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Depression in Late-Life: a Focus on Prevention

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Abstract

Depression is a leading cause of disease burden, disability and distress for millions of older adults. Thus, prevention of late-life depression is a priority research area. This article addresses the science of late-life depression prevention with the following: 1) an introduction to the Institute of Medicine framework of universal, selective and indicated prevention as it pertains to late-life depression, with particular attention to successes of indicated and selective prevention in primary care; 2) a discussion of how biomarkers can be integrated into prevention research, using interferon-alpha-induced depression as a model; 3) an outline for expansion of prevention to non-specialist care delivery systems in Low and Middle Income Countries – thus, extending the reach of current successful approaches; 4) a description of a novel approach to simultaneous testing of universal, selective and indicated prevention in late-life depression, with emphasis on study design features required to achieve practical, scalable tests of health impact.

Introduction

Late-life depression is common, highly disabling, associated with higher health care utilization and costs, and may complicate comorbid conditions that are prevalent in older adults. Prevention is particularly important, as accumulating evidence demonstrates that persistent symptoms and dysfunction from depression remain common among older people, even with appropriate antidepressant treatment. Given the aging of the world's population and the high disease burden associated with depression, a comprehensive approach to prevention of this problem is urgently needed. Considerable success has already been achieved in identifying maintenance treatments as effective strategies for prevention of relapse and recurrence among older adults with established histories of treated depression(1, 2). Yet, critical gaps remain in understanding of optimal approaches to primary prevention, which will thus be a substantial focus of this article. The following work will: articulate the core framework of prevention as it applies to late-life depression – specifically, the concepts of: 1) universal, 2) selective and 3) indicated prevention(3); illustrate how identification of risk biomarkers and addressable risk factors can facilitate prevention, including among at-risk groups; discuss the expansion of flexible late-life depression prevention approaches into

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the more global settings of low- and middle-income countries; and describe how innovations in trial design may permit simultaneous evaluation of all three types of prevention in late-life depression, including among diverse populations.

Part A. The Framework of Prevention

Overview

People have long recognized the potential value in preventing something before it happens, a notion encapsulated in the aphorism of Benjamin Franklin, “An ounce of prevention is worth a pound of cure.”(4) Yet it is only recently that scientific attention has been paid to preventing mental disorders of adulthood, with research on late-life depression paving the way.

Most clinicians are familiar with classifying prevention efforts into the following three categories: *primary*, preventing newly incident disease; *secondary*, detecting disease early and preventing progression; and *tertiary*, preventing or limiting the impact of the disease(5). This scheme, while useful, is based on the status of the disease in question. A more useful framework for preventive interventions can be built around the target population. Such a framework was summarized by the Institute of Medicine (IOM) and entails *universal*, *selective*, and *indicated* prevention. Universal prevention focuses on the general population of interest. Selective prevention focuses on persons at risk to develop the disease. Indicated prevention is directed at people who have some symptoms but are below the symptom threshold that would indicate disease. Furthermore, these types of prevention may be viewed as part of a larger continuum of health promotion, as described by the IOM(3); see Table 1.

What is the evidence regarding prevention strategies in late-life depression? It might seem appealing to try a universal prevention approach of low cost and high acceptability in broad older populations. However, a meta-analysis by Cuijpers et al.(6) reveals, admittedly with a relative paucity of data, an incident risk ratio (IRR) of 0.90 (95% confidence interval [CI]: 0.61 – 1.33), with an estimated number needed to treat (NNT) (i.e., to prevent) of >20. Thus, while universal prevention is inherently attractive as a concept, strategies that have been employed to date appear unlikely to have cost/benefit ratios favoring their general application. Consequently, the most prominent examples in the literature of successful application of depression prevention involve either selective or indicated prevention models.

Selective Prevention

Research groups from the Netherlands and the U.S. have found that identifying persons at high risk for depression, based on risk markers such as medical comorbidity, low social support or functional disability, can yield theoretical NNTs of approximately 5 to 7 in primary care settings (7–10). Furthermore, a few pioneering randomized controlled trials (RCTs) of selective prevention have been conducted in specialty settings – for example, by focusing on high-risk populations with medical comorbidity. In one study, short-term problem-solving therapy (PST) approximately halved the two-month incidence of depression as compared with usual care in patients with macular degeneration(11), the leading cause of age-associated blindness; however, the two groups did not differ significantly at six-month follow-up. In another study among patients who had suffered stroke, selective prevention was tested using a three-group design: escitalopram, PST or placebo control. Those receiving escitalopram had about one-quarter the incidence of major depression at one year compared to placebo-receiving controls; patients who received PST had an intermediate outcome not significantly different from placebo in intent-to-treat analyses(12). However, by six months after discontinuation of preventive intervention, the group that had previously received escitalopram had greater levels of depressive symptoms

than either of the other comparison groups(13). Thus, it is clear that future research needs to identify the optimal methods for achieving a more enduring benefit of preventive interventions.

Indicated Prevention in Primary Care Settings

Since depression incidence is elevated with most chronic medical conditions(14), there is scientific rationale to conduct similar studies in a variety of other medically ill populations. Indeed, the prevalence of subsyndromal depressive symptoms – i.e., core features of depression (e.g., sadness, anhedonia) without the full the complement of symptoms necessary for major depressive disorder (MDD) diagnosis – is known to be high among such persons, and patients with subsyndromal symptoms have a greater than 5-fold increased risk of conversion to MDD within one year, compared to those without such symptoms(15). Furthermore, a focus on the medically ill population may be justified from a public health perspective as well, since many patients with chronic medical conditions receive ongoing subspecialty care, making such settings appropriate to deliver preventive interventions. However, another approach would be to identify at-risk seniors in primary care settings using an indicated prevention strategy. Focusing on primary care recognizes that most older adults with subsyndromal depressive symptoms do see their primary care providers (PCPs) (16); indeed, most seniors who die by suicide have been seen in primary care within a month of their death(17). Accordingly, efforts to improve detection and treatment of late-life depression have focused attention on primary care settings(18).

Studies strongly suggest that primary care-based indicated prevention efforts be as fruitful as what has been observed for selective prevention, and a recent important preventive intervention trial in the Netherlands(19) bears description here. One hundred seventy primary care patients aged ≥75 years with subthreshold depressive or anxiety symptoms were randomized to a stepped care intervention versus usual care. The stepped care intervention began with watchful waiting, increased to home-based bibliotherapy through brief depression-focused psychotherapy and referral back to the PCP for persistent or worsened depressive symptoms. The primary outcome was one-year incidence of any major depressive or anxiety disorder. Compared to usual care, the group receiving the stepped care intervention had one-half the incidence of new disorder. The intervention was well tolerated, yielded an NNT of 8, and cost approximately 500 € per recipient, or 4000 € per disorder-free year(20). Moreover, two-year follow-up showed continued better outcomes for the group that had received the intervention(21), with incident disorders increasing in both groups over the second year, but the active intervention group experiencing approximately half the incidence of usual care.

Summary

Selective preventive interventions in primary care and medical specialty settings can halve the incidence of major depression, and do so in a cost-effective manner. Similarly, it appears that indicated depression prevention strategies can be implemented in primary care settings with desirably low numbers needed to treat. Work remains to be done to demonstrate the longer-term sustainability of such prevention strategies. As well, it must be recognized that care providers for older adults typically face many competing demands on their limited time with patients. Thus, the ideal preventive intervention would have multiple benefits on health in addition to preventing depression; e.g., future work may explicitly address the preventive effects of interventions such as increasing social engagement(22), exercise(23) or diet(24).

Part B. Prevention Opportunities in Biological Psychiatry

Given the promise of selective prevention strategies, a natural question is whether biomarkers or biological information may be applied toward refinement of high-risk populations. This approach is especially appealing where biomarkers may signal modifiable risk targets, which can then be addressed for the purposes of maximizing efficacy of preventive interventions. This article provides a rich illustration on this topic with a discussion of blood biomarkers and their relation to risk of interferon-induced major depression. Major depression that develops during interferon-alpha (IFN-α) therapy – hereafter, IFN-MDD – is especially important among the variety of neuropsychiatric disturbances related to IFN-α therapy(25, 26). Indeed, IFN-MDD is a highly illustrative example of iatrogenic disorder and occurs in about 25–30% of people within a few months of starting IFN-α(27), which is established treatment for hepatitis C disease and used as adjuvant treatment in malignant melanoma(28, 29).

Overview: Interferon-α-induced major depression as a model setting for prevention research

There are several challenges for depression prevention research that may be addressable by focusing on specific depression subtypes such as IFN-MDD. **(i) The problem of heterogeneity**. MDD is probably a heterogeneous disorder. For example, MDD can be associated with psychosocial stress, pain, endocrine illness, circadian disruptions or irregularity, cerebrovascular disease, medication side effects, peri-menopausal changes, and numerous other factors. Heterogeneity may complicate targeted prevention approaches and limit analytic power. However, this heterogeneity can be reduced by prospectively following patient participants who are similarly exposed to IFN-α. **(ii) The problem of low statistical power**. Even among patients with co-morbid medical illness, the annualized incidence of MDD is still less than 2%(30); such low base rates will adversely affect statistical power to demonstrate the efficacy of a given preventive intervention unless sample sizes are very high(31). By contrast, the incidence of IFN-MDD in non-depressed adults is greater than 25% within a few months. **(iii) The importance of mechanistic relevance in identifying modifiable targets**. In the absence of detailed knowledge of biologic mechanisms in the development of depression, preventive approaches have generally relied on examining known depression therapies and testing their efficacy as prophylactics. However, under ideal circumstances, preventive interventions would have intrinsic relevance to depression by relating to biomarkers of plausible elements in the suspected etiology of depression. In addition, some biomarkers may be modifiers of risk. Observational studies have identified numerous risk factors, such as age, gender, marital status, history of stressful life events, adverse events during childhood, family history, and others;(32, 33) however, many are not readily modifiable. Because patient participants can be biologically examined prior to starting IFN-α therapy and before they become depressed, and there is such a high expected incidence of MDD, modifiable risk factors for depression may be more readily identified in this setting. (iv) **The importance of efficiency**. By definition, all forms of primary prevention imply intervening among individuals who are not yet ill. However, there are financial costs and potential side effects for individuals who otherwise would not have progressed to depression. Thus, better targeting of interventions toward very high-risk populations becomes particularly advantageous, and biological psychiatry can facilitate this approach.

Five Lessons from IFN-MDD Research

One lesson learned from both the IFN-MDD context, as well as the above discussed RCT of escitalopram among patients with stroke, is that prophylactic use of antidepressants can indeed be useful for prevention in some contexts. To prevent IFN-MDD, several prevention

trials have utilized selective serotonin reuptake inhibitors (SSRIs). Some of the earliest work addressed SSRI-based depression prevention among patients receiving IFN as adjunctive treatment for malignant melanoma, and initial results were promising(34). A recent meta-analysis found that 47.6% of patients with past, remitted histories of MDD developed IFN-MDD. However, if stably treated with SSRIs prior to initiating IFN-α, then only 20% of those with a past history of MDD in remission developed IFN-MDD.(27) In a meta-analysis of RCTs, 31% of those on placebo developed IFN-MDD, compared to 18% on SSRIs; however, this did not meet statistical significance.(27) Post-*hoc* analyses revealed that most of the benefit occurred among patients with some pre-existing subsyndromal symptoms and/or history of depression.(35) There has since been a larger multi-site RCT of subjects without a history of depression and with minimal pre-existing depression symptoms, where 18% on placebo developed IFN-MDD, compared to 8% on SSRI.(36) Thus, use of SSRIs can about halve the incidence of IFN-MDD but not completely prevent depression. Whether people who already have some subsyndromal depression symptoms obtain the most benefit from SSRI prevention (as suggested by the post-*hoc* analyses) will require additional examination.

A second lesson is that prophylactic treatments may address a subset of symptoms, but not other symptoms. Preliminary results from open-label SSRI treatment for IFN-MDD suggest that antidepressant use may have specific utility for particular kinds of symptoms. In recent work, Lotrich and colleagues observed that: complaints of suicidal ideation and punishment were diminished in 100% of participants treated with SSRIs; worthlessness and having a sense of failure were reduced in about 80%; while effects on neurovegetative symptoms such as anergia, insomnia, and appetite change were *rarely* improved(37). Prior studies examining the role of SSRIs in preventing IFN-MDD are consistent with this observation.(38)

A third and related lesson is that different genes may variably influence specific aspects of vulnerability as well as sets of symptoms. For example, in recent analyses of the serotonin transporter promoter polymorphism (5-HTTLPR), the *S/S* genotype (previously associated with increased risk for IFN-MDD(39, 40) and with diminished antidepressant response to SSRIs) was associated primarily with neurovegetative symptoms during IFN-MDD but not with suicidal ideation, worthlessness, or sadness.(41) In other examples: a functional TNF-α polymorphism increased risk specifically for labile anger and fatigue but not other mood symptoms;(42) an IL-28 polymorphism that has been associated with viral clearance during IFN-α treatment was also associated with neurovegetative symptoms like sleep, appetite, and fatigue but not other depression symptoms;(43) and a functional *Val/Met* brain-derived neurotrophic factor (BNDF) polymorphism was associated with sadness and suicidal ideation but not neurovegetative symptoms of MDD.(41) Thus, it can be anticipated that not all mood symptoms will respond equally to the same preventive interventions.

A fourth lesson from prospective studies of IFN-MDD has been that genetic vulnerability may be mediated by potentially treatable neurophysiological mediators. For example, poor sleep quality, which itself has been strongly associated with risk for subsequent IFN-MDD,(44, 45), may mediate the depression risk conferred by the 5-HTTLPR *S* allele.(40) Thus, rather than resort to genetic therapies to address genotype directly, it may be possible to address mediators such as poor sleep quality. Whether this concept can be fully supported by the evidence remains to be determined, but the hypothesis is certainly testable.

Similarly, increased IL-6 levels have been associated with risk for IFN-MDD,(45) as has an IL-6 gene polymorphism.(39) It is possible that IL-6 levels may mediate the effect of low omega-3 fatty acid availability, as reflected by high arachidonic acid to omega-3 fatty acid ratios.(46) Diet is readily modifiable and thus a feasible intervention target in public health,

and this may offer a safe approach towards depression prevention.(46) Therefore, a fifth lesson is that some biomarkers of depression risk (e.g. IL-6 levels) may be indirectly modifiable, and such a hypothesis is testable.

Summary

Studies of IFN-MDD have been useful in delineating some associated pathophysiological processes that may be targets for prevention (i.e., poor sleep quality and low blood omega-3 fatty acid levels). The five lessons detailed above and summarized in Table 2 will be useful in shaping the design of the next generation of prevention interventions to include information on biomarkers and possible biological mechanisms.

Part C. Prevention Opportunities in Global Psychiatry

Prevention of depression in Low and Middle Income Countries

Prevention of depressive disorders is of great public health significance in Low and Middle Income Countries (LMICs), and represents one of the Grand Challenges in Global Mental Health (grandchallengesinglobalMH@NIH.org). Late-life depression is of particular concern in LMICs due to rapid demographic transitions in countries such as India, where extended life expectancies are much more recent phenomenon; increased prevalence of social conditions that are recognized as risk factors (e.g., living alone or living with a chronic disabling condition); and the weak response of health systems to address the needs (let alone the mental health needs) of the elderly. Furthermore, the mental health care work force is scarce in LMICs. For this reason, there is a need to focus on prevention interventions that can be delivered by non-specialist and lay health workers in non-health care or primary care settings.

A recent study(47), the MANAS trial (“Project to Promote Mental-health” in the Konkani language) conducted in Goa, India demonstrated that the use of lay health counselors, as part of a collaborative stepped-care intervention, increased recovery rates from common mental disorders, including depression, in a mixed-age sample of patients of public primary care facilities. An unanticipated finding was that the MANAS intervention also reduced the incidence of common mental disorders in those with initially subthreshold symptoms. MANAS showed a risk difference at 6 months of 12.3% in the incidence of ICD-10 confirmed common mental disorders (especially mixed anxiety and depression) in a mixed-age sample (mean age in early 40s) in those receiving collaborative stepped care utilizing LHCs (12.7%) versus those receiving enhanced usual care (25.0%). In the context of the shortage of mental health specialists in LMICs, the results from MANAS highlight the important strategy of task shifting – i.e., the rational redistribution of tasks among health workforce teams in order to make more efficient use of lay human resources(48).

The authors have recently established an international consortium for depression prevention researchers (www.preventionofdepression.org)(49) and have reviewed the public health need for depression prevention research in older adults in LMICs: in the review(50), we noted that the number of older adults in LMICs will grow substantially in the next few decades. For example, according to the US Census National Database (http://www.census.gov/ipc/www/idb/informationgateway.php), the age-60+ population in India was about 99.4 million persons (9%). The projections for 2030 are 192.7 million (14.3). The treatment gap for people with mental disorders has been extensively documented, especially in LMICs, where up to 90% of people with mental disorders do not receive cost-effective treatments(47). The great scarcity of mental health specialists in most countries and the inequity of the distribution of these specialists is a major barrier to closing the treatment gap. The existence of the treatment gap and the attendant workforce issues underscore the need for developing effective models of prevention that can be implemented by health workers

with shorter training and fewer qualifications, in order to make more efficient use of the available human resources for health.

Promising interventions and rationale for their use

Brief learning-based approaches, already shown to have efficacy in the treatment of depressive disorders, pain, or insomnia disorders, offer a promising strategy to address the mandate of the Strategic Plan of the National Institutes of Mental Health (NIMH): "to develop and test innovative interventions to reduce risk and positively alter trajectories of illness" (NIMH Strategic Objective 2.3) (http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml#strategic-objective2) As described above, antidepressant medications are the most widely used modality for treating prevalent cases of major depression and have been employed as prophylactic preventive interventions in some contexts, such as IFN-MDD. Nevertheless, their broad use in subthreshold depression may be ill-advised due to 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(51). Thus, psychological interventions may be desirable for reasons of safety and patient preference. For example, problem-solving therapy has been used in depression prevention studies successfully, as described above(52–54). PST involves a key behavioral activation component but may be more easily utilized by older adults than Interpersonal Psychotherapy or Cognitive Behavioral Therapy, and can be readily embedded within service models(55). Teaching coping skills may enhance resilience to stress, by diminishing the sense of loss of control (feeling trapped or helpless). Similarly, teaching strategies for better sleep (because poor sleep is a known and well-established risk factor for depression) may attenuate affective reactivity and enhance cognitive flexibility on the part of both care recipients and caregivers(56, 57). Thus, there may be a synergy between PST-based approaches and those that enhance sleep quality. In this context, Brief Behavioral Treatment of Insomnia (BBTI) seems particularly promising, since it has been shown to improve sleep quality and to reduce symptoms of depression and anxiety(57). Interventions such as PST and BBTI are also practicable: safe, cheap, deliverable by general medical clinicians (including nurses, social workers, and potentially lay health counselors), and more likely to be acceptable to older adults than the use of antidepressant medication.

Summary

The development of depression prevention strategies effective in LMICs would be a means of addressing multiple inequalities (e.g., treatment gaps, workforce barriers) in global mental health. In India, based upon expected incidence rates and the projections above (http://www.census.gov/ipc/www/idb/informationgateway.php) for the year 2030, the projected number of older adults with depression will be 192.7 million x 0.127=24.5 million. A reduction of 50% in incidence could potentially affect over 12 million individuals if effective prevention strategies were widely employed. Even a 25% reduction would have significant impact on a large population. Mental health policies targeting the prevention of depression across the lifespan, including in later-life, could also have large global health implications for other problems in aging. For example, in a recent study, Barnes and Yaffe(58) estimated that prevalent cases of Alzheimer disease (AD) attributable to depression range from 506,000 to 1,078,000 subjects in the U.S. Accordingly, the prevention of 10% and 25% of lifetime cases of depression may reduce the prevalence of AD by 68,000 and 173,000, respectively.

Part D. Opportunities in Prevention Trial Design – Putting it All Together

Thus, we have seen how numerous successes have been achieved in late-life depression prevention research, primarily by focusing on sub-sets of populations with subsyndromal

presentations, or with key risk factors or risk markers for incident depression – that is, these studies have been examples of indicated and selective prevention. Nevertheless, an important outstanding question is whether novel strategies can be developed to allow synchronous examination of potential tools for indicated, selective, *and* universal prevention of depression – thus, addressing the full range of the IOM prevention framework. We describe an ongoing RCT– VITAL-DEP (Depression Endpoint Prevention in the VITamin D and OmegA-3 TriaL, NCT01696435) – as an example of such a strategy using nutritional supplements. Furthermore, we address its implications for future directions in depression prevention research.

Design of a trial for simultaneous testing of indicated, selective and universal prevention

VITAL-DEP is a depression prevention ancillary study of the VITamin D and OmegA-3 TriaL (VITAL, NCT01169259), which is an RCT of vitamin D (in the form of vitamin D3 [cholecalciferol], 2000 IU daily) and marine omega-3 fatty acid (eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA], 1 g daily) supplements in the primary prevention of heart disease and cancer among 20,000 US adults (10,000 men aged 50+ years, 10,000 women aged 55+ years); the randomized treatment period will be 5 years(59). Current evidence from laboratory studies, observational research and limited clinical trials suggest that these particular nutritional supplements have strong plausibility as tools to reduce risk of depression or to improve mood(60–73). However, until the unique opportunity of VITAL-DEP, large-scale prevention trials, with adequate dosing and long-term treatment durations to test the efficacy of these agents in general populations, had been lacking. The trial utilizes a 2×2 factorial design, such that independent main effects as well as possible agent synergies may be explicitly tested: i.e., participants are randomized to one of four groups (n=5000 per group): 1) daily vitamin D3 and omega-3; 2) daily vitamin D3 and omega-3 placebo; 3) daily vitamin D placebo and omega-3; or 4) daily vitamin D and omega-3 placebos. Primary aims are to test whether these agents reduce risk of clinical depressive syndrome and yield better mood scores over time in the full cohort of 20,000. Of note, because the trial cohort includes 20,000 generally healthy late mid-life and older participants who will be followed for occurrence of depression *regardless* of baseline depression risk factor status, the primary aims represent a true test of *universa*l prevention. Indeed, the sample size is large enough to test a modest relative risk reduction of 15% at >85% power.

Secondary aims are also addressed. First, in a sub-set of 1,000 deeply-phenotyped participants examined at a Clinical and Translational Science Center, the study will address whether vitamin D3 or omega-3 can reduce depression incidence and yield better mood scores among persons with key high-risk factors for late-life depression (*selective* prevention) or subsyndromal symptoms (*indicated* prevention). Second, because African-Americans have high particularly risk of vitamin D insufficiency/deficiency(74), VITAL-DEP will specifically test whether vitamin D3 supplementation can reduce depression risk among older African-Americans, who will comprise approximately 25% of the VITAL cohort. Third, using a nested case-control design, the trial will leverage blood samples collected as part of VITAL to examine whether pre-randomization plasma levels of vitamin D and fatty acids are related to depression risk and/or modify the agents' effects. See Table 3 for a summary of advantages of this trial strategy.

Implications for design of prevention research

Thus, the VITAL-DEP design incorporates key principles summarized in Parts A, B and C of this text. First, it addresses the full spectrum of prevention under the IOM Framework, by simultaneously testing the impact of vitamin D and omega-3 for universal, selective *and* indicated prevention of late-life depression. Second, the trial incorporates relevant biological

markers of risk (e.g., baseline insufficient plasma 25-hydroxyvitamin D or low omega-3 fatty acid blood levels) and whether these interact with treatment variables. Finally, the design addresses critical needs articulated in Part C – namely, that preventive interventions ideally should be safe, inexpensive and highly palatable to target populations, especially if they are being considered for broader use; these prerequisites can be summarized by an acronym developed by VITAL-DEP investigators: SEAL (Safety, Evidence for Efficacy, Acceptability, Low-cost). Safety is addressed by employing doses that are within the limits specified by regulatory and government bodies(75–77); dosing also represents an optimal balance of the need for safety with the available biologic, epidemiologic and small trial evidence of efficacy for mood; the agents themselves are popular and have high acceptability with the general public; and both are very low-cost – approximately $15–20 (USD) for a full-year supply at these doses at most retail pharmacies(78).

Summary

Although existing depression prevention research has shown robust successes in employing indicated and selective prevention models, opportunities for universal prevention have been little explored. Thus, future prevention studies would ideally examine possibilities for expanding into universal prevention paradigms. However, because *de novo* trials of this nature are typically cost-prohibitive, due to the large sample sizes and infrastructure required, future universal prevention research might identify creative means to embed tests of depression prevention within existing large RCTs (e.g., those that employ agents with plausible biologic relevance to depression) or cohort studies, or in large-scale public health promotion efforts (e.g., involving modifiable behaviors, such as physical activity/exercise, social activity, dietary factors) that serendipitously produce “natural experiment” opportunities. Finally, an important direction in prevention science would be to conduct further work extending collaborative care approaches. Indeed, such models have already been found effective for management of older patients already diagnosed with depression, as in the IMPACT (Improving Mood-Promoting Access to Collaborative Treatment) trial(79). Furthermore, the PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial) study(80) was a critical early illustration of this method in prevention: collaborative care management reduced rates of suicidal ideation, as well as depression severity, among older primary care patients more effectively than usual care. Thus, collaborative care approaches utilizing a central “hub” of primary care along with an extended network of providers with community ties and/or remote contacts with patients could conceivably be employed to test the value of universal screening and “SEAL”-standard interventions for primary prevention of late-life depression.

Conclusion

Although there has been much progress in treatment of mood disorders, depression continues to be a leading cause of disease burden and disability for millions of older adults in the US and around the world. Despite this, prevention research in late-life depression – and in adult psychiatric disorders overall – is a relatively young field. A comprehensive approach to late-life depression prevention research – i.e., identifying risk factors and markers, defining populations and sub-populations at-risk, and developing and implementing strategies that can be employed narrowly or universally – is now essential. The evidence to date suggests that such prevention tools are either available or can be readily developed and tested. Success in this endeavor would yield substantial reduction in the burden of late-life depression and positive global health impact.

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Table 1

The Framework for Depression Prevention: Application to Late-life Depression

Modality	Target
Indicated Prevention	Persons with subsyndromal depressive symptoms
Selective Prevention	Persons with high-risk factors: e.g., physical/functional impairment, living alone, medical comorbidity
Universal Prevention	General population, regardless of risk status

Table 2

Lessons and Implications Regarding Biological Processes in Depression Prevention Research.

Lesson	Implication
1. Antidepressant therapies can sometimes be used for prevention. There is some evidence that they are best used in subject with pre-existing subsyndromal depression	**1.** Target antidepressant therapies for use as preventions in those with pre-existing subsyndromal depression symptoms.
2. Specific therapies may address some symptoms but not other symptoms.	**2.** Design prevention trials to examine prevention of specific symptom domains.
3. Specific genetic risk factors may increase risk for some symptoms but not others.	**3.** Target prevention therapies to examine prevention of specific symptom domains
4. Some biologic and genetic risk factors (e.g., the short allele in 5-HTTLPR) may be *mediated by* other modifiable factors (e.g., poor sleep).	**4.** Design preventions to target modifiable factors that act as mediators (e.g., treat poor sleep).
5. Some biologic and genetic risk factors (e.g., high interleukin-6) may *mediate* influence of other modifiable risk factors (e.g., low omega-3 levels)	**5.** Design preventions to target modifiable risk factors (e.g., treat low omega-3 levels).

Table 3

Strategies for Universal Depression Prevention Trials.

Approach	Example
Choose the right intervention	Omega-3 supplements and physical activity are examples of interventions with: good **S**afety, plausible **E**vidence of potential efficacy, high **A**cceptability, **L**ow-cost (SEAL).
Leverage research infrastructures	Ancillary studies to existing large-scale trials. Add-in trial within large cohorts or health promotion studies.
Identify at-risk subsets	Testing of selective and indicated prevention among at-risk persons. Utilization of biomarker information to identify mediators and moderators of risk.