Addressing Health Challenges of Women Across the Life Course: Summary of the Women's Health 2018 Preconference Symposium

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Abstract

Although the United States is often ahead in both research and health care fields, it lags behind peer countries in many population health indicators. To address these complex health problems that often reflect the intersection of many socioeconomic and health issues, it is essential that scientists work collaboratively across distinct disciplines. Women's health is but one area which can benefit from such an approach given the multifaceted and complex issues underlying the different aspects of women's health research. The National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) and the Office of Women's Health of the U.S. Food and Drug Administration (FDA) cosponsored a preconference symposium at the Women's Health 2018 Conference, held in May in Arlington, VA, to highlight interdisciplinary approaches to research, how researchers can work collaboratively, and how to apply multifaceted approaches to complex real-world problems. Three speakers presented information on a range of subjects related to the health of women across the life course, including the distinction between multidisciplinary, interdisciplinary, and transdisciplinary approaches; the science behind Team Science and how its findings apply to working collaboratively; and gender inequalities in the opioid epidemic. This article summarizes the major points of the presentations and the subsequent discussions.

Keywords: multidisciplinary; interdisciplinary; transdisciplinary; team science; opioid use disorder; intersectionality

Introduction

DESPITE BEING A LEADER in biomedical research, important population health indicators for the United States are often falling behind peer nations. As an example, since 1980, life expectancy for men and women in the United States has fallen well below average in comparison to other industrialized nations. Moreover, while White men's life expectancy follows the trend of other industrialized nations and has continued to increase over time, White women's life expectancy in the United States has begun to decrease since 1986.^{1,2} Within the United States, geography plays an important role in life expectancy; however, the picture is complex, as other factors, such as education, socioeconomic conditions, and built environment, all affect life expectancy.^{3,4}

Jennifer Montez et al. have found that state-level factors, such as economic conditions, physical infrastructure policies, and tobacco environment, can only account for about a third of this variation in mortality rates.⁵ Another third was accounted for by individual-level factors, such as age, race, ethnicity, income, and marital status; the social context and environment of women are significant contributors to her personal health factors. Thus, adoption of a multifaceted research approach to address the health of women across the life course can identify key intersecting factors affecting health outcomes.

Multidimensional considerations and interdisciplinary approaches are central to the Office of Research on Women's Health (ORWH) vision for the health of women. Women comprise more than 50% of the U.S. population and tend to

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outlive men. Yet, biomedical research has often excluded women from clinical trials over the years, leading to not only gaps in knowledge but also in understanding of sex differences and in disease treatment and response, especially for conditions such as cardiovascular disease, certain cancers, and rheumatoid arthritis.⁶ On December 13, 2016, the 21st Century Cures Act was signed into law mandating that any strategic plan issued by the National Institutes of Health (NIH) institutes or centers (ICs) shall account for women and strive to reduce health disparities among women. The act underscores that researchers must methodically examine and report health data by sex, acknowledge and understand differences in women's health based on race and ethnicity, and provide analysis of longitudinal trends in health data to better understand the changes in a woman's health across the life course. While the historical research model involves an investigator working independently and being rewarded by publication, tenure, and funding for self-contained work, more recently, NIH has recognized the value of an interdisciplinary methodology, examining the intersections of many factors upon health through biomedical, epidemiological, and life course approaches to fill existing knowledge gaps in women's health.

The NIH ORWH and the Office of Women's Health of the U.S. Food and Drug Administration (FDA) cosponsored a preconference symposium at the Women's Health 2018 Conference, held in May in Arlington, VA. Presentations from the symposium, "Addressing Health Challenges of Women Across the Life Course," highlighted the key role interdisciplinary approaches can play to women's health research, how researchers can work collaboratively through team science, and how to apply multifaceted approaches to a complex real-world problem such as opioid abuse. The workshop began with a welcome from Dr. Susan Kornstein, Executive Director of the Virginia Commonwealth University Institute for Women's Health, Editor-in-Chief of the *Journal of Women's Health*, and President of the Academy of Women's Health.

Opening Remarks

Dr. Janine Clayton, Director, ORWH, NIH, opened the meeting, introducing the ORWH mission to address the health of women from head to toe, as well as to honor the legacy of Dr. Vivian Pinn, the first ORWH Director. An important part of Dr. Pinn's legacy is the inclusion of interdisciplinary research to address the entire health of a woman (from physical health to mental and emotional health) and her life course. The health of women in the United States today is declining: maternal mortality in the United States is increasing while it is decreasing in other high-income countries⁷; women are less likely to be administered naloxone; and women are less likely to be given evidence-based treatments than men. These gender inequalities are a complex problem with no easy solution. NIH is trying to bring multiple disciplines together to strengthen the health of women.

Ms. Elizabeth Spencer, Deputy Director, ORWH, NIH, went on to introduce the speakers and provide a brief overview of each presentation. At ORWH, the health of women is considered at every level, from cellular to biomedical, to clinical, to legislative. NIH, made up of 27 ICs, is also adjusting its trajectory to draft a trans-NIH plan to integrate the health of women across the ICs. The trans-NIH plan will be important to ensure that Sex as a Biological Variable is in-

tegrated NIH-wide. The 2018 Vivian Pinn Symposium, which took place on May 16, 2018, is available on the NIH Video-Casting and Podcasting website (<https://videocast.nih.gov/Summary.asp?File=23915&bhcp=1>) and another ORWH resource; the ORWH newsletter, "Women's Health and Focus at NIH," can be found on the ORWH website (newsletter subscription page).

Presentation Summaries

*Introduction to interdisciplinary research:
"multidisciplinary, interdisciplinary, transdisciplinary
research oh my!"*

Dr. Victoria A. Cargill, Associate Director, Interdisciplinary Research, ORWH, NIH, explained the difference between multidisciplinary, interdisciplinary, and transdisciplinary approaches to research. As an example, Dr. Cargill presented a "painful lesson" from her own practice, the case of a young woman who presented pregnant and HIV positive. At the time, the research recommendation to prevent mother to child transmission of HIV was to terminate the pregnancy. The same patient returned a year later at the age of 24, again pregnant, but this time well past the point of termination. While the woman delivered a healthy HIV negative son, she had extensive multidrug resistant HIV, with few options for drug treatment remaining to which her virus was sensitive. Although she was treated with the drug that had the lowest threshold for resistance, the patient developed a severe, near fatal drug reaction. It was not until two years later that examining the data on the drug by sex demonstrated that this drug had a very different and severe side effect profile in women. This key difference was missed because the drug had been tested primarily in men during clinical trials, and the data from women were not analyzed. This example makes the point; women's lives are complex and at the center of the intersection of multiple factors—what research field is best positioned to include these competing demands?

When considering the answer to this question, it is important to keep in mind that women's health requires multiple lenses—social, economic, medical (obstetrics and gynecology, dental, primary care, *etc.*), interpersonal, familial, organizational, community, public policy, and treatment. Multidisciplinary research approaches these challenges by bringing together different disciplines to address the issue(s) under study, while continuing to maintain the separation of the disciplines such that when the study is completed, those disciplines address findings from their unique perspectives. The advantage of a multidisciplinary approach is the value added of having multiple experts from different fields collaborating. The limitation, however, is that the fields remain separated, which can make communication across fields and scientists more difficult, and a solution which synthesizes the various disciplines harder to identify. Using a multidisciplinary approach to provide care for the patient presented earlier, researchers might suggest a peer-led adherence intervention.

In contrast to multidisciplinary research, interdisciplinary research integrates information, data, techniques, and tools of two or more disciplines to advance understanding beyond the scope of any single discipline or practice.⁸ While multidisciplinary approaches remain separate, interdisciplinary approaches move beyond single disciplines to approach

problems in new and different ways, which engage a wider audience, explain more phenomena, and may have predictive value beyond the existing circumstances. Circling back to the patient presented earlier, interdisciplinary approaches would attempt to develop interventions and predict how the patient might react to these, given her background and history. The limitations of interdisciplinary research include the difficulty of learning a new discipline and the required collaboration and coordination of working in teams. Moreover, academic institutions, including promotion and tenure tracks, often favor the independent investigator.

To counteract some of these limitations, funding mechanisms and opportunities, including many from ORWH, encourage interdisciplinary research. ORWH recently issued a funding opportunity announcement (FOA) for understudied, underreported, and underrepresented women (U3 women), which focuses on women who are also marginalized and vulnerable. The FOA stressed on using interdisciplinary approaches and explicitly states “interdisciplinary, transdisciplinary, and multidisciplinary research focused on the effect of sex/gender influences at the intersection of a number of social determinants, including but not limited to race/ethnicity, socioeconomic status, education, health literacy, and other social determinants in human health and illness”⁹ are responsive. Bringing these approaches together, women’s health can be viewed as a tree—with many root determinants such as genetic predisposition; interdisciplinary approaches, like vision science, can reach across the branches of the tree that grow up from these different roots to span the multiple factors that affect women’s health.

Transdisciplinary research is defined as creating a new discipline from two or more existing disciplines. A good example of a transdisciplinary field is bioinformatics, which was created by the blending of computer science and biology. Transdisciplinary approaches move beyond their component disciplines to create something entirely new, which sets them apart from either multidisciplinary or interdisciplinary approaches.¹⁰ Transdisciplinary research allows investigators to capitalize on innovations across various disciplines and increase understanding of a health issue or disease state, while potentially affecting policy change and including important stakeholders. There can be a number of challenges to implementing a transdisciplinary approach as it requires collaboration and stepping out of comfort zones into an entirely new methodology that requires tolerance and respect of new disciplines.¹¹

In conclusion, there are advantages and limitations for each approach. While all approaches bring more to the table than siloed independent research, they also all involve working in teams and can become hampered by the difficulties encountered in research collaborations.

State of the science lecture: the science of team science; building effective collaborations that produce results

Dr. Kara Hall, Program Director, National Cancer Institute, NIH, and her colleagues began the science of Team Science over a decade ago to help build solid collaborations. The multilayered aspects of women’s health can be linked to the structure of Team Science, which is also multilayered; dependent on individual-level factors, such as willingness to engage in teams; interpersonal-level factors, such as com-

munication effectiveness; and organizational/societal structures.¹² In addition, team problems vary by size—teams of two have different problems than teams of 200.

Research conducted on the productivity of Team Science research has demonstrated that cross-disciplinary teams are more productive than single-disciplinary comparison teams, generating more publications over time with greater scientific impact.^{13–17} Moreover, gender heterogeneous teams have 34% more citations, and if teams have at least one female principal investigator, on average, they are more likely to win a grant or produce innovative ideas.^{15,18–21} Although women tend to do more work in collaborative frameworks and participate in interdisciplinary teams more frequently, there are fewer women in science, and women have less seniority than men. In addition, including someone with higher academic rank in a collaboration leads to greater productivity.^{4,7–10} The ways in which teams are constructed, team size, the history of collaboration, the roles different team members play, and the amount of time and focus team members can devote to a project all influence the outcomes that the team can expect.^{15,22–26}

While there is some reason to believe that multi-institutional collaborations lead to higher impact work than co-located teams or individual researchers, this finding is dependent on heterogeneity of the group, as measured by the number of disciplines and institutions.^{27,28} As the number of investigators increases, productivity can decrease if adequate coordination and collaboration mechanisms are not put in place.^{28,29} More coordination mechanisms, including “face to face meetings, division of responsibility, [and] clear roles and expectations,” led to more successful outcomes; however, when researchers examined universities involved in collaborative cross-location teams, they discovered that the greater the number of universities involved in projects, the fewer the number of coordination mechanisms being utilized.^{30,31}

Transdisciplinary researchers working collaboratively often find that their Team Science work challenges them intellectually and as investigative researchers, but also find the work to be difficult in terms of overcoming different values, language, cultures, and operating out of their comfort zone.²⁹ Traditional academic incentive systems do not fit with the collaborative network within which many investigators are now working. The tenure system, authorship contributions, and funding opportunities, to mention a few, may not have caught up with the changes in how transdisciplinary researchers are working collaboratively. To overcome some of these challenges, researchers can develop certain competencies as team scientists, including curiosity, having an open mind, demonstrating critical awareness, evaluating limitations of all disciplines (including one’s own), and flexibility.^{32,33}

Hall et al. developed a four-phase model for transdisciplinary research, as well as a tool kit, to help implement Team Science. The model consists of the developmental, conceptualization, implementation, and translational phases.³⁴ During the often-overlooked developmental phase, it is important to consider who to bring to the table the key concepts that are to be addressed and what the mission and goals of the project will be. The next phase, conceptualization, is the time during which team scientists develop the research questions and hypotheses, create shared mental models and languages, and develop a team ethic.³⁴ An important and

distinct aspect of the implementation phase of Team Science is to manage conflict among researchers from disparate backgrounds and consider team learning. During the translational phase, researchers apply their findings to advance the project and continue development. To help overcome the challenges of working in teams throughout all four phases, Hall et al. identified several options, such as a shared collaboration plan and operating manual and other resources, all of which are included in the Team Science Toolkit available online at teamsciencetoolkit.cancer.gov.³⁵ In summary, Team Science requires more care and consideration than individual work, but can be more rewarding in terms of productivity and innovation. Moreover, by taking advantage of the findings of Team Science research, team scientists can increase competencies through collaboration and coordination.

Substance use disorder and opioids in women: the intersection of biology, culture, gender, and sex

Dr. Kathleen Brady, Distinguished University Professor, Vice President for Research, Medical University of South Carolina; Director, South Carolina Clinical and Translational Research Institute, linked the importance of integrating disciplines and teams into tackling the major problem of substance use disorder (SUD) and the opioid epidemic. Dr. Brady reviewed the history of opioid use, beginning with the Sumerians in 3400 BC, including the Opium Wars in the early 1800s, the introduction of their medicinal use, including morphine, and ending with the outlawing of heroin in 1924. More recently, opioid-related deaths have increased dramatically from 1999 to 2014.³⁶ Part of the contribution to the increase in death rates is the faster development of tolerance to opioids than other drugs. There are also substantial gender inequalities related to opioid use. For example, women have a higher incidence of pain disorders and, thus, are more likely to be prescribed opioids, to use them longer, and to develop a tolerance to opioids.³⁷

In the early 2000s, pain became the fifth vital sign, and prescribers increased their assessment of pain due to external monitoring of patient outcomes. Patients who were in pain or experienced pain that was poorly controlled could and would report poor outcomes. At the same time, OxyContin was released, marketed, and targeted to providers as an opioid with less abuse potential. These converging events led to a rise in the prescription rates of opiates. Now, however, in the face of mounting public pressure, rising opioid deaths, and additional prescribing guidelines, doctors are trying to lower prescription rates, with the intention of lowering opioid overdose rates. However, while opioid prescription rates have fallen in the last 10 years, opioid-related deaths are still on the rise.³⁸ Decreasing opioid prescription rates correlate with the dramatic rise in the illicit opioid market to meet demand. In addition, drugs like fentanyl and carfentanyl, which are far more potent than heroin or morphine, are causing more overdose deaths.³⁹

Although, in general, it is true that prescription opioid use has decreased in the overall population, prescription opioid use among women has increased over 400% since 1999, and women are also more likely to die of prescription opioid use.³⁹ Heroin use among women has also increased over the last four decades, 100% since 2002, now reaching a similar rate to that of men.⁴⁰ Between 1999 and 2015, there was also

an 850% increase in synthetic opioid-related deaths for women.³⁹ Trends in pregnancy and opioid use are striking:

“About 2.3% of women of reproductive age report non-medical opioid use in the last 30 days. About .8% of pregnant women report non-medical opioid use, and about .4% at the time of delivery had opioid misuse or dependence. This is the 24 to 34 age group, ... that’s really been a pretty dramatic increase in the last five years.”^{41,42}

When considered in the wider context of multidimensional health indicators, it is little wonder that the opioid epidemic differentially affects women; women have higher rates of co-occurring psychiatric disorders, they are less likely to receive treatment, and there are gender-specific barriers to entering treatment, such as having less social support, issues surrounding pregnancy, and trauma. Compared to men with lifetime drug dependence, women are more likely to have a co-occurring anxiety disorder, an affective disorder, and drug dependence.⁴³ Opioid use disorder (OUD), especially, is a risk factor for co-occurring mood and anxiety disorders across the life course, with women being 7.5 times more likely to have any mood disorder and 4.2 times as likely to have an anxiety disorder.^{44,45}

“The relationship between childhood adversity and addiction is stronger in women than it is in men.” This finding is true in both relapse outcomes, drug initiation, and addiction over the life course.^{46,47} The influences of Adverse Childhood Experiences (ACES) may very well be related to epigenetic vulnerability; ACES can lead to changes in DNA expression which contribute to individual susceptibility to addiction later in life. One study using mouse models demonstrated that knocking out the DNA ability to make the epigenetic change in the nucleus accumbens following stress increased resilience in female mice.⁴⁸

In general, stress appears to be more related to drug use in women than it is in men; in response to stressful cues, women experience greater craving than men.⁴⁹ Specialized Centers of Research-funded work by Brady et al. demonstrated that women with SUD have a greater stress response, a blunted cortisol response, and an increased heart rate response to stressful stimuli compared to men with SUD. The lowered cortisol response is of particular interest since the release of cortisol stops the stress response in the nervous system. Effectively, women with SUD are stuck in a stressful feedback loop.^{50–52}

The treatment of OUD with methadone and buprenorphine, both of which are very effective treatments for men and women, is currently reaching between 20% and 30% of people with OUD. Naloxone and naltrexone, medicines used to reverse overdoses, are equally effective for women and men, although naltrexone may have more side effects in women. Adrenergic agents, such as clonidine for the treatment of withdrawal and, as new evidence suggests, relapse, may be more effective in women. Fox et al. demonstrated that treatment with guanfacine decreased cocaine cravings in women versus placebo, whereas men saw no effect/increased cravings.⁵³ Similarly, the MOTHER study of pregnant women treated with either methadone or buprenorphine demonstrated that buprenorphine-treated infants had fewer hospital days and shorter duration of treatment for neonatal abstinence, although there were higher maternal dropout rates.⁵⁴

While women tend to do as well as men in treatment, after controlling for comorbidity, economic factors, and other

important individual-level factors, it is important to consider gender-specific barriers to treatment that are unique to women. Women are disproportionately affected by issues, such as child care, lack of resources, partners with SUD, unique health problems for women, parenting classes, and particularly, co-occurring disorders, post-traumatic stress disorder, depression, and anxiety. A recovery model tested by Greenfield that focused solely on women has shown higher satisfaction ratings from women, although treatment outcomes were like other programs. Women-only treatment may not be the answer to the differential effect of OUD on women, but the exclusion of men may have led to higher outcomes due to relational satisfaction.

In conclusion, OUD and opioid-related deaths continue to rise, and while effective treatments, such as medication assisted treatment, are available, they are not widely implemented. Prescribers seem to understand that they need to lessen the extent to which they prescribe opioids, but this alone is not solving the problem. The opioid problem is complicated by comorbidities, psychiatric disorders, and gender differences that require complex and multifaceted solutions.

Discussion and Closing

Following the talks, a Q and A session centered predominantly around the opioid issue, such as ways to facilitate patient transitions off opioids, how to address the gender inequality, and how to apply Team Science to the epidemic and elsewhere. There was a discussion on how to begin to get teams organized and focused, starting with the leadership of the organization. There was also a question about evaluation of coalition work and resources for ensuring that a taskforce is on goal, to which Drs. Cargill and Hall responded with follow-up resources. Many attendees asked about specific issues related to the opioid crisis, such as surgical use of opioids, transgender issues, and medical marijuana, as well as the panel's opinion on specific treatments or resources for dealing with these issues. The panel suggested evidence-based treatments, pointing to specific references from the literature when applicable. Both attendees and panelists agreed that it was difficult to determine the appropriate postsurgical dosage of pain relief and that practice-based guidelines for dosage and length of administration would be helpful. Importantly, the panel highlighted that the opioid problem cannot be solved without interdisciplinary and transdisciplinary approaches that take into consideration the economic, social, cultural, and especially community-level factors affecting SUDs. Dr. Cargill closed the symposium by thanking everyone in attendance, particularly Drs. Hall and Brady.

Author Disclosure Statement

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