Discovery, Design, and Proof-of-Concept: ORBIT Phases I and IIa

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Figure 1. The ORBIT Model for Behavioral Treatment Development
## PROCESS OF DRUG DEVELOPMENT

<table>
<thead>
<tr>
<th>PHASE</th>
<th>GOAL</th>
<th>STRATEGY</th>
<th>MILESTON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>Identify candidate</td>
<td><strong>Integrate clinical need with basic science</strong></td>
<td>Biologic activity</td>
</tr>
<tr>
<td>Non-Clinical</td>
<td>Non-human safety, biologic activity</td>
<td>Animal, in vitro laboratory studies</td>
<td>FDA approval for testing in humans</td>
</tr>
<tr>
<td>Phase I</td>
<td>Human Pharmacology</td>
<td><strong>Small N, healthy, close monitoring, no controls</strong></td>
<td>Safe and biologic activity in healthy</td>
</tr>
<tr>
<td>Phase II</td>
<td>Therapeutic Efficacy</td>
<td><strong>Small N, patients, close monitoring, no controls</strong></td>
<td>Safe and biologic activity in patients</td>
</tr>
<tr>
<td>Phase III</td>
<td>Therapeutic Confirmatory</td>
<td>Randomization efficacy trial with morbidity/mortality outcomes</td>
<td>FDA permission to market drug</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Therapeutic Use</td>
<td>Long-term surveillance, no control, diverse patients</td>
<td>Optimization, refinement</td>
</tr>
</tbody>
</table>
Development of a Lifestyle Intervention for Remission of the Metabolic Syndrome:

Discovery through Proof-of-Concept
Discovery: Significant Clinical Question

Remission of the Metabolic Syndrome

Imbalance

Lifestyle → Anthropometric → Biochemical → Clinical Events

--Diabetes
--Heart Failure
--Cardiovascular Disease

LIFETIME
Discovery: Significant Clinical Question:

**Sustained Change in Lifestyle**

**Interdisciplinary Team**

**BASIC PRINCIPLES**
1. Target diet, physical activity, and stress simultaneously.
2. Real time patient discovery more powerful than education.
3. Immediate benefits more powerful than distal negative consequences.
4. Embed program into medical care.
Standard Strategy for Lifestyle Change

Discovery: Basic Behavioral Science
Standard Strategy for Lifestyle Change

Goal: Fortify

Strategy: Self-management skills

Discovery: Basic Behavioral Science

Hall & Marteaux, 2014
Problem with the Standard Strategy for Lifestyle Change
Revised Strategy for Lifestyle Change
From Neuroscience

Foerde et al., 2015
Guo et al., 2014
Schwabe & Wolf, 2009
Revised Strategy for Lifestyle Change
From Basic Neuroscience

**Desire**
- Goal: Neutralize
- Strategy: Mindfulness

**Intention**
- Goal: Fortify
- Strategy: Self-management skills

**Habit**
- Goal: Form new habits
- Strategy: Real time stimulus-response pairing

**Action**
PROCESS OF BEHAVIORAL TREATMENT DEVELOPMENT

![Diagram of the ORBIT Model for Behavioral Treatment Development](image)

**Figure 1.** The ORBIT Model for Behavioral Treatment Development

Czajkowski, Powell et al., 2015; Powell, Freedland, Kaufmann, in press
**Phase Ia: Define**

### HYPOTHESESIZED TREATMENT PATHWAY

<table>
<thead>
<tr>
<th>Component</th>
<th>Habit (“ELM Leaf”)</th>
<th>Treatment Target</th>
<th>Behavioral Risk Factor</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIET</strong></td>
<td>“Perfect Plate”</td>
<td>½ plate vegetables/day</td>
<td>Vegetable Intake (≥ 3 servings/day)</td>
<td>≥ 50% with remission of metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>“HALT”</td>
<td>Stop and breathe before emotional eating</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PHYSICAL ACTIVITY</strong></td>
<td>“Play”</td>
<td>Engage in enjoyable physical activities and notice sensory experiences</td>
<td>Physical Activity (≥ 150 min moderately vigorous /week)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Use It or Lose It”</td>
<td>30 min moderately vigorous physical activity on most days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Waste Energy”</td>
<td>10,000 steps on most days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STRESS</strong></td>
<td>“Discover this Moment”</td>
<td>Practice staying in the present while engaging in health behaviors</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>“Recognize Hooks”</td>
<td>Put time between a stressor and emotional reaction to it</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Smile First”</td>
<td>Practice kindness to self and others</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Important Trumps Urgent”</td>
<td>Prioritize an ELM hour on most days</td>
<td></td>
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</tbody>
</table>
The ELM Lifestyle Program

Central Fat

Hypertension

↑ Triglycerides

↑ Glucose

↓ HDL Cholesterol

You are invited to the ELM Dinner Club
Phase IIa: Proof-of-Concept

After 6 of intensive treatment:
- 61.5% no longer met criteria for metabolic syndrome
- Energy/vitality, social support, and depression improved
- Drug use decreased

After 2.5 years:
- 53.8% maintained remission of the metabolic syndrome
- 38.5% maintained clinically significant weight loss
- 25% no longer needed anti-hypertensive medications
- Sustained improvement in diet, physical activity, stress, mood, social support, energy/vitality.
- Metabolic syndrome remission was highly related to loss of > 5% of baseline weight

N=26
“A new treatment is born into a hostile environment. It must be kept alive in infancy. It needs to mature until it reaches a point at which it can be brought into contact with the abundance of problems that could undermine it. Scientists should protect early development; not contribute to premature death.”

Feyerabend, 1965
7-Year Follow-Up of Proof-of-Concept Participants

In those in remission at 2.5 years, at 7 years:
50% lost or stayed the same weight

What helped the most?
93%: Nutrition education
86%: Reducing emotional reactivity to stress
71%: Physical activity

Health Network
43%: Still connected with ELM friends
57%: Connected with a health conscious friend > once a week

Technology
43% Use Fitbit for health
Phase Ib: Refine

ELM Experimental Group
N=10

Physical Activity

Cooking Demonstration

Group Discussion (Share a Meal)
Phase Ib: Refine

Update Technology

Goal: 10,000 steps on most days

Goal: 30 active minutes on most days

Support from Friend

Cheer or taunt?
Just help your #FitFriends in finding their fit
## Phase Ib: Refine

### Neutralize Desire With Mindfulness-Based Habits

<table>
<thead>
<tr>
<th>AIM</th>
<th>ELM LEAF (HABIT)</th>
<th>PREPARE FOOD</th>
<th>EATING HABITS</th>
<th>PHYSICAL ACTIVITY</th>
<th>STRESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention Control</td>
<td>“Be Here Now”</td>
<td>Experience taste of salt, fat, sugar.</td>
<td>Become sensitive to emotions that trigger eating.</td>
<td>Notice judgmental thoughts during activity.</td>
<td>Experience body’s reaction to stress and relaxation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Notice smell, aroma, color of vegetables.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotion Regulation</td>
<td>“Stop, Breathe, Be”</td>
<td>Cutting vegetables cues breathing</td>
<td>Stop and breathe before opportunistic eating</td>
<td>Replace judgmental thoughts with deep breathing before activity.</td>
<td>Breathe before reacting to interpersonal “hook”</td>
</tr>
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### Phase Ib: Refine

**Enhance Efficiency While Maintaining Strength**

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<tr>
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</thead>
<tbody>
<tr>
<td>Treatment Strategies</td>
<td>Feedback, Support</td>
<td>Habit Change (added)</td>
</tr>
<tr>
<td>Number of Habits</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Wearable Technology</td>
<td>Pedometers</td>
<td>Fitbits</td>
</tr>
<tr>
<td>Cooking Demonstration</td>
<td>Full meal</td>
<td>Vegetable dishes</td>
</tr>
<tr>
<td>Stress Management</td>
<td>Variety of techniques</td>
<td>2 Mindfulness-Based Habits</td>
</tr>
<tr>
<td>Duration of Sessions</td>
<td>2.5 hours</td>
<td>1.5 hours</td>
</tr>
<tr>
<td>Health Network</td>
<td>Evolved organically</td>
<td>Fitbit-assisted connectivity</td>
</tr>
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Figure 1. The ORBIT Model for Behavioral Treatment Development
Phase IIb: Pilot

Feasibility Pilot Study (N=12)

Aims:
1. To explore feasibility at a different site
2. To explore acceptability to patients and providers
3. To determine rate of recruitment
4. To explore impact on weight and metabolic syndrome after 6 months.

Kevin Masters, PhD
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University of Colorado at Denver
SUMMARY OF THE PROCESS OF BEHAVIORAL TREATMENT DEVELOPMENT USING THE ORBIT MODEL

**DISCOVERY**
- Inter-Disciplinary Development of Concept: 1 y

**PHASES Ia, Ila**
- Define and Proof-of-Concept: 4 years

**PHASE IIIb**
- Refinement Studies: 2 y
- Feasibility Pilot Study: 2 y

**PHASE III**
- Multi-Site Efficacy Trial: 5 y

Timeline:
- 2009: DISCOVERY
- 2010: PHASES Ia, Ila
- 2014: PHASE IIb
- 2016: Feasibility Pilot Study
- 2018: Multi-Site Efficacy Trial
It takes a village . . .

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