In Education, Research, & Clinical Care:

SexXX Makes a Difference

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Lubbock, TX

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Disclosure

✓ No financial disclosures
✓ Representative of Texas Tech Univ HSC
✓ The information provided by the speaker are her own and not meant to represent official statements of U.S. Food and Drug Administration
Learning Objectives

✓ Understand the unique terms sex and gender

✓ Recognize the limitations of applying a one-sex lens in research, education and clinical care

✓ Apply a sex and gender lens to achieve personalized patient-centered care
Starting on the same page

Definitions
Institute of Medicine Definitions

Source: Exploring the Biological Contributions to Human Health: Does Sex Matter (2001)
SEX

- Chromosomal
- Physiological
- Typically binary
  - Male/Female

GENDER

- Environmental
- Society
- Spectrum
  - Masculine/Feminine
  - Man/Woman
  - Both
  - Neither
Sex

Gender

Gender Identity

Transgender

Biological construct

Social construct (external)

Gender conception of self (internal)

Gender identity differs from the person's sex at birth
Women in Practice: The Female Organs

Breast

Uterus

NOT "bikini medicine"
Sex and Gender in Biomedical Research and Health Policy
In 1977, the FDA recommended that premenopausal women capable of becoming pregnant be excluded from early phases of drug trials. *(Including all women using reliable methods of contraception, women whose male partners had had vasectomies or used condoms, and women who were "single."*)

Although the FDA guidelines pertained only to early phases of drug development, in practice the participation of women in all phases was affected.
“the historical lack of research focus on women’s health concerns had compromised the quality of health information available to women as well as the health care they receive”
• **Consider** the inclusion of women in the study populations for all clinical research efforts.
  • Exceptions would be studies of diseases which exclusively affect males or where involvement of pregnant women may expose the fetus to undue risks.
  • General differences **should be** noted and evaluated.
  • If women are not to be included, a clear rationale **should be** provided for their exclusion.

**Source:** NIH Guide for Grants and Contracts (Vol. 16, pp. 2).
Women were significantly underrepresented in drug trials

Even when women were included, data were not analyzed sufficiently

Recommended ensuring drug companies consistently include “sufficient numbers of women in drug testing”
1993 NIH REVITALIZATION ACT

Women & minorities to be included in clinical research

Ensure that valid scientific analysis *could be* performed in determining whether differences existed between women and minorities in relation to other study subjects

Include both sexes in adequate numbers to ensure data *could be* analyzed for an effect of gender on safety and efficacy of proposed intervention or drug.
Food and Drug Modernization Act:
Congress directs FDA to develop guidance on inclusion of women and minorities in clinical trials

Demographic Rule requires sponsors:
- Tabulate the trial population by age group, sex, and race in Investigational New Drug (IND) applications
- Analyze safety and efficacy by age group, sex, race, and other variables as appropriate in New Drug Applications (NDA)
Drug Trials Snapshots

WHAT IS THE PURPOSE OF DRUG TRIALS SNAPSHOTS?

Drug Trials Snapshots provide consumers with information about who participated in clinical trials that supported the FDA approval of new drugs. The information provided in these Snapshots also highlights whether there were

http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm
### % Women Reported in FDA Drug Trial Snapshots

(cardiovascular drugs approved since Jan 2014)

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>INDICATION</th>
<th>WOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPTRAVI</td>
<td>Pulmonary arterial hypertension</td>
<td>80%</td>
</tr>
<tr>
<td>REPATHA</td>
<td>Hypercholesterolemia (HoFH)</td>
<td>50%</td>
</tr>
<tr>
<td>SAVAYSA</td>
<td>Reduce risk of pulmonary embolism in VTE patients</td>
<td>43%</td>
</tr>
<tr>
<td>PRALUENT</td>
<td>Hyperlipidemia</td>
<td>40%</td>
</tr>
<tr>
<td>SAVAYSA</td>
<td>Reduce the risk of stroke in a Afib patients</td>
<td>38%</td>
</tr>
<tr>
<td>KENGREAL</td>
<td>Blood thinner following heart procedure</td>
<td>28%</td>
</tr>
<tr>
<td>CORLANOR</td>
<td>Heart failure</td>
<td>24%</td>
</tr>
<tr>
<td>ENTRESTO</td>
<td>Heart failure</td>
<td>22%</td>
</tr>
</tbody>
</table>

Source: [http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm](http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm)
NATIONAL INSTITUTES OF HEALTH

Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research
• 57% of 2014 NIH-funded clinical trials subjects were women

• **No data element** in NIH’s data system to indicate whether an awardee’s study should or does include plans for an analysis in research outcomes by sex

• NIH **lacks summary data**, such as the percentage of awardees in a given year with trials designed to identify potential differences in clinical outcomes by sex
  
  • **Compromises** NIH’s monitoring of Inclusion Policy implementation

  • **Limits** NIH’s assurance that it is supporting research that can be used to shape improved medical practice for both women and men
NEW RESEARCH POLICY
January 2016

NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

282 | NATURE | VOL 509 | 15 MAY 2014
BIAS in the RESEARCH PIPELINE

Cell-Based → Animal-Based → Human Trials → Clinical Care

**Percentage of articles reporting sex of cells in experiments**
BIAS in the RESEARCH PIPELINE

Cell-Based → Animal-Based → Human Trials → Clinical Care
BIAS in the RESEARCH PIPELINE

Cell-Based → Animal-Based → Human Trials → Clinical Care
Review of Federally Funded RCTs
9 Major Scientific Journals in 2009

1. New England Journal of Medicine
2. Journal of the American Medical Association
3. Annals of Internal Medicine
4. American Journal of Medicine
5. Journal of Clinical Oncology
6. Circulation
7. Clinical Infectious Disease
8. Obstetrics and Gynecology

Sex in Clinical Trials: Inclusion, Analysis and Reporting: n= 87

Coronary Drug Project

To determine whether regular administration of lipid modifying drugs (clofibrate, nicotinic acid, estrogen, dextrothyroxine) to men with a documented myocardial infarction would result in significant reduction in total mortality over a 5 year period.

Source: ClinicalTrials.gov

1973
Flibanserin

- Drug for treatment of hypoactive sexual desire disorder in women
- Safety studies conducted determine interaction of drug with ETOH
  - 18 of 20 subjects were men
- Post-marketing safety studies in women were required by FDA at the time of drug approval

2015
The Issue

When biomedical research is biased our abilities are limited when teaching future clinicians evidence-based care for all
Are men and women really the same?
The Darwin Awards: sex differences in idiotic behaviour

Ben Alexander Daniel Lendrem student, Dennis William Lendrem project manager, Institute of Cellular Medicine, Andy Gray consultant orthopaedic trauma surgeon, John Dudley Isaacs director, Institute of Cellular Medicine
EVIDENCE OF DIFFERENCES

Cardiovascular
Suicide
Sudden Death
Aneurysms
Impulsivity
Cardiomyopathy
Autism
Antisocial

Autoimmune
Depression
Arrhythmia
Hip Fractures
Cholecystitis
Irritable Bowl
Migraine
Alzheimers
Cardiac Resynchronization Therapy in Women: US Food and Drug Administration Meta-analysis of Patient-Level Data

Cardiac Resynchronization Therapy

- Combined 3 clinical trials CRT-D vs. Implantable Cardioverter Defibrillator (ICD) in patients with mild heart failure (New York Heart Class II)

- 22% of the combined subjects were women
CRT-D to ICD HRs for Outcomes by Sex
Combined Study Population

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Heart Failure or Death</th>
<th>P Value Interaction</th>
<th>HR (95% CI) Death</th>
<th>P Value Interaction</th>
<th>Heart Failure or Death Events, No./Total Subjects, No.</th>
<th>Death Events, No./Total Subjects, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td>.002</td>
<td></td>
<td>.03</td>
<td>155/878</td>
<td>54/878</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>712/3198</td>
<td>314/3198</td>
</tr>
<tr>
<td>LBBB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td>.007</td>
<td></td>
<td>130/749</td>
<td>45/749</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>465/2182</td>
<td>205/2182</td>
</tr>
<tr>
<td>Non-LBBB</td>
<td></td>
<td></td>
<td></td>
<td>.95</td>
<td>25/129</td>
<td>9/129</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>247/1016</td>
<td>109/1016</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration &gt;150 ms</td>
<td></td>
<td></td>
<td>.12</td>
<td></td>
<td>98/581</td>
<td>33/581</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration &lt;150 ms</td>
<td></td>
<td></td>
<td>.003</td>
<td></td>
<td>57/297</td>
<td>21/297</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>298/1209</td>
<td>127/1209</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td></td>
<td></td>
<td>.38</td>
<td></td>
<td>68/293</td>
<td>26/293</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>531/2141</td>
<td>248/2141</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonischemic heart disease</td>
<td></td>
<td></td>
<td>.02</td>
<td></td>
<td>87/585</td>
<td>28/585</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>181/1057</td>
<td>66/1057</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRT-D indicates cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; ms, milliseconds. P values represent sex-by-treatment interactions.
Results

• Overall, women benefited more than men.
• Neither group benefited with LBBB and QRS of <130 milliseconds.
• The majority benefited from LBBB with QRS of >150 milliseconds.
Results

• The main difference came in patients with LBBB and a QRS of 130 to 149 milliseconds.

• Women had a 76 percent reduction in heart failure (absolute difference 23%) or death and a 76 percent reduction in death alone (absolute difference 9%), but there was no significant benefit in men.
This finding matters because....

Cardiovascular clinical guidelines limit the Class I indication for CRT-D to patients with LBBB and QRS of 150 milliseconds or longer.
8 out of 10 discontinued medications between 1997-2001
Women experienced the majority of adverse events including death

Source: GAO FDA Study 2001
## Prescription Drugs with Evidence of Greater Health Risks for Women

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Category</th>
<th>Health Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pondimin (fenfluramine hydrochloride)</td>
<td>Appetite suppressant</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Redux (dexfenfluramine hydrochloride)</td>
<td>Appetite suppressant</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Seldane* (terfenadine)</td>
<td>Antihistamine</td>
<td>Torsades de Pointes (potentially fatal irregular heartbeat)</td>
</tr>
<tr>
<td>Posicor (mibefradil dihydrochloride)</td>
<td>Cardiovascular</td>
<td>Lowered heart rate in elderly women and adverse interactions with 26 other drugs</td>
</tr>
<tr>
<td>Hismanal (astemizole)</td>
<td>Antihistamine</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>Rezulin (troglitazone)</td>
<td>Diabetic</td>
<td>Liver failure</td>
</tr>
<tr>
<td>Propulsid\textsuperscript{b} (cisapride monohydrate)</td>
<td>Gastrointestinal</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>Lotronex (alosetron hydrochloride)</td>
<td>Gastrointestinal</td>
<td>Ischemic colitis (intestinal inflammation due to lack of blood flow)</td>
</tr>
</tbody>
</table>

*Note: Seldane is no longer available due to its association with the rare but serious heart rhythm disorder, torsades de Pointes.*
TAKE ONE TAB AT BEDTIME TO HELP YOU SLEEP

AMBBIEN 10MG

QTY 30

NO REFILLS - DR. B
SEX & GENDER
MEDICAL EDUCATION
The Issue

When medical education does not integrate evidence and awareness of sex and gender into curricula it creates a gap in knowledge which ultimately affects the treatment of patients.
2011 Climate Survey
Medical School Faculty*

• Distributed to the 2011 AAMC New Horizons Group + 30 DO Schools (159)
• 70% of responding 46 US medical schools did not have formal sex and gender specific integrated medical curriculum
• 83.1% did not have and integrated women’s health curricula outside of traditional Ob/Gyn
• Overall lack of coverage in health topics where sex and gender-based evidence exists

PI: Jenkins MR. *Funding provided by Laura W. Bush Institute for Women’s Health
Heart

- Endothelial Dysfunction: Normal Coronary MI 7X > women

Bones

- Men are under-screened & under-treated for osteoporosis

Women:

- > organ toxicity
- < amounts over < amount of time

ETOH

RX

- 2014 FDA recommends 1/2 -maximum zolpidem dosing in women
Perspective of Students and Faculty

National Surveys
Sex and gender in medical education: a national student survey

Marjorie R. Jenkins¹*, Alyssa Herrmann², Amanda Tashjian², Tina Ramineni², Rithika Ramakrishnan², Donna Raef¹, Tracy Rokas³ and John Shatzer⁴

[Logos of AMSA, SNA, APAMS, LMSA, and AMWA]
DEMOGRAPHICS

• Students from a total of 205 schools including regional campuses participated

• 153 schools met the final inclusion criteria

• 1,191 students completed the survey

• 1,097 met the final inclusion criteria

<table>
<thead>
<tr>
<th>School Year</th>
<th>MS 1</th>
<th>MS 2</th>
<th>MS 3</th>
<th>MS 4</th>
<th>5+ Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of respondents</td>
<td>25.4</td>
<td>33.7</td>
<td>21.5</td>
<td>17.6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>Male</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of respondents</td>
<td>74.3</td>
<td>25.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Jenkins, MR. et al. *Biol Sex Diff.* (2016)
I am familiar with the topic of sex and gender medicine

Medical education should include teaching of sex and gender

My medical education includes teaching of sex and gender differences

85%

96%

94%

63%

59%

Knowing sex and gender medicine improves one’s ability to manage patients

The majority of medical knowledge is based on data obtained from males
Moderate to Extensive Coverage

<table>
<thead>
<tr>
<th></th>
<th>Medical History</th>
<th>Domestic Violence</th>
<th>Substance Use</th>
<th>Mental Health</th>
<th>Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florida (59)</td>
<td>73.3</td>
<td>64.4</td>
<td>70.7</td>
<td>76.3</td>
<td>36.8</td>
</tr>
<tr>
<td>FSU (2)</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pharm</th>
<th>Pulmonary</th>
<th>Cardiology</th>
<th>Rheum</th>
<th>ID</th>
<th>Endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florida (59)</td>
<td>56.9</td>
<td>59.3</td>
<td>68.4</td>
<td>69.1</td>
<td>62.7</td>
<td>80.7</td>
</tr>
<tr>
<td>FSU (2)</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>
Survey Question:
Are there evidence-based health differences between men and women within these topics?

<table>
<thead>
<tr>
<th>Topic</th>
<th>Yes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptoms of MI</td>
<td>83.5</td>
<td>83.6</td>
</tr>
<tr>
<td>Dosing of Zolpidem</td>
<td>20.4</td>
<td>10.6</td>
</tr>
<tr>
<td>Outcomes after low impact fractures in adults</td>
<td>59</td>
<td>39.3</td>
</tr>
<tr>
<td>Risk factors for the development of osteoporosis</td>
<td>92.2</td>
<td>85.5</td>
</tr>
</tbody>
</table>

Jenkins, MR. et al. *Biol Sex Diff.* (2016)
There are evidence-based health differences between men and women in regard to...YES

<table>
<thead>
<tr>
<th></th>
<th>MI</th>
<th>Aspirin</th>
<th>Domestic Violence</th>
<th>Zolpidem</th>
<th>Narcotic Addiction</th>
<th>Smoking Cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florida (59)</td>
<td>95.2</td>
<td>58.7</td>
<td>71.0</td>
<td>12.9</td>
<td>37.1</td>
<td>46.0</td>
</tr>
<tr>
<td>FSU (2)</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Surveys: Key Points

• Students perceive sex and gender differences are **important** to the ability to manage patient care: 96%
• There is **discordance** between expressed knowledge and perceived amount of exposure within curricular topics
• There is marked **inconsistency** across topics in regard to the reported and observes inclusion of sex and gender differences within medical education.

**Formal approach to integration of sex and gender evidence into medical education is needed.**
PARTICIPANTS’ SURVEY RESULTS

I am familiar with the topic of sex and gender differences in health and disease.

PRE-TEST: 81% Agree/Strongly Agree  POST-TEST: 93% Agree/Strongly Agree

Does your institution require OSCEs or other simulated patient cases in women’s health?

PRE-TEST: 28% No/Unsure/No, but Interested  POST-TEST: 37% No/Unsure/No, but Interested

The FDA should consider recommending dosages based on the sex of the patient.

PRE-TEST: 69% Agree/Strongly Agree  POST-TEST: 97% Agree/Strongly Agree

Sex and gender based medicine is a fundamental aspect of precision medicine.

PRE-TEST: 40% Strongly Agree  POST-TEST: 81% Strongly Agree
Curricular Integration
“A scientific discovery, regardless of its potential, will ever impact patients, prevent deaths, or improve lives without first being transformed into clinical knowledge.

Such transformation occurs in the learning environment!”
A Framework of Translation Education

**T-0 Basic Scientific Discovery**

**T-1 Translational research:** To findings tested for clinical effect and/or applicability

**T-2 Translational research:** T1 tested in controlled environment to support efficacy + optimal settings for guidelines

**T-3 Apply recommendations or guidelines to general practice**

**T-4 Apply recommendations to improve global health**

**Discovery**

**TEd-0 Sex & Gender Scientific Discovery**

**TEd-1 Develop + test educational methodologies for threading SGBM evidence into medical education**

**TEd-2 Develop sex and gender curricular guidelines**

**TEd-3 Implementation of SGBM curricular threads into real-world academic settings**

**Develop Guidelines**

**TEd-4 Global application of sex & gender health through public health integration**

**Proof of Concept**

**Dissemination**

**Public Health**

Team Model for Curricular Change

- Student Champion
- Institutional Leaders
- Curriculum Gatekeeper
- Sex and Gender Content Expert

Change Team
Common Barriers to Integrating New Information into Curricula

- Resources
- Time
- Faculty Development
Resources and Time
Development of a PubMed Based Search Tool for Identifying Sex and Gender Specific Health Literature

Michael M. Song, PharmD, Cheryl K. Simonsen, MLIS, Joanna D. Wilson, DO, and Marjorie R. Jenkins, MD
Username: present_preview
Password: Present_preview

Repository of Sex and Gender Tools for Health Professions

Jenkins M., Casanova R., et. al. www.sgsh.org
Slide Library

- Ready to use
- Speaking points
- Reference articles
- Level of evidence

Jenkins M., Casanova R., et. al. www.sgsh.org
Slide Library

- Peer reviewed
- Add to existing lectures
- Searchable

Jenkins M., Casanova R., et. al. www.sgsh.org
Slide Library
Author Guide
Learning Modules

- IPE
- Built in
- SGSH

Jenkins M., Casanova R., et. al. www.sgsh.org
Learning Modules

• Cases follow male and female patient through disease process

Jenkins M., Casanova R., et. al. www.sgsh.org
Learning Modules

- Pre- and post-test
- USMLE Type Questions
- Attitudes
- Knowledge

Learning Modules

- Interactive
- Peer reviewed
- Stand alone
- Incorporate into existing course

Jenkins M., Casanova R., et. al. www.sgsh.org
Learning Modules

Field Tested
To access these curricular materials

www.sexandgenderhealth.org

Username: present_preview
Password: Present_preview
Sex and Gender in a Medical Emergency: Y Does X Make a Difference?

Alyson McGregor, M.D., MA
Assistant Professor in Emergency Medicine
Brown University

Laura W. Bush
INSTITUTE for WOMEN’S HEALTH
TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER
Publications
2018 Sex & Gender Health Education Summit

Advancing Curricula through a Multidisciplinary Lens

April 8-10, 2018 University of Utah
Salt Lake City, Utah

www.sgbmeducationsummit.org

** faculty travel grants available **

Sponsors:

[Logos of sponsors]
Not Knowing The Difference Doesn’t Mean There Is No Difference
Thank you

Contact information:
sgsh@ttuhsc.edu

or
marjorie.jenkins@ttuhsc.edu