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# Tobacco-induced sleep disturbances: a systematic review and meta-analysis

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## Summary

Even though tobacco-induced sleep disturbances (TISDs) have been reported in previous studies, the present article is the first meta-analysis quantitatively assessing the impact of tobacco on sleep parameters. We conducted a systematic review and meta-analysis of the studies comparing objective (i.e. polysomnography and actigraphy) and/or subjective sleep parameters in chronic tobacco smokers without comorbidities versus healthy controls. Studies were retrieved using PubMed, PsycINFO, and Web of Science. Differences are expressed as standardized mean deviations (SMD) and their 95% confidence intervals (95%CI). Fourteen studies were finally included into the review, among which ten were suitable for meta-analysis. Compared to healthy controls, chronic tobacco users displayed increased N1 percentage (SMD = 0.65, 95%CI: 0.22 to 1.07), N2 percentage (SMD = 1.45, 95%CI: 0.26 to 2.63), wake time after sleep onset (SMD= 6.37, 95%CI: 2.48 to 10.26), and decreased slow-wave sleep (SMD = -2.00, 95%CI: -3.30 to -0.70). Objective TISDs preferentially occurred during the first part of the night. Regarding subjective parameters, only the Pittsburgh Sleep Quality Index (PSQI) total score could be analyzed, with no significant between-groups difference (SMD = 0.53, 95%CI: -0.18 to 1.23). Smoking status should be carefully assessed in sleep medicine, while TISDs should be regularly explored in chronic tobacco users.

**Keywords: Sleep, smoke, dependence, tobacco, systematic review, meta-analysis.**

## Abbreviations

|         |   |       |                                    |
|---------|---|-------|------------------------------------|
| AASM    | American academy of sleep medicine                                    | REM   | rapid-eye-movement                 |
| AI      | arousal index   | SD    | standard deviation                 |
| Cig/day | cigarette per day   | SE    | sleep efficiency                   |
| ESS     | Epworth sleepiness scale  | SLREM | latency to REM-sleep               |
| FTND    | Fagerström Test for Nicotine Dependence                               | SMD   | standardized mean deviation        |
| GABA    | $\gamma$ -aminobutyric acid   | SOL   | sleep onset latency                |
| ISI     | insomnia severity index   | SPT   | sleep period time                  |
| LMI     | leg movement index  | SRBDs | sleep related breathing disorders  |
| N1      | light sleep stage 1   | SWS   | slow-wave sleep                    |
| N2      | light sleep stage 2   | TISDs | tobacco-induced sleep disturbances |
| NOS     | Newcastle Ottawa scale  | TST   | total sleep time                   |
| PRISMA  | Preferred Reporting Items for Systematic<br>Reviews and Meta-Analyses | TUD   | tobacco use disorder               |
| PSG     | polysomnography   | WASO  | wake after sleep onset             |
| PSQI    | Pittsburgh sleep quality index  |       |                                    |

## INTRODUCTION

In 2015, it was estimated that 1.3 billion people used tobacco worldwide<sup>1</sup>. In the vast majority of cases, tobacco is used in its smoked form. Within tobacco products, different compounds may affect individuals' health. Nicotine is considered to be the main active principle of tobacco affecting the central nervous system, and is in particular involved in inducing tobacco dependence<sup>2</sup>. Furthermore, other compounds of smoked tobacco, such as tar, cause a large set of severe medical conditions including lung cancer, chronic bronchitis and cardiovascular diseases<sup>3,4</sup>. Tobacco smoking also affects mental health. For example, smoking is associated with an increased severity of a vast range of psychiatric disorders, such as depression and anxiety<sup>5</sup>, or with an increased risk of developing other psychiatric disorders, such as psychosis<sup>6</sup>. Such psychiatric disorders, in particular psychosis, are associated with increased stigma<sup>7</sup>, but also with reduced access to adequate healthcare, including addiction treatment<sup>8</sup>. In addition, tobacco smoking is frequently associated with impairments in some major physiological functions, such as sexuality<sup>9</sup>, eating habits<sup>10</sup>, or physical exercise<sup>11</sup>.

Sleep is another fundamental physiological function that has been found to be altered by tobacco smoking. Tobacco-induced sleep disturbances (TISDs) have been confirmed with objective sleep measures, i.e. those reported either by polysomnography or actigraphy, as well as with subjective sleep measures, including subjective sleep quality, insomnia, or daytime sleepiness. Several previous systematic reviews have found that tobacco smoking was associated with decreased sleep efficiency (SE)<sup>12-14</sup>, total sleep time (TST)<sup>12,14,15</sup>, slow wave sleep (SWS)<sup>12-15</sup>, rapid-eye-movement (REM) sleep<sup>13-15</sup>, and with increased sleep onset latency (SOL)<sup>12-15</sup>, wake after sleep onset (WASO)<sup>13</sup>, light sleep stages 1 (N1) and 2 (N2)<sup>12</sup>, and latency to REM-sleep (SLREM)<sup>12,14,15</sup>. Other sleep disturbances have been

pointed out in tobacco users, including an increased risk of developing restless legs syndrome, sleep apnea, as well as several unspecific alterations of sleep architecture<sup>16,17</sup>.

The pathophysiology of TISDs is thought to be primarily related to the pharmacological effects of nicotine on brain neurotransmission<sup>18</sup>. Nicotinic activation of cholinergic receptors induces the release of a wide range of neurotransmitters involved in sleep and wakefulness regulation<sup>19</sup>, including the central release of dopamine, norepinephrine, serotonin, acetylcholine, glutamate,  $\gamma$ -aminobutyric acid (GABA) and b-endorphins<sup>20–22</sup>. Specifically, nicotinic actions increase theta and gamma cortical activity, together with waking and REM sleep<sup>23–26</sup>. Activation of nicotinic receptors enhances the noradrenergic inhibition of sleep-promoting neurons in the Ventro Lateral Pre Optic area (VLPO, considered to be a key structure for sleep initiation and maintenance), thereby inhibiting sleep and enhancing wakefulness<sup>27</sup>. Altogether, data show that nicotinic activation of cholinergic receptors in the brain leads to sleep disruption and arousal enhancement either directly, by altering the connections between sleep and wake structures, or indirectly by impairing key internal messages such as the one from the circadian sleep/wake timing system.

Despite the number of previous studies and systematic reviews, the present study is the first meta-analysis conducted on TISDs to provide pooled quantitative estimates of the different sleep alterations related to tobacco smoking. Such estimates would be particularly important for clinical practice, either for sleep or addiction specialists. In sleep medicine, quantitatively estimating TISDs may help to better interpret the results of sleep assessment among chronic tobacco users, and to better disentangle TISDs from alterations resulting from other medical causes. On the other hand, addiction specialists may want to be aware of TISDs in order to better educate patients and to integrate these elements into motivational interviewing and motivation to quit. For all these reasons, we performed a meta-analysis on TISDs, based on both objective and subjective evaluations of sleep.

## MATERIALS AND METHODS

A systematic review and meta-analysis were performed to examine the association between sleep disturbances and chronic tobacco use. This review was conducted, and hereby reported, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>28</sup>. The review protocol was registered in PROSPERO on 28/04/2020 (Registration# CRD42020168974).

### **Search strategy**

A systematic search was conducted in *PubMed*, *PsycINFO*, and *Web of Science*, from inception to 02/07/2020. The search was restricted to English language. Keywords were combined by using the Boolean operators “AND” and “OR”, and filters were used in order to exclude review articles. The algorithm used was the following one: (*"tobacco" OR "cigarette" OR "smoke"*) AND (*"use disorder" OR "dependence" OR "addiction"*) AND (*"polysomnography" OR "actigraphy" OR "sleep" OR "apnea" OR "nightmare" OR "daytime sleepiness" OR "hypersomnia" OR "parasomnia" OR "insomnia" OR "restless leg"*) NOT *"review"* [Publication Type].

### **Search procedure**

The flowchart detailing the selection process of the included studies can be found in **Figure 1**. Two authors (SC and MN) independently performed a broad screening, based on title and abstracts. Duplicates were removed using Zotero and Rayyan. The title and abstract of each potentially eligible record were reviewed independently by two authors (SC and MN).

After this preliminary round of screening, full texts of the selected studies were retrieved and independently reviewed by two reviewers (SC and MN). The final inclusion for review was determined by the two reviewers, based on the inclusion and exclusion criteria

(see below). Disagreements were solved by two senior authors (BR and PG). Studies included in the review consisted of either cohort studies, or retrospective case control studies.

Studies were included only if they compared chronic tobacco users (see definition below) and controls, and if they measured subjective and/or objective parameters of sleep (see below). Clinical trials, case reports, reviews, meta-analyses and animal studies were excluded. Unpublished studies were not searched for, in order to focus on the most rigorous datasets.

### ***Inclusion and exclusion criteria of the selected studies***

Inclusion criteria for the study participants were as follows: (1) age  $\geq 18$  and  $\leq 70$  years: we chose this age range because the physiology of sleep in youngsters and the elderly is specific<sup>29</sup> and this would as been an important source of heterogeneity to including these two ages categories; (2) diagnosis of tobacco dependence, or tobacco/nicotine use disorder, according to either the DSM-III, DSM-IV, DSM IV-TR, ICD-10, or DSM-5 criteria respectively, or a Fagerström Test for Nicotine Dependence (FTND)<sup>30</sup> score of five or more; (3) chronic use of tobacco, i.e. at least five times per week; (4) active use of tobacco, or cessation of use for less than 24 hours; and (5) studies assessing at least one of the sleep parameters defined below. Control participants were either of non-smokers or occasional smokers who did not met the above criteria.

Exclusion criteria were as follows: (1) criteria of concurrent substance use disorder or any other psychiatric disorder, based on either the DSM-III, DSM-IV, DSM IV-TR, ICD-10, or DSM-5 criteria; (2) criteria of any concurrent somatic disease; (3) any other mode of nicotine consumption than smoked cigarettes; and (4) clinical trials or studies that assessed the effectiveness of a drug.

### ***Sleep parameters of interest***



- *Objective sleep parameters*

Objective sleep parameters were either obtained from polysomnography (PSG) or estimated via actigraphy. We retained the most frequently studied and most commonly used parameters, as listed below.

Actigraphy estimated the following parameters<sup>31</sup>: (1) SE in percentage; (2) SOL in minutes; (3) TST in minutes; (4) WASO presented as the percentage of sleep period time (SPT) or in minutes.

PSG assessed the following parameters<sup>32</sup> : (1) SE in percentage; (2) SOL in minutes; (3) TST in minutes; (4) WASO, presented as the percentage of SPT or in minutes; (5) Arousal index (AI), presented as the number of arousals occurring per hour of sleep; (6) N1 percentage; (7) N2 percentage, (8) SWS (=N3) percentage; (9) REM sleep percentage and (10) LREM in minutes. The time spent in each stage is generally presented as a percentage of TST or SPT<sup>33</sup>. PSG also recorded the apnea-hypopnea index (AHI), i.e. the total number of apnea and hypopnea events per hour of sleep<sup>34</sup> and the leg movement index (LMI, or PLMI for periodic movements) i.e. the number of leg movements per hour of sleep<sup>35</sup>.

It is worth mentioning that LMI, AI and SLREM were not mentioned as target parameters in the initial protocol registered on Prospero. We decided to carry out an *a posteriori* extraction and analysis of these parameters in order to integrate all the sleep parameters assessed in the available studies, and to potentially explore additional pathophysiological mechanisms of TISDs in chronic tobacco users.

- *Subjective sleep parameters*

Three predominant rating scales were considered in the selected studies : (1) the Pittsburgh sleep quality index (PSQI)<sup>36</sup>; (2) the Epworth sleepiness scale (ESS)<sup>37</sup>; and (3) the insomnia severity index (ISI)<sup>38</sup>. For each of these scales, only the total score was collected for review and meta-analysis.

### **Data extraction**

For each included study, two reviewers (S.C, S.L) extracted the following parameters, using a standardized extraction form: (a) information about the publication (e.g., authors' name, year of publication, country); (b) study design (cohort, retrospective case–control); (c) sample size and description (e.g., gender, age, origin of population); (d) tobacco use and other addiction-related characteristics (e.g., minimum tobacco consumption needed to participate in the study, criteria of tobacco dependence or tobacco use disorder (TUD), other authorized substance consumption); (e) whether substance consumption was allowed during in the assessment period; (f) paraclinical data (e.g., CO level); (g) main inclusion or exclusion criteria; (h) preinclusion night and results; (i) scoring rules for PSG (e.g., Rechtschaffen and Kales); (i) comparison group description (e.g., matching criteria).

For one study<sup>39</sup>, we combined the mean and standard deviations (SD) of two of the three sub-groups which reported cigarette consumption, respectively between 10 and 20 per day and more than 20 per day. The overall result of all three subgroups was not maintained as it included a subgroup whose consumption of one cigarette per day (cig/day) could not be certified (< 10 per day) in contrast with the other two. When data could not be extracted or calculated from the paper, it was planned to contact the authors via email to request the relevant data, but this procedure was not necessary.

### ***Data analysis***

We synthesized the included studies in agreement with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines<sup>40</sup>. PSG staging parameters were calculated using the scoring rules of Rechtschaffen and Kales. Events scoring for AHI, AI and LMI were calculated using the 2007 American Academy of Sleep Medicine (AASM) criteria<sup>41</sup>. We decided to pool the sleep parameters estimated through actigraphy with those of PSG because a good reliability between the two has been reported for SE, WASO and TST<sup>42</sup>.

### ***Assessment of study quality***

To assess possible biases in prevalence reporting, two authors (SC and SL) independently assessed the quality of each study by using the Newcastle Ottawa Scale (NOS)<sup>43</sup> (Table 9). The NOS contains eight items, categorized into three dimensions: selection, comparability, and, depending on the study type, outcome (cohort studies) or exposure (case-control studies). The total maximum score for these three dimensions is nine points. A study scoring more than seven points was considered to have a low risk of bias<sup>43</sup>.

### ***Statistical analysis***

Data were analyzed using R studio (R software version 4.0.2 with the “meta” package version 4.15-1). We used a random effect model to pool effect estimates. Restricted maximum likelihood estimator for  $\tau^2$  was used. For each study, the compared effect size between the smoking group and the control group was provided by calculating odds ratios for dichotomous outcomes and mean differences for continuous outcomes. When all studies assessed the same outcome but measured it using different scales, the standardized mean difference was used. Heterogeneity was analyzed using  $I^2$  which was interpreted as low, moderate or high, for  $I^2$  values of 25%, 50% and 75%, respectively<sup>44</sup>. If necessary, we imputed the most conservative SD values from the p values of the comparative test according to the Cochrane recommendation<sup>45</sup>.

None of the pre-defined subgroup or sensitivity analyses were performed because of the small number of available studies<sup>46</sup>. Moreover, to investigate the stability of our conclusions, we undertook a sensitivity analysis by removing actigraphy studies and studies that excluded sleep disorders. This sensitivity analysis was not initially planned in our protocol. As previously recommended<sup>47</sup>, publication bias was not assessed because less than ten studies were included in the meta-analysis.

# RESULTS

## *Study selection*

The flow-chart of the systematic search and successive selection process can be found in **Figure 1**. Our search yielded 756 records. After removing duplicates, the titles and abstracts of the remaining 519 articles were screened. A total of 39 studies were selected for full-text review. Of these, 14 articles<sup>39,48-60</sup> were found to meet the inclusion criteria of the systematic review, and 10 of the 14 studies were used in the final meta-analysis<sup>39,48-56</sup>. The excluded studies, and the reasons for their exclusion, can be found in Tables 3 and 4. Four of the studies meeting the inclusion criteria were not included in the meta-analysis, two because the values were not convertible in mean deviation and SD<sup>57,60</sup>, one because it focused on a specific clinical population<sup>58</sup>, and one because the sample contained subjects aged less than 18 years<sup>59</sup>.

Some data could not be included in the meta-analysis. For one study<sup>49</sup>, the SWS was not computable because only stages S3 and S4 of R&K classification were reported, and it was not possible to combine the mean deviation and SD of these two values. For one other study<sup>48</sup>, the WASO could not be included into the analyses because it was expressed as a percentage, not in minutes. Due to insufficient data available in the retained studies, the objective parameters LMI and AI could not be integrated into this meta-analysis. For the same reason, the three subjective scores ISI, AIS and ESS were not analyzed into a quantitative synthesis. All non-analyzable studies were included in the qualitative review (Tables 3 and 4).

## *Study characteristics*

Among the ten selected studies which compared sleep differences between chronic tobacco users and control subjects (Tables 1 and 2), four studies used PSG<sup>48-51</sup>, two studies used actigraphy<sup>52,53</sup>, seven studies used the PSQI<sup>39,48,52-55,61</sup>, while only one used the ESS<sup>50</sup>

and none used other predefined measures. Among the PSG or actigraphy studies, three provided the SE<sup>48,50,52</sup>, four explored the TST<sup>48,52,53,60</sup>, five the SOL<sup>48-50,52,53</sup>, three the N1<sup>48-50</sup>, four the N2<sup>48-51</sup>, two the SWS<sup>48,50</sup>, four the REM<sup>48-51</sup>, two the SLREM<sup>48,51</sup>, three the WASO<sup>49,52,53</sup>, two the AI<sup>48,51</sup>, two the AHI<sup>48,50</sup>, and only one the LMI<sup>48</sup>.

**Table 1. Characteristics of the studies assessing objective sleep parameters**

| 1 <sup>st</sup> author, Country year | Country | Sample  | Population (n)                  | Mean age (SD) [range]                 | % males        | Minimal tobacco use in smokers                | Tobacco use characteristics in mean(SD) : cig/day ; FTND; smoke duration (yr) | Authorized substance consumption or inclusion cut-off  | Biological parameters | Authorized consumption in the assessment         | Accepted comorbidities                               |
|--------------------------------------|---------|---|---------------------------------|---------------------------------------|----------------|---|---|--|-----------------------|--|--|
| <b>Laboratory PSG studies</b>        |         |   |                                 |                                       |                |   |   |  |                       |  |  |
| <b>Soldatos 1980</b> <sup>49</sup>   | USA     | NA  | Smokers (50)<br>Control (50)    | 39.8(NA)<br>[NA]                      | 62<br>62       | « Curent smokers ≥3 yrs »                     | 25(NA)<br>NA  | T +, A+, C+, OID +, M +<br>T +, A+, C+, OID +, M +   | No                    | Yes  | All  |
| <b>Jaehne 2012</b> <sup>48</sup>     | Germany | General population  | Smokers (44)<br>Control (44)    | 30(9.5)<br>29.3(8.3)<br>[18-52]       | 66<br>66       | Dependence FTND ≥5 and DSM-IV                 | 21.2(7.5); FTND:6.4(1.2); 13.1(9.5)<br>NA                                     | T +, A+*, C+*, OID +*, M -<br>T -, A+*, C+*, OID +*, M -<br>*simple use  | Cotinine , nicotine   | not during the PSG recording                     | None   |
| <b>Conway 2008</b> <sup>50</sup>     | Brasil  | Retrospective PSG database from a sleep Institute                         | Smokers (254)<br>Control (948)  | 45.0(8.8)<br>45.6(10.5)<br>[30 –70]   | 31.25<br>37.04 | ≥ 100 cig during life with no discontinuation | NA*<br>0<br>* pack-yrs :22.9(19.7)  | T +, A+, C+, OID +, M +<br>T - A+, C+, OID +, M +  | No                    | No   | Psychiatric, medication, dependence, sleep disorders |
| <b>In-home PSG studies</b>           |         |   |                                 |                                       |                |   |   |  |                       |  |  |
| <b>Zhang 2008</b> <sup>51</sup>      | USA     | Data from cohort on sleep disordered breathing and cardiovascular disease | Smokers (40)<br>Control (40)    | 56.8 (4.21)<br>57.0(4.52)             | 50<br>50       | ≥ 20 cig/day                                  | 25.3(NA)*<br>0<br>*range : [20-50]  | T +, A+, C+, OID +, M -<br>T -, A+, C+, OID +, M -<br>Coffee: S : 95% ; Control : 75%  | No                    | Yes  | Psychiatric, dependence sleep disorders excepted SAS |
| <b>Sahlin** 2009</b> <sup>57</sup>   | Sweden  | Birth cohort from Uppsala   | Smokers (63)<br>Control (323)   | NA<br>NA<br>[20-70]                   | 0<br>0         | ≥ 1 cig/day                                   | NA  | T +, A+, C+, OID +, M +<br>T *, A+, C+, OID +, M +<br>* NA   | No                    | Yes  | None   |
| <b>Zhang** 2006</b> <sup>60</sup>    | USA     | Birth cohort from several sites   | Smokers (779)<br>Control (2916) | 59.6(10.5)<br>63.5(11.5)<br>[40-69]   | 51.90<br>35.90 | « Curent smokers»                             | NA  | T +, A+, C+, OID +, M -<br>T -, A+, C+, OID +, M -<br>Coffee: S : 90.6% ;<br>Control : 74.2%                                       | No                    | Yes  | None excepted SAS                                    |
| <b>Actigraphy studies</b>            |         |   |                                 |                                       |                |   |   |  |                       |  |  |
| <b>Cohen 2018</b> <sup>52</sup>      | Israel  | Student of the Yezreel Valley College                                     | Smokers (40)<br>Control (46)    | 24.03(2.84)<br>22.44(2.23)<br>[19-28] | 30.0<br>30.4   | ≥ 10 cig/day and ≥ 2 yrs                      | 13.35(4.17) ; FTND 4.26(2.23), NA<br>0  | T +, A+*, C+*, OID +*, M -<br>T -, A+*, C+*, OID +*, M -<br>*simple use, mean(SD) drink/wk : S :1.82(1.67), Control:0.93(1.15)     | CO level              | Refrain from smoking 30 min prior to the session | Psychiatric, physic sleep disorders                  |
| <b>Cohen 2019</b> <sup>53</sup>      | Israel  | Student of the Yezreel Valley College                                     | Smokers (38)<br>Control (39)    | 23.92(2.94)<br>23.05(1.82)<br>[19-30] | 26.32<br>25.64 | ≥ 10 cig/day and ≥ 2 yrs                      | 13.18(4.25), FTND 4.14(2.11), NA<br>0   | T +, A+*, C+*, OID +*, M -<br>T -, A+*, C+*, OID +*, M -<br>*simple use ; mean(SD) drink/wk : S : 1.77(1.75), Control: 0.953(1.20) | CO level              | Refrain from smoking 30 min prior to the session | Psychiatric, physic, sleep disorders                 |

A, Alcohol; C, Cannabis; cig, cigarettes; CO, Carbon monoxide; Coffee, percentage of daily coffee consumers; FTND, total score of Fagerstrom Test For Nicotine Dependence; M, medication; "+", consumption authorized or parameters excluded; NA, Non available; OID, Other Illegal Drugs; PLMs, Periodic leg movements; SAS, Sleep apnea syndrome; SD : standard deviation; T, Tobacco; "- ", consumption non-authorized or parameters non-excluded.

**Table 3. Results of the studies assessing objective outcomes**

| 1 <sup>st</sup> author, yr         | First night, results | Outcomes  | Sleep continuity and sleep index : results smokers (VS) controls in mean(SD)  | Sleep architecture  | Matched                        | Other characteristics tested   | Sleep and consumption control over the assessment   | scoring methods                                |
|------------------------------------|----------------------|---|---|---|--------------------------------|--|---|--|
| <b>Laboratory PSG studies</b>      |                      |   |   |   |                                |  |   |  |
| <b>Soldatos 1980</b> <sup>49</sup> | Yes, no result       | <b>Night 2 to 4</b><br>(1) SL ↑*<br>(2) WASO min  | (3) T1<br>(4) T2<br>(5) REM<br>(1) SE : 43.7(38.89) VS 29.8(19.799)<br>(2) WASO : 49.0(29.69) VS 44.1(23.3)   | (3) T1 : 5.7(2.8284) VS 5.1(2.8284)<br>(4) T2 : 64.4(7.07) VS 63.3(6.36)<br>(5) REM : 24.4(4.24) VS 24.5(3.53)  | Age, sex                       | Similar: personality, other drugs<br>Difference: coffee                                | NA  | <b>R &amp; K</b>                               |
| <b>Jaehne 2012</b> <sup>48</sup>   | Yes, no result       | <b>Night 2</b><br>(1) SE<br>(2) SL<br>(3) TST<br>(4) WASO %SPT<br>(5) AHI ↑*<br>(6) AI  | (7) LMI<br>(8) T1 %SPT<br>(9) T2 %SPT<br>(10) SWS %SPT<br>(11) REM %SPT<br>(12) SLREM<br>(1) SE : 87.08(7.51) VS 89.84(7.95)<br>(2) SL : 19.67(17.37) VS 11.66(13.31)<br>(3) TST : 417.2(36.19) VS 430.5(38.15)<br>(4) WASO : 7.04(4.87) VS 6.34(6.46)<br>(5) AHI : 1.2(1.5) VS 0.56(0.9)<br>(6) AI : 11.64(5.03) VS 11.79(5.44)<br>(7) LMI : 4.32(10.79) VS 0.54(2.81) | (8) T1 : 7.99(4.5) VS 6.62(3.62)<br>(9) T2 : 55.43(6.81) VS 55.00(6.54)<br>(10) SWS : 8.19(7.78) VS 10.19(7.35)<br>(11) REM : 20.90(4.86) VS 21.43(4.09)<br>(12) SLREM:71.94(22.71)VS74.20(36.99) | Age, sex                       | Similar: BMI<br>Difference: PLMS   | Habitual bedtime: 10-12 PM, similar with PSQI results. BS :22:30-06:30.None woke up for smoke during the recording. | <b>R &amp; K ;</b><br>AASM 2007 for AHI        |
| <b>Conway 2008</b> <sup>50</sup>   | Unknow               | <b>Night 1 or 2</b><br>(1) SE<br>(2) SL<br>(3) AHI (4) AI<br>(5) T1 ↓*<br>(6) T2<br>(7) SWS ↓*<br>(8) REM                               | (1) SE : 82.6(10.1) VS 82.8(10.5)<br>(2) SL : 17.80(17.60) VS 17.2(22.7)<br>(3) AHI : 17.6(21.5) VS 15.8(20.1)<br>(4) AI : 20.7(17.1) VS 17.0 (15.0)  | (5) T1 : 4.7(3.6) VS 4.1(2.9)<br>(6) T2 : 60.0(11.7) VS 58.0(11.7)<br>(7) SWS : 17.0(10.4) VS 19.0(10.0)<br>(8) REM : 18.4(7.0) VS 18.9(6.9)  | No                             | Similar: BMI, age<br>Difference: gender  | NA  | <b>R &amp; K ;</b><br>AASM 1999 for AI and AHI |
| <b>In-home PSG studies</b>         |                      |   |   |   |                                |  |   |  |
| <b>Zhang 2008</b> <sup>51</sup>    | No                   | <b>Night 2</b><br>(1) TST<br>(2) AHI<br>(3) T2<br>(4) REM<br>(5) SLREM  | (1) TST : 372(45.6) VS 384(46.8)<br>(2) AHI : 1.8 (1.5) VS 1.7 (1.4)  | (3) T2 : 56.5(9.81) VS 55.6(9.35)<br>(4) REM : 22.6(5.6) VS 22.2(4.6)<br>(5) SLREM: 72.2(37.7) VS 63.4(32.6)  | Age, race, BMI, AHI, neck size | Similar: mental health<br>Difference: coffee   | Daily caffeine or alcohol use is collected 4h prior to the assessment   | <b>R &amp; K</b><br>AASM 1992 for AHI          |
| <b>Sahlin** 2009</b> <sup>57</sup> | Unknow               | <b>Night 1 or 2</b><br>(1) SE<br>(2) SL ↑*<br>(3) TST<br>(4) WASO ↓*<br>(5) T1 ↑*<br>(6) T2<br>(7) SWS<br>(8) REM                       | values are expressed as weighted mean   |   | No                             | No   | No  | <b>R &amp; K ;</b><br>AASM 2007 for AHI        |
| <b>Zhang** 2006</b> <sup>60</sup>  | No                   | <b>Night 1 or 2</b><br>(1) SE ↓*<br>(2) SL ↑*<br>(3) TST ↓<br>(4) T1 ↑*<br>(5) T2 ↑*<br>(6) SWS ↓*<br>(7) REM ↓*<br>(8) RDI<br>(9)SLREM | values are expressed as median  |   | No                             | Similar: NA<br>Difference: age, genre, race, education, alcohol, coffee, BMI, diseases | No  | <b>R &amp; K</b>                               |
| <b>Actigraphy studies</b>          |                      |   |   |   |                                |  |   |  |
| <b>Cohen 2018</b> <sup>52</sup>    | -                    | <b>Night 1 to 7</b><br>(1) SE ↓*<br>(2) SL<br>(3) TST<br>(4) WASO in min  | (1) SE : 95.63(3.53) VS 97.23(2.62) ; (2) SL : 12.49 (9.13) VS 11.31(7.75)<br>(3)TST : 429.11(49.46) VS 421.11(72.60) ; (4) WASO: 18.56(15.29) VS 11.21(11.19)  |   | No                             | Similar: anxiety, depression<br>Difference: age, alcohol                               | Sleep diary   | Sadeh et al                                    |
| <b>Cohen 2019</b> <sup>53</sup>    | -                    | <b>Night 1 to 7</b><br>(1) SL<br>(2) TST<br>(3) WASO in min<br>(4) ↑*   | (1) SL : 16.15(10.70) VS 13.97(9.21) ; (2) TST: 393.06(47.63) VS 399.37(61.01)<br>(3) WASO : 17.57(15.48) VS 11.82(11.71)   |   | No                             | Similar: age, sex, BMI, alcohol, alcohol, anxiety                                      | Sleep diary   | Sadeh et al                                    |

\*\* , not analyzable studies included in qualitative review; %SPT, % of sleep period time; SE, sleep efficiency; ↑\*, significantly increase; ↓\*, significantly decrease; BS, bedtime schedule.

|                           |        |                             |               |                         |       |                         |                                      |                        |    |                                       |
|---------------------------|--------|-----------------------------|---------------|-------------------------|-------|-------------------------|--------------------------------------|------------------------|----|---------------------------------------|
| <b>2008</b> <sup>50</sup> | Brasil | Database of sleep institute | Control (948) | 45.6(10.5)<br>[30 – 70] | 37.04 | with no discontinuation | NA mean pack/yr(SD) :22.9(19.7)<br>0 | T-, A+, C+, OID +, M + | No | dependence, sleep disorder but no SAS |
|---------------------------|--------|-----------------------------|---------------|-------------------------|-------|-------------------------|--------------------------------------|------------------------|----|---------------------------------------|

"-" , consumption non-authorized or parameters non-excluded; "+" : consumption authorized or parameters excluded; NA, non-available;"\*\*", not analyzable studies included in qualitative review; A, alcohol; C, cannabis; cig, cigarettes; CO, carbon monoxide; FTND, total score of Fagerstrom Test For Nicotine Dependence; M, medication; NA, not available result; OID, other illegal drugs; PLMs, periodic leg movements; S, smoker group; SAS, sleep apnea syndrome; SD, standard deviations; T, tobacco; Yr, year.

**Table 4. Results of the studies assessing subjective outcomes**

| Author, year              | Substance consumption allowed in the assessment | Results smokers versus (VS) controls in mean (SD)         | Matched                        | Other characteristic tested                                       | Sleep and consumption habits: information over the assessment  | Duration          |
|---------------------------|---|---|--------------------------------|---|--|-------------------|
| <b>PSQI</b>               |   |   |                                |   |  |                   |
| Jaehne 2012 <sup>48</sup> | Yes   | 4.35(NA) VS 2.78(NA) ↑*                                   | Age, sex                       | Similar: BMI<br>Difference : PLMS                                 | Habitual bedtime: 10-12 PM, similar with PSQI results. Bedtime schedule :22:30-06:30.None woke up for smoke during the recording | PSQI over 2 weeks |
| Cohrs 2012 <sup>56</sup>  | Yes   | 4.55(2.78) VS 3.85(2.50) ↑*                               | No                             | Difference: age, sex, BMI, education, depression, AUDIT           | NA   | PSQI over 2 weeks |
| Liu 2013 <sup>55</sup>    | Yes   | 5.77(2.45) VS 4.74(1.75) ↑*                               | Age, gender, educational level | NA  | NA   | PSQI over 1 month |
| Cohen 2018 <sup>52</sup>  | Yes   | 5.35(2.95) VS 6.13(2.69)                                  | No                             | Similar: anxiety, depression<br>Difference: age, alcoholic drinks | Sleep diary, no results  | PSQI over 1 month |
| Cohen 2019 <sup>53</sup>  | Yes   | 5.63(3.25) VS 6.03(2.68)                                  | No                             | Similar: age, sex, BMI, alcohol, anxiety                          | Sleep diary, no results  | PSQI over 1 month |
| Xu 2019 <sup>54</sup>     | Yes   | 4.16(2.45) VS 2.28(2.27) ↑*                               | No                             | Difference: age, education  | No   | PSQI over 1 month |
| Chehri 2020 <sup>39</sup> | Yes   | 2.08(0.43) VS 1.82(0.41) ↑*                               | No                             | Difference: sex   | No   | PSQI over 1 month |
| Tang 2015 <sup>58**</sup> | Yes   | 4.38(2.583) VS 4.07(2.378)<br>**Non-representative sample | Age, gender                    | NA  | No   | PSQI over 1 month |



|  |     |  |    |   |  |                      |
|--|-----|--|----|---|--|----------------------|
| Arbinaga<br>2019 <sup>59**</sup>   | Yes | 9.17(3.10) VS 6.43(3.39) ↑*<br>**17-year-olds and not > 18 | No | NA                                      | 20.8% smoked<br>over the 30 minutes<br>after wake up | PSQI over<br>1 month |
| ESS  |     |  |    |   |  |                      |
| Conway<br>2008 <sup>50</sup>   | Yes | 9.9(5.3) VS 9.4(5.4)                                       | No | Similar: age, BMI<br>Difference: gender | NA   | -                    |
| AUDIT, alcohol use disorders identification test; BMI, body mass index; NA, not available; SD, standard deviation of the mean; ↑*significantly increase; ↓*, significantly decrease. |     |  |    |   |  |                      |

- *Types of study, country, settings, and comparison group*

Six studies, pooling 1,633 participants (466 tobacco subjects and 1,167 controls), provided PSG or actigraphy data<sup>48–53</sup>. Two of these studies were carried out in Israel<sup>52,53</sup>, two in the USA<sup>49,51</sup>, one in Germany<sup>48</sup> and one in Brazil<sup>50</sup>. Seven studies, encompassing a total of 3,109 participants (1,458 tobacco users and 1,651 controls), provided PSQI data<sup>39,48,52–56</sup>. Two of the PSQI studies were carried out in Germany<sup>48,61</sup>, two in Israel<sup>52,53</sup>, one in China<sup>54</sup> and one in Iran<sup>39</sup>. In three studies<sup>50,51,54</sup>, participants were part of a clinical sample, and in six studies<sup>39,48,52,53,55,56</sup>, they were from the general population. Two studies were based on a retrospective database of polysomnography results for AHI<sup>50,51</sup>, and one study was based on patients hospitalized before surgery who had not received specific medication<sup>54</sup>. Information on origin of TUD and on control participants were lacking in a single study<sup>49</sup>.

- *Age and gender*

The mean age of tobacco subjects and controls in PSQI studies were 38.1 years and 36.3 years respectively; age ranged from 22.4 to 47.5 years (reported in 6 studies). In actigraphy/PSG studies, the mean age of participants with TUD and controls was reported in five of the six studies; it ranged from 22.4 years to 57.0 years. Concerning gender, the percentage of males in tobacco subjects and controls ranged from 0.9% to 100% (reported in all studies). Most studies included an equivalent percentage of males and females in both groups, except for two studies<sup>50,56</sup>. One study<sup>54</sup> included only males.

- *Characteristics of the use of tobacco and other substances*

Two studies used an inclusion cutoff of at least one cig/day<sup>55,56</sup>, three studies used a cutoff of at least ten cig/day<sup>52–54</sup>, and one study 20 cig/day<sup>51</sup>. One study<sup>49</sup> defined the inclusion criterion as at least three years of tobacco consumption, regardless of the quantity

of cigarettes smoked. However, in this study, the mean number of smoked cig/day in the smoking group was 25. One other study<sup>39</sup> did not provide a definition of the smoking group, but we were able to integrate the subgroup of participants who smoked at least ten cig/day into the analyses. Finally, one study<sup>48</sup> used a FTND score of five or more and the DSM-5 criteria for TUD as inclusion criteria.

The mean cigarette consumption of chronic tobacco users ranged from 13.2 to 25.3 cig/day. This item was reported in six studies. Only five studies<sup>48,52,53,61,62</sup> reported the FTND score; among these studies, three reported a low or moderate dependence<sup>48,52,53</sup>, one a high level of dependence<sup>55</sup> and one only the number of FTND scores  $\geq 5$ <sup>56</sup>. Smoking duration (in years) was reported in only three studies<sup>48,54,55</sup>. In three studies<sup>49-51</sup>, all other drug abuse or dependence was allowed in both groups. Cigarette consumption was allowed in the control group of two studies<sup>49,61</sup>. Only two studies did not restrict the consumption of drugs that may affect sleep<sup>49,50</sup>. Five studies used urine drug screening in the control and/or TUD group<sup>48,52,53,61,62</sup>.

- *PSG scoring rules and conditions of assessment*

All actigraphy studies and two of the five PSG studies were performed in a home setting. All PSG results were based on one-night recordings, after a first adaptation night. The two actigraphy studies were based on seven-night recordings. The five PSG studies used the R&K scoring rule for all sleep criteria, except for AHI which was scored using the AASM criteria. The two actigraphy studies used the same standard scoring rules<sup>63</sup>.

In all studies, the PSG was performed during active consumption. Chronic tobacco users were allowed to smoke as usual without restriction before the PSQI assessment in all PSQI studies and in only two PSG studies<sup>48,50</sup>. In two PSG studies<sup>48,50</sup>, the participants were not authorized to smoke during the recording; in the two actigraphy studies<sup>52,53</sup>, participants were asked to refrain from smoking for at least 30 minutes prior to the session. Four studies investigated variability in sleep duration and sleep onset/offset<sup>48,50-53</sup>.

The PSQI assessment referred to the previous month in eight studies and to the past two weeks in two studies<sup>48,56</sup>

- *Comorbidities*

Most of the studies investigated the presence of comorbidities that could affect the sleep assessment. Nine out of ten studies had comorbidity exclusion criteria: six for other drug abuse or dependence<sup>39,48,52,53,56,62</sup>, seven for physical criteria<sup>39,48,50,51,54,55,61</sup> five for psychiatric criteria<sup>39,48,54-56</sup>, seven for medication<sup>39,48,51-54,56,62</sup>. Two studies had exclusion criteria for sleep disorders: one specifically for sleep-related breathing disorders<sup>50,51</sup>(SRBD), and the other one for all diagnosed sleep disorders, including SRBD and periodic leg movements<sup>51,54</sup>.

- *Quality assessment*

The Newcastle-Ottawa Scale was used to assess the quality of the included studies. All results are presented in Table S1.

### **Results of the meta-analysis**

Regarding objective parameters in the whole sample, the meta-analysis revealed significantly higher N1 sleep stage percentage (SMD = 0.65, 95%CI: 0.22 to 1.07), N2 percentage (SMD = 1.45, 95%CI: 0.26 to 2.63), WASO (SMD = 6.37, 95%CI: 2.48 to 10.26), and lower SWS percentage (SMD = -2.00, 95%CI: -3.30 to -0.70) in chronic tobacco users than in controls (Table 2;  $p < 0.05$ ). No significant difference was found for SE (SMD = -1.05, 95%CI: -3.41 to 1.31), SOL (SMD = 2.65, 95%CI: -0.04 to 5.35), TST (SMD = -8.53, 95%CI: -18.66 to 1.60), REM percentage (SMD = -0.54, 95%CI: -1.25 to 0.17), REM sleep latency (SMD = 2.40, 95%CI: -8.30 to 13.10), and AI (SMD = 1.76, 95%CI: -2.02 to 5.53) (Table 2;  $p > 0.05$ ). The LMI was not meta-analyzable because it was assessed in only one study. The AHI was not meta-analyzable because two of the three studies evaluating this parameter excluded subjects with AHI > 5 in the adaptation night before the PSG assessment.

The sensitivity analysis of the SE and SOL by subgroup, which did not include actigraphy studies, yielded similar results. In contrast, this sub-analysis found a significantly longer TST in the chronic tobacco users than in controls (SMD = -12.82, 95%CI: -25.15 to -0.49) (Table 3;  $p < 0.05$ ). The sensitivity analysis of the sleep parameters, after removing studies which excluded sleep comorbidities, yielded similar results (Table 4;  $p > 0.05$ ).

Concerning subjective parameters in the whole sample, the meta-analysis showed no significant difference for the PSQI between the two groups (SMD: 0.53, 95%CI: -0.18 to 1.23) (Table 5, Figure S1;  $p < 0.05$ ). ISI and ESS scores were not meta-analyzable because we only found one study with the ESS score, and none with the ISI (Table 2).

**Table 5. Summary of meta-analyses**

|          | No. of datasets | No. of S/C | Mean of S | SD of S | Mean of C. | SD of C | MD     | MD [95%-CI]     | I <sup>2</sup> | I <sup>2</sup> [95%-CI] |
|----------|-----------------|------------|-----------|---------|------------|---------|--------|-----------------|----------------|-------------------------|
| TST min  | 4               | 212/219    | 402.84    | 44.72   | 408.74     | 54.64   | -8.53  | [-18.66 ; 1.60] | 0              | [0% ; 78%]              |
| SOL min  | 5               | 426/1127   | 21.96     | 18.74   | 16.79      | 14.55   | 2.65   | [-0.04 ; 5.35]  | 52             | [0% ; 82%]              |
| SE%      | 3               | 338/1038   | 88.44     | 7.05    | 89.96      | 7.02    | -1.16  | [-2.41 ; 0.09]  | 36             | [0% ; 79%]              |
| N1%      | 3               | 348/1042   | 6.13      | 3.64    | 5.27       | 9.4     | 0.65*  | [0.22 ; 1.07]   | 0              | [0% ; 72%]              |
| N2%      | 4               | 388/1082   | 59.08     | 8.85    | 57.98      | 8.49    | 1.45*  | [0.26 ; 2.63]   | 0              | [0% ; 58%]              |
| SWS%     | 2               | 298/992    | 12.60     | 21.10   | 14.60      | 8.68    | -2.00* | [-3.30 ; -0.70] | 0              | NC                      |
| REM%     | 4               | 388/1042   | 21.58     | 5.42    | 22.01      | 4.78    | -0.54  | [-1.25 ; 0.17]  | 0              | [0% ; 62%]              |
| REML min | 2               | 84/84      | 72.07     | 30.21   | 68.8       | 34.80   | 2.40   | [-8.30 ; 13.10] | 14             | NC                      |
| WASO min | 3               | 128/135    | 28.38     | 20.15   | 22.38      | 15.4    | 6.37*  | [2.48 ; 10.26]  | 0              | [0% ; 8%]               |
| AI       | 2               | 348/1042   | 16.17     | 16.17   | 14.45      | 10.22   | 0.26   | [-2.06 ; 2.58]  | 4              | NC                      |
| PSQI     | 6               | 1846/2733  | 4.59      | 2.40    | 4.14       | 2.05    | 0.53   | [-0.18 ; 1.23]  | 86             | [72% ; 93%]             |

\*p < .05

Abbreviations: %, percentage; min, minutes; NC, non-calculable; MD, mean difference; CI, confidence interval; I<sup>2</sup>, I<sup>2</sup> statistic; REM, rapid eye movement sleep; REML, rapid eye movement sleep latency; S/C, chronic smoker/control; TST, total sleep time; SOL, sleep onset latency; SE, sleep efficiency; N1, stage 1; N2, stage 2; SWS, slow wave sleep; WASO, wake after sleep onset; AI, arousal index; PSQI, total score of Pittsburgh sleep quality index.

# DISCUSSION

## *Summary findings*

To our knowledge, this is the first meta-analysis comparing both objective and subjective sleep parameters between regular tobacco users and healthy adults. Overall, when compared to healthy adults, chronic tobacco users had an impaired sleep quality and an impaired sleep architecture. Among the objective sleep parameters found to be altered, SWS was significantly lower, while N1, N2 and WASO were significantly higher in tobacco users. By contrast, we did not find significant differences between tobacco users and controls with respect to SE, SOL, TST, REM, LREM, LMI, AHI and AI. In the subgroup sensitivity analysis including only PSG studies, TST was significantly lower in tobacco smokers than in healthy controls and it was not the case in all other sensitivity analyses. Among the subjective sleep parameters that were explored, only the PSQI could be integrated into a meta-analysis, which revealed no significant difference between chronic tobacco users and healthy controls. Our findings are in line with all the previous qualitative systematic reviews<sup>12,13,15</sup>. These results have important implications for better delineating the detailed pattern of TISDs in chronic tobacco use. Moreover, there was a contrast in our findings between objective sleep parameters, among which several were found impaired, and subjective sleep parameters, essentially the PSQI global score, which was not found to be significantly altered in chronic tobacco smokers compared to healthy subjects. This suggests that TISDs may be insidious, and tobacco users fail to identify and therefore report TISDs.

Further research can build on these results to clarify the pathophysiological mechanisms underlying the impact of tobacco on sleep. Taken as a whole, our results emphasize alterations of the sleep continuity (more WASO, with decreased SWS and increased N1 and N2) rather than alterations of the sleep duration or latency, which could

have been reported<sup>14</sup>. This sleep continuity could be altered by several mechanisms, such as obstructive sleep apnea (OSA). Some authors observed increased OSA in smoking patients, which is associated with more awakenings and less SWS<sup>50,64</sup>. Moreover, nicotine activates acetylcholine neurons of wake-promoting brain regions, what directly leads to a decrease of SWS<sup>51</sup>. The absence of significant alteration in REM sleep could result from a mixed effect between direct nicotine toxicity effect and nicotine withdrawal, which is associated with an increased REM sleep<sup>65</sup>. As reported previously, REM-sleep preferentially occurs in the second part of the night. Similarly, the reason why SWS is particularly affected by tobacco smoking could be because this stage occurs preferentially in the first part of the night. Finally, as suggested by some authors<sup>60</sup>, the reduced alterations found in the second part of the night, compared to those found in the first part, could be related to a short-term action of nicotine, as its blood levels gradually decrease after sleep onset. This reinforces the hypothesis that nicotine plays a predominant role in TISDs.

### ***Strengths***

This study provides a comprehensive approach to tobacco-induced sleep disturbances, combining a review and a meta-analysis of quantitative parameters derived from both PSG and actigraphy, as well as from subjective measures. This holistic strategy allowed to explore some subtle physiological disturbances of sleep, such as alterations of sleep continuity or sleep architecture associated with tobacco use. It also allowed to explore neurological or respiratory abnormalities occurring during sleep, such as leg movements or sleep apnea. Last, the review integrated subjective sleep disorders. Including sleep apnea and leg movements in the review was important because both AHI and LMI are increased in tobacco smokers<sup>17</sup>. This can independently affect other sleep parameters and thereby bias the assessment of the impact of tobacco on these parameters<sup>16</sup>. The diurnal consequences of all these sleep disturbances were also addressed using the ESS. Moreover, combining the actigraphy and PSG data has allowed to more precisely understand the impact of smoking on the SE, TST, SOL and WASO parameters. A subgroup analysis excluding the actigraphy



data allowed to check that there was no bias induced by actigraphy parameters, as actigraphy is for example known to underestimate the WASO<sup>66</sup> and overestimate SE<sup>67</sup>.

Another quality feature was that all the PSG studies reported data from the second night, what avoided the “first night effect” bias. Moreover, they all used the same R&K sleep scoring rules, and the AASM criteria for scoring the AHI. Overall, the criteria used to select the studies were rather restrictive, what contributed to a relative homogeneity of both smoking and control groups, even if this may have contributed to exclude possible studies of interest. In addition, the exclusion criteria of the different studies were relatively homogeneous, in particular with regard to psychiatric comorbidities, other drugs affecting sleep, or premorbid sleep disorders. Even if some discrepancies were noted with respect to the definition of the smoking group, all studies recruited chronic tobacco users. A last characteristic of the studies was that they were conducted in different continents, i.e. America, Europe and Asia. This diversity was important for interpreting the main results of our study, as some physiological disparities of sleep features were reported, depending on the ethnic origin<sup>68</sup>, and missing important population in this meta-analysis would have been a source of concern.

### ***Limitations***

Several limitations of our meta-analysis should be addressed. Most of them pertain to the characteristics of the included populations. First, the total duration of tobacco use was very heterogeneous between studies. This could be a source of concern, even if it is unclear whether this parameter may affect the assessment of sleep over a couple of nights. Moreover, the “addiction” criteria of tobacco / nicotine use disorder were not available in a majority of studies, which led to focus on chronic tobacco use. In practice, daily tobacco smoking is usually associated with TUD criteria, even if some light smokers may not meet

those criteria<sup>69</sup>. In any case, it was impossible to assess whether sleep disturbances were correlated with the severity of TUD.

Second, the precise smoking habits (e.g., timing of smoking) were not available in the studies. It is likely that a predominance of smoking in the evening, or at night, would have a greater impact on sleep quality and architecture than a homogeneous daytime consumption. In the same line, night withdrawal may occur preferentially in some subjects and affect their sleep<sup>65,70,71</sup>, but this was not explored in the included studies. For example, tobacco withdrawal has been associated with an increased REM sleep<sup>65</sup>. As reported previously, REM-sleep preferentially occurs in second part of the night. Similarly, the reason why SWS is particularly affected by tobacco smoking could be because this stage occurs preferentially in the first part of the night. A similar limitation of the majority of the included studies was that they did not use objective measures such as blood or urine cotinine concentrations, what could lead to a gap between declared and real smoking behaviors.

Third, circadian rhythms were not examined in this systematic review, and none of the included studies examined circadian markers or individual chronotypes. The circadian system should be investigated in patients with TUD, not only because it is the main driver of the sleep-wake cycle, but also because links between circadian physiology and substance abuse have been described. For instance, it has been shown that subjects with an evening chronotype use more tobacco and alcohol than those with a morning chronotype<sup>72</sup>, and that they display higher depression scores<sup>73</sup>. Other studies have described strong correlations between chronotype and chronic use of substances (i.e. caffeine, nicotine, and alcohol), and because chronotype and social jetlag are interconnected<sup>74</sup>, they propose that these correlations are most probably a consequence of social jetlag (i.e. the discrepancies between social and biological timing), rather than a simple association with different chronotypes<sup>75</sup>. The role of circadian genes in drug addiction has also been described in a number of studies in animal species, including humans<sup>76</sup>. Specifically, the circadian clock gene PER1 has been

linked to drug dependence and reward<sup>77-79</sup>; the circadian-associated gene (Clock) has been found to regulate the brain rewarding response to cocaine<sup>80</sup>, and Casein kinase 1 epsilon to constitute a genetic susceptibility to heroin addiction<sup>81</sup>. Although circadian rhythmicity was not considered in our meta-analysis, we do not believe that it constitutes a risk of bias in our interpretations, as the studies included in our analysis are relatively homogenous in terms of age range and are therefore expected to have included similar ranges of circadian phenotypes and genotypes.

Fourth, studies were heterogeneous regarding the accepted amount of consumption of alcohol, coffee, other drugs, or other habits (e.g., screen use) that could affect tobacco smoking<sup>82,83</sup>, as well as sleep<sup>87</sup>. However, it is difficult in practice to screen for all the potential confounding determinants of sleep. Regarding PSG data, despite very homogeneous modes of acquisition and procedures, some slight local differences are frequently noted, and may impact the homogeneity of the final result<sup>88</sup>.

Finally, few studies included in our analysis examined anxiety or depression symptoms. Given that tobacco users display more frequently those symptoms<sup>5,82</sup>, which are known to be associated with sleep disorders<sup>88</sup>, this might represent a potential confounding variable. Although exclusion of depression or anxiety disorders may have led to underestimate the impact of smoking on sleep, it would not change our overall conclusion that sleep is significantly altered in chronic smokers.

## **Conclusions and future implications**

In conclusion, our literature review and meta-analysis provide consistent pieces of evidence that tobacco smoking impairs sleep continuity and architecture. More specifically, chronic tobacco smoking increases WASO, N1 and N2 light stages of sleep and reduces SWS. Moreover, tobacco smoking increases sleep fragmentation. No significant differences were found regarding sleep efficiency, total sleep time, REM sleep, sleep latency to REM-sleep, arousal index, leg movement index and subjective sleep quality. For these last eight parameters however, it is unclear whether the absence of association may be related to a lack of effect, power or data. Circadian rhythms were not examined in this systematic review, which focused on sleep quality and physiology. Future studies and meta-analyses should thus explore chronobiology features in tobacco users.

The practical conclusions from this meta-analysis are that a thorough sleep assessment should systematically include tobacco use and tobacco use patterns, and the treatment of sleep disorder should systematically integrate a proposal to support quitting tobacco in subjects with sleep impairment. Similarly, tobacco cessation services should routinely screen for sleep disturbances with simple clinical questions addressing insomnia, chronobiological disturbances, sleep apnea and diurnal consequences such as fatigue or daytime sleepiness, or with more structured questionnaires such as the ISI, ESS or PSQI.

In the initial assessment and longitudinal follow-up of patients, it would be useful to integrate counseling/recommendations on sleep hygiene and sleep improvement in the motivational objectives, and monitor whether sleep parameters have improved after quitting tobacco.

### **Practice points**

- TISDs consist in alterations in sleep continuity and sleep architecture.
- TISDs preferentially occur during the first part of the night, with reduced slow-wave sleep and increased light sleep
- TISDs also consist in an increased number of wakes after sleep onset
- TISDs do not seem to significantly affect REM-sleep
- The subjective parameters of sleep, in particular the PSQI score, were not found to be significantly affected by tobacco smoking

### **Research agenda**

- To explore a dose-effect relationship between the level of tobacco smoking and the level of alteration of the sleep parameters involved
- To investigate the effects of nicotine alone on sleep parameters, and to compare with those of tobacco
- To better distinguish the role of comorbidities, in particular psychiatric comorbidities, in the relationship between tobacco use and sleep quality.
- To quantify electroencephalographic changes in the macro and micro-architecture of sleep, in order to better understand the pathophysiology of TISDs.
- To better explore the role of chronotypes and circadian mechanisms in the occurrence of TISDs.
- To investigate whether some specific TISDs are associated with reduced likelihood of quitting smoking
- To investigate whether quitting tobacco may be rapidly associated with reduced TISDs.
- To investigate whether improving sleep and/or circadian rhythms can improve the rates of smoking cessation

### **Conflicts of interest**

The authors do not have any conflicts of interest to disclose.

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**Figure 1. Flow chart of the study selection process (PRISMA Flow Diagram)**

