotherapy. Thus, a continuing education (CE) module, developed for and delivered by AdventHealth University (AHU) Echelon development media platform, regarding OUD and immunopharmacotherapy was developed by Student Registered Nurse Anesthetists (SRNA) to improve the knowledge base of CRNAs.

Significance and Background of Clinical Problem

Over 2.5 million Americans suffer from OUD, which takes the lives of 130 people daily; it costs over 78 billion dollars annually due to healthcare and criminal justice expenses and loss of workplace productivity (Olson & Janda 2018; Shen, Orson, & Kosten, 2012). Furthermore, the current therapy for opioid abuse has limited success with the potential for significant side effects, illicit use,

costly maintenance, and high attrition rates within the first month (Banks et al., 2018; Olson & Janda, 2018). As a result, only 10% of Americans suffering from OUD are receiving treatment, causing OUD to have the highest addiction relapse rate, in an estimated 91% of those in recovery (American Addiction Centers, 2018). Within the first week of sobriety, 59% of people will have an opiate-related relapse, and 80% will relapse within a month of being discharged from a recovery program (American Addiction Centers, 2018). Overall, those that relapse from OUD have a ten-fold higher mortality rate than the general population (American Addiction Centers, 2018). Consequently, the United States' life expectancy has decreased for the first time in over 20 years due to the rise in unintentional death rates from opioid misuse (Griffis et al., 2017).

The significant impact on mortality from OUD led the U.S. Department of Health and Human Services (HHS) (2017) to declare the opioid epidemic a public health emergency. The HHS, along with the National Institute of Health (NIH), National Science and Technology Council (2018), Center for Disease Control and Prevention (CDC), Substance Abuse and Mental Health Services Administration (SAMHSA), and the World Health Organization (WHO) emphasized the need for provider education and additional research regarding OUD: non-opioid alternatives to manage chronic pain, and new treatments for opioid addiction and overdose-reversals (Griffis et al., 2017; HHS, 2017).

Immunopharmacotherapy, a new treatment for opioid addiction in the pre-clinical phase, elicits an immune response, and as a result, lacks abuse potential (Banks et al., 2018). The vaccinations have a longer duration of therapeutic effect, which decreases relapse mortality, unlike traditional treatments (Banks et al., 2018). It effectively prevents a specific opioid from acting on central receptors due to formed antibodies. If a CRNA does not understand the treatment, the patient's pain could be inefficiently treated (Nguyen et al., 2017; Raleigh, Pentel, & LeSage, 2014).

For CRNAs to provide safe, effective patient care, they must be educated on OUD, opioid prescribing, and upcoming treatments with associated drug pharmacodynamics and its potential impact on pain management (AANA, 2018; Griffis et al., 2017). CRNAs pain management responsibilities

include both treatments for acute and chronic pain (Griffis, Giron, & Darna, 2017). An online education module, developed for and delivered by AHU, regarding OUD and immunopharmacotherapy approved for CE credits by the AANA delivers digital education at low cost and flexibility to CRNAs. An increase in evidence-based knowledge ideally translates into improved competence of the anesthesia provider and enhanced patient safety by providing effective pain management. An AANA CE module had not been developed under the Echelon platform by an SRNA at AHU. Therefore, a feasibility study was conducted to assess resources, weaknesses, and the prospect of the intervention.

PICOT Evidence Review Questions

Two PICOT questions assisted with the review of the literature. The first addressed the problem: In people with opioid use disorder (P), what is the effect of anti-opioid vaccinations (I) compared to current FDA-approved medications, like methadone (C) on opioid addiction (O)?

The second question addressed the intervention: At AdventHealth University (P), what is the feasibility of a Student Registered Nurse Anesthetist developed one-hour (T) online module regarding the potential treatment of opioid addiction with immunopharmacotherapy (I) being approved for continuing education by the American Association of Nurse Anesthetists (O)?

Search Strategy/Results

The search strategy included government websites, CINAHL, ProQuest, and PubMed databases. A total of 142 studies were initially retrieved, ten of which met inclusion criteria. Inclusion criteria included OUD, immunopharmacotherapy, opioids, and within the last ten years. Key search terms included: *opioid* AND *immune-pharmacotherapy*. MESH Terms included*: opioid, crisis, learning module, continuing education, online learning, immunopharmacotherapy*. Search Limits were: English language, research article, and date within the last ten years.

GRADE Criteria

The literature was classified using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria (see Appendix A for GRADE evidence matrix tables). The majority of studies were randomized control in design, so an initial GRADE of four was assigned. The literature warranted a downgrade to a three due to limitations from indirectness and publication bias. Limited generalizability due to animal subjects is related to indirectness. Publication bias occurred due to funding by the Institute of Drug Abuse/Addiction.

The literature was upgraded due to the large effect and recognition of confounders that increase the confidence in this intervention. The studies concluded a significant decrease in the addictive effects of opioids and their overdose-induced lethality. A final GRADE criterion of three was established. Due to consistent results in pre-clinical trials, it is recommended that immunopharmacotherapy should be considered by anesthesia providers within the community as a possible future treatment of OUD.

Literature Review and Synthesis of Evidence

OUD & Current Treatments

OUD is a diseased state in which physical dependence on opioids leads to compulsive and repetitive use despite negative consequences to the person's mental state, health, or social life (Shen et al., 2012). The disease is considered a chronic, relapsing disorder in which substantial therapeutic efforts are required to maintain sobriety (Shen et al., 2012). The U.S. Food and Drug Administration (FDA) approved opioid antagonists, like naloxone, to treat of opioid overdose reversal (Banks et al., 2018). Also approved for treating opioid abuse are, methadone and buprenorphine, which are complete opioid receptor agonists, meaning they activate the receptors similarly to the abused opioid (Banks et al., 2018). For this reason, these treatments are associated with illicit use and unfavorable side effects, leading to high attrition rates within the first month and overall limited success (Olson & Janda 2018).

Immunopharmacotherapy

In contrast, immunopharmacotherapy, the pioneering treatment for OUD in pre-clinical animal studies, prevents specific targeted drugs from crossing the blood-brain barrier and eliciting the desired addictive psychoactive effects, so it lacks abuse potential and has a longer duration of therapeutic effect (Kimishima et al., 2017; Nguyen et al., 2018; Raleigh et al., 2014). Furthermore, immunopharmacotherapies are beneficial in clinical pain management situations because they are selective for one targeted opioid, unlike naloxone, an antagonist for all opioids (Banks et al., 2018; Olson & Janda, 2018).

Anti-opioid immunopharmacotherapies sequester specific drugs peripherally, preventing the opioid from reaching targeted receptors in the brain (Banks et al., 2018). The vaccinations individually target drugs of abuse, like heroin, oxycodone, hydrocodone, or fentanyl, to induce a tailored IgG antibody, deterring analgesic effects within the brain (Banks et al., 2018; Bremer et al., 2016; Nguyen et al., 2017; Raleigh et al., 2014). Overall, opiate-selective vaccinations reduce potency and decrease brain concentration levels (Banks et al., 2018).

effective dose 50 & self-administration rates.

Single conjugate, opiate selective vaccinations elicit high levels of antibodies that allow significant protection from lethal drug doses by reducing potency (Banks et al., 2018; Bremer et al., 2016; Kimishima et al., 2017; Nguyen et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018; Raleigh et al., 2014; Shen et al., 2012). The effective dose (ED50) is the amount of drug required to produce a therapeutic effect in half of the users; it was significantly increased nearly 30-fold in the vaccinated test group of rats (Bremer et al., 2016; Kimishima et al., 2017; Nguyen et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018). This ED50 shift to the right of the selected opioid decreases drug potency and limits over-dose induced lethality (Bremer et al., 2016; Kimishima et al., 2017; Nguyen et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018). Self-administration rates in the rat subjects

decreased because significantly larger doses of the drug were required to obtain desired psychoactive effects (Bremer et al., 2016; Kimishima et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018).

plasma and brain concentration levels.

The targeted-opioid in the vaccination is sequestered by immunopharmacologic antibodies (Nguyen et al., 2018). Within the immunoconjugate vaccinated test group, brain concentration levels of the targeted opioid were nearly 50% lower than the control group who received the same dose of the opioid (Bremer et al., 2016; Kimishima et al., 2017; Olson & Janda, 2018). Limiting the dose beyond the blood-brain barrier decreases neurological impact and drug abuse behaviors (Bremer et al., 2016; Nguyen et al., 2018).

outlook.

Despite statistical significance in the success of the vaccinations against opioid-use disorder in animal trials, barriers to extensive utilization of these vaccinations remain due to regulatory and societal stigmas toward the treatment of addiction as a disease (Banks et al., 2018; Olson & Janda, 2018). Although anti-opioid vaccinations decrease the rate of opioid self-administration in pre-clinical studies, it is unknown if the single-target drug vaccination will decrease alternative opioid choice behaviors (Banks et al., 2018). Furthermore, a lack of financial investment in safety profiling and large-scale vaccine production, due to previous failures of nicotine and cocaine vaccinations, further hinder the current progression of clinical trials (Olson & Janda, 2018).

impact on pain management.

Immunopharmacotherapy decreases selected opioid drug potency and limits neurological impact (Banks et al., 2018; Bremer et al., 2016; Kimishima et al., 2017; Nguyen et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018; Raleigh et al., 2014; Shen et al., 2012). Due to formed antibodies, the vaccinations effectively prevent a specific opioid from acting on central receptors and providing analgesic effects (Nguyen et al., 2017; Raleigh, Pentel, & LeSage, 2014). It is essential to provide

information regarding immunopharmacotherapy to CRNAs because if the targeted opioid is administered, the patient's pain would be inefficiently treated (AANA, 2018; Griffis et al., 2017).

Role of the CRNA

In addition to new abuse-deterrent formulations, the FDA also emphasized a need to address the insufficient education regarding OUD and potential treatments by prescriber-capable advanced registered nurse practitioners (ARNP), such as CRNAs (Griffis et al., 2017). According to the AANA Code of Ethics (2017), CRNAs possess the skill and ability to prevent patient harm. Also, CRNAs can enhance the safety of their practice and combat OUD through several elements: experience, education, and multi-modal approach (Griffis et al., 2017).

experience & education.

First, as clinicians with expertise in pain management, CRNAs can serve as patient educators and advocates for responsible opioid prescribing. Per the Substance-Use Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT), CRNAs can prescribe medication-assisted treatment (MAT) to combat OUD (AANA, 2018; HHS, 2017). Immunopharmacotherapy is specific for a selected opioid, like fentanyl or oxycodone, which is why CRNAs must be knowledgeable about the impact of the opioid-vaccinations on anesthetic care, pain management, and drug interactions (American Addiction Centers, 2018; Banks et al., 2018; Griffis et al., 2017).

multi-modal approach.

As a result, knowledge regarding immunopharmacotherapy would indicate the use of multi-modal, opioid-alternative treatments to effectively relieve pain (Kimishima et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018). Alternative pharmacological analgesic classes and opioid sparing-techniques, like regional anesthesia, can reduce opioid administration, which results in a shortened hospital stay and fewer patient complications ((Griffis et al., 2017). Through ongoing continuing education and awareness of OUD and evidence-based treatments, CRNAs can enhance the safety of their prescriptive practices and treatment of acute or chronic pain (Griffis et al., 2017).

Online CE Modules

Digital education offers extensive access at low cost and flexibility to CRNAs (Dunleavy et al., 2019; Sun & Chen, 2016; Tudor et al., 2019). It provides opportunities to enhance the quality of educational structures, improve cost-effectiveness, provide convenient access to learning, and deliver educational campaigns to specific target resources, especially when offered through professional organizations, like Echelon (Dunleavy et al., 2019; Sun & Chen, 2016; Tudor et al., 2019). This scholarly project examined the development of an online education module approved for CE credits by the AANA in order to determine the feasibility to offer current information on immunopharmacotherapy to CRNAs.

Applicability to Practice & Contribution to Professional Growth

According to the AANA (2018), anesthesia providers are responsible for providing safe, quality care for their patients; this process includes a thorough pre-operative assessment, review of current medications, and an understanding of those drugs with possible interactions/implications. Awareness of current research and treatment options for OUD allows the CRNA to make evidence-based decisions in the care and pain management of patients undergoing immunopharmacotherapy should it receive approval (Dunleavy et al., 2019; Tudor et al., 2019).

Immunopharmacotherapy is specific for a selected opioid, like oxycodone, hydrocodone, or fentanyl (American Addiction Centers, 2018). If the CRNA chooses the same vaccination-conjugate opioid, a patient's pain would be inadequately treated because the analgesic effects are blocked by elicited antibodies (Banks et al., 2018). Therefore, knowledge regarding the therapy would indicate the use of multi-modal or opioid-alternative treatments to effectively relieve pain (Kimishima et al., 2017).

Project Aims

The primary aim of this scholarly project was to evaluate the feasibility of an evidence-based AHU SRNA developed online module regarding the treatment of opioid addiction with immunopharmacotherapy approved for CE credits by the AANA. The objectives were as follows:

Objective 1: Develop an evidence-based one-hour online module, including pre/post-test, developed for and delivered by AHU through the Echelon platform, regarding the treatment of OUD with immunopharmacotherapy by April 2020.

Objective 2: Apply for CE credit approval by the AANA by August 2020.

Objective 3: Complete written feasibility study, with evidence-based recommendations, for an AHU SRNA developed online module approved for CE credits by the AANA by March 2021.

Methods

Feasibility studies determine whether an intervention is appropriate, relevant, and sustainable (Bowen et al., 2009; Tickle, 2013). These studies analyze the likelihood and manner that an intervention can be implemented the way in which it was planned (Bowen et al., 2009; Tickle, 2013). Feasibility studies objectively assess resources, weaknesses, and prospects for the success of a proposed intervention where there is limited existing data (Bowen et al., 2009; Tickle, 2013).

Feasibility studies have been adopted within the healthcare and business setting because they allow time and cost-effective testing interventions (Bowen et al., 2009; Tickle, 2013). They involve obtaining information from multiple resources throughout the project to evaluate whether a process is beneficial from an economic or operational standpoint (Bowen et al., 2009). Feasibility studies result in no pre-determined sample size, and there were no ethical considerations, like informed consent (Bowen et al., 2009; Tickle, 2013).

The viability of an SRNA developed one-hour online module using the Echelon platform on immunopharmacotherapy, obtaining approval by the AANA for CE credits, was examined through a descriptive, narrative feasibility study. The location was at AHU in Orlando, Florida, mainly Echelon, a division of AHU specializing in online CE and media development. The involvement of SRNAs within the Doctor of Nurse Anesthesia Program (DNAP) at the university was specifically examined.

Information gathered assisted in determining if projects of this nature are sustainable within the DNAP scholarly project timeframe. If the Echelon platform was determined to be viable, it would

impact future CE module development and research and development by AHU SRNAs while potentially generating revenue for the institution. Throughout the CE module development process, narrative qualitative data was gathered, including process assessment, barriers, facilitators, and costs and resources needed. All further data collection was through interviews, meetings, and emails, which are stored on a password-protected AHU- drive set to automatically delete in five years. Scholarly project members: Brianne Beacham, Candice Dykes, and Dr. Sarah Snell are the only individuals with access to the Microsoft Teams. All prior interviews of key players were required in the DNAP791 course; verbal consent was obtained prior to audio recording, and the interviews were stored on password-protected laptops.

For the purposes of this scholarly project, the four phases of project management outlined by the Harvard Business Review were utilized. The Harvard Business Review (2016) recognizes four project management phases in a feasibility study: planning, build-up, implementation, and closeout.

Planning & Procedures

Planning

This step identified what problems need to be solved, who would be involved, and what will be done. First, the preliminary analysis of development asked the question, *can it work*? – At AHU, what was the feasibility of an SRNA developed one-hour online module regarding the potential treatment of opioid addiction with immunopharmacotherapy being approved for CE credits by the AANA? Next, a literature review determined *does it work?* – what was the effect of anti-opioid vaccinations compared to current FDA-approved medications, like methadone, on opioid addiction?

Stakeholders were identified and interviewed. Key players aided in recognizing potential barriers, resources, and facilitators. Key stakeholders were identified: Lori Polizzi, director of Echelon; Dr. David Greenlaw, founder and former president of AHU, as well as Dr. Martin Rivera, AHU faculty member, and CRNA. A scholarly project, preliminary PowerPoint was presented to stakeholders in the DNAP793 course (see Appendix B for GANTT chart).

Once the topic, immunopharmacotherapy for OUD, and the required identifying activity value-form were approved by Echelon's committee, the CE module transcript development began. Institutional Review Board (IRB) approval was not deemed necessary by AHU as there was no research data collection, involvement of identifiable, private information human subjects, or publication expectation.

Build-up

A project committee, which included a project chair, mentor, and reviewer, was formed. Objectives were defined to set manageable goals; resources had been gathered and a budget developed, along with a curriculum vitae (CV). After identifying gaps and the current problem state, the desired goals/learning outcomes, instructional strategies, and a module outline was designed. These topic details were submitted to Echelon's review committee for further review and input.

budget.

Resources allotted consisted mostly of time (see Appendix C). There was a $299 charge per prior approval Provider Directed Independent Study (PDIS) application, and a one-time fee of $500 to $1,000 for CE credits (AANA, 2018). The cost per credit ranged based on the number deemed approved by the ANNA: 1, 1.5, or 2 credits. The PDIS CE credit for online media expires after three years (AANA, 2018). Per Mrs. Pollizi, creating the one-hour online CE module and submitting it to the AANA through the Echelon platform was time consuming. Still, there was no monetary cost for AHU students (see Appendix C1).

Implementation

Once the topic received site approval from Lori Polizzi, Director of AHU Division - Echelon, the development of the online module transcript began. A transcript was formed using the written objectives, module outline, and pre/post-test assessment. These questions underwent face validation. Face validation included a review by three individuals in the DNAP class of 2021 cohort, one CRNA

or theoretical end user, two DNAP faculty members, and one faculty member outside the DNAP department.

Once the documents underwent review by the scholarly project committee members and Director of Echelon, they were converted into portable document formats. The AANA Standard and Criteria Official Application, program information (see Appendix D), program transcript (see Appendix E), educational planning table (see Appendix F), references, and curriculum vitae and conflict of interest forms of the scholarly project chair and SRNAs were submitted directly, with the assistance of Lori Polizzi and Echelon, to the AANA.

Closeout

The AANA accreditation team's review and response to the application took approximately 60 days. After receiving approval by the AANA for 1.00 Class A CE credit and 1.00 CE credit in pharmacology, the Echelon content development team began to transform the written module documents into a digital media format.

Finally, given the evidence presented in the feasibility development, the question *will it work?* was applied, and the implementation of the intervention was determined (Bowen et al., 2009). A written feasibility study and evidence-based recommendations for process management of SRNA developed a one-hour online module approved for CE credits by the AANA and potential implications for AHU were completed (see Appendix C).

Overall, there was limited variation between the initially proposed timeline and the final timeline (see Appendix B for GANTT charts).

Facilitators & Barriers

AHU and Echelon personnel, namely Mrs. Polizzi and the project chair, were vital contributors to the project's success. The primary anticipated barrier to the implementation of this scholarly project was identified via the key player interviews. The DNAP scholarly projects span over two years, but the process involved an unfamiliar, designated platform. An AHU SRNA had yet to develop and submit an

online education module under the Echelon platform and the AANA. However, there were very few standards or frameworks to assist with developing a feasibility study (Bowen et al., 2009). So, the four phases of project management outlined by the Harvard Business Review were used as the framework for this scholarly project.

Results/Findings

An evidence-based one-hour online continuing education module was developed and submitted to the AANA for CE credit approval. The scholarly project, Immunopharmacotherapy for Opioid-Use Disorder: Applicability to Practice, received approval by the AANA for 1.00 Class A CE credit and 1.00 CE credit in pharmacology/therapeutics, effective until October 31, 2022. The online module also received accreditation with the following: Florida Board of Nursing (FBN) – 1.00 CNE General, American Nursing Credentialing Center (ANCC) – 1.00 CNE Pharmacology, and California Board of Registered Nursing (CBRN) – 1.00 CE Pharmacology. Therefore, at AHU, an SRNA developed one-hour online module regarding the potential treatment of opioid addiction with immunopharmacotherapy being approved for continuing education by the AANA has been deemed feasible (see Appendix C).

Applicability to Practice & Contribution to Professional Growth

OUD has become a national crisis, and the current therapy for opioid abuse has limited success with significant side effects, illicit use, and high attrition rates. It effectively prevents a specific opioid from acting on central receptors due to formed antibodies, but if the treatment is not understood by healthcare providers, especially CRNAs, the patient's pain could be inefficiently treated (Nguyen et al., 2017; Raleigh, Pentel, & LeSage, 2014).

An awareness of current research and treatment options for OUD would allow providers to make evidence-based decisions in the care and pain management of patients undergoing immunopharmacotherapy should it receive approval. However, an AANA CE module had not been developed under the Echelon platform by an SRNA at AHU. The purpose of this feasibility study was,

therefore, to determine the viability of AHU - Echelon SRNA developed digital education at low cost and flexibility to healthcare providers on the treatment of OUD with immunopharmacotherapy to increase knowledge while enhancing patient safety with evidence-based care.

Overall, this study recommends the establishment of SRNA developed CE modules at AHU Echelon Division accredited by the AANA (see Appendix C). The cost/benefit analysis justifiably reveals that the non-monetary benefits far outweigh the time and costs involved in CE module development approved by the AANA for credits. The long-range benefits of this process for AHU, its SRNAs, and healthcare professionals are positive.

It is projected to generate revenue as a give-back to the University, increase name recognition and overall branding, and offer extensive access to evidence-based knowledge at low cost and convenience to healthcare providers while supporting the healing mission of the University and enhancing patient safety and pain management. The project also contributes to the process of doctoral scholarly project module development by SRNAs for future progress and analysis and the rapidly growing, high demand online CE module industry containing current, evidence-based information for healthcare providers.

For CRNAs to provide safe, effective patient care, they must be educated on OUD and upcoming treatments with associated drug pharmacodynamics and its potential impact on pain management (AANA, 2018; Griffis et al., 2017). An increase in evidence-based knowledge ideally translates into improved provider competence and enhanced patient safety by providing effective pain management. An online education module, developed by SRNAs and delivered by AHU – Echelon, regarding OUD and immunopharmacotherapy approved for CE credits by the AANA delivers digital education at low cost and flexibility to providers while benefiting the University and studying SRNA.

Recommendations for process improvement of CE module development by AHU SRNAs via Echelon include ensuring efficient organization and alignment of all document content with AANA expectations. When choosing a module topic, ensure that it is capable of changing knowledge, skill, or

practice that is relevant to the profession, as well as provide measurable outcomes with reporting metrics.

Conclusion & Limitations

Limitations

Although having limited external validity, feasibility studies have been adopted in healthcare and educational settings because they allow for a time and cost-effective means of testing interventions (Bowen et al., 2009). However, the specificity of this process involving SRNA developers and the AHU Echelon development platform may limit the generalizability of this feasibility study.

Conclusion

Based on the AANA's approval for CE credit and the analysis of the cost/benefit considerations, the development of a CE module by SRNAs at AHU submitted to the AANA for credit was deemed feasible and desirable. AHU SRNA developed online modules approved by the AANA for CE credits offer numerous benefits to AHU, SRNAs, and healthcare professions. With time, continued SRNA module development, both the increased quantity and strength of content, would generate revenue as a give-back to the university, but the intangible benefits far outweigh the time and costs involved in the CE module developed approved by the AANA for credits.

Dissemination

The findings and recommendations of the feasibility scholarly project were disseminated at a national level through the AANA CE platform, as well as within the local AdventHealth community during March 2021 at AHU. The project was presented to the AHU faculty, collaborating Echelon faculty, and key players through an oral PowerPoint presentation and poster via an online media platform, and a written feasibility study (see Appendix C).

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Appendix A: GRADE Evidence Matrix

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Nguyen, J., Bremer, P., Ducime, A., Creehan, K., Kisby, B., Taffe, M., & Janda, K. (2017). Active vaccination attenuates the psychostimulant effects of α-PVP and MDPV in rats. *Neuropharmacology*, *116*, 1-8.

Nguyen, J., Hwang, C., Grant, Y., Janda, K., & Taffe, M. (2018). Prophylactic vaccination protects against the development of oxycodone self-administration. *Neuropharmacology, 138*, 292-303.

Purpose	Variables	Setting/Subjects	Measurements & Instruments	Results	Evidence Quality
Study One Assess immuno-therapeutic strategies for attenuating psychostimulant effects of cathinone derivatives in rats **Study Two** Determine if immuno-pharmacotherapy against oxycodone alters anti-nociception and self-administration of opioid rates	**Study One** **Independent** - Control group (19): Administration of alpha-PVP and MDPV - Test group (12): administration of alpha-PVP-KLH and MDPV-KLH vaccines **Dependent** - Locomotor rat activity on wheels - Self administration rate of alpha-PVP by the trained rats - Antibody titer level **Study Two** **Independent** - Control: Exposure to oxycodone (TT; 24) - Experimental: Exposure to oxytocin vaccination (Oxy-TT; 24) **Dependent** - Plasma titer analysis - Self-administration rates - Tail withdrawal latency: nociception	**Study One** **Subjects:** Male, Sprague-Dawley rats age 10-11 weeks **Setting:** Charles River, New York over a 12-week period **Study Two** **Subjects:** Male, adult Wistar rats age ~13 weeks **Setting:** Charles River, New York over an 8-week period	**Study One** - Locomotor activity: 1-hour access to wheel quarter rotations mark - Daily 1-hour access to alpha-PVP self-infusion (0.025 mg/kg) - Antibody titer: enzyme-linked immunosorbent assay (ELISA) with Biomek - Group data analyzed with two-way repeated-measure Analysis of Variance **Study Two** - Antibody titer: enzyme-linked immunosorbent assay (ELISA) with Biomek - IV self-administration measured with repeated-measure Analysis of Variance (rmANOVA) - Tail withdrawal nociception pre/30 minutes post oxycodone injection	**Study One** - Wheel rotations increased in control group ($P < 0.01$) - Significant decrease after week 8 vaccination of self-drug infusions ($P=0.005$; >80% discrimination among groups) - Plasma antibody titer increased after vaccinations ($P < 0.005$) **Study Two** - Vaccine decreases brain penetration of oxycodone (unpaired t-test $P < 0.0001$) - Vaccination group was protective against self-administration of oxycodone ($P=0.0013$) by decreasing motivation ($P=0.0475$) - Vaccine attenuates antinociceptive effects of oxycodone ($P=0.0194$)	**Study One** **Methodological flaws:** None **Inconsistency:** None **Indirectness:** Animal study, not human **Imprecision:** None **Publication bias:** None **Study Two** **Methodological flaws:** None; golden standard **Inconsistency:** None **Indirectness:** Animal study, not human **Imprecision:** None **Publication bias:** None
Design **Study One** Randomized control animal trial **Study Two** Randomized control animal trial				**Implications** **Study One** rug-conjugate vaccines which generate antibodies to neutralize cathinone derivates **Study Two** Providing further interpretation of the efficacy of anti-drug vaccination in pre-clinical models for eventual trials	

<table>
<tr><td colspan="6">Bibliography
Kimishima, A., Wenthur, C., Zhou, B., & Janda, K. (2017). An advance in prescription opioid vaccines: Overdose mortality reduction and extraordinary alteration of drug half-life. ACS Chemical Biology, 12(1), 36.
Peterson, B., Schreiber, S., Fumo, N., & Brooke Lerner, E. (2019). Opioid deaths in milwaukee county, wisconsin 2013-2017: The primacy of heroin and fentanyl. Journal of Forensic Sciences, 64(1), 144-148.</td></tr>
<tr><th>Purpose</th><th>Variables</th><th>Setting/Subjects</th><th>Measurement and Instruments</th><th>Results</th><th>Evidence Quality</th></tr>
<tr><td><u>Study One</u>
Evaluate active PO vaccines in their effectiveness of eliciting high-affinity anti-opioid antibodies

<u>Study Two</u>
To assess leading cause of non-natural deaths reported by the United States Medical Examiner</td><td rowspan="2"><u>Study One</u>
Independent
- Control group: Administration of traditional pharmacologic strategies: methadone, buprenorphine
- Test group (Oxy-TT): small molecule-immunogenic protein conjugate vaccine

Dependent
- Hot plate and tail flick antinociception assay
- Drug half life

<u>Study Two</u>
Independent
Use of prescription opioids, heroin, or fentanyl

Dependent
Death, autopsy report of analysis of non-natural death reports</td><td rowspan="2"><u>Study One</u>
Subjects: Adult male rats; negated further subject criteria

Setting: United States; further information regarding laboratory location negated

<u>Study Two</u>
Subjects: Reported deaths due to non-natural opioid causes reported 2013 to 2017

Setting: Milwaukee County Medical Examiner’s Office</td><td rowspan="2"><u>Study One</u>
- Hot plate and tail flick antinociception assays, supraspinal and spinal analgesic potency of opioid drugs quantified by measuring a response latency to the heat stimulus
- Serial blood sampling over the course of 24 hours quantified with LCMS for plasma drug levels

<u>Study Two</u>
- Toxicology laboratory analysis by the American Board of Forensic Toxicology (ABFT) in detail of assessment of cause</td><td><u>Study One</u>
- Hot plate and tail flick antinociception assay: ED50 increased 10-fold in the experimental group
- Drug half-life: 68 to 268-fold increase in experimental group
<u>Study Two</u>
- Drug deaths increased from 220 in 2013 to 401 in 2017
- 82% increase in opioid related deaths
- In 2013, heroin or fentanyl was present in 116 (48%) of opioid deaths, but by 2017 increased three-fold 300 (89% of opioid deaths)</td><td rowspan="2"><u>Study One</u>
Methodological flaws: None
Inconsistency: None
Indirectness: Animal trials
Imprecision: None
Publication bias: National Institute on Drug Abuse funded study

<u>Study Two</u>
Methodological flaws: None
Inconsistency: None
Indirectness: Discusses opioid epidemic but not new treatment research
Imprecision: Singular, location may be difficult to adopt
Publication bias: None</td></tr>
<tr><td>Design
<u>Study One</u>
Randomized control, animal study

<u>Study Two</u>
Retrospective analysis of database/ reports</td><td>Implications
<u>Study One</u>
These vaccines can result in significant blockade of opioid analgesic activity, protection in lethal overdose by increasing serum half-life

<u>Study Two</u>
With increased awareness of the opioid crisis within the United States, death tolls rapidly increasing over less than 5-year timeframe enforces the need to alternative treatment methods</td></tr>
</table>

<table>
<tr><td colspan="6">Bibliography
Bremer, P., Kimishima, A., Schlosburg, J., Zhou, B., Collins, K., & Janda, K. (2016). Combatting synthetic designer opioids: A conjugate vaccine ablates lethal doses of fentanyl class drugs. Angewandte Chemie International Edition, 55(11), 3772-3775.
Barry, C., Kennedy, A., Gollust, S., Niederdeppe, J., Bachhuber, M., Webster, D., & McGinty, E. (2016). Understanding americans' views on opioid pain reliever abuse. Addiction, 111(1), 85-93.</td></tr>
<tr><th>Purpose</th><th>Variables</th><th>Setting/Subjects</th><th>Measurement and Instruments</th><th>Results</th><th>Evidence Quality</th></tr>
<tr><td><u>Study One</u>
Evaluate the effectiveness of immunotherapy for reducing psycho active effects of fentanyl class drugs

<u>Study Two</u>
Examine Americans' personal experience with opioid use disorder and their views of the problem</td><td rowspan="2"><u>Study One</u>
Independent
- Control group: Administration of fentanyl
- Test group (Fent-TT): small molecule-immunogenic protein conjugate vaccine and similar, high doses of fentanyl

Dependent
- Antinociception assay/ ED50 shifts

<u>Study Two</u>
Independent
Survey questions (January 31 to February 28, 2014) – pilot tested

Dependent
Respondents answers of opioid abuse and opinion</td><td rowspan="2"><u>Study One</u>
Subjects: Adult rodents; neglected further subject information

Setting: United States; further information regarding laboratory location negated

<u>Study Two</u>
Subjects:
1,111 U.S resident adults age 18 or greater

Setting: United States online panel through ARG survey group</td><td rowspan="2"><u>Study One</u>
- At 6-week post vaccination and 10 weeks analysis of anti-drug titers plasma levels analyzed after increased doses of fentanyl administration

<u>Study Two</u>
- Study participants were sampled randomly from online panel based on address sampling of 97% of American households
- Computer and internet access provided to all participants
- Responders received $10 for answering
- Definition of opioid abuse provided</td><td><u>Study One</u>
- Largest doses of fentanyl were administered to experimental group; resulting in 55% fatality in control group
- ED50 shift in experimental group, 30-fold increase ($p < 0.001$)
<u>Study Two</u>
- 28.2% of Americans abused opioid pain relievers in the last 12 months
- 69.5% have abused them in their lifetime
- 17.3% reported using medication that was not prescribed to them
- 58% ranked the abuse as a serious problem in the nation</td><td rowspan="2"><u>Study One</u>
Methodological flaws: None
Inconsistency: None
Indirectness: Animal, not human study based
Imprecision: None
Publication bias: Funded by National Institute on Drug Addiction

<u>Study Two</u>
Methodological flaws: Potentially dishonest answers or reports by respondents; survey fatigue
Inconsistency: Survey included numerous issues like HIV, guns, cancer, mental illness
Indirectness: None
Imprecision: Doesn't examine solutions, like vaccination against opioids and the public's opinion
Publication bias: None</td></tr>
<tr><td>Design
<u>Study One</u>
Randomized control, animal study

<u>Study Two</u>
Public opinion survey</td><td>Implications
<u>Study One</u>
Vaccinated protection against lethal doses of fentanyl can aid in opioid abuse
<u>Study Two</u>
Americans view the problem of opioid abuse as a serious problem and epidemic, enforcing the support and need to medical, law enforcement, disease and public health members to find solutions</td></tr>
</table>

<table>
<tr><td colspan="6">Bibliography
Raleigh, M., Pentel, P., & LeSage, M. (2014). Pharmacokinetic correlates of the effects of a heroin vaccine on heroin self-administration in rats. PLoS One, 9(12).
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<tr><th>Purpose</th><th>Variables</th><th>Setting/Subjects</th><th>Measurement and Instruments</th><th>Results</th><th>Evidence Quality</th></tr>
<tr>
<td><u>Study One</u>
Evaluate the effects of a morphine-conjugate vaccine on heroin self-administration in rats

<u>Study Two</u>
Examine the limitations of current treatment options to opioid use disorder, like buprenorphine availability and overdose deaths

Design
<u>Study One</u>
Randomized control, animal study

<u>Study Two</u>
Cross sectional study</td>
<td><u>Study One</u>
Independent
- Control group: unconjugated heroin drug (KLH) (n = 12)
- Expirimental group: M-KLH: 25 mcg heroin vaccine (n = 13)

Dependent
Plasma and brain heroin levels

<u>Study Two</u>
Independent
Availability of buprenorphine providers

Dependent
Opioid-related overdose deaths</td>
<td><u>Study One</u>
Subjects: 25 Male Holtzman rats (350 grams)

Setting: Information regarding laboratory location negated

<u>Study Two</u>
Subjects:
- Buprenorphine providers within the United States able to prescribe through Substance Abuse and Mental Health Services Administration
- Persons reported deaths due to opioid-related over dose ages 15 years and older

Setting: United States</td>
<td><u>Study One</u>
- Animals were anesthetized 1 week after final vaccination; blood was drawn from jugular catheters
- Rats were decapitated for collection of brain blood 4 minutes after heroin dose
- Two-way analysis t-tests between groups

<u>Study Two</u>
- Provider availability for buprenorphine administration found through Substance Abuse and Mental Health Services Administration Buprenorphine Treatment Practitioner Locator compared to:
- Overdose reported deaths analyzed between 2013 and 2015 from Center for Disease Control and Prevention database
- Counties with fewer than 10 deaths excluded for privacy</td>
<td><u>Study One</u>
- Vaccination shifted the heroin dose-response to the right and reducing heroin potency; heroin and its active metabolites were retained in the plasma and reduced in the brain
- Mean plasma concentrations were 39-fold greater in vaccinated rats ($p < 0.01$)
<u>Study Two</u>
- 846 counties, 49 states (83% of US population)
- 51,688 recorded deaths due to opioid overdose (20 per 100,000)
- Buprenorphine provider median 5.9 per 100,000
- Treatment availability and rate of deaths weak (correlation coefficient 0.18, $p < 0.001$)

Implications
<u>Study One</u>
Vaccination against heroin in animal studies can lead to distinct treatment option for heroin addiction in humans
<u>Study Two</u>
Current treatment for opioid abuse, like buprenorphine, have barriers, weak correlation to current treatment availability and overdose deaths, emphasizing the need for alternative treatments</td>
<td><u>Study One</u>
Methodological flaws: None
Inconsistency: None
Imprecision: Animal based study, implied implication to humans
Publication bias: None

<u>Study Two</u>
Methodological flaws: None
Inconsistency: None
Indirectness: None
Imprecision: Does not discuss vaccinations, but current barriers of treatments approved
Publication bias: None</td>
</tr>
</table>

<table>
<tr><td colspan="6">Bibliography
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Dunleavy, G., Nikolaou, C., Nifakos, S., Atun, R., Law, G., & Tudor C. (2019). Mobile digital education for health professions: Systematic review and meta-analysis by the digital health education collaboration. Journal of medical Internet research, 21(2).</td></tr>
<tr><th>Purpose</th><th>Variables</th><th>Setting/Subjects</th><th>Measurement and Instruments</th><th>Results</th><th>Evidence Quality</th></tr>
<tr>
<td><u>Study One</u>
Literature review of digital problem-based learning DPBL in improving the health professional’s knowledge, skills, and attitude.

<u>Study Two</u>
Literature review of the effectiveness of Mobile learning on health professions education.

Design
<u>Study One</u>
Systematic review of RCT using standard Cochrane methodology.

<u>Study Two</u>
Systematic review using standard Cochrane methodology.</td>
<td><u>Study One</u>
Independent
Digital problem-based learning

Dependent
Knowledge, skills and attitude

<u>Study Two</u>
Independent
Mobile learning methods

Dependent
Learners knowledge, skills, attitude and satisfactio</td>
<td><u>Study One</u>
Subjects: Nine RCT studies with 890 medical students

Setting: Electronic Database MEDLINE, Elsevier, Cochrane Central Register of Controlled Trials, PsycINFO, Ebsco, and Web of Science Core Collection

<u>Study Two</u>
Subjects: 29 studies, including 3175 learners. A total of 25 studies were RCTs and 4 were cluster RCTs

Setting:
7 major bibliographic databases from January 1990 to August 2017 and included randomized controlled trials (RCTs) or cluster RCTs.</td>
<td><u>Study One</u>
Cochrane method with two reviewers independently performing each of the steps. RCT issued between January 1990 to August 16, 2017

<u>Study Two</u>
A total of 2 reviewers independently extracted relevant characteristics related to participants, intervention, comparators, outcome measures, and results from all the included studies using a standard data collection form</td>
<td><u>Study One</u>
The pooled analysis comparing the effect of DPBL to traditional learning on postintervention knowledge outcomes favored DPBL (SMD 0.67, 95% CI 0.14-1.19)

<u>Study Two</u>
The pooled estimate of the studies favored mLearning over traditional learning in terms of postintervention knowledge scores (SMD=0.43, 95% CI 0.05-0.80, N=11 studies

Implications
<u>Study One</u>
DPBL improves students’ postintervention knowledge scores in comparison to traditional learning.

<u>Study Two</u>
The evidence base suggests that Mobile Learning is as effective as traditional learning or possibly more so.</td>
<td><u>Study One</u>
Methodological flaws: Studies included in this meta-analysis were designed as RCT, but most of them lacked information on the randomization method, allocation concealment, or blinding method
Inconsistency: None
Indirectness: None
Imprecision: None
Publication bias: None

<u>Study Two</u>
Methodological flaws: 86 % of studies did not provide information on the method of randomization and sequence allocation
Inconsistency: None
Indirectness: None
Imprecision: Data availability bias may occur if data is unavailable in the included studies and their unavailability is related to the study results.
Publication bias: None</td>
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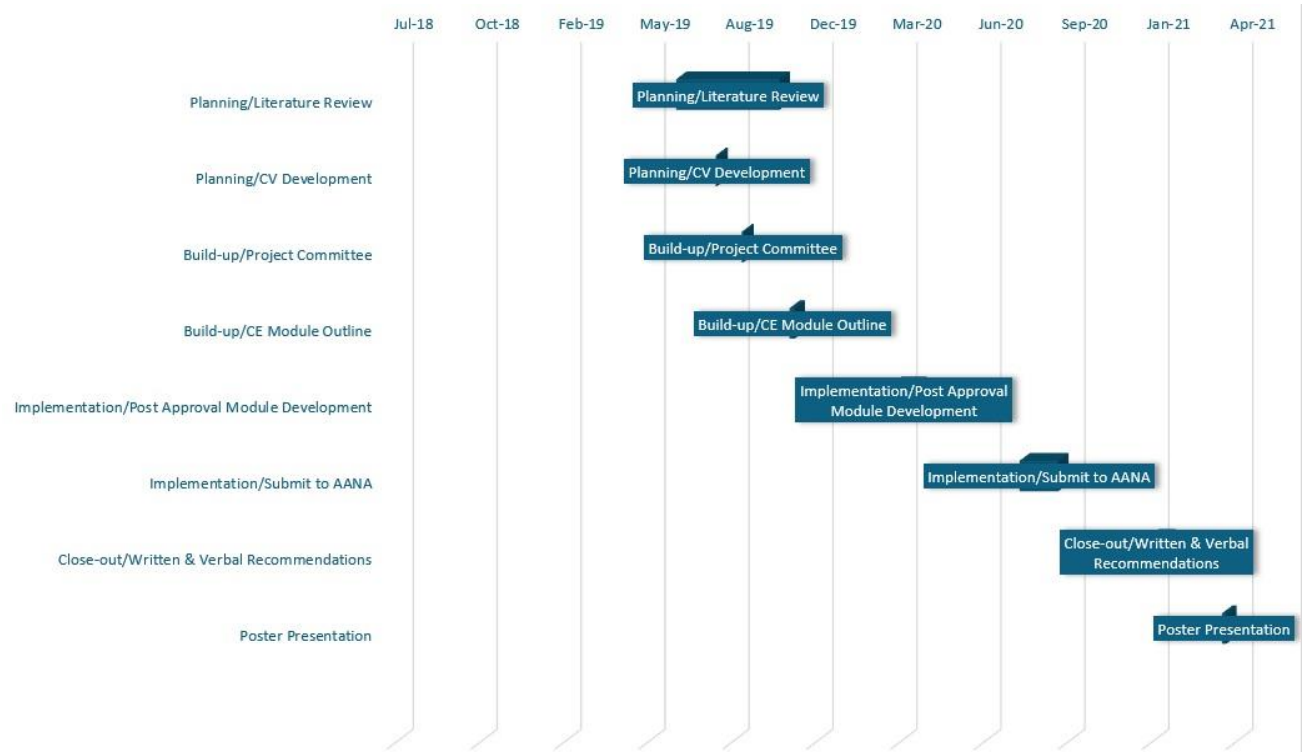
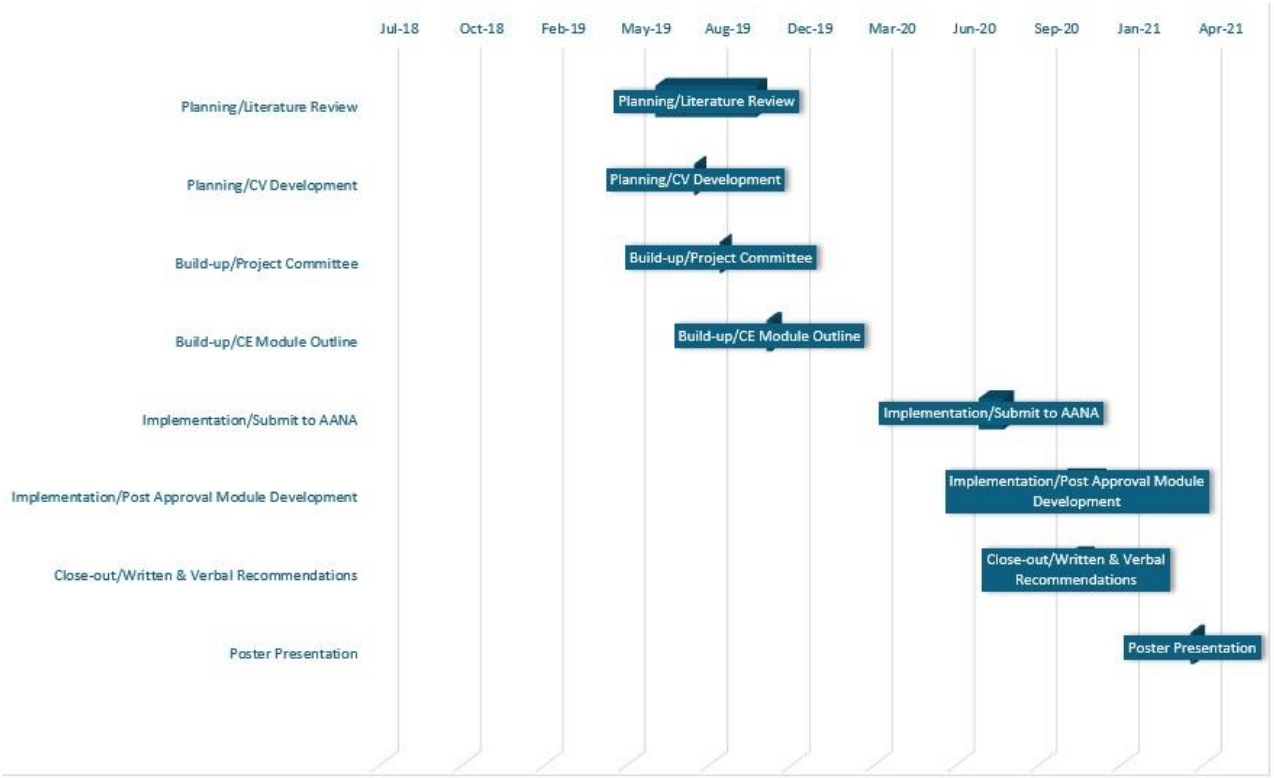
Appendix B

Initial Proposed GANTT Chart/Timeline



Final GANTT Chart/Timeline



Appendix C

Feasibility Study

AdventHealth University Student Registered Nurse Anesthetists Developed Online Continuing Education Module Seeking American Association of Nurse Anesthetists Approval for CE Credit

Doctor of Nurse Anesthesia Practice Program

AdventHealth University

Orlando, U.S.A

Prepared by

Brianne M. Beacham, BSN, SRNA

Candice J. Dykes, BSN, SRNA

Certification

We hereby certify that we have no interest, present or contemplated, in the proposed AdventHealth University Echelon Division, and that to the best of our knowledge and belief, the statements and information contained in this report are correct – subject to the limitations herein set forth.

Brianne M. Beacham, BSN, SRNA

Candice J. Dykes, BSN, SRNA

Table of Contents

Executive Summary

Student Registered Nurse Anesthetists (SRNAs) at AdventHealth University (AHU) had yet to develop an American Association of Nurse Anesthetists (AANA) approved continuing education (CE) module through the Echelon media development platform. The purpose of this study was to contribute to the rapidly growing online CE industry for healthcare providers, as well as, the process of doctoral scholarly project SRNA module development. Overall, this study recommends the establishment of SRNA developed CE modules at AHU Echelon Division accredited by the AANA.

Echelon's established reputation strengthens the ability to enhance professional development and patient care through online CE modules. Still, because an AANA CE module had not been developed under the Echelon platform by an SRNA at AHU, some cost forecasts may have been prone to greater error due to no historical cost figures. The strategy to establish AHU SRNA developed CE modules approved by the AANA will maximize the benefits of the strengths outlined and mitigate the potential effects of the weakness from process improvement recommendations.

The analysis justifiably reveals that the non-monetary benefits far outweigh the time and costs involved in CE module development approved by the AANA for credits. The intangible benefits cause the process to be favorable for AHU, its SRNAs, and healthcare professions. The long-range benefits of establishing this process appear extremely positive for multiply parties. It is projected to generate revenue as a give-back to the University, increase name recognition and overall branding, and offer extensive access to evidence-based knowledge at low cost and flexibility to healthcare providers while supporting the healing mission of the University.

Introduction

Purpose

Student Registered Nurse Anesthetists (SRNAs) at AdventHealth University (AHU) had yet to develop an American Association of Nurse Anesthetists (AANA) approved continuing education (CE) module through the Echelon media development platform. Therefore, a feasibility study on the development of an online education module approved for CE credits by the AANA was conducted to determine the viability of digital education at low cost and flexibility to healthcare providers on the treatment of opioid-use disorder (OUD) with immunopharmacotherapy to increase knowledge, while enhancing patient safety with evidence-based care.

Assumptions

The first assumption made in the proposal of this feasibility study included a sufficient number of future SRNAs interested in CE module development and credit approval by the AANA for increased knowledge analysis. Furthermore, it was assumed that there was a need for accredited evidence-based CE modules for healthcare providers.

Market Potential

Environmental Analysis

In 2025, all Certified Registered Nurse Anesthetists (CRNAs) will require a doctorate in nurse anesthesia to enter the field; currently, a master's degree is required. The master-level nurse anesthesia programs will have to transition to a doctorate program by 2022 to meet this 2025 requirement. With a higher-level degree program also comes new requirements with regards to the DNAP scholarly project.

These projects require SRNAs to demonstrate a synthesis of evidence-based practice in an area specific to the student's specialty. Therefore, there is a potential market for AHU SRNAs

to utilize CE module development, credit application/approval, and analysis to meet this requirement.

The online CE module industry is rapidly growing with significant demand from providers, allowing for a more accessible source of mandatory continued learning for all credentialed or licensed healthcare professional. The current overall industry for continuing medical education (CME) is estimated to be $750 million, but the industry's gross annual product is expected to increase exponentially within the next five years (American Association of Continuing Medical Education, 2020; Iskowitz, 2019).

Strengths and Weaknesses

One of the major strengths of this process is the already established reputation of Echelon, the continuing education division of AHU and AdventHealth. This formed relationship enables the mission-driven Echelon and AHU to serve the CE requirements of individuals, and organizations' training needs by providing high-quality online learning and informational resources to enhance professional development and patient care.

On the other hand, a major weakness included that an AANA CE module had not been developed under the Echelon platform by an SRNA at AHU. Therefore, developing cost forecasts for new ventures with no historical cost figures is considered more difficult and typically subject to greater error than forecasts for projects with cost histories.

Cost of the Process

Production Cost

The success of the CE development and accreditation is partly contingent on the cost of the module. The total overall cost identified as directly relating to the development of the one-hour enduring media CE module was $11,817 (see appendix C1). A cost-saving was that the SRNA developers charge nothing for their contributions to content development (see Appendix C1).

Time Cost

Although the were no monetary cost for AHU students, there was a significant time cost. The estimated time cost per SRNA for the development of the module was 150 hours. AHU Director of Continuing Education – Division Echelon, Lori Pollizi, estimated that her time commitment to the module development was 64 hours. Furthermore, the additional content development by the Echelon team for enduring media was estimated to have been 359 hours.

Conclusion

Risks & Benefits

AHU SRNA developed online modules approved by the AANA for CE credits offer numerous benefits to multiply parties. With time, continued SRNA module development, both the increased quantity and strength of content would generate revenue as a give-back to the University. However, many of the risks and benefits from the module development cannot easily be assigned a monetary value.

institutional.

The SRNA developed and published CE module would increase AHU's name recognition and overall branding. The University's reputation would also be enhanced by promoting graduates with research credentials, a distinction from many other institutions.

However, if SRNAs lack the high level of quality required in academia, then there is a potential that it could reflect negatively on the institution.

SRNA developers.

Throughout the process, SRNAs acquire invaluable knowledge and skills applicable to continued professional development. Also, gaining recognition and approval by accrediting associations, like the AANA validate SRNA time and effort while increasing their confidence.

This process requires significant time and effort on the SRNAs' part. If they are unsuccessful, it could poorly affect their confidence and motivation for continued academic endeavors.

professional contributions.

Digital education offers extensive access at low cost and flexibility to healthcare providers. It allows opportunities to enhance the quality of educational structures, improve cost-effectiveness, and provide convenient access to learning, especially when accredited by the AANA and offered through professional organizations, like Echelon.

Recommendations

Based on the analysis of the benefit/cost considerations, the development of a CE module by SRNAs at AHU submitted to the AANA for credit was deemed feasible and desirable. Determining the viability of this process allows for future development and progression toward research and publication analysis at AHU by SRNAs, as well as increased availability of evidence-based knowledge for healthcare providers.

Our recommendations for process improvement of CE module development by AHU SRNAs include ensuring efficient organization of documents and alignment of all content with AANA expectations. Module content also needs to change knowledge, skill, or practice relevant to the profession and provide measurable outcomes with reporting metrics.

Appendix C1

Cost Estimate for 1 Hour Enduring Media - SRNA Research Online CE

Content Development *(does not include ARNA research time)*	$ 2,957.50
On-Line Content Development	$ 570.00
Media Production - Audio Recording, Design, Build, and Production QA	$ 6,565.00
Project Management	$ 1,040.00
Accreditation	$ 684.00
Technical Support/Maintenance/Hosting	$ -
Total Design and Development Cost	**$ 11,816.50**

Content Development	**Hours**	**Rate**	**Cost**
Content/Curriculum Deliverables			
Content Development *AHU SRNA Research ?*	0.0	$ 45.00	$ -
Content Deliverables: Transcript, Bibliography, Author(s) Bio	40.0	$ 35.00	$ 1,400.00
Curriculum Layout: Bullets, Graphs, Charts	37.0	$ 35.00	$ 1,295.00
Post Test Development	1.5	$ 35.00	$ 52.50
Content QA and Final Review	6.0	$ 35.00	$ 210.00
Estimated Hours for Content Development	84.5	$ -	$ 2,957.50
On-line Content Development	**Hours**	**Rate**	**Cost**
On-Line Deliverables		$ -	
Course Shell Development	4.0	$ 30.00	$ 120.00
Script Editing	7.5	$ 30.00	$ 225.00
Content QA	7.5	$ 30.00	$ 225.00
Estimated Hours of On-Line Content Development	19.0		$ 570.00
Media Production	**Hours**	**Rate**	**Cost**
Design/Build			
Template Design	16.0	$ 30.00	$ 480.00
Art direction/graphics	12.0	$ 30.00	$ 360.00
HTML5 Video Build	160.0	$ 30.00	$ 4,800.00
Upload to Production Files	3.0	$ 30.00	$ 90.00
Estimated Hours for Design/Build	191.0		$ 5,730.00
Audio	**Hours**	**Rate**	**Cost**
Recording	2.0	$ 35.00	$ 70.00
Voice	2.0	$ 30.00	$ 60.00
Audio Editing	8.0	$ 50.00	$ 400.00
Transfer to Wave File	1.5	$ 30.00	$ 45.00
Estimated Hours for Audio	13.5		$ 575.00
	Hours	**Rate**	**Cost**
Production QA			
First run QA	2.0	$ 30.00	$ 60.00
First run QA Fixes	4.0	$ 35.00	$ 140.00
Final Client QA changes	2.0	$ 30.00	$ 60.00
Estimated Hours for Production QA/Changes	8.0		$ 260.00
Total Media Production			**$ 6,565.00**
Project Management	**Hours**	**Rate**	**Cost**
Correspondence/Meetings/Project Coordination	16.0	$ 35.00	$ 560.00
Program Information Build - Resources, Transcript, Program Info, Glossary	8.0	$ 30.00	$ 240.00
Uploading files to LMS/testing functionality	8.0	$ 30.00	$ 240.00
Estimated Hours for Project Management	32.0		$ 1,040.00
Accreditation	**Hours**	**Rate**	**Cost**
Paperwork and accreditation manager's review			
Doc/prep for accrediting for each board 1 CE	11.0	$ 35.00	$ 385.00
Fee per 1 CE	0.0	$ 299.00	$ 299.00
Estimated Hours for Accreditation	11.0		$ 684.00
Technical Support/Maintenance/Hosting	**Hours**	**Rate**	**Cost**
Hosting (fixed cost - for one year)			$ -
Program maintenance (fixed cost - for one year)		$ -	$ -
Client and technical support (fixed cost - for one year)		$ -	$ -
Estimated Costs for LMS			$ -

Total estimated hours for 1 hour enduring media **359.0 hours** **$ 11,817**

Questions contact: Lori Polizzi 407-303-9409 or lpolizzi@echeloned.com

Appendix D

Immunopharmacotherapy Treatment for Opioid-Use Disorder:
Applicability to Practice Program Information

Program Description:

Opioid-use disorder has become a national crisis, killing over 100 Americans daily and costing 78 billion dollars annually. The current therapy for opioid abuse has limited success with significant side effects, illicit use, and high attrition rates. However, research has demonstrated that immunopharmacotherapy (a new treatment for opioid addiction in the pre-clinical phase) elicits an immune response which lacks abuse potential and decreases related mortality.

Program Purpose:

This course is designed to increase awareness and evidence-based knowledge regarding immunopharmacotherapy treatment for opioid-use disorder, and its impact on patient care. Opioid-use disorder, its current state and treatments, immunopharmacotherapy, its mechanism of action with possible drug-interactions, and the provider's vital role in developing adequate pain management and appropriate anesthetic plans to future patients treated with the anti-opioid vaccinations should they receive approval will be discussed.

Program Goal:

Increase the CRNA's awareness and knowledge regarding immunopharmacotherapy for opioid use disorder, and its impact on patient care and development of the anesthetic plan.

Program Outcomes/Objectives:

Upon completion of this course, program participants will be able to:

1. Identify the signs and symptoms of opioid-use disorder.

2. Distinguish between current opioid-use disorder treatments and their side-effects.

3. Define immunopharmacotherapy.

4. Identify the mechanism of action of immunopharmacotherapy/anti-opioid vaccinations.

5. Understand the pharmacodynamics of anti-opioid vaccinations in pre-clinical animal subjects.

6. Distinguish the potential physiological side-effects and impact from treatment with immunopharmacotherapy on opioid analgesics.

7. Incorporate appropriate pain management techniques within an anesthetic plan for surgical patients undergoing immunopharmacotherapy for the treatment of an opioid-use disorder.

8. Identify the provider's role in opioid-use disorder and immunopharmacotherapy.

Educational Module Outline of Intended Content

Immunopharmacotherapy for Opioid-Use Disorder

Module 1. Welcome

Topic 1.1 Course introduction

Topic 1.2 Course objectives

Topic 1.3 Introduction to content

Module 2. Clinical problem/significance: Opioid-Use Disorder

Topic 2.1 Define OUD

Topic 2.2 Signs & symptoms of OUD

Topic 2.3 Current Treatments (Mechanism of action & side effects)

Topic 2.4 Problem significance/impact

Learning Activity: Opioid-use disorder

Module 3. Immunopharmacotherapy

Topic 3.1 Define immunopharmacotherapy

Topic 3.2 Mechanism of action & hapten structure/development

Topic 3.3 Potential physiological impacts

Topic 3.4 Plasma & brain concentration levels

Topic 3.5 Drug half-life

Topic 3.6 Effective dose 50 & self-administration rates

Topic 3.7 Outlook of immunopharmacotherapy and clinical trial progression

Learning Activity: Immunopharmacotherapy

Module 4. Immunopharmacotherapy applicability to practice

Topic 4.1 Impact on appropriate anesthetic plan development and adequate pain management

Topic 4.2 Alternative analgesia treatments

Learning Activity: Patient care & appropriate treatment

Module 5. Role of the CRNA

Topic 5.1 AANA

Topic 5.2 Applicability to practice

Learning Activity: Role of the CRNA

Module 6. Conclusion

Topic 6.1 Case Study: Anesthetic plan development & pain management for intraoperative patient treated with immunopharmacology

Topic 6.2 Rationale of case study

Topic 6.3 Summary

Module 7. Echelon wrap-up

Appendix E

Immunopharmacotherapy for Opioid-Use Disorder: Applicability to practice Transcript

Module 1. Welcome

Topic 1.1 Course introduction

Hello, and welcome to the course! This course was designed after recognizing that there is a gap in knowledge and awareness regarding immunopharmacotherapy in relation to opioid-use disorder among healthcare providers. Per the National Institute of Health, the lack of available resources regarding not only opioid-abuse, but also its upcoming therapies can jeopardize patient safety.

By completing this course, the provider will gain an increased knowledge regarding research on pre-clinical immunopharmacotherapy for the treatment of opioid-use disorder. An alertness toward a potential future encounter with the vaccinations will prepare providers to administer safe, effective patient care and follow-up.

Topic 1.2 Course objectives

Upon completion of this course, program participants will be able to:

- Identify the signs and symptoms of opioid-use disorder
- Distinguish between current opioid-use disorder treatments and their side-effects
- Define immunopharmacotherapy
- Identify the mechanism of action of immunopharmacotherapy
- Understand the pharmacodynamics of anti-opioid vaccinations in pre-clinical animal subjects
- Distinguish the potential physiological side-effects and impact from treatment with immunopharmacotherapy on opioid analgesics
- Incorporate appropriate pain management techniques within an anesthetic plan for surgical patients undergoing immunopharmacotherapy for the treatment of an opioid-use disorder
- Identify the provider’s role in opioid-use disorder and immunopharmacotherapy

Topic 1.2 Introduction to content

Opioid-use disorder has become a national crisis, killing over 100 Americans daily and costing 78 billion dollars annually. The current therapy for opioid abuse has limited success with significant side effects, illicit use, and high attrition rates. However, research has demonstrated that immunopharmacotherapy (a new treatment for opioid addiction in the pre-clinical phase)

elicits an immune response which lacks abuse potential and decreases related mortality. Compared to current treatments, immunopharmacotherapy against a targeted opioid could offer suppression of addiction liability and overdose potential over an extended period of time without placing excessive compliance demands and adverse effects on the person.

This course is designed to increase the provider's awareness and evidence-based knowledge regarding immunopharmacotherapy treatment for opioid-use disorder, and its impact on patient care. Opioid-use disorder, its current state and treatments, immunopharmacotherapy, its mechanism of action with possible drug-interactions, and the provider's vital role in utilizing this knowledge to develop adequate pain management and appropriate anesthetic plans to future patients treated with the anti-opioid vaccinations should the drugs receive approval will be discussed.

Module 2. Clinical problem/significance: Opioid-Use Disorder

Topic 2.1 Define OUD

For this module, opioid-use disorder, also known as OUD, is defined as a diseased state in which physical dependence on opioids lead to compulsive and repetitive use despite negative consequences to the person's mental state, health, or social life. Opioids are either natural or synthetic chemicals that agonize specific receptors on nerve cells within the body and brain in order to produce analgesic effects. The drugs reduce the perception of pain, but they are also associated with side effects, such as, drowsiness, mental confusion, euphoria, nausea, constipation, and respiratory depression.

The opioid class of drugs can refer to prescription pain relivers, man-made opioids, and heroin. Synthetic opioids include fentanyl, methadone, and tramadol. Prescription pain relivers primarily include oxycodone, hydrocodone, codeine, and morphine. Prescription opioids are intended to treat acute and chronic pain, active-phase cancer treatment, palliative care, and end-of-life care.

Unlike other substance disorders, opioids result in physical dependence in one of the shortest amounts of time, as little as 4 to 8 weeks, and they produce some of the highest levels of positive reinforcement via distributed mu-opioid receptors. Therefore, opioid-use disorder is considered a chronic relapsing disorder requiring substantial therapeutic efforts in order to maintain sobriety with serious potential consequences including disability and death.

Topic 2.2 Signs & symptoms of OUD

In order to appropriately recognize OUD, provider's must be able to identify associated signs and symptoms. The Diagnostic and Statistical Manual of Mental Disorders aid in the recognition of someone with OUD as a problematic pattern of opioid-use leading to distress, with at least two of the following occurring within a 12-month period:

- Taking larger amounts of drugs or over a longer period than intended.
- Persistent desire or unsuccessful efforts to control opioid use.
- Craving or urge to use opioids.
- Problems fulfilling obligations at work, school or home.
- Continued opioid use despite ongoing physical or psychological problem caused by opioids.
- Experiencing withdrawal or taking opioids to relieve or avoid unwanted symptoms.

OUD has three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. These stages typically occur in a reoccurring cycle and affect major areas of the brain and neurotransmitters.

The binge or intoxication stage is classified as when an individual consumes an addictive substance. This is when the brain's reward system is triggered, reinforcing frequent opioid use.

Next is the withdrawal or negative affect stage. Excessive use activates stress neurotransmitters, which provide the neurochemical basis for the negative physical and emotional state associated with withdrawal. In chronic opioid abusers, abrupt cessation of the drug or withdrawal symptoms include pain, chills, cramps, diarrhea, restlessness, anxiety, nausea, vomiting, insomnia, mydriasis, and intense cravings.

Lastly is the preoccupation or anticipation stage. This stage involves the over use of the pre-frontal cortex. Constant activation of this area of the brain leads to significant cravings and compulsive opioid seeking, restarting the cycle with the binge or intoxication stage, thus the treatment course is long-term and extensive.

Topic 2.3 Current Treatments

According to the bipartisan bill, Substance-Use Disorder Prevention that Promotes Opioid Recovery and Treatment, also known as SUPPORT, medication-assisted treatment, or MAT, is considered the best treatment approach for OUD. MAT is a comprehensive treatment that combines the use of medications (methadone, naltrexone, or buprenorphine) with counseling and cognitive behavioral therapies. The U.S. Food and Drug Administration approved both opioid antagonists, like naloxone, and opioid-receptor agonists, such as methadone and buprenorphine, for the treatment of opioid overdose reversal.

Naloxone is a non-selective, competitive opioid receptor antagonist. So, the drug blocks the effects of opioids by removing them from the mu-receptor in order to treat related overdose. These effects may last a half an hour. When administered to opioid-dependent individuals, they

will experience symptoms of opioid withdrawal, like agitation, sudden onset of pain, nausea/vomiting, and tachycardia.

On the other hand, methadone and buprenorphine, synthetic opioid analgesics with extensive half-lives, are used for maintenance therapy in dependent individuals via mu-receptor agonism. Methadone is a full agonist, where buprenorphine is a partial agonist, so it has an improved safety profile due to incomplete efficacy; therefore, methadone activates the receptors similarly to the abused opioid in order to decrease cravings. For this reason, these treatments are associated with illicit use and unfavorable side effects, like mental confusion, euphoria, nausea, drowsiness, and constipation, leading to high attrition rates within the first month and overall limited success. As with other opioids, a tolerance and dependence can also develop after repeating dosages which are only available at prescriptive maintenance clinics.

Topic 2.4 Problem significance/impact

The combination of the strong physiological effects of opioids, along with poor current treatment effectiveness, ODU has become a significant problem in the nation. The United States is considered one of the largest global consumers of opiates with an ease of access to prescription opioids and heroin. Each year over 200 million opiate prescriptions are written in the U.S. alone. In relation, it is estimated that over 2.5 million Americans suffer from OUD.

Opioid-abuse takes the lives of over 100 individuals daily, and it costs nearly 80 billion dollars annually due to healthcare and criminal justice expenses, and loss of workplace productivity. In 2017, both the U.S. President and the Department of Health and Human Services declared the opioid epidemic a national state of emergency due to the overwhelming statistics associated with opioid abuse.

As discussed, the current treatments for opioid abuse are associated with unfavorable side effects, illicit use, and costly maintenance. Therefore, only 10% of Americans suffering from OUD are receiving treatment, causing OUD to have the highest rate of addiction relapse. Within the first week of sobriety, more than half of people will actually have an opiate-related relapse, and 80% of those that attend an inpatient recovery program will relapse within a month of being discharged. Overall, those that relapse from OUD have a ten-fold higher mortality rate than the general population.

In consequence, the United States' life expectancy has decreased for the first time in over 20 years due to the rise in unintentional death rates from opioid misuse!

Learning Activity: Opioid-use disorder

1. According to the Diagnostic and Statistical Manual of Mental Disorders, which is a characteristic of someone with opioid-use disorder?

a. Ability to control desire of opioid use
b. Capability to fulfill obligations at work
c. Development of an opioid tolerance
d. Decreased opioid use after psychological problems

Answer: C
Objective: 1, Module 2, Topic 2.1
Learning Activity: Opioid-use disorder

Rationale: The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2018) aid in the recognition of someone with opioid-use disorder as a problematic pattern of opioid-use leading to distress, with at least two of the following occurring within a 12-month period: Taking larger amounts of drugs or over a longer period than intended, unsuccessful efforts to control opioid use, problems fulfilling obligations at work, school or home, or continued opioid use despite ongoing physical or psychological problem caused by opioids.

2. Which characteristic is associated with naloxone in comparison to methadone and buprenorphine?

a. Complete opioid-receptor agonist
b. Competitive opioid-receptor antagonist
c. Non-competitive opioid-receptor agonist
d. Incomplete opioid-receptor antagonist

Answer: B
Objective: 2, Module 2, Topic 2.3
Learning Activity: Opioid-use disorder

Rationale: Naloxone is a non-selective, competitive opioid receptor antagonist. Methadone is a full agonist, where buprenorphine is a partial agonist. They are associated with illicit use and unfavorable side effects similar to abused-opioids (Banks et al., 2018; Whelan & Remski 2012).

Module 3. Immunopharmacotherapy

Topic 3.1 Define immunopharmacotherapy

In response to the OUD public health emergency, the National Institute of Health released an initiative to combat the crisis by emphasizing three research areas: improvement of overdose-reversal interventions, alternative strategies to safely manage chronic pain, and new treatments for opioid addiction, like to be discussed: immunopharmacotherapy.

Immunopharmacotherapy, in general terms is the treatment or prevention of a disease by increasing the immune system's functionality. The concept of anti-opioid vaccinations was first discovered in 1974, when self-administration of heroin by a rhesus monkey was decreased with a

conjugate vaccine. However, it was not until the 1990s, with vaccinations for cocaine and nicotine, that the immunopharmacological field reignited interest. Although unsuccessful in clinical trials, these early studies highlighted important features of immunopharmacological vaccinations against drugs of abuse, and became the foundation of subsequent research efforts.

Immune therapy is evolving as a promising treatment for OUD in pre-clinical animal studies. Specifically, immunopharmacotherapy against opioid abuse induces a tailored IgG antibody response. The antibodies bind to specific freely-circulating opioid molecule, like heroin, oxycodone, hydrocodone, or fentanyl. The formed antibodies peak concentration levels occur two to four weeks after injection. The antibodies triggered by the vaccinations sequester the specific targeted drugs peripherally and prevent them from crossing the blood-brain barrier and eliciting the desired addictive psychoactive effects.

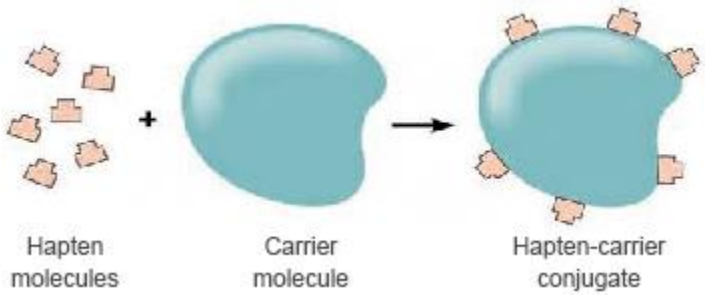
This new therapy would not only be beneficial in those with OUD, but these antibodies could also be used to protect police enforcement, emergency medical technicians, and other first responders from inadvertent acute exposure, especially from fentanyl. It is the hope that a person can be vaccinated with either one or a combination of anti-opiate vaccinations. These vaccinations compared to current, traditional treatments are considered superior because they block an opioid's activity without direct interaction with mu-opioid receptors, they have fewer adverse side-effects, and could provide protection for up to a year with booster injections.

Topic 3.2 Mechanism of action & hapten structure/development

In order to understand more of how immunopharmacotherapy prevents opioid-abuse, the molecular structure of the vaccinations should be examined. There are several fundamental components to the development of a successful anti-opioid vaccine. First, the vaccine's protective quality must not be surmounted by a higher dose of the opioid, next the antibodies must display high binding affinities for the drug and its metabolic profile, and lastly, sufficient antibody concentrations must be achieved in order to produce the desired effect. In order for adequate antibody concentrations to be achieved, a vigorous T-helper-type immune response is required. This step is enabled with the right choice of immunogenic carrier protein, adjuvant, and dosing schedule.

A conjugate, or carrier protein like bovine serum albumin, is essential for opioid vaccination effectiveness because it converts the hapten into a T-cell dependent antigen. The hapten is considered the most important component because it serves as the immune response or antibody development activating agent.

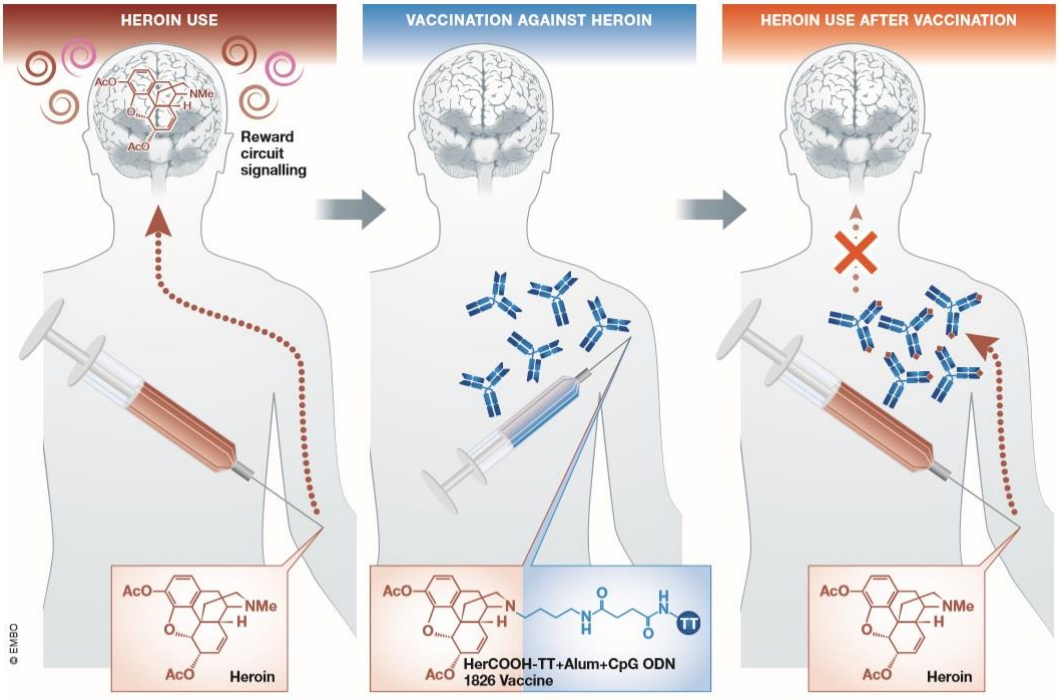
Haptens are small molecules that elicit an immune response only when attached or conjugated to a large carrier, like a protein. When in contact with the hapten-carrier protein adduct, the body will generate antibodies. In the case of anti-opioid vaccinations, the design aspect maximizes structural similarity to the abused drug in order to increase the likelihood of producing antibodies with a high affinity for the opioid. Drugs of abuse and their metabolites, like heroin, oxycodone, hydrocodone, or fentanyl are individually targeted because the vaccine hapten mimics the molecular structure of these native drugs.



https://www.creative-diagnostics.com/Hapten.htm

In addition to the hapten-protein conjugate, adjuvant formulations are additionally essential for anti-opioid vaccines. Without this component, the vaccinations would only elicit a weak immune response. The most successful adjuvant formulations involve colloidal aluminum salts and cytosine-phosphodiester-guanine oligonucleotide which enhance the immune response and downstream injection site activation.

A final consideration for developing effective opioid vaccines is the immunization schedule. Opioid vaccination requires the continued maintenance of antibody concentrations with high affinity for the drug. Vaccines for drugs of abuse require more frequent booster injections when compared to those for infectious diseases. A vaccination schedule of at least three injections at least four weeks apart with antibody titers every two to four months was recommended during the pre-clinical animal trials.

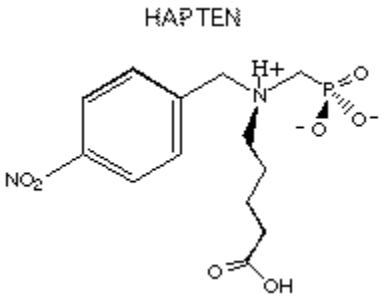


https://www.embopress.org/doi/pdf/10.15252/embr.201745322

Topic 3.3 Potential physiological impacts

An example of a hapten molecule is urushiol, a toxin found in poison ivy. Urushiol is absorbed into the skin and generates the actual hapten through a secondary reactive molecule. Exposure causes effector T-cells, generating an immune reaction. Therefore, a person develops blisters after coming in contact with poison ivy. Interestingly, haptens can also produce autoimmune disease. Examples include the potential for lupus erythematosus induced by hydralazine and halothane-related hepatitis.

These physiological effects from the hapten molecule have not presented in the animal-trail studies, so if the vaccinations progress to human trials, the potential for hapten-induced autoimmune disease with should be researched. Haptens have these known potential side-effects, negatively effecting the hepatic system, so providers should note associated lab values, like liver enzymes, when caring for patients undergoing immunopharmacotherapy treatment.



https://biosci.mcdb.ucsb.edu/immunology/Antibody-Antigen/catab.htm

Topic 3.4 Plasma & brain concentration levels

As discussed, the single conjugate, opiate selective vaccinations elicit a high concentration of antibodies. The targeted-opioid in the vaccination is sequestered by these immunopharmacologic antibodies within the plasma. So, the opioid is prevented from entering the brain and attaching onto its targeted receptor. Rather, the opioid concentrations remain elevated within the plasma and measured via enzyme-linked immunosorbent assay, also called ELISA**.**

Within the immunoconjugate vaccinated test group, brain concentration levels of the targeted opioid were nearly 50% lower than the control group who received the same dose of the opioid. By limiting the dose beyond the blood-brain barrier, the neurological impact is decreased. The opioid is prohibited from agonizing central receptors, so the vaccination decreases antinociceptive effects traditionally caused by administered opioids.

This pharmacodynamic effect decreases motivation for opioid self-administration within pre-clinical animal trials. Because users will no longer achieve the desired effects from drug-use, there is a limited incentive or behavior to abuse opioids. It is anticipated that in future studies, this feature within humans will also translate to a functional protection against the reinforcing effects from opioids and decrease OUD.

Topic 3.5 Drug half-life

In relation to the previous topic of increased plasma concentrations, how does this impact on the opioid's half-life? The half-life of a drug is known as the time taken for the plasma concentration of a drug to reduce to half its original value. This factor is used to estimate how long it takes for a drug to be eliminated from the body.

The vaccinations sequester free drugs in the periphery which increases plasma rather than brain concentration levels; therefore, the opioid-specific vaccinations were found to prolong drug half-life nearly 68 to 268-fold increase over the unvaccinated animal subjects. The increased half-life in animal subjects is due to increased hapten-protein binding and a decreased rate of hepatic clearance. However, because the vaccinations are neurologically protective from opioids, those under treatment of immunopharmacotherapy do not experience the addictive euphoria from drugs even with a prolonged half-life.

Topic 3.6 Effective dose 50 & self-administration rates

Because the antibodies prevent the drug from entering the brain and attaching to the opioid-receptors, there is a decrease in the drug's neurological impact, so the vaccinations have been found to also provide significant protection from lethal drug doses by reducing overall

potency. Potency can be described in terms of a drugs effective dose, or ED50. The ED50 is the amount of drug required to produce a therapeutic effect in half of the users.

It was concluded that in pre-clinical studies, the ED50 was significantly increased nearly 30-fold in the vaccinated test group of rats. This means that significantly larger doses of an opioid are required to obtain the desired psychoactive effects. The vaccinations cause a shift to the right of a selected opioid's ED50, so the drug's potency and over-dose induced lethality are decreased. Again, by decreasing an opioid's neurological effect, or by requiring a substantially larger amount of opioid intake to achieve the same feeling, self-administration rates and OUD are decreased.

Topic 3.7 Outlook of immunopharmacotherapy and clinical trial progression

In order to have a complete understanding regarding the research on immunopharmacotherapy for OUD, there must be an awareness of not only its mechanism of action and pharmacokinetics, but also its projected future toward approval and potential limitations. By increasing the provider's knowledge base regarding anti-opioid vaccinations, a foundation to continue to follow-up on the literature is created. If treatment progresses to human trials, the provider can update their knowledge and compare the animal findings.

In its current stance of pre-clinical animal trials, despite statistical significance throughout the literature in the success of the vaccinations against OUD, there remain several potential barriers to extensive utilization of these vaccinations. The first is due to regulatory and societal stigmas toward the treatment of opioid addiction as an actual disease.

Secondly, although anti-opioid vaccinations decrease the rate of opioid self-administration in pre-clinical studies, it is unknown if the single-target drug vaccination will decrease the potential for abuse. The concept of treating someone with multiply vaccinations or contaminating a vaccination with an additional opioid-specific hapten is a discussed solution within the literature.

Lastly, there is a lack of financial investment thus far in the immunopharmacotherapy research arena due to the failures of nicotine and cocaine vaccination. These pioneering immunopharmacotherapy studies lacked safety profiling and capability of large-scale vaccine production.

Learning Activity: Immunopharmacotherapy

1. Immunopharmacotherapy is the process by which a disease is prevented or treated by inhibiting the body's immune system. How are the number of available antibodies effected by the therapy?
    a. Decreased

b. Eliminated
c. Increased
d. Unchanged

Answer: C
Objective: 3, Module 3, Topic 3.1

Rationale: Immunopharmacotherapy is the treatment or prevention of a disease by increasing the immune system's functionality. This immune therapy induces a tailored IgG antibody response which then sequester the specific targeted drugs peripherally and prevent them from crossing the blood-brain barrier and eliciting the desired addictive psychoactive effects (Banks et al., 2018; Bremer et al., 2016; Nguyen et al., 2017; Raleigh et al., 2014).

2. Which are the main components of anti-opioid specific vaccine development? (Select 2)
a. Benzene ring
b. Effector T-cells
c. Hapten
d. Large carrier protein

Answer: C & D
Objective: 4, Module 3, Topic 3.2

Rationale: There are several fundamental components to the development of a successful anti-opioid vaccine. Haptens are small molecules that elicit an immune response only when attached or conjugated to a large carrier, like a protein (Olson & Janda, 2018). The vaccinations produce a proliferated T-cell response in the body. Benzene ring is unrelated to the topic discussed.

3. Which of the following is an important component in the development of immunopharmacotherapy vaccinations?
a. Aromatic ring
b. Hapten molecule
c. Lipid bilayer
d. Small carrier-protein

Answer: B
Objective: 4, Module 3, Topic 3.2

Rationale: There are several fundamental components to the development of a successful anti-opioid vaccine, but the hapten is considered an important concept. Haptens are small molecules that elicit an immune response. They are important in the purification and production of antibodies (Olson & Janda, 2018).

4. Which consideration impacts the use of the hapten molecule?
a. A bound, conjugated hapten can trigger an immune response
b. Chicken pox causes blisters due to produced haptens
c. Halothane hepatitis does not involve the hapten concept
d. Haptens cannot elicit an autoimmune response

Answer: A

Objective: 4, Module 3, Topic 3.2 & 3.3

Rationale: A well-known example of a hapten molecule is urushiol, a toxin found in poison ivy. Urushiol is absorbed into the skin and generates the actual hapten through a secondary reactive molecule. Exposure causes effector T-cells, generating an immune reaction. Therefore, a person develops blisters after coming in contact with poison ivy. Interestingly, haptens can also produce autoimmune diseases. Such examples that providers may be familiar with is lupus erythematosus induced by hydralazine and halothane-related hepatitis.

5. In anti-opioid vaccinated rat test subjects, which effects lead to a decrease in opioid-self-administration rates? (Select 2)

a. Decrease in plasma concentration levels
b. Decrease in brain concentration levels
c. Increase in the ED50
d. Increase in opioid potency

Answer: B & C

Objective: 5, Module 3, Topic 3.4 & 3.6

Rationale: The targeted-opioid in the vaccination is sequestered by immunopharmacologic antibodies, so the opioid is prevented from entering the brain and attaching onto its targeted receptor. Within the immunoconjugate vaccinated test group, brain concentration levels of the targeted opioid were nearly 50% lower than the control group who received the same dose of the opioid. It was also concluded that the ED50 was significantly increased nearly 30-fold in the vaccinated test group of rats. The vaccinations cause a shift to the right of a selected opioid's ED50, so the drug's potency and over-dose induced lethality are decreased (Banks et al., 2018; Bremer et al., 2016; Kimishima et al., 2017; Nguyen et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018; Raleigh et al., 2014; Shen et al., 2012).

Module 4. Immunopharmacotherapy applicability to practice

Topic 4.1 Impact on appropriate anesthetic plan development and adequate pain management

Based on the information discussed regarding the pharmacodynamics of the vaccinations, if the targeted opioid is administered to someone who is being treated for OUD with that specific vaccination, the patient's pain will be inefficiently treated. The patient would experience no pain relief because although they were treated with an opioid, the analgesic effects are blocked by elicited antibodies. When pain is undertreated, it can lead to negative health effects and a decreased quality of life.

Knowledge regarding this potential upcoming therapy would, therefore indicate that the provider would recognize the drug interaction. Then, the provider would be able to make an evidence-based decision to incorporate a multi-modal or opioid-alternative approach within their plan of care to effectively relieve pain.

Topic 4.2 Alternative analgesia treatments

Immunopharmacotherapy is specific for a selected opioid, like fentanyl or oxycodone, which is why the provider must be knowledgeable about the impact of the opioid-vaccinations on drug interactions and pain management. So, when caring for a patient who has been treated with immunopharmacotherapy for OUD, it would indicate the use of multi-modal or opioid-alternative treatments.

Multi-modal therapy would ensure that the patient's acute or chronic pain is effectively relieved because when used alone, the opioid would be insufficient in controlling pain in person treated with immunopharmacotherapy for OUD. Furthermore, according to the 2016 National Pain Strategy, multi-modal pain management fully addresses the range of an individual patient's biopsychosocial challenges, by providing various therapies that may include medical, surgical, psychological, behavioral, and integrative approaches as needed.

Opioid-sparing treatments could include alternative pharmacological analgesic classes and regional anesthesia. These techniques would not only avoid the dilemma of administering an ineffective opioid or other potential form of abuse and relapse, but other treatments also result in shortened hospital stays and fewer patient complications. Such examples of multi-modal or pharmacological alternatives to opioids include: acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentin, ketamine, and other adjuvant medications (muscle relaxants, corticosteroids, antidepressants, local anesthetics, alpha-2 adrenergic agonists, and N-methyl-D-aspartate (NMDA) receptor antagonists). These alternative pain management strategies enhance patient-centered care to reduce the surgical stress response and limit the need for non-vaccine specific opioids.

Non-pharmacological strategies can also be encouraged and serve to augment pharmacologic therapy. Similar to the MAT for opioid-abuse, physical modalities and cognitive-behavioral therapy can also be utilized in treatment for acute pain management. Examples of physical modalities include massage, physical therapy, and applications of heat and cold. Cognitive-behavioral therapy can embrace distraction techniques, imagery, music, relaxation, and meditation. Nonpharmacologic interventions have been shown to reduce anxiety, improve mood, improve sleep, increase a person's sense of control over their pain, decrease fatigue, restore hope, and enhance quality of life.

Learning Activity: Patient care & appropriate treatment

1. An anesthesia provider is conducting an anesthesia pre-operative assessment of a patient undergoing a cholecystectomy. During the interview, they find that the patient has a negative health history except-for opioid-addiction, specifically fentanyl. The patient states last month

they started a new treatment of anti-opioid vaccinations. Which medications should the provider consider for their anesthetic plan? (Select 2)

a. Fentanyl
b. Ketorolac
c. Methocarbamol
d. Oxycodone

Answer: B & C
Objective: 6 & 7, Module 4, Topic 4.1 & 4.2
Rationale: Immunopharmacotherapy is specific for a selected opioid, like oxycodone, hydrocodone, or fentanyl (American Addiction Centers, 2018). If the provider chooses the same vaccination-conjugate opioid, a patient's pain would be inadequately treated because the analgesic effects are blocked. Antibodies bind to drug peripherally, preventing the drug from entering the brain and agonizing its analgesic receptors (Banks et al., 2018).

2. An anesthesia provider is providing care for a surgical patient with a negative health history except for oxycodone abuse for which they are receiving immunopharmacotherapy treatment. Which medication should the provider incorporate into their plan of care?

a. Acetaminophen
b. Fentanyl
c. Hydrocodone
d. Oxycodone

Answer: A
Objective: 6 & 7, Module 4, Topic 4.1 & 4.2
Rationale: Immunopharmacotherapy is specific for a selected opioid, like fentanyl or oxycodone. If the same vaccination-conjugate opioid is chosen, a patient's pain would be inadequately treated because the analgesic effects are blocked secondarily by antibodies. Therefore, if the provider is caring for a patient who has been treated with immunopharmacotherapy for opioid-use disorder, it would indicate the use of multi-modal, or opioid-alternative treatments within their care plan. Multi-modal therapy would ensure that the patient's acute or chronic pain is effectively relieved. Opioid-sparing treatments include alternative pharmacological analgesic classes and regional anesthesia. These techniques would avoid the dilemma of administering an ineffective opioid or other potential form of abuse (Griffis et al., 2017; Kimishima et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018).

Module 5. Role of the CRNA

Topic 5.1 AANA

According to the American Association of Nurse Anesthetists, providers have a responsibility to provide safe, quality care for their patients. This process includes a thorough pre-operative assessment, including a comprehensive evaluation of the patient's general health, allergies, current medication use, pre-existing conditions, and prior anesthesia. The pre-operative assessment and evaluation will provide the insight necessary to develop an optimal plan of care and effective post procedure analgesia based on a review of current medications and an understanding of potential side effects and complications.

When obtaining a health history or pre-operative assessment from the patient, it is important to ensure that the provider follows several recommendations when discussing addiction specifically. First, attempt to establish a rapport by being an open ear in listening to their story, use open-ended questions in a non-judgmental fashion because a patient may feel guilt, shame, or fear, assess past problems and treatment attempts, and lastly, listen for any patient concerns about bias or stigma with medical care of an addict.

In addition to being up to date in understanding a patient's medication history, the provider must also grow in their knowledge of new potential treatments. Education for prescriber-capable advanced registered nurse practitioners is supported by both the National Institute of Health and the Food and Drug Administration who emphasize the need to address the insufficient resources specifically regarding OUD and potential treatments. There is a lack of resources regarding upcoming immunopharmacotherapy treatment for OUD. So, this module was developed in order to provide concise information on current research. But, how is the future presence of immunopharmacotherapy directly applicable to providers?

Topic 5.2 Applicability to practice

Lack of knowledge about pain and its treatment can be a major barrier to adequate pain management. In order to provide safe, effective patient care, the provider must be educated on OUD, prescribed treatments, and upcoming therapies. Understanding the possible future drug's pharmacodynamics and its potential impact on pain management is important. An awareness and increased knowledge will allow the provider to make evidence-based decisions in the care and pain management of future patients undergoing immunopharmacotherapy should it receive approval.

Combating OUD and enhancing patient safety can be done through several elements: experience, education, and as just discussed, a multi-modal approach. By taking this module, the provider will already have increased education regarding the opioid-crisis. Furthering the knowledge about potential treatment using immunopharmacotherapy will allow the follow-up on literature as it progresses through clinical trials. Lastly, if the drug gains approval, then the provider will expand their experience caring for patients treated with the vaccinations. As discussed, utilization of multi-modal approach to pain management is the most efficient care.

Learning Activity: Role of the CRNA

1. An anesthesia provider can enhance the safety of their practice, patient care, and combat opioid-use disorder through which actions? (Select 2)
    a. Education
    b. Follow-up interviews

c. Multi-modal approaches
d. Opioid administration

Answer: A & C
Objective: 8, Module 5, Topic 5.1 & 5.2
Rationale: In addition to new abuse-deterrent formulations recommended by the National Institute of Health, the Food and Drug Administration also emphasized the need to address the insufficient education regarding opioid-use disorder and potential treatments by prescriber-capable advanced registered nurse practitioners (Griffis et al., 2017). According to the AANA Code of Ethics (2017), the provider possesses the skill and ability to intervene in the prevention of patient harm. Also, they can enhance the safety of their practice and combat opioid-use disorder through several elements: experience, education, and multi-modal approach (Griffis et al., 2017).

2. According to the American Association of Nurse Anesthetists, advanced registered nurse practitioners have a responsibility to provide safe, quality care for their patients. Which components are part of this process? (Select 2)

a. A knowledge of medications and possible interactions
b. Appropriate health insurance authorization
c. Post-operative assessment
d. Review of current medications

Answer: A & D
Objective: 8, Module 5, Topic 5.1 & 5.2
Rationale: According to the American Association of Nurse Anesthetists (2017), providers have a responsibility to provide safe, quality care for their patients. This process includes a thorough pre-operative assessment, review of current medications, and an understanding of those drugs with possible interactions. This will allow the provider to give the best care and plan accordingly. Obtaining health insurance authorization does not influence the safety of a patient's care.

Module 6. Conclusion

Topic 6.1 Case Study: Anesthetic plan development & pain management for intraoperative patient treated with immunopharmacology

The anesthesia provider is preparing for the next surgical case, a laparoscopic, possible open appendectomy on a 32 years-old male patient. The provider goes to the pre-operative area and begins the assessment and interview. The patient has a negative health history, but when asked about any tobacco, alcohol, or recreation drugs use, he admits to having a prior opioid addiction, specifically abusing fentanyl. He states having been on methadone, but within the past few months, he now goes to his doctor for injections as a new treatment instead.

The provider suspects and confirms that the patient is receiving immunopharmacotherapy, or anti-opioid vaccinations for fentanyl abuse. Knowing this

information, consider the anesthetic plan. Should the provider use fentanyl on induction to blunt airway reflexes? What will be the provider's plan for pain management? Will the provider use fentanyl, could they choose an alternative opioid, or what other modalities could be incorporated to provide this surgical patient with the best, safest care?

Topic 6.2 Rationale of case study

As discussed, the anti-opioid vaccinations utilize hapten-carriers coupled with immunogenic protein complexes which individually target drugs of abuse and their metabolites, like heroin, oxycodone, hydrocodone, or fentanyl. In this case study, the patient has been treated with a fentanyl-conjugate vaccination. If their body is exposed to fentanyl, the produced antibodies in response to the treatment sequester the drug peripherally. There will be an increased plasma concentration and half-life of fentanyl because it is prevented from crossing the blood-brain barrier and eliciting the desired addictive psychoactive effects. So, fentanyl should be avoided because if it is administered to this patient, it will have no analgesic effect.

Although the vaccination is opiate specific, other opioids should be avoided as the patient has a history of related addiction. However, as a last resort, opioids other than fentanyl can be administered for analgesia. Rather, a multi-modal, opioid-sparing treatments for pain should be utilized as best, evidence-based practice. Alternative pharmacological analgesic classes and regional anesthesia can effectively treat pain.

Topic 6.3 Summary

More than half of drug-related deaths in the United States involve opioids, but current treatments for OUD, like non-selective opioid antagonists, have limited success. This epidemic led to the declaration of a state of emergency which increased research on pain and addiction management. Newly developed pre-clinical, immunopharmacotherapy or anti-opioid vaccinations have shown to effectively elicit antibodies against target opioids which prevent the drug from acting on receptors.

But, if the anti-opioid vaccinations are not fully understood by the provider, the patient's pain could be inefficiently treated. So, the use of multi-modal or opioid-alternative treatments is required to effectively relieve pain. In conclusion, increased knowledge, awareness, and follow-up on related literature regarding the potential future therapy is essential!

Module 7. Echelon wrap-up

Appendix D

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Continuing Education & Professional Development

Echelon® Curriculum Chart for Live/Enduring Media
SRNA/AANA – Educational Planning Activity Form

Title of Activity: Immunopharmacotherapy for Opioid-Use Disorder: Applicability to Practice

Identified Gap(s): There is a lack of provider directed educational resources, like CE modules and peer-reviewed journals regarding recent, preclinical immunopharmacotherapy treatment for OUD.

Description of current state: Opioid-use disorder (OUD) has become a national crisis, killing over 100 Americans daily and costing 78 billion dollars annually. Yet, the current therapy for opioid abuse has limited success with the potential for significant side effects, illicit use, costly maintenance, and high attrition rates within the first month. As a result, only 10% of Americans suffering from OUD are receiving treatment, causing OUD to have the highest rate of addiction relapse with an estimated 91% of those in recovery. On the other hand, immunopharmacotherapy, a new treatment for opioid addiction in the pre-clinical phase, elicits an immune response. Immunopharmacotherapy lacks abuse potential and decreases related mortality. But, due to the clinical state of the vaccinations, there are limited resources and knowledge regarding the topic among the health care team.

Description of desired/achievable state: The provider possesses an understanding of immunopharmacotherapy in relation to OUD and are knowledgeable about the impact of the anti-opioid vaccinations on anesthetic care, drug interactions, pain management, and patient safety. An awareness of immunopharmacotherapy pharmacodynamics and their potential impact on pain management allows for appropriate care of patients and necessary follow-up of related literature. Application of this knowledge increases safe, effective patient care because proper care and patient safety begin with improved provider competence of not only their training and skills, but also their knowledge regarding upcoming medications.

Gap to be addressed by this activity: __X__ **Knowledge** __X__ **Skills** __X__ **Practice** _____ **Other: Describe** This course is designed to increase awareness and evidence-based knowledge regarding immunopharmacotherapy treatment for opioid-use disorder, and its impact on patient care. Opioid-use disorder, its current state and treatments, immunopharmacotherapy, its mechanism of action with possible drug-interactions, and the provider's vital role in developing adequate pain management and appropriate anesthetic plans to future patients treated with the anti-opioid vaccinations should they receive approval will be discussed.

Instructional Strategies Used: Enduring material utilizing Provider-directed, learner-paced direct instruction and interactive instruction/activities.

Learning Outcome (s): This course is designed to increase awareness and evidence-based knowledge regarding immunopharmacotherapy treatment for opioid-use disorder, and its impact on patient care. Opioid-use disorder, its current state and treatments, immunopharmacotherapy, its mechanism of action with possible drug-interactions, and the provider's vital role in developing adequate pain management and appropriate anesthetic plans to future patients treated with the anti-opioid vaccinations should they receive approval will be discussed.

Select all that apply: ☒ Nursing Professional Development ☒ Patient Outcome ☐ Other: Describe _____

Outcomes	CONTENT (Topics)	Test Questions	TEACHING METHODS/LEARNER ENGAGEMENT STRATEGIES
List learner's outcomes	Provide an outline of the content		List the learner engagement strategies to be used by Faculty, Presenters, Authors
1. Identify the signs and symptoms of opioid-use disorder.	**Module 2. Clinical problem/significance: Opioid-Use Disorder** Topic 2.1 Define OUD Topic 2.2 Signs & symptoms of OUD	1. According to the Diagnostic and Statistical Manual of Mental Disorders, which is a characteristic of someone with opioid-use disorder? e. Ability to control desire of opioid use f. Capability to fulfill obligations at work g. Development of an opioid tolerance h. Decreased opioid use after psychological problems **Answer: C** **Objective: 1, Module 2, Topic 2.1 & 2.2** *Rationale: The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2018) aid in the recognition of someone with opioid-use disorder as a problematic pattern of opioid-use leading to distress, with at least two of the following*	***Learning Activity: Opioid-use disorder***

		occurring within a 12-month period: Taking larger amounts of drugs or over a longer period than intended, unsuccessful efforts to control opioid use, problems fulfilling obligations at work, school or home, or continued opioid use despite ongoing physical or psychological problem caused by opioids.	
2. Distinguish between current opioid-use disorder treatments and their side-effects.	**Module 2. Clinical problem/significance: Opioid-Use Disorder** Topic 2.3 Current Treatments (Mechanism of action & side effects)	2. Which characteristic is associated with naloxone in comparison to methadone and buprenorphine? e. Complete opioid-receptor agonist f. Competitive opioid-receptor antagonist g. Non-competitive opioid-receptor agonist h. Incomplete opioid-receptor antagonist **Answer: B** **Objective: 2, Module 2, Topic 2.3** *Rationale: Naloxone is a non-selective, competitive opioid receptor antagonist. Methadone is a full agonist, where buprenorphine is a partial agonist. They are associated with illicit use and unfavorable side effects like abused opioids (Banks et al., 2018; Whelan & Remski 2012).* 3. Which is associated with the current treatments for opioid abuse? a. Low associated attrition rates b. Low-cost maintenance clinics c. No illicit use or abuse d. Unfavorable side effects **Answer: D** **Objective: 2, Module 2, Topic 2.3** *Rationale: The current therapy for opioid abuse has limited success with the potential for significant side effects, illicit use, costly*	***Learning Activity: Opioid-use disorder***

		maintenance, and high attrition rates within the first month (Banks et al., 2018; Olson & Janda 2018). 4. Per the Substance-Use Disorder Prevention that Promotes Opioid Recovery and Treatment, medication-assisted treatment effectively combines which elements? (Select 2) a. Avoiding addiction support groups b. Cognitive behavioral therapy c. Gambling as a replacement for opioid use d. Methadone or naltrexone **Answer: B & D** **Objective: 2, Module 2, Topic 2.3** *Rationale: Per the Substance-Use Disorder Prevention that Promotes Opioid Recovery and Treatment, also known as SUPPORT, medication-assisted treatment, or MAT, is considered the best treatment approach for opioid-use disorder. MAT is a comprehensive treatment that combines the use of medications (methadone, naltrexone, or buprenorphine) with counseling and cognitive behavioral therapies (AANA, 2018; HHS, 2017).*	
3. Define immunopharmacotherapy	**Module 3. Immunopharmacotherapy** Topic 3.1 Define immunopharmacotherapy	5. Immunopharmacotherapy is the process by which a disease is prevented or treated by inhibiting the body's immune system. How are the number of available antibodies effected by the therapy? e. Decreased f. Eliminated g. Increased h. Unchanged	***Learning Activity: Immunopharmacotherapy***

		Answer: C **Objective: 3, Module 3, Topic 3.1** *Rationale: Immunopharmacotherapy is the treatment or prevention of a disease by increasing the immune system's functionality. This immune therapy induces a tailored IgG antibody response which then sequester the specific targeted drugs peripherally and prevent them from crossing the blood-brain barrier and eliciting the desired addictive psychoactive effects (Banks et al., 2018; Bremer et al., 2016; Nguyen et al., 2017; Raleigh et al., 2014).* 6. Which research areas were emphasized by the National Institute of Health in order to combat the opioid crisis? (Select 2) a. Continue current overdose-reversal interventions b. Develop new treatments for opioid addiction c. Focus on animal versus human research results d. Identify alternative strategies to safely manage chronic pain **Answer: B & D** **Objective: 3, Module 3, Topic 3.1** *Rationale: The National Institute of Health (NIH), National Science and Technology Council (2018), Center for Disease Control and Prevention (CDC), Substance Abuse and Mental Health Services Administration (SAMHSA), and the World Health Organization (WHO), emphasized the need for provider education and additional research regarding opioid-use disorder: non-opioid alternatives to manage chronic pain, and new treatments for opioid addiction and overdose-reversals (Griffis et al., 2017; HHS, 2017).*	

		7. Vaccinations for which drugs were created during the 1990's? (Select 2) a. Cocaine b. Fentanyl c. Heroin d. Nicotine **Answer: A & D** **Objective: 3, Module 3, Topic 3.1** *Rationale: Immunopharmacotherapy, in general terms is the treatment or prevention of a disease by increasing the immune system's functionality. The concept of anti-opioid vaccinations was first discovered in 1974, when self-administration of heroin by a rhesus monkey was decreased with a conjugate vaccine. However, it was not until the 1990s, when vaccinations for cocaine and nicotine, that the immunopharmacological field reignited interest (American Psychiatric Association, 2019; Olson & Janda, 2018).*	
4. Identify the mechanism of action of immunopharmacotherapy/anti-opioid vaccinations.	**Module 3. Immunopharmacotherapy** Topic 3.2 Mechanism of action & hapten structure/development Topic 3.3 Potential physiological impacts	8. Which are the main components of anti-opioid specific vaccine development? (Select 2) e. Benzene ring f. Effector T-cells g. Hapten h. Large carrier protein **Answer: C & D** **Objective: 4, Module 3, Topic 3.2** *Rationale: There are several fundamental components to the development of a successful anti-opioid vaccine. Haptens are small molecules that elicit an immune response only when attached*	***Learning Activity: Immunopharmacotherapy***

		or conjugated to a large carrier, like a protein (Olson & Janda, 2018). The vaccinations produce a proliferated T-cell response in the body. Benzene ring is unrelated to the topic discussed. 9. Which of the following is an important component in the development of immunopharmacotherapy vaccinations? e. Aromatic ring f. Hapten molecule g. Lipid bilayer h. Small carrier-protein **Answer: B** **Objective: 4, Module 3, Topic 3.2** *Rationale: There are several fundamental components to the development of a successful anti-opioid vaccine, but the hapten is considered an important concept. Haptens are small molecules that elicit an immune response. They are important in the purification and production of antibodies (Olson & Janda, 2018).* 10. Which consideration impacts the use of the hapten molecule? e. A bound, conjugated hapten can trigger an immune response f. Chicken pox causes blisters due to produced haptens g. Halothane hepatitis does not involve the hapten concept h. Haptens cannot elicit an autoimmune response **Answer: A** **Objective: 4, Module 3, Topic 3.2 & 3.3**	***Learning Activity: Immunopharmacotherapy*** ***Learning Activity: Immunopharmacotherapy***

		Rationale: A well-known example of a hapten molecule is urushiol, a toxin found in poison ivy. Urushiol is absorbed into the skin and generates the actual hapten through a secondary reactive molecule. Exposure causes effector T-cells, generating an immune reaction. Therefore, a person develops blisters after coming in contact with poison ivy. Interestingly, haptens can also produce autoimmune diseases. Such examples that providers may be familiar with is lupus erythematosus induced by hydralazine and halothane-related hepatitis (Nijoku et al., 2005).	
5. Understand the pharmacodynamics of anti-opioid vaccinations in pre-clinical animal subjects.	**Module 3. Immunopharmacotherapy** Topic 3.4 Plasma & brain concentration levels Topic 3.5 Drug half-life Topic 3.6 Effective dose 50 & self-administration rates	11. In anti-opioid vaccinated rat test subjects, which effects lead to a decrease in opioid-self-administration rates? (Select 2) e. Decrease in plasma concentration levels f. Decrease in brain concentration levels g. Increase in the ED50 h. Increase in opioid potency **Answer: B & C** **Objective: 5, Module 3, Topic 3.4 & 3.6** *Rationale: The targeted-opioid in the vaccination is sequestered by immunopharmacologic antibodies, so the opioid is prevented from entering the brain and attaching onto its targeted receptor. Within the immunoconjugate vaccinated test group, brain concentration levels of the targeted opioid were nearly 50% lower than the control group who received the same dose of the opioid. It was also concluded that the ED50 was significantly increased nearly 30-fold in the vaccinated test group of rats. The vaccinations cause a shift to the*	***Learning Activity: Immunopharmacotherapy***

		right of a selected opioid's ED50, so the drug's potency and over-dose induced lethality are decreased (Banks et al., 2018; Bremer et al., 2016; Kimishima et al., 2017; Nguyen et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018; Raleigh et al., 2014; Shen et al., 2012). 12. What effects does the pharmacodynamics of anti-opioid vaccinations cause? a. Less opioid is required to produce the desired effect b. The opioid's drug half-life is increased c. There is a decrease in the opioid's ED50 d. There is an increase in the number of blocked opioid receptors **Answer: B** **Objective: 5, Module 3, Topic 3.4, 3.5 & 3.6** *Rationale:* T*he ED50 was significantly increased nearly 30-fold in the vaccinated test group of rats. The vaccinations cause a shift to the right of a selected opioid's ED50, so the drug's potency is decreased. This means more drug is required to produce the desired effect. The opioid-specific vaccinations prolong drug half-life 68 to 268-fold increase over the unvaccinated animal subjects. The targeted-opioid in the vaccination is sequestered by immunopharmacologic antibodies, so the opioid is prevented from entering the brain and attaching onto its targeted receptor. The vaccinations do not cause a direct blockage or antagonist on the opioid-receptors, rather the antibodies bind to the opioid and prevent it from acting on the receptors (Banks et al., 2018; Bremer et al., 2016; Kimishima et al., 2017; Nguyen et al.,*	

		2017; Nguyen et al., 2018; Olson & Janda, 2018; Raleigh et al., 2014; Shen et al., 2012). 13. Where do the antibodies sequester the vaccine-hapten - opioid unit and increase its primary concentration? a. Mu-opioid receptors b. Adipose tissue c. Brain d. Plasma **Answer: D** **Objective: 5, Module 3, Topic 3.5** *Rationale: The vaccinations sequester free drugs in the periphery which increases plasma rather than brain concentration levels (Kimishima et al., 2017). The opioid-specific vaccinations prolong drug half-life 68 to 268-fold increase over the unvaccinated animal subjects (Kimishima et al., 2017). The increased half-life in animal subjects is due to increased hapten-protein binding and a decreased rate of clearance (Kimishima et al., 2017).* 14. When treated with an anti-opioid vaccination, what happens to the effective dose 50 of the selected opioid? (Select 2) a. Decrease in the ED50 of the opioid b. Increase in the ED50 of the opioid c. Shift to the right in the ED50 of the opioid d. Shift to the left in the ED50 of the opioid **Answer: B & C** **Objective: 5, Module 3, Topic 3.6**	

		Rationale: The effective dose (ED50) is the amount of drug required to produce a therapeutic effect in half of the users; it was significantly increased nearly 30-fold in the vaccinated test group of rats. This ED50 shift to the right of the selected opioid decreases drug potency and limits over-dose induced lethality. Self-administration rates in the rat subjects decreased because significantly larger doses of the drug were required to obtain desired psychoactive effects (Bremer et al., 2016; Kimishima et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018).	
6. Distinguish the potential physiological side-effects and impact from treatment with immunopharmacotherapy on opioid analgesics.	**Module 3. Immunopharmacotherapy** Topic 3.3 Potential physiological impacts **Module 4. Immunopharmacotherapy applicability to practice** Topic 4.1 Impact on appropriate anesthetic plan development and adequate pain management Topic 4.2 Alternative analgesia treatments	15. An anesthesia provider is conducting an anesthesia pre-operative assessment of a patient undergoing a cholecystectomy. During the interview, they find that the patient has a negative health history except-for opioid-addiction, specifically fentanyl. The patient states last month they started a new treatment of anti-opioid vaccinations. Which medications should the provider consider for their anesthetic plan? (Select 2) e. Fentanyl f. Ketorolac g. Methocarbamol h. Oxycodone **Answer: B & C** **Objective: 6 & 7, Module 4, Topic 4.1 & 4.2** *Rationale: Immunopharmacotherapy is specific for a selected opioid, like oxycodone, hydrocodone, or fentanyl (American Addiction Centers, 2018). If the provider chooses the same vaccination-conjugate opioid, a patient's pain would be inadequately*	***Learning Activity: Patient care & appropriate treatment*** ***Learning Activity: Patient care &***

		treated because the analgesic effects are blocked. Antibodies bind to drug peripherally, preventing the drug from entering the brain and agonizing its analgesic receptors (Banks et al., 2018). 16. An anesthesia provider is providing care for a surgical patient with a negative health history except for oxycodone abuse for which they are receiving immunopharmacotherapy treatment. Which medication should the provider incorporate into their plan of care? e. Acetaminophen f. Fentanyl g. Hydrocodone h. Oxycodone **Answer: A** **Objective: 6 & 7, Module 4, Topic 4.1 & 4.2** *Rationale: Immunopharmacotherapy is specific for a selected opioid, like fentanyl or oxycodone. If the same vaccination-conjugate opioid is chosen, a patient's pain would be inadequately treated because the analgesic effects are blocked secondarily by antibodies. Therefore, if the provider is caring for a patient who has been treated with immunopharmacotherapy for opioid-use disorder, it would indicate the use of multi-modal, or opioid-alternative treatments within their care plan. Multi-modal therapy would ensure that the patient's acute or chronic pain is effectively relieved. Opioid-sparing treatments include alternative pharmacological analgesic classes and regional anesthesia. These techniques*	***appropriate treatment***

		would avoid the dilemma of administering an ineffective opioid or other potential form of abuse (Griffis et al., 2017; Kimishima et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018). 17. A provider is caring for a patient undergoing immunopharmacotherapy treatment for opioid-use disorder. Which of the following lab values should the provider check, if they are concerned about potential side-effects from the hapten vaccination component? a. Urinalysis b. Calcium c. Liver enzymes d. Magnesium **Answer: C** **Objective: 6, Module 3, Topic 3.3** *Rationale: A well-known example of a hapten molecule is urushiol, a toxin found in poison ivy. Urushiol is absorbed into the skin and generates the actual hapten through a secondary reactive molecule. Exposure causes effector T-cells, generating an immune reaction. Therefore, a person develops blisters after coming in contact with poison ivy. Interestingly, haptens can also produce autoimmune disease. Examples include the potential for lupus erythematosus induced by hydralazine and halothane-related hepatitis. Although these physiological effects from the hapten molecule have not presented in the animal-trail studies, this information should be considered and followed-up if the vaccinations progress to*	

		human trials. Haptens have these known potential side-effects, negatively effecting the hepatic system, so providers should note associated lab values, like liver enzymes, when caring for patients undergoing immunopharmacotherapy treatment (Nijoku et al., 2005).	
7. Incorporate appropriate pain management techniques within an anesthetic plan for surgical patients undergoing immunopharmacotherapy for the treatment of an opioid-use disorder.	**Module 4. Immunopharmacotherapy applicability to practice** Topic 4.1 Impact on appropriate anesthetic plan development and adequate pain management Topic 4.2 Alternative analgesia treatments **Module 5. Role of the CRNA** Topic 5.2 Applicability to practice	15. An anesthesia provider is conducting an anesthesia pre-operative assessment of a patient undergoing a cholecystectomy. During the interview, they find that the patient has a negative health history except-for opioid-addiction, specifically fentanyl. The patient states last month they started a new treatment of anti-opioid vaccinations. Which medications should the provider consider for their anesthetic plan? (Select 2) a. Fentanyl b. Ketorolac c. Methocarbamol d. Oxycodone **Answer: B & C** **Objective: 6 & 7, Module 4, Topic 4.1 & 4.2** *Rationale: Immunopharmacotherapy is specific for a selected opioid, like oxycodone, hydrocodone, or fentanyl (American Addiction Centers, 2018). If the provider chooses the same vaccination-conjugate opioid, a patient's pain would be inadequately treated because the analgesic effects are blocked. Antibodies bind to drug peripherally, preventing the drug from entering the brain and agonizing its analgesic receptors (Banks et al., 2018).*	***Learning Activity: Patient care & appropriate treatment*** ***Learning Activity: Patient care & appropriate treatment***

		16. An anesthesia provider is providing care for a surgical patient with a negative health history except for oxycodone abuse for which they are receiving immunopharmacotherapy treatment. Which medication should the provider incorporate into their plan of care? a. Acetaminophen b. Fentanyl c. Hydrocodone d. Oxycodone **Answer: A** **Objective: 6 & 7, Module 4, Topic 4.1 & 4.2** *Rationale: Immunopharmacotherapy is specific for a selected opioid, like fentanyl or oxycodone. If the same vaccination-conjugate opioid is chosen, a patient's pain would be inadequately treated because the analgesic effects are blocked secondarily by antibodies. Therefore, if the provider is caring for a patient who has been treated with immunopharmacotherapy for opioid-use disorder, it would indicate the use of multi-modal, or opioid-alternative treatments within their care plan. Multi-modal therapy would ensure that the patient's acute or chronic pain is effectively relieved. Opioid-sparing treatments include alternative pharmacological analgesic classes and regional anesthesia. These techniques would avoid the dilemma of administering an ineffective opioid or other potential form of abuse (Griffis et al., 2017; Kimishima et al., 2017; Nguyen et al., 2018; Olson & Janda, 2018).*	

		18. An anesthesia provider, who is unfamiliar with immunopharmacotherapy for fentanyl abuse, administers fentanyl to a surgical patient being treated for abuse with the anti-opioid vaccinations. Which would be a likely reaction for that patient? a. Delirium b. Malignant hyperthermia c. Pain d. Severe hypotension **Answer: C** **Objective: 7 & 8, Module 4 & 5, Topic 4.1 & 5.2** *Rationale: If the opioid that the treatment vaccination is targeted to act upon is administered, then the patient's pain would be inefficiently treated (AANA, 2018; Griffis et al., 2017). Due to formed antibodies, the vaccinations effectively prevent a specific opioid from acting on central receptors and providing analgesic effects (Nguyen et al., 2017; Raleigh, Pentel, & LeSage, 2014).*	
8. Identify the provider's role in opioid-use disorder and immunopharmacotherapy.	**Module 5. Role of the CRNA** Topic 5.1 AANA Topic 5.2 Applicability to practice	19. An anesthesia provider can enhance the safety of their practice, patient care, and combat opioid-use disorder through which actions? (Select 2) e. Education f. Follow-up interviews g. Multi-modal approaches h. Opioid administration **Answer: A & C** **Objective: 8, Module 5, Topic 5.1 & 5.2**	***Learning Activity: Role of the CRNA***

		Rationale: In addition to new abuse-deterrent formulations recommended by the National Institute of Health, the Food and Drug Administration also emphasized the need to address the insufficient education regarding opioid-use disorder and potential treatments by prescriber-capable advanced registered nurse practitioners (Griffis et al., 2017). According to the AANA Code of Ethics (2017), the provider possesses the skill and ability to intervene in the prevention of patient harm. Also, they can enhance the safety of their practice and combat opioid-use disorder through several elements: experience, education, and multi-modal approach (Griffis et al., 2017). 20. According to the American Association of Nurse Anesthetists, advanced registered nurse practitioners have a responsibility to provide safe, quality care for their patients. Which components are part of this process? (Select 2) e. A knowledge of medications and possible interactions f. Appropriate health insurance authorization g. Post-operative assessment h. Review of current medications **Answer: A & D** **Objective: 8, Module 5, Topic 5.1 & 5.2** *Rationale: According to the American Association of Nurse Anesthetists (2017), providers have a responsibility to provide safe, quality care for their*	***Learning Activity: Role of the CRNA***

		patients. This process includes a thorough pre-operative assessment, review of current medications, and an understanding of those drugs with possible interactions. This will allow the provider to give the best care and plan accordingly. Obtaining health insurance authorization does not influence the safety of a patient's care.	

If Live: Note: Time spent evaluating the learning activity may be included in the total time when calculating contact hours.

Total Minutes ____divided by 60=____contact hour(s)

If Enduring:

Method of calculating contact hours:

__X__ **Pilot Study** __X__ **Historical Data** _____ **Complexity of Content** _____ **Other: Describe**_____

Estimated Number of Contact Hours to be awarded: __1___

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