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CLINICAL REVIEW

Effects of nicotine on sleep during consumption, withdrawal and replacement therapy

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SUMMARY

Smoking constitutes the most important behavioural health risk in the Western world. By acting on various neurotransmitter systems, nicotine consumption also influences sleep and mood. Studies on the relationship between smoking, sleep disturbances, sleep-related disorders and depression led to dissimilar results. The aim of the present work is to provide a descriptive overview of the existing data regarding the relationship of nicotine consumption, withdrawal, replacement therapy and sleep disturbances in both animals and humans. Primarily symptoms of insomnia, such as increased sleep latency, sleep fragmentation and decreased slow wave sleep with reduced sleep efficiency and increased daytime sleepiness, were observed during nicotine consumption. Furthermore, most studies indicated a nicotine induced rapid eye movement (REM) sleep suppression. The effects on sleep due to therapeutic nicotine substitution after smoking cessation were often masked by withdrawal symptoms. Depressive non-smokers experienced a mood improvement under nicotine administration comparable to the effect of anti-depressants. In turn, depressive symptoms and sleep impairment during nicotine withdrawal had a negative impact on abstinence rates. Smoking was also associated with an increased prevalence of sleep-related respiratory disorders, which further worsened sleep quality and daytime sleepiness. The partly inconsistent findings of the analysed 52 studies result mostly from different methodology, necessitating a more unified approach with regard to subjects' assessment of smoking status, control for co-morbidity and use of medication as well as outcome criteria.

Introduction

Cigarette smoking is a major public health problem. One half of all long-term smokers die prematurely as a consequence of tobacco consumption.[1] In industrialised countries smoking is recognised as the most significant avoidable single cause for a multiplicity of chronic diseases.[2] Although the health consequences of smoking are well documented, the influence of nicotine consumption, nicotine withdrawal and substituted nicotine on sleep have not been extensively studied.

Nicotine stimulates cholinergic neurotransmission via the widespread α7 and α4β2 nicotinergic acetylcholine (ACh) receptors and indirectly alters the glutaminergic, dopaminergic and serotonergic systems in the brain.[3] Chronic nicotine consumption is usually coupled with physical and psychological dependence. Withdrawal symptoms include sleep disturbances, the craving for tobacco, dysphoria, fear, anhedonia, irritability or restlessness and increased appetite. Insomnia complaints during nicotine withdrawal are reported in up to 39% of cases.[4,5]

Additionally, depressive symptoms are common in prolonged nicotine withdrawal,[6] and there is a complex relationship between nicotine dependence and depression. Not only do depressive patients smoke more frequently, but during nicotine withdrawal there is also an increase in depressive episodes.[7] Furthermore, sleep disturbances and changes in REM sleep are common in depressive patients; and the presence of depressive symptoms is associated with lower nicotine abstinence rates.[8]

It is speculated that the negative health effects of smoking could at least partly be related to the effects of nicotine on sleep.[9] Disturbed sleep due to nicotine use in turn might worsen the withdrawal process, and may therefore be a relevant risk factor for

Abbreviations: ACH, acetylcholine; MSLT, multiple sleep latency test; NRT, nicotine replacement therapy; PSG, polysomnography; REM, rapid eye movement; NREM, non-REM; SWS, slow wave sleep; TST, total sleep time.

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relapse. This implies the necessity to adapt smoking cessation therapies to the specific requirements of groups at risk, e.g., smokers with depression (most of whom also have insomniac symptoms) or sleep problems.

The present descriptive review aims to provide an overview of investigations on smoking and its effect on sleep as well as smoking cessation with and without nicotine substitution. Also included in the review were studies, which investigated patients with depression, looked at nocturnal respiration in smokers and examined the therapeutic use of nicotine.

Methods

The electronic data bases Medline+ (Ovid), PreMedline (Ovid), Cumulative Index to Nursing & Allied Health Literature – CINAHL (Ovid), PsycINFO (Elton B. Stephens Company – EBSCO), and Embase were searched in October 2007 for relevant publications regarding the effects of nicotine on sleep. The keywords included "sleep", "sleep disturbance", "insomnia", "smoking", "smoking cessation", "nicotine", "nicotine withdrawal", "tobacco" and "tobacco withdrawal". Both German and English original articles were included. Investigations that used substances other than nicotine replacement therapy (NRT) during nicotine withdrawal, such as bupropion, were excluded. Pre-clinical animal studies were only considered when nicotine was administered directly and sleep EEG or sleep regulatory mechanisms were examined. The quality of the search was assessed by screening the reference lists of the original publications and cross-checking with the reference lists from available overviews on the topic.[10–12] There was a notable lack of studies which investigated sleep disturbances as a side effect of nicotine replacement therapies as that term was only occasionally mentioned in the abstracts. A search with the keyword "insomnia" yielded another four articles.[13–16] Altogether, 52 studies were analysed in this review.

Results

Studies investigating the effects of nicotine on sleep in animals

Out of the eight studies in animals, six investigated in vivo nicotine effects on the sleep EEG, one specified the nicotine receptors relevant to sleep in knock-out mice, and one reported on neural sleep regulation on the basis of rat midbrain slices (see Table 1). Lena et al.[17] showed that the effects of nicotine on sleep in β2-AchR-knock-out mice were transmitted mainly by the β2 subunit of the ACh receptors. Several of the studies described a dose-dependent effect of nicotine on sleep, with increased REM-sleep duration, shortening of the REM latency and a reduction of wake time.[18–21] Higher nicotine doses, however, led to REM-sleep suppression, to an increase in the time awake and to a reduction in total sleep time.[19,20,22] A REM rebound was observed after cessation of chronic nicotine administration.[20]

Vazquez and colleagues[22] showed a dose-dependent suppression of the ponto-geniculo-occipital (PGO) spikes by nicotine, which are characteristic of REM sleep and generated by cholinergic projections from the pedunculo-pontine (PPT) and latero-dorsal (LDT) neurons. It was assumed that the suppression of the PGO waves is caused by a nicotine mediated inhibitory effect of the dorsal raphe nucleus on the LDT and PPT neurons. Mihailescu et al.[23] confirmed the inhibition of PGO spikes after the administration of nicotine as a result from serotonergic blocking of the PPT and LDT neurons. Guzman-Marin and co-workers[24] found a connection between REM sleep and serotonergic activation when observing an increased firing rate of the dorsal raphe nucleus and prolonged REM periods after nicotine application.

The methodological inconsistency between the studies is noteworthy. Apart from the small subject numbers, various other limitations to the comparability of the results arose, e.g., the type of nicotine application (subcutaneous, intravenuous, intraperitoneal, transdermal) and thus differing pharmacokinetics, the use of different mammalian species (cats, rats, mice), various study designs and different EEG recording times and duration.

In summary, animal data suggest dose-dependent effects of nicotine on REM sleep, i.e., lower doses stimulating REM sleep and higher doses suppressing it, followed by rebound effects upon nicotine discontinuation. Furthermore, nicotine seems to enhance wake time during sleep and decrease SWS, thus indicating an arousing effect of the substance.

Studies investigating the effects of nicotine on sleep in humans

Of the 44 retrieved publications on the relationship between nicotine and sleep in humans, nine addressed nicotine consumption, eight nicotine withdrawal (one study investigated both consumption and withdrawal) and 16 nicotine replacement therapy (including two studies in healthy non-smokers). In seven studies the connection between nicotine, sleep and depression was examined. A further five articles focussed on the influence of nicotine on the sleep of patients with sleep apnoea syndrome. Twenty-four of these studies employed polysomnographic methods, whereas the remainder relied on the subjective assessment of sleep by questionnaires.

Influence of nicotine consumption on sleep

Studies investigating nicotine consumption and sleep with subjective measurements. The longitudinal cohort study of Wetter and Young[25] studied a large sample of participants and showed that smokers have approximately double the risk of experiencing sleep disturbances, manifested primarily as difficulties falling asleep and daytime sleepiness (see Table 2).

Likewise, Kaneita et al.[27] found a twofold increase in sleep disturbances in pregnant smokers. Phillips and Danner[28] and Riedel and co-workers[29] reported similar results and noted an association between smoking, coffee and alcohol consumption as well as depressive and anxiety symptoms. The risk of chronic insomnia and changes of some sleep parameters (TST and time in bed) seemed to differ between moderate and heavy smokers. One explanation could be a larger variability of consumption in light smokers. Additionally smokers with a higher and more regular consumption obviously developed some tolerance to the effects of nicotine on sleep.[29] The longitudinal cohort study of Patten and colleagues[30] found that smoking, depressive symptoms, female gender and Asian ethnicity were predictive for the development of sleep problems in adolescents. Rieder et al.[31] observed nightly awakening due to nicotine craving in 20% of heavy smokers.

PSG studies investigating the effects of nicotine consumption on sleep. Soldatos and colleagues[32] found an increased sleep latency and time awake in smokers under controlled conditions. These findings were confirmed by a large longitudinal cohort study of Zhang et al.[33], where smokers exhibited an extended sleep latency, a decreased TST, an extension of REM-sleep latency, a decrease in SWS as well as a reduced sleep efficiency compared to non-smokers. (see Table 2). A spectral analysis of sleep EEGs showed an increase of α-frequencies and reduction of δ-frequencies, which was most pronounced at the beginning of the sleep period.[34]

Summarising, according to both subjective and objective sleep assessments, smokers showed a higher prevalence of sleep disturbances. Polysomnography revealed an impairment of SWS and sleep

Table 1
Animal experiments on the influence of nicotine on sleep.

Author	Study sample	Methodology	Results
Domino and Yamamoto[18]	cats $n=9$	EEG: indwelling brain electrodes; i.v. via jugular vein: -saline -0.005–0.01 mg/kg nicotine -nicotine after administration of mecamylamine; recording for 24 h	Saline: No effects on EEG and behaviour Nicotine: -1–3 min: EEG-activity ↑ + arousal -5 min: deep SWS -15–30 min: REM ↑ mecamylamine: no effects from nicotine observed
Jewett and Norton[19]	Cats: 50 μg/kg; $n=1$; 100 μg/kg $n=2$; 200 μg/kg $n=1$	EEG: implanted electrodes, EMG: electrodes in posterior neck muscles; s.c. nicotine bitartrate (NB); control recordings 24 h prior, recording 5 h	NB 50 μg/kg: -REM ↑, alert time ↑ NB 100 μg/kg: -REM ↑, alert time ↓ NB 200 μg/kg: -REM ↓, alert time ↑, TST ↓+ tremor observed all concentrations: -EMG ↑
Velazquez-Moctezuma et al.[21]	Cats $n=7$	EEG: implanted electrodes; 9 administrations of Ringer's solution and 9 × nicotine (9.2 μg) for 10 min via a bilaterally implanted cannula in the pons; recording 3 h	nicotine: -REM ↑ -wake time ↓ -SWS 1 ↓ -REM latency ↓ -SWS 2 ↔
Vazquez et al.[22]	Cats $n=10$	EEG, EOG: implanted electrodes, EMG: electrodes in posterior neck muscles, ponto-geniculo-occipital (PGO)-spikes activity: electrodes in lateral geniculate nucleus; nicotine patch (NP) 2 h before sleep, either 17.5 mg; 35 mg; 52.5 mg crossover (min. of 4 d in between); recording of baseline, intervention night, recovery night, each for 8 h	35mg; 52.5 mg NP: -total REM ↓ 17.5 mg NP: -total REM ↔ -REM period duration ↑ -REM frequency ↓ -REM latency ↓ -PGO spikes disappear all NPs: total wake time ↑ post patch: PGO spikes reappear, PGO spike density ↓, REM period duration enhanced with increasing dose
Salin-Pascual et al.[20]	Rats *control:* saline $n=7$ *dose response:* nicotine 0.1 mg/kg $n=5$ 0.25 mg/kg $n=8$ 0.5 mg/kg $n=6$ 1 mg/kg $n=8$ *chronic group*: nicotine 0.1 mg/kg $n=5$ 0.5 mg/kg $n=5$ *block group:* mecamylamine 0.5 mg/kg $n=8$ 1 mg/kg $n=8$ mecamylamine 0.5 mg/kg + nicotine 1 mg/kg $n=8$	EEG: implanted electrodes, EMG: electrodes in posterior neck muscles; *dose response group:* s.c. administration of nicotine 10 min before sleep, recording for 4 h *chronic treatment group:* s.c. nicotine daily at 10am for 4 d, adaptation night, recording of baseline night, 4 intervention nights, recovery night *block group*: 1)i.p. mecamylamine, 2 different doses, recording of baseline, intervention and recovery nights 2)mecamylamine and nicotine 30 min later, recording of baseline, intervention and recovery nights	*dose response group*: 0.5 mg/kg and 1 mg/kg: -REM ↓ -SWS ↓ -Wake time ↑ -REM latency ↑ 0.1 mg/kg and 0.25 mg/kg: -no effect chronic treatment group: 0.1 mg/kg: -REM ↑ -Wake time and SWS ↓ 0.5 mg/kg: -REM ↓ (rebound in recovery night) -Wake time ↑ -SWS ↓ block group: 1). no changes 2). no effect from nicotine
Guzman-Marin et al.[24]	Rats $n=6$	EEG and EMG: implanted electrodes, activity of discharge rate of DRN and PSN: implanted electrodes, measuring 16 cells out of 36, which met criteria; s.c. nicotine 0.1 mg/kg; recording for 2 h	nicotine effect on PSN: -firing rates during REM and NREM/REM transition ↑ -firing rate during wake time and NREM ↔ general nicotine effects: -REM period duration ↑ -REM frequency ↔

(*continued on next page*)

Table 1 (*continued*)

Author	Study sample	Methodology	Results
Mihailescu, et al.[23]	37 experiments on coronal midbrain slices from rats	baseline firing rates of DRN, PPT and LDT cholinergic neurons recorded 5 min prior to intervention, pressure injection of a nicotine solution (2 mM) for 2 ms into the DRN of the brain slices; recording of DRN, PPT and LDT firing rates, serotonin concentration	nicotine: -firing rate DRN neurons ↑ after transient ↓ -firing rate LDT ↓ after transient increase -firing rate PPT ↓ after transient increase -serotonin release ↑ -serotonin induced reciprocal changes in LDT/PPT firing rates
Lena et al.[17]	Mice $n = 14$ WT $n = 18$ β2-AchR-knock-out	EEG: epidural implanted electrodes, EMG: electrodes in posterior neck muscles, ECG: subcutaneous electrodes, baseline condition i.p. nicotine 1–2 mg/kg, behavioural manipulation (sleep deprivation and immobilisation), recording for 48 h	baseline: knock-out vs. WT longer REM episodes, less micro arousals in NREM, more stable REM and NREM WT after nicotine: -1st. h: ↑ wakefulness, NREM and REM ↓ -2nd. h: rebound ↓ of wake time, NREM ↑ -3rd. and 4th. h: no effect knock-out mice after nicotine: -1st. and 2nd. h no changes

Abbreviations: d, days; DRN, dorsal raphe nucleus; h, hour; i.p., intraperitoneal; i.v. intravenous; LDT, laterodorsal tegmental cholinergic neurons; min, minute; NB, nicotine bititrate; NREM, non-REM; PSG, polysomnography; PPT, pedunculopontine cholinergic neurons; PSN, putative serotonergic neurons; REM, rapid eye movement; s.c., subcutaneous; SWS, slow wave sleep; TST, total sleep time; WT, wild type.

efficiency while in subjective reports insomnia symptoms dominated.[25,28] Smoking was confirmed to be a predictor for the development of sleep disturbances in studies with population-representative cohorts and large subject numbers.[26,30] Smokers also seem to make other unhealthy lifestyle choices, such as more frequent use of alcohol and caffeine, which may further augment sleep problems. It is difficult to compare the results of the eligible studies as the degree of dependence, smoking history and the smoking cessation times varied between the investigations. Alcohol consumption, caffeine intake as well as depression were at least partly controlled for, whereas in most studies somatic co-morbidity, use of psychotropic medication and drug consumption were not taken into account. None of the investigations determined the actual serum nicotine concentrations in the subjects. Furthermore, differing age-distributions of the samples studied and the lack of control for menstrual cycle in females may have added more error variance.

Effects of nicotine withdrawal on sleep

Studies investigating the effects of nicotine withdrawal on sleep with subjective measurements. During complete nicotine abstinence, a decreased sleep quality, frequent and extended awakenings as well as increased symptoms of depression were reported[35–38] (see Table 3).

After withdrawal, the initial daytime sleepiness gradually decreased over 20 days, with strong smokers reporting this symptom more frequently than moderate smokers.[39] Persistent insomnia complaints were more common in subjects with subsequent relapse.[39] Hatsukami et al.[36] showed an association between nicotine plasma levels and the development of nicotine withdrawal symptoms and the time awake at night. Shiffman and colleagues[38] found a similar relationship between withdrawal symptoms and nicotine exposure, observing a shorter TST, an increased amount of nocturnal awakenings and a decreased subjective sleep quality in smokers consuming more than 20 cigarettes per day before abstinence. The study of Grove et al.[40] examined the effect of exercise on insomnia complaints after nicotine cessation. Women, who exercised daily for 30–50 min during the withdrawal period, reported fewer difficulties falling asleep than the control group.

PSG studies of nicotine withdrawal. Soldatos and colleagues[32] found a slight increase of REM sleep, a reduction of the total wake time with no change in arousals and a reduction of the sleep latency in smokers during nicotine withdrawal (see Table 3). In contrast, Prosise et al.[41] noticed an increase in the number of relative arousals (i.e., EEG change in sleep to wake, α-frequency or movement without consideration of duration), an increase of nocturnal awakenings and enhanced frequency of sleep stage changes with an unchanged TST. The Multiple Sleep Latency Test (MSLT) showed a significant reduction of sleep stage 1 latency and an increased daytime sleepiness.

Recapitulating the main points, subjective impairments of sleep during nicotine withdrawal were reported in all studies. The severity of sleep disturbance was related to the degree of nicotine consumption and dependence, as well as the duration of the abstinence. PSG did not consistently reproduce these findings and were contradictory regarding sleep duration, sleep efficiency, frequency of sleep stage changes and arousal frequency.[32,33,41] Beyond that, other influences of nicotine on sleep, such as craving or anxiety, need to be considered. Further restrictions arise from the small sample sizes in the PSG studies. Comparability of the studies is additionally impaired by inconsistent measurements of the degree of nicotine dependence and withdrawal symptoms, i.e., the variety of psychometric instruments used and assessment times.

Future investigations should take into account that nicotine withdrawal symptoms usually begin after 6–12 h after discontinuation, reach maximum intensity within one to three days and can last up to three weeks[4] or in individual cases even longer.[5] The available studies examined only the first three to four withdrawal nights, thereby covering merely the initial part of the withdrawal phase. Furthermore, only one study[39] explored the relationship between insomnia complaints during withdrawal and relapse rates. It is possible that an increased frequency of insomnia symptoms during withdrawal from nicotine might enhance the risk for a relapse to smoking.

Effects of nicotine administration on PSG sleep in healthy non-smokers

Transdermal nicotine application in non-smokers resulted in a dose-dependent reduction of REM sleep,[42,43] increased sleep stage 2 and earlier wake-up times. In the following nights after cessation of nicotine administration a REM rebound was found, whereas sleep latency, TST and sleep continuity remained unchanged[42] (see Table 4).

Table 2
Influence of nicotine on sleep.

Authors	Subjects	Methodology	Results
Surveys			
Wetter and Young[25]	$n = 3516$ *non-smokers*: $n = 1647$ *former smokers*: $n = 1013$ *smokers*: $n = 791$ age 20–69 yrs return rate 82%	longitudinal cohort study; questionnaires on insomnia, hypersomnia, parasomnias; outcome frequency of symptoms occurring: very frequent >16 × days/month frequent: 5–15× not frequent: 2–4× rare: 1 or <1×	smokers (male/female): - difficulty getting to sleep, non-restorative sleep, difficulty waking up smokers (male): - nightmares and disturbed sleep smokers (female): - excessive daytime sleepiness no difference between former and non-smokers
Phillips and Danner[28]	$n = 484$ *smokers*: $n = 115$ *non-smokers*: $n = 369$ *students*: $n = 99$, age < 18 yrs, 38 % smokers *adults*: $n = 385$, age 18–84 yrs, 20 % smokers	mailed out questionnaires to random sample 1000 households; students questioned directly; adapted SSS and assessment of wakefulness, questions on health problems	smokers: - more frequent problems with staying asleep - increased daytime sleepiness - depressive symptoms - higher caffeine intake - more minor accidents
Patten et al.[30]	$n = 7960$ adolescents age 12–18 yrs response rate 82% *current smokers*: 9.9% *non-smokers*: 51% *experimenting smokers*: 34% (“Have you ever smoked, tried or experimented smoking, even single puffs?”)	longitudinal cohort study; telephone follow-up 1989 and 1993, questionnaire on sleep problems and depressive symptoms, nicotine use	predictor for development of sleep problems: - depressive symptoms, nicotine use (dose dependent), female sex, rebelliousness predictor for persistence of sleep problems: - depressive symptoms, female sex, Asian ethnicity, nicotine use
Rieder et al.[31]	$n = 14$ smokers with nocturnal sleep disturbance nicotine craving male = 13; female = 1 mean age 38; mean 40.7 cig/d	pilot study; questionnaire on nocturnal sleep disturbance nicotine craving (NSDNC), frequency of NSDNC	frequency of NSDNC: - daily $n = 4$ - several times/week $n = 5$ - several times/month $n = 5$ - general sleep disturbance $n = 11$ - sleep problems at quit attempt $n = 9$
Riedel et al.[29]	$n = 769$ *current smokers*: 21 % *light smokers* (<15 cig/d): 38% *heavy smokers* (>15 cig/d): 62 % return rate 49 %	randomized prospective study; sleep diary for 2 weeks, BDI, STAI, demographic and health information, health problems, nicotine consumption	light smokers: - time in bed (TIB) and TST ↓ - increased OR for chronic insomnia heavy smokers: - more caffeine intake - TIB and TST as non-smokers smokers: - younger population, higher BDI scores, higher STAI scores, higher alcohol consumption, - sleep latency, number of awakenings, wake time + sleep efficiency not different from non-smokers
Kaneita et al.[27]	$n = 16.000$ pregnant Japanese women *smokers during pregnancy*: 9.9%, *smokers before pregnancy*: 25,7%	survey with questionnaire assessing 1. drinking behaviour, 2. smoking behaviour, 3. sleep status 4. personal data;	smoking only: increased OR for - subjective insufficient sleep - difficulties initiating and maintaining sleep - short sleep duration - excessive daytime sleepiness - RLS - early morning awakenings combination of smoking and drinking: even more increased OR for all the above
PSG studies			
Soldatos et al.[32]	$n = 50$ smokers, $n = 50$ non-smokers matched for age and sex mean age 39.8 yrs; 1.25 packs/d	randomized study; duration 4 nights (1 adaptation, 2, 3 and 4 PSG, incl. EMG and EOG), questionnaires: MMPI, sleep history	smokers: PSG: - time awake ↑, sleep latency ↑ MMPI: - increased caffeine consumption

(*continued on next page*)

Table 2 (*continued*)

Authors	Subjects	Methodology	Results
Zhang et al.[33]	$n = 6442$ *never smoked*: $n = 2916$ *former smokers*: $n = 2705$ current smokers: $n = 779$ age > 40 yrs	multi-center longitudinal study (2 yrs); home-PSG, questionnaires on alcohol and caffeine consumption, medication use (incl. psychotropic), health status (incl. cardio-vascular diseases), quality of life instruments	smokers: PSG: - sleep latency ↑, TST ↓, NREM 1 & 2 ↑, NREM 3 & 4 ↓, sleep efficiency ↓, amount of REM not different; no differences between never smoked and former smokers
Zhang et al.[34]	*smokers* (>20 cig/d): $n = 40$ *non-smokers*: $n = 49$; age < 65 yrs	controlled study, matched for age, gender, BMI, apnoea–hypopnoea index and neck circumference; home-PSG 1 night; EEG spectral analysis	smokers: subjective data: - more often non-restful sleep - increased caffeine consumption spectral analysis: - α-power ↑ - δ-power ↓ - differences greatest in the early part of sleep, decreased towards end

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; d, day; MMPI, Minnesota Multiphasic Personality Inventory; NREM, non-REM; OR, odds ratios; PSG, polysomnography; REM, rapid eye movement; RLS, restless legs syndrome; SSS Stanford Sleep Scale; STAI, State Trait Anxiety Inventory; SWS, slow wave sleep; TIB, time in bed; TST, total sleep time.

Davila et al.[43] described an increase in sleep latency, a decreased TST and a reduced sleep efficiency without affecting arousals, although the findings of the second intervention night in the placebo group could be due to rebound effects from the nicotine patches during the first night.

The healthy control groups (see Table 6) in the studies by Salin-Pascual and co-workers[44] and Salin-Pascual and Drucker-Colin[45] showed, besides an increased sleep fragmentation, a REM suppressing effect during acute nicotine administration, leading to REM-sleep rebound during withdrawal.

Effects of nicotine replacement therapy on sleep in smokers during nicotine withdrawal

Studies with nicotine gum on subjective sleep variables. The randomized study of Hughes et al.[46] did not show an alleviation of insomnia complaints through nicotine gum during withdrawal compared to placebo (see Table 5).

Gross and Stitzer[47] described only a slight improvement of sleep complaints in the nicotine group versus placebo. The sample of this study was characterised by a high nicotine dependence, i.e., on average 24 years of smoking more than 30 cigarettes/day, and displayed a high drop-out rate during withdrawal.

Studies investigating the effect of nicotine patches on subjective sleep variables during withdrawal. Subjects using nicotine patches during withdrawal seemed to exhibit significantly more sleep disturbances than those using placebo[13–15] (see Table 5). However, it should be noted that in two of these investigations[13,14] additional smoking was not an exclusion criterion, and that no objective abstinence control was performed. Therefore, effects of nicotine consumption by smoking and withdrawal effects might have been confounded with the effects of the patches, thus leading to very high nicotine levels. No separate analysis for the chronological occurrence of sleep disturbances was performed in any of the above mentioned studies. Jorenby et al.[16] noted persistent sleep disturbances after a controlled smoking cessation program with the use of nicotine patches for five weeks. Sleep disturbances occurred even more frequently in the placebo group, designating them as a withdrawal effect.

Most subjects in the study of Gourlay et al.[48] reported sleep problems in the first week of nicotine replacement therapy, which decreased with continuing abstinence and the use of low-dose nicotine patches. Female gender, higher dependency scores and length of nicotine abstinence were identified as predictors for side effects, including sleep disturbances. Fredrickson et al.[49] demonstrated a positive correlation of sleep disturbances with plasma cotinine levels. Participants with sleep disturbances showed higher levels while using nicotine replacement than those without. As both nicotine consumption and withdrawal can affect sleep in a similar way, it is difficult to differentiate the effects.

PSG studies investigating the effect of nicotine patches on sleep in withdrawal. Wetter et al.[50] found an increased number of arousals under placebo during withdrawal with unchanged frequency of sleep stages, REM-sleep time, TST and total awake time (see Table 5). With ongoing abstinence using nicotine patches they observed a linear decrease in arousals and sleep stage 2 as well as a simultaneous increase of SWS. Contrary to the PSG results, participants in both groups reported more frequent night awakenings and a reduced sleep quality during the withdrawal protocol. The placebo group stated an increased sleep onset latency and the intervention group longer wake times.

Actigraphy showed a shorter time in bed with no effect on sleep efficiency and increased wrist activity with higher cotinine levels.[51] Likewise, the subjective sleep quality improved with higher nicotine doses. When applying nicotine patches exclusively at night, total wake time and number of arousals increased, whereas REM sleep decreased and dream activity was more intensive than under placebo.[52]

An important influencing factor could be the time of application of nicotine patches: nicotine substitution during the day mimics a smoker's behaviour with steady nicotine supply during the day and abstinence at night. The nocturnal fall in nicotine levels thus may result in withdrawal symptoms. Rieder et al.[31] identified sensations of nicotine craving as a cause for awakening at night in heavy smokers.

Twenty-four compared to 16 h nicotine patches led to decreased craving in the morning and lower Profile of Mood Scores (POMS) but no differences in the subjective sleep evaluation[53] during withdrawal. Both application types resulted in a prolonged sleep latency and a shortened TST compared to baseline.[54] While on the 24 h patch, arousals were significantly decreased, total NREM-sleep time and SWS time increased. REM density was particularly increased during the first third of the night. Spectral analysis showed a reduced β-activity during REM sleep using the 16 h patch, however, an increase of β-activity with the 24 h patch.

Table 3
Influence of nicotine withdrawal on sleep.

Authors	Subjects	Methodology	Results
Studies without PSG			
Hatsukami et al.[35]	$n = 27$ smokers *experimental group*: $n = 20$, 2 dropouts *control group*: $n = 7$ mean 46 yrs; mean 35.2 cig/d	randomized controlled study; experimental group: days 1–3: smoking (1st night adaptation, 2 & 3 baseline) days 4–7: abstinence; control group: no change in smoking; no alcohol, caffeine consumption regulated, CO monitoring, SJWQ, POMS, SSS	*abstinence*: sleep: - ↑ number and duration of awakenings other parameters: - heart frequency ↓, concentration ↓, appetite and caloric intake↑, depressive mood, confusion ↑
Cummings et al.[39]	$n = 33$ *heavy smokers* (>20 cig/d): $n = 17$ *light smokers* (<20 cig/d): $n = 16$ age 19–63 yrs, return rate 19%	prospective study; day 1: baseline, 20 days abstinence; withdrawal diary including self-developed checklist of withdrawal symptoms (including sleepiness and sleeplessness)	sleepiness: - ↑ in heavy smokers, trend decreasing across time sleepiness: - tendency to ↓, no difference heavy and light smoker
Hatsukami et al.[36]	$n = 20$ smokers mean age 34 yrs; mean 36.9 cig/d	clinical study; smoking 3 days, abstinence 4 days; day 2: 4× nicotine and cotinine blood levels before and after smoking; day 3: nicotine and cotinine blood levels directly, 15, 30 and 60 min after smoking to determine metabolic half-life; all days: nicotine exposure measured, SJWQ, POMS, SSS	half-life: - shorter half-life related to ↑ confusion and number of awakenings/night smoke exposure: - greater exposure related to number of awakenings/night withdrawal symptoms: - more craving related to higher blood levels and higher changes in pre/post smoking levels
Hatsukami et al.[37]	$n = 32$ *abstinence group*: $n = 11$ mean age 23.7, 26.3 cig/day *reduction group*: $n = 11$ mean age 23.2, 26.2 cig/d *low nicotine group*: $n = 10$ mean age 25.8, mean 25.7 cig/d	randomized study; reduction group: 50% reduction in number of cigarettes; low nicotine group: 'light' cigarettes; day 1: adaptation, days 2 & 3: baseline, days 4–8: experiment; no alcohol, caffeine consumption in all groups regulated, CO analysis, saliva cotinine, POMS, self-developed withdrawal questionnaire	abstinence: - number of awakenings/night ↑ - heart frequency ↓ - weight ↑ - withdrawal symptoms higher compared to reduction group - anger and hostility ↑ low nicotine group: no effects observed
Shiffman et al.[38]	*'chippers'* (<5 cig/d at least 4 d per week): $n = 26$, mean 8 cig/d *regular smokers* (20–40 cig/d): $n = 25$, mean 26.4 cig/d, mean age 29.2 yrs	2 conditions with smoking and abstinence 2 days and 3 nights each, 1 week apart; 5 times per day hand-hold computer for self-developed sleep questionnaire (withdrawal DSM-III-symptoms, cognitive and motor performance, mood disturbance), cotinine validation	Withdrawal in regular smoker vs. 'chippers': - number of waking episodes ↑ - sleep-quality ↓
Grove et al.[40]	$n = 27$ women, 5 drop-outs *sports group*: $n = 12$ *control group*: $n = 10$ age 25–55 yrs, mean 29 cig/d	randomized matched pair study; week 1: adaptation, weeks 2–6: sports training, week 7: acute nicotine withdrawal, weeks 8–11 abstinence, sports 30–50 min/d; sleep-quality questionnaire, CO analysis, cotinine levels	both groups: - difficulties falling and staying asleep, control group significantly more in week 8 sports group: - less difficulties and no peak in week 8
PSG studies			
Soldatos et al.[32]	$n = 8$ male smokers, mean age 30 yrs, 2 packs cig/d *extended abstinence group*: $n = 4$	non-controlled study; days 1–4: baseline (1 night adaptation), days 5–9: abstinence, days 10–16: extended abstinence; PSG nights 5–9, 15, 16	days 5–7: - 45%↓ total time awake, sleep latency ↓, slightly REM ↑ days 8–9: - 33%↓ total time awake days 15–16: - no significant difference
Prosise et al.[41]	$n = 18$, 2 dropouts; mean age 41.3 yrs; mean 32 cig/d	non-controlled study; week 1: baseline (1 adaptation night, PSG for 3 nights), week 2: abstinence (PSG for 3 nights); MSLT after every PSG night, sleep loss assessment, POMS, STAI, withdrawal symptoms, urine cotinine	abstinence: PSG: - relative arousals ↑, number of stage changes ↑, number of awakenings ↑, slightly higher restless leg syndrome index MSLT: - NREM 1 latency ↓ mood: - anxiety ↑, tension and irritability ↑, craving ↑

Abbreviations: cig, cigarettes; d, day; MSLT, Multiple Sleep Latency Test; NREM, non-REM; OR, odds ratios; POMS, Profile of Mood States; PSG, polysomnography; REM, rapid eye movement; SJWQ, Shiffman-Jarvik-Withdrawal Questionnaire; SSS Stanford Sleep Scale; STAI, State Trait Anxiety Inventory; SWS, slow wave sleep; TST, total sleep time; yrs, years.

Table 4
Polysomnographic investigations of the influence of nicotine patches on sleep in healthy non-smokers.

Authors	Subjects	Methodology	Results
Gillin et al.[42]	$n = 12$ non-smokers mean age 30 yrs	double-blind randomized cross-over study; d1: adaptation, d 2: baseline, d 3–8: experimental night with a subsequent recovery night; conditions (9 pm to 7 am): placebo, 7 mg NP, 14 mg NP; PSG, POMS, HAM-D, dream report	7 mg and 14 mg NP: - REM sleep duration, REM % ↓ - NREM 2 % ↑ (only 14 mg) - no change in TST - sleep end time earlier 7 mg and 14 mg recovery night: - REM latency and NREM 2 ↓ - REM sleep and REM % ↑ - sleep end time return to normal 7 mg recovery night: - REM density ↓ 14 mg recovery night: - TST ↑ mood and number of dreams did not differ
Davila et al.[43]	$n = 20$ snoring non-smokers male = 10; female = 10; age 28–70 yrs; mean BMI 35.1	double-blind randomized cross-over study; day 1: adaptation, days 2–3: experimental night; conditions (6 pm to 6 am): placebo,15 mg NP/24 h; serum nicotine levels, PSG, snoring index;	nicotine patch: - TST ↓ - sleep latency ↑ - sleep efficiency ↓ - REM % ↓ - females had higher nicotine levels - mean snoring intensity ↓ - disordered breathing event duration correlated negatively with nicotine serum concentration - oxygen saturation correlated positively with nicotine serum concentration both conditions: - females longer time in NREM 3 & 4

Abbreviations: cig, cigarettes; d, day; HAM-D, Hamilton scale for depression; h, hour; NP, nicotine patches; NREM, non-REM; POMS, Profile of Mood States; PSG, polysomnography; REM, rapid eye movement; TST, total sleep time; yrs, years.

When looking at gender differences and use of NRT, Wetter et al.[55] observed a temporal linear decrease of sleep fragmentation in men, while it remained constantly increased in women. Women using nicotine replacement also exhibited more total wake time during the first withdrawal night than women on placebo and men in general. Likewise, men in both placebo and intervention groups had an increased sleep efficiency, while women using nicotine patches showed no improvement, thereby actually experiencing a worsening of symptoms during nicotine replacement therapy.

To sum up, due to their different designs, e.g., length of abstinence, additional smoking while on nicotine replacement, application time and nicotine dosage, the studies described above are hardly comparable. In most of the investigations an individually adapted dosage of nicotine replacement did not take place due to standardised protocols. An individual variability of nicotine metabolism might have led to differences in nicotine serum concentrations, thereby suggesting that partial withdrawal symptoms were confounded by nicotine effects on sleep.

Two well-designed and comparable studies[50,54] arrived at similar results. Application of nicotine patches over 16 and 24 h respectively reduced the frequency of arousals and prolonged time spent in SWS, with the 24 h application being even more beneficial. Beyond that, the application time of the patch can be important as maximum plasma concentrations are only reached after 8–10 h.[56,57] Investigations into the direct comparison of day and night application have not yet been carried out.

Nicotine patches as a therapeutic strategy during nicotine withdrawal may counteract disturbed sleep by decreasing the frequency of arousals and prolonging SWS. Furthermore, there seems to be a discrepancy between subjective and objective sleep parameters. During nicotine withdrawal both with and without nicotine patches, increased sleep disturbances were subjectively reported. However, polysomnographic investigations point to at least a partially positive effect. Presumably, the subjectively experienced impairment of sleep might be closely linked with other withdrawal symptoms, like craving.

Effects of nicotine on PSG sleep in depressed patients

Following the acute use of nicotine patches, depressive non-smoking patients displayed a significant increase in REM sleep with no changes in other sleep parameters, compared to healthy controls[44,58] (see Table 6). The increase of REM sleep was highest during the fourth night of nicotine exposure.[45] Those patients, who had the largest increase of REM sleep (>50% over baseline), showed the strongest decrease in Hamilton Rating Scale for Depression (HAM-D) scores and also a shorter REM latency. Salin-Pascual and Galicia-Polo[58] observed a significant increase of REM-sleep duration and a decrease of sleep stage 2 in the second night with nicotine patches in depressed non-smokers. During nicotine withdrawal, women with a previous depression presented a small non-significant increase in REM sleep, while REM-sleep latency remained unaffected.[59] Healthy smokers showed a shortened REM latency and an increase of depressive symptoms during the withdrawal period.[60]

Haro and Drucker-Colin[61] observed a return to baseline REM-sleep durations along with an increase in TST, higher sleep efficiency and more SWS sleep when nicotine administration was ceased after nine months. REM-sleep latency, which was shorter at baseline in depressive subjects, normalised around the fifth month and showed no change up to the 24-month follow-up. In a comparison of nicotine and fluoxetine as treatment, depressive non-smokers showed a reduction of wake time, sleep stage 1 and arousals, while SWS, REM-sleep latency, TST and sleep efficiency increased during nicotine application.[62] Both nicotine and fluoxetine improved depressive symptoms, however, fluoxetine therapy

Table 5
Influence of nicotine replacement therapy on sleep during nicotine withdrawal.

Authors	Subjects	Methodology	Results
Nicotine gum			
Hughes et al.[46]	$n = 100$ smokers (>10 cig/d) 1 dropout 1–1.5 packs/d for at least 15 yrs mean age 36.7 yrs	double-blind randomized study; 2 mg nicotine gum, mean >10/d; d 1: BL, d 2: nicotine tolerance and plasma levels, d 3: smoke stop with nicotine gum or placebo; d 3, 4, 6: POMS, withdrawal symptom rating list, subjective sleep, CO control	placebo: insomnia ↑ nicotine: - irritability, anxiety, somatic complaints ↓ - withdrawal discomfort - craving, hunger, overeating and insomnia ↔
Gross and Stitzer[47]	$n = 87$ smokers (>10 cig/d), 47 dropouts (unable to quit, relapse) mean age 41.8 yrs 33.9 cig/d, smoked for 24 yrs	double-blind randomized study; placebo or 2 mg nicotine gum, 5–15/d for 10 wk; 2 wk prior cessation, BL, then twice/wk self-report withdrawal symptoms, somatic complaints, CO control, saliva cotinine, thiocyanate level	placebo: - total withdrawal score↑ during wk 1, then ↓ until wk 5, then stable - higher dropout rate due to relapses - at BL more heavy smokers nicotine: - no ↑ total withdrawal score over 10 wk and less than placebo during wk 4–5 - irritability, anxiety, craving, somatic complaints, sleep disturbance ↓ in wk 1 - appetite and excessive eating ↓ over 10 wk
Nicotine patches – studies without PSG			
ICRF General Practice Research Group[13]	$n = 1686$ patients in 19 surgeries $n = 966$ (57.3 %) dropouts $n = 260$ completed full 12 wk age 25–64 yrs mean 24 cig/d, smoked for 25 yrs	double-blind placebo controlled randomized study; 12 wk duration, 4 wk 21 mg NP, 4 wk 14 mg NP, 4 wk 7 mg NP + either pamphlet or booklet; BL, follow-up wk 1, 4, 8 and 12, evaluation of adverse effects and withdrawal symptoms, cotinine levels;	nicotine at wk 1: - craving ↓, irritability, moodiness, tenseness and difficulties concentrating ↓ adverse effects of NP at wk 1: - sleep disturbances ↑, skin reactions ↑
Hurt et al.[15]	n = 240 44 dropouts, mean age 43.2 yrs mean 29.8 cig/d	double-blind placebo controlled randomized study; 8 wk duration, 22 mg NP + individual counselling; BL, nicotine and cotinine levels, weekly follow-up, CO control, BDI, Hughes–Hatsukami Withdrawal Scale, alcohol consumption	adverse effects: NP 87.5 % Placebo: 68.3 % - skin reactions , headaches (more in placebo group), vomiting and other gastrointestinal complaints, sleep disturbances nicotine: - withdrawal symptoms ↓
Fredrickson et al.[49]	$n = 40$ smokers (>20 cig/d), 2 dropouts mean age 47.4 yrs 32.4 cig/d, smoked for 28.8 yrs	open outpatient study; 8 wk duration, 24 h NP, wk 1–5: 44 mg/d, wk 5–9: 22 mg/d, +self-help booklet; Hughes–Hatsumaki Withdrawal Questionnaire, diaries, nicotine and cotinine levels at BL, CO control	44 mg NP: - problems falling and staying asleep ↑, unusual dreams ↑ 22 mg NP: - same as above, but in less subjects and less pronounced - positive correlation between cotinine levels and sleep disturbances
Gourlay et al.[14]	$n = 629$ relapsed smokers after previous treatment with NP mean age 41.4 yrs 27.7 cig/d	double-blind placebo controlled randomized study; 12 wk duration, 24 h NP (could be removed at night if persistent insomnia), 4 wk 21 mg NP, 4 wk 14 mg NP, 4 wk 7 mg; BL, follow-up at wk 4, 8, 12 and 26, evaluation of adverse effects, CO and cotinine levels	adverse effects: NP $n = 179$ Placebo $n = 143$ - sleep disturbances, headaches (more in placebo), gastrointestinal complaints, musculoskeletal pain
Jorenby et al.[16]	$n = 211$ smokers (> 20 cig/d), 41 dropouts, mean age 41.2 yrs 30.2 cig/d	double-blind placebo controlled randomized study; 5 wk duration, 24 h NP (could be removed at night if persistent insomnia), 21 mg NP + group therapy 2–3 x/wk; two different withdrawal scales daily, cotinine levels, CO control	adverse effects: - sleep disturbances (11.4% NP, 14.2% placebo) - insomnia, nightmares in both groups withdrawal symptoms: - ↑ during 1. wk irritability, anxiety, difficulties concentrating, restlessness (all higher in placebo) - ↑ for 4 wk sleep disturbances, appetite (no group difference), weight gain (less in NP)

(*continued on next page*)

Table 5 (*continued*)

Authors	Subjects	Methodology	Results
Gourlay et al.[48]	$n = 1392$ smokers (>15 cig/d for at least 3 yrs) mean age 41 yrs, mean 32 cig/d	cohort study; 12 wk duration, 24 h NP (34.7% removed NP before sleep), 4 wk 21 mg NP, 4 wk 14 mg, 4 wk 7 mg NP, + brief counselling & booklet; BL, follow-up wk 1, 4, 8, 12 and 26, random nicotine and cotinine levels, CO control, report adverse effects;	sleep disturbances: 21 mg NP 96.7 % 14 mg NP 3.1 % 7 mg NP 0.1 % - nightmares ↑, other sleep problems ↑, predictor for sleep disturbances: female and abstinence concurrent smoking: - headache ↑, sleep problems ↓
Nicotine patches — PSG studies			
Wolter et al.[51]	$n = 71$ smokers *light smokers* (10–15 cig /d): $n = 23$ *moderate smokers* (16–30 cig/d): $n = 24$ *heavy smokers* (30 cig/d): $n = 24$, mean age 47.5 yrs, mean 25.5 cig/d	double-blind randomized stratified study; 10 wk duration, 24 h NP, placebo, 11 mg/d NP, 22 mg/d NP or 44 mg/d NP; wk 1 BL outpatient, wk 2 NP inpatient, wk 3–10 NP outpatient, wk 11 off patch, follow-up at mths 3, 6, 9 and 12; subjects on placebo: from wk 3 onwards 11 mg/d NP or 22 mg/d NP, subjects on 44 mg/d NP reduced to 22 mg/d NP at wk 6; CO-control, nicotine and cotinine levels, actigraphy wk 2, 10, 11 and 1 wk prior to mth 6 follow-up, subjective sleep	actigraphy: - no difference in sleep efficiency - no dose differences for changes from BL to wk 3 - bedtime wrist activity higher in 22 mg/d NP than 11 mg/d NP in wk 10 - ↓ daytime wrist activity in wk 3, 10 and 11 - change in daytime wrist activity and nicotine percentage correlates positively subjective sleep quality: - better with higher NP dosage
Wetter et al.[50]	$n = 43$ smokers (>20 cig/d), 2 dropouts *active group*: $n = 17$ *placebo group*: $n = 17$ *repeated assessment group* (continued smoking): $n = 9$ mean age 41.8 yrs, mean 30.5 cig/d	double-blind randomized study 6 wk duration, 24 h NP, 22 mg/d NP + group and individual counselling; BL d 7 and 5 prior quitting, recording d 1, 3 and 5 post quitting; PSG, sleep diaries, POMS, Questionnaire of Smoking Urges, CO control	PSG: - arousals ↑ in placebo, arousals ↓ in NP, NREM 2 ↓ in NP, NREM 3 and 4 ↑ in NP, REM latency, sleep latency, TST, time awake ↔ sleep diaries: - sleep latency ↑ in placebo, time awake↑ in NP, sleep duration ↔, more awakenings in nights 1, 3 and 5, daytime sleepiness ↑
Wetter et al.[55]	$n = 34$ smokers (>20 cig/d) mean age 41.9 yrs, mean 30.5 cig/d	double-blind placebo controlled randomized study; 24 h NP, 22 mg/d NP + 3 × pre- and 4 × post-quit individual counselling; BL d 7 and 5 prior quitting, recording d 1, 3 and 5 post quitting; PSG, sleep diaries, POMS, Questionnaire of smoking urges, CO control, cotinine levels	PSG: - arousals males ↑ d 1, then ↓, less in NP, sleep stages ↔, time awake males ↓ after d 1 (both groups), time awake females ↓ in placebo, ↑ in NP, sleep efficiency males ↑ (both groups), sleep efficiency females ↑ in placebo, ↓ in NP sleep diaries: - no differences or changes
Aubin et al.[53];	$n = 20$ smokers mean age 32.9 yrs, mean 26 cig/d	randomized open-label cross-over study; design see Staner et al.[54] PSG, Karolinska Sleep Diary, Questionnaire of Smoking Urges, POMS	PSG: - SWS ↑ in 24 h NP, ↓ in 16 h NP - POMS-Score ↓ (24 h >16 h NP) subjective data: no differences
Page et al.[52]	$n = 16$ smokers, 1 dropout mean age 25.8 yrs	randomized placebo controlled blind study; 24 h NP, 14 mg/d (if < 10 cig/d) or 21 mg/d (if >10 cig/d) or placebo; 2 nights abstinent at the sleep laboratory with 1 wk in between (smoking allowed); PSG , dream report (6x/night)	PSG: - REM ↓ in NP - TST, NREM 1,2,3,4 ↔, time awake ↑ in NP, micro arousals ↑ in NP, REM latency ↔ dream report: - more vivid dreams during REM in NP, no differences in NREM 2 dreams
Staner et al.[54]	$n = 20$ smokers mean age 32.9 yrs, mean 26 cig/d	randomized open cross-over study; 21 mg/24-h-NP or 15 mg/16 h NP, 1 d BL, 2 × 2 d smoke free + NP, 4 d in between (smoking allowed), no alcohol & caffeine; PSG, Karolinska Sleep Diary	21mg/24 h-NP: - NREM and SWS ↑, REM density ↑, micro arousals ↓ 15 mg/16 h NP: - micro arousals ↑, REM ↑, SWS ↓ both NP: - sleep latency ↑, TST ↓, sleep efficiency ↓

Abbreviations: BDI, Beck Depression Inventory; BL, baseline; cig, cigarettes; d, day; h, hour; NP, nicotine patch; NREM, non-REM; POMS, Profile of Mood States; PSG, polysomnography; REM, rapid eye movement; SWS, slow wave sleep; TST, total sleep time; wk, week; yrs, years.

Table 6
Investigations of the influence of nicotine in depressed patients.

Authors	Subjects	Methodology	Results
Salin-Pascual et al.[44]	non-smokers major depressed patients (HAM-D >18): $n=8$, mean age 39.6 yrs healthy subjects: $n=8$, mean age 31.5 yrs	randomized double-blind cross-over study; 17.5 mg NP applied 2 h before bedtime, removed after 24 h; 1st.night adaptation, 2nd. night baseline, 3rd. night placebo or nicotine, 4th. night follow-up; PSG, HAM-D	depressives with nicotine: - REM and REM-sleep average duration ↑, short time mood improvement with HAM-D ↓ healthy subjects with nicotine: - wake time ↑, TST ↓, NREM 1 ↓, REM sleep time and total REM ↓, REM latency ↓ (also in follow-up night)
Salin-Pascual and Drucker-Colin[45]	$n=12$ non-smokers *healthy subjects*: $n=6$, mean age 42.6 yrs *major depressed patients* (HAM-D > 18): $n=6$, mean age 35.2 yrs	controlled study 17.5 mg NP applied 2 h before bedtime, removed after 24 h; 1st.night adaptation, 2nd. night control, 4th, 5th and 6th. night nicotine, 7th. night withdrawal; PSG, HAM-D	depressives with nicotine: - REM sleep time ↑ in all nights, highest 4th. nicotine night normal volunteers with nicotine: - REM ↑, highest in withdrawal, NREM 2 ↓ between night 4 and 7, NREM 3 ↓ between night 3 and 5, HAM-D ↓, insomnia ↓
Salin-Pascual and Galicia-Polo[58]	$n=15$ major depressed non-smoking patients (HAM-D >18) mean age 36.6 yrs	non-controlled study; 17.5 mg NP applied 2 h before bedtime, removed after 7.00 in the morning; 1st.night adaptation, 2th. night baseline, 3rd. night nicotine; PSG, HAM-D	- REM-sleep-time ↑ - NREM 2 ↓ - $n=10$ mood improvement after nicotine with REM enhancement above baseline values - $n=8$ REM sleep latencies <60 min of baseline
Wetter et al.[59]	$n=14$ female smokers with history of depression: $n=7$ without depression: $n=7$, 1 dropout mean age 44.2 yrs, mean 22.1 cig/d	controlled study; adaptation night 10 d pre cessation, baseline 5 d pre cessation, d 3, 5,and 10 after quitting daily morning and evening diaries, SSS, Wisconsin Smoking Withdrawal Scale, CO levels, PSG;	Both groups: - number of awakenings, number of sleep stage shifts, time awake after sleep onset peaked on d 3 and then ↓ - TST, NREM 1 ↓ across withdrawal, NREM 3,4 ↓ over 3 d, then ↑ history of depression group: - REM% ↑ d 5–10 no depression group: - REM latency ↑ across d 3–5, then ↓ subjective data: - sleep disturbances ↑, restorative value of sleep ↓ - more awakenings in depression history group
Haro and Drucker-Colin[61]	$n=14$ non-smoking major depressed patients (HAM-D >18) mean age 38.1 yrs	single-blind study; 17.5 mg NP applied at 21.00, were renewed daily at the same time, 5 d/wk until mths 6, 3 d/wk in mth 7, once/wk in mth 8, nicotine free patch once/wk mths 9–24; PSG, monthly HAM-D;	baseline and results up to 9. mth: described in Haro and Drucker-Colin[62] mth 10: - TST, sleep efficiency ↑ - wakefulness, NREM 1↓ NREM 3 and 4, REM latency ↑ up to mth 9 compared to BL - REM duration transiently ↓during withdrawal - other parameters unchanged during withwrawal
Haro and Drucker-Colin[62]	*non-smoking depressed patients* (HAM-D >18): $n=24$ mean age 38.4 yrs *healthy subjects*: $n=30$	double-blind study; $n=12$: 17.5 mg NP applied at 21.00, were renewed daily at the same time, 5 d/wk until mths 6, 3 d/wk in mth 7, once/wk in mth 8, nicotine free patch once/wk mths 9–14; $n=12$: 20 mg fluoxetine at the same frequency and duration as nicotine, from mths 9–14 placebo; PSG, monthly HAM-D	baseline depressive vs. healthy: - TST ↓, wakefulness ↑, sleep efficiency ↓, sleep latency ↑, NREM 1, 3, 4 ↓, total-REM duration ↑, REM latency ↓ NP: - mth 1: wakefulness ↓, NREM 1 ↓, NREM 3–4 ↑, REM latency ↑ - mths 2–6 : as in mth 1. + TST ↑, sleep efficiency ↑ - mths 7–9 : as in previous mth - mths 11–13 : REM-duration ↓, REM latency ↓ to mth 4 values - HAM-D: similar reduction nicotine vs. fluoxetine: wakefulness ↓, EEG-awakenings ↓, NREM 1,2,3, ↓, NREM 4 ↑, REM-Sleep ↑, REM latency ↓

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Table 6 (*continued*)

Authors	Subjects	Methodology	Results
Moreno-Coutino et al.[60]	$n=15$ smokers without depression, mean age 39 yrs, mean 27.1 cig/d ($n=7$ completely abstinent after 1 yr, $n=3$ partially abstinent, 5 dropouts in partial abstinence)	non-controlled study; baseline, 1, 2, 4, 6, 9 and 12 month follow-ups; PSG, urinary cotinine, HAM-D; linear mixed regression model	- HAM-D ↓ in total and partial abstinent smokers - REM latency ↓ - NREM 2 ↑ in abstinence - percentage REM ↑ in abstinence in mths 4, 6, 9, and in partial abstinence in mths 1, 2, 12 - NREM 1 ↓ in abstinence in mths 2, 4, 6 - NREM 3, 4 ↓ in abstinence in mths 1, 4, 6, 12, and in partial abstinence after mths 2 - HAM-D correlates inversely with NREM 1 and REM latency - HAM-D correlates positively with REM sleep time and stage shifts

Abbreviations: BL, baseline; cig, cigarettes ; d, day; HAM-D, Hamilton scale for depression; h, hour; mth, month; NP, nicotine patches; NREM, non-REM; PSG, polysomnography; REM, rapid eye movement; SSS Stanford Sleep Scale; TST, total sleep time; wk, week; yrs, years.

worsened sleep by increasing wake time, number of arousals and sleep stage 1 and reducing TST and REM sleep. Nicotine administration led to a prolonged REM latency.

In summary, depressive non-smokers experienced an improvement of mood under nicotine administration comparable to the effect of anti-depressants. The most consistent finding was an increased REM sleep during nicotine therapy maintained over several months.

Nicotine consumption and sleep apnoea

Sleep apnoea syndrome (SAS) is characterised by the interruption of breathing during sleep and thus a decrease in oxygen saturation. Occurrence of apnoeas leads to serious sleep fragmentation with frequent arousals and sleep stage changes and usually to daytime sleepiness.

In a longitudinal cohort study,[26] the prevalence of SAS was 40 times higher in smokers than in non-smokers (see Table 7).

In a regression analysis former smokers showed no increased risk for impaired breathing during sleep after controlling for other risk factors, such as coffee consumption, body mass index, etc.[26,63] The use of nicotine gum led to a significant decrease in apnoea time and reduced obstructive and mixed apnoeas without change in the number of central apnoeas.[64] In an investigation of non-smokers nicotine patches influenced the volume but not the frequency of snoring and sleep apnoeas.[43] In this study, the placebo night followed the nicotine night; therefore withdrawal effects cannot be excluded. The overnight application of a nicotine patch resulted in a small but significant increase in the mean oxygen saturation and a non-significant reduction in the apnoea–hypopnoea index in smokers.[65] When supplying toothpaste containing nicotine to non-smokers, Zevin et al.[66] observed an extended sleep onset latency and an increased time spent in stage 1. The apnoea–hypopnoea index did not change and daytime sleepiness only tended to improve with higher nicotine doses.

Outlook

Both in population-representative samples and under controlled conditions, smoking and acute nicotine application led to complaints of insomnia, increased sleep fragmentation and sleep onset latency, decreased sleep efficiency, reduced SWS time and increased daytime sleepiness. These symptoms appear to be reversible after cessation.[40,33]

Similar sleep changes were also observed during acute nicotine withdrawal. The extent of the sleep impairment correlated with individual plasma nicotine concentrations,[15,39,49] the severity of nicotine dependence[48] and female gender.[48,55,30] To what extent menstrual cycle affects sleep disturbances after smoking cessation is not yet clear. On one hand, an exacerbation of withdrawal symptoms during the luteal cycle phase was observed[67]; whereas Pomerleau et al.[68] and Snively et al.[69] found no difference in symptom intensity between follicular and luteal phase. This factor should be taken into account in future investigations.

Nicotine replacement therapy affects the sleep of non-smokers and previous smokers in the same manner. Two studies[54,55] indicated an improvement of withdrawal-related sleep disturbances when using nicotine replacement devices. In order to reduce withdrawal symptoms and achieve a better sleep quality it might be crucial to adapt the individual effective NRT dosage within the range of under- or overdosing.

Little is known about the underlying mechanisms of disturbed sleep during nicotine withdrawal. Pharmacokinetic issues, such as the uptake or metabolism of nicotine, do not seem to be of importance. There is evidence of differences between acute and chronic application[44,61] and of changing effects during the course of withdrawal.[32,51] While subjects experienced remarkably disturbed sleep, the effects of nicotine withdrawal on PSG parameters were less impressive.

Sleep-related breathing disorders represent another possibility of how nicotine affects subjective sleep quality as there is a clear correlation of SAS with smoking.[26,63] Although chronic nicotine exposure leads to a reduction of the hypoxic sensitivity and to a delay of hypoxia-induced arousals,[70,71] none of the investigations found an association between sleep disturbances and apnoea–hypopnoea index or oxygen saturation during sleep.

Sleep may also be disturbed in periodic limb movement disorder (PLMD; for an overview see Hornyak et al.[72]). PLMs are supposed to be related to an impaired dopaminergic function with a decreased number of D_2 receptors in the striate cortex[73] and a reduced nightly urine excretion of dopamine.[74] Like dopamine agonists, nicotine could therefore influence PLM symptoms via the central dopamine system. Smoking (>20 cigarettes/day) was strongly associated with the occurrence of a restless legs syndrome (RLS),[75] a neurological disorder in which PLMs are highly prevalent. Further studies on the relationships between PLM, RLS and nicotine and the possible therapeutic use of nicotine in reducing PLMs are therefore required.

Beyond the occurrence of insomnia complaints, there are inconsistent findings regarding the effect of nicotine and withdrawal symptoms on different sleep stages. According to the reciprocal interaction model of McCarley and Hobson,[76] REM-sleep results from cholinergic stimulation of neurons in the gigantocellular tegmental field, while noradrenergic neurons of the raphe nucleus inhibit REM and induce NREM sleep. The direct stimulation of the central Ach receptors through nicotine corresponds to the findings of reduced SWS time, an increase of the NREM stages 1 and 2[33] as well as a decreased power of low-sleep EEG frequencies in favour of high-frequency activity.[34]

Nicotine has anti-depressive effects, and it is postulated that chronic smokers try to control depressive symptoms by nicotine

Table 7
Relationship of nicotine and sleep apnoea.

Authors	Subjects	Methodology	Results
Prevalence studies			
Wetter et al.[26]	$n = 811$ *non-smokers*: $n = 340$ *former smokers*: $n = 323$ *current smokers*: $n = 158$	longitudinal epidemiological study; PSG, oral/nasal air flow, oxymetry, inductance plethysmography	*relative risk for mild sleep-disordered breathing* : former vs. never-smokes: OR 1.14, smoker vs. never-smokers: OR 2.09, heavy smokes (>40 cig./day): OR 6.74 *relative risk for moderate sleep-disordered breathing*: former vs. never-smokes: OR 1.86, smokers vs. never-smokes: 4.44, heavy smokers: OR 40.47 *relative risk snoring*: former vs. never-smokes: OR 1.26, smokers vs. never-smokes: OR 2.29, heavy smokers: OR 3.06
Kashyap et al.[63]	patients with OSA (AHI >10/h): $n = 108$, 35% smokers mean age 51.9 yrs healthy subjects: $n = 106$, 19 % smokers mean age 47.4 yrs	retrospective case-control study; PSG, sleep questionnaire, smoking and drinking behaviour	relative risk for obstructive sleep apnoea: current vs. never-smokes: OR 2.8 current vs. never or former smoker: OR 2.5
Intervention studies			
Gothe et al.[64]	*patients with OSA*: $n = 8$ males, never-smokes $n = 3$, occasional smokers $n = 2$, stopped smoking before study $n = 3$ mean age 45 yrs	controlled cross-over study: 2 mg nicotine gum for 20 min in hourly intervals starting at 15:00, additional 4 mg chewing gum 30 min before sleep, total dose 14 mg, control and test on separate nights 1 wk apart; PSG, inductive plethysmograph, oronasal air flow, O_2 saturation, pCO_2	nicotine: - total number of apnoeas in 1st. and 2nd. h ↓ - central apnoeas ↑ in 4 and ↓ in 4 subjects - sleep apnoea time ↓ - obstructive apnoeas disappeared in 4 subjects in 1 h after nicotine and remained absent in 5 subjects in 2 h - time apnoeic while asleep ↓ - no effect on O_2 and CO_2 saturation - no changes in sleep stages
Hein et al.[65]	$n = 8$ OSA patients, smokers, mean age 57 yrs	controlled study; nicotine patch 35 mg administered at 21:00 1.night control, 2. night nicotine; PSG	nicotine: - no changes in apnoea index - O_2 saturation ↑
Zevin et al.[66]	$n = 11$ male non-smokers (6 former cigarette and 1 former pipe smoker) with OSA mean age 50 yrs	double-blind randomized cross-over study; 2mg vs. 4.3 mg nicotine toothpaste; baseline assessment, 2 mg and 4.3 mg toothpaste in separate nights after a 3–7 d wash out period; PSG, oral/nasal air flow, O_2 saturation, abdominal-chest wall movement, nicotine levels, ESS, sleep quality, snoring, sleepiness	PSG: - sleep latency shorter at baseline compared with both active treatments, no difference between both dosages - no effect on AHI and sleep stages - no differences in ESS, trend towards lower score in higher dose

Abbreviations: AHI, apnoea hypopnoea index; d, day; ESS, Eppworth Sleepiness Scale; HAM-D, Hamilton scale for depression; h, hour; NREM, non-REM; OSA, obstructive sleep apnoea; POMS, Profile of Mood States; PSG, polysomnography; REM, rapid eye movement; SWS, slow wave sleep; TST, total sleep time; wk, week; yrs, years.

consumption.[60] Animal experiments on the regulation of REM sleep can help to interpret nicotine's influence on sleep and its anti-depressive effect. The stimulation of serotonergic neurons in the dorsal raphe nucleus by nicotine leads to an inhibition of the PPT and LDT neurons, which is responsible for REM onset, and the suppression of the PGO spikes.[23,24] Based on the assumption of a relative serotonin deficiency as a pathogenic factor in depression, the activity of the dorsal raphe nucleus would not be sufficient to suppress REM, leading to an increase of REM-sleep percentage and a shortened REM latency. Nicotine consumption is supposed to increase serotonin release in the dorsal raphe nucleus, thereby reducing REM sleep. Haro and Drucker-Colin[62] found an increase of REM sleep and a significant shortening of REM latency at baseline in depressive non-smokers. After chronic nicotine application, REM latency gradually increased up to the values of healthy individuals; REM duration showed a continuous decrease to normal values after an initial increase. Mood improvement correlated with the increase of REM latency in this study. Notably, nicotine rather than fluoxetine led to a normalisation of PSG-sleep parameters. Salin-Pascual and colleagues[44] also observed in depressive subjects using nicotine a shortened REM latency and an improvement of depressive symptoms accompanied by an increase of REM duration compared to baseline.

Likewise, Guzman-Marin et al.[24] found an extension of REM periods despite suppressed PGO spikes, suggesting a direct cholinergic stimulation of the REM onset neurons by acute nicotine application. The application time is possibly crucial to the 'brightening up' effect of nicotine: while in the first weeks an increase of REM sleep was observed in depressed patients, several months of application led to a REM suppressing effect, similar to the effect of anti-depressive drugs. According to the hypothesis of Haro and Drucker-Colin[61] a cholinergic effect might prevail in an early phase, while chronic nicotine application suppresses the hyperactivity of the cholinergic system and the serotonergic effect on sleep takes over.

In summary, sleep disturbances represent a frequent phenomenon among smokers. Smoking is associated with the occurrence of insomnia and sleep apnoea syndrome, and, in addition, could also be considered as self medication with regard to depressive symptoms. On the other hand, sleep disturbances during withdrawal are a risk for relapse or continuing consumption. Further investigations on these relationships and possible implications for treating sleep disturbances in smokers during nicotine withdrawal are needed.

Practice points

1. In both animals and humans, nicotine consumption is associated with sleep disturbances. Symptoms of insomnia, like increased sleep onset latency and sleep fragmentation, as well as decreased SWS and increased daytime sleepiness are reported.
2. Nicotine withdrawal also leads to insomnia complaints, the severity of which is related to the severity of nicotine dependence, the occurrence of other withdrawal symptoms, the individual nicotine levels and the duration of the abstinence. Subjective effects may be more pronounced than the severity of PSG documented sleep abnormalities.
3. Therapeutically applied nicotine impairs sleep as well. To what extent sleep disturbances under nicotine therapy are caused by withdrawal effects after smoking cessation or by direct action of nicotine cannot be differentiated at this time.
4. Nicotine effects on REM sleep were investigated in different study designs. The most consistent finding is that nicotine consumption suppresses REM sleep with a rebound during early withdrawal.
5. Depressive non-smokers experience a mood improvement by the intake of nicotine comparable to that found when using anti-depressive medication. The effect seems to be reversible after nicotine cessation.
6. Despite an increased prevalence of sleep-related respiratory disorders in smokers, there was no investigation of changes in those disorders after smoking cessation. There is also no evidence for a positive effect on these symptoms when nicotine was applied in non-, former or occasional smokers.

Research agenda

1. Comparison of exclusively day or night application of nicotine and the effects on sleep, particularly with regard to therapeutic application of nicotine.
2. Assessments of additional variables, such as degree of dependence, abstinence control, co-morbidity, age, gender and menstrual cycle.
3. Control of the actual nicotine exposure, preferably by nicotine or cotinine levels.
4. Comparable assessments for the effectiveness of nicotine substitution.
5. Investigations for a better understanding of the discrepancies between PSG findings and subjective sleep complaints.
6. Investigations of motor function during sleep after nicotine consumption and withdrawal.
7. Investigations of the relationship between sleep disturbances and relapse frequency.
8. Investigations of possible anti-depressive actions of nicotine other than its effect on sleep.
9. Investigations of changes of sleep-related breathing disorders in smokers after smoking cessation.

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