Role for Multicomponent Interventions

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Disclosures

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• Other: Speaker at
  – AUA Foundation Meeting: UI in Primary Care
  – American College of Physicians meeting through an un-restricted educational grant from Astellas
Outline

1. Significance
2. State-of-the-Art Knowledge
3. Knowledge Gaps and
4. Research Opportunities
Multicomponent Interventions: Standardized Framework

- **Multicomponent Intervention**: not a MESH term
- **Clinical Trial (Intervention Study)** are both MESH terms: . . . in which participants are assigned to receive one or more interventions
- Other modifying terms: *multifaceted; complex; behavioral plus drug*

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Definitions-
AHRQ Focus Group

• Terminology agreement around: Complex, multicomponent, health system interventional trials

• The word multicomponent, by contrast, was generally recommended by the interviewees¹

  – “I think, that the value about distinguishing multicomponent interventions are because there are questions about the interaction of the components, which components are critical and variation across the individual components, across different studies. So thinking about them and how to collect information is useful.”

Definitions - AHRQ Focus Group

• Terminology agreement around: multicomponent

• The word multicomponent, by contrast, was generally recommended by the interviewees\(^1\)
  
  — *Interaction of the components*
  
  — *Which components are critical*
  
  — *Variation across the individual components*
  
  — *How that differs across studies*

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MTOPS (α-blocker + 5-αRI) for BPH sx’s: a multicomponent intervention?

Must the interventions come from different domains? 3 or more? Include behavioral?
State-of-the-Art Knowledge

• Multicomponent interventions common
  – Smoking cessation, asthma management, reducing buzzed-driving, weight loss, HIV elimination

• Conditions with multiple, interacting risk factors
  – Geriatric conditions specifically- falls, delirium, functional dependence, urinary incontinence\(^1\), insomnia\(^2\)

• Multicomponent interventions for achieving multiple outcomes

\(^1\)Burgio et al. JAGS 2011, \(^2\)Tyagi JAGS 2014
State of Art Knowledge: Role for Multicomponent Interventions

- Conditions with multiple, interacting risk factors
- Where single intervention less effective/ineffective: delirium
  - No clear evidence on cholinesterase inhibitors, antipsychotic medication or melatonin to reduce incidence
  - Strong evidence supporting multi-component interventions to prevent delirium in hospitalised patients\(^1\)
- Targeting multiple outcomes\(^2\)

\(^1\) Siddiqi et al. Dementia and Cognitive Improvement Group. 2016
\(^2\) Wenger et al. Primary Care intervention for Falls, UI, Dementia. 2009
State of the Art Knowledge: Multiple Interacting Risk Factors

A. Linear

- Risk Factor
- Early Disease
- Advanced Disease

B. Concentric

- Risk Factor A
- Risk Factor B
- Risk Factor C
- Risk Factor D
- Clinical Phenotype

C. Interactive Concentric

- Risk Factor A
- Risk Factor B
- Risk Factor C
- Risk Factor D
- Clinical Phenotype

Modified from Decker, Sausville. Ann NY Acad Sci 2005

Geriatric Syndromes: Clinical, Research and Policy Implications of a Core Geriatric Concept

A. Linear

Hypertension ➔

Congestive Heart Failure ➔

Symptomatic Congestive Heart Failure with Nocturia
Geriatric Syndromes: Clinical, Research and Policy Implications of a Core Geriatric Concept

**B. Concentric**

- Risk Factor A
- Risk Factor B
- Risk Factor C
- Risk Factor D

Clinical Phenotype

**Nocturia**

- Nocturnal Polyuria
- Low Bladder Capacity
- Global polyuria
Geriatric Syndromes: Clinical, Research and Policy Implications of a Core Geriatric Concept

C. Interactive Concentric

Risk Factor Synergism

Risk Factor A

Risk Factor B

Risk Factor C

Risk Factor D

Targeted Interventions

Clinical Phenotype

Parent Study
(N=55)

Nocturia

0-1 episodes nocturia
(N=0)

2-3 episodes nocturia
(N=34)

4+ episodes nocturia
(N=21)

LOW bother
(N=13)

Medium bother
(N=10)

HIGH bother
(N=11)

Interaction between voiding and sleep → *bother from nocturia*

<table>
<thead>
<tr>
<th>Sleep Characteristic</th>
<th>LOW Bother (± s.d.)</th>
<th>HIGH bother (± s.d.)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to sleep (min)</td>
<td>16.1 (± 11.4)</td>
<td>28.8 (± 13.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fatigue- Morning</td>
<td>5.7 (±0.9)</td>
<td>4.7 (±0.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Higher # better*

A MULTIFACTORIAL INTERVENTION TO REDUCE THE RISK OF FALLING AMONG ELDERLY PEOPLE LIVING IN THE COMMUNITY

MARY E. TINETTI, M.D., DOROTHY I. BAKER, Ph.D., R.N., C.S., GAIL MCAVAY, M.S., ELIZABETH B. CLAUS, Ph.D., PATRICIA GARRETT, M.H.S., R.N.-C., MARGARET GOTTSCALK, P.T., MARIE L. KOCH, M.S., P.T., KATHRYN TRAINOR, M.S., AND RALPH I. HORWITZ, M.D.
Experimental Designs

- Test multicomponent interventions for multifactorial health conditions
- Identification and selection of modifiable risk factors related to the outcome of interest
  - Known risks → targeted risk factors (foot problems\(^2\), palmomental reflex\(^2\), sedative use\(^{2,3}\), polypharmacy\(^3\), hearing loss)
- Selection of intervention components to reduce the deleterious effects of the modifiable risk factors

\(^1\)Allore et al. Clinical Trials 2005; \(^2\)Tinetti NEJM 1988, \(^3\)Tinetti NEJM 1994
### Table 1 Elements of the nine illustrative multicomponent intervention trials

<table>
<thead>
<tr>
<th>Author, year (location)</th>
<th>Outcome</th>
<th>Prevalence of risk factors</th>
<th>Correlation among risk factors</th>
<th>Were risk factors grouped?</th>
<th>No. of intervention components</th>
<th>Measurement of predetermined risk factors at follow-up</th>
<th>Eligibility Treatment assignment</th>
<th>Blinded allocation and assessment</th>
<th>Sample size or power</th>
<th>Assignment of components</th>
<th>Estimated component effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinetti et al. 1999 [8] (USA)</td>
<td>Falls</td>
<td>Yes</td>
<td>Correct for in analysis</td>
<td>Yes</td>
<td>8</td>
<td>Yes</td>
<td>Restrictive Matched</td>
<td>Blinded allocation and assessment</td>
<td>Not provided</td>
<td>Standardly tailored</td>
<td>Effect of risk factor reduction</td>
</tr>
<tr>
<td>Inouye et al. 2000 [7] (USA)</td>
<td>Delirium</td>
<td>Yes</td>
<td>Not reported</td>
<td>Not reported</td>
<td>7</td>
<td>Not reported</td>
<td>Broad Randomized by physician</td>
<td>Blinded allocation and assessment</td>
<td>Provided</td>
<td>Standardly tailored</td>
<td>Effect of risk factor reduction</td>
</tr>
<tr>
<td>Beyth et al. 2000 [17] (USA)</td>
<td>Warfarin-related bleeding</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>2</td>
<td>Not reported</td>
<td>Restrictive Stratified randomization by subject</td>
<td>Blinded allocation</td>
<td>Provided</td>
<td>Standardly tailored</td>
<td>Effect of risk factor reduction</td>
</tr>
<tr>
<td>Counsell et al. 2000 [14] (USA)</td>
<td>Functional decline</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
<td></td>
<td>Broad Randomized by subject</td>
<td>Blinded allocation</td>
<td>Provided</td>
<td>Participants received all components</td>
<td>Effect of risk factor reduction</td>
</tr>
<tr>
<td>van Haastrecht et al. 2000 [15] (Netherlands)</td>
<td>Falls and impaired mobility</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>8</td>
<td>Not reported</td>
<td>Broad Randomized by subject</td>
<td>Blinded allocation</td>
<td>Provided</td>
<td>Participants received all components</td>
<td>Effect of risk factor reduction</td>
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<tr>
<td>Strandberg et al. 2001 [10] (Finland)</td>
<td>Cardiovascular disease</td>
<td>Yes</td>
<td>Not reported</td>
<td>Not reported</td>
<td>8</td>
<td>Not reported</td>
<td>Restrictive Randomized by subject</td>
<td>Blinded allocation</td>
<td>Not provided</td>
<td>Participants received all components</td>
<td>Effect of risk factor reduction</td>
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<tr>
<td>Timonen et al. 2002 [18] (Finland)</td>
<td>Strength, balance and mobility</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>7</td>
<td>Not reported</td>
<td>Broad Randomized by facility</td>
<td>Blinded allocation</td>
<td>Provided</td>
<td>Participants received all components</td>
<td>Effect of risk factor reduction</td>
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<tr>
<td>Jensen et al. 2003 [16] (Sweden)</td>
<td>Falls and injury</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>4</td>
<td>Yes</td>
<td>Restrictive Stratified randomization by subject</td>
<td>Blinded allocation and assessment</td>
<td>Provided</td>
<td>Participants received all components</td>
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<tr>
<td>Shaw et al. 2003 [9] (UK)</td>
<td>Falls and injury</td>
<td>Yes</td>
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### Elements of Multicomponent Trials

#### Table 1: Elements of the nine illustrative multicomponent intervention trials

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<td>Outcome</td>
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<td>Risk factor prevalence &amp; correlation</td>
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<td># components and assignment</td>
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<tr>
<td>Measurement of risk factors at follow-up</td>
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<td>Sample size or power</td>
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<td>Assignment of components</td>
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<td>Estimated component effects</td>
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</table>

- Outcome
- Risk factor prevalence & correlation
- # components and assignment
- Measurement of risk factors at follow-up
- Blinded allocation and assessment
- Sample size and power
- Estimated component effects
Targeting of **Multiple** Outcomes with Multiple Interventions

Proposed USPSTF Framework for multiple outcomes

1. Adults aged ≥65 y
2. Screening for multiple risk factors
3. High risk
4. Low risk
5. Adverse effects

- Home inspections
- Exercise and rehabilitation programs
- Multifactorial risk assessment and management
- Comprehensive geriatric assessment
- Medication management programs

- Improved geriatric syndromes
  - Reduced falls
  - Improved functional limitation

- Adverse effects

* Risk factors include increasing age, baseline functional impairment and limitations, incontinence, polypharmacy, medical risks, or sensory and cognitive deficits.

Knowledge Gaps

• Standardized definition, MESH term
• Methodological concerns about meta-analyses of multicomponent trials
• Which elements belong?
• How multicomponent strategies fit together (macro)- National strategy for HIV; Alzheimer’s disease
Combined Multicomponent: Vision; Goals; Indicators

Goals of the National HIV Strategy

1. Reduce New Infections
2. Increase Access to Care and Improve Health Outcomes for People Living with HIV
3. Reduce HIV-Related Health Disparities and Health Inequities
4. Achieve a More Coordinated National Response to the HIV Epidemic

### Goals → Steps: Multicomponent Interventions

<table>
<thead>
<tr>
<th>STEP 1.B</th>
<th>Expand efforts to prevent HIV infection using a combination of effective, evidence-based approaches.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.B.1</td>
<td>Design and evaluate innovative prevention strategies and combination approaches for preventing HIV infection in high-risk populations and communities, and prioritize and promote research to fill gaps in HIV prevention science among the highest risk populations and communities.</td>
</tr>
<tr>
<td>1.B.2</td>
<td>Support and strengthen integrated and patient-centered HIV and related screening (sexually transmitted infections [STI], substance use, mental health, intimate partner violence [IPV], viral hepatitis infections) and linkage to basic services (housing, education, employment).</td>
</tr>
<tr>
<td>1.B.3</td>
<td>Expand access to effective prevention services, including pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP).</td>
</tr>
<tr>
<td>1.B.4</td>
<td>Expand prevention with persons living with HIV.</td>
</tr>
</tbody>
</table>

Meta-analysis Consideration - AHRQ Framework (9 points)

• Holistic- look at effectiveness of whole bundle

• Intervention features or factors- group by components (exercise + PT); active components (home monitoring); theory; context
  – PICOTS framework (Patient population, Intervention, Comparator, Outcomes, Timing, Setting); they focus on ways of categorizing the intervention or its components, the setting, or both.

• Factors influencing success or behavior- realistic (evidence informed care), mechanism of action, configurational (needed, but not sufficient)

Choosing Multicomponent Elements

- Multiphase optimization strategy (MOST)
- Sequential experimentation with results feeding forward
- Calculated risks for speed
- Move intervention science fastest, even if slower progress in the short run
- Standardized RCT only following optimization

Research Opportunities

• MESH heading, standards
• Look at AlzDz and HIV models for overarching strategy for progress as potential model
• Collaborative efforts with behavioral scientists, implementation science
• Packaging UI/LUTS outcome measures to be integrated into other trials
  — SPRINT, LIFE, SOF
Future Research Framework

Table 3  Areas for future research and questions and issues to be addressed

<table>
<thead>
<tr>
<th>Areas for research</th>
<th>Unanswered questions and issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting of multicomponent intervention trials</td>
<td>Develop a common terminology for the elements of multicomponent intervention trials.</td>
</tr>
<tr>
<td>Study design</td>
<td>Develop reporting standards.</td>
</tr>
<tr>
<td>Study design</td>
<td>Can full or fractional factorial designs be applied to multifactorial geriatric syndromes and what</td>
</tr>
<tr>
<td>Study design</td>
<td>are their limitations?</td>
</tr>
<tr>
<td>Selection of modifiable risk factors</td>
<td>How many risk factors can be studied in a single trial?</td>
</tr>
<tr>
<td>Selection of modifiable risk factors</td>
<td>What is the minimum prevalence of a risk factor?</td>
</tr>
<tr>
<td>Selection of modifiable risk factors</td>
<td>What is an acceptable level of correlation among risk factors?</td>
</tr>
<tr>
<td>Selection of modifiable risk factors</td>
<td>How can risk factors be grouped?</td>
</tr>
<tr>
<td>Selection and assignment of intervention components</td>
<td>How many components can be studied in a trial?</td>
</tr>
<tr>
<td>Selection and assignment of intervention components</td>
<td>How to determine which risk factors an intervention may affect?</td>
</tr>
<tr>
<td>Selection and assignment of intervention components</td>
<td>How to best assign components to participants in a trial?</td>
</tr>
<tr>
<td>Selection and assignment of intervention components</td>
<td>By how much does a component need to reduce the risk of the targeted risk factor to be effective?</td>
</tr>
<tr>
<td>Sample size determination</td>
<td>How can high adherence with component assignment be achieved?</td>
</tr>
<tr>
<td>Sample size determination</td>
<td>How to determine the sample size needed to estimate component effects?</td>
</tr>
<tr>
<td>Estimation of component effects</td>
<td>How to extend sample size determination for clustered and other types of designs?</td>
</tr>
<tr>
<td>Estimation of component effects</td>
<td>What is the appropriate comparison group?</td>
</tr>
<tr>
<td>Estimation of component effects</td>
<td>What methods will provide unbiased estimates of individual component effects?</td>
</tr>
</tbody>
</table>

1Allore et al. Clinical Trials 2005
Future Research Framework

- Terminology, reporting standards
- Design issues
- Ideal # risk factors, correlation, grouping
- How many components, assignment
- Sample size, comparison group
- Effect of individual components, bundle of components

1Allore et al. Clinical Trials 2005
Recap: Multicomponent Interventions

1. Significance
2. State-of-the-Art Knowledge
3. Knowledge Gaps and
4. Research Opportunities