Opioid Analgesics Association with Serotonin Syndrome in Patients Taking Antidepressant Medications

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Abstract

Serotonin syndrome (SS) is a potentially life-threatening condition that is often under-diagnosed in the clinical setting. Serotonin toxicity occurs when there is an excessive amount of serotonin in the body leading to neuronal hyperstimulation. In the United States, there is widespread use of serotonergic psychiatric medications in the general population. This is a particular concern to anesthesia providers, not only in the perioperative setting, where many serotonergic medications are administered, but also in pain clinics where the prescribing of opioids is a common practice. Recent publications, including several case studies, literature reviews, and randomized control trials have indicated that there is an increased risk of SS when opioids are used in patients already taking serotonergic antidepressant medications. Continuing education is vital to the professional development of anesthesia providers and it is imperative to educate not only on potential drug interactions, but the signs and symptoms as well as treatment options for patients that develop SS. Continuing education in the form of online modules provides advantages including self-paced learning, lower cost, and a more comfortable learning environment. The aim of this project was to assess the feasibility of an AdventHealth University (AHU) Student Registered Nurse Anesthetist (SRNA) developed one-hour module on opioid analgesics association with SS in patients taking serotonergic antidepressant medications being approved for continuing education (CE) credit by the American Association of Nurse Anesthetists (AANA). Information was obtained from multiple resources: experts in continuing education, a feasibility study, and professional guidance in writing objectives and test questions, through interviews, both in person and virtually.

Contents

Serotonin Syndrome

Serotonin syndrome (SS) is an under-diagnosed and potentially life-threatening condition (Adler, Charnin, & Quraishi, 2015; Baldo, 2017; Volpi-Abadie, Kaye, & Kaye, 2013). In the perioperative setting, there is an increased risk of SS when opioids are used in patients taking serotonergic antidepressant medications. Further, with the widespread use of serotonergic psychiatric medications in the general population and the changes in the prescriptive authority of Advanced Practice Registered Nurses (APRN) for controlled substances in Florida, it is imperative that anesthesia providers are well informed, not only on potential drug interactions, but the signs and symptoms and treatment options for patients that develop SS. Emphasis should be placed on completing a thorough medication reconciliation prior to surgery, or the prescribing of opioids in a pain clinic, to avoid potential drug interactions.

Significance and Background of Clinical Problem

SS occurs when there is an excessive accumulation of serotonin in the synaptic cleft leading to neuronal overstimulation (Warner et al., 2017). The exact number of cases and deaths related to SS is often under-reported due to misdiagnosis, mild symptoms, and physician unawareness (Beakley, Kaye, & Kaye, 2015). A report by the Toxic Exposure Surveillance System in 2004 revealed that SSRIs caused toxic effects in more than 8,000 people and caused more than 100 deaths (Watson et al., 2005). Recent studies have shown an increased risk of SS when opioids are administered to patients already taking serotonergic medications, including antidepressants. According to the Center for Disease Control and Prevention (2017), antidepressant use has increased by nearly 65% over a 15-year time frame, between 1999-2014. With the increasing number of patients in the United States taking prescribed antidepressants who present for surgery or for treatment at pain clinics, it is important for anesthesia providers to

be able to identify the signs and symptoms of serotonin toxicity and effectively manage, or prevent cases of SS (Adler et al., 2015). An online education module on opioid analgesics and their association with SS, specifically in patients taking serotonergic antidepressant agents, could increase the knowledge base and skills of anesthesia providers to effectively recognize and manage SS.

PICOT Evidence Review Questions

Two questions posed in PICO format have assisted in a systematic review of the literature. The first addresses the clinical problem: In patients prescribed antidepressants (P) does the use of opioid analgesics (I) increase the risk of serotonin syndrome (O)? The second question addresses the intervention: At AdventHealth University (P) what is the feasibility of a Student Registered Nurse Anesthetist (SRNA) developed one-hour online module regarding opioid analgesics association with serotonin syndrome in patients taking antidepressant medications (I) being approved for continuing education by the American Association of Nurse Anesthetists (AANA) (O) by December 2020 (T)?

Search Strategy/Results

The search strategy included the following databases: PubMed, MEDLINE, CINAHL, and Google Scholar. A total of 146 articles were initially retrieved. Five studies were randomized clinical trials (RCTs) and meta-analyses that met the studies inclusion criteria. Inclusion criteria included serotonin syndrome, opioids, serotonergic drugs, antidepressants, and studies within the last 10 years. Key Search Terms and MeSH combinations included: *Serotonin syndrome, opioids, opioid analgesics, serotonin toxicity, drug interactions, antidepressant medications, serotonergic agents,* AND *anti-depressive agents.* The Search Limits were English language, research article, and 10 years.

GRADE Criteria

The grading of recommendations assessment, development, and evaluation (GRADE) criteria was used to assess the quality of the studies while conducting the literature review. Limitations included few RCTs found within the last 10 years, and the most recent literature consisted mostly of case-studies. Methodological flaws included SS being an underreported and misdiagnosed condition. Inconsistencies in the studies included the lack of information regarding the exact dosage of each opioid or serotonergic agent that can potentiate SS. Opioids such as tramadol, fentanyl, methadone, and meperidine are serotonin reuptake inhibitors (SSRIs) and with the concurrent administration of other serotonergic drugs, can lead to SS (Abadie et al., 2015; Adler et al., 2015; Beakley et al., 2015; Rastogi, Swarm, & Patel, 2011; Rickli, Liakoni, Hoener, & Liechti (2018); Smischney, Pollard, Nookala, & Olatoye, 2018; Warner et al., 2017; Werneke, Jamshidi, Taylor, & Ott, 2016). In summary, the quality of evidence is moderate, but the recommendation of a CE module to decrease the knowledge deficit of anesthesia providers regarding the association between SS and opioids administration is high.

Literature Review and Synthesis of Evidence

Several studies have shown an increased risk of SS when opioid analgesics are administered to patients taking prescribed serotonergic antidepressants. SS is caused by excess serotonin in the peripheral and central nervous system **(**Smischney et al., 2018). SS symptoms can range from mild to severe, and failure to treat SS in a timely manner can be life-threatening. Opioids analgesics are drugs that act on the nervous system to relieve pain and are among the most commonly administered drugs in hospitals (Baldo, 2017). Patients taking serotonergic medication, such as serotonergic antidepressants, are at an increased risk of developing SS. Antidepressants are medications prescribed to reduce symptoms of depressive disorders.

Selective serotonin reuptake inhibitors (SSRIs) in particular, are commonly prescribed antidepressants that work by increasing the concentration of serotonin in the synaptic cleft to enhance mood (Warner et al., 2017).

The professional development of healthcare providers and the safety of patients relies on continuing education. Online continuing education modules are interactive educational tools that allow healthcare providers to gain knowledge and skills that contribute to their professional growth**,** stay current in their field, keep their certifications active, and provide quality care for their patients (National Health Career Association, 2019). A primary focus of the AANA, is enhancing the professional competence of healthcare providers (AANA, 2018). This project assessed the feasibility of a SRNA developed one-hour online CE module on opioid analgesics association with SS being approved for CE credits. Feasibility studies are often used to assess the practicality of a proposed project, and, as a CE module has not been developed by an AHU SRNA, a feasibility study was the most appropriate data collection method for this project. The SRNA developed CE module, approved for CE credit by AANA, could potentially fill the gap in knowledge on opioid analgesics association with SS in patient's already taking serotonergic drugs.

Opioids Associated with SS

Although the literature presents several medications that can interact with serotonergic drugs, the primary goal of this synthesis review was to analyze the effects of widely used opioids that interact with the serotonin transporter. The opioid analgesics that were commonly mentioned included tramadol, fentanyl, methadone, and meperidine. This paper will focus on commonly administered or prescribed opioids that are associated with serotonin toxicity in patients already taking serotonergic antidepressants.

Tramadol is a synthetic opioid analgesic medication used to treat moderate to severe pain. Despite tramadol's reputation of having a lower risk for addiction and respiratory depression in comparison with other synthetic opiates, it can still cause other issues (Beakley et al., 2015). Tramadol inhibits serotonin reuptake leading to increased serotonin at the synaptic cleft, therefore, its administration alone can contribute to serotonin toxicity (Adler et al., 2015; Beakley et al., 2015; Rickli et al., 2018; Smischney et al., 2018).

Fentanyl is a short-acting synthetic opioid and is considered to have an association with SS (Abadie et al., 2015; Adler et al., 2015; Beakley et al., 2015; Koury et al., 2015; Rastogi et al., 2011; Rickli et al., 2018; Smischney et al., 2018; Warner et al., 2017). Rickli et al. (2018) stated that although fentanyl did not interact with the serotonin in vitro, it was still linked to SS.

Methadone is a synthetic piperidine opioid (Rastogi et al., 2011). Methadone is also considered an inhibitor of serotonin reuptake and has been associated with SS (Beakley et al., 2015; Rastogie et al., 2011; Rickli et al., 2018; Smischney et al., 2018; Werneke et al., 2016).

Meperidine is a synthetic piperidine opioid used for the short-term management of pain and often used by emergency clinicians (Baldo, 2017). Meperidine has also been considered a potent inhibitor of serotonin reuptake for the last 36 years (Baldo, 2017). According to Smischney et al. (2018), Warner et al. (2017), and Werneke et al. (2016), meperidine has been associated with SS. Adler et al. (2015), Rastogi et al. (2011), and Rickli et al. (2018) stated that meperidine might cause SS when combined with other serotonergic medications.

Diagnosis & Treatment

The classic triad presentation of SS is autonomic dysfunction, neuromuscular excitation, and altered mental status (Volpi-Abadie et al., 2013). Autonomic dysfunction typically presents as hypertension, tachycardia, tachypnea, diaphoresis, vomiting, diarrhea, and hyperthermia.

Neuromuscular excitation presents as tremors, clonus, hyperreflexia, muscle rigidity, and akathisia. The last sign in the classic triad is altered mental status, which can appear as anxiety, restlessness, confusion, or disorientation (Volpi-Abadie et al., 2013). While there is no specific diagnostic test for SS, there are three diagnostic classification systems available including the Sternbach Criteria, Radomski Criteria, and Hunter Criteria (HC) (Baldo, 2017; Werneke et al., 2016). Of these, HC was found to be more sensitive and specific of clinical features to diagnose SS (Dunkley, Isbister, Sibbritt, Dawson, & Whyte, 2003) A patient meets HC when they are taking a serotonergic agent and experience neuromuscular symptoms such as clonus, tremor, hyperreflexia, diaphoresis, and temperature more than 38 degrees Celsius (Baldo, 2017). The treatment for SS includes discontinuing all serotonergic agents, maintaining adequate oxygenation and hemodynamics, initiating cooling measures, sedating with benzodiazepines, and administering serotonin antagonists such as cyproheptadine. For severe symptoms, an esmolol or nitroprusside drip can be administered for severe hypertension and tachycardia. Intubation may be required to support the airway and may lead to an admission to the intensive care unit. After adequate treatment, SS is usually resolved within 24 hours (Volpi-Abadie et al., 2013).

In 1999, a survey confirmed that 85% of physicians were unaware of SS (Mackay, Dunn, & Mann, 1999). SS untreated, can lead to severe consequences that include rhabdomyolysis, acute renal failure, disseminated intravascular coagulopathy, and death (Adler et al., 2015). More recently a study by Takata et al. (2019) stated that among anesthesiologist, serotonin syndrome is not widely recognized compared to malignant hyperthermia (MH) and neuroleptic malignant syndrome (NMS). Providers should always review their patient's medications, and if possible, prescribe an opioid medication that will have less drug to drug interactions or weigh the risk and benefits. Opioids that are phenanthrenes analogues such as morphine, hydromorphone,

oxymorphone, and buprenorphine do not act as direct SSRIs and are considered safe analgesics for patients taking prescribed serotonergic antidepressants **(**Adler et al., 2015; Beakley et al., 2015; Rastogi et al., 2011; Rickli et al., (2018); Warner et al., 2017) Analgesia education is essential and patients should be aware of side effects of opioids and potential drug interactions when taking psychiatric serotonergic medications (Abadie et al., 2015; Adler et al., 2015; Beakley et al., 2015; Rastogie et al., (2011); Rickli et al., 2018; Smischney et al., 2018).

Project Aims

The primary aim of the proposed project was to assess the feasibility of an AHU SRNA developed one-hour CE module on opioid analgesics association with SS in patients taking serotonergic antidepressants being approved for CE credits by the AANA. The specific objectives of this scholarly project were:

Objective 1: Identify the budget and resources needed for project development by conducting interviews by June 2019.

Objective 2: Develop an evidence based one-hour CE module with Echelon (including obtaining expert guidance on writing clear objectives and test questions) on opioid analgesics association with serotonin syndrome by April 2020.

Objective 3: Submit CE module and application for CE credit approval with the AANA by June 2020.

Objective 4: Complete a written feasibility report identifying limitations and making recommendations to assist with decision-making regarding the project's viability and implications to the university by March 2021.

Methods

The proposed project was a feasibility study taking place at AdventHealth University, specifically Echelon, a division of AHU specializing in online continuing education and training, integrating course design and media development incorporating the highest credentialing standards (Echelon, 2019). The design for this feasibility study has been adopted from business models, in which feasibility studies are commonly used to determine a project's viability. A feasibility study using a qualitative, process analysis approach was the best method for this project, as a SRNA developed CE module, especially one approved for CE credit by the AANA, is a nascent process.

Conducting a feasibility study involved obtaining information from multiple resources at several different times throughout the project. The students met with key players to identify potential barriers and facilitators to implementing their project, including Echelon, AANA, and individuals with experience in feasibility studies and CE module project development. All of the data collection was through interviews, meetings, and emails, thus, there is no pre-determined sample size. The students obtained verbal consent from the interviewees to audio record the interviews so the students can reference them as needed. The recordings and email interactions were stored on the student's personal laptops, which are password protected and can only be accessed by the students conducting the study. The data from audio recorded interviews will be destroyed from personal laptops after 5 years. As human subjects were not involved in this project, there were no ethical considerations, such as obtaining informed consent.

The CE module transcript was developed and distributed through the AHU Echelon platform. The students worked closely with the accreditation team at Echelon providing transcripts and revisions of the CE module as necessary throughout the development process. Test questions as well as objectives for the module were face validated and reviewed by experts.

The face validated questions will not be administered to end-users of the module, as this study was a narrative feasibility assessment.

Throughout the CE module development process, the students gathered data including any barriers and facilitators encountered and evaluated costs and resources needed throughout the project's timeline. An outline of the anticipated project timeline can be found in Appendix B. The information gathered from this feasibility study was then used as an analytical tool that included recommendations and limitations, which are then utilized to assist the decision-makers when determining if the project was viable. The proposed project's viability could impact future CE module development by SRNAs which could potentially generate revenue and recognition for the institution.

Planning and Procedures

Planning was essential in project development. In addition to completing a literature review on the topic, the students identified key stakeholders including Lori Polizzi, Director of Echelon, Dr. Martin Rivera, AHU faculty member and CRNA, as well as Dr. David Greenlaw, founder and former president of AHU. Several interviews were conducted to identify barriers and facilitators to implementing the project as well as the resources needed to help with the project's success. A module outline was developed and presented to Echelon's accreditation committee who determined the value of the CE module activity. Once the topic was approved by Echelon, the development of the CE module transcript began, which also included expert assistance by Charlotte Henningsen on writing objectives and test questions. The test questions were face validated and the CE module was reviewed by subject matter experts (SMEs) and continuing education experts. After several revisions to the CE module transcript, the Echelon accreditation team determined the module was ready for submission to the AANA. The

accreditation committee, along with Echelon director, Lori Polizzi, then assisted the students with submitting the module to the AANA for approval for CE credits.

Some of the barriers encountered during the student's feasibility study included time, communication, and organization of documents required for CE module submission to AANA. Students had to remain diligent in communication with Echelon, often requiring multiple emails or meetings. As the students had projected timelines for the study, it was important to stay organized and use time wisely to stay on track. A facilitator for the student's project was Lori Polizzi, who guided the students through the module creation process and provided expert advice, however, at times it was difficult to receive timely feedback from Echelon. A major variation in the project timeline included the anticipated date for submission to AANA. Issues that delayed submission to AANA included: multiple revisions made to the CE module transcript, time to hear back from Echelon's accreditation team, and ever-changing documents required by AANA. Thus, the projected date of submitting to AANA in June of 2020 did not occur until October 2020. The completed project timeline can be found in Appendix C.

Results/Findings

CE module development had not been done by an SRNA before, thus, this was a new process in which we were assessing if it was feasible. Collaboration with different departments to understand the costs, human resources, and technological resources needed was challenging.

The students worked closely with Echelon's accreditation team and were in communication with Lori Polizzi frequently throughout the project. The student's original timeline (Appendix B) did not align with the completed timeline of events (Appendix C) due to communication delays with Echelon, and changes with the AANA CE application documentation requirements. For example, our original scheduled date to submit to AANA was

July 8, 2020. However, documents that were originally sent to AANA in PDF format were then requested in Word format. Documents required for AANA CE module submission required collaboration with Echelon, the Project Chair, and Project Mentor, including documents such as Conflict of Interest, Curriculum Vitae, and a biography. These documents that had previously been submitted to Echelon were requested again in August 2020, and delayed submission to AANA further. Thus, organization of documents/steps for the AANA application process in collaboration with Echelon is essential. IRB/SRC submission was not indicated for this project due to the lack of human subjects, as the students are not having end-users take the module pre or post-test as part of this study. Approval of the CE module transcript by the Echelon accreditation committee was time consuming, involving multiple revisions and submissions and took six months to complete. On October 13, 2020, the students completed application and CE module transcript was submitted to AANA and on November 23, 2020 the module was approved for accreditation by the AANA for CE credit in the Pharmacology/Therapeutics category.

Applicability to Practice/Contribution to Professional Growth

Anesthesia providers have a great responsibility to provide safe, high-quality care for their patients. This starts with a thorough assessment, including a review of the patient's current medications. Many prescription medications can lead to increased serotonergic activity and place the patient at higher risk for serotonin toxicity (Warner et al. 2017). Additionally, as nurse anesthetists in Florida now have prescriptive authority, the prescribing of opioids in patients already taking serotonergic medications must be done carefully, whether it be in the surgical setting or seeing a patient for pain services. In April 2016, house bill (HB) 423 was passed allowing graduate-level ARNPs to prescribe controlled substances within the state of Florida under the supervision of a physician. HB 423 allows ARNPs prescribing privileges for controlled

substances listed in Schedule II, limited to a seven-day supply and does not include the prescribing of psychotropic medications for children under 18 years of age unless prescribed by an ARNP who is a Psychiatric Nurse (Florida Board of Nursing, 2016). As more providers obtain prescriptive authority, the need for education and awareness regarding the life-threatening risks of prescribing opioids and serotonergic antidepressants concomitantly is ever-present.

Proper patient education must include appropriate medication administration and safe dosages, as well as signs and symptoms of which to be cognizant. Although the number of RCTs on opiates association with SS in patients on serotonergic antidepressants in the literature is lacking, the ample amount of case studies reporting misdiagnosis and potential for patient harm or death confirm the knowledge deficit in healthcare professionals and the need for education.

Conclusions & Limitations

CE module development has not been done by an SRNA before, thus, this was a new process in which we were assessing if it was feasible. Collaboration with different departments to understand the costs, human resources, and technological resources needed was challenging. There are several areas where limitations were identified. To start, when conducting the literature review, a limited amount of RCTs within the last 10 years were found. Additionally, there was limited information available in the literature regarding feasibility studies. Time was another major limitation as it took six months for the CE module transcript to be approved by the Echelon accreditation committee, as well as another month to get approved by the AANA. CE module development in itself is time costly, requiring multiple transcript revisions and the approval of several reviewers, including subject matter experts (SMEs). Communication proved to be another limitation as it often took several weeks, sometimes months, to get a response back.

Professional development is a lifelong activity for nurse anesthetists. An online CE module on the potential risk of SS when opioids are used in patients already taking serotonergic antidepressants could provide anesthesia personnel the knowledge and skills to properly identify SS and how best to care for patients experiencing serotonin toxicity. The CE module would also educate providers on how to differentiate between other common syndromes such as malignant hyperthermia and the neuroleptic malignant syndrome that closely resemble SS using the more widely used diagnostic tool, HC (Werneke et al., 2016). Online CE modules are not only convenient and cost-effective but allow for the education of the community as a whole, rather than within one's institution alone. Additionally, the feasibility of this project could aid AHU SRNAs in future scholarly projects that involve CE module development with Echelon and the AANA.

Dissemination Plan

The student's project was disseminated on the national level by submitting the completed CE module transcript and application to the AANA. On November 23, 2020, the module was approved by the AANA for one CE credit in Pharmacology/Therapeutics under the "Anesthetic Complications" category and is effective through December 31, 2023. The online program also met the guidelines/criteria for accreditation with the Florida Board of Nursing, American Nursing Credentialing Center, and the California Board of Registered Nursing, for one CE credit. The team at Echelon will develop the enduring media from the module transcript which will then be available on the Echelon website for users to complete and receive continuing education credit. In the Spring of 2021, the student's project, including the written feasibility report (Appendix D), will be disseminated as a poster presentation and narrated online PowerPoint presentation through the AHU website.

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Appendix A
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Purpose	Variables	Setting/Subjects	Measurement and Instruments	Results	Evidence Quality
Study One: Systematic review of all cases of serotonin syndrome (SS) and toxicity published between 2004-2014, using Pubmed and Web of Science. **Study Two:** To determine the potencies of different opioids to inhibit the SERT and NET in vitro using human transporter-transfected HEK293 cells. Also, assess clinical cases of SS associated with each opioid. **Design** **Study One**: Systematic review and meta-analysis. **Study Two:** Retrospective analysis and Test-tube lab research.	**Study One:** **Primary outcome:** Serotonin syndrome reports from case studies. **Study Two:** **Primary Outcome:** Incidence of Serotonin Syndrome by HEK293 cells.	**Study One:** **Setting:** Department of Clinical Sciences. Umea, Sweden **Subjects:** Case studies from 2004-2014 using Pubmed and Web of Science. Total of 299 cases. **Study Two:** **Setting:** Division of Clinical Pharmacology and Toxicology, University Hospital Basel located in Basel, Switzerland. **Subjects:** In vitro using human transporter-transfected HEK293 cells.	**Study One:** Three diagnostic classification systems: Sternbach (SC), Radomski (RC), and Hunter criteria (HC). **Study Two:** Hunter Criteria and Sternbach Criteria.	**Study One:** Combination antidepressant-opiate 16.1%, overdoses 15.4%, combination antidepressant with another potentially serotonergic agent 13%, and combination of different antidepressants 7.7% **Study Two** The opioids that were most frequently reported in association with SS either alone or in combination with other drugs (e.g. SSRIs) were tramadol, fentanyl, tapentadol, oxycodone, methadone, and dextromethorphan. **Implications** **Study One:** "It is important to withhold drugs likely to cause serious adverse effects. On the other hand, it is important not unnecessarily to withhold medicines patients need for exaggerated fear of SS". **Study Two:** Some synthetic opioids interact with the SERT and NET at potentially clinically relevant concentrations. SERT inhibition by tramadol, tapentadol, methadone, dextromethorphan, and pethidine may contribute to the serotonin syndrome. Direct effects on 5-HT1A and/or 5-HT2A receptors could be involved with methadone and pethidine.	**Study One:** **Methodological flaws:** None **Inconsistency:** Different hypothesis and diagnostic systems. **Indirectness:** No information about which opiates caused the highest risk of SS. **Imprecision:** Not specific about dosages of drugs that caused SS. **Publication bias:** No **Study Two:** **Methodological flaws:** **Inconsistency:** Underreporting is common, and the true incidence of SS can't be estimated from the present data. **Indirectness:** No **Imprecision:** No **Publication bias:** No

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Abadie, D., Rousseau, V., Logerot, S., Cottin, J., Montastruc, J., & Montastruc, F. (2015). Serotonin syndrome: Analysis of cases registered in the French pharmacovigilance database. *Journal of Clinical Psychopharmacology, 35*(4), 382. https://doi.org/10.1097/JCP.0000000000000344

Purpose	Variables	Setting/Subjects	Measurement and Instruments	Results	Evidence Quality
Study One: To test whether opioids or ketamine inhibit the human 5-HT transporter and whether this increases free plasma 5-HT concentrations. **Study Two:** To analyze characteristics of SS French pharmacovigilance reports, especially involved drugs and nature of drug-drug interactions **Design** **Study One:** Test-tube lab research. Uptake in vitro and on the plasma 5-HT. **Study Two:** Retrospective analysis of SS.	**Study One:** **Primary outcome:** Serotonin Syndrome by increase concentration in free plasma. **Study Two:** **Primary outcome:** Serotonin syndrome occurrences.	**Study One:** **Setting:** Department of Anesthesiology and Intensive Care Medicine. The University of Bonn. Bonn, Germany. **Subjects**: Transfection and cell culture **Study Two:** **Setting**: Department of Medical and Clinical Pharmacology in Toulouse, France **Subjects:** Retrospective analysis of SS cases registered in the French pharmacovigilance database between January 1, 1985, and May 27, 2013. Total cases: 203.	**Study One:** 5-HT uptake in HEK293 cells and 5-HT uptake in platelets **Study Two:** Three diagnostic classification systems: Sternbach (SC), Radomski (RC), and Hunter criteria (HC). **Results** **Study One:** Tramadol, pethidine, and ketamine (high dose) there was an increase in plasma 5-HT concentrations. In contrast, alfentanil, fentanyl, morphine, and hydromorphone at concentrations up to 10 µM had no effect on free 5-HT plasma concentration 5 min after the addition of 100 nM 5-HT.	**Study Two:** non-psychotropic medications were also involved, generally opioids (14.8%, mainly tramadol). Most of the cases (59.2%) resulted from pharmacodynamic DDIs, most often involving SRIs + opioids (mostly paroxetine + tramadol) Other opioids: tramadol (20), dextropropoxyphene (5), methadone (3), fentanyl (2), and remifentanil (1). **Implications** **Study One:** Effects on human 5-HT plasma levels ex vivo are corresponding: drugs which inhibit the transporter in vitro such as tramadol and pethidine (but not alfentanil, fentanyl, hydromorphone, and morphine) also caused an increasee of free plasma 5-HT by inhibition of 5-HT uptake in platelets. It has to be determined whether these effects contribute to serotonin-mediated adverse events. **Study Two:** This is the first study about SS based on a large pharmacovigilance database and published in English. The results revealed not only the frequent involvement of antidepressants and tramadol, the importance of DDIs (both pharmacodynamic and pharmacokinetic), but also the significant risk of SS even with a single serotonergic drug used at the normal dose.	**Study One:** **Methodological flaws:** No **Inconsistency:** No **Indirectness:** No **Imprecision:** No **Publication bias:** No **Study Two:** **Methodological flaws:** No **Inconsistency:** **Indirectness:** No **Imprecision:** No **Publication bias:** No

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Koury, K. M., Tsui, B., & Gulur, P. (2015). Incidence of serotonin syndrome in patients treated with fentanyl on serotonergic agents. *Pain Physician, 18*(1), E27. Retrieved from https://www.painphysicianjournal.com/linkout?issn=1533-3159&vol=18&page=E27

Purpose	Variables	Setting/Subjects	Measurement and Instruments	Results	Evidence Quality
Study One: To fix the mistake in previous diagnosis and bring awareness of the incidence of perioperative serotonin syndrome (SS) has transitioned from a rare diagnosis to one that should be considered as a differential diagnosis for any patient displaying signs of neuroexcitation. **Study Two:** To understand the incidence of serotonin syndrome in patients who receive fentanyl while on serotonergic agents. **Design** **Study One:** A case study. **Study Two:** Retrospective analysis from 2012-2013. Chart review.	**Study One:** **Primary:** Incidence of SS in the perioperative setting. **Study Two:** **Primary:** incidence of SS as diagnosed using the Hunter Serotonin Toxicity Criteria. **Secondary:** Pts exhibiting s/s of SS.	**Study one:** **Setting:** Department of Anesthesiology and Perioperative Medicine, Rochester, MN. **Subjects:** A 70-year-old man (ASA 2) with a history of benign prostatic hyperplasia, vestibular migraines (treated with high-dose venlafaxine), and gastroesophageal reflux disease presented to the outpatient surgery center for a planned green-light photo-selective vaporization of the prostate. **Study Two:** **Setting**: 900 bed tertiary care academic center (Massachusetts General Hospital). **Subjects:** 112,045 pts on serotonergic agents, 4,538 of them treated with both fentanyl & a serotonergic agent.	**Study One:** The anesthesia team felt confident diagnosing the patient's symptoms as serotonin syndrome secondary to fulfilling the Hunter Criteria. **Study Two:** The Hunter Serotonin Toxicity Criteria.	**Study One:** Upon awakening after the procedure, the patient had myoclonic jerks in bilateral upper and lower extremities. To treat for possible postoperative shivering, meperidine 25 mg was administered intravenously. The myoclonic jerks became worse, and hypertonia increased after receiving meperidine. **Study Two:** Over 2yr period: 112,045 pts on serotonergic agents, 4,538 of them treated with both fentanyl & a serotonergic agent. 23 pts had some symptoms but only 4 [95% CI 1-10] of these pts truly met criteria for SS. 5 additional cases of SS were found, but none of these patients were treated with fentanyl. **Implications** **Study One** Patient with a history of rigidity/movement disorders during the perioperative period may have experienced serotonin toxicity. It is possible, for this history to have been labeled as an allergy to a perioperative medication. Clinicians should remain vigilant for patients at risk of developing SS, such as those taking outpatient medications that increase neuronal serotonin. **Study Two:** The incidence of SS in patients who receive both fentanyl & a serotonergic agent is low.	**Study One:** **Methodological flaws:** This was a case study. **Inconsistency:** Pt had previous "allergy" of propofol and propofol was given on induction. **Indirectness:** No **Imprecision:** No **Publication bias:** No **Study Two:** **Methodological flaws/limitations:** Represents a single institution, although it is a large academic center. Underdiagnosis of serotonin syndrome. Unable to further study the association of a number of agents used, dose, or duration of therapy as potential risk factors due to the small number of cases that could support an association. **Inconsistency:** No **Indirectness:** No **Imprecision:** No **Publication bias:** None

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Rastogi, R., Swarm, R. A., & Patel, T. A. (2011). Case scenario: Opioid association with serotonin syndrome. *Anesthesiology,* 130(6), 3-11 https://doi.org/10.1097/ALN.0b013e31823940c0

Purpose	Variables	Setting/Subjects	Measurement and Instruments	Results	Evidence Quality
Study One: To describe the occurrence of serotonin syndrome (SS) after fentanyl use in two patients taking multiple serotonergic agents. **Study Two:** To illustrate the concern of potential iatrogenic adverse interactions of serotonergic drugs with commonly prescribed opioids in chronic pain pts **Design** **Study One:** Two case studies **Study Two:** Two case studies	**Study one:** **Primary outcome:** incidence of serotonin syndrome. **Secondary:** management of SS with naloxone administration. **Study two:** **Primary:** identification & diagnosing SS. **Secondary:** Treatment options, management of SS symptoms.	**Study one:** **Setting:** Case #1: Outpatient facility Case #2: Outpatient dental facility **Subjects:** Case #1: 72y/o male taking multiple serotonergic medications Case #2: 19y/o male taking multiple serotonergic medications **Study two:** **Setting:** Case #1: pain clinic Case #2: emergency department **Subjects:** Case #1: 45y/o male with chronic pain on multiple serotonergic medications Case #2: 58y/o male with chronic pain on multiple serotonergic medications.	**Study one:** The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. **Study two:** The two most commonly used criteria for diagnosing SS are: Sternbach's Criteria (sensitivity 75%, specificity 96%) & The Hunter Serotonin Toxicity Criteria (sensitivity 84%, specificity 97%t).	**Study one:** Case #1: SS developed immediately after fentanyl administration and resolved promptly with naloxone administration Case #2: The presentation of serotonin syndrome was delayed after the administration of fentanyl possibly because of concomitant administration of a large dose of midazolam. **Study two:** Case #1: After discontinuing pts duloxetine and reducing methadone dose, symptoms resolved within 2 days. Case #2: Replacement of serotonergic opioids (fentanyl & oxycodone) with non-serotonergic opioids (morphine) despite continuation of other serotonergic agents (resulted in complete resolution of SS symptoms. **Implications** **Study one:** Anesthesiologists must consider the compounding serotonergic effects of fentanyl (& other opioids) when it is administered to pts taking serotonergic medications and herbal supplements & have a heightened vigilance for the signs and symptoms of SS. **Study two:** Early & accurate diagnosis, d/c of suspicious offending agents leads to resolution of S/S w/in 24hrs.	**Study one:** **Methodological flaws:** no methods used- this was a review of two case studies **Inconsistency:** No Naloxone was used as an effective treatment in one of the cases but not the other. **Indirectness:** None **Imprecision:** None **Publication bias:** None **Study Two:** **Methodological flaws:** no methods used- this was a review of two individual case studies. In the second case, the patient was misdiagnosed on two occasions, implying the limitations & complexities in the diagnosis of SS and lack of awareness among clinical practitioners. **Inconsistency:** No **Indirectness:** No **Imprecision:** No **Publication bias:** No

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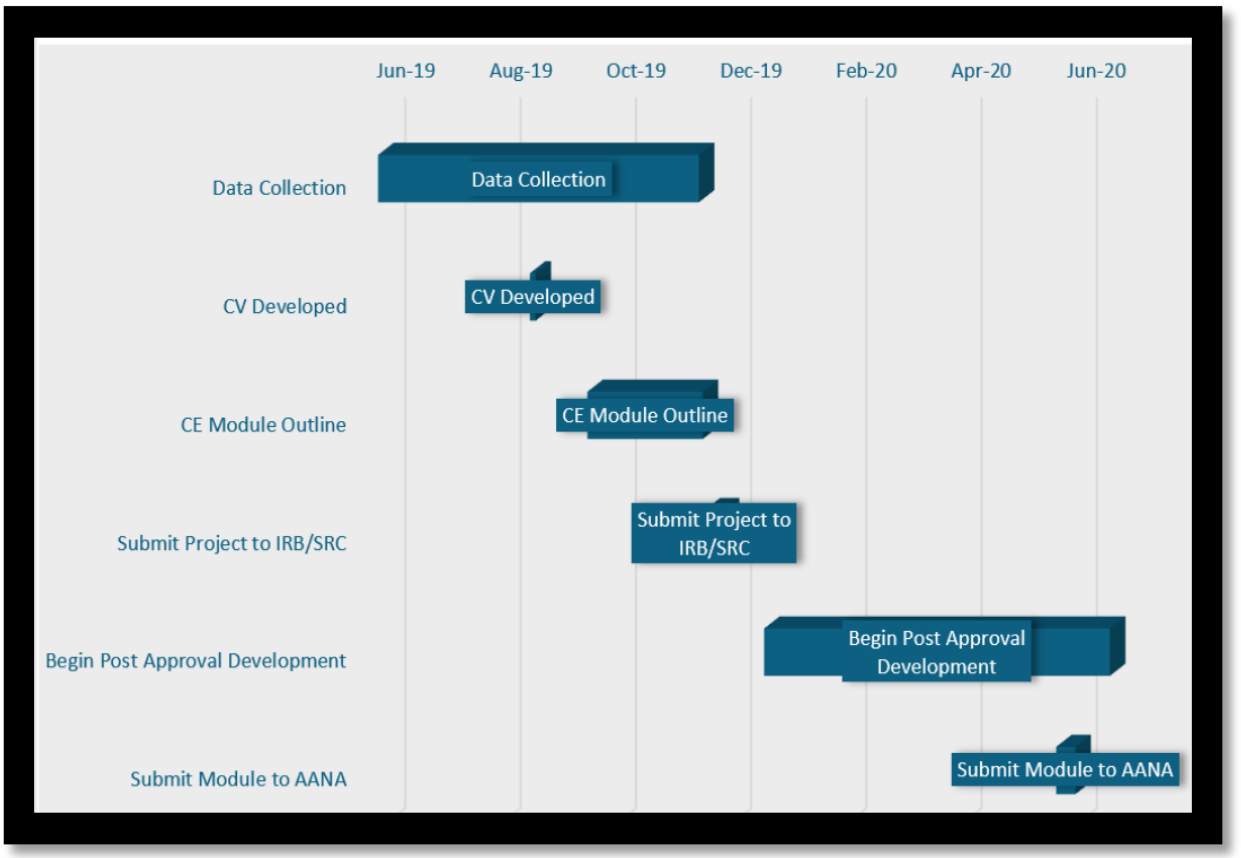
Beakley, B. D., Kaye, A. M., & Kaye, A. D. (2015). Tramadol, pharmacology, side effects, and serotonin syndrome: A review. *Pain Physician, 18*(4), 395. Retrieved from https://pdfs.semanticscholar.org/2203/7814fb97947e3e12983cdd38b6ed35695e4b.pdf

Purpose	Variables	Setting/Subjects	Measurement and Instruments	Results	Evidence Quality
Study One: To recognize the importance of interactions between selective serotonin reuptake inhibitors (SSRIs) and common perioperative medications that may trigger SS. **Study Two:** To make physicians more alert and aware of the potential side effect of SS in patients prescribed tramadol. **Design** **Study One:** One case study review **Study Two:** Review article	**Study one:** **Primary:** Development and diagnosis of SS from the interaction between fluoxetine and a combination of perioperative medications (Zofran, fentanyl, methylene blue, Reglan, and Flagyl). **Secondary:** Treatment for SS after misdiagnosis of malignant hyperthermia (MH). **Study Two:** **Primary Outcome:** Pts taking tramadol are at increased risk of SS. **Secondary outcome:** Poor metabolizers of tramadol are at risk for elevated tramadol levels, associated with serotonergic activity.	**Study one:** **Setting:** Massachusetts General Hospital **Subjects:** Caucasian male in his 20's scheduled for an emergent laparoscopic appendectomy. Pt was on fluoxetine 40mg daily. **Study Two:** **Setting**: Louisiana State University School of Medicine, New Orleans, LA. **Subjects**: Patient's taking tramadol and SSRIs.	**Study One:** Pt demonstrated postoperative hyperthermia and ocular clonus, therefore satisfying the Hunter Criteria Decision Rules. **Study Two:** Describes how diagnosis by a medical toxicologist is the gold standard. Explains importance of thorough history and physical/neuro exam. Diagnostic criteria including the Hunter Serotonin Toxicity Criteria has replaced the originally used Sternbach Criteria d/t increased sensitivity & specificity.	**Study One:** The patient was treated initially with dantrolene d/t concerns for MH, then after persistent fevers, treated with cooling blankets and cyproheptadine after suspecting SS d/t pts history of taking fluoxetine daily and medications used intraoperatively. **Study Two:** The concurrent use of SSRIs with tramadol has been shown to induce SS through synergistic serotonergic action, along with CYP2D6 inhibition, increasing levels of tramadol enantiomer associated with serotonergic activity. **Implications** **Study One:** SS is often underrecognized and may be confused with MH or neuroleptic malignant syndrome (NMS). Awareness of risks, signs and symptoms, and treatment options of SS for anesthesia providers is crucial given the increasing prevalence of SSRI use in the general population. **Study Two:** With the increasing incidence of SS, prescribing physicians should be aware of and educate their patients on the potential s/e of tramadol, especially if patient is already taking serotonergic drugs.	**Study One:** **Methodological flaws:** no methods, as this was a review of a single case study **Inconsistency:** No **Indirectness:** No **Imprecision:** No **Publication bias:** No **Study Two:** **Methodological flaws:** None, this was a review of tramadol pharmacology and its concern when concurrent use of SSRIs. **Inconsistency:** None **Indirectness:** No **Imprecision: No** **Publication bias:** No

Appendix B

GANTT Chart (Anticipated Timeline)



Appendix C

Completed Project Timeline

FEASIBILITY REPORT

Opioid Analgesics Association with Serotonin Syndrome in Patients Taking Antidepressant Medications

Jennifer Huddlestun, BSN, RN, SRNA & Joselline Garcia, BSN, RN, SRNA

PROJECT FEASIBILITY REPORT

Executive Summary

Serotonin syndrome (SS) is a potentially life-threatening condition that is often under-diagnosed in the clinical setting. Serotonin toxicity occurs when there is an excessive amount of serotonin in the body leading to neuronal hyperstimulation. In the United States, there is widespread use of serotonergic psychiatric medications in the general population. This is a particular concern to anesthesia providers, not only in the perioperative setting, where many serotonergic medications are administered, but also in pain clinics where the prescribing of opioids is a common practice. Recent publications, including several case studies, literature reviews, and randomized control trials have indicated that there is an increased risk of SS when opioids are used in patients already taking serotonergic antidepressant medications. As continuing education is vital to the professional development of anesthesia providers, it is imperative to educate not only on potential drug interactions, but the signs and symptoms as well as treatment options for patients that develop SS. Continuing education in the form of online modules provides advantages including self-paced learning, lower cost, and a more comfortable learning environment. This feasibility report will outline the nascent process of an AdventHealth University (AHU) Student Registered Nurse Anesthetist (SRNA)-developed online education module as well as the process of submitting to a national organization for accreditation.

Background of the Study

Professional development is a lifelong activity for nurse anesthetists. An online CE module on the potential risk of SS when opioids are used in patients already taking serotonergic medications could provide anesthesia personnel the knowledge and skills to properly identify SS

and how best to care for patients experiencing serotonin toxicity. The CE module would also educate providers on how to differentiate between other common syndromes such as malignant hyperthermia and the neuroleptic malignant syndrome that closely resemble SS using the more widely used diagnostic tool, Hunter Criteria (Werneke et al., 2016). Online CE modules are not only convenient and cost-effective but allow for the education of the community as a whole, rather than within one's institution alone. Additionally, SRNA development of the educational module will bring recognition to and generate revenue for the University and provide useful information for future projects in continuing education development.

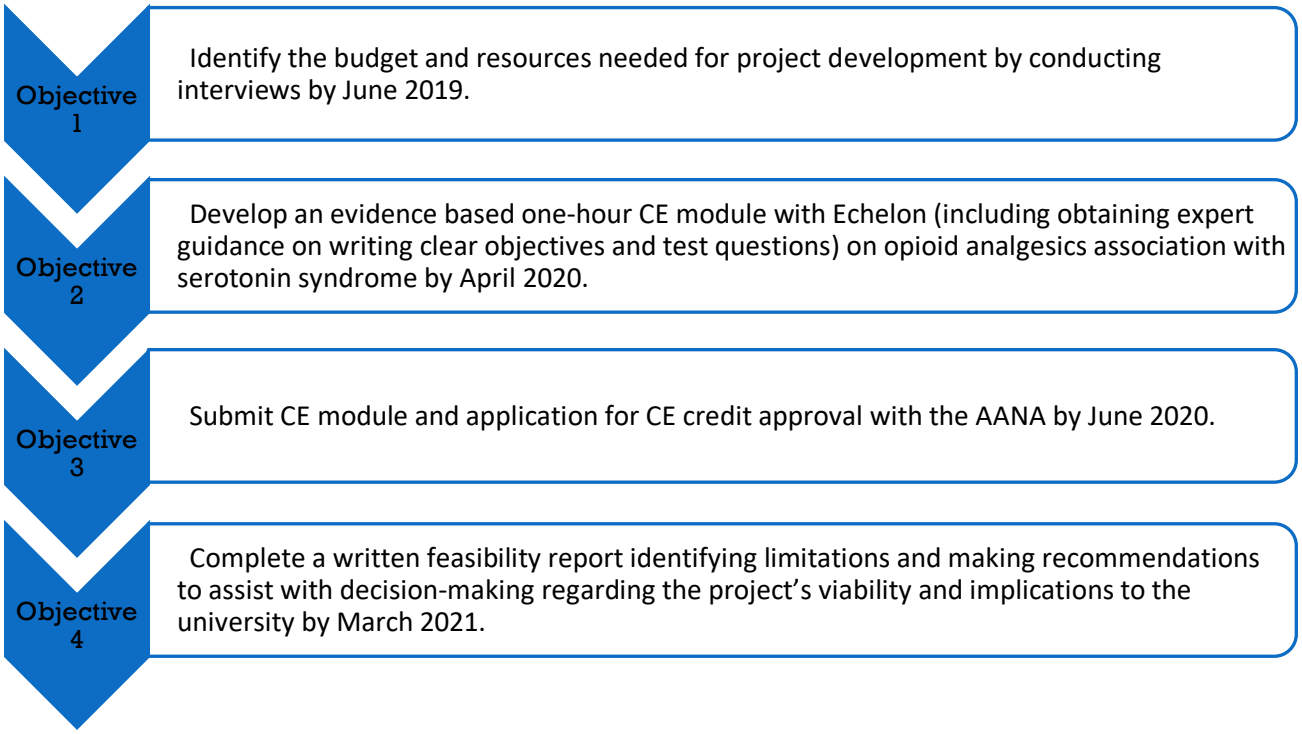
Statement of the Problem

With the increasing number of patients in the United States taking prescribed antidepressants who present for surgery or for treatment at pain clinics, it is important for anesthesia providers to be able to identify the signs and symptoms of serotonin toxicity and effectively manage, or prevent cases of SS (Adler et al., 2015). An online education module on opioid analgesics association with SS, specifically in patients already taking antidepressant agents, could increase the knowledge base and skills of anesthesia providers to effectively recognize and manage SS. The creation of an accredited CE module by AHU SRNAs was a new process being analyzed for feasibility purposes. By presenting the findings of this feasibility study, students hope to improve the process for future student endeavors in CE module development.

Objectives of the Study

The aim of this project was to assess the feasibility of an AHU SRNA-developed one-hour module on opioid analgesics association with SS in patients taking antidepressant medications being approved for continuing education (CE) credit by the American Association

of Nurse Anesthetists (AANA). With information gained from several resources, namely experts in continuing education, feasibility studies, as well as obtaining professional guidance in writing objectives and test questions, this feasibility study was conducted through multiple interviews at AdventHealth University and virtually.



Significance of the Study

This feasibility study provides several benefits to many different parties and stakeholders. The content provided in the educational module holds value and will benefit those who complete the online program by increasing their knowledge and skills. The feasibility study itself, however, will benefit Echelon, AdventHealth University, and future SRNAs wanting to develop an online educational module. By submitting the module transcript to multiple state and national organizations for accreditation, the students will gain recognition not only for themselves, but Echelon and AdventHealth University. This is particularly advantageous to AHU and Echelon, as it will generate revenue each time someone takes the online course created by the students.

Methodology

The proposed project was a feasibility study taking place at AdventHealth University, specifically Echelon, a division of AHU specializing in online continuing education and training, integrating course design and media development incorporating the highest credentialing standards (Echelon, 2019). The design for this feasibility study has been adopted from business models, in which feasibility studies are commonly used to determine a project's viability. A feasibility study using a qualitative, process analysis approach was the best method for this project, as a SRNA developed CE module, especially one approved for CE credit by the AANA, is a nascent process.

Conducting a feasibility study involved obtaining information from multiple resources at several different times throughout the project. The students met with key players to identify potential barriers and facilitators to implementing their project, including Echelon, AANA, and individuals with experience in feasibility studies and CE module project development. All of the data collection was through interviews, meetings, and emails, thus, there is no pre-determined sample size. The students obtained verbal consent from the interviewees to audio record the interviews so the students can reference them as needed. The recordings and email interactions were stored on the student's personal laptops, which are password protected and can only be accessed by the students conducting the study. The data from audio recorded interviews will be destroyed from personal laptops after 5 years. As human subjects were not involved in this project, there were no ethical considerations, such as obtaining informed consent.

The CE module was developed and distributed through the AHU Echelon platform. The students worked closely with the accreditation team at Echelon providing module transcripts and revisions of the CE module as necessary throughout the development process. Test questions as well as objectives for the module were face validated and reviewed by experts. The face

validated questions will not be administered to end-users of the module as part of this narrative feasibility study. Throughout the CE module development process, the students gathered data including any barriers and facilitators encountered and evaluated costs and resources needed throughout the project's timeline.

Scope and Limitations

As this feasibility study was an innovative project for AHU SRNAs, there were several limitations and barriers identified. Time was a major limitation, as SRNAs have many obligations and there were many hours put into research, module creation, transcript revision, and interviews to make this study possible. It also took several weeks, sometimes months to get feedback from the Echelon accreditation committee and another thirty days to get a response from the AANA. SRNAs have had no prior training on educational module development, so students relied heavily on guidance from Echelon director, Lori Polizzi and her team. Identifying resources and obtaining information regarding budget and other important data also proved to be challenging, as well as communication. Additionally, the AANA has very strict guidelines and requirements for approving Class A CE credit, so many revisions had to be made.

Marketing

The development of a continuing education module by SRNAs using the Echelon platform included several different costs. A budget table has been provided below which outlines the costs for the development of the one-hour enduring media content by Echelon. Content development, including extensive research, was conducted by SRNAs and was time costly. In the long run, content development by SRNAs decreases overall costs for the enduring media development. Additionally, the development of the online module by AHU SRNAs provides national recognition for the University, which cannot be quantified.

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

Conclusion

The development of a one-hour continuing education module by AHU SRNAs on opioid analgesics association with serotonin syndrome in patients already taking antidepressant medications being approved for CE credit by the AANA is feasible. On November 23, 2020, the module was approved by the AANA for one CE credit in Pharmacology/Therapeutics under the "Anesthetic Complications" category and is effective through December 31, 2023. The online program also met the guidelines/criteria for accreditation with the Florida Board of Nursing, American Nursing Credentialing Center, and the California Board of Registered Nursing, for one CE credit. The team at Echelon will develop the enduring media from the module transcript which will then be available on the Echelon website for users to complete and receive continuing education credit.

Recommendations

Several recommendations have been made based on the SRNAs experiences during the feasibility study, as well as feedback from Echelon director, Lori Polizzi.