

# Mental Health in an Aging Population: The NIMH Perspective

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Throughout the world, improved public health measures and medical treatments are contributing to increasing longevity. Combined with decreasing fertility rates in many countries, this trend is producing rapid demographic shifts in which older persons are becoming a substantially larger proportion of many nations' populations. Although the National Institute of Mental Health (NIMH) has a long history of supporting and conducting research focused on disorders of cognition and emotion in late life, these changes in demography add urgency to our mission. The goal of biomedical and behavioral research for aging populations must not be limited to extending longevity but must attend to preventing disability and enhancing individuals' capacities to function well in diverse life roles.

Recent years have seen an increasing appreciation of the role that disorders of cognition and emotion play in generating disability and degrading life quality. Although this is not surprising in light of disorders such as Alzheimer disease (AD), the World Health Organization has generated substantial and compelling data demonstrating that illnesses traditionally classified as mental disorders, such as major depression, have a disproportionately large impact on disability and overall disease burden (1). Also, there is increasing evidence that depression may negatively affect the course of general-medical disorders, such as cardiovascular disease. Despite its impact on disability, morbidity, and mortality, depression is too often seen as a normal part of the aging process rather than what it is—a serious disease deserving aggressive treat-

ment. Overall, failure to recognize and treat mental disorders can lead to progressive deterioration of functioning in multiple spheres of life.

This commentary highlights areas in which NIMH would welcome innovation and increasing depth in its research portfolio: epidemiology and diagnosis, pathophysiology, experimental therapeutics and clinical trials, suicide prevention, behavioral research, health-services research, and issues related to elderly persons with mental illness and their caregivers.

## **EPIDEMIOLOGY AND DIAGNOSIS**

Although there have been many studies of cognition with aging (2–5), there persists an inadequate understanding of the interactions among different aspects of physical health, cognition, and emotion as people age (6, 7). There are compelling epidemiologic data, for example, that myocardial infarction and certain other serious medical disorders increase the risk of depression and, conversely, that major depression increases the risk of reinfarction and death in people who have had myocardial infarction (8–10). Initial data suggest, moreover, that this morbid interaction between cardiovascular disease and depression does not result simply from the depressed individual's difficulties in adhering to treatment and rehabilitation, but may reflect pathophysiologic impacts of the mood disorder, perhaps mediated by elevations in cortisol, peripheral catecholamines, and altered platelet function (11–13). Although substantial research is under way on the relationship between

disorders of mood and the cardiovascular system, results to date underscore the need to examine more broadly the interactions among general-medical disorders, depression, anxiety disorders, and other disorders of cognition and emotion. Important “issue” questions include the question of whether late-onset depression can result from cerebrovascular disease, whether late-onset depression can be a harbinger of AD or Parkinson disease (PD), and what the pathophysiologic relationship among these may be.

Another unanswered question concerns possible causal relationships among chronic or recurrent mood and anxiety disorders, elevated levels of the stress hormone cortisol, hippocampal atrophy, and deficits in explicit memory as a person ages. In general, the need exists to understand how late-life general-medical and classically neurological conditions affect the development of mental disorders and vice versa.

Prompted by these needs, NIMH, in collaboration with the National Institute on Aging and the National Institute of Neurological Disorders and Stroke, has initiated support for a comprehensive review of the literature on aging, cognitive functioning, mental health, and vascular status; this review is expected to suggest directions for additional longitudinal studies of cognition and emotion in health and disease with aging. Prevention research is dependent on epidemiologic studies of risk factors; thus the goal of uncovering the relationships among general-medical and neurological disorders, cognition, and emotion is to provide a firm basis for research on prevention and early intervention in disease. If, for example, depression proved to be a harbinger of AD or PD, it would be important to develop tools for documenting that trajectory and intervening appropriately. Improved identification of ongoing risk factors for mental disorders among elderly persons is necessary, for example, to respond to circumstance that might trigger a recurrence of a mood, anxiety, or substance use disorder.

As epidemiologic research on disorders of aging progresses, it will become increasingly important to revisit criteria for late-onset disorders to ensure that they are relevant and differentiate accurately and appropriately between what is normal and what is abnormal. Given the well-documented extent of current failures in recognition and diagnosis (14, 15), the need exists for generalizable approaches to accurate diagnosis that will lead to provision of appropriate interventions when mental disorders are present; this challenge includes the need to account for the variations in idioms of distress in elderly patients.

## NEW APPROACHES TO PATHOPHYSIOLOGY

As suggested above, chronic or recurrent mood and anxiety disorders may affect brain structure and functioning over time; moreover, late-onset mental disorders may be pathophysiologically different from early-onset illness. Thus, as epidemiologic research elucidates the natural history of mood and anxiety disorders and their relationship to brain structure and functioning, we must also investigate the underlying disease mechanisms at the cellular and molecular levels. Such pathophysiologic investigation ideally will lay the groundwork for new therapies, and will be aided by such modern technologies as functional genomics using DNA microarrays and proteomics in the context of careful postmortem studies of the brain.

As alluded to above, early evidence suggests that chronic or recurrent depression or posttraumatic stress disorder may lead to hippocampal atrophy, with a negative impact on explicit memory function; it has also been hypothesized that hippocampal damage lowers the threshold for recurrent depressive episodes (16–18). Furthermore, because evidence suggests that cognitive performance is maintained in aging persons by more extensive recruitment of cortical areas, compared with younger individuals, elderly persons suffer enhanced risk of significant loss in functional capabilities after such brain insults (19). Assuming that these observations are confirmed, we must understand the mechanisms involved.

As another example, a vascular hypothesis has been proposed for a subset of late-onset depressions, suggesting that they may be the result of multiple small strokes in certain anatomic locations (20). This hypothesis would suggest that treatment of atherosclerosis might be an important aspect of depression prevention and treatment; but, once again, new approaches to understanding pathophysiology are prerequisite to testing these hypotheses and developing new therapies.

Central to the success of the NIMH clinical neuroscience portfolio, as we consider mental disorders at any age, is a need to bring the strongest possible cognitive and affective neuroscience to bear on imaging studies, with the aim of identifying specific circuits involved in mental disorders. Cognitive neuroscience must be developmentally sensitive, and research on mental disorders in aging populations is no exception. Cognitive and emotional stimuli and tasks needed to identify vulnerable brain circuits must be specifically developed for research on aging populations. Cognitive neuroscientists would do well to focus specifically on mental disorders in older persons and not assume

without further evidence that approaches to studying normal and abnormal cognition and emotion in adult populations can be transferred directly to elderly populations.

## EXPERIMENTAL THERAPEUTICS

In recent years, NIMH has ceded much research on the development of new pharmacologic interventions to industry and has not paid adequate attention to the use of existing therapies for new indications. Limited federal involvement may have biased the development of new therapeutics toward larger markets (e.g., to adult depression or psychotic disorders) and away from more specialized markets (e.g., disorders of aged populations or children.) Moreover, industry has diminished incentive to study older compounds, especially compounds that are off-patent, for new indications. If, for example, epidemiologic and pathophysiologic studies support a role for cerebrovascular disease in at least some geriatric depression, a significant effort should be made to identify treatments—likely cholesterol-lowering agents and drugs that affect platelet function, that could prevent progression, while using more traditional antidepressants symptomatically. NIMH is currently engaged in discussion of how to support new treatment development in a way that would ultimately justify large-scale trials of efficacy. A significant challenge in such efforts will be improving our ability to recruit elderly people into clinical trials and attending carefully to ethical issues in research that may be specific to this population.

Much of the focus in treatment development has been limited to syndromes defined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (21). However, the strength of the DSMs is in their reliability, not in the delineation of valid disease entities. Moreover, many patients seek clinical help with particular symptoms, such as agitation or disorganization, either apart from or in addition to DSM syndromes. Building on a foundation of NIMH-supported research on noncognitive dimensions of AD, including psychosis, depression, circadian disruption, and agitation (22), the FDA has begun to consider indications for isolated symptoms that occur in the context of syndromal disorders, for example, the psychosis that commonly occurs as a part of AD. To help foster treatment research, NIMH is also developing diagnostic criteria for the depressive syndrome that co-occurs in AD. Muchwork is warranted in defining useful therapeutic endpoints (including neurocognitive ones), choosing candidate compounds, and defining

doses, before we initiate large-scale randomized, controlled trials.

Age-related variability in treatment response is a significant consideration in clinical therapeutics. Research in age-related effects on pharmacokinetics and pharmacodynamics is critically important, as is an understanding of the interaction of aging effects with pharmacogenetic variability.

It is imperative also for NIMH to stimulate the development of psychosocial therapies targeted specifically to aging populations. Many older adults take multiple medications, making additional psychotropic medications difficult to prescribe at therapeutic levels. For these persons, psychosocial interventions may present therapeutic alternatives with fewer side effects and particular benefits for improved self-care overall. Psychosocial interventions for elderly patients must take into account ways in which older persons differ from younger individuals, for example, in terms of the structure of their families, relationships, and social networks. A particularly salient issue regards the ability to avoid crippling traumatic grief reactions after bereavement. Studies of the factors that promote resiliency among older adults, including social networks and religiosity, can enhance efforts at prevention of disorders in these populations.

NIMH is teaming up with the National Institute of Neurological Disorders and Stroke (NINDS) to develop treatment research to combat symptoms of PD. There is increased recognition that up to 90 percent of individuals with PD commonly experience both depressive and psychotic symptoms (23). Unfortunately, perhaps because these problems lie at a watershed between neurology and psychiatry, neither specialty has focused much systematic research on them. With the approval for marketing of atypical antipsychotic drugs, medications now exist that can treat psychosis in PD. NIMH will continue to work closely with NINDS to help set a research agenda that advances the psychiatric treatment of PD.

## CLINICAL TRIALS: THE RISE OF EFFECTIVENESS STUDIES

Although there are significant gaps in the NIMH research portfolio with respect to the development of new pharmacologic therapies, the Institute long has had a strong portfolio of randomized, placebo-controlled trials aimed at establishing the intrinsic efficacy of a given pharmacologic or psychosocial intervention. NIMH remains committed to adequately powered “efficacy” trials for psychosocial or combined treatments or for pharmacologic treatments where they complement the efforts of indus-

try. We recognize, however, that this critical step in interventions research cannot be the final step. Many classical efficacy trials have specifically excluded aged individuals (and children); others exclude persons of any age if they have co-occurring medical or psychiatric illnesses or a substance use disorder.

Trials with broader inclusion criteria, ideally with the power to separately analyze older individuals, are welcome. Of course, the inclusion of more generalizable populations brings with it more confounding variables, and likely higher costs. Thus, the optimal design of “effectiveness” trials is a matter of real intellectual challenge.

Just as classic efficacy trials tended to sacrifice generalizability of sample for internal validity, they also tended to sacrifice generalizability of setting. The majority of randomized controlled trials we have supported were conducted in academic health centers. However, most psychiatric treatments are administered in general medical settings or community clinics rather than in specialized psychiatric care settings in academic health centers. Thus, we must demonstrate that treatments can be transported with fidelity to diverse settings.

Finally, most of the randomized, controlled trials that NIMH has supported in recent years were of relatively short duration—typically in the 6- to 12-week range. Yet, for chronic and recurrent disorders, such as mood, anxiety, or psychotic disorders, short-term trials afford only an initial glimpse of the course of treatment. This is true for all age groups—not only in elderly subjects, but among aged populations in general, side effects and drug-drug interactions that affect cognition, for example, may not be apparent early in the course of treatment.

In summary, trials are needed that will include older subjects and ensure adequate power for separate analysis. Trials are also needed that will focus on different subgroups of elderly patients—for example, samples of individuals with co-occurring general-medical, neurological, and psychiatric disorders—and trials must be designed so as to be relevant to diverse settings, including primary care settings. These issues helped to generate development of the AD clinical trial that is part of the NIMH contract: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; <http://www.catie.unc.edu>).

## SUICIDE

The issue of suicide remains a critical one in geriatric psychiatry; older white men have a suicide rate that is six times the overall national U.S. rate. Older Americans who commit suicide are less likely to have sought mental health specialty care

and more likely to have seen a primary health care provider relative to other age groups within a short period of time before committing suicide. In addition to behavioral research, such as discussed below, and improvements in primary care practice to respond more effectively to suicide risk, research is needed to address specifically how best to encourage the discussion of suicidality in primary care and other medical encounters and to develop effective prevention strategies. An example of needed research is seen in the NIMH-funded PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial), an approach to reducing the risk of suicide by intervening in depression in elderly primary care patients (24).

Although suicide is highest among older adults relative to all other age groups (24, 25), individuals who are suicidal typically have been excluded from traditional efficacy trials. Substantial ethical and liability-related issues must be taken into consideration in recruiting suicidal subjects into trials, but without a willingness to confront the challenges and enroll suicidal patients, improved interventions for suicidal individuals will not be developed.

## BEHAVIORAL RESEARCH

In addition to psychotherapy research, mentioned above, a multitude of important topics relevant to mental disorders in aging require behavioral and social science expertise. Evidence suggests, for example, that older patients may be more susceptible to the stigmatization of mental disorders and therefore less likely to seek help (26). Urgently needed are new strategies for addressing and overcoming stigma and shame that are more generally effective than those currently used in most medical settings. Issues of treatment adherence play an enormous role in the treatment of chronic illnesses, including mental illnesses; however, among older patients, for whom memory disorders may be a complicating factor, and among elderly people with mental disorders, where helplessness, psychotic symptoms, or pain may play a role, research that will help patients adhere to complex and often discomfiting treatment regimens is especially needed. Research on improving adherence that takes into account the roles of families, clinic staff, and broader social networks is very much in need.

## HEALTH SERVICES RESEARCH: NEW FRONTIERS OF CONTEXT AND IMPLEMENTATION

As trends in the delivery of services for mental disorders among elderly patients shift increasingly toward community-based care, it is critical to iden-

tify barriers that older individuals encounter in seeking access to appropriate treatment. An immediate challenge is to improve the abilities of an array of providers—and, particularly, primary care providers—to recognize mood and other mental disorders, including substance abuse disorders, among elderly patients. Problems in recognition are compounded by frequent “competing demands” in primary care, from both providers’ and patients’ perspectives. One, for example, is physical illness, which can affect the initiation of treatment. Understanding these competing demands, the bases upon which priorities are agreed upon, and how problems may be addressed over the course of a series of visits, represent important research questions (27). The nature of many disorders affecting older populations, moreover, underscores the importance of research that lends itself to improving practice quality and fostering a shift from acute treatment models to chronic-disease management models. Such models must take into account, among other things, difficulties with treatment adherence over time, the need to prevent the onset of disability and relapses, and the use of alternative treatments and/or services. Identifying barriers to implementing chronic-disease management models—especially as they are informed by specific needs of different, interested parties—is a key research issue.

Disparities in outcome on the basis of ethnicity and race have become an important topic of investigation across NIH, and this is certainly true for NIMH. An example of a documented disparity is seen in findings that African-American and Hispanic men are less likely than majority populations to fill a prescription for antidepressants, despite the presence of depressive symptoms (28). Also, inclusion criteria for clinical dementia trials have been shown to preferentially select subjects who are not ethnic minorities (29). The origin and significance of such disparities is unclear, and whether they exist among aging populations remains largely uninvestigated. Further research is imperative to ensure that all Americans, including elderly persons, have access to and are receiving appropriate treatment interventions.

### THE AGING OF MENTALLY ILL PATIENTS AND CAREGIVER BURDEN

Just as healthy people are, in general, living longer, so are people with chronic mental disorders, such as schizophrenia or bipolar disorder. As these individuals age, more research attention must also be directed to identifying the needs of aging care-

givers; a substantial part of the shift to community-based care consists of home-based care, where persons requiring care may be either adult children with severe mental disorders or spouses or other family members with mental and degenerative disorders. Studies are needed to understand how best to support aging care providers, maximizing their ability to function, and minimizing their distress.

### CONCLUSION

NIMH has a strong history of research focused on mental disorders and mental health in aging. The Institute established a pioneering intramural research program in aging research with the “Normal Aging” Study in the 1950s, and, in the mid-1970s, created an extramural program in aging research. Over the next two decades, it became one of the keynote programs in the Institute (30). There are, however, new challenges and opportunities ahead, including the need to work more closely with primary care providers and with the discipline of neurology. At the same time, new technologies have emerged and, as I have described, the NIMH has been rethinking the ways in which it conducts clinical trials. Through these times of change, NIMH staff will work closely with researchers in the field to help identify models and mentors for training as the scientific approaches and opportunities evolve, as well as identifying obstacles to choosing research careers in geriatrics. The Institute is committed to these and other initiatives that will re-emphasize the priority warranted by research focusing on mental disorders and health in aging.

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