MEASURING SLEEP QUALITY

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OVERVIEW

- Defining “Sleep Quality”
- Utility of Measuring “Sleep Quality” in Clinical Trials
- Methods for measuring “Sleep Quality” in Clinical Trials
- Key Unresolved Issues and Future Directions.

Defining “Sleep Quality”: No Standard Definition

- Overall summary of sleep
  - May include sleep time, sleep latency, awakenings, wake time
  - May include sleep disruptive events such as arousals, apneas, etc
  - Score on the Pittsburgh “Sleep Quality” Index
- Domain of objective indices other than polysomnographic sleep onset latency (SOL), awakenings, wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE%)
  - These have plausible self-reported correlates
  - What is the self-report correlate of slow wave sleep percentage?
- Rating of the aspect of sleep experience orthogonal to “Quantity”
  - Commonly included in sleep diaries
  - Single item on the Pittsburgh “Sleep Quality” Index

The Problem of Defining Sleep Quality

- Definition for the purposes of this talk: What you get in response to: “Rate the Quality of Your Sleep”
- Use of measures to assess sleep onset and maintenance are well-established and accepted by FDA and are necessary for indications for either or both. Been used repeatedly successfully as outcomes for trials leading to FDA approvals with these indications. No need to review here.
  - Onset: PSG-Latency to persistent sleep, Self-Report-diary-based sleep onset latency
  - Maintenance: PSG-WASO, WASO-6; Self-Report-diary-based WASO, in one case they accepted total sleep time
- Goal of this talk: Examine physiologic correlates of Sleep Quality ratings

Why Care About Sleep Quality?

- Ratings of Quality can vary independently of other ratings of sleep
  - May help characterize some aspects of sleep experience
- Correlations of Quality with other diary ratings for 292 nights in 124 subjects (60 Normals; 64 Insomnia)

SOL	TST	WASO
-0.48	0.45	-0.53

Krystal et al., Sleep. 2007;30:A237

Why Care About Physiologic Measures of Sleep Quality?

- Currently accepted objective indices of sleep quantity (SOL, TST, Awakenings, WASO) don't explain peoples' experiences with their sleep
  - Example: 37-50% of those with insomnia cannot be differentiated from normals with these indices[1-4]

1.Carskadon et al., Am J Psychiatry. 1976;133:12:1382-1388; 2.Coleman et al., JAMA. 1982;247(7):997-1003; 3. Frankel et al. Arch. Gen. Psychiatry.1976;33:615-623.4. Krystal et al., Sleep. 2002;25:630-640.

Potential Measures

- Polysomnogram scored as specified by AASM Scoring Guidelines
  - TST, SOL, WASO, Awakenings, Stage1, Stage2, SWS (Slow-wave Sleep), REM, REM Latency, Apneas/Hypopneas, Periodic Movements of Sleep etc.
- While extremely valuable for many applications, provides a limited picture of the physiology of sleep

AASM. AASM manual for scoring sleep and associated events. Version 2.6.

Sleep Stages?

- There has long been significant interest in slow-wave sleep (N3) or REM time or percentages of total sleep time as indicators of quality
- No clear relationship between these indices and self-reported sleep measures including sleep quality has been seen in clinical trials
- Examples:
  - Tiagibine, GABA reuptake inhibitor, significantly increased slow-wave sleep (N3) and decreased Stage 1 (N1) without affecting any sleep self-report measures.
  - Gaboxadol, extrasynaptic GABA-A positive allosteric modulator, significantly increased N3 in 2 studies without having a significant effect on sleep quality ratings.
  - APD125, selective 5HT2A antagonist significantly increased N3 without significantly improving quality ratings.

Walsh JK, Perlis M, Rosenthal M, Krystal A, et al., . Tiagabine increases slow-wave sleep in a dose-dependent fashion without affecting traditional efficacy measures in adults with primary insomnia. J Clin Sleep Med. 2006 Jan 15;2(1):35-41. Lankford et al,. Sleep. 2008 Oct;31(10):1359-70. Rosenberg et al.,. Sleep. 2008 Dec;31(12):1663-71. \

Data Reduction Involved in Standard (AASM Guidelines Based) Scoring of PSG

- Brain: Over 100 billion neurons;[1] 15 quadrillion bits of data in 30 seconds = 15 Petabits
  - Gross over-simplification – each one is either on or off with a refractory period of 0.2 msec
  - In 30 seconds corresponds to 150,000 bits/neuron
- PSG: 30 seconds = 4.32 Megabits
  - 12 channels sampled at 500 Hz with 24 bit resolution
- Scored Epoch of PSG: 5 bits
  - Wake, Stage1, Stage2, SWS or REM represents 3 bits
  - Add 2 additional bits for binary possibility of respiratory event or periodic movement of sleep in that 30 seconds

Scientific American Book of the Brain. New York: Scientific American, 1999: 3.

Other Potential Measures

- Non-REM EEG Spectral Power
  - Correlated with Sleep Quality ratings only in insomnia subgroup that tended to under-estimate sleep time vs PSG
- CAP
- Others?

Perlis et al., Sleep. 2001 Feb 1;24(1):110-7. Krystal et al., Sleep. 2002 Sep 15;25(6):630-40. Terzano and Parrino. Sleep. 1992 Feb;15(1):64-70. Acebo and LeBourgeois. Respir Care Clin N Am. 2006 Mar;12(1):23-30,

Problem for Potential Measures of Sleep Quality

- Self-report measures tend to be highly correlated
  - May correlate with non-sleep factors
  - Correlation of Mood ratings (average of 4 assessments) with non-concurrent sleep-log derived TST, SOL, WASO, Quality (292 nights in 124 subjects; 60 Normals; 64 Insomnia)

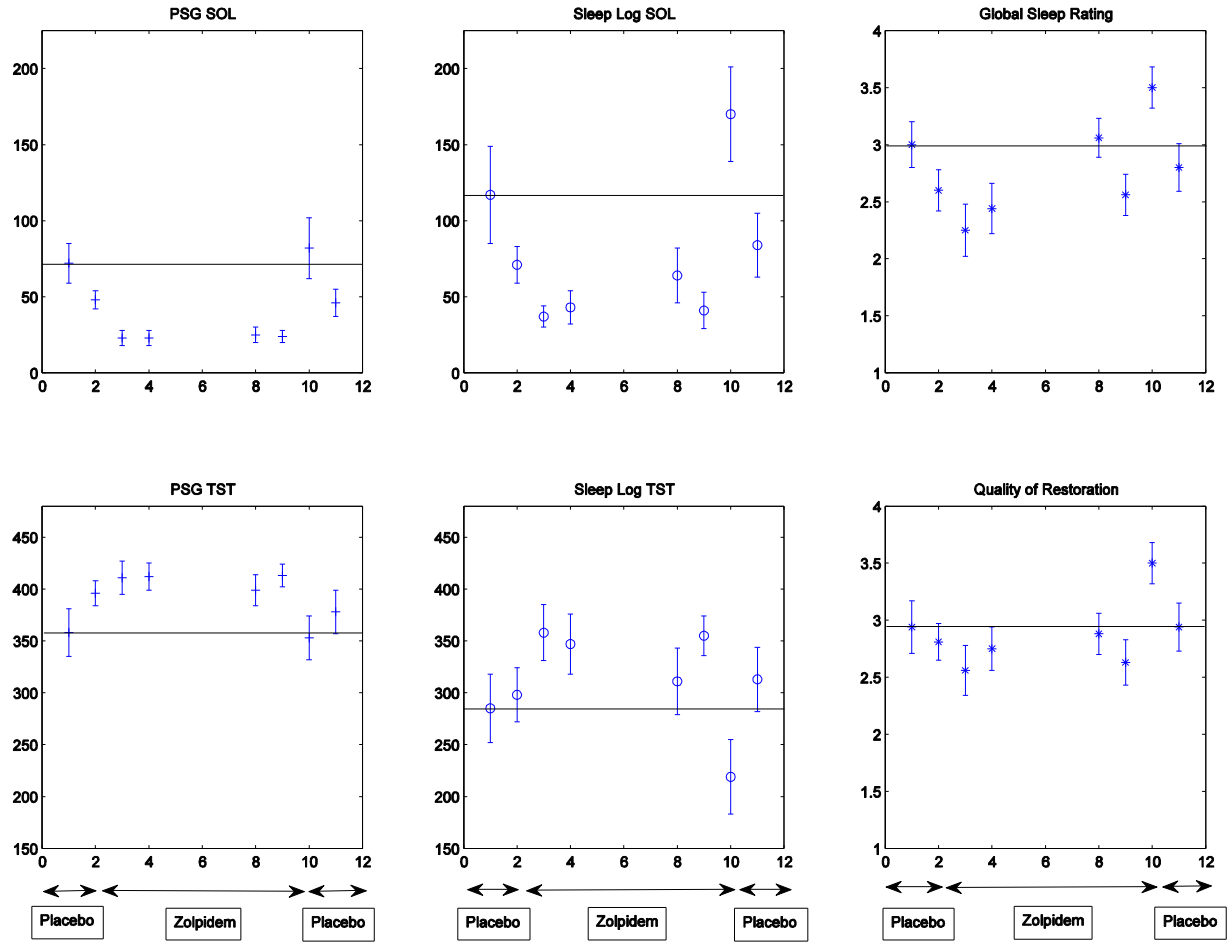
SOL	TST	WASO	Quality
-0.15	0.18	-0.25	0.26

- It is unlikely that a global rating of the quality of sleep will be consistently related to a single physiologic aspect of sleep
  - Consider: Patient with sleep onset insomnia vs patient with sleep maintenance insomnia

Krystal et al., Sleep. 2007;30:A237

PSG vs Self-Report Assessment of Sleep Self-Ratings Tend to Be Highly Correlated

Treating Sleep Onset Difficulty: Quality Ratings Mirror PSG and Log SOL



Data from Kryger et al., Sleep. 1991;14:399-407

Study Assessed Ability To Predict Sleep Quality Ratings with All PSG-Derived Measures

- Included data from two randomized, double-blind, three-month trials of suvorexant and placebo in 1158 patients with insomnia (65% female, mean age 56.4) and two randomized,double-blind,1-month trials of gaboxadol and placebo in 903 patientswith insomnia (63% female,nmean age 57.5)
- Overnight 8-h PSG included for baseline (with placebo) and then after dosing on multiple nights during treatment.
- Best predictor for both suvorexant and gaboxadol studies was total sleep time which accounted for 14% of variance.
  - Magnitude of correlation between each PSG parameter and quality ratings generally increased with the strength of their associations with TST

Svetnik et al.,. How well can a large number of polysomnography sleep measures predict subjective sleep quality in insomnia patients? Sleep Med. 2020 Mar;67:137-146. .

We Carried Out A Similar Analysis In Untreated Healthy Controls and Insomnia Patients

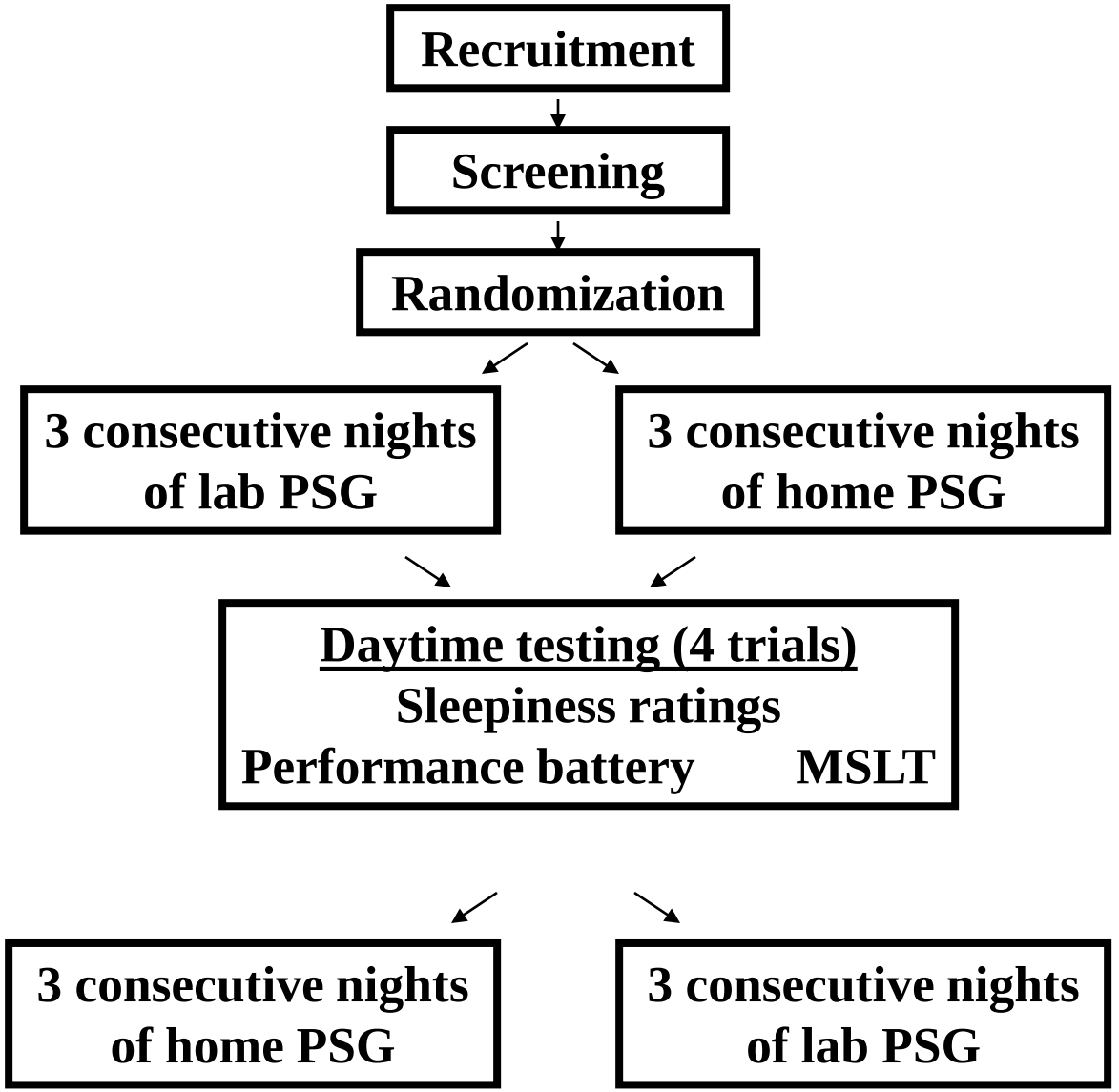
- Evaluated multiple regression of PSG indices with Quality Ratings with the standard set of objective PSG-derived measures plus non-REM Sleep spectral measures
  - TST, LPS, WASO, SE% Stage 1%, Stage 2%, SWS %, REM %, REM Latency
  - Non-REM EEG Relative Spectral Power
    - δ,α,σ,β,γ

Study Patient Population

- 64 Primary Insomnia Patients
  - Met criteria for PI
  - No evidence of other sleep disorder
  - No evidence of sleep-disruptive co-morbid condition
- 60 Normal Sleepers
  - No evidence of sleep complaints or sleep disorder
  - No evidence of sleep-disruptive co-morbid condition
- Subject screening
  - Structured sleep and psychiatric (SCID) interviews
  - Medical exam + thyroid
  - 2 nights of PSG to R/O OSA

Krystal et al., Sleep. 2007;30:A237

Study Design



Krystal et al., Sleep. 2007;30:A237

Demographics and PSG Data

	Primary Insomnia	Normal Sleepers
N	64	60
Age (years)	47 (17)	40 (16)
PSG TST (min)	387 (68)	395 (64)
PSG SOL (min)	28 (30)	20 (30)
PSG WASO (min)	44 (36)	33 (35)
PSG SE%	85 (11)	85 (10)
Quality (1-5)	3.0 (0.9)	3.6 (0.9)

Krystal et al., Sleep. 2007;30:A237

Relationship of PSG Measures with Quality Rating (N=124; 292 Nights of PSG)

Group	Total R^2	Stage 1%	Stage 2%	SWS %	REM %	REM Latency	LPS	TST	WASO	SE %	δ	α	σ	B	Γ
All Subjs	0.09		*	*			*	*	*	*					

Stage1% = Percentage of Stage 1 Sleep; Stage2% = Percentage of Stage 2 Sleep; SWS% = Percentage Slow Wave Sleep; REM% = Percentage REM Sleep; LPS = Latency to Persistent Sleep; TST=Total Sleep Time; WASO=Wake After Sleep Onset; SE%=Sleep Efficiency (Total Sleep Time/Time in Bed); δ=Delta non-REM EEG Relative Spectral Power; α= Alpha non-REM EEG Relative Spectral Power; σ Sigma non-REM EEG Relative Spectral Power; B= Beta non-REM EEG Relative Spectral Power; Γ= Gamma non-REM EEG Relative Spectral Power

Only correlations significant at $p<0.05$ are included in the table *$r<0.3$; **$0.3<r<0.5$; ***$r>0.5$

Conclusions

- Very little of the variance in Sleep Quality ratings is explained by the objective measures studied
- It will be important to study how other potential measures might relate to quality ratings: actigraphy, CAP, etc.
- It is unclear what sleep quality ratings are reflecting. They are correlated with other self-rated measures of sleep but have no physiologic correlate.
  - Preliminary data from our lab suggests that individuals are taking into account different aspects of sleep when they do these ratings
    - For a person with sleep onset difficulty, they reflect their ability to fall asleep, for a person experiencing “light sleep” they reflect sleep depth, for an individual with difficulty staying asleep they are dominated by their experience with sleep maintenance.
- It is not surprising that these ratings are not accepted as a study endpoint by FDA as a basis for an indication

Conclusions

- Should we reserve “Quality” specifically for the circumstance where subjects are instructed to rate the aspects of sleep other than the amount of sleep obtained and the ability to fall and stay asleep?
  - Unlike psychiatric conditions like depression, the FDA requires a physiologic correlate for any sleep outcome measure to provide assurance that it is reflecting some aspect of sleep.
    - Can this change?
      - Only if it can be shown that what is being measured is orthogonal to other aspects of sleep and sleep quality ratings are not.
      - Only if it can somehow be convincingly demonstrated that it is linked to sleep

Conclusions

- A measure that reflects different things in different people is problematic
  - If used, specifically instruct subjects to consider all aspects of their sleep experience and specifically list them
    - Total amount of sleep, difficulty falling asleep, staying asleep, depth of sleep etc
  - Call this something other than “Sleep Quality”: Global Assessment of Sleep?