Summary of the Symposium of Sex and Gender in Physiology and Pharmacology Held at the Royal Swedish Academy of Sciences in Stockholm, October 2018

Introduction

Karin Schenck-Gustafsson, MD, PhD

1Professor of Cardiology, Chair Centre for Gendermedicine, Karolinska Institutet

The Royal Swedish Academy of Sciences, established in 1700, is responsible for the appointment of Nobel Laureates in Physiology and Chemistry. In the old saloons you can find pictures of old Swedish scientists like Linné and of course of Alfred Nobel himself, the man who endowed the Nobel Prize in 1901.

The aim of this symposium was to highlight the differences between men and women regarding the occurrence of various diseases and responses to drug treatment. For this purpose, we invited representatives of various clinical specialities in medicine, surgery, clinical pharmacology, and neuroscience.

Here are short summaries of the lectures those experts delivered at the symposium.

Janusmed Sex and Gender—A Knowledge Bank on Medical Drugs

Linnéa Karlsson Lind, PhD

1Health and Medical Care Administration, Stockholm, Sweden

Background

Reports on lack of knowledge about sex and gender aspects in drug treatment prompted the regional politicians in Stockholm County to contact the regional gender equality strategist, Prof. Karin Schenck-Gustafsson. She was encouraged to start working on incorporating sex and gender perspective into health care and to develop a knowledge bank to support prescribing physicians.

Method

The process of creating the content of the knowledge bank is presented in Figure 1 and can be summarized as follows: (1) standard literature searches are performed according to a template and the collected knowledge is summarized in a text document for each substance; (2) different information sources are used, such as scientific articles, product labels, and clinical textbooks; (3) each document is discussed in a panel with clinical experts and is also assigned to a classification based on the available evidence; (4) information is collected in a database and linked to national registers of pharmaceutical substances and products approved in Sweden; (5) the information is presented on the website Janusinfo (note 1), provided by the regional Drug and Therapeutic Committee in Stockholm. There are also plans to integrate the knowledge base to electronic health record systems.

Prioritized are medications recommended by the regional drug and therapeutic committee and medications commonly used in Sweden.
Results

Janusmed Sex and Gender is the first evidenced-based knowledge bank on sex and gender aspects for individual medical substances. It covers information on pharmacokinetics, dosage, effects, adverse effects, sex-divided data on dispensed prescriptions, and references to underlying data. The website is also available in English (note 2; Figure 2).

So far about 350 medical substances have been analyzed. Around 15% of all the substances showed clinically relevant sex differences (Figure 3). In half of the cases, no clinically relevant differences were found. In about one-third of the cases, open scientific data are lacking.

Conclusions

It is now well recognized that men and women, boys and girls differ as it comes to biology meaning disparities in etiology, prevalence, symptom presentation, treatment response, and prognosis in different diseases. There are also sex differences in absorption, metabolism, and elimination of medications as well as in effects or adverse effects. Therefore, it is important to analyze drug utilization from a sex and gender perspective.

However, information on sex and gender aspects for specific medical substances are often difficult to find, and sometimes findings vary. A sex-specific analysis of data is often lacking in clinical drug studies and clinical treatment guidelines. In some scientific articles, it is unclear whether sex differences have been studied or the sex distribution of the participants may be poorly reported. A lack of knowledge on how to amend for sex and gender when prescribing medications has been expressed by primary care physicians. Therefore, we have collected all available knowledge in one place, as a support to the prescribing physicians.

The main goals of Janusmed Sex and Gender are (1) to improve medical treatment with the right choice of drug, the right dosage regimen related to patient’s sex; (2) to create greater awareness among prescribers about sex/gender aspects on drug treatment; and (3) to contribute to fewer adverse events and more patient safe care.
Notes
1. http://www.janusinfo.se/genus.
2. http://www.janusinfo.se/genus/in-english.

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Figure 2. The Swedish version and the English version.

Figure 3. Distribution of substances according to classification categories.
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**Sex and Gender in Analgesic Drugs**

**Carl-Olav Stiller, MD, PhD**

1Clinical Pharmacology Department of Clinical Pharmacology, Chair of the Stockholm Expert Council of Analgesic Drugs, Stockholm, Sweden

For a long time, sex differences in pain and analgesia did not attract much interest, but this field has expanded more rapidly since 1980s to 2008.1 Epidemiological data derived from large surveys indicate a higher prevalence of back pain, migraine, and musculoskeletal pain in women compared to men.2 In laboratory tests on pain sensitivity, females have a lower pain threshold and lower pain tolerance as compared to males. Furthermore, intensity rating as well as unpleasantness rating were higher in females. Females are more sensitive to cold pain, heat pain, pressure pain, and muscle pain.

Statistics from the Swedish National Board of Health and Welfare indicate a 30% to 50% higher number of females with a prescription of morphine, oxycodone, or codeine as compared to males (Figure 1-3).

Clinical trials on sex differences in μ-opioid analgesia were a subject of meta-analysis.3 Some studies indicate higher doses of opioids in female patients and other higher doses in male patients. The largest study with 2344 men and 1993 women indicted a 0.02 mg/kg higher morphine requirement in women.4 Similar results were also presented in another trial on postsurgical analgesia.5 In contrast, a large Chinese study with 1444 females and 854 males reports higher postoperative dose of morphine in men.6 Higher consumption of epidural opioids in men was also reported by a large cohort study from Germany with 6506 women and 8482 men.7 However, women had a higher incidence of postoperative nausea and vomiting.

One of the reasons for sex differences in opioid sensitivity could be the sexual dimorphism8 of opioid analgesia and interaction of opioid receptors and estrogen receptors.9 Many factors influence the sense of pain including psychological, social, cultural, genetic, molecular, cellular, physiological, body/organ, sex hormones.4,5,10 It is clear that both sex and gender will influence the experience of pain.

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**Figure 1.** Number of patients with a morphine prescription in Sweden.

**Figure 2.** Number of patients with an oxycodone prescription in Sweden.

**Figure 3.** Number of patients with a kodein/paracetamol prescription in Sweden.
Summary

Women appear to use more pain-relieving medication than men. Women may be more sensitive to certain painful stimuli. Sometimes women use higher doses of analgesic and sometimes lower doses than men. Differences in analgesic efficacy may be related to body composition, metabolism, hormonal profiles, or genetic factors.

Recommendations

Separate and systematic assessment of analgesic effects and side effects of analgesic drugs should be part of clinical development of analgesic drugs.

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Sex and Gender in Clinical Medicine

Karin Schenck-Gustafsson, MD, PhD, FESC, DrHeC

The publication 2001 by IOM, United States: “Exploring the biological contribution to human health: Does sex matter” became an eye-opener also in Europe. However, as a clinical cardiologist and head of the CCU at Karolinska, I had already since the late 80s experienced that women were underresearched, underdiagnosed, and undertreated. The EU statistics showed that 50% of the deaths were caused by cardiovascular disease (CVD) for both sexes. Still, the mean survival for women in Sweden has been longer than that for men since 1750. However, this survival gap has diminished over the last 2 decades. If you compare internationally, the increased survival rate during the latest 20 years in Swedish men is unique. There might be several reasons for this; one is the length of telomeres. The telomeres are situated at the ends of the DNA molecule, and the longer they are, the longer life. Women have longer telomeres explaining the longer survival. However, 2 female Nobel Prize laureates (Blackburn and Greider 2009) showed that increased stress will shorten the telomeres and be one of the explanations for the actual decreased gender gap in survival.1,2 Sex hormones can also play a role for the sex differences in survival. Women contract CVD 8 to 10 years later than men. The role of estrogen’s protecting effect is still debated. However, still no recommendations for estrogen as CVD protection exist. Lipid levels, especially LDL and total cholesterol, may play a role in the sex differences in survival. At ages less than 50 years, the cholesterol levels are much higher in men, but thereafter, women’s levels exceed the levels of men. This might explain an increase of CVD after the menopause.

The risk factors for CVD are the same for both sexes but have another impact. For example, diabetes mellitus type 2 will induce more CVD complications and at an earlier stage in women. Smoking will increase mortality 25% in women and much more than in men. There are also specific future female risk factors coupled to reproduction in women, for example, preeclampsia, gestational diabetes, not to breastfeed, premature menopause, polycystic ovarian syndrome. Also cardiovascular disease can be induced by cytostatics and radiation in breast cancer treatment.3

Sex differences exist in the heart, the brain, and in all organs in both humans and animals, as well as all cells including stem cells.4,5

With regard to diagnostic studies, recent important publications illustrate differences between the sexes. In a 10-year follow-up of MRI scans,6 it was found that men’s heart muscle became bigger and thicker than contrast to that of women’s that became smaller. In a thesis from Karolinska Institutet 2018, it was shown using heart MRI scanning that the blood flow was higher and the transport distance of oxygen to the heart muscle cells was longer in women than men.7 Concerning ECG, it is known that women have higher pulse rate (at least during the fertile age), longer QTc, shorter P wave duration, PR interval, QRS duration, and ST-segment. For arrhythmias, women have more AVNRT, SND, AT, and LQTS and men more AF, AVRT, VF/SCD, and septal VT.8
There are different kinds of myocardial infarction: More women than men have myocardial infarction without obstructive stenosis, microvascular disease, prolonged coronary spasm, spontaneous coronary artery dissection, Takotsubo, paradoxical embolization. Therefore, coronary angiography is not always diagnostic for investigating ischemic heart disease in women.9-12

Symptoms may differ between men and women: almost half of the women with myocardial infarction don’t have typical chest pain. This may be the reason why the ambulance comes later to women compared with men having myocardial infarction. Delay in reporting symptom by women have been shown in several European studies.13

Recent studies from NIH/FDA and Sweden show that still too few women are included in CVD trials.14,15 In particular, older women don’t get recommended treatment and have higher mortality rates.14 We have now the first web-based knowledge bank initiated by the Swedish Government16 about sex and gender in drug utilization covering all recommended medicines in Sweden. It is also available in English (www.janusinfo/gender).

What About the Future?
Examples of progress:

- The Swedish Research Council and some other research councils has finally decided (December 2018) that applications for funding should consider sex and gender in their protocols, as is the case for research councils in Canada and United States.
- We have now mandatory gender-specific cardiovascular education for undergraduate and graduate students at Karolinska Institutet.
- At least 4 PhD dissertations on gender medicine came out during 2018 from the medical faculty at the Karolinska Institutet. Examples of dissertations in Gender Medicine during 2018 at Karolinska Institutet (fig):
  - “Diagnostic precision and sex differences in cardiovascular magnetic resonance,” Thesis by Jannicke Nickander, MD
  - “Antiepileptic drug utilization: Need of sex-specific information and decision support,” Thesis by Linnea Lind Karlsson, Pharmacist
  - Karolinska Institutet, Stockholm, October 2018
  - “Sex and gender differences in patients undergoing ablation of atrial arrhythmias,” Thesis by Carina Carnlöf, RN, Karolinska Institutet, Stockholm, November 2, 2018
  - ACS with normal coronaries, Thesis by Maria Daniel, MD
In conclusion, not taking sex and gender differences into account could be a matter of life and death. Finally, there has been more but still not enough attention to these issues in Sweden.

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Atherosclerotic diseases, more nonobstructive coronary disease, higher rates of periprocedural complications during PCI, more depression, and less rehabilitation.

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Sex and Gender Differences in Stroke

Mia von Euler, MD, PhD
1Department of Medicine, Karolinska University Hospital, Solna & Clinical Science and Education, Södersjukhuset, Stockholm, Sweden

Background
Stroke may be of ischemic or hemorrhagic origin, 85% of stroke cases are caused by cerebral infarction (emboli or thrombosis), 10% by intracerebral hemorrhage, and 5% by subarachnoid hemorrhage.

In Sweden, as in most countries, women are older than men when having a stroke 1,2 (Figure 1)

Prevalence and mortality for stroke have decreased in Sweden in both men and women.

Risk factors for stroke are the same for both sexes, although diabetes, smoking, and atrial fibrillation seem to carry a higher risk for women.

Men have been shown to more often have an unhealthy diet, a higher prevalence of atrial fibrillation, diabetes, and hypertension at younger age. More women reach a higher age and are physically active. Also, more women have migraine with aura, obesity, psychosocial stress factors, and risk factors related to reproduction such as pregnancy, use of oral contraceptives, and HRT.

Presentation of Stroke

When presenting with stroke, some studies show that more women than men have cognitive disturbances such as difficulties with speech. In a Swedish prehospital study, patients with stroke not arriving with stroke alarm, more women than men were found lying down 3 (Figure 2).

Treatment of stroke has the same impact in men and women. Prehospital identification of acute stroke increases the possibility of early acute treatment and good outcome. Chance for reperfusion (thrombolysis and/or thrombectomy) is higher for patients arriving as stroke alarams to the emergency department. 4

Before the introduction of the new anticoagulants (NOACs) instead of warfarin, women with AF in Sweden were undertreated with warfarin. However, with the introduction of these new medications, the sex differences disappeared. 5
Rehabilitation

There are indications that women spend less time in rehabilitation compared to men. Whether this reflects differences in age (women being older at time of stroke), a larger proportion of women living alone or in assisted housing or is due to other factors is not clear and needs to be further studied.

Summary

- More men than women have stroke and men are younger at the time of stroke although, as women live longer, the life time risk is higher in women.
- Speech difficulties in some, but not all, studies have been shown to be more common in women.
- Reperfusion treatment is shown to have equal effect in men and women.
- Better utilization of preventive medication of stroke results in less differences between men and women.

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Sex and Gender in Psychiatry

Mikael Landén, MD, PhD

Psychiatry is a medical specialty concerning diagnosis, prevention, and treatment of mental disorders. In psychiatry, we deal with severe mental illnesses, where there is no doubt—not even for the nonprofessional—that something is amiss. A homeless woman on the street who shouts loud, vehemently arguing despite that there is no one there listening, might be disputing with her inner voices and suffer from schizophrenia. A perspiring, wild-eyed—but still charming and witty—man fervently trying to seduce the bus driver, and possibly even succeeding in doing so, might suffer from a manic episode as part of bipolar disorder. A mute woman lying on her bed in a rigid pose, but who maintain a limb position placed by someone else, not drinking, not eating might be suffering catatonia.

But psychiatry also deals with conditions that we all might endure sometime in our lives, or ailments that we recognize in ourselves even though we might have less severe symptoms. Depression is a public health issue that afflicts almost one-fifth of the population. Personality disorders are personality traits taken to the extreme, but where it is difficult—maybe even not possible—to separate normal from pathological behavior. Similar behaviors might be encountered in individuals for whom a diagnosis of a “mental disorder” would be inappropriate. Whether a person crosses that line or not might thus depend not only on the symptoms, but by the person’s ability to cope, by the support from the workplace or next of kin, by the psychiatrist’s view on what is normal and what is not, by whether there is a treatment to offer or not, and perhaps not least important, by the person’s sex.

There are clear sex differences with respect to the prevalence of psychiatric disorders.1 Table 1 shows Swedish data from 2017. If we first look at the number of diagnoses in psychiatric outpatient care, we see that there are slightly more women than men who have any psychiatric diagnosis. But if we break it down by diagnostic group, we find that women are clearly overrepresented in some diagnostic groups, whereas men dominate others. There are more women than men diagnosed with mood disorders, anxiety disorders, and personality disorders. Men are overrepresented among substance abuse disorders and child-onset psychiatric disorders.

In Table 2, we break down figures into specific diagnoses. The differences are even more pronounced. We note that women are overrepresented in all mood and anxiety disorders, but especially recurrent depression and anxiety disorders. And there is a staggering female predominance among personality disorders. It was not possible to get data for specific personality disorders, but probably most of the female preponderance is accounted for by borderline personality disorder. And when it comes to eating disorders—anorexia nervosa or bulimia nervosa—this is almost an entirely female phenomenon. By contrast, men dominate the alcohol abuse category and several child onset disorders: mental retardation, learning and speech disorders, and ADHD.

Hence, the spectrum of psychiatric disorders seems to display clear differences across sexes. But are these “real” differences? Or could it be that other factors influence the likelihood of making a diagnosis? Pertaining to mood disorders, it could be that women are more likely to seek help than men for depression or that depression is more readily detected in women?

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Table 1. Diagnoses in Swedish Specialized Outpatient Care, No. of Patients/100 000, 2017.

| Diagnosis                      | Men   | Women  | Total |
|-------------------------------|-------|--------|-------|
| F00-F99 Psychiatric disorders | 3744  | 4028   | 52%   | 7772  |
| F10-F19 Substance abuse       | 607   | 315    | 34%   | 922   |
| F20-F29 Schizophrenia spectrum disorders | 320 | 272    | 46%   | 593   |
| F30-F39 Mood disorders        | 724   | 1210   | 63%   | 1933  |
| F40-F48 Anxiety disorders     | 751   | 1405   | 65%   | 2156  |
| F60-F69 Personality disorders | 94    | 227    | 71%   | 322   |
| F90-F98 Child-onset disorders | 1107  | 774    | 41%   | 1881  |

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Table 2. Specific Diagnoses in Swedish Specialized Outpatient Care, No. of Patients/100 000, 2017.

| Diagnoses                      | Men   | Women  | Total |
|--------------------------------|-------|--------|-------|
| F10 Alcohol abuse              | 332   | 173    | 34%   | 505   |
| F31 Bipolar disorder           | 218   | 387    | 64%   | 605   |
| F32 Depressive episode         | 311   | 470    | 60%   | 781   |
| F33 Recidivande repression      | 211   | 391    | 65%   | 602   |
| F34 Chronic depression         | 45    | 34     | 57%   | 79    |
| F40 Phobic syndromes           | 43    | 64     | 60%   | 107   |
| F41 Anxiety syndromes          | 427   | 802    | 65%   | 1229  |
| F42 Obsessive compulsive disorders | 58   | 78     | 57%   | 136   |
| F43 Stressor-related disorders | 230   | 495    | 68%   | 725   |
| F44 Dissociative syndromes     | 5     | 14     | 73%   | 19    |
| F50 Eating disorders           | 9     | 117    | 93%   | 126   |
| F60 Specific personality disorders | 47  | 175    | 79%   | 223   |
| F72 Severe mental retardations | 5     | 39     | 8     | 8     |
| F80 Disorders of speech and language | 23 | 10   | 30%   | 33    |
| F81 Learning disorders         | 6     | 59     | 41%   | 11    |
| F90 Hyperactivity disorders    | 995   | 708    | 42%   | 1702  |
| F91 Conduct disorders          | 14    | 69     | 31%   | 20    |

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* Statistics from the Swedish National Board of Health and Welfare 2018.
A recent thesis by Lena Thunander Sundbom (2018, Uppsala University, The influence of gender and depression on drug utilization) studied the influence of sex on depression. She sent out a questionnaire to 16,000 people. Quite surprisingly, she found that men were actually more likely to report depression (odds ratio: 1.23; confidence interval: 1.06-1.41) than women. But in line with what is known, twice as many women (9.8%) had been prescribed an antidepressant than men (5.3%; \( P < .0001 \)). The interpretation of these findings is not straightforward. It could be that women have better access to treatment—or are more likely to seek health care and therefore are less depressed. Depression in men might be less likely to be detected and thus treated less frequently than depression in women. This study focused on drug treatment, but I assume that the difference would have been even more pronounced if one would have included whether or not the patient had had psychotherapy. Hence, one factor might be that depression in men is less likely to be detected, or that men receive a less favorable treatment in psychiatry. But possible gender bias in care is not the only factor.

The Possible Role of Sex Hormones

There is actually no reason to believe that prevalence figures should be 50-50 between men and women. There might be physiological differences that drive differences in psychiatric symptoms over the life course. Below is a table of the number of outpatient visits in psychiatry in Sweden across the life span. Three things can be concluded without any statistical analyses. First, boys are much more likely than girls to pay visits to psychiatric clinics. Before puberty, boys outnumber girls in psychiatry by a factor 2 to 1. Second, in adolescence, this pattern suddenly flips: There are twice as many teenage women in psychiatric treatment as there are men. Third, this female preponderance continues up to 55 years of age, after which the number of women and men visiting psychiatrists is roughly equal, although with a slight female dominance. These dramatic switches co-occur with hormonal changes: puberty onset among girls and boys and menopause in women at age 50 to 55. This has led many to suggest that the female sex hormones during the fertile period make women more vulnerable to mood and anxiety disorders.

Does Testosterone Impact on the Risk for Psychiatric Disorders?

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting reproductive-age women characterized by the presence of symptoms of hyperandrogenism (such as hirsutism, adult acne, and abdominal obesity), oligo-ovulation or anovulation, and frequently polycystic ovaries in the absence of other causes of high androgen activity. Depending on the diagnostic criteria used, the prevalence of PCOS varies from 5% to 15% in women of fertile age.

Some years ago, we set out to test the testosterone hypothesis of psychiatric disorders and conducted a clinical study of 40 women with PCOS and 40 healthy controls. We found that depression and some anxiety disorders were more common among women with PCOS. We repeated the investigation in a register-based study (Cesta et al) and found that 22.4% of women with PCOS had received at least one psychiatric diagnosis compared with 15.7% among the matched comparison individuals. Autism spectrum disorders and schizophrenia were more common in women with PCOS, whereas anorexia nervosa was less common. This seemed to fit with the hypothesis that excess testosterone would cause a more male pattern of psychiatric morbidity. But bipolar disorder, depression,
anxiety disorders, personality disorders, and suicide attempts were also more common in women with PCOS, that is, disorders that are more common in women in the general population. PCOS seem to be associated with increased risk for almost all types of psychiatric morbidity, rather than with a male psychiatric pattern.

**Female Sex Hormones and the Risk for Psychiatric Disorders**

There are some undisputable examples of how sex hormones influence mental health, simply because these disorders do not exist other than in women of fertile age: premenstrual dysphoric disorder (PMDD), postpartum depression and the milder variant postpartum blues, and postpartum psychosis. These are disorders clearly related to hormonal fluctuations.

Interestingly, selective serotonin reuptake inhibitors (SSRIs) are extremely effective in alleviating the irritability and affect liability in PMDD despite that the symptoms are clearly related to hormonal fluctuations. A study that Elias Eriksson’s group in Gothenburg conducted demonstrated that the symptom reduction was almost 90% and clearly separated from placebo (Landén et al.). This is different from when SSRIs are used for depression. In fact only one-third of patients respond to the first-line SSRI when it is used to treat depression.

Another striking difference between PMDD and depression is that it usually takes 2 to 4 weeks to respond to an SSRI when it is used for depression. However, we have shown that when SSRIs were given to PMDD, the symptom reduction was almost instant, within the first day. From day 2 onward, there was a clear separation compared to placebo (Landen, Erlands-
son, Bengtsson, Andersch, & Eriksson, 2009).

To conclude, symptoms of premenstrual dysphoric disorder are clearly related to fluctuations in sex hormones. Despite this, PMDD responds well to drugs that increase serotonin neurotransmission and the pattern of response is different compared to when SSRIs are given for depression. This tells us that there is an interaction between sex hormones and the serotonin system that might be of importance also for other conditions that are more common in men than women, for example, anxiety disorders and depression. Interestingly, there have been reports that women respond better to SSRIs than men, but that this difference disappears after menopause.

In summary, it should not be taken for granted that psychotropic drugs exert exactly the same effect in men and women. But this is a field that needs much more data by analyzing data for each sex separately. We do not routinely tailor treatment according to sex in psychiatry today.

**Does Psychiatric Treatment Differ Depending on Sex or Gender?**

Bipolar disorder is a serious, lifelong disorder characterized by recurrent episodes of mania and depression, interspersed by euthymic periods during which the mood is normal. There is a range of treatment options available, among them mood stabilizing drugs, antidepressants, antipsychotic drugs, anxiolytic drugs, ECT, and psychotherapy. There are no data to suggest that treatment should be adjusted according to sex but a recent study showed that that was definitively the case (Karanti et al., 2014). Women with bipolar disorder were more commonly treated with electroconvulsive therapy, antidepressants, lamotrigine, and benzodiazepines. Men were also much less likely to be treated with psychotherapy (OR: 0.67, 95% CI: 0.60-0.74). The only treatment that was more common among men was lithium. These findings are odd because there are no data to suggest that these treatments should work better in women than men.

**Does Risk Factor for Suicide Differ Between Men and Women?**

Another facet of bipolar disorder is the high suicide risk: The suicide risk is 15 to 20 times higher than in the normal population. There is therefore a need to identify risk factors for suicide. But do men and women have the same risk factors for suicide? We studied risk factors for suicide stratified by sex (Hansson et al., 2018) and found that some risk factors are present in both sexes, but there were also differences. Comorbid substance use disorder was a predictor in men (OR: 1.95, 95% CI: 1.11-3.44) but not women, while comorbid personality disorder predicted suicide attempt in women (OR: 2.29, 95% CI: 1.42-3.69), but not men. Social problems related to the primary group predicted attempted suicide in women only (OR: 1.60, 95% CI: 1.15-2.24).

**Conclusions**

- There are clear sex differences in the prevalence of most psychiatric disorders.
- The reason might be biological (eg, sex hormones), psychological, sociological, but also that gender influences the interpretation of reported symptoms.
- Men and women might respond differently to treatment and clinical studies should therefore stratify results on sex.
- Prognostic factors/risk factors might differ between men and women.
- The actual treatment might also differ for no known reason.

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***Sex and Gender in Aortic Diseases***

Rebecka Hultgren, MD, PhD\(^1\)

\(^1\)Theme Heart and Vascular Theme, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden

**Abdominal Aortic Aneurysm**

*Prevalence, risk factors, treatment, and outcome*

Abdominal Aortic Aneurysms (AAA) are more prevalent in men, regardless of which age groups that are analyzed, with a male:female ratio of 4-6:1.\(^1,2\) The prevalence of AAA in specific age groups are well known in selected populations (United Kingdom and Sweden) due to the ongoing population based screening programs (2% in 65-year-old men vs 0.5% in 70-year-old women).\(^1,3\)

The most influential modifiable risk factor for development of AAA is smoking. The established nonmodifiable commonly found risk-factors in AAA populations are male sex, increasing age, heredity, coronary heart disease, and hyperlipidemia.\(^1\)

Unfortunately, the association between exogenous and endogenous sex-hormone levels and risk for AAA is not well understood, even if some investigations indicate that female sex-hormone replacement therapy could have a protective effect against AAA development, and lower testosterone levels in men could be a risk factor for AAA.\(^4,5\)

As has been shown for other cardiovascular risk groups, growing evidence now also confirm that a deprived socioeconomic position can negatively influence the treatment and outcome in AAA groups; however, more in-depth analysis in the area is needed, especially regarding sex-differences.

Women with AAA have a lower chance to be eligible for endovascular repair than men, resulting in a higher rate of open repair, which influences their poorer postoperative outcome. This is partly dependent on morphological sex differences.\(^1,2\) Outcome, measured as 30-day and 1-year mortality after treatment is often reported to be worse in women than for men.\(^2,6,7\) The poorer outcome could depend on other factors in the care of women: such as the association between socioeconomic, primary prevention, healthseeking behavior and secondary prevention. The true influence by the morphological sex differences or the effect by sex differences in the aortic wall on outcome are still not understood.\(^7\)

**The Paradox**

Within the AAA patient group, 2 challenging findings present an AAA paradox, namely the much higher prevalence and earlier onset found in men, but on the other hand, the higher rupture risk in the much smaller cohort of women, and poorer outcome in women.\(^1,2,3,6,7\)

The high prevalence and early onset in men are addressed in clinical care by the introduction of population screening in men in some countries, which does lower the aneurysm and all-cause mortality in men. However due to the late onset in elderly women, one cannot generally support implementation of screening in women.\(^1,3\)

But, in recent years increasing interest toward targeted screening in risk groups, which can include women is debated. Siblings to AAA patients have a high prevalence of AAA, compared to the general population, and this can be as cost-effective as screening in 65-year-old men, and will also include women at high risk. This screening can give the following absolute risk reduction: 6 prevented death/1000 invited versus 1 to 2 in 65-year-old men.\(^8\)
**Pathogenesis and sex-difference**

The pathogenesis is multifactorial and complex, therefore direct sex-differences are difficult to detect. Corresponding to shown associations between the delayed onset of disease development in other cardiovascular disease groups and female sex-hormones, the obvious disease patterns in AAA groups could support a similar “protective effect” by female sex-hormones.

Animal models support that endogenous estradiol prevent disease development and inhibit expansion of aneurysms. Few aortic wall-analysis in humans with a sex-perspective have been published. However, a relative deficit in female sex-hormones and upregulated androgen receptors have been shown. This could influence expansion rates and rupture but remains to be confirmed in larger series.4,6,9,10

Some direct effects on the aortic walls by sex-hormones are reported, such as the involvement in inflammatory responses in both women and men, however possible differences in the effects by exo versus endogenous sex-hormones are poorly investigated. Shown effects by sex-hormones are for example the dilatation in the descending aorta in the pregnant women, and the increased and earlier relative dilatation in men, paired with an earlier development of aortic stiffness in men.

### Keynote Lecture
**The Science of Sex and Gender in Human Health: State of the Art**

**Marjorie R. Jenkins, MD, MEdHP, FACP**

1Laura W. Bush Institute for Women’s Health Associate Dean for Women Faculty, Texas Tech University Health Sciences Center, Lubbock, TX, USA

**Sex and Gender Variables: Not Interchangeable or Synonymous Terms**

Sex and gender have been uniquely defined by the 2001 by IOM, United States: Exploring the Biological Contribution to Human Health: Does Sex Matter? “Sex matters” and “Being male or female is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of health-related research.”

Sex is a biological variable, including chromosomal, physiological, and hormonal differences and, in the majority, sex is a variable represented by the terminology, male/female.

Gender is a social construct, taking into consideration environmental, cultural, and societal influences. Gender occurs across a spectrum. Terms such as masculine, feminine, man, woman, other, neither are utilized to describe gender as are a multitude of other terms.

Interchanging terms creates ambiguity within the published literature.

There are challenges when analyzing published scientific evidence about sex and gender due to misrepresentations of these 2 terms as synonymous or interchangeable which is not
the case. Sometimes the word gender is used regarding basic research (cell, tissue, animal) instead of the correct term of sex.

Males and females differ in biology (anatomy, physiology), disease (onset, risk factors, prevalence, severity, signs/symptoms, comorbidities), hormones (menarche to menopause, endogenous, HRT/contraceptives), pharmacokinetics, and pharmacodynamics. There are also differences in the genetics and epigenetics between males and females, but it is not just differences in the number of genes that differ. It is how the genes function which may lead to clinically applicable sex differences. In 2017, a group of researchers found 6500 genes with sex differential expression across 53 tissues (45 common to both and 8 sex-specific). An area that is rapidly moving toward personalized genetic therapies is cancer immunotherapy. It is important to consider sex differences in the influence of genes and hormones before starting therapy per a recent review by Kim H-I. *Biomol Ther.* 2018;26(4):335-342.

Without the data, science cannot find the answer.

In scientific publications, up to 76% cell and tissue studies are of unspecified sex, 80% performed in male animals, 67% males across all phases of clinical trials (Figure 1 in Song et al, 2016). This is the case despite women being 51% of the population and 80% of the health-care consumers (Figure 2). Every cell, tissue, and animal has a sex, yet the majority of scientific publications do not require sex of the study materials to be identified. A case-in-point is research publications focusing on the cardiovascular system, an organ system which has long had undisputed sex differences. Miller et al found that across 10 cardiovascular journals with high-impact factor cell-based studies, 28% of cells were unspecified, 68.9% were male, and none utilized exclusively female. Jenkins underlined the importance of using the terms sex and gender appropriately as science must be presented with precision if it is to achieve maximum impact (Taylor, 2011).

Moreover, the myth that female animals have higher variability than males, which has been utilized as a justification of the over 75% of males in animal-based research, has been debunked (Berry 2018; Becker et al 2016).

Here is a quick snapshot of federal reports, regulations, and health policies regarding sex and gender inclusion and reporting: NIH GAO report 2015: 57% of 2014 NIH-funded CT subjects were women. The executive summary of the report concluded that there was a lack of tracking as to whether the study included plans for analysis by sex, lack of summary data to identify potential sex differences, and limited assurance that NIH is supporting research that can inform medical practice for both women and men.

In May 2014, NIH announced a policy to promote sex as a biological variable (SABV) in cell and animal preclinical research through requiring researchers to balance male and female efforts in non-sex-specific research. In 2015, NIH published a Guide Notice NOT-OD-15-102 which expands on the integration SABV in both animal and human studies.
As stated within NOT-OD-15-102, “This notice focuses on NIH’s expectation that scientists will account for the possible role of sex as a biological variable in vertebrate animal and human studies.”

FDA has issued several guidance which have greatly improved demographic reporting in clinical trial applications. Guidance documents represent the agency’s current thinking on a subject. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. Since 1993, FDA Center for Drug Evaluation Research guidance for clinical trial sponsors stating that women are expected to be included in clinical trials and clinical trial data need to be reported by gender, age, and race. FDA Center for Devices and Radiological Health (CDRH) guidance on sex-specific evaluation of data on medical devices was issued in 2014.

Inclusion, reporting, and analysis of clinical trial data by race, age, and gender, in support of New Drug Applications, is codified as mandatory under the Demographic Rule (discussed below). The Demographic Rule passed in 1998 (21 CFR 314.50 (d)(5)) revised the New Drug Application Content (NDA) and format regulations at 21 CFR 314.50 to require effectiveness data to be presented by gender, age, and racial subgroups and dosage modifications be identified for specific subgroups. It also requires that safety data be presented by gender, age, and racial subgroups and that safety data from other subgroups of the populations of patients treated be presented, as appropriate.

These and other regulatory actions and guidance have clearly impacted inclusion and data analysis by gender as evidenced in the 2013 FDA authored FDASIA Section 907 Report, which revealed that 100% of clinical pharmacology analyses, 97% of efficacy analyses, and 90% of safety analyses for FDA drugs and biologics included analyses by sex. Similarly, 88% of FDA medical device approvals had included sex analyses.

A recent publication in which Jenkins served as coauthor provided clarity and transparency about the participation of women in cardiovascular (CV) clinical trials and the safety and efficacy of 36 drugs approved for 6 CV indications. In addition, this work examined CV clinical trial inclusion and exclusion criteria. In this decadal review, it was found that FDA received adequate data to ensure safety and efficacy for both men and women in relation to the drugs and CV disease states reviewed and study inclusion/exclusion criteria did not disproportionately exclude women but, when percentage of women in trials was compared to disease prevalence women, were underrepresented in several cardiovascular diseases (ACS, CHF, MI; Scott P et al. JACC, 2018)

Providing healthcare through a sex and gender lens:

Dr Jenkins proposed 6-step Sex and Gender Diagnostic Framework:

You must consider the following:

I. Sex and gender: Must be considered at the outset of a patient encounter.

II. Clinical presentation: Is there evidence that sex and/or gender influences disease presentation.

III. Risk profile: Create a sex- and gender-specific profile.

IV. Differential diagnosis: Develop a differential diagnosis utilizing the personalized risk profile.

V. Diagnostics: Recognize sex and gender influences which can impact type of testing and interpretation of results.

VI. Select optimal therapeutic choices: Know if sex differences exist or whether there is a lack of evidence (one-sex data) for the selected therapeutic interventions.

Example of sex and gender difference in diagnosis and treatment plans for MI: “High sensitivity troponin I assay as compared to the contemporary troponin I assay noticeably increased the diagnosis of myocardial infarction in women (from 11% to 22%; P < .001) but had a minimal effect in men (from 19% to 21%, P = .002)”. Dr Jenkins pointed out that this is an example of a sex difference. In this study, women diagnosed with MI were managed differently from men with a diagnosis of MI, in that they were less often referred to a cardiologist (80% vs 95%, P = .004), less likely to undergo coronary angiography (47% vs 74%, P = .001) or PCI (29% vs 64%, P < .001), or to be prescribed statin treatment on discharge (60% vs 85%, P = .001). This difference in management is not a sex differences as both the men and women were diagnosed with myocardial infarction. Dr Jenkins highlighted that these disparities between men and woman in referral, diagnostic testing, and treatment are an example of gender not sex differences (Anoop SV, Shah et al. BMJ, 2015:350:bmj.g7873). These results are the same as in many European studies.

Another example is the zolpidem case. A sedative hypnnotic approved in 1995 with maximum approved dose of 10 mg in adults. Early pharmacokinetic studies revealed a 40% sex difference in metabolism; however, the clinical impact of this PK difference could not be fully assessed in part due to the limited technology available in the mid-90s, while a relook at the issue in 2014 prompted the FDA to recommend women be prescribed a maximum of 5 mg of zolpidem. In other words, with advancing science and technology, a previous finding without clear clinical application became clinically meaningful as science and technology evolved. The PK difference is a sex difference and the gender difference is that women are more likely to engage with their healthcare environments and more likely to report and suffer from difficulty sleeping.

The above examples highlight how sex and gender matter if we are to provide the most precise care to all. There are many more examples and here are a few. Dr Jenkins pointed out that one-sex medicine and gender-blind delivery of care does not benefit either men, women, or boys, girls. Here are a few examples that illustrate how both sex and gender matter in health.
Examples of other sex and gender differences are as follows:

Heart: Endothelial dysfunction and myocardial infarction with “normal” coronary angiography are 7 times more common in women.

Bones: Men with osteoporosis underdiagnosed and undertreated but have higher mortality within 1 year post osteoporotic hip fracture.

Brain: Depression is underdiagnosed in men and can have a different presentation between genders.

Alcohol use: End-organ damage more likely in women with same amount and length of use as compared to men.

**Future: Educating the Next Generation of Scientists and Clinicians**

Research in and of itself does not save lives. It is the application of research findings within the patient care environment which allows research to impact lives. This is achieved when clinically meaningful evidence is translated within an educational environment (Figure 2).

Healthcare professionals’ attitudes and perceptions are important.

In a report from 2016 (Jenkins MR, et al. Biol of Sex Diff. 2016), the majority of students also agreed that content in their curriculum is primarily related to males (63.2%). And, nearly all respondents agreed that knowing sex and gender medicine improves one’s ability to manage patients and should be included as a part of the medical school curriculum (96.0% and 94.2%, respectively). In this same study, only 13.4% of fourth-year senior medical students recalled hearing about a dosing difference for zolpidem. This is an obvious example of clinically relevant information not reaching the next generation of providers.

The Institute for Gender and Health, Canada, has an educational program focusing on the integration of sex and gender into biomedical research. The program found at http://www.cihr-irsc-igh-isfh.ca/, touts “Every Cell is Sexed and Every Person is Gendered.”

The Laura W. Bush Institute is a global leader in the development and dissemination of national peer-reviewed educational materials including didactic slide presentations, video modules, student assessment tools, case simulations, textbook, and journal listings. These resources can be found and utilized free of charge at www.sexandgenderhealth.com.

NIH ORWH has courses available and will release new training modules focusing on sex as a biological variable (SABV) in research. A separate course co-directed by FDA’s Office of Women’s Health will consist of a 6-module continuing education course focusing on sex and gender integration across the research and clinical care continuum. The 2018 Sex and Gender Interprofessional Education Summit welcomed faculty and students across 5 disciplines. A slide tool kit for messaging sex and gender in health professionals education can be found at www.sexandgenderhealth.com. The third National Sex and Gender Health Education Summit will take place in Philadelphia, Pennsylvania, September 11-13, 2020.

**Summary**

Dr Jenkins’ keynote highlighted the importance of utilizing sex and gender terminology appropriately and correctly within research and clinical care. She noted great progress in federal policies and regulations across discovery science and product development research continuum. Her 6-step clinical care framework can be readily applied in today’s patient care environment. She emphasized the need for robust sex and gender integration within research platforms and accountability in reporting of sex and gender but pointed out that it is not the research discoveries per se but their application which impacts lives. Lastly, she emphasized the lack of formal sex and gender integration across US medical schools, student support of teaching sex and gender evidence, and educational resources from a variety of federal and academic organizations to narrow this gap.