



Insomnia: Key Questions to be Answered by Large Clinical Trials and Feasibility

Charles M. Morin, Ph.D.
Université Laval, Québec, Canada

Outline

- What considerations should guide the decision to conduct single vs. multi-site clinical trials?
- Major research questions that are best addressed by large multi-centre trials
- Methodological challenges

What Considerations Should Guide Our Decision To Conduct Single vs. Multi-Site Insomnia Research?

- Feasibility (availability of resources, patients)
- Expertise
- Timeliness of a research question
- Nature of research question
 - Epidemiology – prevalence, risk factors, natural history, morbidity
 - Etiology and mechanisms
 - Treatment efficacy vs. effectiveness

From Laboratory to Health-Services Research

Efficacy

Research subjects
Solicited
Stringent

University/
research center
Highly controlled

Narrow end
points



Effectiveness

- Sample
- Recruitment
- Selection criteria
- Treatment
 - Setting
 - Implementation/
monitoring
- Outcome
Assessment

Clinical patients
Unsolicted
Fairly liberal

Clinical practices
Treatment as
usual

Broad outcome
assessment

NIH State-of-the-Science Conference on Manifestations and Management of Chronic Insomnia

- Treatments endorsed by NIH for chronic insomnia:
 - Cognitive Behavioral Therapy
 - FDA-approved benzodiazepine receptor agonists (at least for short-term use)
- Treatments not endorsed for insomnia (due to limited efficacy data and/or safety concerns):
 - Complementary and alternative medicines
 - Antihistamines (OTC and prescription)
 - Antidepressants
 - Antipsychotics

Current State of Evidence on Insomnia Therapies

- CBT and hypnotic medications (BzRAs) are efficacious for short-term treatment of chronic insomnia
- Sleep changes well sustained over time with CBT, but little evidence of long-term efficacy with medication
- Despite high rates of treatment responders, few patients achieve complete remission with any single treatment
- Little evidence of generalizability of treatment outcomes

National Institutes of Health. State-of-the-Science conference statement on the manifestations and management of chronic insomnia in adults. *Sleep* 2005; 28:1049-57.

Morin CM et al. Psychological and behavioral treatment of insomnia: Update of the recent evidence (1998-2004). *Sleep* 2006; 29:1398-1414.

Generalizability of Outcome Evidence

- Patients: Most studies conducted with solicited, young, otherwise healthy, unmedicated, primary insomniacs
 - Small sample size in CBT studies (mean sample size = 60)
 - Limited evidence with older adults, comorbid insomnia, chronic hypnotic users
- End Points: Outcome documented primarily with narrowly defined end points (SOL, WASO, TST)
 - Little evidence of improved daytime functions, reduced morbidity
- Trajectory of Changes: Outcome usually measured over brief intervals, with short-term or no follow up data
 - Median tx duration of 7 days for drug studies (Nowell et al., 1997)
- Treatment Implementation: Typically implemented in highly-controlled university/research settings
 - Limited information on “Treatment As Usual”, as implemented in clinical practices

Major Research Questions

(Medication and Cognitive-Behavior Therapy)

- Which treatment works best for what patient?
- What should be our first-line therapy in the management of insomnia?
- How best to proceed with second-stage therapy for those who fail to respond to initial therapy?
- How generalizable are treatment benefits to patients with comorbid medical and psychiatric illnesses?
- What are the short- and long-term effects of treating comorbid or residual insomnia in MDD, GAD, PTSD?
- Relative cost-effectiveness of CBT and medication

Major Research Questions

(Pharmacotherapy)

- What is the long-term efficacy of BRAs medication (or other hypnotic agents)?
- How effective/safe are sedating antidepressants in treating insomnia?
- What are the risks/benefits of over-the-counter (antihistamines) and complementary and alternative medicines (e.g., herbal/dietary supplements)?

Major Research Questions

(Cognitive-Behavior Therapy)

- How effective/feasible is CBT in primary care medicine?
- What are the active/specific therapeutic components of CBT (e.g., curtailment of time in bed, change in sleep beliefs, reduction of worries) ?
- What are the most cost-effective treatment implementation methods (individual vs. group therapy, self-help approaches, internet)

Combined Hypnotics and CBT

(Unresolved/controversial issues)

- Should we integrate behavioral/pharmacological approaches in the management of insomnia?
- What is the evidence supporting combined therapies relative to monotherapies?
- Does medication enhance or impede CBT long-term outcome?
- How can we best integrate these approaches (treatment dosage, duration, sequencing)?

Methodological Challenges in Multi-Site Clinical Trials (Quality Control)

- Communication, management, leadership
- Accountability and engagement of all sites/investigators
- Standardization of assessment and treatment procedures across sites
- Data integrity and safety monitoring
- Use of centralized resources for:
 - Training and monitoring assessors/therapists
 - PSG scoring
 - Data management (CRF, shared data website)
 - Data and safety monitoring board

Benefits and Advantages of Multi-Site Clinical Trials

- Feasibility (larger sample size)
- Speed of patient recruitment
- Broader generalization
- Making effective treatment available more rapidly to patients
- Opportunities for collaboration with colleagues, for gaining additional expertise, joint publications and for research training for students and fellows

Summary and Conclusions

- Insomnia is a prevalent public-health problem with significant burden for the individual and society
- There are efficacious/effective therapies available, yet insomnia remains for the most part untreated
- There is limited evidence on the effectiveness of these therapies for comorbid insomnia, for treating insomnia in primary care, and on long-term outcomes
- Large, multi-site clinical trials, could provide useful information on these questions