

Objective and Subjective Measurement of Sleep in Clinical Trials

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Disclosures

- Adam Savitz is the Chief Medical Officer of Alto Neuroscience and holds equity in the company
- Adam Savitz is a former employee of Janssen Research & Development, a Johnson & Johnson company and owns stock in Johnson & Johnson.
- The opinions expressed in this presentation are Adam Savitz's. Neither Alto Neuroscience nor Janssen R&D reviewed the presentation.

Why measure sleep in MDD?

- Sleep problems are common in many psychiatric disorders.
 - Major Depressive Disorder (MDD) is being used as an example in this presentation.
- In MDD, 60-70% of patients have sleep problems, most often insomnia (trouble sleeping) but sometimes hypersomnia.
 - In most studies, it is the second most common symptom after depressed mood.
- Patients with sleep problems and MDD will often take longer to recover and have more disability.
- Additionally, for patients in remission from MDD, sleep problems are often an early symptom of pending relapse.

Objective Measures of Sleep

- Polysomnography is usually considered the gold standard for measuring sleep
 - Rarely done in clinical practice to assess sleep (such as for insomnia symptoms or sleep problems in MDD) unless sleep apnea or other sleep disorder is suspected
 - Relatively expensive and significant burden (multiple overnights in a sleep center) to participants
- Actigraphy measures movement and so is an indirect measurement of sleep
 - Studies in MDD have used just actigraphy though modern wearables often include heart rate to improve accuracy and allow sleep stages
 - Lower burden to the participant though not all people can tolerate wearing them (particularly larger devices) at night.

Comparing Polysomnography and Actigraphy

- American Academy of Sleep Medicine recommends the use of actigraphy for insomnia disorder as well as other sleep disorders.
 - In a meta-analysis, they reported that “actigraphy provides objective data this is consistent with PSG” (Smith et al 2018)
- McCall & McCall (2012) compared polysomnography, actigraphy, and sleep logs in patients with insomnia and MDD (average age 41, ISI-20.5, HDRS24-27) and showed good correlation between the two objective measures.

Variable	Acti (minutes)	PSG (minutes)	Mean Difference	Pairwise comparison
SLO	24.2	28.4	4.19 (NS)	0.31 (p<0.05)
LPS	24.2	35.2	11.0 (p<0.05)	0.44 (p<0.001)
SE	82.7	80.7	2.0 (NS)	0.48 (p<0.001)
WASO	61.2	61.1	0.1 (NS)	0.59 (p<0.001)
TST	122.4	127.5	15.0 (NS)	0.54 (p<0.001)

Patient Reported (“Subjective”) Measurement of Sleep

- Syndromal measures of insomnia
 - Examples include the Leeds Sleep Evaluation Questionnaire (LSEQ), Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), and PROMIS-Sleep Disturbance (SD)
 - The PSQI and ISI can be used to diagnose insomnia.
- Scales reporting daytime problems due to poor sleep such as the Epworth Sleeping Scale and the PROMIS-Sleep Related Impairment
- Daily Sleep Diaries including the Consensus Sleep Diary report details of sleep from the patient’s perspective.

Examples: ISI and CSD

For each question below, please circle the number corresponding most accurately to your sleep patterns in the **LAST 2 WEEKS**.

For the first three questions, please rate the **SEVERITY** of your sleep difficulties.

1. Difficulty falling asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

2. Difficulty staying asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

3. Problem waking up too early in the morning:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

4. How **SATISFIED/DISSATISFIED** are you with your current sleep pattern?

Very Satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood).

Not at all Interfering	A Little Interfering	Somewhat Interfering	Much Interfering	Very Much Interfering
0	1	2	3	4

6. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	A little Noticeable	Somewhat Noticeable	Much Noticeable	Very Much Noticeable
0	1	2	3	4

7. How **WORRIED/DISTRESSED** are you about your current sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

Today's date	4/5/11
1. What time did you get into bed?	10:15 p.m
2. What time did you try to go to sleep?	11:30 p.m
3. How long did it take you to fall asleep?	55 min.
4. How many times did you wake up, not counting your final awakening?	3 times
5. In total, how long did these awakenings last?	1 hour 10 min.
6. What time was your final awakening?	6:35 a.m.
7. What time did you get out of bed for the day?	7:20 a.m
8. How would you rate the quality of your sleep?	<input type="checkbox"/> Very poor <input checked="" type="checkbox"/> Poor <input type="checkbox"/> Fair <input type="checkbox"/> Good <input type="checkbox"/> Very good
9. Comments (if applicable)	I have a cold

Comparing Consensus Sleep Diary and ISI

- Baseline data from a MDD trial
- ISI of 15 is considered the cutoff for moderate insomnia.
- Participants with higher ISI had more subjective problems with falling asleep, waking up after sleep onset, and total sleep.

Subjective ratings from CSD	ISI \geq 15 patients mean (SD) N=54	ISI<15 patients mean (SD) N=32
SOL (minutes)	58.5 (42.20)	42.6 (43.23)
Number of Awakenings	2.6 (1.27)	2.0 (1.31)
WASO (minutes)	60.6 (53.13)	28.5 (31.00)
TST (minutes)	339.6 (109.16)	406.6 (123.57)

Abbreviations: SOL – sleep onset latency; TST - total sleep time; WASO – wake after sleep onset

Comparing Polysomnography and Sleep Diaries

- In the American Academy of Sleep Medicine (Smith et al) reported large differences between PSG and sleep diaries in a meta-analysis and that objective measures were “unique from patient reported data”
- McCall & McCall showed larger differences between PSG and sleep diaries than PSG and actigraphy with lower correlations

Variable	Diary (minutes)	PSG (minutes)	Mean Difference	Pairwise comparison	ACT-PSG Difference
SLO	64.3	28.4	35.8 (p<0.001)	0.31 (p<0.05)	4.19 (NS)
LPS	64.3	35.2	29.1 (p<0.001)	0.44 (p<0.001)	11.0 (p<0.05)
WASO	85.4	61.1	24.3 (p<0.05)	0.59 (p<0.001)	0.1 (NS)
TST	333.1	387.5	54.3 (p<0.001)	0.54 (p<0.001)	12.8 (NS)

Comparing Actigraphy and Sleep Diaries

- Kung et al studied two weeks of sleep diaries vs actigraphy in depressed subjects
- The only measure that correlated was total time in bed
- Commonly, self-reports report much longer latency to sleep than objective measures and poorer sleep efficiency and lower total sleep time

Table 1: Comparisons of Sleep Parameters by Using the 2-Week Daily Sleep Log and Wrist Actigraphy (N=30)

	2-wk daily sleep log	Wrist actigraphy				
Variable	(Mean ± SD)	(Mean ± SD)	Paired t-test	p	r	p
Sleep-onset latency, minutes	45.17 ± 32.44	12.12 ± 9.57	5.09	0.00**	-0.19	0.31
Waking episodes, number of times	2.1 ± 2.04	13.36 ± 6.17	-9.08	0.00**	-0.16	0.41
Waking after sleep onset, minutes	NA	61.09 ± 30.03	-	-	-	-
Total time spent in bed, minutes	507.86 ± 117.02	550.71 ± 70.89	-2.23	0.03*	0.46	0.01*
Total sleep time, minutes	336.00 ± 130.98	489.62 ± 89.45	-5.46	0.00**	0.06	0.75
Sleep efficiency, %	66.81 ± 20.74	90.09 ± 6.60	-5.89	0.00**	0.02	0.93
Sleep quality (0-5 points)	2.97 ± 1.13	NA	-	-	-	-

NOTE. NA: not applicable; SD: standard deviation* p<0.05 ** p<0.001

Subjective vs Objective Characteristics

- Depressed patients were characterized as having “sleep disorder” based on ISI>15 and subjective sleep onset latency of >30 minutes for 3 out of 7 nights
- Despite significant differences in subject reporting of symptoms, the PSG findings were similar between the groups including latency to persistent sleep with the major difference being wake after sleep onset.

Parameter	Sleep Disorder Positive (N=73)		Sleep Disorder Negative (N=51)	
	mean	80% CI	mean	80% CI
LPS (min)	33.48	27.76 - 39.2	30.24	25.19 - 35.29
TST (min)	399.46	391.01 - 407.91	412.53	404.05 - 421.01
WASO (min)	55.47	48.33 - 62.61	40.47	33.6 - 47.34
Awakenings (per hour)	2.87	2.64 - 3.1	2.28	2.09 - 2.47

Abbreviations: LPS –latency to persistent sleep; TST - total sleep time; WASO – wake after sleep onset

Discussion

- Problems with sleep are common in multiple psychiatric disorders often leading to increased symptoms and at least in MDD, more difficult to treat illness.
- Since many medications impact sleep, one needs to consider measuring sleep in CNS trials.
- In MDD and Insomnia Disorder (likely in other disorders), subjective and objective assessments of sleep appear to assess different concepts with low or no correlations.
- Careful consideration needs to be made in choosing how important it is to capture an objective measure of sleep vs a patient's perspective on their sleep. Objective is not necessarily "better."