SLEEP MEDICINE RESEARCH

Using Sleep Actigraphy for the Validation of Wellness

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A growing body of evidence suggests that innate immunity contributes to insomnia and that sleep disturbances contribute to alterations in innate immunity.[1] These reciprocal interactions are in part mediated through the adrenals.[1] Given that immunosenescence (cortisol mediated innate immune aging) at the level of tissue macrophages may be causally related to age-associated chronic diseases,[2] it can be inferred that improvements to sleep architecture may benefit overall health and vice versa. For over 20 years, Immune System Management Clinic & Lab (ISM) has been helping clients regain and maintain wellness with Aminomics™ therapy (AT) along with client counselling. AT involves building a custom amino acid powder based on blood testing, which then is provided along with other supplements to rebalance the amino acid profile, counteract the effects of stress, improve sleep and restore optimal metabolism. Clients undergo follow-up testing to validate improvements to the amino acid profile whereby changes to the formulation are made when needed. Actigraphy may potentially allow tech-savvy clients the option to follow improvements to and the maintenance of their health related to the use of AT by monitoring their sleep architecture.

In order to assess whether or not sleep actigraphy could be used to monitor wellness related to the use of AT, actigraphy studies were conducted with the Fitbit Versa on an individual diagnosed with chronic fatigue syndrome (CFS) in 1998 who had been on AT

consistently since 2012 and compared with a 'dechallenge' (off of AT after a three day wash out period).

For the baseline on AT for this patient with CFS, there were notable variations in various sleep parameters, whereby 'atypical' sleep nights clearly stood out from the rest (summarized in **Table 1** and see **Figure 1 A, B)**. For example, for seven atypical nights the % Sleep Efficiency (% SE) was 85.6 % (+/-1.3 % standard error) which was statistically lower and showed more variance than for seven typical nights, at 89.6 % (+/- 0.5 % standard error) where p=0.0148. Indeed, eight of the seventeen parameters were found to be significantly different. The factors rendering poorer sleep nights (atypical) in this case were known and included: persistent ear ache with or without naproxen or acetaminophen (4 consecutive nights), spring time change (sleep initiated Monday night March 11), overdosing at dinner on maple syrup related to Shrove Tuesday (March 6), and the adverse simultaneous combination of naproxen (220 mg) with acetaminophen (325 mg) just before bed (for the ear ache) which appeared to be toxic (1 night). The latter sleep architecture was highly abnormal (**Figure 1B).** Accordingly, sleep data should be excluded when interfering factors can be easily identified which was the case for 'atypical' sleep nights. No atypical sleep nights were identified during the dechallenge. Care was also taken to exclude from analysis for the 'typical nights', the first night's sleep after a 'atypical' night due to rebound[3] which provided more favorable sleep parameters.

In **Table 1** the sleep architecture data for this 65-year-old female are presented showing that while on AT, her sleep parameters were better than normal for her age when compared with other Fitbit users.[4] Indeed, the sleep parameters were similar or better than much younger adults (age 13-22) based on Fitbit summary data (see footnote e in **Table 1)** that had been performed in April 2017 on millions of users.[4] While the % SE was significantly lower for the CFS patient off

therapy than on, interestingly, it was slightly better than the average Fitbit user.[4] The latter may serve as a reminder that Fitbit users are not necessarily healthy. In contrast, the % REM for the patient with CFS while off AT was lower than that reported for all age groups of Fitbit users.[4] For Fitbit users, there is little effect of age on % REM sleep which was reported to be about 21 % at all ages from 13 to 71.[4] While Della Monica et al. reported a % REM of about 21% for healthy females aged 31 to 64, in healthy females 65-84 years of age, this value dropped to about 17 % and was 18.5% in 20 to 30 year-olds.[5] In the latter study, great efforts were taken to validate that participants were healthy, without medications and for the elders, that they did not have cognitive decline.[5] However, the data (n=200) obtained by della Monica et al. had used 7 consecutive nights of actigraphy to pre-screen potential participants for inclusion to the study based on the validation of sleep habits and sleep duration prior to a single night polysomnographic (PSG) assessment[5] raising the issue of an intrinsic bias in this study. Nevertheless, for the most part, the parameters for the patient with CFS while on AT also exceeded that reported for females in all age groups in the della Monica et al. study (20 to 84 years). One of the exceptions was for the % SWS values at about 19 to 20% (+/- about 6%) for the female 31-64 and 65-84 age groups,[5] but the value in Table 1 was within range at 17.5% +/- 1.2%. The other exception also in range was a SWS time of 85 minutes (+/-11) in comparison with the 92 to 96 minutes (+/- 5 minutes) reported for the same female age groups.[5] The sleep parameters for the patient with CFS on AT were also better than that recently reported for 2162 participants 51 years of age (+/-8.1) with ideal cardiovascular health as determined by PSG at home, except the % SWS which was 21.8 % +/-8% but within range of the 17.5 % +/- 1.2 % SWS reported here.[6] Interestingly, the 65 year-old patient with CFS has genetic high cholesterol,

which was not being treated with pharmaceutical interventions, and exhibited normal blood pressure levels on AT and during the dechallenge (see footnotes in **Table 1**).

The question arises as to how to know how long one should take for a wash-out period for the dechallenge. In this case as shown in **Figure 1 A, C, D**, the histograms revealed late deep sleep cycles at 1.5 hours or less from awakening when the patient was on AT therapy. After 3 days of washout, these signatures were absent (**Figure 1, E, F,** and data not shown) suggesting the timing chosen for wash-out was appropriate.

DISCUSSION

Non-restorative sleep is a hallmark of CFS, a primary insomnia disorder, yet a review of the polysomnography (PSG) data have for the most part, failed to establish differences in sleep parameters between patients with CFS and healthy age-matched controls.[7] There were 15 studies cited where 6 used a single night of PSG, 8 used two nights of PSG and one used three nights of PSG. The high variance in these PSG studies (frequently 30 to 50% for the standard error of the means for healthy controls or patient groups) often precluded statistical interpretation, and the use of medications permitted in some of these studies only served to further confound interpretation. The unfamiliar environment of sleep clinics could also impact sleep quality. In contrast, in the actigraphy results presented here for 7 nights of evaluation at home as shown in Table 1, the co-efficient of variation was generally under 5% and often less. Provided atypical nights of sleep and the following rebound nights are excluded, sleep actigraphy appears to increase the likelihood of obtaining statistically interpretable sleep data over PSG.

Nevertheless, using PSG one group[8] reported that patients with CFS (without fibromyalgia, mean age of 37) who were not on any medications, may have 39 less minutes of Total Sleep Time (TST), 7 % less % SE (compare 78% to 85% SE), and a decreased REM time by 24 minutes which were found to be significant when compared with healthy age-matched controls. On the other hand, no significant differences were detected in SWS.[8] Here it is reported for the patient with CFS while off AT (during the dechallenge), there was a significantly reduced % SE, % REM and REM time (by 26 minutes), with no significant effect on SWS when compared with the use of AT. There was no difference in the TST in Table 1 during the dechallenge possibly because the patient's blood pressure remained the same over the short dechallenge and the lack of hypertension is associated with a TST of about 420 to 440 minutes[9] as was observed for the patient in **Table 1**. Overall this may be the first substantiation of the work of Togo et al. for discerning abnormal sleep parameters associated with CFS.[8]

In conclusion, the possibility exists that the general public may be able to monitor the beneficial effects of certain interventions on health provided they are not toxic, by following improvements to sleep parameters with actigraphy. Clearly however, more studies are required to follow a larger number of patients prospectively rather than by dechallenge to better address this issue. This preliminary work also may identify AT as a candidate non-toxic and non-habit forming intervention for counteracting disease-associated and/or age-associated adverse changes to sleep architecture.

SLEEP MEDICINE PEARLS

1. Sleep is very sensitive to interference by unpredictable influences from the environment and/or unusual dietary or other physiological changes in individuals, resulting in atypical sleep nights. To better estimate sleep architecture baselines by actigraphy then, one may need to keep a sleep diary and record any factors which might potentially adversely affect sleep. As well, due to rebound issues, the first night after a night of interference should not be included in the analysis. With these caveats, it remains to be determined if sleep actigraphy can be used more generally to monitor improvements to health.
2. Preliminary evidence suggests Aminomics™ therapy, which serves to counterbalance stress and rebalance the amino acid profile for better metabolism, may be a non-toxic, candidate intervention which may improve sleep but which should be investigated further.
3. The current paucity of internationally recommended sleep interventions may reflect in part that polysomnography assessments frequently relating to a single observation night at a clinic in an unfamiliar environment, may not accurately represent typical nights of sleep. This may result in high variance in the sleep parameters, may preclude obtaining statistical significance, and thereby may result in the failure to identity sleep interventions which may benefit society.

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DISCLOSURE STATEMENT

All costs except the supplements, including time for compiling data, data analysis were borne by the author. The author is contract employed at ISM and owns a small percentage of shares.

Table 1 — Sleep Parameters in a Patient with CFS by Actigraphy

Parameter Time in minutes (')	Aminomics™ Therapy [a] **'Atypical Nights'**	Aminomics™ Therapy [a,e] **'Typical Nights'**	No Aminomics™ Therapy [b,e] **'Dechallenge'**
Replicates (n)	**7**	**7**	**7**
TSP'	**445** +/-14	**474** +/-27	**480**+/-11
SL'	**20** +/-6	**15** +/-3	**15** +/-2
TST' [c]	**386** +/-14	**425** +/-24	**422**+/- 9
% SE [d]	**85.6%** +/- 1.3% *	**89.6%** +/-0.5%	**87.9%** +/- 0.6% *
Awake Time'	**64** +/-8	**49** +/-3	**58** +/-2
% Awake [d]	**14.4%** +/-1.3% *	**10.4%** +/-0.5 %	**12.1%** +/-0.6% *
WASO	**44** +/-5	**34** +/-4	**43** +/- 4
% SF	**11.4%** +/-1.2% *	**7.9%** +/- 0.6%	**10.2%** +/-1.0%
Light Time'	**254** +/-9	**227** +/-13	**256** +/-15
% Light [d]	**57.0%** +/-0.7% &	**47.9%** +/-0.8%	**53.2%** +/-2.7%
SWS Time'	**52** +/-3 *	**85** +/-11	**78** +/-6
% SWS [d]	**11.8%** +/-0.8% #	**17.5%** +/-1.2%	**16.3%** +/- 1.4%
SWS Latency'	**43** +/- 25	**9** +/-3	**33** +/- 17
REM Time'	**75** +/-4 &	**113** +/-4	**87** +/-11 *
% REM [d]	**16.7%** +/-0.8% &	**24.2%** +/-1.2%	**18.1%** +/-2.2% *
REM Latency'	**165** +/-24	**108** +/-17	**125** +/-26
REM'/SWS'	**1.44** +/-0.11	**1.44** +/-0.15	**1.12** +/-0.11

When compared with 'Typical Nights': *significant at $p<0.05$; #significant at $p<0.01$; & significant at $p=$ or $<$ 0.0003. Significance calculated by GraphPad QuickCalcs unpaired t test with two tails.

TSP=total sleep period includes time awake (including sleep latency), Light sleep, REM and SWS times; TST= total sleep time; SL=sleep latency; % SE= % Sleep Efficiency calculated as TST/TSP x100; WASO= Wake After Sleep Onset ; % SF=% Sleep Fragmentation=WASO/ TST x 100; SWS=slow wave sleep also referred to as deep sleep; REM=rapid eye movement.

a) CFS client (female, 65 years-old, BMI 27.2, blood pressure of 122/66) had been on AT variably (for 3 months at a time) since fall 1998 related to amelioration of occasional polyneuropathy episodes. Client had been diagnosed with CFS in 1998. In 2011-12, she suffered adrenal exhaustion with low blood pressure, and recovered on AT. She has been on AT consistently since the adrenal exhaustion and has not suffered any further polyneuropathy episodes, nor any persistent insomnia or fatigue. No drugs, herbal medicines or alcohol were used during these studies except where noted for naproxen and /or acetaminophen captured in the data for atypical nights.

b) CFS client off AT for 7 days following a 3-day wash-out period. At 9-days off therapy her blood pressure was 123/68. There were no factors identified which may have interfered with sleep for these 7 days. As well the dechallenge data are consistent with changes ascribed to patients with CFS.[8]

c) The optimal Total Sleep Time (TST) to reduce the risk of hypertension appears to be roughly about 420 to 440 minutes for the ages 35 to 74 years for both sexes.[9] The reported TST on or off AT in Table 1 falling in between 420 to 440 minutes for this CFS patient is consistent with the lack of hypertension on or off AT. Note that for the 'Atypical Nights' the TST is 386 minutes or 47 minutes shorter, representing about an 11% decrease in TST which falls outside the optimum.

d) Calculated based on Total Sleep Period (TSP) as the denominator.

e) According to Fitbit user data on millions of users polled in April 2017[4] in users 52 to 71 years of age, the means for key sleep parameters were: TST =393', % Light =54%, % SWS=13% and % REM= 21% using the Total Sleep Period as the denominator. For Fitbit users 13 to 22 years of age, the corresponding means were: TST=417', % Light = 50%, % SWS =17% and % REM=21%. The average Fitbit user had a TST=398', %SE=86.0%, % Light = 51% (235'), % SWS=15% (67'), and % REM =21% (97').

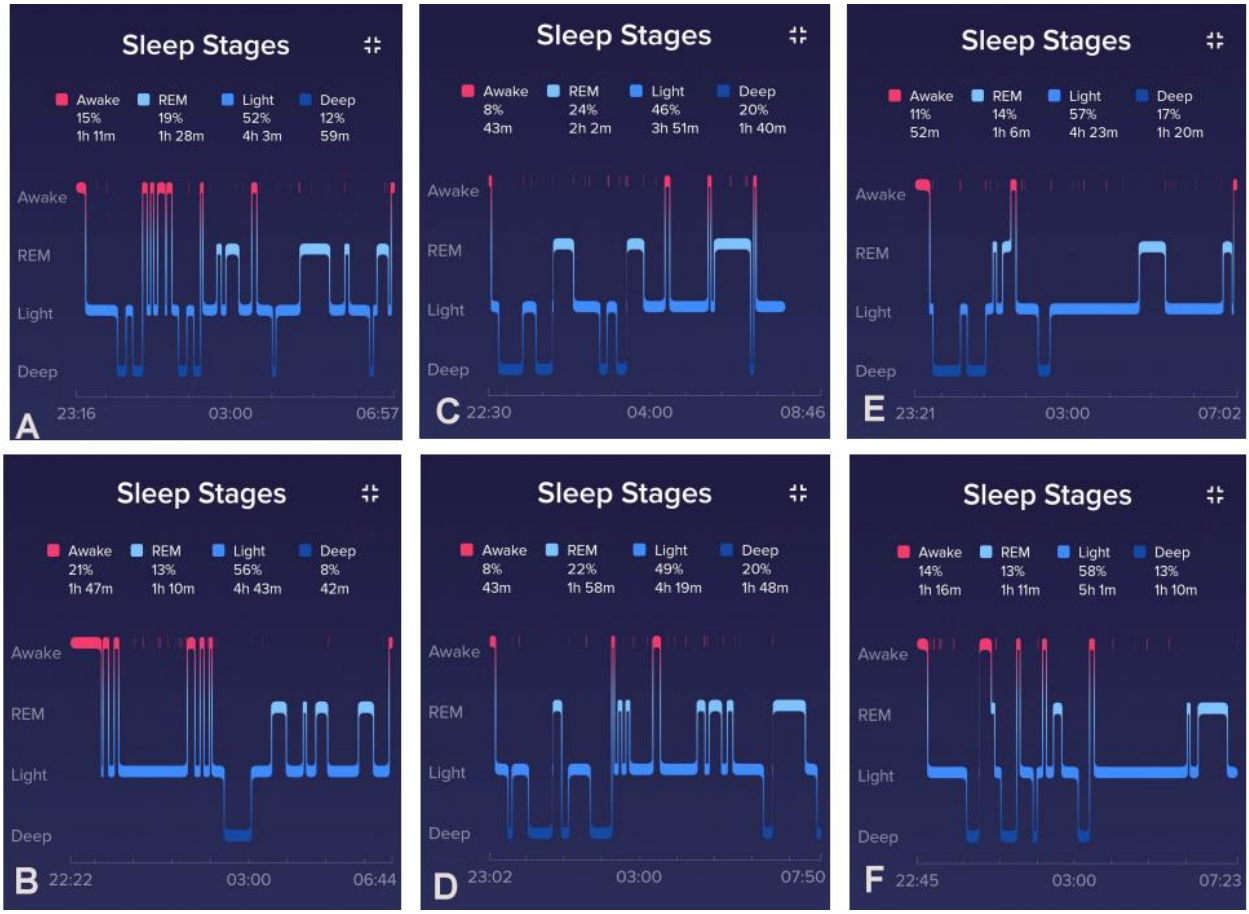

Figure 1 — Representative Actigraphy Sleep Architecture Histograms

Sleep architecture by Fitbit Versa representing: A, B Atypical Sleep on Aminomics™ therapy (A= earache no drugs, B= toxic combined use of naproxen with acetaminophen prior to initiating sleep); C, D Typical Sleep on Aminomics™ therapy; E, F Sleep During Dechallenge without Aminomics™ therapy (after a 10 and 9 day washout). Note the presence of deep sleep cycles within the last 1.5 hours of the sleep cycle in A, C, D but not E and F, associated with being on Aminomics™ therapy. These disappeared after the 3-day washout and were not present in the dechallenge sleep monitoring histograms (data not shown).