ONLINE SUPPLEMENT

Effects of suboptimal adherence of CPAP-therapy on symptoms of obstructive sleep apnea: a randomized, double-blind, controlled trial.

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Methods

Screening

Patients were screened at the following institutions: 1) University Hospital Zurich (internal search performed by us); 2) Independent association of "Lunge Zürich" (who, on our behalf, provided a pre-selection of potential participants derived from their data base after written permissions from the following referring hospitals had been obtained: Spital Männedorf, Zürcher RehaZentrum Wald, Spital Triemli and Spital Horgen); 4) Kantonsspital Aarau, Kantonsspital Graubünden, Kantonsspital Schaffhausen, Kantonsspital Münsterlingen and "Lunge Glarus" (external search performed by us after written permissions had been obtained within the scope of trans-regional collaborations).

Confirmation of relevant OSA

The patients had to wear wrist pulse oximeters (Pulsox-300i, Konica Minolta Sensing Inc., Osaka, Japan) at home during each night of the four-night period off CPAP. Regular CPAP therapies had to be resumed for at least two weeks prior to minimization/allocation.

Randomization and masking. The MS-DOS program MINIM (London, UK) was used to allocate participants by two minimization criteria: maximal off-CPAP $ODI_{4\%}$ </> 30/h (from four consecutive CPAP withdrawal nights) and body mass index (BMI) </> 30 kg/m^2. After random allocation, every participant received the same model of CPAP-machine. Each device was marked with a random 5-digit code (generated via random.com) masking the allocation for patients and investigators throughout the whole trial. Regular controls of our RCT were performed by an external monitor who was otherwise not involved in the study.

Respiratory polygraphies (RPs)

Baseline inpatient RPs were performed under therapeutic CPAP in both arms. Follow-up RPs were performed after two weeks under either therapeutic (control arm) or subtherapeutic CPAP (intervention arm) settings. Inpatient RPs were recorded by Alice 6 Diagnostic System (Philips Respironics, PA, USA), scored with validated Somnolzyer 24x7 software (Philips Respironics, PA, USA)[1] and reviewed manually. The recommendations of the American Academy of Sleep Medicine from 2007 were applied (AASM 2007 Version B)[2] with quantification of OSA-severity by AHI and $ODI_{4\%}$.

CPAP device

For this trial we used AirSense AutoSet S10 by ResMed (San Diego, CA, USA). All patients were trained to operate the study CPAP-device and explicitly advised to continue their usual CPAP routines. Participants, as well as outcome assessors, remained blinded to the arm-assignment until completion of the data analysis.

Patient diaries

During the two weeks of intervention, the patients had to keep a diary to record their systolic and diastolic blood pressure (BP) and heart rate (HR) values three times a day (morning, midday, evening) with three subsequent measurements at a time, as well as note special occurrences (if any). For measuring BP and HR, each participant was provided with the same, clinically validated device (OMR-M7-IT, HEM-7322T, Omron, Advance AG, Switzerland) and trained in its use.

Vigilance tests

Immediately after each RP (at baseline and on the follow-up visit) a one-time Oxford Sleep Latency Test (OSLER) and a one-time Multiple Unprepared Reaction Time (MURT) test were performed. The clinical circumstances of those tests were controlled to ensure low external stimulation: 1) Performance in the same, darkened room with sound insulation and observation via infra-red camera; 2) Confiscation of cell phones, smart devices and watches prior to testing;

3) Testing prior to breakfast, morning medication or the habitual use of stimulants in the morning (e.g. tobacco, caffeine). The participants were allowed to freely change their bodily positions for the duration of the tests.

Sleepiness and QoL questionnaires

After each RP, the participants had to fill out the same bundle of three questionnaires: the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ-10) and the 36-Item Short Form Health Survey (SF-36) to retrospectively assess their previous two weeks.

Bayesian analysis

To supplement the classical analysis, we also considered historical data. Historical trials were identified via a systematic review of the literature.

Eligibility criteria of randomized controlled trials

- Aged ≥18 years
- Diagnosis of obstructive sleep apnea (OSA) defined by an apnoea–hypopnoea index (AHI) ≥5/h
- Random assignment to any combination of continuous positive airway pressure (CPAP, fixed or autotitrating), or an inactive control (sham-CPAP, any other type of placebo [e.g. placebo tablet], no treatment, or usual or standard care)
- RCTs of patients with a concurrent disease (eg, heart failure and stroke) were eligible for inclusion
- Assessment of Epworth Sleepiness Scale (ESS), or Short Form (36) Health Survey (SF-36), or arterial blood pressure (ambulatory, office measurements) at baseline and a follow-up visit and reported with some measure of variability (eg, standard deviation or error) either the average number (i.e. points, standardized score, or mmHg) at each visit, the average change in each group at follow-up compared with baseline, or a treatment effect for the difference in the change of the number between groups
- Parallel or crossover randomized controlled trial design

Comment: If two eligible trials contained a significant overlap in patients, the larger of the two trials was used in the analysis.

Databases

- MEDLINE (from inception to December 1, 2018)
- Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3 (from inception to December 1, 2018)
- Bibliographies of eligible trials

Search terms used for MEDLINE and Cochrane library

MEDLINE:

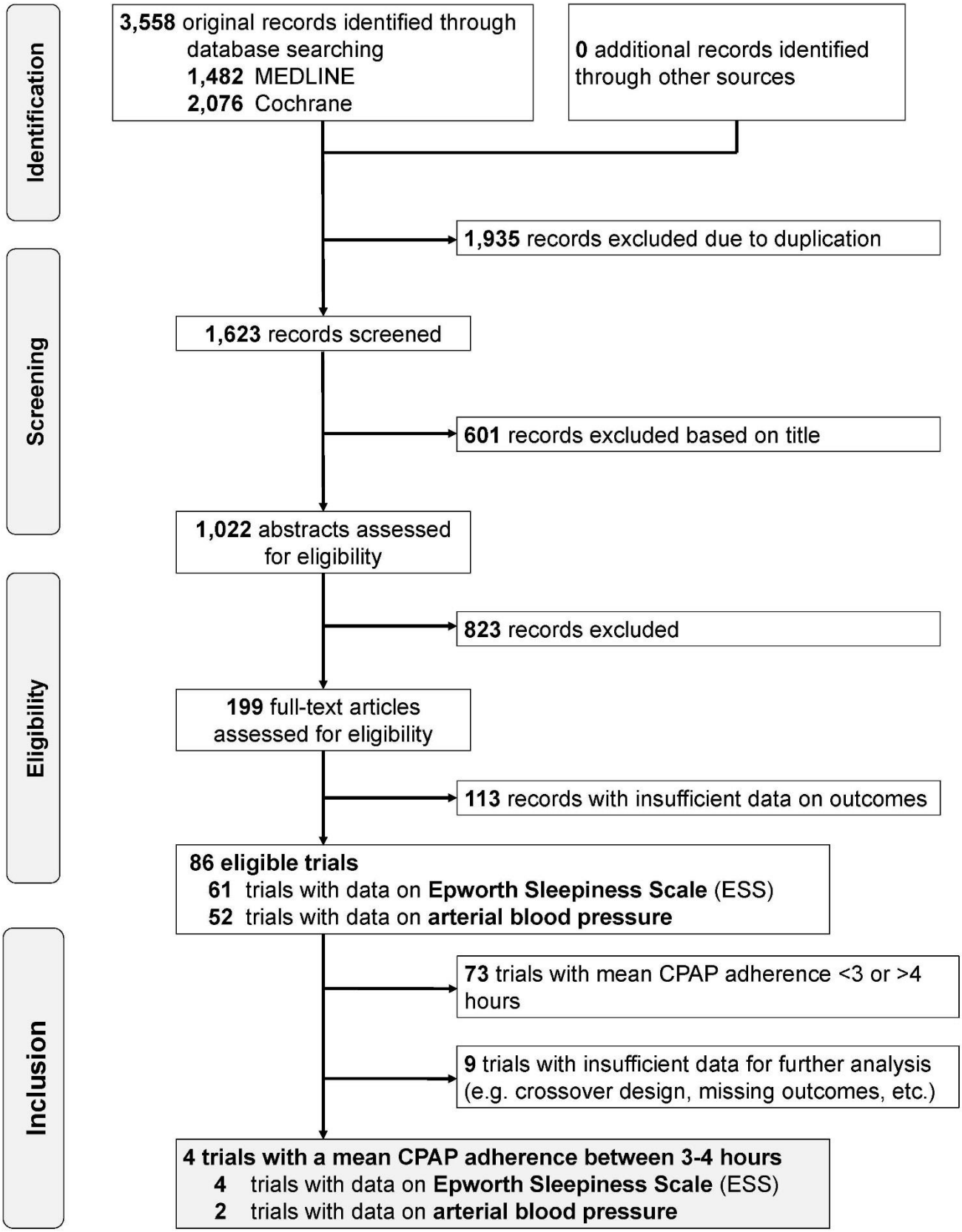
1. 1.(apn* or OSA* or SAHS or hypopn*).af.
2. 2.(randomized controlled trial or controlled clinical trial).pt. or randomized.ab,ti. or placebo.ab,ti. ortrial.ti. or clinical trials as topic.sh. or randomly.ab,ti.
3. 3.(*CPAP or positive airway pressure).af
4. 1 and 2 and 3

Cochrane Library:

1. Apn* or OSA* or SAHS or hypopn*
2. randomized or placebo or randomly or trial
3. *CPAP or positive airway pressure
4. 1 and 2 and 3

Key: af = all fields, pt = publication type, ab = abstract, ti = title, sh = MeSH subject heading, OSA = obstructive sleep apnoea, SAHS = sleep apnoea/hypopnoea syndrome, CPAP = continuous positive airway pressure.

Figure S1. Detailed PRISMA study flow-chart.



Statistical methods

We combined data from the current study and the historical trials with a Bayesian analysis. We followed the idea of Baeten et al.[3], but modified it in two major ways. First, we applied the *bayesmeta* R package for Bayesian random-effects meta-analysis[4] instead of using MCMC sampling. Second, we considered both the control arm and the CPAP arm individually to compute priors based on historical data. We then calculated posterior probability of superiority of therapeutic CPAP versus sham CPAP. In addition, we quantified the probability of improvement in each of the treatment arms separately. Since Hoyos[5] did not report standard deviations for change from baseline, we estimated these from pooled standard deviations for the treatment estimates. Data were analyzed with R (R Core Team (2018), R version 3.4.4 (2018-03-15)).

Data from four trials were included for ESS[5-8], while only two provided historical data for BP[5,6]. Standard errors for the Hoyos trial[5] were estimated from the confidence intervals reported for the treatment estimates, otherwise data were used as reported. In the current study data, we observed a difference in ESS between the treatment arms of about 3 (mean sham CPAP 2.2, therapeutic CPAP -0.9), while in the historical data, there was a mean difference about about 1 (sham -0.8, CPAP -2.1). Small differences in blood pressure were also observed in the current study data (SBP: mean sham -0.3, CPAP -2.9; DBP: sham 2.1, CPAP -0.5), and in the historical data (SBP: sham 1.3, CPAP -0.01; DBP: sham -0.1, CPAP -0.7). The posterior mean [variance] ESS for the CPAP arm was -1.1 [0.17], and for the sham CPAP arm 0.06 [0.15]. The posterior mean systolic (diastolic) BP for the CPAP arm was -0.5 [0.92] (-0.7 [0.45]), and for the sham CPAP arm 1.2 [0.62] (0.1 [0.44]). Sampling from the posterior distributions, and computing the differences between the treatment arms, we obtained a median difference in delta ESS of 0.825 (sham - CPAP, positive favors CPAP) (95% Credible Interval -0.41 to 2.05). The posterior probability of superiority of therapeutic CPAP vs sham CPAP was 90.4% with a Monte Carlo

error of 0.0009. Similarly for systolic (diastolic) BP, the median difference in change was 1.6 [-0.8 to 4.0] (0.8 [-1.0 to 2.7]). The posterior probability of superiority of therapeutic CPAP vs sham CPAP for systolic (diastolic) BP was 90.2% (80.3%) with a MC error of 0.0009 (0.0013). Based on the posterior distributions, we also calculated the probability for each treatment arm that the mean difference was less than 0 (that is, that the outcome at follow-up was less than at baseline). With sham CPAP, the probability of a lower ESS score was only 44%, while with real CPAP, the probability was 99%. For systolic (diastolic) BP, the probability of a lower BP was 7% (44%) with sham, and 68% (86%) with real CPAP.

We amended the approach of Baeten et al.[3] for the two following reasons: 1) when applying *bayesmeta*, we do not need to consider burn-in or convergence diagnostics as *bayesmeta* is a numerical approach to Bayesian analysis, and 2) we use historical knowledge not only in the control group, but also in the treatment group. Baeten et al.[3] planned the trial to include the historical data, while we performed a post-hoc analysis of a conventionally planned study. The choice of the half-normal heterogeneity prior with scale 0.5 was suggested by Friede et al.[6] They also provided satisfactory robustness analysis for this choice of prior. In our study however, we provided a robustness check, by computing the results with and without the Hoyos trial[5]. Incorporation of historical data into current increases the probability of reproducibility.[7]

Table S1. Studies for the Bayes analysis (historical data)

Author	**Design**	**Follow-up** (months)	**Mean CPAP adherence** (hours)	**N*** (overall)	**N*** (CPAP)	**N*** (Sham)	**ESS data**	**BP data**
Hoyos et al. 2012[5]	Parallel	3.0	3.6	65/52	34/28	31/24	Yes	Yes
McEvoy et al. 2016[8]	Parallel	44.4	3.3	2409/2324	1221/1166	1188/1158	Yes	Yes
Redline et al. 1998[9]	Parallel	2.0	3.1	111	59	52	Yes	No
Weaver et al. 2012[10]	Parallel	2.0	4±2	281/223	141/113	140/110	Yes	Yes

* depending on the outcome (ESS data / BP data)

Results

Table S2. Comorbidities of patients included in the final analysis.

	Subtherapeutic CPAP (sham) n=26	**Therapeutic CPAP (real)** n=26
Active smokers	6 (23.1%)	4 (15.4%)
Ex-smokers	10 (43.5%)	11 (52.4%)
Smoking start, age	24.1 ± 12.6	18.1 ± 4.4
Smoking stop, age	42.8 ± 16.2	40.9 ± 10.9
Pack years of smoking	16.6 ± 19.5	15.8 ± 14.9
More than one alcoholic standard drink per day	16 (61.5%)	18 (69.2%)
Obesity	17 (65.4%)	20 (76.9%)
Arterial hypertension	17 (65.4%)	18 (69.2%)
Dyslipidemia	9 (34.6%)	11 (42.3%)
Diabetes	22 (84.6%)	22 (84.6%)
Metabolic syndome	2 (7.7%)	3 (11.5%)
Cerebrovascular event	3 (11.5%)	2 (7.7%)
Atrial fibrillation	3 (11.5%)	4 (15.4%)
Coronary artery disease	4 (15.4%)	2 (7.7%)
Heart failure	1 (3.8%)	0 (0.0%)
Aneurysm	2 (7.7%)	1 (3.8%)
Chronic obstructive pulmonary disease	2 (7.7%)	1 (3.8%)
Asthma	2 (7.7%)	2 (7.7%)
Cancer *(for more details see Table S7)*	4 (15.4%)	2 (7.7%)
Depression *(for more details see Table S8)*	2 (7.7%)	3 (11.5%)
Schizophrenia *(for more details see Table S8)*	1 (3.8%)	0 (0%)
Dementia *(for more details see Table S9)*	0 (0%)	1 (3.8%)
Narcolepsy (treated)	0 (0%)	1 (3.8%)
Miscellaneous		
Shift workers *(for more details see Table S10)*	1 (3.8%)	1 (3.8%)

Data are n (%), or mean (SD) as appropriate.

Table S3. Medication of patients included in the final analysis.

	Subtherapeutic CPAP (sham) n=26	**Therapeutic CPAP (real)** n=26
Beta blocker	7 (26.9%)	5 (19.2%)
Alpha blocker	1 (3.8%)	1 (3.8%)
Angiotensin-converting-enzyme inhibitor	6 (23.1%)	4 (16.0%)
Calcium channel blocker	2 (7.7%)	10 (38.5%)
Angiotensin II receptor blocker	5 (19.2%)	6 (23.1%)
Aldosteroneantagonist	0 (0.0%)	1 (3.8%)
Diuretics	4 (16.0%)	6 (23.1%)
Statins	7 (26.9%)	10 (38.5%)
Insulin	2 (7.7%)	2 (7.7%)
Oral antitiabetics	5 (19.2%)	4 (15.4%)
Oral anticoagulation	4 (15.4%)	4 (15.4%)
Aspirin	6 (23.1%)	6 (23.1%)
Sodium oxybate	0 (0%)	0 (0%)

Data are n (%)

Table S4. Blood pressure profiles by study arms.

		Subtherapeutic CPAP (sham) n=26	**Therapeutic CPAP (real)** n=26	**p-value**
Morning	Systolic blood pressure, mmHg	133.2 ± 16.2	130.2 ± 13.0	0.477
	Diastolic blood pressure, mmHg	81.5 ± 7.4	81.7 ± 9.4	0.941
	Heart rate, bpm	72.6 ± 9.1	71.9 ± 11.5	0.827
Noon	Systolic blood pressure, mmHg	130.2 ± 12.1	130.8 ± 12.5	0.850
	Diastolic blood pressure, mmHg	79.8 ± 7.6	81.0 ± 8.2	0.592
	Heart rate, bpm	75.4 ± 9.1	75.5 ± 11.8	0.974
Evening	Systolic blood pressure, mmHg	134.6 ± 15.0	132.0 ± 16.1	0.709
	Diastolic blood pressure, mmHg	79.2 ± 8.3	80.1 ± 8.1	0.687
	Heart rate, bpm	78.3 ± 10.9	76.6 ± 9.5	0.550

Table S5. Suboptimal CPAP-adherence profiles of all study participants.

Profile	n (%)	Examples
Lifestyle	28 (49%)	Shift workers with unregular sleep cycles, falling asleep while watching TV, decision to use CPAP only "*on demand (… when symptomatic)*"; "*seasonal*"; or "… *at the beginning of the night*", social restrictions (bed-partner, children, etc.), frequent traveling (to places without electricity)
Comorbidities	25 (44%)	Sleep-related neurological disorders (e.g. narcolepsy), cognitive disabilities (incl. dementia, depression, claustrophobia, etc.), airway-related diseases (e.g. chronic sinusitis, chronic cough), nocturia, craniofacial abnormalities (operations etc.), gastroesophageal reflux disease, substance abuse (alcohol, drugs, etc.), schizophrenia, untreatable cancer, etc.
Technical	4 (7%)	Mask-related issues (leakages), suboptimal pressure settings, skin irritation, beards, CPAP not working properly

Table S6. Recruitment details on average CPAP adherence by center. Ultimately, 1,035 patients from nine Swiss sleep laboratory centers were recruited by the investigators at the study site in Zurich.

Recruiting site	Subjects screened	Average CPAP adherence
Kantonsspital Aarau	294	2.7 ± 1.4
Kantonsspital Glarus	37	2.8 ± 1.1
Kantonsspital Graubünden	131	2.8 ± 1.2
Spital Horgen	16	2.9 ± 1.7
Spital Männedorf	10	2.8 ± 1.6
Kantonsspital Schaffhausen	8	3.6 ± 1.3
Stadtspital Triemli	151	3.2 ± 1.2
Universitätsspital Zürich*	268	3.2 ± 1.4
Zürcher RehaZentrum Wald	120	2.9 ± 1.3
	Sum: 1035	**Average all centers: 3.0 ± 1.4**

* study site

Table S7. Additional information on the subgroup population with cancer (12%, n=6).

Case	Cancer (Type)	Date of first diagnosis	Stage	Treatment	Follow up?	Involvement of the CNS	Cancer related medication during the trial	Insomnia, sleeping pills
1	Urothelial carcinoma of the bladder	May 2012	pT1 G3	Transurethral resection (May 2012) and epirubicin in May 2012.	Confirmed complete remission in June 2016.	No.	None.	No insomnia. Depression diagnosed in 2010 treated with SNRI.
5	Breast cancer	1993	pT2 pN0 (0/3) M0 L1 Pn0 R0 G2 HR+ Herz2- Ki67 20%	Mastectomy 1993, chemotherapy (unclear) 1993, radiotherapy (unclear) 1993 and hormonal therapy (Tamoxifen) since 1993	Confirmed complete remission in November 2014.	No.	Tamoxifen	No.
13	Testicular cancer	1993	Stage I	Inguinal orchiectomy	Confirmed complete remission in 2010.	No.	No.	No.
27	Breast cancer	July 2011	pT1c(m) pN2a(5/15) G3 / ER 100% / PR 100% / HER2(IHC) 1+, MIB1 20%	Mastectomy 2011, chemotherapy (Sparano-Regime) 2011-2012, radiotherapy (27x2=54Gy) 2012 and hormonal therapy (Tamoxifen) since 2012	Confirmed complete remission in December 2015.	No.	Tamoxifen.	No.
32	Prostate cancer	January 2017	T1 No M0	Transurethral resection 2017	No follow-up due to recent diagnosis	No.	No.	No.
43	Breast cancer	November 1996	pT1, pN0, M0, G1	Quadrantectomy 1996, chemotherapy	Confirmed complete remission in 2013.	No.	No.	No insomnia. Depression diagnosed in 2009 treated with SSRI.

Table S8. Additional information on the subgroup population with depression (10%, n=5) and schizophrenia (2%, n=1).

Case	Diagnosis	Date of first diagnosis	Treatment	Use of hypnotics
1	Depression	unclear	SSRI	No
2	Depression	2011	SNRI, psychotherapy	No
3	Depression	2009	SSRI	No
4	Depression	2005	SSRI, psychotherapy	No
12	Depression	2010	NDRI, psychotherapy	No
20	Schizophrenia	>20 years ago	Psychotherapy, no pharmacotherapy	No

NDRI, Norepinephrine-dopamine reuptake inhibitor
SSRI, Selective serotonin reuptake inhibitor
SNRI, Serotonin–norepinephrine reuptake inhibitor

Table S9. Additional information on the subgroup population with dementia (2%, n=1).

Case	Diagnosis	Diagnostics	Pharmacotherapy	Use of hypnotics
4	Mild cognitive impairment	Mini–Mental State Examination	Gingko leaves	No

Table S10. Additional information on the subgroup population of shift workers (4%, n=2).

Case	Profession	In this profession	Type of shifts	Use of hypnotics
17	Postal employee	Since >10 years	Permanent night shifts (1 AM to 9 AM)	No
52	Nurse	For >10 years	Alternating day and night shifts during the trial, no changes to usual habits	No

Table S11. Additional information on the subgroup population (29%, n=15) with central nervous system (CNS) medications.

Case	Substance	Dosage	Administration	Indication	Changes*
1	Escitalopram	10 mg	1x daily, oral	Depression	No
2	Duloxetine	60 mg	1x daily, oral	Depression	No
3	Escitalopram	10 mg	1x daily, oral	Depression	No
3	Valproate	300 mg	1x daily, oral	Epilepsy	No
4	Escitalopram	20 mg	1x daily, oral	Depression	No
4	Ginkgo biloba	unclear	1x daily, oral	Mild cognitive impairment	No
6	Cetirizine	10 mg	1x daily, oral	Rhinitis	No
10	Quetiapine	25 mg	1x daily, oral	Bipolar disorder	No
12	Trazodone	25 mg	1x daily, oral	Insomnia	No
19	Levetiracetam	100 mg	2x daily, oral	Epilepsy	Dose increase to 3x daily at V4
19	Fentanyl	2 mg	1x daily, dermal	Pain	No
19	Trazodone	25 mg	1x daily, oral	Insomnia	No
25	Escitalopram	20 mg	1x daily, oral	Obsessive-compulsive disorder	No
29	Bupropion	150 mg	1x daily, oral	Depression	No
31	Oxycodon	10 mg	2x daily, oral	Pain	No
33	Venlafaxine	150 mg	1x daily, oral	Anxiety disorder	No
40	Escitalopram	10 mg	1x daily, oral	Obsessive-compulsive disorder	No
46	Amitriptyline	25 mg	2x daily, oral	Migraine	No
46	Pregabalin	300 mg	1x daily, oral	Pain	No
46	Lorazepam	1 mg	1x daily, oral (on demand)	Insomnia	No
46	Pramipexole	0.125 mg	1x daily, oral	Parkinson	No
47	Trazodone	150 mg	1x daily, oral (on demand)	Insomnia	No

* Changes during the trial (V1 to V4) as noted on CRF

References

1. Punjabi NM, Shifa N, Dorffner G, Patil S, Pien G, Aurora RN. Computer-Assisted Automated Scoring of Polysomnograms Using the Somnolyzer System. *Sleep.* 2015;38(10):1555-1566.
2. Iber C A-IS, Chesson AL, Qaun SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications (1st edn). *Westchester: American Academy of Sleep Medicine.* 2007.
3. Baeten D, Baraliakos X, Braun J, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2013;382(9906):1705-1713.
4. Röver C. Bayesian random-effects meta-analysis using the bayesmeta R package. 2017; https://arxiv.org/abs/1711.08683. Accessed 10.04.2019, 2019.
5. Hoyos CM, Killick R, Yee BJ, Phillips CL, Grunstein RR, Liu PY. Cardiometabolic changes after continuous positive airway pressure for obstructive sleep apnoea: a randomised sham-controlled study. *Thorax.* 2012;67(12):1081-1089.
6. Friede T, Rover C, Wandel S, Neuenschwander B. Meta-analysis of two studies in the presence of heterogeneity with applications in rare diseases. *Biom J.* 2017;59(4):658-671.
7. McShane BB, Böckenholt U. Single-Paper Meta-Analysis: Benefits for Study Summary, Theory Testing, and Replicability. *Journal of Consumer Research.* 2017;43(6):1048-1063.
8. McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *The New England journal of medicine.* 2016;375(10):919-931.
9. Redline S, Adams N, Strauss ME, Roebuck T, Winters M, Rosenberg C. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. *American journal of respiratory and critical care medicine.* 1998;157(3 Pt 1):858-865.
10. Weaver TE, Mancini C, Maislin G, et al. Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial. *American journal of respiratory and critical care medicine.* 2012;186(7):677-683.