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P. I. Musey

S. D. Linnstaedt

T. F. Platts-Mills

J. R. Miner

A. V. Bortsov

See next page for additional authors

Authors
P. I. Musey, S. D. Linnstaedt, T. F. Platts-Mills, J. R. Miner, A. V. Bortsov, D. C. Lee, C. S. Nam, R. G. Patel, R. B. Fillingim, S. A. McLean, and +12 additional authors

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Gender Differences in Acute and Chronic Pain in the Emergency Department: Results of the 2014 *Academic Emergency Medicine* Consensus Conference Pain Section

Paul I. Musey Jr, MD, **Sarah D. Linnstaedt, PhD**, **Timothy F. Platts-Mills, MD, MSc**, **James R. Miner, MD**, **Andrey V. Bortsov, MD, PhD**, **Basmah Safdar, MD, MSc**, **Polly Bijur, PhD, MPH**, **Alex Rosenau, DO, CPE**, **Daniel S. Tsze, MD, MPH**, **Andrew K. Chang, MD, MS**, **Suprina Dorai, MD**, **Kirsten Engel, MD**, **James A. Feldman, MD, MPH**, **Angela M. Fusaro, MD**, **David C. Lee, MD**, **Mark Rosenberg, DO, MBA**, **Francis J. Keefe, PhD**, **David A. Peak, MD**, **Catherine S. Nam**, **Roma G. Patel, MPH**, **Roger B. Fillingim, PhD**, and **Samuel A. McLean, MD, MPH**

Department of Emergency Medicine, Indiana University School of Medicine, (PIM) Indianapolis, IN; TRYUMPH Research Program (SDL, SAM), Department of Anesthesiology (SDL, AVB, SAM), Department of Emergency Medicine (TFP), University of North Carolina, Chapel Hill, NC; Department of Emergency Medicine, University of Minnesota, (JRM) Minneapolis, MN; Department of Emergency Medicine, Yale University, (BS) New Haven CT; Department of Emergency Medicine, Albert Einstein College of Medicine, (PB) Bronx, NY; Department of Emergency Medicine, Lehigh Valley Health Network (AR, SD) Allentown, PA, Morsani School of Medicine, Univ. Of South Florida, (AR) Tampa, FL; Department of Pediatrics, Columbia University College of Physicians and Surgeons, (DAT) New York, NY; Department of Emergency Medicine, Montefiore Medical Center, (AKC) Bronx, NY; Department of Emergency Medicine, Northwestern Universiy, (KE) Chicago, IL; Depatment of Emergency Medicine, Boston Medical Center, Boston University School of Medicine, (JAF, CSN) Boston, MA; Department of Emergency Medicine, Emory Univeristy School of Medicine, (AMF) Atlanta, GA; Department of Emergency Medicine, North Shore University Hospital, (DCL) Manhasset, NY; Department of Emergency Medicines, St Joseph's Regional Medical Center, (MR) Paterson NJ, and New York Medical College, (MR) Valhalla NY; Department of Psychology and Neuroscience, Duke University, (FJK) Durham, NC; Department of Emergency Medicine, Massachusetts General Hospital, (DAP) Boston, MA; University of Minnesota Medical School, (RP) Minneapolis, MN; University of Florida College of Dentistry, (RBF) Gainesville, FL

Correspondence: Paul I Musey Jr., MD. Indiana University School of Medicine, Fifth Third Faculty Office Building, Third Floor. 720 Eskenazi Avenue, Indianapolis, IN 46202. Pmusey@IU.edu. Office (317) 880-3900. Fax (317) 880-0545.

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A. Consensus Conference Workgroup (alphapetical order):
Polly Bijur, Andrey V. Bortsov, Andrew K. Chang, Kathia Damiron, Luda Diatchenko, Suprina Dorai, Kirsten Engel, James A. Feldman, Roger B. Fillingim, Benjamin W. Friedman, Angela M. Fusaro, Christopher Griggs, Francis J. Keefe, David C. Lee, Sarah D. Linnstaedt, Samuel A. McLean, James R. Miner, Paul I. Musey Jr., Catherine S. Nam, Roma Patel, David A. Peak, Clair Pearson, Timothy F. Platts-Mills, Alex Rosenau, Mark Rosenberg, Basmah Safdar, Daniel S. Tsze

B. List of Pain Breakout Session Attendees (alphabetical order):
Lance Becker, Polly Bijur, Suprina Dorai, Roger Fillingim, Andy Fischer, Colleen Kalynych, David Lee, Hyett Lee, Samuel McLean, James Miner, Paul Musey, Summer Paradise, Roma Patel, Alex Rosenau, Basmah Safdar, Daniel Tsze

Scribes/Tech support assistants: Andrew Fischer, Suprina Dorai, Summer Paradise

Abstract

Pain is a leading public health problem in the United States, with an annual economic burden of more than $630 billion, and is one of the most common reasons that individuals seek emergency department (ED) care. There is a paucity of data regarding sex differences in the assessment and treatment of acute and chronic pain conditions in the ED. The *Academic Emergency Medicine* consensus conference convened in Dallas, Texas in May of 2014 to develop a research agenda to address this issue among others related to sex differences in the ED. Prior to the conference, experts and stakeholders from emergency medicine and the pain research field reviewed the current literature and identified eight candidate priority areas. At the conference, these eight areas were reviewed and all eight were ratified using a nominal group technique to build consensus. These priority areas were: 1) gender differences in the pharmacologic and non-pharmacologic interventions for pain, including differences in opioid tolerance, side effects, or misuse; 2) gender differences in pain severity perceptions, clinically meaningful differences in acute pain, and pain treatment preferences; 3) gender differences in pain outcomes of ED patients across the lifespan; 4) gender differences in the relationship between acute pain and acute psychological responses; 5) the influence of physician-patient gender differences and characteristics on the assessment and treatment of pain; 6) gender differences in the influence of acute stress and chronic stress on acute pain responses; 7) gender differences in biologic mechanisms and molecular pathways mediating acute pain in ED populations; and 8) gender differences in biologic mechanisms and molecular pathways mediating chronic pain development after trauma, stress, or acute illness exposure. These areas represent priority areas for future scientific inquiry, and gaining understanding in these will be essential to improving our understanding of sex and gender differences in the assessment and treatment of pain conditions in emergency care settings.

INTRODUCTION

Pain is a leading public health problem in the United States, with an annual economic burden of more than $630 billion, and is one of the most common reasons that individuals seek emergency department (ED) care.[1] There is a paucity of data regarding sex and gender differences in the assessment and treatment of acute and chronic pain conditions in the ED. In population-based studies, females have been consistently found to experience more severe acute and chronic pain across a range of conditions.[2–4] Similarly, in laboratory-based studies, women have been found to exhibit greater pain sensitivity, enhanced pain facilitation, and reduced pain inhibition compared with men. The magnitude of these sex differences varies across studies. While data are limited, some evidence also suggests there are sex differences in the responses to pharmacological and non-pharmacological pain treatments.[5,6]

Multiple biopsychosocial mechanisms are hypothesized to contribute to sex differences in acute and chronic pain outcomes, including differences in the influence of sex hormones on central and peripheral nervous system function,[2,7,8] and gender differences in stress-induced hyperalgesia vs. analgesia,[8–10] psychological responses to stress and pain,[7,8,11] endogenous opioid function,[12,13] and pain reporting.[2,7] The majority of studies that have evaluated biopsychosocial mechanisms mediating gender differences in pain assessments, outcomes, and/or treatment responses were performed in settings that differ markedly from the ED

(e.g., studies of healthy volunteers or population-based studies). Although studies are needed to address these important areas of research in the ED setting, it is not clear how the myriad potential research areas should be prioritized. The goal of this consensus group was to use a consensus process to identify priority research areas related to the influence of gender on pain assessment, treatment, and outcomes in ED populations. Priority areas were defined as those areas most relevant to clinical emergency medicine (EM). In the following sections, we describe the priority areas identified through this consensus process.

METHODS

Consensus was reached on priority themes and questions in the area of sex- and gender-specific research as related to acute and chronic pain using the four-stage nominal group technique.[14] A group of EM and non-EM experts in pain research (see note for listing) nominated and refined these questions through discussions over conference calls and electronic exchanges in the months prior to the conference. In a second iteration, an anonymous web-based survey with the selected questions was sent to all the conference registrants two weeks prior to the survey. On the day of the consensus conference, 16 members (listed in the note) assembled to vote on the questions that were then mapped to priority themes for future research. This group included six females, 11 faculty, three residents, and two medical students. Anonymous responses on written surveys were used in this breakout session to tally the votes. Each question was based on a four-point Likert scale, with 1 being rated as least important and 4 being most important. Weighted vote tallies were calculated for each question by summing the product of the points on the Likert scale (1–4), and the number of votes received. Online pre-conference voting (n = 20) as well as day of consensus conference voting (n = 13) were included for a total 33 surveys tallied. Please see the executive summary elsewhere in this issue for further details of the consensus process.[14]

RESULTS

In the following sections, we describe the priority areas identified through this consensus process. Priority research areas are presented in rank order; this rank order was determined at the conference based on group responses to the 17 pre-conference derived survey questions (Table 1). Thirteen of these questions ultimately were felt to be most relevant by conference participants. These questions were each then mapped to a candidate priority area, shown in Table 2. Eight priority areas were identified and appear in rank order, and are discussed below.

Priority Area 1

Gender differences in the pharmacologic and non-pharmacologic interventions for pain, including differences in opioid tolerance, side effects, or misuse

Rationale: Decades of research indicate that there are gender differences in pain experiences and the effects of analgesics.[15,16] These data suggest that sex- and gender-specific pain treatments might improve patient care. The standard approach for treating moderate to severe pain is to titrate IV opioid analgesics to analgesic effect.[17,18] However,

this approach is often not feasible in the ED given the time-intensive nature of titration and high patient to staff ratios. This issue is particularly problematic given that underdosing of ED opioids is ubiquitous. Knowledge of optimal treatments and doses based on gender, if clinically relevant, could improve ED pain treatment. There is wide variation in individual responses to opioid medications, making the detection of gender differences in the clinical response challenging in light of the complexity of the physiological, genetic, and hormonal determinants of the response. Studies of pain interventions need to build on developing an understanding of the underlying mechanisms of the gender-related differences in pain and response to analgesics, and in the measurement of pain responses. Evidence suggests that women experience more adverse responses to IV opioids than men, particularly nausea and vomiting.[16,19] In the context of acute pain, there is also mixed evidence of greater efficacy of morphine and strong evidence of greater analgesic efficacy of mixed-action opioid agonist-antagonists (pentazocine, nalbuphine, and butorphanol) in women compared to men.[20–24] However, comprehensive data regarding gender differences in responses to μ-opioid analgesics and non-opioid analgesics are lacking.

Additionally, oral opioids are also commonly prescribed from the ED to treat acute pain. While 90% of opioid prescriptions written for ED patients are for appropriate indications, ED providers occasionally have to confront patients seeking opioid analgesics for nonmedical use, and direct appropriate resources for their care.[25] Women progress from use to dependence more quickly than men, suffer more severe emotional and physical consequences of opioid use, and yet underutilize rehabilitation options.[26] More women are prescribed opioids in the ED, have higher dosages prescribed in the ED, and are more likely to have multiple and overlapping prescriptions that put them at risk of abuse.[25] The relationship between gender and vulnerability to opioids is therefore important to understand.

Adult men are two to three times more likely than women to have drug dependence disorders, but the rate of escalation of drug use is higher in women.[27] Women prone to opioid misuse exhibit greater functional impairment, more psychiatric comorbidities, and higher likelihood of using opioids to cope with psychiatric symptoms and pain than men. Women are more likely than men to use opioids consistent with their prescription instructions (i.e. per indicated use to manage their pain), are more likely to use via the intended route of administration (orally or sublingually as opposed to crushing and snorting it), and are more likely than men to have first obtained opioids via legitimate prescriptions.[26] Women also report greater use of prescription co-drugs (e.g. barbiturates, sedatives), which increases their risk of drug interactions. Drug Enforcement Agency (DEA) 2012 data show that the annual retail sales of prescription opioids for nonmalignant pain have increased seven-fold between 1997 and 2006. In addition, the number of fatal overdoses from prescription opioids has also quadrupled during this period, exceeding those from cocaine or heroin. While women are more likely to be regular as well as long-term opioid users,[28,29] and have higher craving for opioids,[30] men are more prone to non-medical abuse of opioids,[31] as well as fatal opioid overdoses.[32,33] Gender differences mediating these findings remain poorly understood, but notable differences have been found in the stress and reward systems of the brain.[34]

Understanding gender-specific differences to pain and therapy may lead to improved pharmacologic and non-pharmacological interventions. In this regard, priority areas for future research include gender differences in:

1. The analgesic response to opioid analgesics and non-opioid analgesics.
2. The adverse events related to the use of analgesic treatments.
3. The response to non-pharmacological interventions for specific pain conditions.
4. Subsequent medication misuse after the initiation of opioid pain treatment in the ED.
5. Risk factors for subsequent medication misuse after the initiation of opioid pain treatment in the ED.
6. Signs and symptoms of opioid misuse.

Priority Area 2

Gender differences in pain severity perceptions, clinically meaningful differences in acute pain, and pain treatment preferences

Rationale: The appropriate management of patients with acute pain relies on being able to accurately interpret self-reported measures of pain and changes in pain scores reported with therapy. Clinical decisions regarding when to administer analgesics, as well as the types of analgesics to administer, are frequently made based on the category of pain severity (i.e. mild, moderate, or severe). This category in turn corresponds to an isolated and self-reported numerical rating scale (NRS) pain score, typically on a range from 0 (no pain) to 10 (worst pain possible).[17,18,35] Instead of using these categories of pain severity as a proxy for the patient's actual desire for analgesia, clinicians may choose to make decisions regarding pain management based on pain scores that provide a more explicit threshold, representing a patient's desire for analgesia.[36–39] If this approach is used, it is important that potential patient misconceptions related to pain treatment be addressed.[40]

The change in pain score that represents an adequate improvement in pain after an analgesic administration (pain relief) is important to identify. For research purposes, the clinically significant difference is also necessary to determine measurement precision to compare the efficacy of different analgesics and modalities of pain control to establish the effect size.[41–47] Research is needed to determine if sex differences exist in responses to commonly used analgesics. If such differences exist, then an evaluation of sex differences may be important to include in trials of new analgesic medications.

It has been shown that sex differences exist in how both adults and children describe and quantify pain, their pain thresholds and tolerances, and their perceptions and sensitivities to pain.[6,24,48–50] If these differences exist in how pain severity, desire for analgesics, and changes in pain scores are perceived, then the use of sex-specific measures could lead to improved care and more precise research measurements. Defining the sex differences for clinically meaningful changes in pain and pain relief would also improve the validity of clinical research investigating pain interventions.

Future research is needed to evaluate both the magnitude and clinical significance of sex-specific differences in pain assessment metrics using validated and developmentally appropriate self-report measures of pain. This indeed is an opportunity for research to directly affect patient-centered outcomes. Priority research in pain assessment should include sex differences in:

1. The correlation of pain scores with different categories of pain severity.
2. Patient threshold of desire for pain treatment.
3. Pain scales that represent adequate analgesia.
4. Pain scale changes that are clinically significant.

Priority Area 3

Gender differences in pain outcomes of ED patients across the lifespan

Rationale: Improving our understanding of gender differences in pain across the life span, from childhood to old age, would create opportunities to better understand and improve the treatment of pain in the ED, and would also shed light on the pathophysiology of pain, which could inform the development of new pain treatments. Among children, the emergence of sex differences in chronic pain conditions begins around puberty, with increasing differences in chronic pain prevalence observed during adolescence.[51] Girls also report higher pain intensity and experience greater behavioral and psychosocial consequences of acute pain conditions.[52–54] There is very limited information available on sex-related differences in treatment effects among children. Among older adults (60 years and above), the prevalence of both acute and chronic pain are also higher among females than males, with 66% of females reporting pain in the past 4 weeks vs. 57% of males, which parallels the higher rate of chronic pain in females than in males among younger adults.[55–58] Differences in responses to treatment for acute pain among the older vs. younger adults have not been well described, nor has the neurobiologic basis of differences in pain experienced between genders among the older adults. Priority areas of research on pain through the lifespan should in include:

1. Gender differences in acute pain for pre-pubertal children and older adults in relation to what has already been observed among adolescents and middle aged adults.
2. Gender differences in how gonadal hormone levels contribute to pain experiences among pre-pubertal children and older adults.
3. How pubertal development rather than age alone contributes to gender differences in pain in the pediatric population.
4. The relationship of gender schemas and their effect on a child's perception and experience of pain.
5. Differences in parental behaviors and responses to a child's experience of pain based on the child's gender and what influence that has on a child's experience of pain.

6. Psychosocial factors that may predict high sensitivity to acute pain and vulnerability to persistent pain differing between girls and boys as well as older adults.

Priority Area 4

Gender differences in the relationship between acute pain and acute psychological responses

Rationale: The psychological response to acute pain depends on both the context in which the pain occurs, and the psychological composition and health of the individual experiencing the pain.[59] Evidence from a variety of sources suggests that adverse acute psychological responses to pain, such as high levels of distress, vary by sex. The preponderance of evidence suggests that women have greater psychological vulnerability to acute pain.[60] Men and women also appear to have different coping mechanisms in response to pain,[61] and women with chronic pain may be more likely to experience depression related to daily pain severity.[62] Acute psychological responses to pain are important not only because they influence the severity of acute pain but also because they may affect risk of progression to chronic pain.[63–65] In addition, acute psychological responses to pain are important because they are potential targets for intervention. In this regard, optimal interventions may differ by sex.[66–69] Effective treatment of pain, patient education, reassurance, and addressing fears about future pain can all help patients control their psychological responses to acute pain, and may improve long-term outcomes.[67,70]

Emergency providers are uniquely positioned to provide therapies that hasten the recovery from acute pain and prevent long-term sequelae. Increased awareness among providers of the distress that commonly accompanies acute pain conditions, and sensitivity to gender differences in distress responses, has the potential to improve both the quality of care and health outcomes. Several specific areas of further research on gender and acute pain include:

1. ED-based studies evaluating gender differences in distress and dissociation in response to acute pain, and, if present, bio-psychosocial factors mediating such differences.
2. ED-based studies evaluating gender differences in clinically relevant responses to acute pain.

Priority Area 5

The influence of physician-patient gender differences and characteristics on the approaches and treatments of pain

Rationale: Studies have demonstrated that patients with pain are markedly undertreated in the ED.[71] Several studies suggest patient and provider gender may interactively contribute to variation in ED provider pain treatment practices. For example, Bernardes et al. found that gender of the treating practitioner influenced pain management practices in the treatment of back pain in clinical vignettes,[72] and another study found that nurses were more likely than physicians to rate pain higher and more willing to administer opioid analgesics to male patients.[73] Marquie et al. found a three-way interaction among physician expertise,

physician gender, and patient gender.[74] Safdar et al. found that female ED practitioners were more likely to administer any analgesics and to use opioids when treating female patients. Male physicians used more opioids when treating male patients.[75]

Despite the above examples, research on this topic is sparse, especially in the ED setting. A focus on physician gender influences in pain management is paramount, as the numbers of female ED physicians increase and the number of ED visits with pain complaints also increases. The knowledge of a potential physician gender bias can alert emergency care practitioners to be more cognizant when providing analgesic care. Additionally, as the work force in the ED shifts to include more physician assistants, nurse practitioners, and in-training residents, it will be important to learn how these differing educational backgrounds and training affect pain treatment. Priority areas for future research on physican-patient gender interactions include:

1. How the gender of the physician affects pain treatment.
2. How the interaction of the gender of the physician and patient influences how analgesia is provided.
3. How the gender of the prehospital health care provider affects the type or amount of pain medication given in the prehospital setting.
4. How the gender of the direct medical oversight physician affects the type or amount of pain medication given in the prehospital setting.
5. How the gender of these two health care providers interact with the patient's gender to influence pain treatment.
6. How the gender of different types of providers in the ED effect pain management.

Priority Area 6

Gender differences in influence of acute stress and chronic stress on acute pain responses

Rationale: Stress-induced analgesia is the phenomenon of reduced pain sensitivity in response to stress exposure. However, hyperalgesia rather than analgesia (i.e., increased rather than decreased pain sensitivity) may also occur following acute stress.[10] Males are more likely to exhibit stress-induced analgesia than females.[76,77] These differences may be modulated by sex hormones,[78] and they are mediated by different neurobiologic mechanisms.[79] Neurobiologic mechanisms that mediate these phenomena in clinical settings and that determine whether analgesia or hyperalgesia occurs remain poorly understood. Most studies evaluating neurobiologic mechanisms have been performed using animal models or have occurred in experimental settings using healthy human volunteers. Because the generalizability of such findings to the ED setting is unclear, studies performed in ED clinical populations are critical. These studies should use a range of methods, including functional genomic, neurophysiologic, neuroendocrine, and pharmacologic approaches. Priority areas of future research on stress and pain should:

1. Evaluate gender differences in stress-induced analgesia and hyperalgesia in common acute pain presentations in the ED.

2. Elucidate the specific neurobiologic mechanisms mediating gender-specific differences in pain sensitivity in response to acute trauma or stress exposure and risk of transition to chronic pain.

3. Evaluate gender-specific differences in how post-stress pain responses are influenced by previous episodes of stress and pain (hyperalgesic priming), and the effect of such responses on the transition from acute to chronic pain.

Priority Area 7

Gender differences in biologic mechanisms and molecular pathways mediating acute pain in ED populations

Rationale: It has been shown that women are more likely to report pain, and when they do, they report more severe pain, more frequent pain, and longer duration of pain than men.[6,61,80–83] Sex steroids contribute to these differences. For example, individuals taking exogenous estrogen as part of gender reassignment experience increases in pain sensitivity, and those taking testosterone often experience improvements in pain.[84] Pain sensitivity also varies across the menstrual cycle.[81] Endogenous opioid system responses also differ between the sexes.[12,13]

Future studies are needed to determine how biologic differences by sex have a clinically relevant role in the assessment of acute pain experiences and in the selection of optimal treatments or treatment doses for individuals presenting with acute pain conditions to the ED. Priority questions for this line of research investigation include:

1. How measurement of acute pain in the ED differs according to gender.

2. How the effects of common acute pain treatments used in the ED differ according to gender.

3. How the rate of adverse effects of pain treatments differ according to gender.

4. How the rate of transition to chronic pain varies by gender for common acute pain conditions.

Priority Area 8

Gender differences in biologic mechanisms and molecular pathways mediating chronic pain development after trauma, stress, or acute illness exposure

Rationale: Contemporary evidence suggests that the transition from acute to chronic pain after trauma, stress, or acute illness exposure results from complex interactions between neurologic, endocrine, and immune systems. Few large-scale studies have directly addressed the role of sex in the transition from acute to persistent pain in ED populations.[85] However, studies have shown that there is no association between sex and poor three-month pain outcomes among ED patients with low back pain or primary headache disorders.[86,87] In addition, research to date demonstrates important sex differences in related biological processes, supporting the potential importance of this research.[88–94] For example, studies

have shown that hormonal variations related to the menstrual cycle affect both neural plasticity and immune system function.[88,93]

Specific areas of inquiry that would help to inform understanding of sex differences in biologic mechanisms mediating the transition from acute to chronic pain after trauma, stress, or acute illness exposure include the following:

1. Longitudinal human cohort studies that use molecular epidemiologic and related approaches to identify biological pathways differentially contributing to chronic pain development in males vs. females.
2. Longitudinal pre-clinical studies that use molecular methods to evaluate biological pathways differentially contributing to chronic pain development in males vs. females.
3. Longitudinal pre-clinical studies where sex-dependent hormone levels can be manipulated (e.g., estrogens, androgens) to determine the effect of such changes on molecular mechanisms mediating the transition from acute to chronic pain.

CONCLUSIONS

Using a consensus process, eight priority research areas were identified that are relevant to clinical emergency care and that have significant knowledge gaps. We recommend that efforts be directed at answering these questions, as they are essential to improving our understanding of the interaction of gender and pain. As with most consensus processes, this list of priority areas is neither definitive nor exhaustive. This list may also not be representative of what all emergency physicians and researchers would find important, and may not be applicable to all practice settings. However, this document should serve as a valuable guide to both researchers and stakeholders seeking important areas of future gender-specific pain research.

There is a great need to advance research in the area of gender and pain. Advancing research in this area has great potential to improve our understanding of pain and pain treatment in the ED. Extramural funding should be sought to address the priority areas discussed and affirmed by the 2014 *AEM* consensus conference group.

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Table 1

Ranked ballot questions from consensus conference

Top Questions	Weighted Vote Tallies*
1. As a clinician how important is it for you to understand sex-specific differences in the vulnerability to opioid tolerance, side effects, or misuse?	120
2. As a clinician, how important is it for you to understand how side effects to commonly used analgesics differ in males and females?	115
3. As a clinician, how important is it for you understand the differential response to oral μ-opioid analgesics and non-opioid analgesics in the ED by male and female patients?	115
4. As a clinician, how important is it for you to understand the differential response to non-pharmacologic interventions for acute pain by males and females?	115
5. As a clinician, how important is it for you to know if there are differences in how males and females self-report pain?	110
6. As a clinician, how important is it for you to know if there are gender -specific differences in the desire for analgesics or types of pain interventions?	107
7. As a clinician, how important is it for you to understand whether gender influences how children experience pain and the optimal pain treatments for children?	107
8. As a clinician, how important is it for you to understand whether gender influences how older adults experience pain and the optimal pain treatments for older adults?	104
9. As a clinician, how important is it for you to understand sex differences in how acute psychological responses affect acute and chronic pain outcomes?	104
10. As a clinician, how important is it for you to be aware of how the gender of physician and patient influence the type and total amount of analgesics provided.	103
11. As a clinician, how important is it for you to understand sex-specific differences in how acute and chronic stress influence pain severity and duration after acute illness or injury?	101
12. As a clinician, how important is it for you to understand the neurobiologic mechanisms mediating sex-specific differences in pain sensitivity in response to acute trauma/stress exposure?	96
13. As a clinician, how important is it for you to understand how sex-specific differences in biological, psychological, and social factors interact to influence the transition from acute to chronic pain?	92
14. As a clinician, how important is it for you to understand the epidemiology of gender-specific differences in factors that influence the development of common chronic ED pain conditions?	84**
15. As a clinician, how important is it for you to understand the biological (nociceptive pathways, physiology, perceptual sensitivity) mechanisms that influence sex differences in acute and chronic pain?	82**
16. As a clinician, how important is it for you to understand the epidemiology of gender-specific differences in factors that influence the development of common acute ED Pain conditions?	81**
17. As a clinician, how important is it for you to have access to information regarding how biological pathways differentially contribute to chronic pain development in males versus females?	61**

These questions were developed by the workgroup pre-conference and voted upon. Each question was based on a four-point Likert scale with 1 being rated as least important and 4 being most important.

*Weighted vote tallies were calculated for each question by summing the product of the point on the Likert scale (1-4) and the number of votes received. Online pre-conference voting (n=20) as well as day of consensus conference voting (n=13) were included for a total 33 ballots tallied.

**Question withdrawn by participants at the conference after discussion.

Table 2

Priority areas created from mapped ranked questions

Survey Question # from Table 1	Corresponding Priority Area
1–4	Priority Area 1: Gender differences in the pharmacologic and non-pharmacologic interventions for pain including differences in opioid tolerance, side effects, or misuse.
5,6	Priority Area 2: Gender differences in pain severity perceptions, clinically meaningful differences in acute pain, and pain treatment preferences.
7,8	Priority Area 3: Gender differences in pain outcomes of ED patients across the lifespan.
9	Priority Area 4: Gender differences in relationships between acute pain and acute psychological responses.
10	Priority Area 5: The influence of physician-patient gender differences in characteristics on the approaches and treatments of pain.
11	Priority Area 6: Gender differences in the influence of acute stress and chronic stress on acute pain responses.
12	Priority Area 7: Biologic mechanisms of molecular pathways mediating gender differences in acute pain in ED populations.
13	Priority Area 8: Gender differences in biologic mechanisms and molecular pathways mediating chronic pain development after trauma stress or injury.