



Modeling Hypnotic Use in Insomniacs

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Scholarly Report submitted in partial fulfillment of the MD Degree at Harvard Medical School

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Scholarly Report Title: Modeling Hypnotic Use in Insomniacs

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Abstract

TITLE: Modeling Hypnotic Use in Insomniacs

Frank Gonzalez, Matt T. Bianchi

Purpose: Chronic insomnia is a heterogeneous disorder that includes subsets in which patients exhibit sleep misperception where there is a mismatch between subjective total sleep time (sTST) and objective total sleep time (oTST) and may mis-attribute subjective sleep gains to hypnotics instead of their sleep homeostat. Coupled with evidence night-to-night variability is present in many adults with insomnia, approach to management may be more complicated than gestalt patterns suggest. There is a need to determine the role of sleep homeostasis and night-to-night variability as well as to identify those who are taking hypnotics and suffering the detrimental side effects of those agents. To that end, we developed a model aimed at capturing key features of chronic insomnia and the extent to which misattribution of hypnotic effects may play a role in the evolution of over-use longitudinally.

Methods: We used MATLAB to design a predictive model to simulate oTST, sTST, and hypnotic use longitudinally with data from each night being incorporated into the subsequent night. Weights were assigned to variables to create clinically relevant sleep phenotypes (SPs), which were then compared using two-tailed t-Tests after conducting 100 runs of 180 day simulations as well as 50 runs of 7 day simulations for each phenotype.

Results: We analyzed six SPs that differed in the presence or absence of: anxiety, tendency towards habit formation, and sleep homeostat. In 180-day simulations, all phenotypes differed in oTST ($p < 0.05$), while sTST and misattribution events were not consistently phenotype-dependent. In SPs with tendency towards hypnotic addiction, we observed an average increase of 34% in hypnotic use as compared to SPs without tendency towards addiction. 7-day simulations, to mimic the shorter durations typical of clinical research, did not consistently differentiate between phenotypes for oTST, sTST, or misattribution events. However, there was an average 29% increase in hypnotic use in SPs with potential towards addiction when compared to those without potential.

Conclusions: The constructed sleep model can simulate and capture night-to-night variability for clinically relevant sleep phenotypes, including addictive personalities. Misattribution events do not appear to occur frequently enough to substantively explain medication overuse. Simulations involving shorter time frames did not capture patterns evident in longer simulations. Although we observed statistically significant differences in sleep time between phenotypes, the absolute magnitudes were small and thus may not be clinically significant. Nevertheless, because real world experiments lasting multiple months are not currently feasible, modeling allows a testing ground for hypothesis explorations.

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Introduction

Insomnia is a sleep disorder that is characterized by a complaint of insufficient sleep as well as daytime symptoms and adverse functional consequences [1]. It has been estimated that the prevalence of insomnia in the general US population ranges from 1% to 20%, depending on the population studied and the criteria used, and can be as high as 33% in elderly populations [1, 2]. Individuals with insomnia have decreased quality of life as a result of troubles with sleep in domains including bodily pain, social functioning, and mental health [1]. Considering the high prevalence and the diverse consequences of insomnia, there are substantial economic and functionality burdens on not just the individual but the population as a whole [3, 4].

In current practice, the treatment, unfortunately, more often involves pharmacological therapy as opposed to the gold standard, cognitive behavioral therapy for insomnia (CBT-I) [5]. However, there is little information to suggest that the use of pharmacological agents, or hypnotics, has a durable and positive effect in chronic insomnia management [5, 6]. Additionally, the side effect profile of hypnotics is far-ranging and includes the potential for abuse, particularly in those individuals with a history of substance abuse or comorbid psychiatric conditions [7].

Another consideration is that the various subsets of insomnia include a sizeable portion of patients who exhibit some degree of sleep misperception, in which there is a mismatch between subjective total sleep time and objective total sleep time, such that they tend to underestimate the amount of time actually spent asleep [5, 8, 9]. When this information is coupled with the growing evidence that there is prominent night-to-night variability in many adults with insomnia [10-13], the approach to management may be more complicated than often assumed by using gestalt patterns or even careful diary tracking. We can consider factors contributing to nightly variability in sleep, and daily variability in patient experience, in several categories for model generation (including physiological arousal, the weight an individual places on past experience [pessimism], recent objective sleep duration (homeostasis), tendency towards habit formation [addiction], and the effect of hypnotic medication on subjective total sleep time [reactivity]). For example, in those with intact homeostatic drive for sleep response to recent sleep loss, one or more poor nights of sleep may be followed by a “recovery” night due to mounting sleep pressure. If an individual decided to take a sleeping pill after one or more nights of frustrating

difficulty sleeping, they might misattribute the subsequently improved night's rest to the hypnotic instead of their homeostatic drive. Homeostasis is a well-studied process in which the pressure to sleep increases from a daily minimum upon awakening that increases over time awake and makes sleep more likely towards the evening [5, 14, 15]. Studies suggest there is a temporal patterning where there is a certain number of bad night's rest followed by a certain number of good night's rest that can be at least partially attributed to sleep homeostasis building over one or more poor nights [16, 17].

There is a growing need to determine the role of sleep homeostasis and other factors in shaping night-to-night variability as well as patterns of hypnotic use (and over-use), especially given the risks associate with short-and long-term pharmacotherapy [18]. To that end, we developed a model aimed at capturing key features of chronic insomnia including stochastic night-to-night variability in total sleep time per night, the role of homeostatic pressure in night-to-night sleep variability, as well as how anxiety and tendency towards habit formation impact sleep times. Additionally, we hope to model the extent to which misattribution of hypnotic effects, versus other categories influencing self-administration, may play a role in the evolution of over-use longitudinally.

Student Role

The student was involved in creating the predictive model by assisting with the formulation of equations. Once the equations were determined, he worked within MATLAB to code a functioning model that incorporated all previously discussed variables. He then used the simulation and conducted multiple runs in order to collect data. This data was then analyzed within GraphPad Prism and compiled into tables, graphs, and figures. He scripted a draft of the results and with the editing assistance of the PI, Dr. Bianchi, the student was able to submit a final manuscript.

Materials and Methods

Model architecture

The graphical user interface of MATLAB (The Mathworks Inc., Natick, MA, USA) was used to design a predictive model and simulate objective total sleep time (oTST), subjective total sleep time (sTST), as well as hypnotic use (Hyp) over a given time-period with the data from each night being incorporated into each subsequent night. oTST as well as sTST were set to a baseline mean with standard deviation. Hypnotic use was binary (1 for yes, 0 for no) and dictated each night by the probability of taking a hypnotic (pHyp). Night-to-night variability was included in the model with the addition of a variable with Gaussian distribution that modified both oTST and sTST for each night. Each of the simulated components was then updated according to a variety of sleep factors as follows:

1. oTST: physiological arousal (σ), homeostat (s), and hypnotic influence
2. sTST: pessimism (β) and hypnotic influence
3. hypnotic use: reactivity (α) and habit (Θ)

Figure 1 is a diagram of the sleep factors and how they relate to the simulated components.

Equations

Each of the sleep factors was then assigned a weight and used to determine the probability of taking a hypnotic on a given night according to the formula below. A random number generator was used and if the value was greater than or equal to $phyp1$ then a hypnotic was taken on that night. If the value was less than $phyp1$ then a hypnotic was not taken.

Equation used to calculate probability of taking a hypnotic. Variables represent sleep factors and can be found in Figure 1.

$$pHyp_1 = \beta * pHyp_0 + (1 - \exp(-r^{1-H_0} * \theta r^{H_0} * f)) * (1 - \beta)$$

Certain conditions are required for misattribution to be possible: at least one night of reduced oTST and non-use of hypnotic, followed by a night of increased oTST and use of hypnotic. When this combination occurs, there is potential for misattribution. For nights on which those conditions were met, the difference in subjective total sleep time was taken and counted as a misattribution event.

Equation used to calculate misattribution events (and hours).

$$\textit{Hypnotic Attributed Benefit} = sTST_{N1|+hyp} - sTST_{N0|no hyp}$$

$$\textit{(Homeostat + Hypnotic) benefit} = oTST_{N1|+hyp} - oTST_{N0|no hyp}$$

To capture the variability that can present within patient populations, a subset of sleep phenotypes was created according to the presence or absence of anxiety (A), potential towards addiction (P), and functioning homeostat (H) (Table 1). From here on out, the sleep phenotypes will be referred to by the presence or absence of these three variables. SP1 = A+P+H-, SP2 = A+P+H+, SP3 = A-P-H+, SP4 = A-P+H+, SP5 = A+P-H+, SP6 = A+P-H-. Variability was captured by manipulating the weights on these additional factors, affecting the oTST, sTST and the probability of taking a hypnotic within the sleep simulation.

Data Collection and Analysis

We conducted 100 runs for each of the six sleep phenotypes with each run consisting of 180 nights or data points. A second set of data was obtained consisting of 50 runs for each of the six sleep phenotypes with each run consisting of only 7 nights. Means for objective total sleep time, subjective total sleep time, as well as misattribution events were calculated for each sample run. The different sleep phenotypes were then compared using two-tailed t-Tests with a two-tailed p-

value <0.05 indicating significance. t-Tests and graphs were conducted with GraphPad Prism (GraphPad software, La Jolla, California, USA).

Results

Objective total sleep time for 180 day simulations (100 runs)

The mean oTST for each sleep phenotype (SP) is presented in Table 2 and is as follows: A+P+H- = 8.18, A+P+H+ = 8.22, A-P-H+ = 6.30, A-P+H+ = 6.49, A+P-H+ = 8.01, and A+P-H- = 7.92. There was a significant difference in oTST between A+P+H- and A+P+H+ ($p<0.001$; $df = 99$), A-P-H+ and A-P+H+ ($p<0.001$), as well as A+P-H+ and A+P-H- ($p<0.001$) (Figure 2).

Subjective total sleep time for 180 day simulations (100 runs)

The mean sTST for each SP is presented in Table 2 and is as follows: A+P+H- = 6.00, A+P+H+ = 6.02, A-P-H+ = 3.77, A-P+H+ = 4.30, A+P-H+ = 5.47, and A+P-H- = 5.38. There was a significant difference in sTST between A-P-H+ and A-P+H+ ($p<0.001$; $df = 99$) as well as between A+P-H+ and A+P-H- ($p<0.001$). However, there was no statistical difference in sTST between A+P+H- and A+P+H+ ($p=0.44$) (Figure 3).

Misattribution events for 180 day simulations (100 runs)

The mean number of misattribution events, as calculated in the methods section, for each sleep phenotype over 180 days is also presented in Table 2 and is as follows: A+P+H- = 26.64, A+P+H+ = 28.32, A-P-H+ = 6.03, A-P+H+ = 6.57, A+P-H+ = 25.45, and A+P-H- = 24.81. There was a statistical difference between A+P+H- and A+P+H+ ($p<0.05$) but not between A-P-H+ and A-P+H+ ($p=0.11$) or between A+P-H+ and A+P-H- ($p=0.25$) (Figure 4).

Hypnotic use for 180 day simulations (100 runs)

The mean percentage for number of nights on which a hypnotic was taken is presented in Table 2 and is as follows: A+P+H- = 55.23, A+P+H+ = 56.83, A-P-H+ = 22.01, A-P+H+ = 56.53, A+P-H+ = 21.40, and A+P-H- = 21.66. In the sleep phenotypes with potential towards addiction there was an average 34% increase in the number of nights on which a hypnotic was taken as compared to those without potential towards addiction (Figure 5).

Objective total sleep time for 7 day simulations (50 runs)

To explore potential differences between longitudinal simulations above, and shorter tracking times more typical of clinical practice and clinical research, we repeated simulations using only 7 days. The mean oTST for each sleep phenotype SP is presented in Table 3 and is as follows: A+P+H- = 8.20, A+P+H+ = 8.14, A-P-H+ = 7.62, A-P+H+ = 7.84, A+P-H+ = 8.00, and A+P-H- = 7.92. There was a significant difference in oTST between A-P-H+ and A-P+H+ ($p < 0.001$; $df = 49$) as well as between A+P-H+ and A+P-H- ($p < 0.05$). However, there was no statistical difference in sTST between A+P+H- and A+P+H+ ($p = 0.21$) (Figure 6).

Subjective total sleep time for 7 day simulations (50 runs)

The mean sTST for each SP is presented in Table 3 and is as follows: A+P+H- = 5.96, A+P+H+ = 5.82, A-P-H+ = 5.12, A-P+H+ = 5.71, A+P-H+ = 5.50, and A+P-H- = 5.38. There was a statistical difference between A-P-H+ and A-P+H+ ($p < 0.001$; $df = 49$) but not between A+P+H- and A+P+H+ ($p = 0.19$) or between A+P-H+ and A+P-H- ($p = 0.12$) (Figure 7).

Misattribution events for 7 day simulations (50 runs)

The mean number of misattribution events for each sleep phenotype over 7 days is also presented in Table 3 and is as follows: A+P+H- = 1.24, A+P+H+ = 1.14, A-P-H+ = 0.90, A-P+H+ = 0.84, A+P-H+ = 1.14, and A+P-H- = 0.90. There were no statistically significant differences when

comparing A+P+H- and A+P+H+ ($p=0.58$; $df = 49$), A-P-H+ and A-P+H+ ($p=0.70$), as well as A+P-H+ and A+P-H- ($p=0.09$) (Figure 8).

Hypnotic use for 7 day simulations (50 runs)

The mean percentage for number of nights on which a hypnotic was taken is presented in Table 3 and is as follows: A+P+H- = 52.86, A+P+H+ = 39.42, A-P-H+ = 22.68, A-P+H+ = 63.74, A+P-H+ = 25.40, and A+P-H- = 20.86. In the sleep phenotypes with potential towards addiction there was an average 29% increase in the number of nights on which a hypnotic was taken as compared to those without potential towards addiction (Figure 9).

Discussion

The model can simulate and capture night-to-night variability for multiple sleep phenotypes including addictive personalities

There has long been an attempt to classify insomnia into subtypes, such as childhood-onset or psychophysiological, with the clinical implication that different classes of insomnia could be treated effectively with differing therapies [8, 9]. With the most recent edition of the DSM-V removing the distinction between primary and secondary insomnia, there is a larger emphasis on treating insomnia as its own disorder instead of as secondary to other medical conditions. One challenge to subtyping insomnia is that there are a variety of sleep and awake factors that contribute to any one individual's insomnia. These can be difficult to identify and patients may not be able to assess or prioritize potentially modifiable contributors to their sleep difficulties. We modeled a selection of "sleep phenotypes" to subtype insomnia based on the variables contained within the simulation, known to contribute to sleep trouble and consistent with both physiological and cognitive models of insomnia [19, 20]. There was an observable difference in stochastic, night-to-night variability as well as oTST and sTST that was dependent on the phenotype-specific variables of anxiety, tendency towards habit formation, and sleep homeostat. In particular, there were significantly observable differences in hypnotic use between the personalities with tendency towards habit formation compared to those without addiction

potential. Those results support the theory that it is possible to model human personality traits and their impact on sleep time dynamics longitudinally.

Misattribution events do not occur at a high enough frequency to be captured

Our definition of misattribution cannot be calculated when individuals take a hypnotic nightly, or never take hypnotics. The optimal method to determine misattribution would thus require intermittent hypnotic use that is frequent enough during the period of study to allow for analysis but also not completely clustered (because hypnotic use needs to alternate with non-use). Despite the relatively large number of runs performed, this sleep model was unable to consistently detect a difference in misattribution events between SPs. This is not due to model lacking sufficient homeostatic drive but rather due to the low frequency of misattribution events. In 7-day runs, misattribution events occurred in less than half of all runs. Because hypnotic use was consistently higher in the simulation SPs with anxiety, the opportunity for identification of misattribution was decreased, raising the problem of how to accurately identify “misattributers” within a real-life patient population.

Simulations involving shorter time frames are more susceptible to interpretations based on extremes.

Although 180 days of objective and subjective sleep tracking for 100 patients is not typically performed experimentally, 7 days of tracking data for 50 patients is commonly performed in research studies[21]. However, when evaluating shorter time frames, long term patterns may not be evident and there is an increased probability of outliers affecting data interpretation[22]. This can present as either false positives or lack of power to detect significant differences. Our model supports this theory with an increase in variability across sleep phenotypes in the 7 day runs as compared to the 180 day runs, particularly in hypnotic use. There was not an issue with false positives but differences that were present in SPs only became evident after increasing simulation length and number of simulations.

Statistically significant differences in sleep time between SPs may not be clinically significant

In the main modeling section, based on 180-day long runs, we found statistically significant differences, often of $p < 0.001$, among many sleep phenotypes for subjective and objective sleep. However, it is unlikely that these small differences, despite the p-values, would be clinically significant. Studies have proposed the idea of an insomnia identity in which there is the conviction that one has insomnia, regardless of objective measures of decreased sleep times, which are often unavailable. In other words, if two people have the same sleep onset latency, total sleep time, and awakenings during the night, only the one bothered by their sleep could be said to have insomnia. In those cases, there is an uncoupling between sleep physiology and sleep appraisal that can lead to a variety of deleterious clinical symptoms [23, 24]. The small differences being noted in this simulation are not likely to matter to individuals but they might still self-identify as an insomniac, exposing themselves to a range of negative sequelae such as self-stigma, depression, and hypertension.

Limitations

The weights assigned to each variable for the sleep phenotypes were designed to closely mimic predictive impact on sleep quality but are not concretely known. Only sleep factors, and of those only a small handful, were incorporated into the model and we did not focus on any awake factors.

Future directions

This sleep model is a framework that allows for long term predictions in night-to-night sleep variability with the potential to identify insomnia subtypes based on subjective and objective sleep times. Though actigraphy based recording devices have been around for decades, the limitations of such technology, including tendency to overestimate sleep and misjudging sleep times as awake (perhaps secondary to paroxysmal sleep disorders), have made information obtained through these means difficult to interpret [25]. With advancements to wearable sleep technology, these products are becoming readily available to the public. As individuals present to

clinic with larger amounts of data, it will be up to the clinician to make sense of the data and identify which patients stand to gain benefit from cognitive restructuring versus standard CBT-I. Future studies that use this model can focus on comparing long term observation of patient sleep times gathered by way of at-home sleep tracking devices to determine if there is a good fit with any of the proposed sleep phenotypes. Because real world experiments this long are not currently feasible, modeling allows a testing ground for hypothesis explorations. As data from longitudinal monitors becomes more available, restrictions on parameters based on actual data can be layered onto models as needed. Considering the large range of parameters included with the sleep model, it is possible that at least some aspects of a patient's personality can be simulated making for a more individualized treatment plans and giving each patient an idea of their true sleep patterns. From the patient perspective, modeling is beneficial in that it provides a framework to analyze and interpret a variety of patient preferences and behaviors.

Acknowledgements

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Figures and Graphs

Figure 1. Interacting variables that affect an individual’s sleep and how they relate to the prior night’s sleep. N_0 corresponds to the previous night while N_1 corresponds to the current night. “Obj” represents objective sleep, “Subj” represents subjective sleep, and “Hyp” represents hypnotic use (present or not on any given night). The variables connecting N_0 to the N_1 represent the sleep factors considered within the model that affected objective sleep time, subjective sleep time, and the probability of taking a hypnotic.

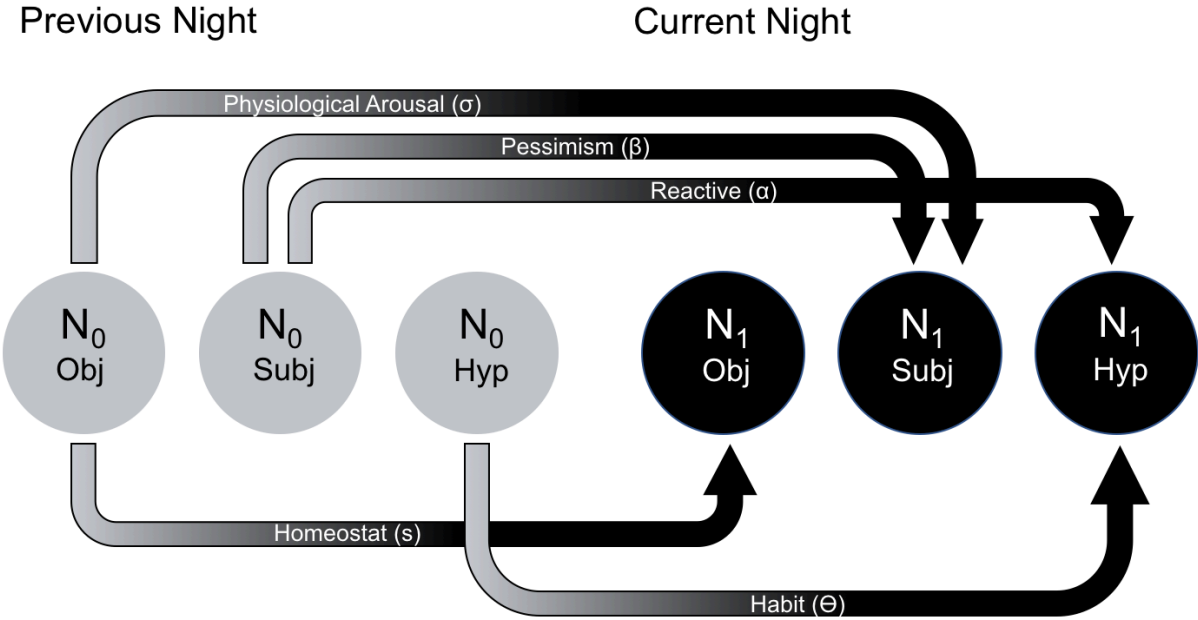


Table 1. Sleep phenotypes simulated within the sleep model. Each sleep phenotype was a combination of a variety of characteristics but the ones considered for analysis focused on “anxiety”, tendency towards habit formation (or “addiction”), and sleep “homeostat”. These variables are binary and were either present (+) or absent (-) and contributed towards sleep time as well as probability of taking a hypnotic.

<i>Sleep Phenotype Characteristics</i>			
	Anxiety	Addiction	Homeostat
Sleep Phenotype 1	+	+	-
Sleep Phenotype 2	+	+	+
Sleep Phenotype 3	-	-	+
Sleep Phenotype 4	-	+	+
Sleep Phenotype 5	+	-	+
Sleep Phenotype 6	+	-	-

Table 2. Average oTST, sTST, misattribution events (per 180 days), and percent of days on which hypnotics were taken for each sleep phenotype calculated over 100 runs.

	SP1	SP2	SP3	SP4	SP5	SP6
oTST	8.18	8.22	6.30	8.01	6.49	7.92
sTST	6.00	6.02	3.77	5.47	4.30	5.38
Misattribution	26.64	28.32	6.03	25.45	6.57	24.81
% Hypnotic Use	55.23	56.83	22.01	56.53	21.40	21.66

Figure 2. Mean objective sleep times for the six simulated sleep phenotypes over 100 runs.

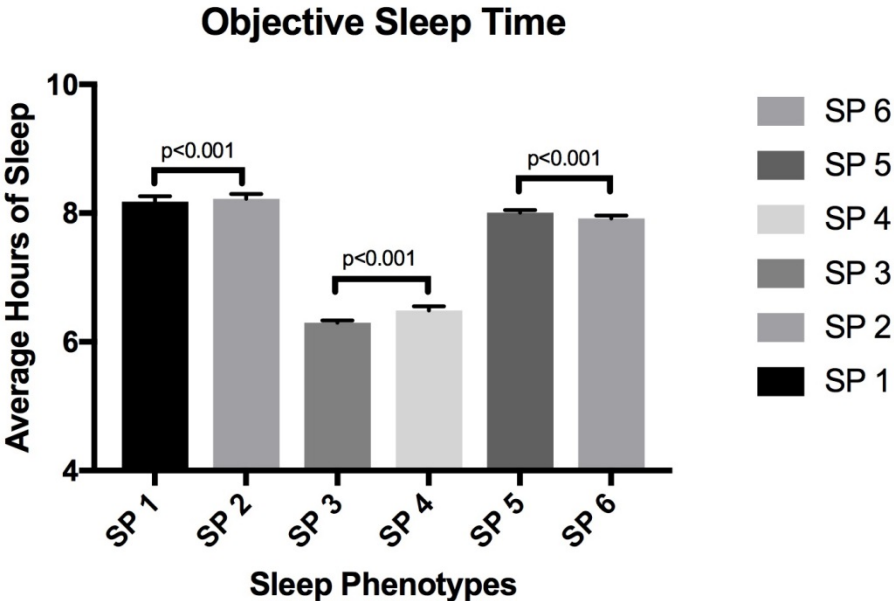


Figure 3. Mean subjective sleep times for the six simulated sleep phenotypes over 100 runs.

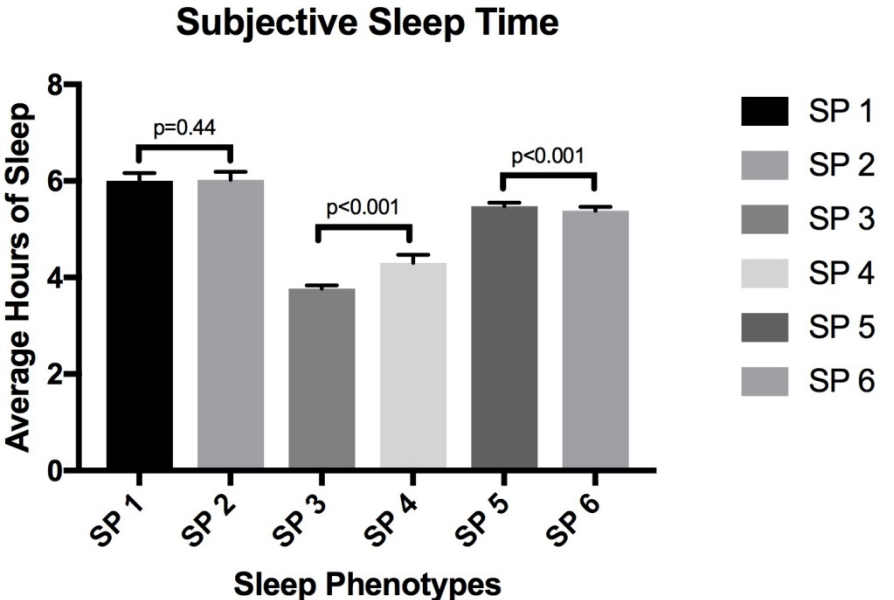


Figure 4. Mean number of misattribution events for the six simulated sleep phenotypes over 100 runs.

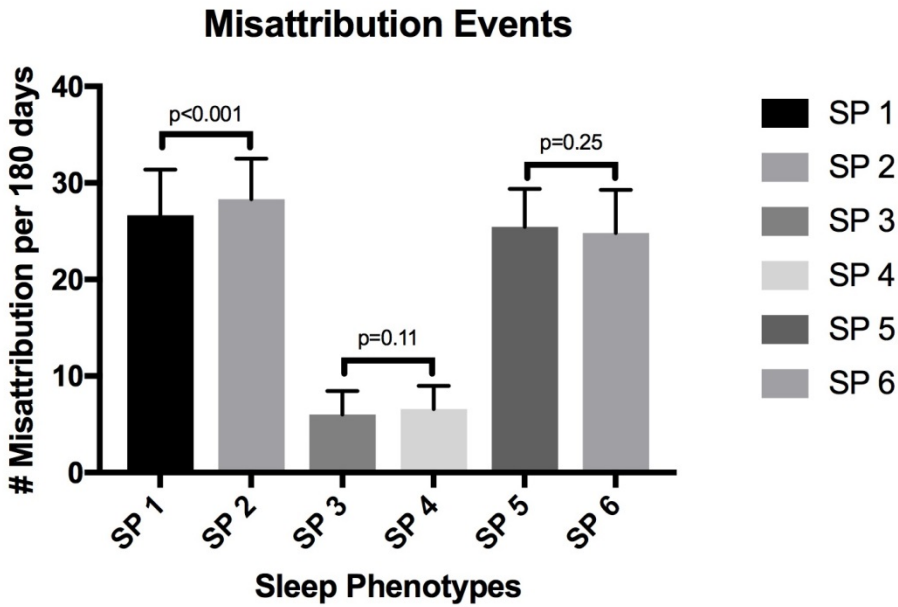


Figure 5. Percent of nights on which a hypnotic was taken for the six simulated sleep phenotypes over 100 runs.

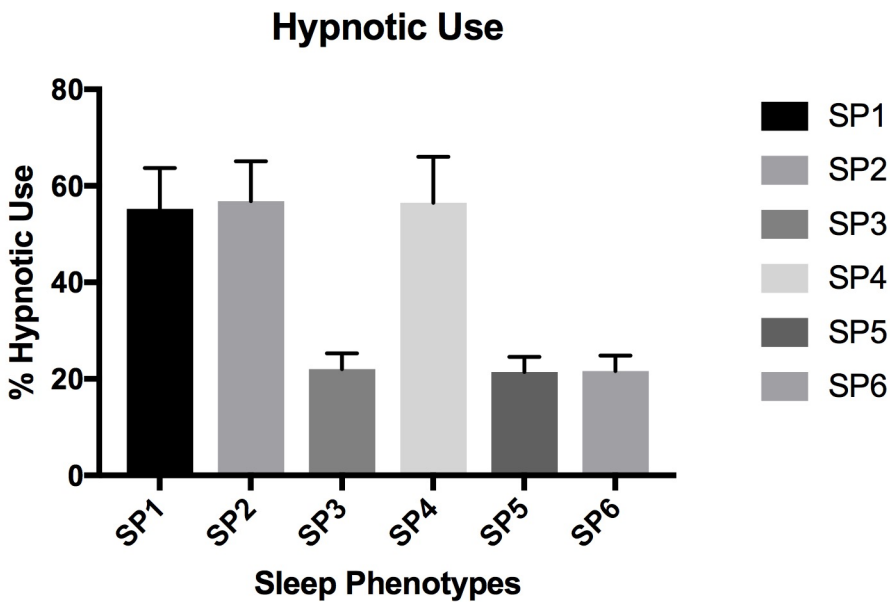


Table 3. Average oTST, sTST, misattribution events (per 180 days), and percent of days on which hypnotics were taken for each sleep phenotype calculated over 50 runs.

	SP1	SP2	SP3	SP4	SP5	SP6
oTST	8.20	8.14	7.62	7.84	7.99	7.92
sTST	5.96	5.82	5.12	5.71	5.50	5.38
Misattribution	26.64	28.32	6.03	25.45	6.57	24.81
% Hypnotic Use	55.23	56.83	22.01	56.53	21.40	21.66

Figure 6. Mean objective sleep times for the six simulated sleep phenotypes over 50 runs

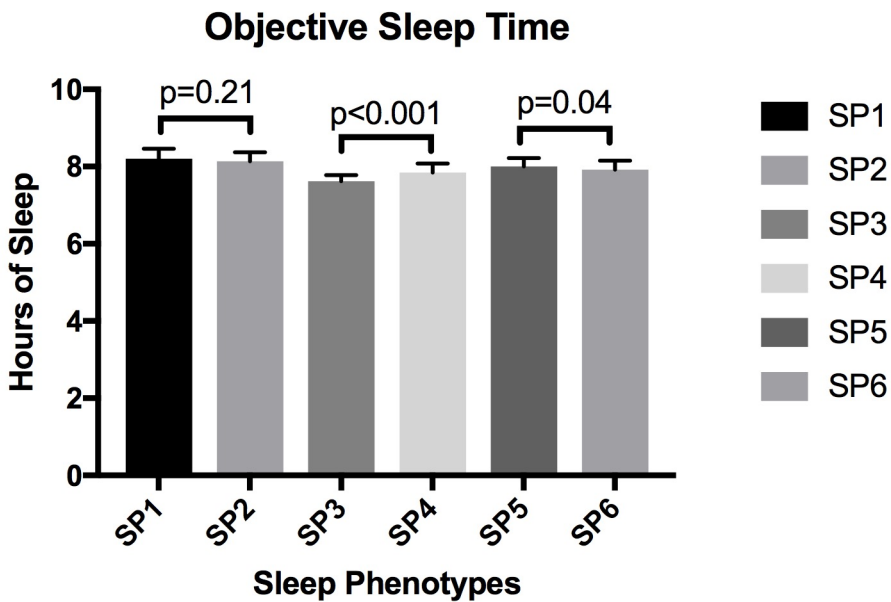


Figure 7. Mean subjective sleep times for the six simulated sleep phenotypes over 50 runs

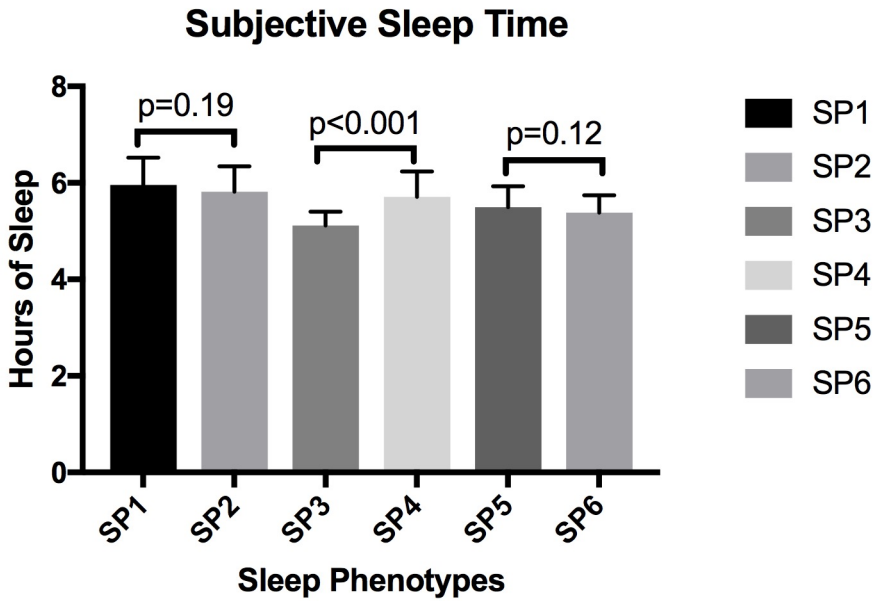


Figure 8. Mean number of misattribution events for the six simulated sleep phenotypes over 50 runs.

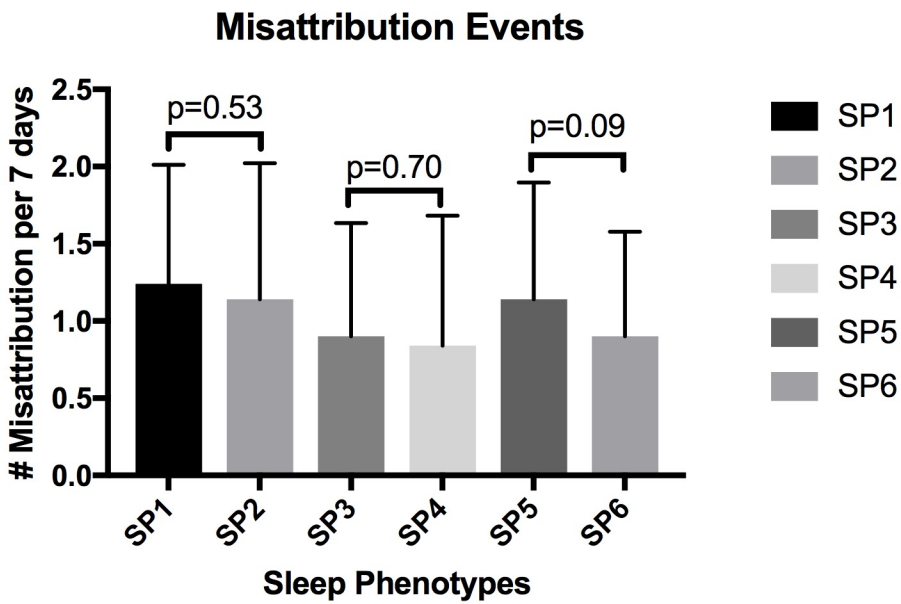


Figure 9. Percent of nights on which a hypnotic was taken for the six simulated sleep phenotypes over 50 runs.

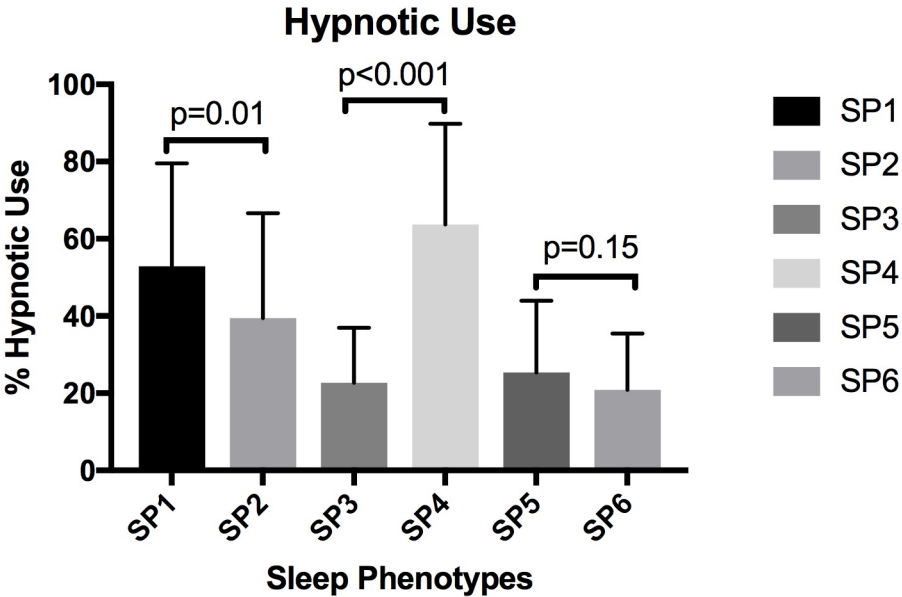


Figure 10. Example objective and subjective total sleep time with hypnotic use on days 3 and 6. (A) represents the increased subjective sleep time the individual potentially attributes to the hypnotic while (B) represents the objective amount of increased total sleep time, which may in part be due to hypnotic use. The difference between (A) and (B) allow for the possibility of misattribution.

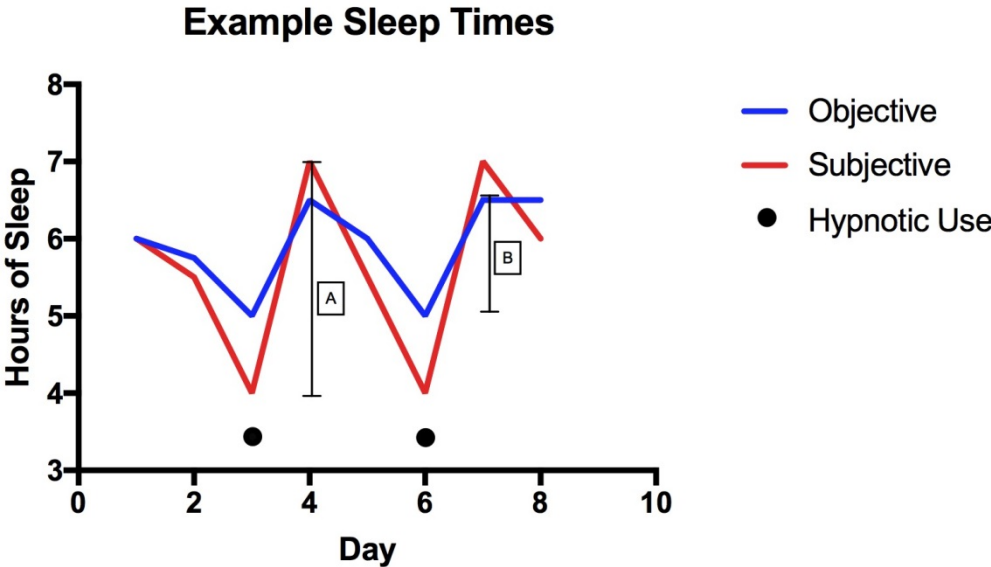


Figure 11. Sample simulations with the top graph demonstrating the probability of taking a hypnotic on any given night, the middle graph demonstrating the total subjective and objective sleep times, and the bottom graph demonstrating the number (hours) of misattribution events. (A) is a sample run from sleep phenotype 3 (not anxious, no tendency towards habit formation, and functioning homeostat) while (B) is from sleep phenotype 2 (anxious, tendency towards habit formation, and functioning homeostat).

