Outline of Talk

With regard to tobacco dependence treatment research, I will:

- Discuss evidence of slow progress
- Discuss reasons for the slow progress
- Suggest theoretic and methodologic strategies that *could* enhance progress
  - These are unproven: Talk is conceptual
- and, I have nothing to declare…
So, is there a problem?

Slow progress

- There has been progress, but
  - Clinical counseling interventions for smoking
    - Types frozen in time
    - Understanding?
    - Certainty that they work?
  - How to combine counseling & pharma optimally?
  - Cessation rates set in stone

Why?

- Research methods are often inefficient
- Lack of integration of research & theory
SOP

SOP Methods

- E.g., an RCT/CET with 2-3 groups; e.g.,
  - **Study 1: Medication focused**
    - Drug A + behavioral counseling
      (support, skill training+adherence, contracting, relaxation, pamphlet…….)
    - Drug B + behavioral counseling
    - Placebo + behavioral counseling
  - **Study 2: Behavioral RX: focused**
    - NRT + Aggressive behavioral intervention
      - MI training, mindfulness/acceptance, skill training, withdrawal exposure, social support
    - NRT + Contact-matched Usual Care
SOP Measures

Primary outcome = 6 month point-prevalence

- Whether someone is smoking 6-months post-treatment
  - Plus additional smoking outcome measures: survival, continuous abstinence

- Some measures of the usual suspects (putative mechanisms): self-efficacy, withdrawal, affect, perceived interpersonal support, stress
  - To assess potential mechanisms: e.g., urge suppression, coping skill execution
Virtues of SOP

Design: RCT’s have strong virtues

- When unconfounded, permit strong inferences about causality with regard to manipulated interventions
- Have the capacity to test whole, integrated packages of intervention components such as would be used in real world: **net effects of components**
- Staff have to master only a small # of different treatments combinations (e.g., 2-3)
Outcome: 6-month point prevalence

- Has vital public health value:
  - Is strongly related to even longer abstinence--screens out evanescent effects
  - Long-term abstinence indexes disease risk reduction

Adjunct measures

- Can reflect effects of a treatment package on a broad range of functioning
SOP: Accentuate the Negative

Inefficient

- Each study takes 3-4 years to test differences amongst 2-3 treatment packages
  - Does not promote programmatic tests of individual treatment components
    - To isolate a single intervention component you need a whole study arm (of 2 or 3)
  - We keep swinging for the fences with multicomponential block-buster packages — “Let’s make sure something in our package works!”
SOP Limitations (cont.)

Insensitive outcome measures

- A strength is the public health relevance, a weakness is insensitivity
  - Distal measure (6-month follow-up)
    - When do treatment effects occur? (Jorenby et al., JAMA, 2006, vol. 296)
    - What causes abstinence to change after this?
    - Virtually no one has shown that treatment affects the future trajectory of relapse
    - Binary measures constrain power
  
- We should be clear about what we are trying to do: forecast future disease risk or detect treatment effects?
Brief individual counseling trial

Cumulative survival vs Days post-cessation

- Dashed line: Active patch
- Solid line: Placebo patch
SOP Limits on Theory

- **SOP:** Where do our hypotheses come from?
  - 4 sessions work well, how about 8?
  - Sessions over 2 months work well, how about if we extend them for 6 months?
  - Let’s try one more element in the package!

- **Such pragmatic hypothesis are not accidental:**
  - RCT’s are not ideal for theory testing & development
  - Because each experimental arm is so costly, we do not systematically test intervention components
  - Ergo: behavioral counseling has grown-up like Topsy
SOP Limitations (cont.)

Why aren’t RCT’s good for theory testing?

- Limited by inefficiency
- Can’t test interactions amongst elements of a package
  - Contracting vs. MI????
  - Limited by design & use of multicomponential treatments encouraged by inefficiencies
- Are a poor platform for testing mediation
SOP Mediational Model

X -> M -> Y

X: Mindfulness, skill training, relaxation, distress tolerance, adherence, support

M: Rated Perceived Support

Y: 6-month Point Prevalence
Consequences of Barren Theory

SOP’s discourage theory integration & this has profound effects

- Insensitive measures: generic vs. theoretically tuned
- Don’t know where to go next
  - When a treatment doesn’t work, what do we do?
  - When it works?: Dismantling?
- We have trouble validating our model of treatment
- Because we do not test our theories strongly, we have not refined them or generated new, more powerful theories
Methods: Beyond SOP

Linda Collins’ MOST approach
(Multiphase Optimization STrategy)

- Based on engineering research principles
  - More efficient designs
  - Programmatic/sequenced approach to intervention development across repeated experiments
  - Permits more specific tests of mechanism
More Efficient Designs

Use of Factorial Designs

- Each person is randomized to an **on or off condition** of each tested intervention component.

- Thus, each person is used to evaluate every intervention component.
  - But, the testing of multiple components yields multiple combinations of interventions.

- Allow the tests of intervention main effects & interactions.
**Design of One Study**

<table>
<thead>
<tr>
<th>Condition Status</th>
<th>Patch</th>
<th>Gum</th>
<th>Counseling</th>
<th>In-Person Counsel.</th>
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Random assignment to all conditions in a fractional factorial design results in…….
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<th>Precessation Medication Type (Ad Lib NRT vs. none)</th>
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</table>
Is it Efficient?

Alternatives for 6 intervention components

- 6 separate RCT’s
  - Rx1 vs. control, Rx2 vs. control, Rx3 vs. control, etc.

- 1 Comparative effectiveness experiment
  - 1 study with 1 control condition compared with 6 different intervention components
## Comparison of Features of Design Alternatives

### Table 2

<table>
<thead>
<tr>
<th>Design</th>
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<th>Number of Experimental Conditions</th>
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</table>
Limitations of a Factorial Design

- Do not allow powerful testing of **packages** of intervention components
- Components are not tested against a single, uniform condition (e.g., Usual Care/placebo)
  - but instead against an abstraction: all other conditions statistically controlled
- This calls for iterative rounds of sequential experiments using
  - Factorial designs to **screen** interventions
  - Factorial designs to “**Refine**” them
  - RCT’s or comparative effectiveness studies to test packages vs. meaningful comparators (e.g., placebo, usual care)
  - Start all over again: the “Optimization Cycle”
Enhanced Methods ➔ Theory

Methods often fuel theory:
- Leeuwenhoek’s microscopes & animalcules
- Wet-form X-ray diffraction images of purines/pyrimidines

“MOST” methods allows for theory development
- More efficient experiments permit sequential tests of specific components
- Theories of synergies and subtractive interactions
- Isolating individual components permits more specific tests of mechanism

But, such affordances call for theoretical development
- Not just for individual intervention components
  - E.g., Pharmacotherapy eases withdrawal
- But, also meta-theory to guide the tests and assembly of multiple interventions
  - Which interventions will work together when, why, & with whom
Our Approach: Phase Based Framework

Most any behavior change involves different phases that each offer different challenges and opportunities.

Smoking

- The disinterested/happy smoker
- The ambivalent smokers
- The interested/motivated smoker
- The quitting smoker
- The successful/struggling smoker
- The lapsing smoker
- The relapsed smoker
- The happy quitter

Odds that a single intervention will be effective for each?
Phase Based Framework (cont)

How to assemble optimal, coordinated interventions & apply extant theories more effectively:

- Evaluate the challenges posed at each cessation phase
- Identify interventions that might address principal challenges at each phase: based on the putative mechanisms activated by each treatment
- Apply the intervention at the appropriate phase
- Sensitively measure the targeted intervention effects on potential mediators and outcomes
  - With measures selected based on the phase-based challenge, the intervention, the mechanism
Phase-Based Framework to Guide the Testing & Building of Smoking Interventions

![Longitudinal Phase-Based Model of Intervention](image-url)
<table>
<thead>
<tr>
<th>Phase</th>
<th>Exemplar Challenges</th>
<th>Exemplar Intervention Components</th>
<th>Exemplar Measures of Mechanism</th>
<th>Exemplary Treatment Selection Measures</th>
</tr>
</thead>
</table>
Advantages of this Meta-Model

Each intervention component is evaluated based on specific intended actions

Assessment

- Tilt towards sensitivity vs. public health
- Specific to type and timing of intervention effects
  - E.g., Precession treatment is intended to affect early withdrawal and initial cessation: Therefore, tested with smoking in 1st 2 weeks
  - Guiding principle: the best treatment will comprise the components that are most effective at each phase
  - Targets both outcomes and mediation—are the treatments working as per our treatment model
MOST Mediational Model

X
Precessation
NRT
Vs.
No Precessation
NRT

M
PostQuit
Withdrawal
Craving

Y
Smoking
Heaviness
at 2-wk
Postquit
Is this the Stages of Change Theory?

Yes & No

- Clearly similar to it & inspired, in part, by it
- But, the Phases Framework is not a theory: e.g., no obligatory “processes of change”
- It is only a framework: “just add theory”
- Not intended to capture core elements of all theories of behavior change
- The “contents” of the framework may come from anywhere - - and should change with disorder
3 Other Methodologic Features

- All the research occurs in PCC’s
  - We wanted to achieve the goals of efficacy research within the context of effectiveness research
- Too much information: Designing new methods of intervention component selection
- Need technologic integration to support the efficient deliver of so many intervention combinations \((2 \times 2 \times 2 \times 2 \times 2 \times 2)\) for 6 components, full factorial
How do you do it?

Technology allows

- It does appear to be feasible!
  - EHR prompts MA to identify smokers and deliver recruitment script (records performance)
  - Telephonic consent, assessment, and induction
  - CITRIX prompts, guides, & times each case manager/intervener via internet connected laptop to deliver the correct treatment combination to each patient
  - CITRIX collects proper assessment information telephonically at proper time-point (real time symptoms etc via IVR)
  - Helping Hand gathers real time assessment of NRT use
  - Telephonic delivery of interventions
Conclusion

“Why are our handle bars like this?”

Need to constantly question research SOP’s

- Should try to move in the direction of
  - More efficient designs
  - More sensitive measures that are psychometrically sound but “purpose built”
  - Sequential, programmatic cycles of experiments that gradually build optimal interventions that are ultimately tested in RCT’s
  - Better use of technology to facilitate the above
Relevant Articles


Phase Based Model

Specific content not important—only the purposes it attempts to serve.

The phases can be somewhat arbitrary, but are selected to aid treatment development and testing (the proof of the pudding).

- Do they correspond to real somewhat distinct challenges that have implications for:
  - types of treatments that should be used at each phase
  - Assessments for each phase-intervention pairing
Summary: Methodologic Improvements that Foster Theory

More efficient Experimental Designs

More sensitive and strategic assessments

- Timing and nature of assessments designed to enhance sensitivity to **effects of specific interventions for specific purposes**
  - Ideal for mediational analyses
- Use of **short-term surrogate outcomes** for greater efficiency
  - David Kessler on Cancer vs. AIDS research efficiency (viral load)

Mediatational analyses focus on individual intervention components

+ Leaping the translation gap

- Translation often requires 15-20 years for behavioral interventions
- Testing treatments in effectiveness context
- Using technology to evaluate and delivery treatments
Table 2

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E.g., Precession

Timing: 2-3 weeks prequit??

Challenges: the person is highly dependent, and is unprepared.

Opportunities: reduce dependence via smoking reduction, replacement of cigarettes w/NRT, elimination of smoking in key contexts, practice of coping, exposure to withdrawal via practice quit attempts

Measurement implications:
- Assess dependence, withdrawal severity, coping skills pre- & early post-quit
- Cessation early in the course of the quit attempt
Cessation

Withdrawal motivational challenge

- **Timing**: 1st 2 weeks
- **Challenge**: major determinant of lapses/relapse within 2 week period
- **Opportunity**: can be effectively reduced via medications
- **Measurement implications**: 2 week measures of
  - Withdrawal symptoms, anhedonia, conditioned withdrawal reactions
  - **Short-term** cessation

Full model: ……