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Preventing Depression in Later Life: State of the Art and Science Circa 2011

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That our ability to understand, treat, and even cure disease has reached its current state and improves still further every year is remarkable. Nonetheless, the ultimate goal of medicine and health care is prevention of illness: the reduction of incidence through preempting new cases of illness, in addition to protection from downstream consequences of already established illness. The 2008 National Institute of Mental Health (NIMH) Strategic Plan (<http://www.nimh.nih.gov/about/strategic%2Dplanning%2Dreports/>) includes prevention as one of its key objectives with respect to mental disorders such as depression. By preventing depression, one hopes ultimately to enhance health span and life span.

Because unipolar major depression is among the leading contributors to the global burden of illness-related disability,¹ and is predicted to be the greatest contributor to illness burden by 2030,² it is a matter of public health significance to identify people at high risk for depression and/or who are already mildly symptomatic, and to discover ways of implementing timely and rational risk reduction strategies to preempt major depression.³ In this article, the published literature is reviewed to summarize what is known about depression prevention in older adults, and, ultimately, to inform future research.

PUBLIC HEALTH CONTEXT AND RATIONALE FOR DEPRESSION PREVENTION IN LATER LIFE

Two questions provide the organizing framework for depression prevention research and practice in older adults: (1) Can early intervention targeted to older individuals at increased risk or already living with subthreshold symptoms of depression reduce incidence, severity, or duration of incident major depression to a clinically significant degree? and (2) How are interventions to prevent major depression in a community-dwelling elderly population best organized and implemented?

The goals of research in this area are to improve accuracy in predicting major depression in older adults and their caregivers, to guide the timely introduction of risk reduction strategies, and to determine whether there are additional health and economic benefits to prevention of major depression in older adults. These could include slower progression of cognitive decline, better control of pain, better indicators of cardiovascular and cerebrovascular health, less caregiver burden, and less cost to the health care delivery system. All of these are significant downstream burdens that could be mitigated through depression prevention in later life.

From a public health perspective, prevention of major depression in later life is important for the following reasons³: (1) depressive episodes in older adults are prevalent and disabling (6%–10% in primary care settings), 30% in medical and long-term care settings; it is estimated that incidence rates of new episodes are about half of prevalence; (2) depression is associated with significant excess mortality after myocardial infarction, stroke, and cancer, and it is the major risk factor for suicide in old age; (3) available treatments are only partially satisfactory in reducing symptom burden, sustaining remission and health-related quality of life, and in averting years lived with disability; (4) milder or subthreshold states increase the risk of developing the full clinical disorder but may be more reversible than the advanced clinical state and may be associated with neurobiological changes at an earlier and more modifiable stage of development; (5) the geriatric mental health workforce issues confronting the nation drive the imperative for devising effective, scalable, depression prevention models that can be implemented by general medical rather than mental health specialty clinicians⁴; and (6) preventing depression in older adults may be cost-effective.⁵

By preventing depression in older adults, the aim is to prevent the downward spiral of depression to disability and death and thereby enhance and prolong older adults' capacity for independence. Because depression diminishes both health span and life span, the ultimate goal of depression prevention is to protect and enhance both.³

The doubling of the number of older adults living with a mental disorder by 2030 is only part of the public health challenge of, and rationale for, preventing clinically significant depressive syndromes in old age. Specifically, older adults of lower socioeconomic status have increased risk for chronic illnesses and for depression. The social worlds that put older adults at risk for depression, especially poverty and living in dangerous neighborhoods, also act to reduce the effectiveness of antidepressant treatment.⁶ Thus, studies of depression prevention must also involve adults on low income (who are often racial minorities). For example, a randomized controlled prevention trial evaluating problem-solving therapy (PST) to prevent episodes of major depression, diminish disability, and improve health-related quality of life in adults on lower income who have risk factors for depression and are already living with mild symptoms of depression is currently under way.⁷ The control condition is health education in dietary practices, chosen because of the high rate of obesity among participants and the need to provide an attentional control. Relative to white participants in the trial, black participants have (1) lower household income and less formal

years of education, (2) higher rates of health hazards (obesity, diabetes, hypertension), (3) higher rates of physical disability, and (4) more frequent histories of alcohol or substance abuse.⁸ About one-third of both blacks and whites report a remote prior history of major depressive episodes. Subjects are being followed for 2 years, with booster sessions of PST or health education every 6 months. As reviewed later, successful depression prevention research requires an infrastructure of community partnerships with primary care and social service agencies that reach the vulnerable populations most in need of preventive interventions.

RATIONALE FOR SELECTIVE AND INDICATED PREVENTION

The literature suggests that depression prevention in later life may be most efficiently accomplished by targeting the elderly who experience risk factors, particularly functional limitations as a result of illnesses such as stroke or macular degeneration, have a small social network, and/or have subthreshold symptoms.^{9,10} Efficiency of interventions to prevent depression encompasses both the effect of the intervention and the effort required to implement it. The effect is reflected in the proportion of cases that would be prevented if the adverse effects of the targeted risk factor were completely blocked (attributable fraction). Effort is reflected by the number of persons who would need to receive a depression prevention intervention to avoid 1 new case of late-life depression (number needed to treat [NNT]). Schoevers and colleagues¹¹ have estimated that the risk factor for which preventive interventions would have the greatest effect and least effort is subthreshold depressive symptoms (NNT of 3–4 vs NNT of 7–9 in selective prevention).¹¹ That is, preventive interventions may have a greater effect in older adults with subthreshold symptoms (indicated prevention) than in patients without such symptoms who may have other risk factors such as disabilities from medical illness (selective prevention). For example, a recent, randomized, controlled prevention trial from Amsterdam has shown the effectiveness of stepped-care prevention of anxiety disorders and major depressive disorders in 170 primary care patients aged 75 years and older with subthreshold symptoms not meeting the full diagnostic criteria for syndromal disorders.¹² This intervention was implemented by mental health nurses for 1 year and encompassed a stepped-care algorithm of 3 months of watchful waiting, 3 months of bibliotherapy, 3 months of PST, and referral to a general practitioner if symptoms persisted. It thus allowed the parsimonious use of resources as needed for older patients with persistent symptoms of depression or anxiety. The intervention reduced the incidence of anxiety disorders and major depressive episodes by 50% in 1 year, relative to care as usual (24% vs 12%).

Clinically, depression merits considerable effort in prevention because of its contributions to disability, morbidity, and mortality. In patients suffering terminal illnesses, such as cancer, depression is a major source of suffering coexistent with all the discomforts and burdens of cancer therapy. For such individuals already undergoing distressing treatment, the prevention of a major source of suffering is a worthwhile clinical objective. Depression has also been linked with increased risk of mortality in congestive heart failure,¹³ stroke,¹⁴ various forms of cancer,¹⁵ suicide during treatment of cancer,¹⁶ and reduced quality of life for terminally ill patients such as those suffering from brain tumors.¹⁷ It is apparent, therefore, that whether as the patient's presenting illness or a comorbidity significantly altering the treatment and outcome of another disease, the effect of depression is worth preempting by preventive measures.

Before discussing depression prevention further, however, the limitations of current depression treatment need to be discussed. Assume that, in a given primary care setting, evidence-based interventions are practiced with 100% insurance coverage providing for all types of interventions, both mainstream and experimental. Even in this idealized scenario,

however, one study shows that the burden of depression, which is measured in years lived with disability, would be averted only by 34%.¹⁸ Such a success rate in ideal circumstances is clearly inadequate. Now, however, assume a more realistic situation in which insurance coverage is only 70%. In such a situation, years averted with disability decreases to around 25%.¹⁸ This finding is even more concerning, in that it underscores the limited access to, and effectiveness of, existing treatments and the need for better preventive interventions.

There are additional important shortcomings of current depression treatment that underscore the need for prevention. These are the findings that full remission occurs only in one-third of those treated with a newer antidepressant and that each subsequent drug intervention is associated with progressively poorer response rates.¹⁹ Compounding this already troubling dilemma, there is the problem of dissemination of treatment: the limited access that certain populations, especially older, racial, and ethnic minorities, have to evidence-based mental health care.

In summary, currently available treatment, even if it were to be administered in an ideal evidence-based way and available to all populations, remains only partially satisfactory in assuaging depression-related disability. From a public health perspective, depression prevention is needed to reduce incidence rates, that is, to preempt episodes of major depression in those with known risk factors (and perhaps already mildly symptomatic), and thereby to mitigate the global burden of depression's illness-related disability.

OBJECTIVES OF DEPRESSION PREVENTION

Implicit in the discussion of depression prevention in older adults are 3 underlying objectives: the preemption of incident episodes of depression, the prevention of recurrent episodes of depression, and, protection from depression's medical and psychosocial complications.³

Several types of depression prevention were outlined by the Institute of Medicine in both its 1994²⁰ and 2009²¹ reports: universal, selective, and indicated prevention. In universal prevention, the entire population base, regardless of whether they are at risk for depression, is targeted. An example would be outreach through media to educate the general population about the early warning signs of depression, to dispel stigma about depression, and to encourage help seeking; or educational outreach to primary care physicians to educate them about the risk factors (such as depression) for suicide in older adults.

As opposed to this wide-scale intervention, selective prevention focuses on those patients presenting with established susceptibility, based on a set of risk factors. For example, in the case of late-life depression, such well-known risk factors include disability, social isolation, bereavement, and chronic insomnia.^{9,11} Moving toward greater severity of risk are preventive measures directed to patients already living with some symptoms of depression, although remaining subsyndromal; so-called indicated prevention. To date, most of the limited data in the literature are derived from studies of selective and indicated prevention. The sample size requirements for studies of universal prevention are substantially greater than the samples of 150 to 300 generally seen in studies of selective and indicated prevention.

THE FEASIBILITY OF DEPRESSION PREVENTION

Using PubMed (searching for "depression prevention" and using limits such as "randomized controlled trials") and cross-referencing with published papers, we were able to identify 30 randomized controlled trials of depression prevention, of which only 4 were conducted in older adults.^{8,10,12,22}

Capturing the state of the field, 1 meta-analytic review of 19 trials using mixed-aged samples reported a pooled incidence rate ratio of 0.78 (95% confidence interval [CI] 0.65–0.93), indicating a reduction in incidence of diagnosable major depression of nearly 20% in 1 year.²³ Several published papers support the efficacy of selective and indicated prevention of depression in either at-risk or already mildly symptomatic older individuals. Some of the studies have used as their primary outcome variable the occurrence of major depressive episodes (typically studies of indicated prevention), whereas other studies have encompassed both major and minor depressive episodes as their primary outcome (typically studies of selective prevention).

A study exemplifying selective prevention enrolled patients with recent stroke.¹⁰ Depression occurs in 30% to 40% of stroke victims, and poststroke depression has been implicated as a contributing factor to impaired recovery of stroke victims, along with increased mortality. In the study, nondepressed patients receiving placebo were significantly more likely to suffer a major or minor depressive episode in a 12-month period than those patients administered either a selective serotonin reuptake inhibitor (SSRI) alone (low-dose escitalopram, 5 mg/d), or receiving a course of PST.¹⁰ This study found an NNT of approximately 8.

A recent report from Amsterdam¹² evaluated indicated prevention in Dutch primary care patients older than of 75 years of age. With the objective of determining the efficacy of an indicated stepped-care prevention program, 170 individuals with subthreshold symptom levels of depression or anxiety were followed. Although these individuals did not yet meet the diagnostic criteria for their respective disorders, they were offered either a preventive stepped-care program or usual care. The intervention program comprised 4 sequential steps, each of 3 months' duration: watchful waiting, cognitive-behavioral therapy-based bibliotherapy, PST, and referrals to primary care if the patient so needed. The incidence of major depressive and anxiety disorders was reduced by more than 50% at a 1-year follow-up. Thus, about 24% of patients randomly assigned to treatment as usual experienced the onset of major depressive episodes or of anxiety disorders, compared with 11% of participants receiving the stepped-care for depression prevention.

Despite evidence of efficacy, the question may arise as to whether the benefits of such a preemptive strategy come at an affordable cost. To address this issue, the cost-effectiveness of the stepped-care depression prevention program reported from Amsterdam versus routine primary care was estimated at \$700 per recipient and \$5431 per disorder-free year gained.⁵

Beyond just reducing the incidence of depression, however, prevention also entails protecting older adults from the downstream consequences of depression.³ One such downstream consequence is suicide. The PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial) study^{24,25} portrays the efficacy of prevention strategies of suicide. PROSPECT showed that by exporting depression care management strategies to urban and rural primary care practices in New York, Philadelphia, and Pittsburgh, a 2.2-fold decrease in suicidal ideation was observed within 2 years. The available data, although still limited, suggest the feasibility, efficacy, and affordability of selective and indicated depression prevention in older adults.

FROM RESEARCH TO PRACTICE

Although current evidence supports the feasibility, efficacy, and affordability of depression prevention, there are many issues that need to be addressed before such interventions can become reality in the modern health care system.

The first is the need for more efficacy trials with a longer duration of study than 12 months. The reason for recommending longer trials derives from the goal of preventing depression,

not just delaying it. Moreover, long-term efficacy trials in at-risk patients such as the elderly, low socioeconomic groups, ethnic minorities, and family caregivers are needed to establish the broader clinical usefulness and effect of depression prevention. Moreover, such efforts could assist health care professionals in understanding the specific needs of these groups to better tailor preventive measures to particular patients.

The second issue is the need for better pathophysiological models of depression. A better understanding of the causes of depression should facilitate identifying risk factors for depression. Subsequently, with a better comprehension of risk factors, physicians can better focus their efforts on those with established vulnerabilities, enabling depression prevention, in the long-term, to become more personalized, efficient, and affordable. Examples of this strategy are illustrated by the work of Lenze and colleagues²⁶ and Lotrich and colleagues.²⁷ Even more fundamental than individualizing depression prevention, is the need for pathophysiological models to identify how to prevent depression. To date, most depression prevention strategies have been based on depression treatment strategies (eg, PST and use of SSRIs). What are the causal mechanisms leading to depression that need to be interrupted?

The third issue is that, if depression prevention was practiced throughout all primary care facilities, there still remains the issue of improving the rate of patient participation in such programs. The availability of programs does not mean that patients will choose to take advantage of them. Greater use of strategies aimed at potential participants in depression prevention services, such as media campaigns to reduce stigma (promotion and universal prevention, to borrow from the Institute of Medicine's 2009 lexicon²¹) is needed.

The fourth issue is the opportunity afforded by the Internet.³ With the Internet revolutionizing most aspects of daily life, it is imperative that the mental health community learn to use this powerful tool for the benefit of older adults at risk for depression. Doing so may enable the field to move beyond selective and indicated prevention to universal prevention, by disseminating depression prevention interventions globally to reduce health disparities, especially when the local health care system cannot provide care to those who need it.³ This will entail confirming important ethical issues, such as the need to inform users that Internet-based dissemination is not intended as a vehicle for emergency mental health services.

RECOMMENDATION FOR FUTURE DEPRESSION PREVENTION RESEARCH IN OLDER ADULTS

To move the field forward and to maximize clinical and policy changes, several strategies are recommended: (1) use of fewer exclusion criteria to recruit clinically representative participants with medical, neurologic, and/or psychosocial risk factors/ comorbidities; (2) partnerships with primary care practices and community-based agencies reaching low-income adults where public health need is greatest; (3) use of lean assessment batteries with low respondent burden and appropriate for people with less formal education; (4) specification of prevention-relevant outcomes beyond symptom ratings, such as burden of coexisting medical illness (especially cardiovascular and cerebrovascular illness), cognitive and functional impairment, and caregiver burden; (5) follow-up periods of at least 12 months and, preferably, 24 months to derive more accurate and clinically meaningful estimates of true incidence reduction; and (6) use of a structured but flexible menu of approaches to be carried out by general medical clinicians (rather than mental health specialists). Research projects need to be powered to detect moderately large effect sizes of interventions on the cumulative incidence of major depression for 1- and 2-year follow-up periods. Based on the limited published data, this means sample sizes of 150 to 300 participants (or 75–150 in each of the experimental and control arms).

General Approach

Because of the diversity of challenges inherent in risk for depression in later life, interventions need to allow for some degree of tailoring to meet the specific needs of the individual and his/her caregiver. Thus, a structured but at the same time tailored approach to delivering the interventions responsive to individual needs is appropriate. There are important synergies, for example, to be attained by simultaneously intervening with the caregiver and the care recipient. That is, dyadic intervention may have greater potential because of effects on factors such as effective support seeking and support provision within the dyad.²⁸

Interventions that have already been shown to promote self-efficacy and resilience in prior studies of depression treatment seem to be promising candidates. The focus should be on assessing the value of such strategies before older adults become ill, in the face of the most pervasive risk factors for depression in old age: disabilities related to medical and cognitive impairments, social isolation, caregiving burden, bereavement, and poor sleep.^{9,11}

Promising Interventions

Simple, brief, learning-based approaches, already shown to have efficacy in the treatment of depressive disorders, pain, or insomnia disorders, seem promising to address the mandate of the NIMH Strategic Plan (2.3) “to develop and test innovative interventions to reduce risk and positively alter trajectories of illness.” Although antidepressant medications are the most widely used modality for treating prevalent cases of major depression, their use in subthreshold depression may be ill-advised because of a lack of evidence for efficacy in mild depression, as well as adverse effects in older adults such as hyponatremia, risk for falls, bone demineralization, and cataracts.²⁹ Psychological interventions may be preferable for reasons of safety and patient preference. PST has been used successfully in depression prevention studies,^{10,12,22,30} is more easily learned than interpersonal psychotherapy or CBT, and can be embedded within a clear service model.³¹ Teaching coping skills may diminish the sense of loss of control (helplessness) at the core of depression. Similarly, teaching strategies for better sleep (because poor sleep is a known and well-established risk factor for depression) may diminish affective reactivity and enhance cognitive flexibility on the part of both care recipients and caregivers.³² In this context, brief behavioral treatment of insomnia (BBTI) is particularly promising, because it has been shown to improve sleep quality and reduce symptoms of depression and anxiety.³² Moreover, learning-based interventions are effective for prevalent cases of depression and insomnia. Interventions such as PST and BBTI are also practicable, that is, safe, cheap, deliverable by general medical clinicians (including nurses and social workers), and more likely to be acceptable to older adults than the use of antidepressant medication before major depression is diagnosable. An important caveat in this discussion, however, are data that SSRI pharmacotherapy is effective in the prevention of recurrent episodes depression, an enormously important clinical issue in the care of older adults.³³

Important Measurement Domains

The literature suggests a core of shared measurement domains in keeping with the general logic model articulated here: depression and anxiety (both categorical measures and dimensional measures of severity), comorbid medical burden, social and physical disability, insomnia, pain, cognitive status, social isolation/support, care-giver burden, self-efficacy, problem-solving skills, and promising biopredictors of depression (eg, proinflammatory cytokines).^{7,8,27} Biopredictors of depression may enable depression prevention to focus on individuals at highest risk and offer guidance as to when and where in the pathway to depression one might best intervene.

Need to Personalize Depression Prevention Strategies

Because most older adults do not get depressed after a disabling medical event or negative life event such as bereavement, the efficiency of depression prevention efforts need to be further enhanced. To address the question of which patients are most likely to benefit from depression prevention, it seems important to investigate biosignatures of depression risk and of response to prophylactic interventions (eg, cytokine activity, sleep). That is, the field should seek to understand biological correlates of (1) the likelihood of depression, (2) time period of risk, and (3) risk reduction using psychosocial or biological strategies. This is in keeping with the general goal of research, to develop models for estimating depression risk (using sociodemographic, clinical, and biological variables easily obtained in community settings), to guide the rationale, and timely and clinically appropriate introduction of risk reduction strategies in persons who need them most.

As suggested earlier, an important dimension of risk for depression and anxiety is poor sleep.³⁴ Insomnia is known to be a potent risk factor for depression and anxiety, not simply a prodrome. What is not yet known is whether protecting sleep or improving sleep quality prevents depression in older adults. Poor sleep is also highly prevalent in later life, especially among those living with social and financial strain, in those living with chronic pain and related medical disabilities, and in those with mild cognitive impairment and progressive cognitive disability. Poor sleep also affects caregivers, often leading to a decision to place a family member in long-term care. Furthermore, there seems to be a bidirectional relationship between poor sleep and increase in proinflammatory cytokine activity. Both seem to be depressogenic.²⁷ Thus, improving sleep fits well into the conceptual framework of depression prevention articulated here.³² Good sleep is important for affective regulation, decreasing stress reactivity, and helping to mitigate chronic pain. It is also essential to information processing, cognitive flexibility, and problem solving. Insomnia is a modifiable precursor and risk factor for depression occurrence and reoccurrence. Teaching people healthy sleep habits, getting them to understand and experience first hand how changing behavior affects health, is a unique entry to sustainable, health-promoting life styles. In this context, the authors have recently published clinical trial data showing that curtailing time in bed and allowing less sleep is associated with poorer health outcomes in adults aged 75 years and older, during a 30-month period of observation.³⁵ There seem to be close relationships between sleep duration/quality, health span and lifespan.

SUMMARY OF METHODOLOGICAL CHALLENGES FOR THE FUTURE

Implicit in this review are important methodological challenges to progress in depression prevention research in older adults. The missions and related methodological challenges of late-life depression prevention are summarized in Table 1.

Paramount among these challenges is the need for a better understanding of the nature and interrelationships among risk factors to target when and how to intervene. Also needed is a wider range of strategies to deliver prevention interventions (eg, using the Internet), together with evidence bearing on the appropriate timing and sequencing of interventions. Methods for better engagement of underserved older adults in interventions and improved engagement of health care and services providers in prevention programs need to be developed and tested. Strategies to facilitate the transportability of prevention interventions into the community for sustained use are much needed.

SUMMARY

Depression is a disorder with a significant public health burden that not only reduces the duration and quality of life of those with depression but also negatively affects the course of comorbid illnesses. Current modalities of depression prevention, although efficacious, fall short of the ideal, especially regarding the need to personalize intervention. In the future, a better understanding of the pathophysiological risk factors for depression that help to identify when and how to intervene in at-risk patients, along with a mastery of the Internet as a powerful dissemination tool, may pave the way to making depression prevention a widely practiced and effective intervention. What is now still revolutionary may become mainstream practice.

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Table 1
Methodologic challenges confronting depression prevention research in older adults

Components of the Mission	What is Needed to Address the Mission	Related Methodologic Challenges
Prevention of episodes of depression	<p>Better understanding of the nature of and interrelationships among risk factors to target when and how to intervene</p> <p>Wider range of strategies to deliver prevention interventions</p> <p>Appropriate timing/sequencing of interventions</p>	<p>Identification, modification, validation of efficient (low burden, feasible, strong psychometrics) assessments for multiple domains of factors</p> <p>Development of statistical methods to better characterize complex sets of risk factors and their trajectories over time</p> <p>Development of classification techniques that allow care providers to efficiently gauge risk for depression in their clients</p> <p>Migration of traditional face-to-face intervention delivery to telemedicine-based formats without loss of fidelity and effectiveness</p> <p>Development/adaptation of research designs and analytic strategies</p> <ul style="list-style-type: none"> • to incorporate multiple durations and sequences of treatments • to accommodate care provider/patient preferences
Depression prevention in the community, particularly in underserved, low-income populations	<p>Accurate identification of change in clinical status</p> <p>Better engagement/retention of underserved older adults in interventions; facilitation of their response to intervention</p> <p>Engagement of community-based health care and services providers as prevention partners</p>	<p>Determination of efficient, low cost measures acceptable to patients/providers and sensitive to change</p> <p>Determination of whether depression outcome and risk factor assessments are feasible, acceptable, and valid</p> <p>Development/adaptation of research designs and analytic strategies to accommodate patient preferences for preventive care</p> <p>Determination of acceptability of depression and risk factor assessments to community-based assessors/care providers</p>
Sustainability of depression prevention efforts	<p>Strategies to facilitate transportability of prevention interventions into the community for sustained use</p> <p>Training of the next generation of researchers conducting effectiveness and dissemination studies</p>	<p>Refinement/application of a standardized approach to characterize intervention delivery and content</p> <p>Evaluation of costs and reimbursability of prevention interventions</p> <p>Development of assessments for depression outcomes and risk factors that can be easily used by community-based care providers</p> <p>Development/adaptation of research designs and analytic strategies to accommodate patient/care provider preferences for preventive care</p> <p>Dissemination of approaches to increase intervention transportability to new settings, populations, and care providers</p> <p>Dissemination of new assessment tools, research design strategies, and analytic tools for prevention effectiveness trials</p>