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Improving the Pharmacologic Management of Pain in Older Adults: Identifying the Research Gaps and Methods to Address Them

M. C. Reid, MD, PhD[1], **David A. Bennett, MD**[2], **Wen G. Chen, PhD**[3], **Basil A. Eldadah, MD, PhD**[4], **John T. Farrar, MD, PhD**[5], **Bruce Ferrell, MD**[6], **Rollin M. Gallagher, MD, MPH**[7], **Joseph T. Hanlon, PharmD, MS**[8], **Keela Herr, PhD, RN, FAAN, AGSF**[9], **Susan D. Horn, PhD**[10], **Charles E. Inturrisi, PhD**[11], **Salma Lemtouni, MD, MPH**[12], **Yu Woody Lin, MD, PhD**[13], **Kaleb Michaud, PhD**[14], **R. Sean Morrison, MD**[15], **Tuhina Neogi, MD, PhD, FRCPC**[16], **Linda L. Porter, PhD**[17], **Daniel H. Solomon, MD, MPH**[18], **Michael Von Korff, ScD**[19], **Karen Weiss, MD, MPH**[12], **James Witter, MD, PhD**[20], and **Kevin L. Zacharoff, MD**[21]

[1]Division of Geriatrics and Gerontology, Weill Cornell Medical Center, New York, NY

[2]Department of Neurological Sciences, Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL

[3]Sensory and Motor Disorders of Aging, Behavioral and Systems Neuroscience Branch, Division of Neuroscience, National Institute on Aging, Bethesda, MD

[4]Division of Geriatrics and Clinical Gerontology, National Institute on Aging, Bethesda, MD

[5]Departments of Epidemiology and Neurology, University of Pennsylvania, Philadelphia, PA

[6]Division of Geriatrics, UCLA School of Medicine, Los Angeles, CA

[7]Philadelphia VA Medical Center, Penn Pain Medicine Center, and the Departments of Psychiatry and Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA

[8]Department of Medicine (Geriatrics), University of Pittsburgh, Pittsburgh, PA and the Geriatric Research Education and Clinical Center, VA Pittsburgh Health System, Pittsburgh, PA

[9]John A. Hartford Center of Geriatric Nursing Excellence, The University of Iowa College of Nursing, Iowa City, IA

[10]Institute for Clinical Outcomes Research, Salt Lake City, UT

[11]Department of Pharmacology, Weill Cornell Medical College, New York, NY

[12]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Washington, DC

[13]Division of Clinical Neuroscience and Behavioral Research, National Institute on Drug Abuse, Bethesda, MD

[14]University of Nebraska Medical Center, Omaha, NE, National Data Bank for Rheumatic Diseases, Wichita, KS

[15]Brookdale Department of Geriatrics and Palliative Medicine, Mount Sinai School of Medicine, New York, NY

Corresponding Author: Dr. Cary Reid, Division of Geriatrics and Gerontology, 525 East 68th Street, Box 39, Weill Cornell Medical Center, New York, NY, 10065, Phone: 212-746-1378, Fax: 212-746-4888, mcr2004@med.cornell.edu.

[16]Sections of Clinical Epidemiology Research and Training Unit, and Rheumatology, Boston University School of Medicine, Boston, MA

[17]National Institute of Neurologic Disorders and Stroke, Bethesda, MD

[18]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts Division of Rheumatology, Brigham and Women's Hospital, Boston, MA

[19]Center for Health Studies Group Health Cooperative, Seattle, WA

[20]Division of Skin and Rheumatic Diseases, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD

[21]Inflexxion, Inc. Newton, MA

Abstract

Objective—There has been a growing recognition of the need for better pharmacologic management of chronic pain among older adults. To address this need, the National Institutes of Health Pain Consortium sponsored an "Expert Panel Discussion on the Pharmacological Management of Chronic Pain in Older Adults" conference in September, 2010, to identify research gaps and strategies to address them. Specific emphasis was placed on ascertaining gaps regarding use of opioid and non-steroidal anti-inflammatory medications because of continued uncertainties regarding their risks and benefits.

Design—Eighteen panel members provided oral presentations; each was followed by a multidisciplinary panel discussion. Meeting transcripts and panelists' slide presentations were reviewed to identify the gaps, and the types of studies and research methods panelists suggested could best address them.

Results—Fifteen gaps were identified in the areas of treatment(e.g., uncertainty regarding the long-term safety and efficacy of commonly prescribed analgesics), epidemiology (e.g., lack of knowledge regarding the course of common pain syndromes), and implementation(e.g., limited understanding of optimal strategies to translate evidence-based pain treatments into practice). Analyses of data from electronic health care databases, observational cohort studies, and ongoing cohort studies (augmented with pain and other relevant outcomes measures) were felt to be practical methods for building an age-appropriate evidence base to improve the pharmacologic management of pain in later life.

Conclusions—Addressing the gaps presented in the current report was judged by the panel to have substantial potential to improve the health and well being of older adults with chronic pain.

Keywords

Analgesic use; chronic non-cancer pain; older adults

INTRODUCTION

There has been a growing recognition of the critical need for better management of chronic pain in the aging population. Up to 50% of community-dwelling older adults report experiencing pain that interferes with normal function, and half of all nursing home residents report experiencing pain on a daily basis[1,2]. Older adults have the highest rates of chronic analgesic use[3,4];however, they are also the most susceptible to adverse effects of analgesic treatment, which increase in the setting of multiple morbidities, polypharmacy, physiologic vulnerability, and functional impairment [5,6].

Recently released guidelines have synthesized available research evidence and expert opinion to inform the clinical management of chronic pain [7,8]. The majority of recommendations found in the guidelines, however, are based on medium-or low-quality evidence. Basic questions, such as the long-term safety and effectiveness of analgesic treatments, reliable predictors of treatment response, and effective management of pain among individuals with multiple morbidities or cognitive impairment, remain largely unanswered. Within the broad assortment of pharmacologic and non-pharmacologic interventions for moderate-to-severe pain, opioids and nonsteroidal anti-inflammatory medications (NSAIDs)are the most commonly administered treatments, but evidence regarding their safe and effective use in older adults is disproportionately lacking.

Given this background, the National Institute on Aging (NIA), National Institute of Drug Abuse (NIDA), National Institute of Neurological Disorders and Stroke (NINDS), and National Institute on Nursing Research (NINR) jointly sponsored a two-day conference entitled “Expert Panel Discussion on the Pharmacological Management of Chronic Pain in Older Adults” in September of 2010 in Bethesda, Maryland. The meeting was held under the aegis of the National Institutes of Health (NIH)Pain Consortium, a working group of NIH officials seeking to enhance pain research and promote collaboration among researchers across the many NIH Institutes and Centers that have programs and activities addressing pain. The objective of the expert panel discussion was to identify research priorities that could, if addressed, lead to improved pharmacologic management of chronic pain in older adults. A specific emphasis was placed on establishing research priorities regarding the appropriate use of opioid and NSAID medications, because of continued uncertainties regarding their risks and benefits. Although the panel recognized the need for similar efforts in the area of non-pharmacologic interventions for pain, a focus on pharmacotherapies was deemed most important at this time given the high prevalence of analgesic medication use in later life [3,9]and expanding evidence regarding the risks associated with both opioid and NSAID medication use [10,11].

The conference began with presentations and discussions focused on the rationale for (and challenges associated with)improving the pharmacologic management of pain in older adults. This was followed by presentations and discussions directed at identifying knowledge gaps and research needs in this area. The remainder of the conference focused on the role of specific methodologic approaches that could be employed to address the identified gaps, as well as various initiatives (e.g., Food and Drug Administration’s Safe Use Initiative) that the hosting Institutes felt were important for the panel to review and discuss.

The current article summarizes the panel presentations and discussions, as well as its outcomes, which include the identified knowledge gaps, as well as recommended studies and methodologic approaches that panel members felt could help to address the gaps. The outcomes of the conference were generated by, and reflect the collective knowledge and perspectives of, a multidisciplinary panel whose expertise spanned the fields of pain management, aging, pharmacoepidemiology, and health services research. The target audience for this work includes funders, researchers, policy makers, as well as other stakeholder groups interested in improving the care of older adults with chronic pain.

Rationale for Focus on Improving Understanding of Analgesic Medications in Older Adults

Chronic pain is a highly prevalent, costly, and frequently disabling disorder in later life [12–14]. While arthritis and arthritis-related diseases are the most common causes of pain in older adults [15], other pain producing conditions also occur commonly in this age group, including neuropathies (e.g., diabetes, herpes zoster), vertebral compression fractures, cancer and cancer treatments, as well as advanced chronic illness[16–20]. The deleterious consequences of inadequately treated pain are far-reaching and include poor self-rated

health, depression, impaired quality of life, as well as decreased cognition and mobility [21–26]. Pain is by far the most frequently cited symptom causing activity of daily living disability in later life [27].

The high prevalence of off-label prescribing for various pain disorders [28], uncertain role of direct-to-consumer advertising of analgesic medications[29], and cost of many prescription pain medicines [30] provide additional support for efforts that seek to increase health care providers' and policy makers' understanding of the risks and benefits associated with the use of analgesic medications in older adults. By far the most important rationale, however, is the fact that the existing evidence base for rational treatment is scant[31–33]. As a consequence, clinicians managing pain in older adults must attempt to extrapolate findings from studies of younger adults, particularly the potential risks inherent in implementing an analgesic trial. Translating results generated in analgesic studies of younger adults to older populations can be hazardous because of age-associated decline in the systemic clearance of analgesics due to decreased renal excretion and liver metabolism, as well as greater pharmacodynamic sensitivity to analgesic central nervous system effects [33,34]. It is important to note that these changes do not uniformly affect all older adults. An important tenet of geriatric medicine is that chronologic age does not equal biologic age, a construct often referred to as aged heterogeneity. The Text Box describes three cases involving older adults with diverse pain problems. While each patient is the same age, they differ in important ways, including physiologic reserve. Clinicians treating these types of patients must tailor their pain treatment son a case-by-case basis. An evidence base that clinicians can access to guide treatment decision-making across the diverse spectrum of older adults encountered in clinical practice is currently lacking.

Text Box

Cases illustrating the diversity of pain problems and issues that arise in managing pain in later life

- An 85year old female develops mobility-limiting back pain secondary to spinal stenosis. She remains independent, but has begun to experience difficulties with advanced activities of daily living (e.g., walking long distances)on account of the pain. She carries a diagnosis of osteoarthritis and takes acetaminophenon an as-needed basis. She does not take any prescribed medication. The patient is not interested in surgery, but is willing to try interventions, including analgesic medications that could help to relieve the pain and improve her mobility status.
- An 85 year old male develops persistent herpetic neuralgia. He has diabetes, hypertension, renal insufficiency, and atrial fibrillation. He is currently taking 8 prescription medications daily, including warfarin. His pain is debilitating, particularly at night. Over a period of several months, the patient's ability to perform basic activities of daily living decreases on account of the pain (and poor sleep). He voices concern about his ability to remain independent in his own home, and asks for help in identifying ways to decrease his pain and improve his function. His daughter contacts you with questions about whether the patient would be better off in an assisted-living facility given his declining functional status.
- An 85 year old female with a gait/balance disorder, osteoarthritis, and dementia presents with worsening gait due to advanced osteoarthritis of both knees. The patient is able to self-report pain and experiences considerable pain on ambulation and at night. Her daughter (who is the primary caregiver) relates that despite her mother's impairments, the patient's quality of life seems good. The daughter is looking for help in how best to manage her mother's pain. The

patient appears content, happy, and occupied when she's not in pain, but distressed when she reports experiencing pain. The daughter feels her mother is suffering on account of poorly treated pain, which is a significant stressor for the daughter.

Factors Complicating the Study of Pain Management in Later Life

Several factors can negatively impact research methods and procedures, measurement approaches, and interpretation of findings. A non-exhaustive list includes the following:

Research challenges—Many investigations employ an upper age limit as an exclusion criterion for study entry and fail to examine potential confounders of differential treatment effects by age [35]. Studies of healthy older adults are the norm, but are not representative of the larger population of older adults, particularly those over age 75. Studying frail, older adults constitutes one of the biggest challenges because of problems with recruitment and consent, the limited ability of many older adults to tolerate complicated protocols, a frequent need to accommodate for sensory, motor, or cognitive impairment, and problems identifying age-appropriate pain measures [36].

Multiple sites and causes of pain—It is the rare older adult who has only one site of pain. Pain has been reported in multiple sites by 28% to 59% of older adults with women reporting greater number of pain sites [37–39]. The number of pain sites magnifies the overall effect of pain [40]. Moreover, older (versus younger) adults are more likely to report pain at multiple sites [41,42]and have pain-causing diseases and injuries associated with more than one mechanism (e.g., nociceptive, inflammatory, neuropathic, visceral), often requiring more than one type of pain medication for optimal treatment. Multiple sources and mechanisms of pain complicate both the study of individual pain conditions and evaluation of treatment response. Separate types of pain(i.e. neuropathic vs nociceptive)should be distinguished and measured separately using questioning regarding pain quality and characteristics and/or validated scales that differentiate these pain types and when possible, controlled for in studies examining pain intervention effectiveness.

Multimorbidity—Older adults are often excluded from analgesic trials on account of co-existing morbidities. Prevalence of chronic medical conditions increases with age, as noted in one study of 1.2 million Medicare beneficiaries aged 65 years and older, which found that 82% had at least one chronic health condition, while 65% had2 or more[43]. Additionally, hospitalized older adults frequently have undiagnosed coexisting geriatric syndromes (i.e., prevalent, morbid conditions occurring in older adults that do no fit within discrete disease categories but have multifactorial etiologies such as delirium, falls, urinary incontinence) that can negatively impact treatment outcomes [44]. Common age-related health conditions and associated treatments, raise concerns regarding the possibility of drug interactions, adverse effects, and difficulty studying analgesic interventions safely. However, studies of healthy older adults, as happens in most drug trials, do not help us to understand the way older persons with comorbidities will respond to treatment. Rather than being a reason for excluding these individuals from trials, comorbidities should be measured and their effect on the results examined as secondary analyses in primary studies and as the central component in age-specific trials.

Polypharmacy—Because most older adults experience multiple chronic conditions and receive medical treatment for them, polypharmacy is a significant issue. Individuals ages 60 and above were prescribed an average of 41 medications per year in one survey [45] and the incidence of adverse effects increases with the number of concurrent medications [46,47].

Given that the typical community-dwelling older adult has over three comorbid medical problems and takes an average of seven different medications [48], the impact of multiple concomitant medications must be considered in interpretation of adverse effects and response to analgesic treatments.

Cognitive impairment—Cognitive impairment is common among older adults [49–51]and presents serious barriers to accurate assessment and measurement of both pain and pain-related outcomes. Cognitive impairment can result in underreporting of pain due to problems recalling, interpreting, or communicating pain symptoms and inability to communicate qualitative characteristics and associated features of pain that impact treatment decisions [52]. Standard assessment techniques can be used effectively in older adults with mild-to-moderate cognitive impairment; however, obtaining a reliable pain report becomes more difficult as cognitive impairment worsens [52,53].

For cognitively impaired older adults unable to reliably report the presence of pain, other strategies must be used to study pain and pain treatments, predominately focused on the observation of behaviors. Many tools have been developed to evaluate pain in those with advanced cognitive impairment, but few have established sufficient psychometric properties to register confidence as a sole outcome measure [54]. A hierarchical approach to assess pain in older persons unable to self-report has been recommended that incorporates multiple data sources, but a standardized method for use in research has not been established [55]. Research is ongoing to refine relevant indicators and establish tools to measure pain in nonverbal older adults. Frequency of behavior presentation and key behaviors, such as facial grimacing or expression, are beginning to emerge as important factors to detect and judge severity of pain in those with dementia [56–58].

Because of issues of reliability in pain reports from persons with advancing cognitive impairment, proxy reports are considered a major data source when studying pain in this population. Although surrogate or proxy judgments, such as that from health care providers and family members, can effectively recognize presence of pain, they do not accurately rate its severity, particularly in those with severe dementia [59–62]. Thus, researchers are challenged to identify approaches to measure pain outcomes for those with advancing cognitive impairment.

Although pain outcome measures in intervention research often focus on pain intensity or pain interference, a more comprehensive evaluation that addresses multiple pain problems and comorbidities, as well as quality of life attributes impacted by pain, is needed. High symptom burden experienced by many frail older adults complicates not only the gathering of information relevant to the study, but also interpretation of study findings.

Attitudinal barriers—Provider and patient attitudes regarding analgesic use can negatively impact the study of pain treatments. Fears and concerns about analgesic appropriateness affect providers' prescribing behaviors and patient/caregiver adherence to the treatment plan. Although health care providers may have legitimate concerns regarding opioid efficacy and impact on function, they often harbor misconceptions about the appropriate use of opioids in older populations[63,64]. Finally, older adults commonly fear the negative consequences of analgesic use, including loss of cognitive abilities and other adverse effects, and frequently endorse a fear of addiction[65,66]. These barriers can have a significant negative impact on studies of analgesic effectiveness; incorporating measures of attitudes regarding pain treatment that may influence analgesic adherence and thus study outcomes are therefore strongly encouraged.

METHODS

The multidisciplinary panel consisted of 18 researchers from institutions or organizations across the country and 26federal representatives from the NIH, Food and Drug Administration(FDA), Veterans Administration (VA), and Agency for Healthcare Research and Quality (AHRQ). A list of conference participants appears in Appendix A. Participants were selected through a consensus-driven process by a program committee consisting of representatives from several institutes and centers in the NIH Pain Consortium. Participants were selected for their expertise in pain management, aging, pharmaco-epidemiology, and/or health services research.

The conference proceedings were audio-tape recorded and transcribed. One panel member (MCR) carefully reviewed the meeting transcript in its entirety, as well as the slide shows of all18 presenters, abstracting the research gaps reported during the meeting, as well as corresponding studies and methodologic approaches that panel members suggested could help to address them. To ensure the accuracy of this process, a list of the abstracted gaps and recommended studies was circulated to all panel members for review. This exercise confirmed the accuracy of the abstraction process and led to the addition of one gap and 5 additional studies not included in the draft list. This review process did not lead to any deletion of gaps or recommended studies identified at the conference. Thus, the final list of gaps and recommended studies (see Table 1) reflect a consensus opinion of all conference participants. Co-authors reviewed each draft of the manuscript to ensure that the information presented accurately reflected their presentations and contributions, and approved all parts of the final manuscript.

A taxonomy of research gaps was developed for purposes of presentation to include continued uncertainties in three specific domains: treatment; epidemiology; and implementation. In cases where multiple studies were recommended to address a given research gap, no attempt was made to prioritize the recommended studies (or rank the identified gaps), as this was not the purpose of the conference; rather, the meeting was designed with the expectation that investigators across a variety of research backgrounds would be informed by the conference proceedings and would pursue those projects most relevant to their areas of expertise.

RESULTS

Research Gaps and Recommended Studies to Address Them

Table 1 shows the 15research gaps, as well as 35 studies that panelists felt could help to address them. Most of the gaps involved uncertainties in the area of treatment, including a lack of knowledge regarding the long-term safety and efficacy of commonly prescribed analgesic medications, how to minimize or prevent analgesic-related side effects, and the prevalence and impact of opioid abuse/misuse behaviors in older populations. Panel members called for studies to ascertain the long-term safety, efficacy, and cost of commonly prescribed analgesic medications. Investigations that include sufficient details regarding participants' demographic, clinical, pain, and functional status, as well as medication exposures and care settings, were recommended to identify patient-level, medication-level, and system-level predictors of treatment response. Studies that determine whether specific co-therapies (e.g., use of various physical therapy, educational and psychotherapeutic interventions when starting an opioid medication), age-or renally-adjusted analgesic dosing, as well as mobile health technologies could minimize or prevent side effects were also recommended. The panel called for epidemiologic studies to ascertain the extent and impact of opioid abuse/misuse in older populations, as well as investigations to develop and test age-appropriate methods of detection.

Uncertainty regarding the incidence, prevalence, and course of common pain syndromes (e.g., back pain, post-herpetic neuralgia) was identified as a primary epidemiologic gap in our understanding of later life pain. Panel members advocated for studies to determine the natural history of specific pain disorders in older populations, as well as investigations that examine the subjective experience of pain in later life and its relation to behavioral and social factors. Alack of knowledge regarding ways to effectively translate evidence-based pain treatments into practice was identified as an important implementation gap. Panel members called for studies to identify and overcome barriers to translating evidence-based pain protocols, as well as studies that compare various methods of dissemination.

Strategies to Address the Gaps

While randomized controlled trials (RCTs) remain the gold standard to understand the efficacy and value of health care interventions, panel members acknowledged limitations associated with using RCTs to study analgesic medication use[67,68].These limitations include:1) sample sizes that are too small to detect uncommon risks; 2) follow-up periods that are typically too short to assess an analgesic medication's long-term benefits and risks; 3) problems with generalizability, because higher-risk patients are typically excluded from trials and levels of monitoring are far more rigorous than what is customarily done in routine practice; 4) high rates of medication discontinuation, which occur commonly and limit investigators' ability to conduct intention-to-treat analyses and long-term analgesic trials; and finally 5) many commonly prescribed opioids and NSAIDs have achieved generic status, making it unlikely that their manufacturers will undertake long-term safety or effectiveness studies since these investigations are not currently required by the FDA.

Despite these relative limitations, panel members agreed that RCTs will continue to play an important role in determining the short-term safety and efficacy of newly developed or understudied analgesic agents. However, given significant gaps in knowledge regarding the long-term safety and efficacy of most analgesics prescribed for the treatment of chronic pain in older adults, panel presentations and discussions focused on other methods that could generate data(in a timely manner) to guide decision making. The methods are described briefly below and include:1) electronic health care databases;2) observational cohort studies with existing pain measures; and 3) augmenting existing cohort studies with measures of pain and other relevant outcomes.

Electronic Health Care Databases—There are five requirements to use large electronic health care databases as tools to study analgesic safety and efficacy, including the ability to: 1) identify and track study populations over time; 2) measure analgesic exposures over time; 3) assess health status, health behaviors, and other relevant health factors in order to control for potential confounders; 4)assess pain-relevant outcomes over time; and 5) ascertain both positive and negative outcomes over time.

Three primary sources of electronic health care data are available for research on NSAID and opioid use in older populations in the U.S.:1) large health systems with electronic medical record (EMR) data, including various health maintenance organizations (HMO) and the VA; 2) insurance (e.g., Medicare and Medicaid)claims data; and 3) clinical pain registries. Table 2 summarizes the attributes of each data source with respect to requirements for conducting comparative analgesic effectiveness and/or safety research. Information about the data elements of, methods of data collection for, and access to each data source appear in Appendix B.

As with all health information databases, each data source has its own strengths and weaknesses that should be considered in the planning of any study. The capture of medication data in any database present challenges that are specific to the type of data

collected: Administrative databases accurately record the prescription medications that were dispensed and paid for; EMR data accurately record prescriptions that were written through the EMR, but it is unknown if they are actually filled; patient survey databases supply medication use as reported by the patient but depends on memory which is often inconsistent. Surveys conducted in person, such as the National Health and Nutrition Examination Survey, sometimes ask patients to present all of their medication bottles to try to improve the data collection process. As for non-prescription medications, administrative databases generally do not include over-the-counter medications (OTC) or complementary therapies, while EMR and patient surveys will have some of this information but with variable accuracy depending on the method used to collect the data. These databases would also not capture 'free' prescriptions provided by some physician practices and pharmaceutical companies, which could also constitute a source of bias. The same applies to the ascertainment of side-effects. In general, milder side-effects are poorly recorded in all datasets, while more serious side-effects and especially those that result in hospitalization are captured more dependably. In all databases, the continued enrollment of an individual patient can be problematic. If a patient changes insurance or healthcare provider, moves to a new location, or dies it may not be recorded in a data set. Continued medical records of any sort from a patient are used to indicate continued participation but this can be more or less problematic, depending on the data source. If death is not actively recorded, the data can sometimes be obtained via a link to the National Death Index, using full name and date of birth, when available. However, many health plans with electronic data link their ever enrolled files to state death registries on an annual basis, so they have reasonably complete death data already. Ideally, the strengths and weaknesses of a database are documented by validation studies, or can be before they are used. The appropriate choice will depend on the specific questions to be addressed by a research study. In all database studies it is important that the limitations of each data type, and the possible effect on the results, be carefully considered when publishing the results.

Large Health System Databases—Large health care systems with EMR data, principally the VA and health plans in the HMO Research Network (HMORN), satisfy many of the data requirements for conducting comparative safety and effectiveness research on opioid and NSAID medications(Table 2). In the absence of primary data collection, these databases are typically better suited to evaluate questions of analgesic safety as opposed to analgesic effectiveness. Large health system databases can be used as a sampling frame from which to sample large numbers of people receiving chronic opioid therapy. For example, among the 11 million persons within HMORN health plans, there are currently more than 300,000 patients receiving chronic opioid therapy. Since these individuals can be readily identified through health plan electronic data resources organized for research use, the HMORN and VA populations represent important resources for comparative effectiveness and safety research on analgesic medications.

Relative advantages and limitations using large health system databases—HMORN and VA research centers have extensive experience using these data resources for epidemiologic, health services, and clinical research. The data are of high quality, with thousands of NIH and VA funded research projects employing these data resources over the past several decades. The HMORN and VA databases cover millions of persons, including minority populations and large numbers of persons over the age of 65. The data are already organized in archival files suitable for research use. HMORN and VA data resources can be used as a sampling frame, permitting enrollment of patients in studies requiring primary data collection. The research value of these data resources and capabilities has been previously demonstrated through thousands of peer-reviewed publications assessing drug safety and effectiveness. Limitations include restricted ability to capture patients' health behaviors

(other than smoking status), severity of illness, and over-the-counter NSAID use, as well as ascertain most pain outcomes. Finally, developing information on participants' functional and cognitive status, along with severity of illness, would require medical record abstraction.

Insurance Claims Databases—Many health care and pharmacy insurance providers make administrative claims data available, including Medicare, Medicaid, Blue Cross Blue Shield through HealthCore, and United Health. These databases contain information on all health care encounters in which billable services were delivered.

Relative advantages and limitations using insurance claims databases—Medicare and Medicaid cover tens of millions of people and have the ability to provide information about opioid and prescription NSAID exposures and adverse events over extended periods of time, including hospitalizations and mortality (Table 2). These databases can provide population-based estimates for various outcomes, which is a particular strength. Given the large number of enrollees, these databases can also provide outcome data on diverse subpopulations (Medicare in particular). Limitations include the possibility of exposure misclassification, e.g., on account of unmeasured use of over-the-counter NSAIDs and ability to capture relevant pain outcomes. In addition, information on pain, functional and cognitive status, severity of illness, and health behaviors cannot be obtained and can operate as important unmeasured confounders. Finally, Medicare provides little information on enrollees' prescription drug use prior to 2006.

Clinical Registries—Clinical registries are databases that systematically collect and store health-related information on specific patient populations, most often defined by a particular illness, or are the recipients of a specific procedure (e.g., arthroplasty), or are managed within a given health care system. Because the clinical registries represent a new approach to researching issues related to the pharmacologic management of pain and some of the registries are still under development, validation studies will be needed to confirm the accuracy of their data elements. There are many pain registries; a brief summary of three registries are presented below. As this conference was intended to highlight a variety of potential research approaches rather than dictate specific strategies, these registries were only three of many examples of emerging data sources selected because of the conference organizers' familiarity with the registries' developing efforts.

PainCAS™—With support from NIDA, the Pain Assessment Interview Network – Clinical Advisory System (PainCAS™) registry was developed with the intention of standardizing the approach to pain assessment and treatment. In addition to other data points, it measures the "five C's" of pain: 1)Condition or diagnosis; 2) Context of pain that the patient is experiencing in their daily lives, what they think they need to do, or what will constitute a successful treatment for them; 3) Cognition level; 4) Comorbid conditions; and 5) Compliance (e.g., adherence, abuse, misuse, other aberrant drug-related behaviors such as diversion.) PainCAS™ is aclinically based tool developed to put data in the hands of health care providers that could help to automate the assessment process for patients with chronic pain. It can provide suitable reports for both health care providers and their patients and can interface with a health care system's medical records. It also provides de-identified, HIPAA compliant patient data that can be used for clinical, administrative, and research purposes. In addition, PainCAS™ provides decision support using either existing care paths in the clinical setting and/or guidelines for treatment as health care providers conduct patient assessments. The initial thrust was to create a framework for providers at a clinical setting based on care paths or accepted guidelines, and then measure how well providers adhered to or deviated from those care paths or guidelines. A fully functioning version of the tool is expected to be available for commercial use in 2012.

A key component of PainCAS™ is going to be its ability to track treatments and outcomes over time. It will capture information such as over-the-counter NSAID use to the degree that the medical record gathers these data. It will also capture information on pain, physical functioning, emotional functioning, participant ratings of improvement, satisfaction with treatment, symptoms, adverse effects, adherence to treatment regimen, and compliance with follow-up visits.

Relative advantages and limitations of PainCAS™—An advantage of using this approach includes incorporation of data capture utilizing existing patterns of workflow in a standardized way, thereby minimizing the likelihood of clinician and clinic setting variability. PainCAS™ will also allow for analysis of any combination of data captured as part of a usual clinical assessment at the provider, clinic setting, and aggregate data levels. Additionally, and importantly, data will include both positive and negative treatment outcomes. Data capture will be based on patient report which is the standard for pain outcomes and as such will be as reliable as assessments used currently. A comprehensive measure of patient severity of illness is not included at the present time.

National Data Bank for Rheumatic Diseases (NDB)—Founded in 1998, the NDB was developed with a focus on obtaining patient-reported data and measures in a purposeful, organized, systematic way for patients with rheumatoid arthritis, fibromyalgia and osteoarthritis. Since 2000, the NDB has added patients with systemic lupus erythematosus and all diagnoses seen by a rheumatologist. Patients are referred primarily by U.S. and Canadian rheumatologists and the NDB currently contains approximately 40,000 patients.

Relative advantages and limitations of the NDB—An important feature of this registry is that it captures all over-the-counter and prescribed medications that the patient has taken recently. Additional advantages include the extensive and detailed questionnaires measuring a patient's quality of life, health status, utilities, costs, and more. Relative limitations include underrepresentation of minority patients and those with lower education and income levels [69]. NDB data do not usually include physician-reported measures, although physician validation of important events is a key NDB process. Like all observational cohort studies, problems with confounding and selection bias can affect results. Further details about the NDB can be found on its web site (http://www.arthritis-research.org) and in summary publications [69,70].

New York City Tri-Institutional Chronic Pain Registry—The Tri-Institutional Chronic Pain Registry (TI-CPR) is another registry that was developed recently and is being used currently in four pain clinics. This registry uses Practice-Based Evidence (PBE) study methods [71,72] and includes patients with chronic non-cancer or cancer-related pain receiving longitudinal care from one of four New York City-based pain clinics. The registry's data elements can be used both for routine patient care documentation, as well as for comparative effectiveness and safety analysis purposes.

Relative advantages and limitations of TI-CPR—An advantage of this registry is that it allows for rapid patient accrual because all patients attending one of the clinics are enrolled. The registry includes large amounts of detail about enrolled patients(e.g., demographic, clinical, disease-specific severity of illness, pain, and functional status), treatments, and outcomes from routine practice so the findings related to better treatments are easily translatable into practice because they come from practice(Table 2). In addition, patient-reported data on pain, function, adverse events, hospitalizations, emergency department visits, other medical care visits, and interventions (including prescribed and over-the-counter medications, non-medication therapies, etc.) employed by patients between

visits and outcomes of these treatments are collected by survey prior to each patient encounter. The registry is longitudinal so it can be used to assess the long-term safety, effectiveness, and costs of commonly prescribed analgesic medications and other therapies among older adults, determine how to minimize or prevent analgesic-related side effects, and estimate the prevalence and impact of opioid abuse/misuse behaviors in older populations. As with all data collection approaches, the data are only as good as the details that are recorded. By providing templates for most of the data collected by providers and patients, the corresponding results can be exported from existing EMRs and used over time to determine and refine those interventions associated with better outcomes. A potential limitation is that the patients in these pain clinics may not be representative of the older adult population with chronic pain who self-medicate or are satisfactorily managed by primary care. They are a selected group of patients referred for specialty pain care by their primary care or other providers because of one or more factors such as complexity, risk, treatment resistance, co-morbidities, or to obtain pain procedures. Increasingly pain patients who require opioids are being referred to pain clinics. There may be a socioeconomic selection bias based upon ability to pay or insurance limitations. After use and refinement of the elements in the registry developed in the four pain clinics, there are plans to implement the registry in primary care practices and additional pain clinics in the US.

Observational Cohort Studies—Population-based observational cohort studies are well suited for providing information regarding the long-term safety of commonly used or prescribed analgesic medications. For instance, Cox-2specific inhibitors have been associated with increased risk of blood pressure destabilization in a study using National Health and Nutrition Examination Survey (NHANES)III data [73], while long-term use of NSAIDs has been associated with reduced risk of Alzheimer's disease in some [74], but not all [75,76] studies, and of breast cancer [77].In comparison to RCTs, cohort studies have many advantages for identifying adverse health outcomes associated with analgesic medication use. Most importantly, follow-up for a wide range of adverse health outcomes can be obtained over years and in some cases decades. Second, many cohort studies are relatively large with many hundreds or even thousands of participants. Thus, in concert with the relatively long follow-up, cohort studies can detect adverse events of small-to-moderate effect sizes that could not be identified in typical RCTs. Third, population-based observational studies often include subjects with a wide range of co-morbidities. Thus, observational cohort studies can evaluate associations with adverse outcomes due to interactions with comorbid conditions and specific analgesic medications.

Cohort studies can also ascertain etiologic factors underlying the variability of pain management effectiveness and/or adverse treatment outcomes. For example, low back pain has been associated with spinal stenosis, but is unrelated to other common pathologies noted on imaging, such as spondylosis or spondylolisthesis [78–80]. Meniscal lesions in the knee, a common reason for knee surgery, was shown to be a common finding that was as likely to be found in non-painful knees as in painful knees[81], calling into question the appropriateness of surgical intervention of these lesions.

Determining the consequences of pain in older adults can help to guide the selection of salient outcomes for use in future studies; some may serve as proxy measures of treatment effectiveness. For example, chronic widespread pain has been associated with increased risk of falls [82], incident self-report and performance-based disability [83,84], and progression of disability among disabled women [85], and could serve as meaningful outcomes in studies of analgesic effectiveness. In addition, the use of long-acting opioids has been associated with improved functional status and social engagement with no increase in adverse events or side effects relative to either no analgesic or nonopioid analgesic use

among nursing home residents [86], suggesting that effective pain management may help prevent these adverse outcomes.

A major caveat in the interpretation of findings regarding pharmacologic interventions in cohort studies is the issue of confounding by indication. That is, persons who take (or are prescribed) a certain medication are systematically different than those who do not take (or are not prescribed) the medication. Another caveat is "depletion of susceptibles," which refers to the fact that those who experience adverse events, or are at risk of doing so, are less likely to continue in the study long-term, and therefore long-term safety data do not necessarily reflect the true risks for the overall population[87]. Third, details about medication use may be less than ideal in observational cohort studies. For instance, it is important to know if medications prescribed are actually filled and taken as prescribed. Fourth, participants are typically only evaluated at certain time intervals, and therefore any medications used in between the study visits are not typically captured. Finally, substantial inter-individual variation in the pain experience occurs commonly and frequently necessitates novel study designs and analytic approaches. For example, one study(using a novel approach) found that knee pain was strongly associated with radiographic severity[88], despite the long-held belief of a symptom-structure discordance. Understanding what pathologies may contribute to pain provides insight into treatment targets. Despite these relative limitations, cohort studies can provide important insight into various aspects of pain and pain management in later life.

Add-Ons to Observational Cohort Studies—One approach to taking advantage of ongoing cohort studies involves adding additional measures to studies of pain and analgesic-medication use. Examples include the Study of Osteoporotic Fractures, Multicenter Osteoarthritis Study, and Osteoarthritis Initiative. All three studies focus on conditions associated with pain and include the same standard pain assessments to allow for uniform phenotyping of pain across studies. A second approach involves adding measures of pain and pain medication use to existing cohort studies of other common chronic conditions with a focus on (or that include a large proportion of) older adults. Examples of this approach include the Health, Aging and Body Composition (Health ABC) study, Framingham studies, and the Rush Memory and Aging Project.

Both approaches have unique strengths and weaknesses. Studies of pain will have excellent measures of pain and pain medication use, possibly including pain onset and transition to persistent pain. Further, these data may be supplemented by imaging and other modalities that can document potential causes of pain. However, these studies may be limited in the amount of other adverse health outcome data available and the investigators maybe reluctant to add additional measures because of concerns about undue participant burden. These issues are similar but reversed for studies of common chronic conditions, which assess the exposures and conditions of interest well, along with potential confounders, typically including medication use. These two add-on approaches are best seen as complementary. Ideally, the convergence of findings from add-on studies to both types of cohorts would provide the strongest evidence of analgesic-outcome associations.

Identifying a Core Set of Measures for Use in Longitudinal Cohort Studies—Panel members discussed various recommendations regarding a core set of pain measures for use in new studies or as add-on measures in ongoing cohort studies. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) provides guidance regarding core outcome domains to be studied in pain research[89], including: 1) pain; 2) physical functioning; 3) emotional functioning; 4) participant global ratings of improvement and satisfaction with treatment; and 5) symptoms and treatment-related adverse events. Supplemental domains include interpersonal-social functioning, coping,

clinician global rating, biological markers (quantitative sensory testing), cognitive functioning, and economic measures [90]. IMMPACT recommends that the following specific outcomes also be employed in clinical trials investigating pain interventions and therefore should be considered for observational studies of pain as well: 1) pain intensity rated on a 0–10 numerical rating scale, unless a well-accepted disease-specific measure of pain intensity is available; 2) the amount of any rescue analgesics used;3) physical functioning assessed by the Multidimensional Pain Inventory Interference Scale or the Brief Pain Inventory pain interference items unless a well-accepted disease-specific measure of physical functioning is available;4) emotional functioning assessed by the Beck Depression Inventory and the Profile of Mood States;5) participant ratings of overall improvement assessed by the Patient Global Impression of Change scale;6) adverse events using passive capture of spontaneously reported events and open-ended prompts; and finally 7) participant disposition assessed in accord with the CONSORT recommendations, including documentation of treatment adherence and reasons for premature withdrawal [91]. The IMMPACT website provides comprehensive details about this initiative (http://www.immpact.org).

A new effort in this area, i.e., the Patient-Reported Outcomes Measurement System (PROMIS), is being spearheaded by the National Institutes of Health(PROMIS; http://www.nihpromis.org). PROMIS measures have undergone rigorous psychometric evaluation and include pain measures (e.g., pain behaviors, interference, and quality) that could be used as predictors or outcomes in studies involving older adults. The NIH Toolbox (http://www.nihtoolbox.org)represents an additional effort in this area and seeks to develop and test comprehensive tools to measure participants' motor, cognitive, sensory and emotional function for use in epidemiologic and intervention studies. Many of the measures in this 'toolbox' may be relevant for research on pain and pain management in later life.

Initiatives that Can Inform Future Studies—Two federally supported initiatives, i.e., Analgesic Clinical Trials Innovations, Opportunities, and Networks (ACTION)and the Safe Use Initiative, seek to improve the pharmacologic management of pain using different mechanisms, and can inform the development of future studies germane to older persons with pain.

ACTION (http://www.actionppp.org) was conceived by the U.S. Food and Drug Administration (FDA) to create a public-private partnership(PPP)for the advancement of pain care in the U.S. ACTION seeks to streamline the discovery and development of new pain treatments with improved safety and efficacy. This multi-year, multi-phased initiative is intended to address major gaps in scientific information which slow down analgesic drug development. ACTION seeks to identify important scientific and clinical research needs regarding the design, performance, analysis, and interpretation of analgesic clinical trials and will issue (beginning in 2011) periodic requests for proposals to provide funding for investigations focused on critical methodologic aspects of analgesic clinical trials.

The Safe Use Initiative(http://www.fda.gov/Drugs/DrugSafety/default.htm) is a new FDA initiative. The objective of this program is to collaborate with diverse stakeholders to focus on mechanisms to identify and reduce harm from medications, by identifying specific candidate cases associated with significant amounts of preventable harm. The cases are analyzed to identify processes whereby a set of coordinated FDA/stakeholder actions can lead to better management of related risks and harm reduction by the development of appropriate activities and evaluation metrics. For example, it is known that certain analgesics increase fall risk among older adults[92–94]; this association may serve as a model for the implementation of a strategy to prevent (or reduce) the risk of this debilitating and costly adverse effect. More needs to be done to protect older adults from the harm

associated with analgesic medications without restricting their access to appropriate pain care. Participants in the healthcare community at large include patients, consumers, caregivers, healthcare practitioners, pharmacists, healthcare systems, health insurers, drug manufacturers, FDA, and other Federal agencies. Each stakeholder has a role in managing medication risks. Under the Safe Use Initiative, FDA will participate in and coordinate efforts in a systematic manner to prevent (or reduce) medication errors or misuse across all sectors of the medication distribution and use system.

DISCUSSION

A number of clinical practice guidelines [7,8,95,96] have been published on the topic of managing chronic pain, including the American Geriatric Society's Pharmacologic Management of Persistent Pain in Older Persons in 2009[8]. The panels that developed these guidelines acknowledged the general absence of high quality scientific evidence in the area of pharmacologic pain management and that their recommendations were infrequently supported by rigorous evidence. This NIH-sponsored conference was convened in an effort to address this evidence gap by identifying specific research needs that could, if addressed, improve the pharmacologic management of later life pain. Conference outcomes included the identification of 15research gaps that panel members unanimously agreed highlight important unanswered questions in this area, as well as 35 studies that panelists felt could help to address the gaps. Most of the gaps involved deficits in our understanding of treatment issues, including uncertainties regarding the long-term safety and effectiveness of opioid and NSAID medication use, reliable predictors of treatment response, and effective methods to prevent or reduce the occurrence of deleterious, treatment-related side effects. Epidemiologic (e.g., uncertainties regarding the incidence, prevalence, and course of common pain syndromes)and implementation (e.g., lack of knowledge regarding how best to translate evidence-based pain treatments into practice) gaps were also identified.

Addressing the identified gaps was deemed to have substantial dividends at multiple levels. For healthcare providers faced with the task of caring for aging adults with chronic pain, generating an age-appropriate evidence base could improve the quality of care they deliver and reduce the significant frustration endorsed by many clinicians when caring for patients with chronic pain [97,98]. The recommended studies, if conducted, could help providers by fostering the development of age-appropriate risk stratification tools, instruments to better monitor older patients newly started on analgesics with narrow risk-to-benefit ratios, practical tools to communicate analgesic risks and benefits to older patient or their caregivers, as well as evidence-based approaches to discontinuing opioid therapy. The panel called for research focusing on each of these areas, as well as work examining the concomitant use of nonpharmacologic interventions as a means of moderating analgesic treatment outcomes, which could also help to improve the quality of delivered care.

At the patient level, generating knowledge regarding the long-term safety and effectiveness of opioid, NSAID, as well as over-the-counter analgesic medications and ascertaining strategies to minimize or prevent treatment-related side effects could provide substantial benefits, including improved treatment outcomes. Generating this information could also provide substantial dividends at the system level, to include helping insurers determine which treatments to reimburse and for how long, and improving the quality of evidence underlying current pain management guidelines, which could help to promote their adoption and reach in diverse practice settings.

Many of the gaps identified during the conference represent uncertainties regarding the pharmacologic management of chronic pain across all age groups, not just older adults. The panel did not intend to discuss gaps that were exclusively geriatric in focus, but rather, took

care to be as inclusive as possible of geriatric issues within the universe of pain research and, where appropriate, to identify issues that were particularly important for older adults. Reflecting this inclusivity, the gaps presented in this report are similar to those generated by an American Pain Society and American Academy of Pain Medicine initiative [68] on research gaps related to the use of opioid therapy for chronic pain independent of patient age. Of note, the current report also illustrates that many (if not most) of the identified gaps pertain not only to opioid medications, but prescribed NSAIDs and over-the-counter analgesics as well. Gaps pertaining mainly to older adult populations include a lack of knowledge regarding optimal approaches to pharmacologically manage pain in persons with advanced chronic disease and those at the end of life; as well as strategies to overcome established barriers to analgesic medication engagement and adherence. The latter gap is a significant problem among older adults [99,100], but may be less of an issue with aging baby boomers.

Because of the extremely limited number of pain management studies involving older adults [7,32], and difficulties translating results generated in studies of younger adults to older populations, the NIH conference panel felt strongly that future investigations seeking to address the gaps do so by enrolling representative samples of older adults. Panel members also called for funding agencies to support pain research that specifically targets vulnerable groups of older adults. Newly initiated studies should be encouraged to adopt strategies that efficiently screen, consent, and enroll vulnerable groups of older persons[101,102]. Analyses of electronic health care databases and data from cohort studies that specifically enrolled older adults with one or more of the above attributes, e.g., Women's Health and Aging Study [103], were strongly encouraged. A consensus regarding the value of specific research methods was also reached. Panel members felt that many of the identified research gaps could be successfully addressed by analyzing data from electronic health care databases and observational cohort studies, as well as by adding-on relevant measures to ongoing cohort studies. Analyses of electronic healthcare databases and observational cohort study data were deemed to be particularly important tools to help detect adverse associations that require long-term cumulative exposure, identify relatively rare events, and ascertain important interactions (e.g., between co-morbidities and concomitant medication use). This report summarizes the relative advantages and disadvantages of using these approaches to address pressing research issues related to the pharmacologic management of later life pain and can help to guide the selection of a particular method (or methods)in future research. The panel acknowledged that other types of research approaches will be needed to fully address all of the identified gaps. For example, certain questions might best be addressed through the use of randomized controlled trials(e.g., identifying optimal methods for initiating and titrating specific analgesic medications), qualitative research (e.g., identifying patient and provider treatment barriers)or by initiating new observational cohort studies (e.g., identifying the natural history of specific pain syndromes).

In conclusion, this report highlights the presence of significant gaps in our understanding of optimal pharmacologic strategies for managing chronic pain in later life. Addressing these gaps was judged by the panel to have substantial potential to improve not only the quality of care delivered to older persons with chronic pain but also the quality of life for affected individuals. It is hoped that these findings prove valuable to funding agencies, researchers, and policy makers interested in improving the care of older adults with chronic pain.

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Appendix A. Conference Participants

David A. Bennett, Rush University Medical Center, Chicago, IL

Ann Berger, National Institutes of Health Clinical Center, Bethesda, MD

Marie A. Bernard, National Institute on Aging, Bethesda, MD

Simon H. Budman, Inflexxion, Inc.

Wen G. Chen, National Institute on Aging, Bethesda, MD

Elizabeth L. Cobbs, George Washington University Medical Center, Washington, DC

Richard A. Denisco, National Institute on Drug Abuse, Bethesda, MD

Basil A. Eldadah, National Institute on Aging, Bethesda, MD

John T. Farrar, University of Pennsylvania School of Medicine, Philadelphia, PA

Bruce A. Ferrell, University of California Los Angeles, Los Angeles, CA

Rollin M. Gallagher, Veterans Administration and University of Pennsylvania, Philadelphia, PA

Diane St. Germain, National Cancer Institute, Bethesda, MD

Evan Hadley, National Institute on Aging, Bethesda, MD

Joseph T. Hanlon, University of Pittsburgh, Pittsburgh, PA

Keela Herr, The University of Iowa, Iowa City, IA

Susan D. Horn, Institute for Clinical Outcomes Research, Salt Lake City, UT

Michael J. Iadarola, National Institute of Dental and Craniofacial Research, Bethesda, MD

Charles Inturrisi, Weill Cornell Medical College, New York, NY

Lyndon Joseph, National Institute on Aging, Bethesda, MD

John W. Kusiak, National Institute of Dental and Craniofacial Research, Bethesda, MD

Audrey Kusiak, Department of Veterans Affairs, Washington, DC

Salma Lemtouni, US Food and Drug Administration

Yu “Woody” Lin, National Institute on Drug Abuse, Bethesda, MD

Susan Marden, National Institute of Nursing Research, Bethesda, MD

Kaleb Michaud, University of Nebraska Medical Center, Omaha, NE

R. Sean Morrison, Mount Sinai School of Medicine, New York, NY

Marcelle Morrison-Bogorad, National Institute on Aging, Bethesda, MD

Tuhina Neogi, Boston University, Boston, MA

Lis Nielsen, National Institute on Aging, Bethesda, MD

Ann M. O'Mara, National Cancer Institute, Bethesda, MD

Linda L. Porter, National Institute of Neurological Disorders and Stroke, Bethesda, MD

Bob A. Rappaport, US Food and Drug Administration

M.C. Reid, Weill Cornell Medical College, New York, NY

Sergei V. Romashkan, National Institute on Aging, Bethesda, MD

Sherry Sherman, National Institute on Aging, Bethesda, MD

Scott R. Smith, Agency for Healthcare Research and Quality, Rockville, MD

D. Stephen Snyder, National Institute on Aging, Bethesda, MD

Daniel Solomon, Harvard Medical School, Boston, MA

Roma Tickoo, Memorial Sloan Kettering Cancer Center, New York, NY

Michael Von Korff, Group Health Research Institute, Seattle, WA

Molly V. Wagster, National Institute on Aging, Bethesda, MD

Karen D. Weiss, US Food and Drug Administration

James Witter, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD

Kevin L. Zacharoff, Inflexxion, Inc.

Appendix B

This appendix contains information about specific data elements of, methods of data collection for, and access to large health system databases; insurance claims data; and the clinical pain registries listed in the article.

Large Health Systems

Data elements

Research centers located within the 15 HMO Research Network (HMORN)health plans in the United States and the 14 health services research centers located within the regions of the VA are able to access data sets with extensive information on the millions of persons served by their respective health care delivery systems. Available data in these archives include: 1) Enrollee data, including name, a unique enrollment number that is linked across all periods of enrollment, contact information (address, telephone number), age, sex, race/ethnicity in some health plans, primary care physician, and enrollment/disenrollment dates; 2) Ambulatory visit data, including date of visit, diagnoses, procedures, provider identification, type of provider, care setting (e.g., primary care, specialty care, emergency room, physical therapy), costs of services provided; 3) Inpatient episode data, including date of admission and discharge, diagnoses, procedures, intensive care unit days, and costs of

care; 4) Pharmacy data, including the date of prescription, prescribing clinician identification, specific medication prescribed, its formulation, days supply, medication costs. Pharmacy records can be used to estimate such things as average daily dose of opioids dispensed over a defined period of time; 5) Biometric and health status data, now being captured by electronic medical records include blood pressure, height and weight, and more recently some systems are now capturing depression severity and pain ratings in relevant visits; 6) Laboratory and radiographic data, including laboratory tests and radiographic tests performed and their results; and finally 7) Electronic medical records data. With the implementation of electronic medical records (EMRs)in the HMORN and VA health plans, it is possible to directly access the entire medical record of enrollees for medical records abstraction. This can be used to validate diagnoses and health events that are ascertained on health care visit or inpatient episode records. Natural language processing is now being used with some success to analyze text data in health plan EMRs to improve the efficiency and accuracy of identification of diagnoses and health events.

Data collection

Archival data available through HMORN and VA research centers have been collected as part of routine care processes that generate electronic health care records documenting the care provided (e.g., visits, inpatient episodes, medications dispensed, and laboratory/imaging tests). With implementation of EMRs, additional clinically relevant information is becoming routinely available, such as blood pressure readings, weight and height. More recently, some plans have implemented standardized electronic forms for assessing depression severity and pain severity. When these standardized electronic forms are used in clinical care, it is possible to capture the results of these assessments for research use.

Access

The electronic health care databases of health plans in the Health Maintenance Organization (HMO) Research Network are accessed through research centers affiliated with each of the plans, generally through collaborative research with investigators in health plan research centers. Each research center has its own procedures for considering research proposals using health plan data, including human subjects protection review. The research centers in the HMO Research Network have developed a virtual data warehouse to facilitate analyses of data across multiple plans, employing common data definitions and algorithms that can be applied across health plan data sets. There are a variety of research consortia funded by the federal agencies that use HMO Research Network data through diverse funding mechanisms. These include: the Center for Education and Research on Therapeutics (funded by the AHRQ); the Vaccine Safety Datalink (CDC); the Mini-Sentinel network (FDA);cancer, cardiovascular disease, and mental health research networks (NCI, NHLBI, NIMH); and the NIH-HMO Collaboratory (NIH), among others.

“Researchers not employed by the VA have two options for access to the VA patient care datasets. The first is to request data under provisions of the Freedom of Information Act. Requests are considered on a case-by-case basis, with review by the data steward and possibly the VHA Privacy Officer. Further information can be requested from the World Wide Web (www.va.gov/foia). A second option for non-VA researchers is to establish research collaborations with VA researchers and, with appropriate administrative arrangements, to become employed on a “without-compensation” basis. In this capacity, a researcher would then be eligible to request access to the inpatient and outpatient medical SAS datasets as a VA employee” [1].

Insurance Claims Data

Data elements

Specific data elements include diagnosis and procedure codes, laboratory and radiology orders(not the results), ambulatory and inpatient visits, and pharmacy dispensings.

Data collection

Data are routinely collected because of administrative purposes, such as billing.

Access

Insurance claims databases are available from the Center for Medicare and Medicaid Services for those programs. As for other insurance data, many companies are amenable to making arrangements with researchers to use their data.

Clinical Registry: PainCAS™

Data elements

Registry items will include all standard data components of typical assessments performed at both initial and follow-up visits. These items will also be able to be customized based on the clinic settings individual care paths or guidelines. Examples include chief complaint, symptoms, diagnosis, patient characteristics (e.g., age, gender, race), prior and current treatments/interventions (e.g., prescriptions, over-the counter medications, and patterns of drug use over time, interventional procedures performed), and functional impact at initial visit and outcomes at follow-up visit (e.g., pain rating, adverse effects, functional status, and overall quality of life) at each visit.

Data collection

PainCAS™ data are collected in a non-proprietary IT format that is modular, customizable, proprietary to the end user, and handled by a competent data warehouse. One goal of PainCAS™ is to help standardize practice, making sure that components like the risk assessment are not left out, and to provide information to the clinician about best practices.

Access

This clinical registry is still under development. As for the maintenance of the data, it will be maintained by Inflexxion in a secure, fully HIPAA and HITECH compliant fashion. Clinicians (and their administrators) will have access to only their own identified data sets, with other analyses only available in de-identified form, for research purposes. Inflexxion has a significant amount of experience in this arena, with its ASI-MV Connect tool used in over 500 substance abuse treatment centers across the country.

Clinical Registry: National Data Bank for Rheumatic Diseases (NDB)

Data elements

Registry items include patient characteristics (e.g., age, gender, income, alcohol use, body mass index, comorbidity and general health status), treatments/interventions (e.g., dose and duration of all pharmacotherapies to include start/stop dates) and specific outcomes (e.g., somatic symptoms, disability level, hospitalizations and pain status).

Data collection

Patients constitute the primary data source and undergo a comprehensive assessment upon enrollment, followed by semi-annual interviews occurring by mail, telephone, or Internet. All hospitalizations, as well as medical events deemed significant, are validated by medical record reviews conducted by NDB staff. A particular strength of this database is its strong focus on capturing treatments, pain-related status, somatic symptoms, functional and health status, quality of life measures, and mortality.

Access

The NDB has an active group of collaborating researchers that have access to non-identifiable data for their research. Physicians have access to all of their patient data in the NDB for clinical care as well as for their research purposes. Interested investigators can contact the NDB about using data for grants, manuscripts and related projects. The NDB receives funding by private and public sources as well as by tax-deductible donations.

Clinical Registry: New York City Tri-Institutional Chronic Pain Registry

Data elements

Registry items include patient characteristics (e.g., age, gender, race, payer, diagnoses, and severity of illness), treatments/interventions (e.g., prescriptions and patterns of drug use over time, procedures performed), and outcomes (e.g., pain, functioning, adverse events, and other outcomes) at and in between each visit. Clinicians who treat patients with chronic pain played an important role in the selection of the registry's data elements to make certain that they were perceived as useful for both patient care and research purposes. The registry includes all treatments with the date, dose, intensity, and route, and both drug and non-drug combinations of therapy. Validated outcome tools were included so that comparisons could be made across the participating pain clinics and also to the literature, and include the Brief Pain Inventory, Condensed Memorial Symptom Assessment Scale, EQ-5D, and Current Opioid Misuse Measure. These surveys contain items that identify changes in health status factors such as cognitive status, depressive symptom severity, or frailty, so that together with the clinician's notes, they can serve to generate appropriate follow up.

A unique feature of this registry is the use of the disease-specific severity of illness system called the Comprehensive Severity Index (CSI®) to control for confounding by indication or selection bias. CSI® is age and disease-specific, independent of treatments, and provides an objective, consistent method to define patient severity of illness levels. CSI severity levels are calculated from relevant health indicators based on over 2,200 signs, symptoms, and physical findings related to a patient's disease(s) [principal and all secondary diagnoses], not just on diagnostic information (ICD-9-CM coding). The CSI® has been validated extensively in diverse healthcare settings [2–4]. The detailed comprehensive nature of this index allows for detection of differential responses to interventions that may be obscured by either a more unidimensional or a composite severity score. Selection bias is ameliorated by controlling for patient differences statistically rather than by restricting subject inclusion.

Data collection

Data elements are obtained from a combination of existing electronic medical records (EMR) data elements and patient survey; they are provided by both patients and providers. Providers document patient visits using standardized documentation templates so these data can be exported readily. In addition, patient-reported data on pain, function, adverse events, hospitalizations, emergency department visits, other medical care visits, and interventions (including prescribed and over-the-counter medications, non-medication therapies, etc.) employed by patients between visits and outcomes of these treatments are collected by

survey prior to each patient encounter. All data elements are considered standard of care documentation within the participating clinics. Thus, documentation for the registry is not an add-on, because it is very difficult to sustain a registry if it requires duplicate or add-on documentation, particularly for clinicians. The electronic medical record system requires the interviewing clinician to verify that the patients' medication list is current (Attending Physician Acknowledgement Statement). Point-of-care physicians emphasized that this was one of the most important pieces of patient data that they wanted included in the registry. In addition, the TI-CPR has access to all patient encounters that occur in the three institutions clinic environment as well as any outside encounter information that are requested by clinicians and scanned into the EMR. Adverse events are found in the EMR sections on allergies, review of systems, and the physical examination. Along with the validated patient survey questions related to interference with activities of daily living and drug or treatment related adverse effects, the registry captures longitudinal information on incidence, severity, and persistence of adverse effects. Change in "active patient status" is obtained by either (1) patient inclusion in the National Death Index, (2) notification by patient and inclusion of a last follow-up note in the EMR, or (3) attempt at follow-up with patients who miss scheduled clinic visits or do not respond to patient pre-visit survey.

Access

Consistent with the NIH resource sharing plan, all information will be made available to interested parties via a request to the Principal Investigator, Charles E. Inturrisi, PhD in writing, or by email. The sharing of unpublished information may be subject to confidentiality issues relating to our collaborations with other scientists in academic or corporate laboratories, and will need to be discussed with the appropriate institutions before any request is granted, wholly or in part.

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Table 1

Research gaps and studies to address them

Treatment	Panel Recommended Studies That:
Lack of knowledge regarding the long-term safety and efficacy of commonly used analgesics	• Determine the long-term safety, efficacy, and costs of commonly prescribed NSAIDs and opioids • Assess potential medical and psychosocial adverse effects of long-term opioid use including: opioid use disorders; respiratory effects (e.g., overdose, sleep-disordered breathing); endocrine effects (e.g., hypogonadism, impaired sexual function, infertility, osteoporosis, depressed mood); gastrointestinal effects (e.g., chronic constipation, fecal impaction); pain modulation effects (hyperalgesia); clinically apparent immunosuppressive effects (e.g., pneumonia, sepsis); effects on cognition (e.g., sedation, delirium, dementia); movement and balance effects (e.g., falls, fractures); and behavioral effects (e.g., apathy, depression, behavioral deactivation) • Determine the effects of chronic opioid therapy on doctor-patient alliance and on management of comorbid chronic conditions other than chronic pain (e.g., hypertension, diabetes) • Compare the safety and effectiveness of specific medication classes (e.g., non-selective NSAIDs vs. coxibs vs. opioids), individual drugs (e.g., morphine vs. oxycodone), medication regimen (e.g., opioid dose, use of short-acting vs. extended release formulations) and methods of drug delivery (e.g, transdermal vs. oral) among older adults with common pain disorders (e.g., back pain, knee OA, chemotherapy induced neuropathy) • Examine the long-term safety and efficacy of over-the-counter analgesics
Uncertainty regarding factors that predict positive (or negative) treatment outcomes	• Identify patient-level (e.g., age, comorbidity, frailty status, renal function, pharmacogenomic profiles), medication-level (e.g., initiating dose, titration method, specific pattern of analgesic use) or system-level (e.g., use of guideline recommended prescribing) factors that increase the likelihood of experiencing positive or negative treatment outcomes • Determine whether opioid treatment administered early in the course of a chronic pain disorder (vs. initiating therapy after the development of disabilities) is associated with improved outcomes • Develop and evaluate laboratory tests that help to predict analgesic efficacy or side effect occurrence
Lack of knowledge regarding optimal approaches to prevent or minimize side effects	• Determine whether co-administration of additional therapies (e.g., use of physical therapy during the initiation and titration phases of opioid treatment) can minimize or prevent side effect occurrence(e.g., falls, fall-related injuries) • Examine the role of mobile health technologies (e.g., smart phones, actigraphy) in monitoring for and/or reducing occurrence of side effects during analgesic initiation and dose titration • Ascertain whether age-and/orrenal-adjusted dosing reduce side effect occurrence • Determine the value of co-administration of proton pump inhibitors when prescribing NSAIDs to reduce risk of gastrointestinal complications
Uncertainty regarding the pharmacokinetics of specific opioids	• Determine the pharmacokinetics of levorphanol, methadone, and oxymorphone, as well as specific opioid/non-opioid combination products (e.g., codeine + aspirin or acetaminophen, hydrocodone + aspirin or acetaminophen)where the target populations include healthy older adults; individuals taking liver metabolized medications; and those with potentially interacting diseases
Limited understanding regarding the extent, impact, and factors that increase risk of, as well as methods of detection for, opioid abuse/misuse	• Develop and test age-appropriate measures of opioid misuse and abuse • Ascertain the prevalence and specific types of opioid misuse and abuse in older populations • Identify patient-level (e.g., age, degree of social isolation, depressive symptomatology, cognitive status), medication-level (e.g., type of opioid agent, duration of exposure, specific patterns of use), and/or system-level (e.g., use of opioid contracts or use of contracts combined with urine toxicology screens) factors that increase or decrease risk for opioid misuse/abuse

Treatment	Panel Recommended Studies That:
	• Determine the degree to which prescribing opioid medications for older adults constitutes a route for opioid diversion • Ascertain factors that contribute to accidental and intentional opioid misuse (e.g., non-prescribed dose escalation, purposeful oversedation, concurrent excess alcohol consumption, non-prescribed polypharmacy)
Uncertainty regarding how best to discontinue chronic opioid therapy and effects of stopping treatment	• Studies of difficulties with and support for opioid discontinuation among patients not benefiting from moderate-to-high dose chronic opioid therapy regimens or who wish to discontinue opioid use
Lack of knowledge regarding optimal approaches to pharmacologically manage pain among persons with advanced chronic disease or at the end of life	• Examine factors that promote or impede appropriate use of opioids to reduce suffering among persons with advanced chronic disease (e.g., heart, lung, kidney) or at the end of life
Lack of knowledge regarding optimal treatment approaches for breakthrough pain	• Determine the efficacy and safety of specific treatments for breakthrough pain associated with chronic non-cancer pain disorders
Uncertainty regarding the role of opioid rotations when treating chronic pain	• Ascertain the safety and efficacy of employing specific opioid rotations in the treatment of chronic non- cancer pain disorders
Limited information concerning strategies to overcome older patient barriers to analgesic medication engagement/ adherence	• Estimate the prevalence and specific types of older patient beliefs and attitudes (e.g., risk of addiction, fear of side effects) that negatively impact treatment engagement and adherence and that develop and test educational interventions to successfully address them • Determine whether use of mobile health technologies (e.g., smart phones) can enhance adherence during the initiation and titration phases of therapy and whether other technologies (e.g., electronic pill boxes) can enhance analgesic adherence in older adults with memory impairment
Limited knowledge regarding provider-level barriers to prescribing analgesics in older adults & strategies to overcome them	• Estimate the prevalence and specific types of provider beliefs/attitudes that negatively impact on provider willingness to treat pain pharmacologically in older adults(e.g., fear of contributing to patient addiction, belief that pain is an expected part of aging) and that develop and test educational (or other types of) interventions to successfully address them
Lack of practical tools to communicate analgesic risks & benefits	• Develop and test decision support tools that providers can use to help older patients (or their caregiver) understand analgesic risk-benefit profiles and make informed choices regarding use of specific analgesic agents
Uncertainty regarding most appropriate target(s) for intervention	• Develop and evaluate clinical tests to identify pain-specific mechanisms that could guide treatment decision making • Determine whether disease specific treatment approaches (e.g., treatment of specific OA conditions) or generic approaches (pain as a syndrome) lead to superior outcomes
Epidemiology	
Lack of knowledge regarding the incidence, prevalence, and course of common pain syndromes in later life	• Determine the natural history of specific pain disorders (e.g., post-herpetic neuralgia, back pain, chemotherapy induced neuropathy) to help determine the level of treatment intensity needed • Estimate the incidence and prevalence of common pain syndromes in later life and reproducible methods to identify them Examine the subjective experience of pain in older adults and its relation to behavioral and social factors
Implementation	
Lack of knowledge regarding ways to effectively translate evidence-based pain treatments into practice	• Translate evidence-based pain practices (e.g., stepped-care or collaborative-care models) into diverse clinical practice settings, as well as those that ascertain and/or attempt to modify specific barriers to translating evidence-based pain protocols into practice

Treatment	Panel Recommended Studies That:
	• Determine the role of specific acute pain management protocols (e.g., post-arthroplasty pain) in the management of chronic pain disorders • Test or compare methods of disseminating evidence-based pain protocols in to practice • Determine the role of cluster randomized controlled trials as a means of facilitating dissemination of evidence-based pain protocols in practice

Table 2

Attributes of Electronic Health care Databases

	Large Health Systems (Electronic Medical Record)	Medicaid	Medicare	Clinical Registries		
				PAINCAS™	National Data Bank for Rheumatic Diseases	New York City Tri-Institutional Pain Registry
Demographic factors						
Age, sex	Yes	Yes	Yes	Yes	Yes	Yes
Race/ethnicity, socioeconomic status	Variable	Variable	No	Yes	Yes	Yes
Clinical, functional & other health status factors						
Major comorbidities	Yes	Yes	Yes	Yes	Yes	Yes
Body mass index	Yes	No	No	Yes	Yes	Yes
Functional status	EMR abstraction	No	No	Yes	Yes	Yes
Cognitive status	EMR abstraction	No	No	Yes	Yes	Yes
Depressive symptom severity	Variable	No	No	Yes	Yes	Yes
Frailty	EMR abstraction	No	No	Yes	Limited	Yes
Health status	Yes	Limited	Limited	Yes	Yes	Yes
Smoking and body mass index (BMI)status	Yes	No	No	Yes	Yes	Yes
Other health behaviors	Variable	No	No	Yes	Yes	Yes
Ability to refine above factors by record review	Yes	No	No	Yes	Yes	Yes
Ability to refine above factors by patient interview	Yes	No	No	Yes	Yes	Yes
Pain variables						
Pain severity	Variable	No	No	Yes	Yes	Yes
Pain extent	No	No	No	Yes	Yes	Yes
Non-articular pain	No	No	No	Yes	Yes	Yes
Articular pain	No	No	No	Yes	Yes	Yes
Medication & medication-relatedoutcomes						
Opioid exposure(s)	Yes	Yes	Yes	Yes	Yes	Yes
NSAID exposure(s)	Limited	Limited	Limited	Yes	Yes	Yes
Other medication exposures(s)	Variable	Yes	Yes	Yes	Yes	Yes

	Large Health Systems (Electronic Medical Record)	Medicaid	Medicare	Clinical Registries		
				PAINCAS™	National Data Bank for Rheumatic Diseases	New York City Tri-Institutional Pain Registry
Current & cumulative dose estimation	Variable	Yes	Yes	Yes	Yes	Yes
Adverse event identification	Yes	Yes	Yes	Yes	Yes	Yes
Ability to confirm by medical record review	Yes	No	No	Yes	Yes	Yes
Ability to confirm by patient interview	Yes	No	No	Yes	Yes	Yes
Other						
Population size covered	Millions	Millions	Millions	*	40,000	2,500
Enrollment status tracked	Yes	Yes	Yes	Yes	Yes	Yes
Diverse population	Yes	Yes, but mostly young & poor	Yes	Variable	Variable	Variable
Ability to contact subjects for interviews, examination and/or collecting biological samples	Yes	Yes	Yes	Yes	Yes	Yes
Ability to access laboratory & radiology results	Yes	No	No	Yes	Variable	Yes
Initial identification from ICD/CPT codes	Yes	No	No	Yes	Yes	Yes
Potential to interview cases and controls for additional information	Yes	No	No	Yes	Yes	Yes
Links to death registry	Yes	Yes	Yes	No	Yes	No
Diagnosis and exclusion codes	Yes	Yes	Yes	Yes	Yes	Yes
Confirmation of diagnosis and exclusion by medical record	Yes	Yes	Yes	Yes	Yes	Yes

*Still being tested.