Meditation & Exercise to Prevent Acute Respiratory Infection (MEPARI) or Aging, Stress, Colds & Flu

October 11, 2011

Madison, Wisconsin

Bruce Barrett MD PhD
Associate Professor of Family Medicine
U.W. School of Medicine & Public Health
Can we prevent
Cold and Flu?
(acute respiratory infection)
Q. What is a cold?

- A #1: Acute respiratory illness caused by one of many respiratory viruses*
- A #2: A constellation of symptoms (syndrome) usually including nasal congestion/drainage and/or sore throat (that isn’t allergy) and general malaise, lasting 1 to 14 days

*Rhinovirus, coronavirus, adenovirus, enterovirus, influenza, parainfluenza, respiratory syncytial virus. Metapneumovirus & bocavirus ID’d more recently

Metapneumovirus reported 2004, Bocavirus in 2006


Q. What is the flu?

- A #1: Acute respiratory illness caused by influenza virus (influenza types A & B with many subtypes)
- A #2: A constellation of symptoms (syndrome) including sore throat and/or cough and/or nasal congestion/drainage AND often including fever, headache & muscle aches AND often more abrupt & severe than illness due to other viruses*
- The term “influenza-like illness” (ILI) can be used for this symptom complex. When ILI occurs during a known influenza epidemic, “influenza” can be diagnosed presumptively
Iceberg concept of infection

- Severe symptoms
- Mild symptoms
- Infection but no symptoms
- Exposure but no infection
<table>
<thead>
<tr>
<th>Wisconsin Upper Respiratory Symptom Survey</th>
<th>WURSS-44, WURSS-21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. How sick do you feel today?</strong></td>
<td>12. Body aches</td>
</tr>
<tr>
<td>15. Chills</td>
<td>25. Ear discomfort</td>
</tr>
<tr>
<td>16. Feeling feverish</td>
<td>27. Eye discomfort</td>
</tr>
<tr>
<td>20. Sinus pain</td>
<td>31. Heaviness in chest</td>
</tr>
<tr>
<td>21. Sinus pressure</td>
<td>32. Lack of energy</td>
</tr>
<tr>
<td>22. Sinus drainage</td>
<td>33. Loss of appetite</td>
</tr>
<tr>
<td>34. Think clearly</td>
<td>35. Speak clearly</td>
</tr>
<tr>
<td>36. Sleep well</td>
<td>37. Breathe easily</td>
</tr>
<tr>
<td>38. Walk, climb stairs, exercise</td>
<td>39. Accomplish daily activities</td>
</tr>
<tr>
<td>40. Work outside the home</td>
<td>41. Work inside the home</td>
</tr>
<tr>
<td>42. Interact with others</td>
<td>43. Live your personal life</td>
</tr>
<tr>
<td>44. Compared to yesterday</td>
<td>Barret, B The Wisconsin Upper Respiratory Symptom Survey. <em>Journal of Family Practice</em> 51(3); 1-10, 2002</td>
</tr>
</tbody>
</table>
Symptoms experienced in first 3 days of community-acquired colds (n=230)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal</td>
<td>223</td>
<td>97%</td>
</tr>
<tr>
<td>Throat</td>
<td>201</td>
<td>87%</td>
</tr>
<tr>
<td>Cough</td>
<td>150</td>
<td>65%</td>
</tr>
<tr>
<td>Headache</td>
<td>142</td>
<td>62%</td>
</tr>
<tr>
<td>Chilliness</td>
<td>87</td>
<td>38%</td>
</tr>
<tr>
<td>Malaise/tiredness</td>
<td>184</td>
<td>80%</td>
</tr>
</tbody>
</table>

B. Barrett et al.. Validation of a short form Wisconsin Upper Respiratory Symptom Survey (WURSS-21). *Health and Quality of Life Outcomes* 7 (76), 2009
Very first symptom experienced in N=230 community-acquired colds

Throat  42%
Nasal    46%
Cough    3%

Mean annual incidence of respiratory infections

Respiratory viruses are seasonal

Rhinovirus

Adenovirus

Credit: Wisconsin State Lab of Hygiene (WSLH)
Respiratory viruses are seasonal

Parainfluenza 1

Parainfluenza 2

Parainfluenza 3
Respiratory viruses are seasonal

Influenza

Respiratory Syncytial Virus

Credit: Wisconsin State Lab of Hygiene (WSLH)
Anatomy

- Ethmoid cells
- Frontal sinus
- Frontal sinus ostia
- Ethmoid bulla
- Maxillary ostium
- Uncinate process
- Nasal septum
- Middle turbinate
- Maxillary sinus
- Inferior turbinate
- Osteomeatal complex
Influenza virus
Influenza is a deadly disease

The influenza pandemic of 1918-1919 killed an estimated 70 million people, more than the number that died in all first World War battles combined (1914-1918).

“Pandemic” = Global epidemic
Influenza is a deadly disease

Each year in the U.S., approximately 30,000 deaths and 500,000 hospitalizations are associated with influenza infection.

Flu shots save lives
Antivirals for influenza

• Adamantanes - amantidine and rimantidine
  Effective only against influenza A
  Resistance in several Flu A strains
• Neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza)
• Influenza A & B sensitivity to the “—amivirs” varies
• All influenza antivirals must be given within 48 hours of first symptom to be effective
• And then, only slightly-to-somewhat effective
• Should only be used during high prevalence (otherwise we would be ineffectively treating non-influenza infections)
ANTIBIOTICS
THE END OF MIRACLE DRUGS?

WARNING
NO LONGER EFFECTIVE AGAINST KILLER BUGS
Outpatient Abx use in US and EU

Figure 1. Total outpatient antibacterial use in the United States and 27 European countries in 2004 (total use for Greece, Iceland, and Bulgaria, 2002 data for Poland, and 2003 data for Italy). DDD, defined daily dose; MLS, macrolides, lincosamides, and streptogramins; TMP, trimethoprim. *Includes amphenicols (J01B), aminoglycosides (J01G), combinations of antibacterial agents (J01R), and other antibacterial agents (J01X).

Mediterranean diet = good; Mediterranean abx Rx pattern = bad

courtesy Jochen WL Cals – NAPCRG 2008
Conventional drug therapies for common cold

- Antihistamines (diphenhydramine, loratadine, etc)
- Decongestants (pseudophedrline, etc)
- Antitussive (DM – dextromethorphan, codiene)
- Expectorant (guaifenesin)
- Analgesics (aspirin, ibuprofen, naproxen, acetaminophen)
- Combination cold formulas
- Side effects, costs and lack of evidence of effectiveness limit enthusiasm
The Common Cold

Vitamin C

Common Cold

Zinc Lozenge Plus Formula

Echinacea flower

Garlic
Ascorbic acid
Vitamin C

- At least 30 RCTs with more than 8,000 randomized participants
- Variable quality & outcomes
- First Cochrane reviewers conclude: “Vitamin C does not prevent the common cold, but probably shortens the length of the illness”
- Latest update more cautious

R.M. Douglas et al. “Vitamin C for preventing and treating the common cold” Cochrane Review 2003
Zinc
Zinc - Systematic Reviews

• 13 treatment RCTs (n=966)
• 3 preventive RCTs (n=394)
• Majority of trials report benefit
• Methodological quality has varied
• Cochrane review concludes benefit for both treatment and prevention

Echinacea

Echinacea purpurea

Echinacea angustifolia
18 randomized trials; many positive


Medical profession applauds safe herb miracle!

ECHINACEA CURES Colds & Flu

‘Try it as a front-line treatment for colds, flu & sore throats’

- TOP NATURAL HEALTH AUTHOR DR. ANDREW WEIL

‘Echinacea helps you get over colds & flu much faster than any other treatment’

- PURDUE UNIVERSITY RESEARCH GROUP

‘Protects against colds, flu & boosts immune system’

- PRESIDENT CLINTON’S COMMISSION ON DIETARY SUPPLEMENT LABELS

‘Supercharge Echinacea’s amazing healing power with Goldenseal’

- DR. MICHAEL MURRAY, BASTYR COLLEGE, SEATTLE
Wrong way to use echinacea
Nasal saline

Demonstrated benefit for chronic sinus symptoms, by unproven for treating or preventing cold-n-flu illness

D. Rabago, A. Zgierska, M. Mundt, B. Barrett, J. Bobula & R. Maberry

D. Rabago, T. Pasic, A. Zgierska, M. Mundt, B. Barrett & R. Maberry.
Ginger  *Zingiber officinale*
Garlic  (*Allium Sativum*)
Lemon  *Citrus limon*
Chamomile
Peppermint  *Mentha piperita*
≥ 7 randomized controlled trials (n ≥ 896) report benefit; all from same manufacturer?


Astragalus

*Astragalus* genus = >3,000 species

Traditional Chinese medicine

Many uses; “immune stimulant”

No randomized trial I am aware of for cold-n-flu
Pelargonium siloides
Umckaloabo

South African traditional remedy; Three randomized trials in adults (N = 746) and three in children (N = 819) yield positive yet inconsistent results


Cold-n-Flu Treatment

Many options, many claims

Nothing proven to provide meaningful benefit
Q: How about prevention?
Q. Are there proven preventive methods?
A: Yes.......and......... No

- Contact avoidance
- Hand-washing
- *Enhance physical health*
- Exercise
- Nutrition
- *Enhance mental health*
- Stress reduction
- Self-care
- Relationships

- Immunization is impractical because too many viruses
- There are no known effective immune enhancing drugs
- Immune enhancing herbs (echinacea) and supplements (vitamins) are unproven
Stress & immunity to colds & flu

- Stressed people have more frequent and more severe cold and flu illness episodes
- Stress negatively influences several immune system processes

Stress hits at multiple levels

Body
- headaches
- frequent infections
- taut muscles
- muscular twitches
- fatigue
- skin irritations
- breathlessness

Mind
- worrying
- muddled thinking
- impaired judgement
- nightmares
- indecisions
- negativity
- hasty decisions
- loss of confidence
- more fussy
- irritability
- depression
- apathy
- alienation
- apprehension
- smoking more

Emotions

Behavior

http://ecohealthwellness.com
Immune system

Highly complex
Widely distributed
Poorly understood

http://www.microbiologybytes.com
Immune system

Antibodies = Immunoglobulins

http://www.biology-innovation.co.uk

http://en.wikipedia.org/wiki/Monoclonal_antibodies
Immunosenescence
Some immune processes decline with aging

http://www.blisstechniques.com/
Stress may accelerate aging

Meditation may reduce stress, & thereby prevent or ameliorate cold-n-flu

Exercise may stimulate the immune system,* & thereby prevent or ameliorate cold-n-flu

*directly, and/or by reducing stress

http://technorati.com/lifestyle/article/running-to-lose-weight/
MEPARI trial

- Meditation or
- Exercise to
- Prevent
- Acute
- Respiratory
- Infection
• **OBJECTIVE**

• To evaluate potential preventive effects of mindfulness meditation or sustained moderate intensity exercise on incidence, duration and severity of acute respiratory infection
Mindfulness based stress reduction

MBSR

Standardized 8 week course

Incorporates aspects of meditation & yoga

Aims to enhance awareness of body & mind

Attention to sensation, thought, emotions

2.5 hours in class each week

45 minutes daily practice

Pioneered by Jon Kabat-Zinn PhD
Center for Mindfulness in Medicine, Health Care
University of Massachusetts Medical School
Exercise

Matched to MBSR by:

• Duration (8 weeks)
• Attention (weekly 2½ hour group sessions)
• Intensity (daily 45 minute at-home practice)
• Location (UW Research Park)

• Aimed at sustained moderate intensity exercise
• Jogging, fast walking, biking, swimming, etc
MEPARI = randomized controlled trial

- Community recruited adults aged 50 years or older were randomized to 1 of 3 conditions:
  - 8-week training in mindfulness meditation
  - matched 8-week training in moderate intensity sustained exercise
  - wait-list observational control

Not eligible if already trained in meditation or exercising regularly
Randomized using statistical algorithm

With this much grant money, only experiment we can do is "flip a coin"!
NIH NCCAM ARRA funding

- National Center for Complementary & Alternative Medicine (NCCAM)
- National Institutes of Health (NIH)
- American Recovery & Reinvestment Act (ARRA) of 2009 “Economic Stimulus” funding
- Original proposal was for 4 to 5 year project
- ARRA required data collection over 1 year, and full project finished within 2 years
- Aimed for Employment as well as Science
- Medical research “soft money” = New jobs
Many people involved in MEPARI

- Shari Barlow, Michele Gassman, Lori Wilson, Kati Krome, Tola Ewers, Chidi Obasi MD MSPH, Becky West PhD APRN, undergrad students
- Exercise & Mindfulness trainers/coordinators
- Nursing & Lab personnel at UW Hospitals
- Grant management, Personnel, UW support
- Principal Investigator: Bruce Barrett MD PhD, Co-Investigators: Chris Coe PhD, Mary Hayney PharmD, Dave Rakel MD, Daniel Muller MD PhD, Roger Brown PhD, Zhengjun Zhang PhD, Ann Ward PhD, Aleksandra Zgierska MD PhD, James Gern MD, Richard Davidson PhD
2009-2010 cold/flu season

- Primary outcomes: incidence, duration, and global severity (area-under-the-curve) of all cold/flu illness episodes over a single cold/flu season

- Wisconsin Upper Respiratory Symptom Survey (WURSS-24) assessed illness severity daily

- Nasal wash collected during ARI illness was assayed for neutrophils, interleukin-8 & tested for nucleic acid to identify specific viruses

- Cohort 1 – September to May

- Cohort 2 – January to May
Figure 1. CONSORT diagram

Cohort 1 Screened n=465
- Reasons for exclusion
  - Too much exercise n=225
  - Meditation practice/training n=40
  - Scheduling issues n=24
  - Declined to participate n=8
  - Other n=42

Cohort 1 Run-In Trial n=126
- Excluded n=32
  - Declined to participate n=22
  - Failing inclusion criteria n=10

Total Randomized n=94
- Assigned to Exercise n=31
  - n=2 withdrew
    1) uterine cancer diagnosis
    2) need to take care of elderly parents
  - Received exercise intervention and included in analysis n=29
- Assigned to Meditation n=31
  - n=1 withdrew unhappy with allocation
  - Received meditation intervention and included in analysis n=31
- Assigned to Control n=32

Cohort 2 Screened n=418
- Reasons for exclusion
  - Already had flu shot n=155
  - Too much exercise n=70
  - Meditation practice/training n=20
  - Declined to participate n=33
  - Other n=62

Cohort 2 Run-In Trial n=78
- Excluded n=18
  - Declined to participate n=17
  - Failing inclusion criteria n=1

Total Randomized n=60
- Assigned to Exercise n=20
  - n=2 withdrew
    1) conflict with work schedule
    2) interest in a different study
  - Received exercise intervention and included in analysis n=18
- Assigned to Meditation n=20
  - Received meditation intervention and included in analysis n=20
- Assigned to Control n=20
  - Received control intervention and included in analysis n=20
Participant Characteristics of N=149 MEPARI trial finishers

<table>
<thead>
<tr>
<th></th>
<th>Exercise</th>
<th>Mindfulness</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years) mean (SD)</strong></td>
<td>59.0 (6.6)</td>
<td>60.0 (6.5)</td>
<td>58.8 (6.8)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Female n (%)</strong></td>
<td>39 (83.0)</td>
<td>42 (82.4)</td>
<td>41 (80.4)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Non smokers n (%)</strong></td>
<td>43 (91.5)</td>
<td>48 (94.1)</td>
<td>48 (94.1)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Race φ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black n (%)</td>
<td>3 (6.4)</td>
<td>1 (1.9)</td>
<td>2 (3.9)</td>
<td>0.52</td>
</tr>
<tr>
<td>White n (%)</td>
<td>43 (91.5)</td>
<td>49 (92.5)</td>
<td>48 (94.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>Other n (%)</td>
<td>1 (2.13)</td>
<td>3 (5.7)</td>
<td>1 (2.0)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Ethnicity Non-Hispanic n (%)</strong></td>
<td>47 (100)</td>
<td>51 (100)</td>
<td>49 (96.1)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>BMI mean (SD)</strong></td>
<td>29.0 (6.9)</td>
<td>29.0 (6.0)</td>
<td>29.8 (6.8)</td>
<td>0.77</td>
</tr>
</tbody>
</table>
Figure 2 - MEPARI Trial Main Results

Error bars represent 95% confidence intervals.
<table>
<thead>
<tr>
<th>Main outcomes</th>
<th>Exercise n=47</th>
<th>Meditation n=51</th>
<th>Control n=51</th>
<th>Between-group difference</th>
<th>Mediation vs. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals with ARI illness (per cent of sample) (95% CI)</td>
<td>17 (36%)</td>
<td>21 (41%)</td>
<td>28 (55%)</td>
<td>0.19 (-0.01, 0.37)</td>
<td>0.14 (-0.06, 0.32)</td>
</tr>
<tr>
<td>Number of ARI episodes</td>
<td>26</td>
<td>27</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean global severity (95% CI)</td>
<td>248 (77, 419)</td>
<td>144 (62, 225)</td>
<td>358 (221, 495)</td>
<td>110 (-105, 324)</td>
<td>214 (56, 372)</td>
</tr>
<tr>
<td>Total days of ARI illness</td>
<td>241</td>
<td>257</td>
<td>453</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ARI illness days (95% CI)</td>
<td>5.13 (2.64, 7.62)</td>
<td>5.04 (2.25, 7.83)</td>
<td>8.89 (5.76, 12.02)</td>
<td>3.76 (-0.24, 7.75)</td>
<td>3.85 (-0.29, 7.99)</td>
</tr>
</tbody>
</table>
# MEPARI Secondary Outcomes

## Biomarker and viral identification data from nasal secretions

<table>
<thead>
<tr>
<th></th>
<th>Exercise n=47</th>
<th>Meditation n=51</th>
<th>Control n=51</th>
<th>Between-group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-8 mean (95% CI)</strong></td>
<td>694 (484, 904)</td>
<td>910 (696, 1124)</td>
<td>658 (511,806)</td>
<td>Exercise vs. Control: -36 (-282, 211) p=0.39 Meditation vs. Control: -252 (-497, -6) p=0.022</td>
</tr>
<tr>
<td><strong>Neutrophils mean (95% CI)</strong></td>
<td>103.7 (-46.1, 253.5)</td>
<td>107.9 (23.0,192.8)</td>
<td>110.4 (22.9, 197.9)</td>
<td>Exercise vs. Control: 6.7 (-150.8, 164.2) p=0.47 Meditation vs. Control: 2.5 (-119.6, 124.6) p=0.48</td>
</tr>
<tr>
<td><strong>Positive for virus (95% CI)</strong></td>
<td>8</td>
<td>14</td>
<td>19</td>
<td>Exercise vs. Control: 0.12 (-0.15, 0.38) p=0.20 Meditation vs. Control: 0.004 (-0.24, 0.25) p=0.49</td>
</tr>
<tr>
<td><strong>Specific viruses</strong></td>
<td>HRV (7), MPV (1) CoV (2), HRV(10), MPV (1), PIV (2), RSV (1) Adv C (1), CoV (3), Flu A/H1N1 (2), HRV (11), MPV (1), PIV (1), RSV (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Negative for virus</strong></td>
<td>11</td>
<td>12</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>
### Main outcomes

#### Healthcare provider visits and work days lost to illness

<table>
<thead>
<tr>
<th></th>
<th>Exercise n=47</th>
<th>Meditation n=51</th>
<th>Control n=51</th>
<th>Between-group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of episodes of missed work</td>
<td>21</td>
<td>25</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Total number of missed days</td>
<td>91.5</td>
<td>99</td>
<td>144.5</td>
<td></td>
</tr>
<tr>
<td>Mean number of missed days (95% CI)</td>
<td>1.9 (0.8, 3.1)</td>
<td>1.9 (0.7, 3.2)</td>
<td>2.8 (1.5, 4.2)</td>
<td>0.9 (-0.9, 2.7) p=0.16 0.9 (-0.9, 2.7) p=0.17</td>
</tr>
<tr>
<td>ARI-related missed days (95% CI)</td>
<td>32</td>
<td>16</td>
<td>67</td>
<td>0.11 (-0.01, 0.24) p=0.041 0.30 (0.19, 0.40) p&lt;0.001</td>
</tr>
<tr>
<td>Mean ARI-related missed days (95% CI)</td>
<td>0.68 (0.1, 1.2)</td>
<td>0.31 (0.1, 0.5)</td>
<td>1.31 (0.5, 2.1)</td>
<td>0.63 (-0.4, 1.6) p=0.1 1.0 (0.2, 1.8) p=0.011</td>
</tr>
<tr>
<td>Total number of healthcare visits</td>
<td>116</td>
<td>116</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Mean number of healthcare visits (95% CI)</td>
<td>2.5 (1.7, 3.2)</td>
<td>2.3 (1.6, 2.9)</td>
<td>2.4 (1.8, 2.9)</td>
<td>-0.1 (-1.0, 0.8) p=0.42 0.1 (-0.7, 0.9) p=0.41</td>
</tr>
<tr>
<td>ARI-related healthcare visits</td>
<td>15</td>
<td>10</td>
<td>16</td>
<td>0.003 (-0.09, 0.09) p=0.47 0.05 (-0.04, 0.13) p=0.13</td>
</tr>
<tr>
<td>Mean ARI-related healthcare visits (95% CI)</td>
<td>0.32 (0.14, 0.49)</td>
<td>0.20 (0.07, 0.32)</td>
<td>0.31 (0.12, 0.50)</td>
<td>-0.01 (-0.26, 0.25) p=0.48 0.11 (-0.11, 0.34) p=0.15</td>
</tr>
<tr>
<td>Mean Non-ARI-related healthcare visits (95% CI)</td>
<td>2.15 (1.5, 2.8)</td>
<td>2.08 (1.5, 2.7)</td>
<td>2.06 (1.5, 2.6)</td>
<td>-0.09 (-0.89, 0.71) p=0.41 -0.02 (-0.80, 0.76) p=0.48</td>
</tr>
</tbody>
</table>
Conclusions:

- Mind-body behavioral trainings such as mindfulness meditation or sustained moderate intensity exercise may reduce incidence, duration and severity of cold/flu illness.

- If these results are confirmed in future studies there will be important implications for both:
  1) health-related policy & practice, and
  2) scientific understanding of mechanisms of health maintenance and disease prevention.

http://technorati.com/lifestyle/article/running-to-lose-weight