Original Article

Effects of homeopathic medicines on polysomnographic sleep of young adults with histories of coffee-related insomnia

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ABSTRACT

Background: Homeopathy, a common form of alternative medicine worldwide, relies on subjective patient reports for diagnosis and treatment. Polysomnography offers a modern methodology for evaluating the objective effects of taking homeopathic remedies that clinicians claim exert effects on sleep quality in susceptible individuals. Animal studies have previously shown changes in non rapid eye movement sleep with certain homeopathic remedies.
Methods: Young adults of both sexes (ages 18–31) with above-average scores on standardized personality scales for either cynical hostility or anxiety sensitivity (but not both) and a history of coffee-induced insomnia participated in the month-long study. At-home polysomnographic recordings were obtained on successive pairs of nights once per week for a total of eight recordings (nights 1, 2, 8, 9, 15, 16, 22, 23). Subjects ($N = 54$) received placebo pellets on night 8 (single-blind) and verum pellets on night 22 (double-blind) in 30c doses of one of two homeopathic remedies, Nux Vomica or Coffea Cruda. Subjects completed daily morning sleep diaries and weekly Pittsburgh sleep quality index scales, as well as profile of mood states scales at bedtime on polysomnography nights.
Results: Verum remedies significantly increased PSG total sleep time and NREM, as well as awakenings and stage changes. Changes in actigraphic and self-rated scale effects were not significant.
Conclusions: The study demonstrated the feasibility of using in-home, all-night sleep recordings to study homeopathic remedy effects. Findings are similar though not identical to those reported in animals with the same remedies. Possible mechanisms include initial disruption of the nonlinear dynamics of sleep patterns by the verum remedies.

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1. Introduction

Previous studies in many different countries have shown that a substantial proportion of the general population, especially individuals with chronic illnesses, use various types of complementary and alternative medicine (CAM) [1–4]. Among CAM users, insomnia and depression/anxiety are common conditions for which they seek alternative therapies [4,5]. Homeopathy, a 200-year-old whole system of CAM developed by a German physician, is one of the mostly widely known [6] and controversial modalities [7–9] for which clinicians and consumers worldwide claim

therapeutic benefit in sleep disturbances and fatigue, as well as other medical and psychiatric conditions [10–14].

Homeopathic clinicians often rely on subjective changes in sleep quality and increased mental/physical energy as early indications of the actions of homeopathic medicines (termed "remedies") [15]. But the relative lack of objective measures to evaluate homeopathy in human subjects has thus far hindered advances in both clinical care and research. Polysomnography (PSG), which can distinguish divergent findings, if present, between subjective sleep complaints and objective all-night sleep recording assessments in certain types of insomnia [16–18], offers a potentially valuable tool for homeopathic investigations.

Multiple studies on healthy animals have shown measurable effects on sleep of three different homeopathic remedies at potencies prepared to a dilution past Avogadro's number (Histamine, Coffea Cruda, and Nux Vomica) compared with placebo. Each rem-

edy at a 30c potency altered sleep patterns notably with differential effects on electroencephalographic delta frequency (0.5–2.5 Hz) power during sleep [19–22]. Other investigators have demonstrated effects of Nux Vomica 30c on alcohol-induced sleep time in mice [23,24].

Clinically, homeopaths report that Coffea Cruda patients are mild and timid, but also irritable and oversensitive to all types of sensory stimuli, especially noise, as well as to positive emotions [25,26]. Nux Vomica as a homeopathic remedy is used clinically to treat people with competitive, irritable and impatient Type A-like behavioral patterns and tendencies to abuse alcohol, caffeine, and other substances. Both Coffea Cruda and Nux Vomica patients report insomnia in the middle of the night as a symptom [27]. Taken together with the clinical reports, the animal EEG sleep data provide a basis for selecting Coffea Cruda and Nux Vomica as candidate homeopathic remedies to test in the first homeopathic PSG research on human subjects.

The primary purpose of the present within-subjects feasibility study was to examine the PSG effects of one dose of placebo versus either Coffea Cruda 30c or Nux Vomica 30c in relatively healthy young adult human subjects with a past history of coffee-induced insomnia. Because of the importance of person-centered factors in clinical expectations of remedy effects [27,28], inclusion criteria included individual difference traits of increased levels of either anxiety sensitivity or of Type A cynical hostility. Based on the animal studies, the remedy effects were hypothesized to include changes in both quantity and quality (variability in sleep stage changes and in awakenings after sleep onset) of NREM sleep, especially slow wave sleep, after controlling for within-subject baseline sleep patterns and placebo effects.

2. Methods

2.1. Subjects

Potential subjects were identified by screening young adult male and female college students (age range 18–31) enrolled in the introductory psychology class at the University of Arizona, for scores on the 16-item anxiety sensitivity index (ASI) [29], the 27-item Cook–Medley Cynical Hostility Scale (CMHO) [30], and one 5-point rating item on self-rated physical health [31]. All potential subjects had to score $\geqslant 3$ out of 5 on a rating of global health and give a history of coffee-induced insomnia in the past. The anxiety sensitivity and hostility classifications were used to select the study participants, such that individuals were chosen to be high hostile (above CMHO mean, below ASI mean) or high anxiety sensitive (below CMHO mean, above ASI mean). Above- and below-mean cutoffs for inclusion in the high anxiety sensitivity subgroup were $\geqslant 16.8$ for males and $\geqslant 19.1$ for females on the ASI and <11.0 on the CMHO; for the high hostility subgroup <16.8 for males and <19.1 for females on the ASI and $\geqslant 11.0$ on the CMHO. These cutoffs were determined by the study statistician using the mean scores computed from the first 1036 people screened for the study and are comparable to means published with similarly aged samples [32–35]. Subjects were dynamically assigned [36] to one of the two remedies, Nux Vomica or Coffea Cruda, using their CMHO and ASI scores, age, and sex as balancing factors.

The study was reviewed and approved by the University of Arizona Institutional Review Board. Research staff contacted eligible individuals and obtained written informed consent for the 4-week home-based PSG study participation. Because of the belief by some homeopaths that beverage coffee (but not caffeine) sometimes antidotes homeopathic remedies, subjects had to be willing to eliminate drinking coffee for the full duration of the study, although they were encouraged to change to and stabilize prior to the first baseline sleep recording night for at least 1 week on

non-coffee caffeinated beverages to maintain their customary daily caffeine intake without interruption, if necessary. Exclusion criteria were pregnancy or planning to become pregnant, major psychiatric or serious chronic medical conditions, chronic use of medications other than contraceptive drugs, and/or a history of anaphylactic shock. Subjects were paid $300 for their month-long participation. Table 1 summarizes descriptive characteristics of the study participants.

2.2. Procedures

Participants underwent a total of eight all-night PSG and actigraphic recordings in their own homes, distributed as 4 weekly pairs of consecutive nights (Week 1 baseline; Week 2 single-blind placebo pellets on night 8; Week 3 repeat baseline; Week 4 double-blind verum homeopathic remedy pellets on night 22). Thus, PSGs were performed on nights 1–2, 8–9, 15–16, and 22–23 of study participation. Subjects were instructed not to consume alcohol on the day of the recordings and not to consume caffeinated beverages or tobacco for 6 h prior to each PSG, but were otherwise encouraged to maintain their own habitual dietary and sleep–wake patterns in order to obtain naturalistic data.

The inclusion of baseline recordings on nights 1, 2, 15, and 16 enabled the establishment of typical sleep characteristics as a control for detecting effects of taking pellets on nights 8 and 22. Although subjects took no pellets on nights 9 or 23, most homeopaths claim to see evolving changes over time in patients for days to weeks and even months after administration of even a single 30c

Table 1
Demographic and baseline sleep variables.

Variable	Nux Vomica recipients ($n = 28$)	Coffea Cruda recipients ($n = 26$)
Age	19.6 ± 2.2	19.6 ± 2.6
Gender	11 M	16 M
CMHO	12.0 ± 2.2	11.8 ± 3.1
ASI	13.1 ± 7.3	16.2 ± 7.4
PSQI global score	4.1 ± 1.8	4.1 ± 1.6
SE%	90.4 ± 5.2	89.3 ± 3.9
Stage 1%	4.8 ± 2.2	5.5 ± 2.6
Stage 2%	50.0 ± 7.1	51.8 ± 6.1
SWS (stage 3–4)%	23.3 ± 6.1	22.1 ± 7.4
REM%	21.9 ± 5.4	21.8 ± 4.5
TST (min)	382.5 ± 55.5	378.3 ± 63.1
TIB (min)	423.0 ± 52.5	421.9 ± 59.3
SOL (min)	22.8 ± 19.7	23.4 ± 8.7
Stage 1 (min)	18.5 ± 8.6	21.0 ± 10.2
Stage 2 (min)	190.5 ± 33.5	195.7 ± 36.7
SWS (stage 3–4) (min)	88.2 ± 26.6	81.5 ± 28.0
REM (min)	85.1 ± 26.4	84.7 ± 23.3
NREM (min)	297.3 ± 42.5	298.2 ± 48.1
Stage changes	124.9 ± 33.3	120.7 ± 26.7
Awakenings	18.6 ± 6.4	19.1 ± 5.3
Arousal index	8.4 ± 2.6	9.6 ± 4.3
Actigraphy TST	382.5 ± 74.1	394.5 ± 64.9
Actigraphy SOL	23.1 ± 21.1	21.8 ± 11.7
Actigraphy SE	85.2 ± 7.7	86.9 ± 4.4
Actigraphy FI	8.9 ± 2.8	8.6 ± 3.2
POMS fatigue	3.1 ± 2.8	4.4 ± 2.4
Morning sleep diary ratings (3-category scale)	0.98 ± 0.48	1.06 ± 0.47
CMASI	0.67 ± 0.22	0.59 ± 0.26
Daily coffee	61%	42%
Other daily caffeine	82%	69%

There were no significant baseline differences on any of the variables between the remedy treatment groups at $P < 0.05$. CMHO, Cook–Medley Hostility Scale; ASI, anxiety sensitivity index; CMASI, unitary personality score for combination of hostility and anxiety sensitivity (see text); PSQI, Pittsburgh sleep quality index; TIB, time in bed; TST, total sleep time; SOL, sleep onset latency; SE, sleep efficiency; NREM, non-rapid eye movement sleep; SWS, slow wave sleep; REM, rapid eye movement sleep; FI, fragmentation index; POMS, profile of mood states scale.

potency dose to patients [37–41]. Basic science and animal studies offer some empirical support for such an assertion [21,42–44]. Therefore, with the clinical prediction of carryover effects from pellet night 22 to no-pellet night 23, the placebo week with recordings on nights 8 and 9 were similarly structured. Because of the claim of persistent effects of homeopathic remedies for variable periods of days to weeks after the last dose [45], the placebo condition was always placed prior to the 2-arm verum condition in time rather than attempting a simultaneous placebo versus remedy or counterbalanced crossover design (see also Walach's entanglement considerations for homeopathic study designs [46]).

All subjects completed the Pittsburgh sleep quality index (PSQI) [47,48] five times during the study, at baseline prior to the PSG sessions, and at the end of each study week. Prior to lights out on PSG nights, subjects also completed a profile of mood state (POMS) [49] scale. Bedtimes and sleep periods varied in accord with each individual's customary bedtime and waking time habits. Nevertheless, subjects were asked to choose the specific consecutive two days of the week when the weekly recordings occurred and to undergo the PSGs on the same two days of the week for each of the 4 weeks. Subjects completed a daily morning sleep quality rating over the 4 weeks of participation.

Indistinguishable placebo and verum remedy pellets (Coffea Cruda 30c, Nux Vomica 30c) were purchased from Hahnemann Laboratories, Inc. (San Rafael, CA), an FDA-regulated homeopathic pharmacy experienced in collaborating on research study protocols. The #30 lactose–sucrose dry pellets were certified for purity and lack of contaminants by an independent testing laboratory. All vials of placebo and remedy were number-coded, labeled for blinding, and assigned sequentially by subject number on the basis of a design adaptive allocation procedure appropriate for small sample studies [50,51]. Consistent with clinical practice, subjects were asked to dissolve three pellets from their assigned study vials under the tongue on night 8 (placebo) and night 22 (verum). On verum night 22, half of each personality type group received Coffea Cruda 30c and half received Nux Vomica 30c.

2.3. Polysomnographic and actigraphic recordings

Ambulatory PSGs were performed using Cadwell Laboratories Inc. Easy Ambulatory 2 system equipment (Kennewick, WA). Recordings include six unipolar EEG channels (C3, C4, Cz, Pz, O1, and O2 referenced to contralateral mastoids), bilateral electrooculograms (EOG), mental/submental electromyogram, and a two-lead electrocardiogram (bilateral sub-clavicle electrode placement). Electrode impedance levels were kept below 5 kΩ. Equipment settings for data acquisition included an EEG sampling rate of 200 Hz, a low pass filter set at 35 Hz and a high pass filter set at 0.53 Hz. A 60 cycle notch filter was used to eliminate ambient electrical noise.

Actigraphic data were collected using a Mini Mitter Inc., Actiwatch-64 (Bend, OR) worn on the subjects' left wrist. The Actiwatch was programmed to record in 15-s epochs, with movement sampled at 32 Hz. The actigraphs were analyzed using Actiware-Sleep version 3.4 software (Mini Mitter Inc.), with wake-threshold sensitivity set to medium. Actigraph Bedtime and Uptime were entered as the lights out and lights on time, respectively, as determined by the PSG recording.

Technicians performed the hookups in the subjects' homes prior to customary bedtimes and departed until the next day when they picked up the equipment for data downloading. Data were scored in 30-s epochs in accord with standard Rechtschaffen–Kales criteria [52] by a sleep technician certified to 94% inter-rater reliability criteria by a registered PSG technician and blinded to the remedy received. Arousal scoring was performed in accordance with the American Academy of Sleep Medicine guidelines [53]. Subjects initiated a marker for lights out by a button press on the Cadwell

Easy Ambulatory 2 unit. Nights on which subjects had less than 4 h of scorable sleep were not used in the analyses as previous sleep studies have done [54,55]. Setting a minimum threshold for time in bed (TIB) is a common control in ambulatory sleep studies [55] to prevent skewed values of variables dependent on TIB, such as sleep efficiency which is computed as total sleep time (TST) divided by TIB.

2.4. Statistics

Based on the clinical literature and animal studies, primary outcome variables of interest were total sleep time, slow wave sleep, stage changes, and awakenings after sleep onset, as a function of verum remedy versus placebo across all subjects. Given the exploratory and early research phase nature of the current study on human subjects, however, PSG sleep onset and rapid eye movement (REM) latencies, REM and other NREM stages, as well as actigraphic measures of TST, sleep onset latency, sleep efficiency, and fragmentation index, were examined secondarily for possible effects. The focus of the current paper is the effects of remedies themselves. Subsequent papers will report on the interactions between remedy effects and personality types for POMS and individual night effects on spectral EEG.

To facilitate use of personality as a covariate in regression models, a net personality score (CMASI) was computed as a unitary continuous variable, using the values from the ASI and CMHO, where a higher value signified greater hostility and less anxiety sensitivity. CMASI scores are a linear combination of the CMHO and ASI which varied from 0 to 1, with large values denoting high CMHO and low ASI and small values denoting low CMHO and high ASI. Due to the design of the study, CMHO and ASI scores are inversely related.

Using the sleep outcome variables listed above as dependent variables, we tested whether the outcome variable for the verum week (nights 22, 23) differed from means for the placebo week (nights 8, 9) after adjusting for the mean for the four baseline nights (1, 2, 15, 16). Averaging all four baseline nights helped lessen any confounds from first-night effects in the home setting on study night 1 by providing multiple assessments of the subjects' usual sleep patterns without study medications in both Weeks 1 and 3 of the protocol.

We utilized a random effect regression model for analysis, with person as the random effect. The regression equations each controlled for sex, the CMASI net personality score, the baseline value of the outcome variable, and total time in bed. For example, we tested whether a subject's Week 4 (verum) stage changes differed from their Week 2 (placebo) stage changes, after adjusting for their own baseline stage changes, sex, CMASI and total time in bed. Descriptive statistics, t-tests, and χ^2 analyses were used to assess demographic variables. STATA 10.0 was used for all data reduction and analyses.

3. Results

A total of 4279 people were screened for the study. Seventy people met all eligibility criteria, volunteered and enrolled in the study. But 5 participants who started the study were administratively withdrawn due to early protocol violations making them ineligible for study participation (e.g., beginning medication on the exclusion list, an undisclosed health problem on the exclusion list). Three subjects opted out of the study (e.g., schedule conflicts, catching the flu) prior to treatment allocation and 3 subjects were not within the targeted age range for the present study, leaving a total of 59 participants who received the homeopathic treatment and completed the study. Five subjects from the remaining 59

enrolled participants did not meet the criterion for the minimum 4 h of sleep per night and/or did not have enough data on their baseline recordings for analysis. The results reported reflect the findings from the remaining 54 participants (allocated to Coffea Cruda [n = 26] or Nux Vomica [n = 28] on night 22).

In-home recordings pose unique challenges for data quality. Portions of different nights and unavailability for some subjects on certain nights contributed to difficulties obtaining complete data. Individual electrodes or, rarely, the main battery pack cables detached during the sleep period on various nights in different subjects, resulting in partial data loss. On average, out of the 4 possible baseline nights (nights 1, 2, 15, 16) subjects contributed 2.96 ± 1.00 baseline nights. There were two possible nights of data on both placebo and remedy weeks. Subjects on average contributed 1.39 ± 0.74 and 1.33 ± 0.67 days, respectively, on placebo and remedy week. Outcome data on missing nights (due to the absence of data or failure to meet the sleep quality standard) were imputed as follows: any values that had valid data on any preceding or following night in the study design were determined by linear interpolation. Then, any remaining missing values were filled in by carrying the last value forward.

The final sample of young adults ($N = 54$) in the current report had a mean age of 20 SD 2 years (50% female). Table 1 shows that the subsets of subjects who received Coffea Cruda ($n = 26$) versus Nux Vomica ($n = 28$) did not differ in age, gender distribution, CMASI, PSQI, baseline PSG and sleep diary parameters.

Table 2 gives the verum effects in comparison with placebo and significance levels for the effects of the remedies together and separately. These effects are reported using unstandardized coefficients with standard errors to interpret the variables in their unit of measurement. When data from the two remedies were combined, overall PSG for the remedy week showed significantly longer TST, increased NREM sleep including more minutes in stage 2 and increased slow wave sleep (SWS), with a trend toward increased minutes of stage 4 sleep ($\beta = 5.8$, $P < 0.10$) compared with placebo. Remedies also led to more sleep disruptions after sleep onset, with significantly increased awakenings, number of stage changes, and more type 2 arousals compared to placebo.

In the remedy-specific within-subject analyses, Coffea Cruda and Nux Vomica recipients both showed similar significant effects of increasing TST and NREM on verum as compared with placebo nights. But only Nux Vomica effects were significant for increases in type 2 arousals and on the Arousal Index on verum versus placebo nights.

Differences between Nux Vomica and Coffea Cruda treatment groups for remedy week nights 22 and 23 were compared. The only variable with a significant difference was a lower arousal index for the Coffea Cruda recipients ($\beta = -1.24$, 95% confidence interval -2.5 to -0.01, $t = -2.1$, $P = 0.049$). Nux Vomica and Coffea Cruda recipients did not significantly differ on the remaining variables listed in Table 2.

Within-subject analyses of the actigraphic measures, which depend on indications of gross motor activity of the wrist rather than EEG, showed no significant treatment effects on TST, sleep onset latency, sleep efficiency, or fragmentation index.

For the subjective measures, individuals receiving Coffea Cruda showed a trend toward a decrease in POMS fatigue on the post-verum night compared with the post-placebo night (Table 2). Overall, remedy (verum) week was not different from placebo week on the subjective ratings of global sleep quality on the weekly PSQI, after controlling for baseline values. On the daily morning sleep diary ratings (3 possible categories: fatigued, somewhat refreshed, refreshed), the only finding was a trend toward poorer subjective sleep for Nux Vomica compared with placebo in a logistic regression, controlling for personality and sex (OR 0.29, CI 0.08–1.11, $P = 0.07$).

4. Discussion

The current study demonstrates the feasibility of using in-home all-night sleep recordings with ambulatory PSG equipment in young adults to assess the effects of homeopathic remedies. Both remedies led to an increase in TST reflected mainly in increased NREM sleep. The increased NREM time is similar to observations from previous animal sleep studies with Coffea Cruda 30c [19–21]. In addition, consistent with the animal data showing increased variability of EEG sleep after Nux Vomica 30c [56], the human subjects in the present study had a significant increase in stage changes on remedy nights compared to those on placebo nights. The Nux Vomica group also demonstrated a higher arousal index than did the Coffea Cruda subjects. Despite an increase in sleep disruption after sleep onset, manifested by more awakenings on remedy week nights versus placebo nights, POMS fatigue ratings were lower for the remedy nights. Notably, during open-ended exit interviews while still blinded, many subjects reported their perceptions of greater sleep disruption following placebo, compared to remedy nights. The POMS fatigue subscale findings are consistent with the latter qualitative observations.

Table 2
Regression findings for within-subject analyses on means for combined remedy nights (22/23) versus means for combined placebo nights 8/9, controlling for gender, personality scores, total time in bed, and means for combined baseline nights (1/2/15/16).

Outcome variable	Both remedies (n = 54)			Nux Vomica only (n = 28)			Coffea Cruda only (n = 26)		
	β	95%CI	R^2	β	95%CI	R^2	β	95%CI	R^2
TST	69.5***	(39.4, 99.7)	0.52	52.8**	(14.9, 90.8)	0.60	92.7**	(38.3, 147.1)	0.51
Stage 2 (min)	36.6***	(19.6, 53.6)	0.51	29.3**	(8.3, 50.3)	0.60	45.9**	(14.9, 76.8)	0.46
NREM	54.8***	(32.0, 77.6)	0.50	45.9**	(19.4, 72.3)	0.60	67.3**	(24.8, 109.8)	0.44
SWS	13.3**	(5.3, 21.4)	0.46	12.4*	(1.8, 23.0)	0.47	15.2*	(1.5, 28.8)	0.48
Stage changes	22.9***	(12.1, 33.7)	0.47	20.9**	(5.9, 35.8)	0.49	25.0**	(7.3, 42.8)	0.44
Awakenings	4.1***	(2.0, 6.2)	0.49	4.1*	(1.0, 7.2)	0.45	4.1*	(0.9, 7.2)	0.61
Arousal index	0.8†	(−0.6, 1.6)	0.63	1.3**	(0.5, 2.1)	0.77	0.2	(−1.4, 1.8)	0.61
Type 2 arousals	3.1**	(0.99, 5.2)	0.51	3.0*	(0.2, 5.8)	0.49	3.2†	(−0.3, 6.7)	0.55
POMS-fatigue	−1.1*	(−2.0, −0.2)	0.45	−1.0	(−2.3, −0.4)	0.52	−1.3†	(−2.6, 0.04)	0.34
Weekly PSQI global score	−0.2	(−0.9, 0.5)	0.30	−0.2	(−1.3, 1.0)	0.24	−0.3	(−1.2, 0.6)	0.43

TST, total sleep time; SWS, slow wave sleep (stages 3- and 4-min); NREM, non rapid eye movement sleep; PSQI, Pittsburgh sleep quality index (higher scores mean poorer subjective sleep); POMS, profile of mood state scale.
† $P < 0.10$.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

One possible interpretation of the data could be that the seeming changes in sleep during the remedy week resulted from the passage of time and general adaptation of subjects to the study protocol and equipment, rather than that of remedy effects. The objective findings, however, are not fully consistent with a time effect by itself. The regression analyses were controlled for PSG sleep variable findings not only on nights 1–2, but also on nights 15–16. If subjects were simply sleeping better as time passed in the study without a role for the remedies themselves, then awakenings and other measures of transient sleep disturbances during the night should have decreased by the remedy week (study Week 4). Instead, even though TST increased, the number of awakenings, sleep stage changes, and arousal index increased, especially with Nux Vomica 30c.

Moreover, personality type interacted with the specific remedy received to produce differential changes in the POMS; effects are reported elsewhere [57]. Thus, even if the passage of time contributes to some of the apparent differences between the Week 2 placebo and Week 4 remedy findings, the data suggest remedy effects beyond those from the simple passage of time. Individual susceptibility to unique remedy-specific, as opposed to non-specific placebo, symptoms in healthy human subjects appears characteristic of other widely-used homeopathic remedies in 30c potency as well [58].

The use of objective markers of remedy effects such as PSG recordings offers an innovative approach to advancing work in a controversial area such as homeopathy, where most contested clinical studies rely on subjective assessments alone. Waking EEG also has shown promise in documenting the effects of individualized homeopathic remedies on patient populations [59,60]. In the present study, it is notable that the PSG but not the actigraphic measures showed remedy effects above those attributable to placebo. The ability of homeopathic remedies to cause subtle and unique subjective symptoms that conventional standardized questionnaires can miss [58] and the current observation of significant remedy effects on sleep EEG, but not actigraphy, suggest caution in relying solely on actigraphy for future sleep studies of homeopathic remedies. Because of the dependence on muscle movement, actigraphy can underestimate sleep latency, waking periods, and total sleep time as compared with PSG recordings whenever subjects are awake, but physically inactive [61].

The study design was deliberately structured with single-blind placebo preceding allocation to one or the other of the two double-blind remedies in order to address a different potential methodological and theoretical concern, i.e., the reported risk of non-local or entanglement confounds of placebo and remedy effects, when treatment arms are administered double-blind in a closed system of a homeopathic study. Keeping the experimental system open with single-blind placebo may have provided a strategy to reduce the risk of entanglement between placebo and remedy effects [62–65].

The mixed directionality of the sleep changes on remedy nights, i.e., some improvements and some disruptions in PSG variables, is consistent with the clinical literature and practice theory [15,66,67]. That is, homeopaths claim bidirectional and mixed direction effects for their remedies under several common circumstances dependent on (a) initial state of the host; and/or (b) differential direction of global versus local effects (improved global with worsened local changes). Nonlinear, bidirectional effects of homeopathic remedies, especially early in the course of the response, are consistent with state dependency. That is, the same remedy at the same potency (e.g., 30c) can cause a set of transient symptoms in a healthy person, but alleviate similar symptoms in a sick person or animal [66]. Given previous data on evolving nonlinear changes over time after administration of homeopathic remedies [22,68], further examination of the dynamics of the physiological and self-report measures over time will be essential [69]. The brief time period in which the PSG recordings were obtained following remedy administration (2 nights) would reflect only an initial, destabilized transitional phase in the dynamic response to the remedies [70].

In summary, the current findings on human sleep are similar but not identical to previously-reported, objectively-measurable effects of the same two homeopathic remedies on animals. Future studies are needed to evaluate longitudinal changes in EEG dynamics and to examine evolution of sleep patterns over a much longer period of time after remedy administration in persons with primary insomnia and in healthy individuals. Overall, the sleep literature on various forms of alternative medicine, including homeopathy, is very limited, requiring more rigor and more study [71–73]. Moreover, the present findings do not address the question of whether or not either of the homeopathic remedies tested here would be therapeutic for certain people with insomnia. Rather, the data provide initial evidence for feasibility of the PSG methodological approach and the ability of homeopathic remedies to alter objective sleep in human subjects.

New basic science evidence begins to address some of the major concerns of skeptics about the plausibility of biological activity in homeopathic remedies [43,44,74–78]. Several different laboratories have reported measurable physico-chemical changes in the solvent during the succussion (vigorous shaking) procedure in homeopathic remedy preparation, even when the dilution process takes the original source material past Avogadro's number of molecules. Thus, the data open the door to reconsidering the biological as well as psychological effects of adjunctive use of homeopathic remedies in human subjects [79].

References

[1] Menniti-Ippolito FGL, Bologna E, Forcella E, Raschetti R. Use of unconventional medicine in Italy: a nation-wide survey. Eur J Clin Pharmacol 2002;58:61–4.

[2] Becker-Witt C, Lüdtke R, Weisshuhn TE, Willich SN. Diagnoses and treatment in homeopathic medical practice. Forsch Komplementarmed Klass Naturheilkd 2004;11:98–103.

[3] Sirois FM. Provider-based complementary and alternative medicine use among three chronic illness groups: associations with psychosocial factors and concurrent use of conventional health-care services. Complement Ther Med 2008;16:73–80.

[4] Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States 2007. National Health Statistics Reports. Hyattsville, MD: U.S. Department of Health and Human Services; 2008.

[5] Baldwin CM, Long K, Kroesen K, Brooks AJ, Bell IR. A profile of military veterans in the southwestern United States who use complementary and alternative medicine: implications for integrated care. Arch Intern Med 2002;162:1697–704.

[6] Kaul PN. Alternative therapeutic modalities. Alternative medicine. Prog Drug Res 1996;47:251–77.

[7] Merrell WC, Shalts E. Homeopathy. Med Clin North Am 2002;86:47–62.

[8] Fisher P. Homeopathy and The Lancet. Evid Based Complement Altern Med 2006;3:145–7.

[9] Jonas WB, Anderson RL, Crawford CC, Lyons JS. A systematic review of the quality of homeopathic clinical trials. BMC Complement Altern Med 2001;1:12.

[10] Guthlin C, Lange O, Walach H. Measuring the effects of acupuncture and homoeopathy in general practice: an uncontrolled prospective documentation approach. BMC Public Health 2004;4:4.

[11] Witt C, Keil T, Selim D, Roll S, Vance W, Wegscheider K, et al. Outcome and costs of homoeopathic and conventional treatment strategies: a comparative cohort study in patients with chronic disorders. Complement Ther Med 2005;13:79–86.

[12] van Wassenhoven M, Ives G. An observational study of patients receiving homeopathic treatment. Homeopathy 2004;93:3–11.

[13] Itamura R. Effect of homeopathic treatment of 60 Japanese patients with chronic skin disease. Complement Ther Med 2007;15:115–20.

[14] Muller-Krampe B, Oberbaum M, Klein P, Weiser M. Effects of Spascupreel versus hyoscine butylbromide for gastrointestinal cramps in children. Pediatr Int 2007;49:328–34.

[15] Vithoulkas G. The science of homeopathy. NY: Grove Weidenfield; 1980.

[16] Ouellet MC, Morin CM. Subjective and objective measures of insomnia in the context of traumatic brain injury: a preliminary study. Sleep Med 2006;7:486–97.

[17] Rowe MA, McCrae CS, Campbell JM, Benito AP, Cheng J. Sleep pattern differences between older adult dementia caregivers and older adult noncaregivers using objective and subjective measures. J Clin Sleep Med 2008;4:362–9.

[18] Silva GE, Goodwin JL, Sherrill DL, Arnold JL, Bootzin RR, Smith T, et al. Relationship between reported and measured sleep times: the sleep heart health study (SHHS). J Clin Sleep Med 2007;3:622–30.

[19] Ruiz-Vega G, Perez-Ordaz L, Proa-Flores P, Aguilar-Diaz Y. An evaluation of Coffea cruda effect on rats. Br Homoeopathic J 2000;89:122–6.

[20] Ruiz-Vega G, Perez-Ordaz L, Leon-Hueramo O, Cruz-Vazquez E, Sanchez-Diaz N. Comparative effect of Coffea cruda potencies on rats. Homeopathy 2002;91:80–4.

[21] Ruiz-Vega G, Perez-Ordaz L, Cortes-Galvan L, Juarez-G FM. A kinetic approach to caffeine–Coffea cruda interaction. Homeopathy 2003;92:19–29.

[22] Ruiz-Vega G, Poitevin B, Pérez-Ordaz L. Histamine at high dilution reduces spectral density in delta band in sleeping rats. Homeopathy 2005;94:86–91.

[23] Sukul A, Sinhabau SP, Sukul NC. Reduction of alcohol induced sleep time in albino mice by potentized Nux vomica prepared with 90% ethanol. Br Homoeopathic J 1999;88:58–61.

[24] Sukul NC, Ghosh S, Sinhababu SP, Sukul A. Strychnos nux-vomica extract and its ultra-high dilution reduce voluntary ethanol intake in rats. J Altern Complement Med 2001;7:187–93.

[25] Kent JT. Lectures on homeopathic materia medica. New Delhi, India: Jain Publishing Co.; 1972.

[26] Hering C. Dr. H. Gross' Comparative Materia Medica. London: H. Turner and Co.; 1867.

[27] Morrison R. Desktop guide to keynotes and confirmatory symptoms. Albany, CA: Hahnemann Clinic Publishing; 1993.

[28] Lansky AL. Impossible cure: the promise of homeopathy. Portola Valley, CA: R.L. Ranch Press; 2003.

[29] Reiss S, Peterson RA, Gursky M, McNally RJ. Anxiety sensitivity, anxiety frequency, and the prediction of fearfulness. Behav Res Ther 1986;24:1–8.

[30] Cook WW, Medley DM. Proposed hostility and pharisaid-virtue scales for the MMPI. J Appl Psychol 1954;38:414–8.

[31] Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care 1996;30:473–83.

[32] Barefoot JC, Dahlstrom G, Williams RB. Hostility, CHD incidence, and total mortality: a 25-year follow-up study of 255 physicians. Psychosom Med 1983;45:59–64.

[33] Barefoot JC, Dodge KA, Peterson BL, Dahlstrom WG, Williams RB. The Cook–Medley Hostility Scale: item content and ability to predict survival. Psychosom Med 1989;51:46–57.

[34] Scherwitz L, Perkins L, Chesney M, Hughes G. Cook–Medley Hostility Scale and subsets: relationship to demographic and psychosocial characteristics in young adults in the CARDIA study. Psychosom Med 1991;53:36–49.

[35] Telch MJ, Lucas JA, Nelson P. Nonclinical panic in college students: an investigation of prevalence and symptomatology. J Abnorm Psychol 1989;98:300–6.

[36] Aickin M. A simulation study of the validity and efficiency of design-adaptive allocation to two groups in the regression situation. Int J Biostatistics 2009;5. article 19.

[37] Sherr J. The dynamics and methodology of homeopathic provings. 2nd ed. Malvern, UK: Dynamis Books; 1994.

[38] Herrick N. Animal mind, human voices. Provings of eight new animal remedies. Point Richmond, CA: Hahnemann Clinic Publishing; 1998.

[39] Herrick N. Sacred plants, human voices. Point Richmond, CA: Hahnemann Clinic Publishing; 2003.

[40] Owen D. Principles and practice of homeopathy: the therapeutic and healing process. Churchill Livingstone; 2007.

[41] Lewith GT, Watkins AD, Hyland ME, Shaw S, Broomfield JA, Dolan G, et al. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial. BMJ 2002;324:520–3.

[42] Sukul NC, Bala SK, Bhattacharyya B. Prolonged cataleptogenic effects of potentized homoeopathic drugs. Psychopharmacology 1986;89:338–9.

[43] Elia V, Niccoli M. New physico-chemical properties of extremely diluted aqueous solutions. J Therm Anal Calorim 2004;75:815–36.

[44] Elia V, Napoli E, Germano R. The 'Memory of Water': an almost deciphered enigma. Dissipative structures in extremely dilute aqueous solutions. Homeopathy 2007;96:163–9.

[45] Frei H, Everts R, von Ammon K, Kaufmann F, Walther D, Schmitz SF, et al. Randomised controlled trials of homeopathy in hyperactive children: treatment procedure leads to an unconventional study design Experience with open-label homeopathic treatment preceding the Swiss ADHD placebo controlled, randomised, double-blind, cross-over trial. Homeopathy 2007;96:35–41.

[46] Walach H. Entanglement model of homeopathy as an example of generalised entanglement predicted by weak quantum theory. Forschende Komplementarmedizin/Research in Complementary Medicine 2003;10:192–200.

[47] Buysse DJ, Reynolds CF, Monk TH, Berman SR, et al. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.

[48] Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh sleep quality index. J Psychosom Res 1998;45:5–13.

[49] Shacam S. A shortened version of the profile of mood states. J Pers Assess 1983;47:305–6.

[50] Aickin M. Randomization, balance, and the validity and efficiency of design-adaptive allocation methods. J Stat Plan Infer 2001;94:97–119.

[51] Aickin M. A program for balancing the allocation of subjects to treatment in a clinical trial. Comput Biomed Res 1982;15:519–24.

[52] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Los Angeles, CA: UCLA BIS/BRI Publications; 1998.

[53] Task-Force. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992; 15: 173–84.

[54] Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association-of-sleep-disordered-breathing. Sleep apnea, and hypertension in a large community-based study. JAMA 2000;283:1829–36.

[55] Redline S, Sanders MH, Lind BK, Quan SF, Gottlieb DJ, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. Sleep 1998;21:759–67.

[56] Ruiz G, Torres JL. Homeopathic effect on the sleep pattern of rats. Br Homoeopathic J 1997;86:201–6.

[57] Brooks AJ, Bell IR, Howerter A, Jackson N, Aickin M. Effects of homeopathic medicines on mood of adults with histories of coffee-related insomnia. Submitted for publication.

[58] Mollinger H, Schneider R, Walach H. Homeopathic pathogenetic trials produce specific symptoms different from placebo. Forsch Komplementmed 2009;16:105–10.

[59] Bell IR, Lewis DAI, Schwartz GE, Lewis SE, Caspi O, Scott A, et al. Electroencephalographic cordance patterns distinguish exceptional clinical responders with fibromyalgia to individualized homeopathic medicines. J Altern Complement Med 2004;10:285–99.

[60] Bell IR, Lewis DAI, Lewis SE, Schwartz GE, Scott A, Brooks AJ, et al. Electroencephalographic alpha sensitization in individualized homeopathic treatment of fibromyalgia. Int J Neurosci 2004;114:1195–220.

[61] Morgenthaler T, Alessi C, Friedman L, Owens J, Kapur V, Boehlecke B, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep 2007;30:519–29.

[62] Walach H. Entanglement model of homeopathy as an example of generalized entanglement predicted by weak quantum theory. Forschende Komplementarmedizin und Klassische Naturheilkunde 2003;10:192–200.

[63] Mollinger H, Schneider R, Loffel M, Walach H. A double-blind, randomized, homeopathic pathogenetic trial with healthy persons: comparing two high potencies. Forschende Komplementarmedizin und Klassische Naturheilkunde 2004;11:274–80.

[64] Walach H. Generalized entanglement: a new theoretical model for understanding the effects of complementary and alternative medicine. J Altern Complement Med 2005;11:549–59.

[65] Walach H, Mollinger H, Sherr J, Schneider R. Homeopathic pathogenetic trials produce more specific than non-specific symptoms: results from two double-blind placebo controlled trials. J Psychopharmacol 2008;22:543–52.

[66] Bertani S, Lussignoli S, Andrioli G, Bellavite P, Conforti A. Dual effects of a homeopathic mineral complex on carrageenan-induced oedema in rats. Br Homoeopathic J 1999;88:101–5.

[67] Bellavite P. Complexity science and homeopathy: a synthetic overview. Homeopathy 2003;92:203–12.

[68] Hyland ME, Lewith GT. Oscillatory effects in a homeopathic clinical trial: an explanation using complexity theory, and implications for clinical practice. Homeopathy 2002;91:145–9.

[69] Bell IR, Koithan M. Models for the study of whole systems. Integr Cancer Ther 2006;5:293–307.

[70] Hollenstein T. State space grids: analyzing dynamics across development. Int J Behav Dev 2007;31:384–96.

[71] Stevinson C, Ernst E. Valerian for insomnia: a systematic review of randomized clinical trials. Sleep Med 2000;1:91–9.

[72] Freire AO, Sugai GC, Chrispin FS, Togeiro SM, Yamamura Y, Mello LE, et al. Treatment of moderate obstructive sleep apnea syndrome with acupuncture: a randomised, placebo-controlled pilot trial. Sleep Med 2007;8:43–50.

[73] Yeh GY, Mietus JE, Peng CK, Phillips RS, Davis RB, Wayne PM, et al. Enhancement of sleep stability with Tai Chi exercise in chronic heart failure: preliminary findings using an ECG-based spectrogram method. Sleep Med 2008;9:527–36.

[74] Rey L. Thermoluminescence of ultra-high dilutions of lithium chloride and sodium chloride. Physica A 2003;323:67–74.

[75] Rey L. Can low-temperature thermoluminescence cast light on the nature of ultra-high dilutions? Homeopathy 2007;96:170–4.

[76] Roy R, Tiller W, Bell IR, Hoover MR. The structure of liquid water: novel insights from materials research and potential relevance to homeopathy. Mater Res Innov 2005;9:557–608.

[77] Rao ML, Roy R, Bell IR, Hoover R. The defining role of structure (including epitaxy) in the plausibility of homeopathy. Homeopathy 2007;96:175–82.

[78] Rao M, Roy R, Bell IR. Characterization of the structure of ultra dilute sols with remarkable biological properties. Mater Lett 2008;62:1487–90.

[79] Witt C, Albrecht H, editors. New directions in homeopathy research. Essen, Germany: KVC Verlag; 2009.