Prevention of Depressive Disorders: Overview of a Developing Field

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October 3, 2012
Disclosures (past 5 years):

National Institute of Mental Health
National Institute on Aging
National Center for Minority Health and Health Disparities
National Heart, Lung, and Blood Institute
John A. Hartford Foundation
American Foundation for Suicide Prevention
Commonwealth of Pennsylvania
American Association for Geriatric Psychiatry
UPMC Endowment in Geriatric Psychiatry

Forest Laboratories, Pfizer, Lilly, BristolMyersSquibb
(provide pharmaceuticals for NIH-sponsored research)
Overview

- Why is prevention of depressive disorders important?
- Is prevention of depression possible?
- Challenges for the future

www.preventionofdepression.org
Prevention encompasses

- Preemption of incident and recurrent episodes of depression
- Protection from developmental complications of depression
Interrelation of prevention and treatment

Universal prevention
- General population

Selective prevention
- Vulnerable people

Indicated prevention
- People with symptoms

Maintenance therapy
- Recovered patients

Relapse prevention
- Patients in remission

Treatment / therapy
- Diagnosed patients
Why is prevention important?

- Prevalence, persistence, and substantial morbidity/mortality of depression
- Treatment is only partially satisfactory in reducing disability
- Limited access to treatment, especially minorities: social inequalities of risk widen with age—socioeconomic gradient in treatment access, utilization, and response
- Mental health workforce issues: need models of large-scale depression prevention that could be carried out by general medical clinicians or lay health counselors using cost-effective, stepped care approaches
### Averted Years Lived with Disabilities
(current coverage and with Evidence-Based Mental Health)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Current</th>
<th>EBMH</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mood disorder</td>
<td>15%</td>
<td>23%</td>
<td>35%</td>
</tr>
<tr>
<td>Major depression</td>
<td>16%</td>
<td>23%</td>
<td>34%</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>13%</td>
<td>20%</td>
<td>49%</td>
</tr>
<tr>
<td>Any alcohol rel. dis.</td>
<td>2%</td>
<td>5%</td>
<td>34%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>13%</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Any disorder</td>
<td>13%</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Is prevention of depression possible?
Prevention of incidence of new cases of depression

- Meta-analytic review
- 19 trials

Results:
- IRR = 0.78 (95% CI: 0.65~0.93)
- No significant subgroups (type, target population)
- IPT may be somewhat more effective than CBT

Cuijpers et al., Am J Psychiatry, 2008
Prevention of depression in post-stroke patients

Cox proportional Hazards controlled for age, gender, lesion site, ADL score, MMSE and SFE showed treatment was only significant factor.

* HR 4.5, 95% CI, 2.4-8.2, p<.001 for ESC vs PL
† HR 2.2, 95% CI, 1.4-3.5, p<.001 PST vs PL

Robinson et al. *JAMA*, 2008
Depression incidence in macular degeneration at months and 6 months by treatment assignment

- **2 Months**
  - N = 194
  - OR = 0.43 [0.20, 0.95]
  - P = 0.033

- **6 Months**
  - N = 190
  - OR = 0.65 [0.33, 1.39]
  - P = 0.29

Rovner et al, AGP, 2006
Stepped-Care Prevention of Anxiety and Depression in Late Life

A Randomized Controlled Trial

Petronella J. van't Veer-Tazelaar, MA; Harm W. J. van Marwijk, MD, PhD; Patricia van Oppen, PhD; Hein P. J. van Hout, PhD; Henriëtte E. van der Horst, MD, PhD; Pim Cuijpers, PhD; Filip Smit, PhD; Aartjan T. F. Beekman, MD, PhD

Context: Given the public health significance of late-life depression and anxiety, and the limited capacity of treatment, there is an urgent need to develop effective strategies to prevent these disorders.

Objective: To determine the effectiveness of an indicated stepped-care prevention program for depression and anxiety disorders in the elderly.

Design: Randomized controlled trial with recruitment between October 1, 2004, and October 1, 2005.

Setting: Thirty-three primary care practices in the northwestern part of the Netherlands.

Participants: A total of 170 consenting individuals, 75 years and older, with subthreshold symptom levels of depression or anxiety who did not meet the full diagnostic criteria for the disorders.

Intervention: Participants were randomly assigned to a preventive stepped-care program (n=86) or to usual care (n=84). Stepped-care participants sequentially received a watchful waiting approach, cognitive behavior therapy-based bibliotherapy, cognitive behavior therapy-based problem-solving treatment, and referral to primary care for medication, if required.

Main Outcome Measures: The cumulative incidence of DSM-IV major depressive disorder or anxiety disorder after 12 months as measured using the Mini International Neuropsychiatric Interview.

Results: The intervention halved the 12-month incidence of depressive and anxiety disorders, from 0.24 (20 of 84) in the usual care group to 0.12 (10 of 86) in the stepped-care group (relative risk, 0.49; 95% confidence interval, 0.24 to 0.98).

Conclusions: Indicated stepped-care prevention of depression and anxiety in elderly individuals is effective in reducing the risk of onset of these disorders and is valuable as seen from the public health perspective.

Trial Registration: isrctn.org Identifier: ISRCTN26474556.

Arch Gen Psychiatry. 2009;66(3):297-304
Reducing Suicidal Ideation and Depressive Symptoms in Depressed Older Primary Care Patients
A Randomized Controlled Trial

Martha L. Bruce, PhD, MPH
Thomas R. Ten Have, PhD
Charles F. Reynolds III, MD
Ira I. Katz, MD, PhD
Herbert C. Schulberg, PhD
Benoit H. Mulsant, MD
Gregory K. Brown, PhD
Gail J. McAvay, PhD
Jane L. Pearson, PhD
George S. Alexopoulos, MD

PROSPECT’S Intervention: Guideline Management

Identification of Diagnosis
Physician Education
Patient & Family Psycho-Education

DEPRESSION SPECIALIST & TREATMENT ALGORITHM
Reducing Suicidal Ideation and Depressive Symptoms in Depressed Older Primary Care Patients:

- A Randomized Controlled Trial Utilizing Citalopram and Depression Care Management (n = 598)
- Rates of suicidal ideation declined faster (p = .01) in intervention patients compared with usual care patients.
- Differences peaked at 8 months (70.7% versus 43.9% resolution; p = .005)
- PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial).
  Bruce M, Tenhave T, Reynolds CF et al: JAMA, 291(9):1081-1091, 2004
After a median follow-up of 52.8 months, patients with major depressive disorder in intervention practices were less likely to have died than patients in usual care practices:

adjusted hazard ratio = 0.55 (CI, 0.36-0.84)

No effect was seen in patients with clinically significant minor depression.

The benefit seemed to be almost entirely attributable to a reduction in deaths due to cancer.

The mechanism for such an effect is unclear and warrants further investigation.

Survival probability among persons with no depression (red line) or major depression (blue line) in practices randomized to usual care or to the intervention. Data from PROSPECT (1999-2008).

Depression: Risk factor for future dementia?

Ownby, R. L. et al. *Arch Gen Psychiatry*, 2006
Forest plots for random effects meta-analyses
Maintenance Treatment of Depression in Old Age

A Randomized, Double-blind, Placebo-Controlled Evaluation of the Efficacy and Safety of Donepezil Combined with Antidepressant Pharmacotherapy

Charles F. Reynolds III, MD; Meryl A. Butters, PhD; Oscar Lopez, MD; Bruce G. Pollock, MD, PhD; Mary Amanda Dew, PhD; Benoit H. Mulsant, MD; Eric J. Lenze, MD; Margo Holm, PhD; Joan C. Rogers, PhD; Sati Mazumdar, PhD; Patricia R. Houck, MSH; Amy Begley, MA; Stewart Anderson, PhD; Jordan F. Karp, MD; Mark D. Miller, MD; Ellen M. Whyte, MD; Jacqueline Stack, MSN; Ariel Gildengers, MD; Katalin Szanto, MD; Salem Bensasi, BA; Daniel I. Kaufer, MD; M. Ilyas Kamboh, PhD; Steven T. DeKosky, MD

(REPRINTED) ARCH GEN PSYCHIATRY/VOL 68 (NO. 1), JAN 2011 WWW.ARCHGENPSYCHIATRY.COM

Downloaded from www.archgenpsychiatry.com at University of Pittsburgh, on January 14, 2011
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Factors Contributing to Relapsing, Chronic Illness Course in Late-Life Depression

• Psychosocial factors:
  – Role transitions, bereavement, increasing dependency, interpersonal conflicts
• Progressive depletion of psychosocial and economic resources
• Chronic sleep disturbances
• Cerebrovascular disease
• Neurodegenerative disorders
• Limited access to adequate treatment
MTLD-III: Hypotheses

1. Combined pharmacotherapy (escitalopram + donepezil) will be superior to (escitalopram + placebo) in improving or maintaining cognitive performance and functional status over a two-year period.

2. Combined pharmacotherapy may reduce recurrences of major depressive episodes.
Rationale for Study-I

Cognitive impairment in late-life depression:

• has not been adequately addressed in previous pharmacotherapy intervention research;
• is a core feature of the illness;
• contributes markedly to disability and impaired quality of life; and
• is an overlooked but critical target of intervention.
• Depression in old age, with or without overt cognitive impairment, is either a risk factor for or a prodrome to Mild Cognitive Impairment or dementing illness (especially Alzheimer’s dementia or vascular dementia) (Ownby et al., 2005).

• Depression in old age adversely affects basic cognitive operations, including information processing speed, working memory, and episodic memory (Nebes et al., 2000).

• Even after treatment to symptomatic remission and recovery, basic cognitive operations do not improve to the level seen in non-depressed control subjects, i.e., there is room for improvement (Nebes et al., 2000; Butters et al., 2002).

• Despite continuing recovery from depression, cognitive impairment and functional disabilities may progress.
Maintenance Therapies in Late-Life Depression-III: Optimizing and Maintaining Cognitive Functioning

Start antidepressant pharmacotherapy

Elderly Depressed Subjects

N=220

ESCIT + DON
N= 67

ESCIT + PBO
N=63

Response: HRSD- 17 ≤ 10

Randomization

Elderly Non-Depressed Controls

N=46

Cognitive Assessments:

T1: Post-depression treatment

T2: 3 Months

T3: 12 Months

T4: 24 Months

Maintenance Treatment up to 2 years

Reynolds, et al., Arch Gen Psychiatry, 2011
Key Findings in the Cognitive Domain

- Relative to placebo + antidepressant, donepezil + antidepressant temporarily improved global cognition (treatment x time interaction $F = 3.78$, df = 2, 126, $p = .03$), but effect sizes were small (Cohen’s $d = 0.27$, group differences at one year)

- Of 57 participants with Mild Cognitive Impairment, 3/30 on donepezil (10%; 95% CI: 0, 21%) and 9/27 on placebo (33%; 95% CI: 16%, 51%) converted to dementia; Fisher exact $p = 0.05$

- Of 73 cognitively normal subjects, 6/37 (16%) on donepezil experienced cognitive decline (5 MCI, 1 dementia), and 8/36 (22.2%) on placebo showed cognitive decline (all MCI): Fisher exact $p = 0.56$
Key Findings in the Mood Domain

• Donepezil-randomized subjects were more likely to experience recurrent major depressive episodes: 35% versus 19% on placebo; log rank chi squared = 3.97, p = 0.05. Hazard ratio = 2.09 (95% CI: 1.00, 4.41)

• Subjects with MCI had a 44% recurrence rate on donepezil versus 12% on placebo (LR = 4.91, p = 0.03)
Recurrence of Major Depressive Episodes

- **Months from Randomization**
- **Proportion not recurred**
- **Donepezil (n=67)**
- **Placebo (n=63)**

**Normal Cognition**
- **Donepezil (n=37; 11 rec)**
- **Placebo (n=36; 8 rec)**

**MCI**
- **Donepezil (n=30; 8 rec)**
- **Placebo (n=27; 3 rec)**
Preventing Depression: Challenges for the Future
Can prevention be personalized?

Since most adults are resilient to depression after a disabling medical event or other negative life events such as bereavement, how can one improve the cost benefit ratio of prevention efforts?

Example: genetic contributions to (1) likelihood of onset (2) time period of risk and (3) likelihood of risk reduction using psychosocial and psychopharmacologic strategies

Need to understand architecture of both risk and resilience to depression in old age

Courtesy Eric Lenze
What is Cost Effectiveness of Depression Prevention in Old Age?
Cost-effectiveness plane

<table>
<thead>
<tr>
<th>More costs, Less health</th>
<th>More costs, More health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less Costs, Less Health</td>
<td>Less costs, More health</td>
</tr>
</tbody>
</table>

Courtesy Filip Smit
Smit et al., British Journal of Psychiatry, 2006
Stepped-care approach toward preventing depression

't Veer et al. (in prep.) Cost-effectiveness of a stepped-care intervention to prevent onset of depression and anxiety in late life.

Courtesy Filip Smit
Preventive online PST vs WL

Warmerdam et al. (in prep) Cost-utility and cost-effectiveness of internet-based treatments for adults with depressive symptoms

Courtesy Filip Smit
We must go beyond traditional health care: Using the internet

- Interventions that can be used *again and again*.
- Reducing health disparities
  - *especially when the local health care system cannot provide care to people who need it.*
- Interventions that can be shared globally
  - *without taking anything away from local populations*

Preventing Depression
A Global Priority

Pim Cuijpers, PhD
Aartjan T. F. Beekman, MD, PhD
Charles F. Reynolds III, MD

www.preventionofdepression.org
Key domains of vulnerability for late-life depression and intersections with PRC projects. Intersections (shaded areas) will receive learning and skills development-based interventions for depression prevention.

CF Reynolds, PI
Using LHCs to Prevent Incident Major Depression and Anxiety Disorders in LAMIs

Primary Care Patients > 60 Years of Age  
n=120  
Subthreshold depressive symptoms and no MDD in past 12 months

MANAS/DP  
n=60  
Usual Care  
n=60

Assessment Point (time from T1):
T1: baseline
T2: 3 months follows completion of intervention
T3: 6 months
T4: 12 months*

Primary Outcomes
— Incident episodes of major depressive and anxiety disorders
— Level of depressive and anxiety symptoms

Collaboration with Vikram Patel, Alex Cohen, Amit Dias, Neerja Chowdhury and Pim Cuijpers (R34 MH096997-01A1)
Aging Institute

- Collaboration between UPMC Senior Services and the University of Pittsburgh
- Links age-related clinical programs, research, and education initiatives
- Launched July 1, 2002

Administrative Staff
Charles F. Reynolds III, M.D., Director
Deborah Brodine, President, UPMC Community Provider Services
Taafoi Kamara MS, MPH, Administrative Director
Betty Robison MSN, RN-BC, Gerontology Educator
Lisa Meadows MSW, LSW, Senior Information Center Liaison
Carol Davis, Administrative Assistant Sr.
Why Have an Aging Institute?

- catalyst for change in how we think about older patients
- stimulate multidisciplinary aging research and research training
- promote interprofessional education in geriatrics
- foster models of team-based care of complex older adults
Goals of Aging Institute Workgroups

- Palliative Care: improve access to palliative care services across the care continuum. Collaborate with Pitt Geriatric Education Center to develop, implement, and evaluate

- Healthy Aging: Address UPMC Health Plan’s HEDIS measure for osteoporosis management rates for older woman who’ve had a fracture

- Unplanned Readmission: Aims to decrease unplanned readmissions in UPMC skilled nursing facilities by 10%

- Falls Prevention

- Dementia caregivers
“The lesson is pretty clear from my point of view in terms of what the average person should be doing. I strongly believe that with some changes in health-related behavior, each of us can earn the right to have at least 25 years beyond the age of 60 — years of healthy life at good function. The disappointing news is that it requires work and willpower.”

http://www.time.com/time/printout/0,8816,994967,00.html

Thomas Perls, 2011
“Those who allege that old age is devoid of useful activity...are like those who say that the pilot does nothing in the sailing of his ship, because, while others are climbing the masts, or running about the gangways, or working at the pumps, he sits quietly in the stern and simply holds the tiller. He may not be doing what younger members of the crew are doing, but what he does is better and much more important.”

"It is not by muscle, speed, or dexterity that great things are achieved, but by reflection, force of character, and judgment."

"In these qualities old age is usually not only not poorer, but is even richer."

Cato Maior, De Senectute
Cicero
Loeb Classical Library, 1923
We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time
How filled with awe is this place,
and we did not know it.

Shabbat Evening I,
Mishkan T’filah, 2007