Pharmacological Treatment of Post-Anesthetic Shivering:
An Educational Outreach Project.

Cari A. Miller, BSN, RRNA

cari75092@yahoo.com

Capstone Project

DOCTOR OF NURSING PRACTICE

Primary Advisor: Kay K. Sanders, DNP, CRNA
Secondary Advisor: Mark D. Welliver, DNP, CRNA, ARNP

Harris College of Nursing and Health Sciences.

School of Nurse Anesthesia.

Texas Christian University.

October, 2011.

Word Count: 14,113
Abstract

Statement of Practice Problem:
Shivering commonly occurs after anesthesia and can jeopardize the hemodynamic stability and recovery of patients. Meperidine is the most frequently used pharmacological treatment for post-anesthetic shivering (PAS); however, a standard of care does not exist and recommended options for PAS treatment are unknown to many of those caring for the shivering patient.

Proposed Solution:
To increase knowledge among anesthesia professionals and post-anesthetic care (PACU) nurses regarding the etiology, risk factors, consequences, and pharmacological treatment options in the treatment of PAS through the development and dissemination of a journal review course.

Methodology:
The researcher conducted a literature search of full-text articles analyzing pharmacological treatment of PAS. Systematic reviews, meta-analyses and randomized controlled trials published within the past ten years with an adult population focus were reviewed.

Findings:
The literature, which showed meperidine and tramadol are equally effective, also recommended clonidine, nalbuphine, and doxapram for timely cessation of post-anesthetic shivering.

Conclusions:
When meperidine is not a safe, available, or ideal treatment option for PAS, health professionals caring for the shivering post-anesthetic patient can use several other pharmacological modalities, including doxapram, nalbuphine, clonidine, and tramadol.
PART ONE

Introduction

Patients presenting to a Post-Anesthetic Care Unit (PACU) following general or regional anesthesia are at risk for shivering. Clinicians refer to this potential complication as post-anesthetic shivering (PAS) and describe it as spontaneous, uncontrollable muscular shaking, which increases metabolic heat production. Multiple studies estimate the incidence of shivering to be between 5% and 65% and consider shivering one of the leading causes of discomfort in the recovering patient.\(^2\text{-}^4\) Although the exact cause of this phenomenon is not known,\(^1,^2\) patient frustration, discomfort, and physiological disturbances are evident.\(^2\)

Various consequences of PAS exist; however, an increase in oxygen uptake is most important. The amount of oxygen consumed by the patient can increase up to 600%, potentially creating a mismatch between oxygen delivery and oxygen demand.\(^1,^5,^6\) Healthcare professionals, including anesthesia practitioners and PACU nurses, must realize PAS usually coexists with hypothermia.\(^2\) Controversy exists over which of these two, PAS or hypothermia, is responsible for the development of undesirable cardiac and/or respiratory events.\(^2\) In view of this controversy, practitioners should maintain patients’ body temperature in an acceptable range during and following general and regional anesthesia.\(^8\) However, normothermic patients also experience PAS; therefore, vigilance in treating all occurrences of PAS in the PACU is warranted.\(^2\)

In addition to patient warming devices, numerous drugs have shown efficacy in preventing and treating PAS.\(^1,^2,^4,^5,^6,^9\) Currently, meperidine is the most frequently used drug for the treatment of PAS in the United States of America (USA).\(^9\) However, many hospitals are restricting use of this drug due to growing evidence of its associated adverse effects. For this same reason, some hospitals have entirely eliminated it from their pharmaceutical formulary.\(^10\) A critical review of meperidine by Latta and colleagues listed respiratory depression,
tachycardia, xerostomia, agitation, confusion, and chemical dependency potential as side effects of meperidine.\textsuperscript{10} Researchers have associated meperidine with delirium, hallucinations, seizures, and reversible Parkinsonism.\textsuperscript{11} The anti-cholinergic effects of meperidine are likely responsible for its other effects, such as urinary retention, constipation, and mydriasis.\textsuperscript{10,11} Potentially lethal pharmacodynamic effects can occur when meperidine interacts with monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs).\textsuperscript{10,11} The Institute for Safe Medicine Practices (ISMP Canada) reported the treatment of PAS is considered an acceptable reason for the use of meperidine; however, hospital imposed restrictions could affect the availability of this drug.\textsuperscript{10,11,12} Even with ample supply of meperidine, the popularity of this drug could easily decrease due to facility imposed restrictions, practitioner awareness of its adverse effects, and patient population contraindications.

Dwindling access to meperidine and increasing knowledge regarding its adverse effects, makes it prudent to explore pharmacological treatment alternatives for PAS. Fortunately, various studies have explored this problem and exposed a few successful options. Though many studies have examined the efficacy of multiple medications in the treatment of PAS, evidence was only sufficient to recommend tramadol, doxapram, clonidine, and nalbuphine.\textsuperscript{5,13,14,15,16,17}

In an effort to increase knowledge among healthcare professionals caring for the postoperative shivering patient, this project aimed to collect, examine, and disseminate the evidence regarding pharmacological treatment of PAS in the adult patient recovering from general or regional anesthesia.
Overview

Methodology

In an effort to obtain relevant data for analysis, this author conducted a thorough literature search using search engines and databases including CINAHL, Academic SearchComplete, Cochrane Collaboration, PubMed, and Google Scholar. Key terms for searching included “post-anesthetic OR postanaesthetic OR postoperative’ AND ‘shivering OR tremor OR shaking.’” The last electronic search occurred on May 23, 2011.

This author included only full-text articles published within the last ten years, which analyzed pharmacological treatments were included. Scholars define pharmacological treatment as medical intervention given to patients experiencing shivering while recovering from general or regional anesthesia. In these studies, all medications were given intravenously (IV). Exclusion criteria consisted of articles discussing non-pharmacological treatments, randomized controlled trials (RCTs) included in systematic reviews (SRs), and studies on children. Considering the importance of prevention in health care, this author viewed studies with a preventive focus for informational purposes.

Overview

Multiple studies have utilized evidence-based research to explore the effectiveness of multiple drug treatments for the cessation of PAS. The conclusions of these studies and systematic reviews must be disseminated to health care professionals. Therein lies the reason for this project. The evidence-based research paved the way toward a project aimed at the dissemination of knowledge through the submission for publication of a journal review course. The evidence found by this author pointed to five effective pharmacological modalities for treating PAS. Use of meperidine for the cessation of PAS is grounded in tradition; however, through dissemination of research findings, practitioners can encourage efforts to increase
practice based on evidence.\textsuperscript{18} Considering the current national trend toward improved patient outcomes and safety, along with reduced costs, treatments should be patient specific and based upon scientific evidence. To improve outcomes in patients suffering from PAS, recipients of the distributed information must include anesthesia practitioners and PACU nurses.

One way of achieving such dissemination of evidence is through peer-reviewed journal publication, which is an effective way of educating a large population and can lead to widespread implementation of needed changes. This author developed a journal review course that discusses PAS and its etiology, risk factors, consequences, prevention, and pharmacologic treatment options. In the event of publication, this author will evaluate the success of the intervention via course evaluation distribution and grade results.
PART TWO

Literature

Background

As early as 1972,\textsuperscript{7} post-anesthetic shivering was been a well-documented phenomenon; however, its etiology remains controversial.\textsuperscript{1,2,5,6,7,13,14,15,17} A variety of drugs are effective in stopping PAS although their mechanisms of action are mainly speculative. Due to these two unknowns, a gold standard of practice in treating this condition is lacking.\textsuperscript{14 (p458)}

As with all medical complications, prevention is ideal. In an effort to avoid PAS and other thermally associated postoperative complications, Scott and Buckland advocate intraoperative prevention of hypothermia as standard practice, which is accomplished mainly through the use of forced air warmers.\textsuperscript{8 (p1101,1109)} Studies have found the medications tramadol, meperidine, clonidine, nalbuphine, and doxapram are also effective in preventing post anesthetic shivering.\textsuperscript{5,13,14,15,16,17}

When prevention fails or shivering is normothermic, pharmacological intervention is warranted.\textsuperscript{19} Currently, healthcare professionals most frequently use meperidine for PAS cessation\textsuperscript{9} though traditional use of this drug possibly impedes utilization of other therapeutic options. As availability and popularity of meperidine dwindle, coupled with an increased awareness of meperidine’s adverse effects and patient contraindications, healthcare professionals must avert attention away from tradition and focus on evidence-based practice.

A barrier to evidence-based practice (EBP) is the disbelief that it will produce better outcomes than traditional care.\textsuperscript{18 (p16)} A review of 41 systematic reviews discovered educational outreach was an effective intervention to enhance translation of research findings into practice.\textsuperscript{18 (p17)} This project was conducted to discuss current practice, explain the proposed mechanisms of action for the afore-mentioned drugs, examine comparison findings, and discuss the educational outreach intervention which emerged.
**Review of Literature**

Upon initial examination of the accumulated evidence, it was evident an abundance of studies existed. Although the evidence search located many RCTs, the majority of those studies existed in both systematic reviews located by this author, therefore this review does not include those studies. A SR combines results from different RCTs to obtain quantified synthesis. An SR uses a method to insure individual studies are similar enough, although expectation of some variation exists. Research located two SRs: one published in 2002 and the other published in 2009; however, the redundancy of their references warranted careful consideration. The 2009 SR was noted to include all except 2 of the RCTs examined in the 2002 SR. Furthermore, the 2009 SR analyzed an additional 12 RCTs. Clearly the 2009 SR, being a more recent and thorough review, deserved the most attention for the purpose of this paper. In addition to the synthesis of both SRs, this author assessed the quality of the the 2009 SR through use of the Quality of Reporting of Meta-analyses (QUORUM) checklist. Following elimination of redundant referenced studies, a total of 6 studies met inclusion criteria. Searching yielded 2 systematic reviews considered Level I, the highest level of evidence, and 4 studies considered Level II. No evidence-based guidelines for the treatment of PAS have currently been issued.

In addition, resources included text books for pharmacological, physiological and other medical facts and data. Descriptive and educational articles provided information used to guide the process of synthesis and development of the journal course review. Systematic reviews and randomized controlled trials were given close attention in order to reach solid, evidence supported conclusions and recommendations. Highly rated evidence, such as systematic reviews, demonstrate greater scientific rigor and are more influential in the validation or improvement of certain clinical practice methods. The Melnyk and Fineout-Overholt rating system for the
hierarchy of evidence,\textsuperscript{18 (p10)} used to scale evidence in this review, can be found in Appendix A, Table A1.

**Level I Evidence.** Starting with the highest level of evidence, Kranke et al explains the results from a survey given to anesthesiologists. The survey regarding 33 clinical problems ranked PAS frequency eighth and the importance of preventing shivering was ranked twenty-first, suggesting anesthesiologists do not consider shivering a true medical problem.\textsuperscript{14 (p453)} Fortunately, Kranke realized the need for attention to PAS and subsequently performed a SR that analyzed data from 20 RCTs conducted on those recovering from general or regional anesthesia.\textsuperscript{14 (p453)} Meperidine was the most tested medication in the analyzed studies and consistently performed best. Doxapram and clonidine came close to meperidine in terms of efficacy; therefore, studies also considered doxapram and clonidine effective treatment regimens.\textsuperscript{14 (p455)} Kranke stated data on tramadol and nalbuphine were insufficient to draw meaningful conclusions.

Kranke discussed the results and weaknesses of their SR, yet failed to make an official recommendation. Instead, Kranke discouraged the need for more trials to investigate efficacy of other drugs on PAS, stating “simple regimens such as meperidine”\textsuperscript{14 (p459)} were very effective in PAS treatment. The conclusions of this SR were vague and seemingly uncertain. Fortunately, 7 years later a publication by different authors offered a more comprehensive SR that incorporated new evidence.

Published in 2009 by Charuluxanan and colleagues, another SR, a Level I study, investigated pharmacological treatment for PAS studied through 2008.\textsuperscript{13} The SR retrieved 426 reports upon initial search for pharmacological treatment for PAS, and then narrowed its focus to 32 RCTs considered appropriate for systematic review. Pharmacological treatment of PAS was the focus of these 32 RCTs. These RCTs included placebo control, treatment control, or direct comparative studies: all with a 20 person median size of subject groups. All 16 authors
performed an independent search and screening for evidence and analyzation included reports in English and other languages.\(^{14}\) (p352)

Charuluxanan discovered studies relating the effectiveness of each drug, which included 9 RCTs for meperidine; 3 for tramadol, ketanserin, doxapram, and clonidine; and 2 for nalbuphine.\(^{14}\) (p354-357) Evidence for these 6 drugs was found to be sufficient and statistically significant. A “range of dosage” for convenient implication was decided upon due to a high dose variation of treatment regimens.\(^{13}\) (p354) Eleven medications: alfentanil, magnesium sulfate, fentanyl, ondansetron, nefopam, pentazocine, urapidil, morphine, lignocaine, metamizol, and butorphanol were studied by some RCTs yet found to be inadequate for quantitative analysis.\(^{13}\) (p351)

The ability to reach a conclusion in this SR, versus the latter SR discussed, was a result of an increase in directly comparative studies of meperidine and tramadol. This subsequent SR clearly concluded that options for the successful treatment of PAS include meperidine, tramadol, clonidine, ketanserin, doxapram, and nalbuphine.\(^{14}\) (p354-357) Although ketanserin was reportedly effective in the treatment of PAS, this paper excluded it as a recommended treatment option because it is not available in the USA.\(^{21}\) While this SR recommended meperidine 25 milligrams (mg) and tramadol 0.5-1 milligrams per kilogram (mg/kg) as equally effective treatments, it also recommended clonidine 30-150 micrograms (mcg), nalbuphine 0.05-0.1 mg/kg, and doxapram 25-100 mg as effective therapeutic alternatives.\(^{13}\) (p360)

Although an SR, considered the highest level of evidence, made these recommendations, the quality of SRs can be deficient. Therefore, the quality of this SR requires further evaluation through the use of the Quality of Reporting of Meta-analyses (QUORUM) checklist. The QUORUM is a checklist of standards, guided by research evidence, for the method of reporting a systematic review. Included in the checklist are information on searches, selection, validity assessment, data abstraction, study characteristics, quantitative data synthesis, and trial
flow. Appendix B displays the results from utilizing the QUORUM checklist on the systematic review by Charuluxanan and colleagues. Recommendations were drawn from the SR as it was found to be of high quality.

**Level II Evidence.** A RCT published by Dhimar and colleagues\(^\text{15}\) in 2010 compared meperidine and tramadol for the treatment of PAS in the regional anesthetic patient. This Level II study included 60 patients from both genders undergoing various surgeries. The included patients were ASA (American Society of Anesthesiologists) grade I, II, or III patients and received regional anesthesia. An ASA I patient is a normal healthy person. ASA II patients have mild systemic disease yet no functional impairment. ASA III patients are afflicted with a severe systemic disease that causes some functional limitation. This study found tramadol and meperidine to be equally effective; however tramadol stopped shivering sooner than meperidine; therefore, researchers considered it qualitatively superior. Complete disappearance of shivering took 5 minutes in the tramadol group and 20 minutes in the meperidine group. The treatment doses were 1 mg/kg for both drugs. Additionally, Dhimar found the recurrence rate to be lower with tramadol versus meperidine. This RCT concluded tramadol was faster to treat, less likely to be associated with shivering recurrence, and equally effective when compared to meperidine.

Published in 2010 by Mohammadi et al\(^\text{5}\), another RCT also compared tramadol and meperidine. The study included 60 adult patients, ASA I and II, suffering from PAS following general anesthesia for a urological operation. All patients received similar anesthetics and received either tramadol 1 mg/kg or meperidine 0.5 mg/kg for treatment of PAS. This study also found tramadol and meperidine equally effective in alleviating PAS; however, the study did not conclude tramadol was the superior of the two. The authors recommended future performance of larger studies to study and compare the side effects of tramadol and meperidine when treating PAS.
Shrestha, the author of a third RCT, sought to determine if doxapram, meperidine, or placebo was superior in treating PAS. Thirty ASA I or II patients were included in the study and all were recovering from general or orthopedic surgeries performed under general anesthesia. Pre-operative treatments, anesthesia technique and operating room and fluid temperature were similar for each patient. Treatment regimens consisted of doxapram 1.5 mg/kg, meperidine 0.35 mg/kg and 3 milliliters (ml) normal saline. Meperidine performed better than doxapram (yet not in a statistically significant way) so the study concluded both meperidine and doxapram were effective in the pharmacological treatment of PAS.

In 2004, Zahedi conducted and published a larger RCT. This study was a double-blind trial on patients undergoing general anesthesia for cataract surgery. The adult participants were ASA I or II. Like the afore-mentioned RCTs, anesthesia technique was kept similar. In the 120 shivering patients, blind pharmacological treatments included meperidine 0.5 mg/kg and tramadol 1 mg/kg. Zahedi reported tramadol was more effective due to a faster onset, no recurrence of shivering, shorter duration of recovery, and fewer adverse effects.

**Proposed Mechanisms of Action.**

**Meperidine.** Introduced as an antispasmodic drug in 1939, meperidine is central to many PAS protocols. It is a well-known drug, familiar to most medical staff, possesses a reputation as a modality for the treatment of pain and shivering, and has been readily available in the past. Research has provided abundant documentation regarding meperidine’s potent anti-shivering effects; however, the mechanism for these effects is poorly understood. This drug exerts its action on κ-opioid receptors (KOR) and µ-opioid receptors (MOR), whereas pure µ-agonists, such as fentanyl and morphine, only work on MOR. KOR and MOR are types of opioid receptors where opiates bind in order to exert their action. Researchers know meperidine treats PAS better than pure µ-agonists, but they can only speculate about the reason.
Naloxone is an opioid antagonist that blocks MOR and KOR, reversing the effects of opioids bound to these sites. Naloxone has a high affinity for MOR and a low affinity for KOR; therefore, a low dose would only affect MOR. To reach KOR, a higher naloxone dose is needed. Meperidine’s anti-shivering action was inhibited by high-dose naloxone but not by low-dose naloxone; therefore, researchers developed the theory that meperidine’s action on KOR mediates its effect on PAS.7,22,23

Hypothermia causes vasoconstriction that leads to the body’s attempt to preserve heat via shivering. Another reason meperidine ceases shivering is its ability to decrease the shivering threshold almost twice as much as the vasoconstriction threshold,23 (p1049) which means body temperature can drop lower than normal before onset of vasoconstriction and shivering. Additionally, meperidine’s effect on shivering and vasoconstriction thresholds means vasoconstriction will occur at a higher temperature than required to initiate shivering. Although these mechanisms explain meperidine’s effect on hypothermic shivering, they do not clarify meperidine’s effect on normothermic shivering. Nonetheless, meperidine, along with the other recommended drugs for cessation of PAS, has been successful as an anti-shivering regimen in both hypothermic and normothermic patients.

**Tramadol.** Tramadol, a synthetic opioid, was synthesized in 1962 and introduced to the USA in 1995.24 Tramadol is a centrally acting analgesic possessing a dual mechanism of action of activating MORs and blocking norepinephrine and serotonin reuptake.24 (p881) Researchers believe that by blocking the reuptake of norepinephrine and serotonin, tramadol activates descending inhibitory spinal pathways which terminates shivering. Tramadol’s action on MORs is responsible for its analgesic properties. This drug is finding favor in the eyes of researchers worldwide when compared to meperidine for the treatment of PAS. Although tramadol is administered intravenously in many countries, the intravenous (IV) form has not yet been approved in the United States of America (USA) by the Food and Drug Administration (FDA).21
**Doxapram.** In the 1960’s, doxapram was introduced as a strong, dose-dependent, respiratory stimulant. Researchers thought this respiratory stimulant effect was a result of central nervous system (CNS) stimulation; however, controversy still exists as to its principal site of action. Additionally, doxapram treated drug-induced CNS depression and improved arousal and level of consciousness following anesthesia. The use of this drug for the cessation of shivering surfaced in 1993, yet the mechanism for this action isn’t clear. Researchers know doxapram lowers the shivering threshold, allowing the body to reach lower temperatures before shivering occurs. What researchers don’t know is how a CNS stimulant, with a potential side effect of muscular spasticity, can combat PAS, which involves muscular shaking. (p245)

**Nalbuphine.** Nalbuphine, a semisynthetic agonist-antagonist opioid, is best known for its analgesic properties. This drug, like meperidine, acts as an agonist at KORs and has a high affinity for these receptors. Therefore, as with meperidine, nalbuphine’s anti-shivering properties are possibly attributed to KOR agonism, yet it is not completely known. Unlike meperidine, nalbuphine has MOR antagonistic properties similar to naloxone, a drug that reverses the effects of opioids. Nalbuphine also comparably reduces the shivering and vasoconstriction thresholds, another possible reason for its anti-shivering effects. While the mechanism of action for nalbuphine is still up for debate, studies have found this drug effective for the treatment of PAS. (p270)

**Clonidine.** Better known for its anti-hypertensive effects, clonidine is another treatment effective for PAS cessation. While clonidine mainly exerts its action on alpha 2 adrenergic receptors found throughout the body, explanations for clonidine’s anti-shivering effects are merely suggestions. One theory involves the hypothalamus. The hypothalamus, where alpha 2 receptors are found, is responsible for controlling body temperature. Clonidine is thought to work on hypothalamic receptors to inhibit vasoconstriction and shivering or at other CNS levels by altering incoming thermal information. However, most credit is given to clonidine’s ability to
reduce the thermoregulatory thresholds for vasoconstriction and shivering.\(^{28}\) Regardless of which theory is correct, many studies have focused on clonidine for the treatment of PAS.\(^{13,28}\)

**Meperidine: Drug of the past?** In the 1990’s, clinical guidelines began discouraging the use of meperidine and several major institutions severely restricted its use or removed it entirely from their formularies.\(^{29,10}\) In 2002, Latta et al\(^{10}\) published an extensive review of meperidine, examining every paper previously published on this drug. The final conclusion of this review was that “meperidine is a medication whose time has passed in routine pain management and whose use must be questioned in all instances.”\(^{10}\) Though complex, the researchers base their conclusion partially on evidence that meperidine’s metabolite, normeperidine, is neurotoxic and can cause anxiety, myoclonus, seizures, mood changes, and hyperreflexia within 24 hours.\(^{10}\) The authors point to an educational gap as the reason meperidine is still being used despite its documented side effects. According to Latta, many governmental, professional, and accreditation organizations see meperidine use as a negative marker; therefore, health care professionals should look at its use more carefully.\(^{10}\)

The Institute for Safe Medication Practices Canada (ISMP Canada) issued a safety bulletin on meperidine.\(^{12}\) In this 2004 publication, ISMP Canada recommended healthcare facilities evaluate the use of meperidine and limit this drug’s use to treatment of postoperative shivering, treatment of short term pain, and prevention/treatment of drug-induced or blood product-induced rigors. The bulletin also recommended removal of all oral meperidine from the formulary and avoidance of meperidine use in elderly patients. While ISMP considered PAS treatment an appropriate use of meperidine, this bulletin supported the notion that meperidine’s popularity is rapidly declining.

An editorial published in *Hospital Pharmacy*\(^{30}\) added to ISMP Canada’s recommendation by stating meperidine is contraindicated in patients with renal dysfunction or patients receiving monoamine oxidase inhibitors (MAOIs). The editorial continued by stating professionals should
use caution when administering meperidine to patients with “gastrointestinal obstruction, ileus, ulcerative colitis, pre-existing constipation, pulmonary disease, respiratory depression, history of substance abuse, head trauma, increased intracranial pressure, glaucoma, hepatic disease, pregnancy, seizure disorders, cardiac arrhythmias, urinary retention, oliguria, and the elderly.”

Post-anesthetic shivering jeopardizes recovery from general or regional anesthesia. The consequences of shivering include an increase in cardiac demand, carbon dioxide production, and post-operative pain; however, an increase in oxygen consumption is arguably the greatest adverse effect as it can create a mismatch between oxygen supply and demand. Literature identified various pharmacological treatments that succeed in treating PAS in the post-anesthetic patient. Multiple studies demonstrated equal efficacy between meperidine and tramadol; however, tramadol is not available in IV form in the USA at this time. Fortunately, evidence has pointed to doxapram, clonidine, nalbuphine, and tramadol as effective alternatives to meperidine. Considering the growing trend to limit the use of meperidine, those caring for the post-anesthetic shivering patient must be aware of these substitutions. A journal review course explaining PAS and its treatment options would assist in the dissemination of such evidence.

**Synthesis of Literature**

The undesirable effects of PAS are diverse, ranging from difficulty in patient monitoring to increases in heart rate, cardiac output, intracranial pressure, pain, carbon dioxide production, and oxygen consumption. PAS is a common occurrence in the PACU following general and regional anesthesia, thus researchers have studied various pharmacological treatments in an attempt to determine the best treatment for this medical condition.

**Meperidine.** Meperidine has the longest standing history as a medical treatment for PAS. Not surprisingly, meperidine also has the most substantial amount of evidence supporting its use.
as an anti-shivering regimen.\textsuperscript{10} These combined factors explain why it is the most frequently used pharmacological agent for the cessation of PAS;\textsuperscript{9} however, the popularity of meperidine is currently diminishing on account of its undesirable side effects\textsuperscript{10,12,29,30} The referenced studies and systematic reviews support a favorable argument for alternative treatments for PAS, including doxapram, clonidine, nalbuphine, and tramadol. When meperidine is not available or ideal, the treatment of PAS should include these alternative pharmacological agents. The evidence points to many situations in which healthcare professionals should not use meperidine or should use it with caution. Currently, meperidine is considered an acceptable therapy for the treatment of PAS, except in patients with contraindications;\textsuperscript{10,11} however, the progressive movement away from using meperidine in the USA could easily pave the way toward meperidine becoming a drug of the past. In the event meperidine becomes a drug of the past, an alternative course of action must be taken by healthcare professionals.

**Doxapram, clonidine, and nalbuphine: Alternative treatments.** Many anesthesia professionals and PACU nurses may be surprised to learn of these alternative treatments for PAS cessation, as each of these drugs is better known for other therapeutic uses. As with meperidine, researchers do not completely understand the physiological rationale for the success these drugs demonstrate when PAS. The realization meperidine is most frequently used for PAS cessation, coupled with growing evidence regarding this drug’s undesirable effects, points to a need for increased consideration of the alternate drugs. The pharmacological options, discovered through a review of the literature, are currently accessible and reasonable to use in the post-operative setting. Cost, facility policy, or simply the lag time between research and evidence implementation could all factor into the underutilization of these treatment alternatives. Practitioners must encourage evidence-based practice in all areas of today’s health care system and the treatment of PAS is no exception. Following an exhaustive summary of literature, the afore-mentioned SR clearly recommended doxapram, clonidine, and nalbuphine as alternative
treatments for PAS. And, although the evidence also recommended tramadol, a huge barrier, accessibility in the USA, currently stands in the way of its utilization.

**Tramadol: An equal to meperidine?** All studies, whether randomized controlled trials or systematic reviews, found tramadol as effective as, if not superior to meperidine. Although use of tramadol in other countries is extensive, the USA FDA has not currently approved its IV formula. Interestingly though, tramadol use in other medication forms is increasing in the United States; therefore, in the event its IV form becomes available, healthcare professionals should be aware of its effectiveness against PAS. It is not known if and when IV tramadol will be available in USA; therefore, healthcare professionals must translate the evidence in support of alternative treatment options into clinical practice.

**Quality of evidence.** Due to the redundancy of references between studies and SRs, the majority of this project’s evidence findings resulted from the systematic review by Charuluxanan and colleagues. Considering the heavy emphasis upon this single SR in the synthesis of literature and formulation of an intervention, this author assessed its quality using the QUORUM statement checklist. QUORUM assists in evaluating the quality of systematic reviews through the use of a checklist. Available for review in Appendix B, the QUORUM checklist demonstrated the high quality of the Charuluxanan SR, thereby making it an excellent SR upon which to build an intervention.

So many unknowns exist regarding PAS and its treatment. The etiology of PAS is controversial, the mechanism of action of the various pharmacological modalities is obscure, the future demand and supply of meperidine is questionable, and the prospect of tramadol availability in the USA remains unknown. What is known is the need for translating evidence into clinical practice. In the treatment of PAS, the evidence points toward minimizing the use of meperidine and increasing the use of alternative treatments to include doxapram, clonidine, and nalbuphine.
Summary

In summary, the use of meperidine is controversial on account of its vast number of side effects. Although the use of meperidine is considered appropriate for the treatment of PAS, patient contraindications, medication availability, and drug popularity could greatly affect the ability to use meperidine in the PACU setting. Research has shown other medical agents, including tramadol, doxapram, clonidine, and nalbuphine are successful in treating PAS; therefore, researchers consider these drugs appropriate therapeutic alternatives to meperidine. Although tramadol is not an available option in the USA, the remaining drugs are easily available in today’s hospitals and would be practical in many settings.

Choosing an inappropriate treatment for PAS could jeopardize the safety and recovery of a patient, create patient dissatisfaction, delay discharge from the PACU, and increase health care costs. When meperidine is not an option, practitioners must possess the ability to choose an effective, alternative pharmacological treatment for the cessation of PAS. However, to simply implement a suggested treatment, without knowledge regarding other aspects of PAS, would be imprudent.

Healthcare practitioners, including anesthesia professionals and PACU nurses, should possess an understanding of the etiology, risk factors, prevention, consequences, and pharmacological treatment options in the treatment of PAS. The development of a journal review course and its submission for publication emerged from the literature as a realistic method of disseminating the evidence and encouraging its translation into clinical practice.
PART THREE

Intervention

Overview

During the postoperative period, shivering is a frequent occurrence that can create deleterious physiological effects and cause discomfort for the recovering patient.\textsuperscript{19,22,31} A standard of care regarding pharmacological treatment for this complication does not exist; however, healthcare professionals most frequently use meperidine.\textsuperscript{7} Many articles in recent years have highlighted the detrimental effects of meperidine; therefore, a trend to reduce the use of this drug is gaining ground.\textsuperscript{10,12} Although organizations typically consider the treatment of PAS an appropriate use of meperidine, given contraindications don’t exist, the potentially dwindling availability and declining popularity of this drug demand the exploration of substitute treatments.

The uncovered evidence displayed a few successful, realistic alternatives to meperidine for the cessation of PAS. Studies concluded doxapram, nalbuphine, clonidine, and tramadol were reliable, successful pharmacological modalities for the treatment of PAS in the patient recovering from general and regional anesthesia.\textsuperscript{5,13,14,15,16,17} Healthcare professionals typically know each of these drugs for their other physiological responses; therefore, education is needed to bridge the gap between evidence and application into clinical practice.

When healthcare professionals utilize the best and latest evidence to guide practice, patients experience 28\% better outcomes; therefore, there is an urgent need for clinicians to translate research evidence into best practices.\textsuperscript{18 (p4)} In the report, \textit{Crossing the Quality Chasm: A New Health System for the 21st Century}, the Institute of Medicine’s Committee on the Quality of Health Care in America identified strategies for improving the quality of care delivered to Americans.\textsuperscript{32} This report listed “evidence-based decision making” as Rule 5 of the Ten Rules for Health Care\textsuperscript{32 (p8)} because, despite an increase in the amount and quality of research, healthcare providers are doing a poor job integrating research findings into practice. Unfortunately, even as
information technology expands, the translation of research into practice can take as long as 17 years. 18 (p4)

Given the lag time between research evidence and bedside practice, healthcare practitioners must desire to improve patient outcomes, realize the importance of sharing knowledge, and take efforts to disseminate research findings. Facilitators of evidence-based practice must select methods for presenting data in a manner appropriate for the subject matter. To reach healthcare professionals responsible for treating post-anesthetic shivering, the targeted audience should include anesthesia practitioners and post-anesthetic care unit nurses. In addition to pharmacological treatment options, educational efforts must elaborate on the etiology, risk factors, consequences, and prevention of PAS to insure practitioners thoroughly understand the implications of this condition. To succeed in this educational outreach project, creation of a journal review course emerged as the intervention.

**Intervention**

A need to disseminate the evidence regarding the pharmacological treatment of PAS became apparent as the goal for intervention in this study. The method chosen for this intervention was submission for publication of a journal review course. The choice journal was the official, peer-reviewed, scholarly journal of the American Association of Nurse Anesthetists. It is a bimonthly publication that includes an ongoing journal course consisting of 6 successive articles that provide members of the profession with continuing education units (CEUs). 33

Infusing evidence-based practice into the clinical setting is a challenge; however, there is a paradigm shift from traditional practice toward evidence-based practice. 18 (p186) Further facilitating this shift, publication would serve as a means to distribute evidence-based information with the intended purpose of affecting clinical practice and improving healthcare outcomes. Contributing to the intervention decision was the Call for Courses made by the AANA Journal, which encouraged the submission of review courses from interested parties. This author
located the Call for Courses after the journal review course in every *AANA Journal* published in the last year.

**Development of Intervention**

Following idea generation for the inclusion of review course subtopics, this author developed an outline. The *AANA Journal* provided an “Educational Design II Documentation Format” template for generation of objective and content topics, which was used for outlining the course. Readers can find this form in Appendix C. This author located, examined, and followed *AANA Journal*’s “Information for Authors” and “Journal Course Requirements” during all stages of writing and preparation for submission. These documents served to guide the intervention development. Perusal of literature regarding PAS assisted in incorporating necessary information into the article and in supporting the facts upon which the article was written. This author repeatedly visited the evidence to ensure its correct interpretation and translation into the review course manuscript.

Utilizing the expertise of mentors and information found in literature, a review course was generated. The process of question development corresponded with the desired knowledge attainment outcomes for readers. Attention to clinical practice relevance was kept by this author during construction of ten course examination questions. Finalization of the journal review course will include proofreading by an experienced editor/reviewer. (See Appendix E for Journal Review Course.) The ACE Star Model of Knowledge Transformation,\(^\text{34}\) a model dedicated to increasing understanding of the evidence-based practice process, guided the selection and development of the intervention.
Guiding Framework

Put simply, knowledge is complex. Knowledge is displayed in a variety and multitude of forms, possesses demanding terminology, exists in extreme abundance, and presents a challenge in application attempts. Locating, sorting through, analyzing, and integrating knowledge can be tedious tasks. Models of knowledge transformation have been developed to provide a framework for organizing these processes. The Academic Center for Evidence-Based Practice (ACE) at the University of Texas Health Science Center created one such model, named the ACE Star Model of Knowledge Transformation. The ACE Star model (Figure 1) served as the theoretical framework for this project and focuses on improving patient outcomes and safety by bringing research into practice.

---

**ACE Star Model of Knowledge Transformation**

The originators of the ACE Star theoretical framework developed the five-point start to illustrate five stages of knowledge transformation. Moving from point to point on the star, the
user of this model is guided through the organizational process of examining and applying evidence-based practice. The five points correspond to the step of the process including: (1) discovery, (2) summary, (3) translation, (4) integration, and (5) evaluation. The ACE Star model and how it served as a framework for this project is explained below.

**Discovery.** As discussed in the methodology section of this paper, this author located knowledge through a comprehensive search and assessment of available literature. Systematic reviews, meta-analyses, and randomized controlled trials served as the literature foundation upon which the intervention emerged. Additionally, for the generation of knowledge, textbooks, descriptive studies, pharmacological research reviews, and narrative reviews were acquired.

**Summary of Evidence.** Single, concise statements emerged from the discovered literature. Evidence summaries, such as systematic reviews and meta-analyses, served to answer the clinical question regarding the successful pharmacological treatment of PAS with certainty. As IOM stated, “No unaided human being can read, recall, and act effectively on the volume of clinically relevant scientific literature.”\(^ {18 \text{ (p25)}} \) During a time of information overload, systematic reviews and meta-analyses, assist in reducing the volume of literature via summarizing a large amount of studies. Such a summary of evidence identifies bias and increasing reliability and reproducibility of results.\(^ {18 \text{ (p115)}} \) The *Synthesis of Literature* section of this paper expounds upon a synthesis of evidence for this project.

Textbooks, descriptive studies, pharmacological research reviews, and narrative reviews assisted this author in understanding the more rigorous evidence summaries and directing development of recommendations and the interventional process.

**Translation.** The efforts required during the process of discovery and summary of evidence would be considered futile if the process did not continue. An impact can be made by using the discovered and summarized evidence to make clinical recommendations, which is described as the act of translation. Translation provides practitioners with useful and relevant
information upon which to base clinical decisions. An extensive review was performed on information collected during the summation step and conclusive recommendations were reached. Often authors provide recommendation in the form of clinical practice guidelines (CPGs); however, this author translated the recommendations into a journal review course. To ensure a successful translation process, inquiry through the chosen journal will be made to obtain requirements for submission of the review course.

**Integration.** Integration is the method of utilizing research in clinical practice. During this stage, recommendations are followed and put into practice. Consideration of factors prior to integration of recommendations include cost effectiveness, availability, time constraints, and individual expertise. Objectives of this educational outreach project can be met through publication with an appropriate journal. Following such a dissemination of knowledge, integrational change on an individual and/or organization level can occur.

**Evaluation.** To evaluate something is to establish the success of its implementation. Inquiry with the publishing journal regarding number of returned quizzes and grade distribution can determine whether knowledge regarding PAS and its pharmacological treatment increases among anesthesia professionals.

**SWOT Analysis**

**Strengths:** Journals reach a large audience. A review course, especially one offering CEUs, can serve as a motivational tool for readers to participate in learning. Cost of intervention is low and potential for making an impact is high.

**Weaknesses:** The review course manuscript may not gain acceptance for publication. If published, the course material may be considered impertinent material and overlooked by readers. Dissemination through publication adds to the information overload faced by healthcare professionals. Facility policy could affect the implementation of recommendations and practitioner ability to individualize patient treatment based on new knowledge.
**Opportunities:** An opportunity for vast knowledge transformation exists through publication with a nationally distributed journal. Anesthesia professionals may awaken to the importance of PAS and its pharmacological treatment. With increased knowledge and implementation of recommendations, patient outcomes could improve.

**Threats.** Introduction of new pharmacological treatments successful at cessation of PAS could affect the credibility of the review course recommendations. New evidence regarding PAS contradictory to discovered/summarized evidence in this paper could jeopardize the validity of the intervention.
PART FIVE

Evaluation

Discussion

The evidence points to many situations in which healthcare professionals should not use meperidine or should use it with caution. Currently meperidine is considered an acceptable therapy for the treatment of PAS; however, the progressive movement away from using this drug in the USA could easily pave the way toward meperidine becoming a drug of the past. In such an event, healthcare professionals must be prepared to choose an alternative course of action. The referenced studies and systematic reviews support a favorable argument for alternative treatments for PAS, including doxapram, clonidine, nalbuphine, and tramadol. When meperidine is not available or ideal, treatment of PAS should include these alternative agents. The need for translating evidence into clinical practice is clear. In the treatment of PAS, the evidence points toward minimizing the use of meperidine and increasing the use of the alternative, available treatments doxapram, clonidine, and nalbuphine.

Maintaining an educational outreach focus, this author deemed submission for publication of a journal review course as an appropriate interventional goal. The process of developing the journal review course was given great consideration. Recommended guidelines for writing such an evidence-based clinical review were obtained and followed.\textsuperscript{18} (p116-118),36,37 Discovery, evidence summary, and translation assisted in determining information essential for inclusion in the review course, with special consideration given to simplifying information while maintaining validity and eliminating bias.

The “AANA Journal Course Requirements” served as an additional reference upon writing the review course. Prior to submitting the review course for publication, an experienced editor/reviewer will assist in the process of review course development and format.
content and context were evaluated by feedback from this author’s TCU advisors (See Manuscript in Appendix D.)

In addition, the process of composing good, clear multiple-choice questions was a process in itself. The production of high-quality multiple choice questions followed Campbell’s guideline.\(^{38}\) Comparing the written questions with the guideline served to evaluate the process of creating the questions. Feedback from TCU advisors served to evaluate question content and clinical relevance. (See Questions in Appendix F)

The desired outcome for the intervention is acceptance of the journal review course for publication. Success of the review course will be evaluated through inquiry with the publishing journal regarding course distribution, returned quizzes, and quiz grades.

**Process Evaluation**

Numerous modifications were made during the process of constructing the review course and questions. The body of the review course adhered to the stated objectives and the questions remained in alignment with the purpose of the course. During the process of intervention development, the literature was maintained as the focus point. Evaluation of the process in creating an effective, evidence-based review and relevant questions resulted in a product worthy of dissemination.

**Conclusions**

Conclusions drawn from this study are multiple and straight-forward. PAS is a common occurrence with numerous deleterious sequelae and when prevention of PAS fails, pharmacological treatment should occur. Meperidine is the drug most frequently used for the cessation of PAS; however, meperidine is contraindicated in many patient populations and a trend toward reducing the use of meperidine is growing. Fortunately, multiple studies have discovered other effective pharmacological options including doxapram, nalbuphine, clonidine, and tramadol.
Based on the findings, this author recommends the following:

- The prevention of PAS, through intraoperative warming, should be considered standard practice.\(^8\)
- Prior to selecting meperidine for PAS treatment, its potential adverse effects, contraindications and availability should be considered.\(^{10}\)
- When meperidine is not ideal or available to treat PAS, doxapram, clonidine, nalbuphine, and tramadol are effective options. Healthcare professionals should contemplate possible physiological effects of each drug when selecting an appropriate agent.\(^{5,13,14,15,16,17}\)
- More studies are needed regarding side effect profiles of the afore-mentioned drugs, so healthcare professionals can tailor treatment more specifically to the patient.
- Anesthesia practitioners and PACU nurses should understand the etiology, risk factors, prevention, consequences, and pharmacological treatment options in the treatment of PAS in order to best individualize patient treatment and improve patient outcomes.
- FDA approval of Tramadol in the USA would provide practitioners with a pharmacological treatment for PAS that is equally effective to meperidine.\(^{5,13,14,15,17}\)

**Implications**

**Lessons Learned**

The initial topic for this project was emergence from volatile anesthetic agents (VAAs). After a synthesis of the literature failed to reveal new information not already known by most anesthesia professionals, the subject changed to selection of VAAs by anesthesia professionals. Upon attempting to locate literature on this new topic and contemplating how to produce a focused intervention, it became evident too many variables existed to make this topic an appropriate project focus. The time and effort spent on the failed topics taught this author a lesson in patience.
After completing a new evidence synthesis on the pharmacological treatment of PAS, this author learned another lesson. The initial focus of the study was simply the comparison of tramadol and meperidine for cessation of PAS. It wasn’t until intervention development that this author realized IV tramadol isn’t FDA approved in the USA. This author wanted to continue with the same focus; therefore, an intervention of writing a systematic review to submit for publication in a peer-reviewed journal with a worldwide audience was chosen. Quickly that intervention fizzled because a peer-reviewed journal with a worldwide audience had already published such a systematic review. A lesson on the importance of thorough investigation was learned since verifying FDA status of tramadol wasn’t an early thought in the process when researching the literature.

The world of publication is a large one. Confusion and frustration can easily fill any author who is new to this world. Maintaining a focus on FDA information is paramount. This author only learned of a huge factor; AANA Journal will not publish recommendations that are not labeled by FDA for that particular use, after the review course was written. A final learned lesson was letting the evidence speak for itself. Once this author delved into the evidence, the intervention emerged on its own. As a result, using the ACE Star Model for knowledge transformation was a smooth process and an evidence-based intervention was born.

**Future Directions**

In the future, this author is hopeful IV tramadol will gain FDA approval for use in the USA. The inclusion of this drug in the nation’s formulary will provide anesthesia professionals with an equal substitute for meperidine when treating PAS. Additional studies on the comparable efficacy of meperidine, tramadol, doxapram, nalbuphine, and clonidine for the treatment of PAS will provide an increased volume of information upon which to base clinical decisions. Also, future studies are needed to assess the side effect profiles of each of the above mentioned drugs.
Hopefully, the future will find healthcare professionals using evidence, rather than tradition, when choosing treatment for PAS.
References


34. Stevens KR. ACE star model of EBP: Knowledge transformation. Academic Center for Evidence-Based Practice, The University of Texas Health Science Center at San Antonio. 2004.

35. Foster SD, Faut-Callahan M. A professional study and resource guide for the CRNA. AANA Pub; 2001.


Appendix A

Table A1  Evidence Table

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Level of Evidence</th>
<th>Drugs Compared</th>
<th>Major Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kranke, Eberhart, Roewer &amp; Tramer</td>
<td>2002</td>
<td>I</td>
<td>meperidine, clonidine, ketanserin, doxapram.</td>
<td>Meperidine performed consistently best in stopping PAS. Clonidine, ketanserin and doxapram also effective. Insufficient amount of data existed for inclusion of Tramadol.</td>
</tr>
<tr>
<td>Charuluxananan, Trakulthong, Areejunthawat, et al.</td>
<td>2009</td>
<td>I</td>
<td>meperidine, tramadol, clonidine, ketanserin, doxapram, nalbuphine</td>
<td>Tramadol and meperidine were equally effective in stopping PAS. Clonidine, ketanserin, doxapram and nalbuphine were effective alternative treatments.</td>
</tr>
<tr>
<td>Dhimar, Patel &amp; Swadia</td>
<td>2007</td>
<td>II</td>
<td>tramadol, meperidine</td>
<td>Equally efficacious, but tramadol more potent (worked faster), so tramadol qualitatively superior for controlling PAS.</td>
</tr>
<tr>
<td>Mohammadi, Khajavi, Imani, Azodi, Tavakoli &amp; Khashayar</td>
<td>2010</td>
<td>II</td>
<td>tramadol, meperidine</td>
<td>Tramadol and meperidine were equally effective in treating PAS.</td>
</tr>
<tr>
<td>Shrestha</td>
<td>2009</td>
<td>II</td>
<td>doxapram, meperidine</td>
<td>Meperidine more effective than doxapram, although not statistically significant, therefore both alternatives for treating PAS.</td>
</tr>
<tr>
<td>Zahedi</td>
<td>2004</td>
<td>II</td>
<td>tramadol, meperidine</td>
<td>Tramadol superior due to faster termination of PAS, no recurrence and less adverse effects compared to meperidine</td>
</tr>
</tbody>
</table>
Appendix A

Legend for Table A1

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials (RCTs), or evidence-based clinical practice guidelines based on systematic reviews of RCTs</td>
</tr>
<tr>
<td>Level II</td>
<td>Evidence obtained from at least one well-designed RCT</td>
</tr>
<tr>
<td>Level III</td>
<td>Evidence obtained from well-designed controlled trials without randomization</td>
</tr>
<tr>
<td>Level IV</td>
<td>Evidence from well-designed case-control and cohort studies</td>
</tr>
<tr>
<td>Level V</td>
<td>Evidence from systematic reviews of descriptive and qualitative studies</td>
</tr>
<tr>
<td>Level VI</td>
<td>Evidence from single descriptive or qualitative study</td>
</tr>
<tr>
<td>Level VII</td>
<td>Evidence from the opinion of authorities and/or reports of expert committees</td>
</tr>
</tbody>
</table>

### Appendix B

**QUORUM statement checklist**

<table>
<thead>
<tr>
<th>Heading</th>
<th>Subheading</th>
<th>Descriptor</th>
<th>Reported? (Y/N)</th>
<th>Page number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>Identify the report as a meta-analysis [or systematic review] of RCTs</td>
<td>Yes</td>
<td>351</td>
<td></td>
</tr>
<tr>
<td>Abstract</td>
<td>Use a structured format</td>
<td>Yes</td>
<td>351</td>
<td></td>
</tr>
<tr>
<td><strong>Describe</strong></td>
<td><strong>Objectives</strong></td>
<td>The clinical question explicitly</td>
<td>Yes</td>
<td>351-352</td>
</tr>
<tr>
<td><strong>Data sources</strong></td>
<td>The databases (ie, list) and other information sources</td>
<td>Yes</td>
<td>352</td>
<td></td>
</tr>
<tr>
<td><strong>Review methods</strong></td>
<td>The selection criteria (ie, population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication</td>
<td>Yes</td>
<td>352-354</td>
<td></td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals); and subgroup analyses</td>
<td>Yes</td>
<td>353</td>
<td></td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td>The main results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Introduce</strong></td>
<td><strong>Introduction</strong></td>
<td>The explicit clinical problem, biological rationale for the intervention, and rationale for review</td>
<td>Yes</td>
<td>351-352</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td><strong>Searching</strong></td>
<td>The information sources, in detail (eg, databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication)</td>
<td>Yes</td>
<td>352</td>
</tr>
<tr>
<td><strong>Selection</strong></td>
<td>The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design)</td>
<td>Yes</td>
<td>352-354</td>
<td></td>
</tr>
<tr>
<td><strong>Validity assessment</strong></td>
<td>The criteria and process used (eg, masked conditions, quality assessment, and their findings)</td>
<td>Yes</td>
<td>352-354</td>
<td></td>
</tr>
<tr>
<td><strong>Data abstraction</strong></td>
<td>The process or processes used (eg, completed independently, in duplicate)</td>
<td>Yes</td>
<td>352-353</td>
<td></td>
</tr>
<tr>
<td><strong>Study characteristics</strong></td>
<td>The type of study design, participants’ characteristics, details of intervention, outcome definitions, &amp;c, and how clinical heterogeneity was assessed</td>
<td>Yes</td>
<td>354</td>
<td></td>
</tr>
<tr>
<td><strong>Quantitative data synthesis</strong></td>
<td>The principal measures of effect (eg, relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias</td>
<td>Yes</td>
<td>354</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td><strong>Trial flow</strong></td>
<td>Provide a meta-analysis profile summarizing trial flow (see figure)</td>
<td>Yes</td>
<td>353</td>
</tr>
<tr>
<td><strong>Study characteristics</strong></td>
<td>Present descriptive data for each trial (eg, age, sample size, intervention, dose, duration, follow-up period)</td>
<td>Yes</td>
<td>355-356</td>
<td></td>
</tr>
<tr>
<td><strong>Quantitative data synthesis</strong></td>
<td>Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg 2X2 tables of counts, means and SDs, proportions)</td>
<td>Yes</td>
<td>357</td>
<td></td>
</tr>
<tr>
<td>Discussion</td>
<td>Summarize key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg, publication bias); and suggest a future research agenda</td>
<td>Yes</td>
<td>359-360</td>
<td></td>
</tr>
</tbody>
</table>
Appendix C

Review Course

Pharmacological Treatment of Post-Anesthetic Shivering: Is Meperidine Losing Favor?

Keywords: post-anesthetic shivering, post-anesthetic shaking, post-operative shivering, post-operative shaking, meperidine

Abstract:

Shivering is a common occurrence during the immediate period following general or regional anesthesia and can jeopardize the recovery of patients. The detrimental effects of post-anesthetic shivering (PAS) are often underestimated by anesthesia professionals, yet can include an increase in oxygen consumption up to 600%. Two types of shivering have been identified and while one type has traditionally been attributed to hypothermia, the etiology for the other is only theorized. Many presdisposing risk factors have been identified; including young age, orthopedic surgery, duration of surgery, pain and hypothermia. Although meperidine has long been the most frequent pharmacological treatment for PAS, literature regarding its side effects is accumulating and a national trend toward restricting its use is in progress. Fortunately, evidence supports alternative therapeutic interventions, including clonidine, doxapram, nalbuphine and tramadol.

Objectives:

Upon completion of this course, the reader should be able to:

1. Define post-anesthetic shivering (PAS) and discuss its incidence rate.

2. Identify physiological consequences which may result from its occurrence and describe the types of shivering.

3. Discuss PAS etiology theories and predisposing factors which increase the risk for this condition.
4. Identify evidence based interventions for managing PAS, the most common pharmacological treatment for PAS and this drug’s associated side effects.

5. Discuss effective evidence-based pharmacological alternatives for treatment of PAS and their proposed mechanisms of action.

Introduction

Patients presenting to a Post-Anesthetic Care Unit (PACU) following general or regional anesthesia are at risk for shivering. Scholars refer to this potential complication as post-anesthetic shivering (PAS) and describe it as spontaneous, uncontrollable muscular shaking, which increases metabolic heat production. The shivering response involves skeletal muscle contraction which increases metabolic heat production in effort to maintain a normal body temperature within the narrow range of 36.5ºC-37.5ºC.\(^1\) Multiple studies estimate the incidence of shivering varies to be between 5% and 65% and consider shivering one of the leading causes of discomfort in the recovering.\(^2-5\) Although the exact cause of this phenomenon is not known, patient frustration, discomfort and physiological disturbances are evident.\(^1,2,6\)

Consequences of Post-anesthetic Shivering

Apart from being bothersome to the patient, PAS can result in many worrisome physiological effects. Among the various consequences of PAS, an increase in oxygen consumption is the most documented, and arguably the most important, ill effect. The amount of oxygen consumed by the patient can increase up to 600%, potentially creating a mismatch between oxygen delivery and oxygen demand.\(^1,2,5-7\) If oxygen demand exceeds oxygen delivery, the body will begin to compensate by increasing cardiac output and heart rate. If demand is still not met, increased oxygen consumption will occur resulting in decreased SVO2 (mixed venous oxygen saturation). If demand still exceeds delivery, the last compensatory mechanism, anaerobic metabolism and metabolic acidosis, can result. These changes may be benign in the person with adequate
physiologic reserve; however, there is potential for detrimental cardiac effects in those who cannot afford these stressful compensatory mechanisms.\textsuperscript{8}

Additional potentially deleterious sequelae include increased minute ventilation and carbon dioxide production, catecholamine release, tachycardia, and hypertension. Increased intraocular and intracranial pressures, increase in pain from aggravated surgical incisions, and difficulty monitoring patients can also result from PAS.\textsuperscript{5-7,9} Considering these detrimental effects, patients most likely to suffer from PAS include those who cannot tolerate the cardiorespiratory effort or energy expenditure of oxygen. This would include, but are not limited to, weak or respiratory compromised patients, those at risk for myocardial ischemia, and anemic patients.

It is important to realize PAS usually coexists with hypothermia.\textsuperscript{2(p2194),6} Controversy exists over which of these two, PAS or hypothermia, is responsible for the development of undesirable cardiac and/or respiratory events.\textsuperscript{2 (p2194),10} In view of this controversy, practitioners should maintain patients’ body temperature in an acceptable range during and following general and regional anesthesia.\textsuperscript{5,11} However, normothermic patients also experience PAS, and considering its uninviting consequences, vigilance in treating all occurrences in the PACU is warranted.\textsuperscript{2 (p2194),5,6}

**Thermoregulatory Response**

Researchers often refer to normal body temperature as a “set point.” Even slight deviations from this point initiate autonomic thermoregulatory responses such as shivering, vasoconstriction, and sweating. Many pharmacological agents, such as opioids and general anesthetics, increase the sweating threshold while reducing the shivering threshold which means core temperature can rise or fall to a greater degree before sweating or shivering occurs, respectively. The interthreshold range is the range between which these thermoregulatory defenses, shivering and sweating, are not triggered. When body temperature falls outside of this range due to hypo- or hyperthermia, thermoregulatory responses occur.
Hypothermia occurs during surgery as a result of anesthetic-induced inhibition of thermoregulation. Researchers refer to hypothermia induced shivering as thermoregulatory shivering. Thermoregulatory shivering is associated with cutaneous vasoconstriction. The second type of shivering is non-thermoregulatory shivering, which occurs with cutaneous vasodilation. The exact mechanism for this type of shivering is not clear.

**Etiology Theories**

As early as 1972, post-anesthetic shivering has been a well-documented phenomenon; however, its etiology remains controversial. Most authors agree hypothermia is the major contributor to PAS because general and regional anesthesia impair thermoregulation via various mechanisms. A common theory is that when anesthetic induced thermoregulatory inhibition dissolves and the shivering threshold is increased toward normal, shivering occurs as a result of the difference between the low body temperature and now near-normal threshold. While this theory explains thermoregulatory shivering, many shivering patients are normothermic, pointing to a non-thermoregulatory mechanism.

The realization that not all shivering stems from hypothermia led to other theories, including stress, hypoxia, hypocarbia, sympathetic overactivity, and pain. Another theory that gained attention is that of uninhibited spinal reflexes. This theory is based upon the thought that the spinal cord recovers faster than the brain, resulting in spinal reflexes that are uninhibited and manifested as clonic activity. Of these theories, pain is the most supported. To test the hypothesis that postoperative pain facilitates nonthermoregulatory shivering, Horn et al performed a randomized controlled trial (RCT) on 74 adult patients undergoing elective arthroscopic knee surgery. In this study, with anesthetic management and body temperature similar among all participants, no patients administered intra-articular lidocaine and 43% of patients given intra-articular saline shivered, respectively. The study concluded that
nonthermoregulatory shivering was prevented through the reduction of surgical pain. More studies of this kind are needed in order to strengthen theories related to PAS.

**Identifying Patients at Risk**

Fast and efficient efforts to manage a problem are more likely to occur when the complication is predictable. As afore-mentioned evidence suggested, patients with core body temperature below interthreshold range and those experiencing pain are at increased risk for PAS. The more severe the hypothermia; the greater likelihood of PAS. Eberhart and colleagues performed a study aimed at identifying risk factors for PAS after general anesthesia. After recording and analyzing data in 1340 consecutive adult patients, the incidence of PAS was calculated to be 11.6%. These authors identified three major risk factors for the development of PAS, including young age, orthopedic surgery, and core hypothermia. Longer duration of surgery was also associated with an increased risk for shivering, although the authors did not mention exact length of time. Of the three major risk factors, the study identified age as the most important, accounting for over 70% of the predictive power of the model used in the study.

This study used an elaborate formula to estimate likelihood of shivering based on age. Here is a small summary of findings based on age: patients without shivering (n=884) age was 55+/-18; patients with shivering (n=116) age was 40+/-18. Increased risk of PAS was found following endoprosthetic surgeries, particularly those requiring use of bone cement. The authors theorized "bone cement stimulates release of cytokines such as alpha-tissue necrosis factor and interleukin-6; both of which can increase the set point of the thermoregulatory system postoperatively." 17(1855)

While some authors found increased susceptibility for PAS among males, others came to conflicting conclusions regarding this factor. Still another risk factor discovered in the literature points to the anesthetic agent selection. Practitioners may be capable of reducing the risk for PAS by altering which agent is chosen as the administered anesthetic. Research has
linked propofol with a decreased likelihood for PAS, while halogenated agents, pentothal, and small opiate doses have favored PAS. Established guidelines for predicting PAS could not be found by this author; however, Eberhart suggested their study findings can accurately predict a patient’s risk. Remaining cognizant of risk factors for PAS genesis may result in avoided or quickly resolved occurrences; therefore, heightened practitioner awareness of the potential seriousness of this condition is warranted.

Managing Shivering with Evidence Based Interventions

A gold standard of practice in treating PAS is lacking. As with all medical complications, prevention is ideal. In effort to avoid PAS and other thermally associated postoperative complications, Scott and Buckland advocate intraoperative prevention of hypothermia as standard practice. Prevention of hypothermia is accomplished mainly through the use of forced air warmers. When prevention fails or shivering is non-thermoregulatory, pharmacological intervention is warranted. In addition to patient warming devices, numerous drugs have shown efficacy in preventing and treating PAS, including clonidine, doxapram, nalbuphine, tramadol, and meperidine.

Meperidine. Introduced as an antispasmodic drug in 1939, meperidine remains the most frequently used pharmacological agent for PAS cessation and is central to many PAS protocols. It is a well-known drug, familiar to most medical staff, possesses a reputation as a modality for the treatment of pain and shivering, and has been readily available in the past. Research has provided abundant documentation regarding meperidine’s potent anti-shivering effects; however, the mechanism for these effects is poorly understood. This drug exerts its action on κ-opioid receptors (KOR) and μ-opioid receptors (MOR), whereas pure μ-agonists, such as fentanyl and morphine, only work on MOR. KOR and MOR are types of opioid receptors where opiates bind in order to exert their action. Researchers know meperidine treats PAS better than pure μ-agonists, but they can only speculate about the reason.
Naloxone is an opioid antagonist which blocks MOR and KOR, reversing the effects of opioids bound to these sites. Naloxone has a high affinity for MOR and a low affinity for KOR therefore a low dose only affects MOR. A higher naloxone dose is needed to reach KOR. Because the anti-shivering action of meperidine was inhibited by high-dose naloxone but not by low-dose naloxone, the theory that meperidine’s effect on PAS is mediated by its action on KOR was developed.5,10,22

Another reason meperidine ceases shivering is due to its ability to decrease the shivering threshold almost twice as much as the vasoconstriction threshold, which means body temperature can drop lower than normal before onset of vasoconstriction and shivering.22 (p1049) Additionally, it means vasoconstriction will occur at a higher temperature than required to initiate shivering. Although this explains meperidine’s effect on hypothermic shivering, it does not clarify meperidine’s effect on normothermic shivering. Nonetheless, meperidine, along with the other recommended drugs for cessation of PAS, has been successful as anti-shivering regimens for both hypothermic and normothermic patients.

Meperidine: Drug of the Past? Meperidine has been associated with multiple side effects, such as delirium, hallucinations, seizures, reversible Parkinsonism, urinary retention, constipation, and mydriasis. In addition, potentially lethal pharmacodynamic effects can occur when meperidine interacts with monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs).21,23 In the 1990’s, following an increased awareness of meperidine’s side effects, clinical guidelines began discouraging the use of meperidine and several major institutions severely restricted its use or removed it entirely from their formularies.21 (p62),24

In 2002, Latta et al21 published an extensive review of meperidine, examining every paper previously published on this drug. They listed respiratory depression, tachycardia, xerostomia, agitation, confusion, and chemical dependency potential as side effects of meperidine. The final conclusion of this review was that “meperidine is a medication whose time
has passed in routine pain management and whose use must be questioned in all instances.”

Though complex, the researchers base their conclusion partially on evidence that meperidine’s metabolite, normeperidine, is neurotoxic and can cause anxiety, myoclonus, seizures, mood changes, and hyperreflexia within 24 hours. The authors point to an educational gap as the reason meperidine is still being used despite its documented side effects. According to Latta, many governmental, professional, and accreditation organizations see meperidine use as a negative marker; therefore, health care professionals should look at its use more carefully.

The Institute for Safe Medication Practices Canada (ISMP Canada) issued a safety bulletin on meperidine. In this 2004 publication, ISMP Canada recommended healthcare facilities evaluate the use of meperidine and limit this drug’s use to treatment of postoperative shivering, treatment of short term pain, and prevention/treatment of drug-induced or blood product-induced rigors. The bulletin also recommended removal of all oral meperidine from the formulary and avoidance of meperidine use in elderly patients. While ISMP considered PAS treatment an appropriate use of meperidine, this bulletin supported the notion that meperidine’s popularity is rapidly declining.

An editorial published in Hospital Pharmacy added to ISMP Canada’s recommendation by stating meperidine is contraindicated in patients with renal dysfunction or patients receiving monoamine oxidase inhibitors (MAOIs). The editorial continued by stating caution should be used in patients with “gastrointestinal obstruction, ileus, ulcerative colitis, pre-existing constipation, pulmonary disease, respiratory depression, history of substance abuse, head trauma, increased intracranial pressure, glaucoma, hepatic disease, pregnancy, seizure disorders, cardiac arrhythmias, urinary retention, oliguria, and the elderly.”

Although organizations typically consider the treatment of PAS an appropriate use of meperidine, given contraindications don’t exist, the potentially dwindling availability and declining popularity of this drug demand the exploration of substitute treatments.
with ample supply of meperidine, the popularity of this drug could easily decrease due to facility imposed restrictions, practitioner awareness of its adverse effects, and increasing patient population contraindications. Dwindling access to meperidine and increasing knowledge regarding its adverse effects, make it prudent to explore pharmacological treatment alternatives for PAS. Fortunately, various studies have explored this topic, exposing a few successful options. Though many medications have contended for a title of success in treating PAS, evidence was only sufficient to recommend clonidine, doxapram, nalbuphine, and tramadol. A systematic review of 32 RCTs published by Charuluxanan and colleagues concluded meperidine 25 milligrams (mg) and tramadol 0.5-1 milligrams per kilogram (mg/kg) were equally effective treatments, and recommended clonidine 30-150 mcg, nalbuphine 0.05-0.1 mg/kg, and doxapram 25-100 mg as effective therapeutic alternatives.  

**Clonidine.** Better known for its anti-hypertensive effects, clonidine is another treatment effective for PAS cessation. While it is known clonidine mainly exerts its action on alpha 2 adrenergic receptors found throughout the body, explanations for clonidine’s anti-shivering effects are merely suggestions. One theory involves the hypothalamus. The hypothalamus, where alpha 2 receptors are found, is responsible for controlling body temperature. Clonidine is thought to works on hypothalamic receptors to inhibit vasoconstriction and shivering or at other CNS levels by altering incoming thermal information. However, most credit is given to clonidine’s ability to reduce the thermoregulatory thresholds for vasoconstriction and shivering. Regardless of which theory is correct, many studies have focused on clonidine for the treatment of PAS and its use has been successful for the cessation of PAS. Hypotension and bradycardia are possible side effects of clonidine; however, their occurrence appears to be typically mild enough to not warrant treatment.

**Doxapram.** Introduced in the 1960’s, healthcare professionals used doxapram as a strong, dose-dependent, respiratory stimulant; to treat drug-induced CNS depression; and to improve
arousal and level of consciousness following anesthesia. Researchers thought these effects resulted from central nervous system (CNS) stimulation; however, controversy still exists as to its principal site of action. The use of this drug for the cessation of shivering was discovered in 1993, yet the mechanism for this action also isn’t clear. Studies have shown doxapram lowers the shivering threshold, allowing the body to reach lower temperatures before shivering occurs. What isn’t made clear through the evidence is how a CNS stimulant, with a potential side effect of muscular spasticity, can combat PAS, which involves muscular shaking. Revisiting the theory that shivering occurs after general anesthesia because the spinal cord recovers faster than the brain, doxapram’s central nervous stimulation could combat the uninhibited spinal reflexes presumably responsible for shivering.

Some authors anticipate doxapram will find a new niche for managing obstructive sleep apnea, a disorder commonly seen in the PACU setting. Considering the better known effects of doxapram, respiratory stimulation and improving arousal, the use of this drug to treat PAS in the PACU setting may lead to multiple improved patient outcomes; however, it must be a patient specific treatment. Patients with a seizure disorder, head injury, or cerebral vascular injury should not be given doxapram as controversy exists as to whether this drug is proconvulsant. Also, studies have noted agitation in patients with liver insufficiency who were administered doxapram. Although conflicting data exists, doxapram can lead to a slight increase in blood pressure and the occurrence of non-life threatening dysrhythmias. Most importantly, doxapram is contraindicated in patients with mechanical disorders of ventilation as the respiratory stimulant effect does not treat the underlying physiological problem and may worsen respiratory fatigue. Although healthcare professionals should take these precautions, Charuluxanana only describes nausea and vomiting as a witnessed side effect among 32 RCTs.

**Nalbuphine.** Nalbuphine, a semisynthetic agonist-antagonist opioid, is best known for its analgesic properties. This drug, like meperidine, acts as an agonist at KORs and has a high...
affinity for these receptors. Therefore, as with meperidine, nalbuphine’s anti-shivering properties are possibly attributed to KOR agonism, yet is not completely known. Unlike meperidine, nalbuphine has MOR antagonistic properties similar to naloxone, a drug which reverses the effects of opioids. Nalbuphine also comparably reduces the shivering and vasoconstriction thresholds, another possible reason for its anti-shivering effects. While the mechanism of action for nalbuphine is still up for debate, studies have found this drug effective for the treatment of PAS. Each of the pharmacological agents mentioned in this review, except clonidine, is associated with nausea. Nalbuphine is no exception; however, unlike meperidine, nalbuphine was not associated with drowsiness or respiratory depression.

**Tramadol.** Tramadol, a synthetic opioid, was synthesized in 1962 and introduced to the USA in 1995. Tramadol, a centrally acting analgesic, also possesses anti-shivering properties theoretically by blocking serotonin reuptake, inhibiting norepinephrine transport function, and mimicking opioids through weak mu-receptor agonist activity. Researchers believe that by blocking the reuptake of norepinephrine and serotonin, tramadol activates descending inhibitory spinal pathways which leads to termination of shivering. As with meperidine, many potential mechanisms have been postulated to explain tramadol’s effect on the prevention and treatment of PAS, but data is inconclusive. Interestingly, this drug is finding favor in the eyes of researchers worldwide when compared to meperidine for the treatment of PAS.

**A Glimpse into the Future: Meperidine versus Tramadol?** Tramadol is equally effective, if not superior, to meperidine in multiple randomized controlled trials and systematic reviews. Although tramadol use is extensive in other countries, its intravenous (IV) formula is not currently approved in the United States of America (USA) by the Food and Drug Administration (FDA). Tramadol use in other medication forms is increasing in the US; therefore, in the event its IV form becomes available, healthcare professionals should be aware of its effectiveness against PAS.
Summary

Meperidine. Meperidine has the longest standing history as a medical treatment for PAS.\textsuperscript{10} Not surprisingly, meperidine also has the most substantial amount of evidence supporting its use as an anti-shivering regimen.\textsuperscript{21} These combined factors explain why it is the most frequently used pharmacological agent for the cessation of PAS; however, the popularity of meperidine is currently diminishing on account of its undesirable side effects\textsuperscript{21,24-26} Researchers have made a favorable argument for alternative treatments for PAS; including doxapram, clonidine, nalbuphine, and tramadol.

When meperidine is not available or ideal; these alternative pharmacological agents should be used for the treatment of PAS. The evidence points to many situations in which healthcare professionals should not use meperidine or should use it with caution. Although meperidine is currently considered an acceptable therapy for the treatment of PAS, except in patients with contraindications,\textsuperscript{21,23} the progressive movement away from using meperidine in the USA could easily pave the way toward meperidine becoming a drug of the past. In the event this happens, healthcare professionals must be prepared to choose an alternative course of action.

Doxapram, Clonidine, and Nalbuphine: Alternative Treatments. Anesthesia practitioners and PACU nurses may be surprised to learn of these alternative treatments for PAS cessation, as each of these drugs is better known for other therapeutic uses. As with meperidine, the physiological rationale for their success in treating this condition, though studied and theorized, is not known for certain. The knowledge that meperidine is most frequently used for PAS cessation, coupled with growing evidence regarding its undesirable effects, points to a need for increased consideration of the alternate drugs. The pharmacological options discovered through a review of the literature, are currently accessible and reasonable to use in the post-operative setting. Cost, facility policy, or simply the lag time between research and evidence implementation could all factor into the underutilization of these treatment alternatives.
Healthcare professionals, including anesthesia practitioners and PACU nurses, must encourage the use of evidence-based practice in the treatment of all conditions, including PAS.

**Improving Patient Outcomes.** Though frequently observed in PACU settings, the importance of PAS is often underestimated; however, PAS jeopardizes recovery from general or regional anesthesia. In addition to patient discomfort and frustration, undesirable effects of PAS include increased cardiac demand, carbon dioxide production, and post-operative pain. An increase in oxygen consumption is arguably the greatest adverse effect as it can create a mismatch between oxygen supply and demand, placing compromised patients at risk for undesirable cardiac events.\(^6\)\(^,(p615)\),\(^5\)

For many years, healthcare practitioners have considered meperidine the best pharmacological agent for the treatment of PAS; however, the use of this drug is now controversial on account of its vast number of side effects.\(^17\) Although its use for the treatment of PAS is considered appropriate, patient contraindications, medication availability, and drug popularity could greatly affect the use of meperidine in the PACU setting. Research has shown other medical agents, including tramadol, doxapram, clonidine, and nalbuphine were successful in treating PAS; therefore, these drugs are considered appropriate therapeutic alternatives to meperidine. Although tramadol is not an available option in the USA, the remaining drugs are typically available in today’s hospitals and would be practical in many settings.

Choosing an inappropriate treatment for PAS could jeopardize the safety and recovery of a patient, create patient dissatisfaction, delay discharge from the PACU, and increase health care costs. When meperidine is not an option, practitioners must possess the ability to choose an effective, alternative pharmacological treatment for the cessation of PAS. However, to simply implement a suggested treatment, without knowledge regarding other aspects of PAS, would be imprudent. To improve patient outcomes and satisfaction, anesthesia professionals should possess an understanding of the etiology, risk factors, prevention, consequences, and
pharmacological treatment options in the treatment of PAS. When the best and latest evidence is used to guide practice, patients experience 28% better outcomes; therefore, there is an urgent need for clinicians to translate research evidence into best practices. Unfortunately, even as information technology expands, the translation of research into practice can take as long as 17 years. Higher quality care should not be postponed. The time to act is now.

References


15. Drugs @ FDA page. U.S. Food and Drug Administration Web site. Available at:  


Appendix D

**Review Course Questions**

**Answers**

Pharmacological Treatment of Post-Anesthetic Shivering: Is Meperidine Losing Favor?

1. Post-anesthetic shivering is believed to occur in approximately how many patients recovering from general or regional anesthesia? (Objective 1)
   1. <1%
   2. 1-5%
   3. 5-65% *Objective 1*
   4. >65%

2. Select the true statement about post-anesthetic shivering. (Objective 1)
   1. It is described as spontaneous, uncontrollable muscular shaking.
   2. It involves skeletal muscular contraction which increases metabolic heat production.
   3. The exact cause of post-anesthetic shivering is not known.
   4. *All of the above*

3. Which of the following is NOT a consequence of post-anesthetic shivering? (Objective 2)
   1. increased minute ventilation
   2. oxygen consumption increase up to 600%
   3. *nausea and vomiting*
   4. increased post-surgical pain

4. Non-thermoregulatory shivering is associated with: (Objective 2)
   1. *cutaneous vasodilation*
   2. cutaneous vasoconstriction
   3. unsuccessful peri-operative patient warming
   4. controlled intra-operative patient cooling

5. Most authors agree the major cause of post-anesthetic shivering is: (Objective 3)
   1. pain
   2. anti-cholinergics
   3. *hypothermia*
   4. benzodiazepines

6. In Eberhart’s study, which factor was found most important in determining patient risk for shivering? (Objective 3)
   1. hypothermia
   2. male gender
   3. *young age*
   4. orthopedic surgery

7. The most common pharmacological agent for the treatment of post-anesthetic shivering is meperidine, which can have a lethal interaction with these drugs: (Objective 4)
1. neuromuscular blockers
2. anti-cholinergics
3. mono-amine oxidase inhibitors
4. barbiturates

8. Meperidine’s metabolite, normeperidine, is associated with: (Objective 4)
   1. hyperreflexia
   2. anxiety
   3. seizures
   4. all of the above

9. A systematic review by Charuluxanan et al concluded these drugs were effective alternatives for the cessation of post-anesthetic shivering: (Objective 5)
   1. doxapram, clonidine, nalbuphine, tramadol
   2. clonidine, atropine, tramadol, doxapram
   3. atropine, doxapram, tramadol, ondansetron
   4. ondansetron, nalbuphine, clonidine, tramadol

10. Though not currently approved in intravenous form in the USA, this drug has been found equally effective to meperidine in numerous studies: (Objective 5)
    1. clonidine
    2. tramadol
    3. ondansetron
    4. doxapram