FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2016/2017

Miguel José dos Reis Costa

Alterações do Sono em Fumadores de Tabaco: uma Revisão Sistemática

Cigarette Smoking and Sleep Disturbance: a Systematic Review

março, 2017

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Cigarette Smoking and Sleep Disturbance: a Systematic Review

Mestrado Integrado em Medicina

Área: Psiquiatria

Tipologia: Monografia

Trabalho efetuado sob a Orientação de:

Doutor Manuel Esteves

Trabalho organizado de acordo com as normas da revista:

Nicotine & Tobacco Research

março, 2017

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

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Psiquiatria

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Cigarette smoking and sleep disturbance : a systematic Review

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Aos meus pais e a todos aqueles colegas,

que no decorrer desta jornada se tornaram amigos

Cigarette Smoking and Sleep Disturbance: a Systematic Review

Alterações do Sono em Fumadores de Tabaco: uma Revisão Sistemática

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Word Count: 4163

Head Title:

Cigarette Smoking and Sleep Disturbance: a Systematic Review

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ABSTRACT

Background: The influence of cigarette smoking in mental health has not been entirely studied yet. However, sleep disturbance is an established cause of mental illness. This review aims to provide an overview of previous investigations on cigarette smoking and its effect on sleep, and use it as an evidence of its influence on central nervous system.

Methods: Using *Pubmed* as database we selected articles written (1) in English, (2) published after 1997 and (3) stating the relationship between "sleep" and "cigarette smoking" or "sleep" and "nicotine" as main subject.

Results: Outcomes from 33 selected articles were organized according to the different ways in which cigarette smoking can affect sleep and allowed us to establish a correlation between subjective sleep complaints and objective sleep disturbance. Smokers not only seem to have daytime sleepiness more frequently but also less total sleep time, longer latency to sleep onset, and an altered polysomnography pattern (decrease of slow wave sleep, a extension of REM sleep latency, an increase of α-frequencies and reduction of δ-frequencies), comparing to non-smokers. Most of these alterations can also be founded in non-smokers after administration of 24-hour nicotine patches (absence of acute withdrawal) and after exclusion of any kind of breathing disorder.

Conclusion: Sleep disturbance in smokers is manly caused by direct influence of nicotine in sleep-wake cycle neurons. Further investigations targeting a better understanding of how nicotine could affect neural basis of behaviour and biological rhythms are needed.

RESUMO

Introdução: A possível influência do tabaco na saúde mental dos fumadores ainda não foi totalmente esclarecida. Já os distúrbios de sono, são uma causa conhecida de doença mental. Esta revisão procura dar uma visão geral da literatura prévia à cerca de como o tabaco pode afetar o sono, e usar essa evidência como prova de que este tem impacto no equilíbrio do Sistema Nervoso Central.

Métodos: Usando a Pubmed como base de dados, foram selecionados artigos escritos (1) em Inglês, (2) publicados depois de 1997 e (3) onde a relação entre "sono" e "fumadores" ou "sono" e "nicotina" aparecesse como principal tema do trabalho.

Resultados: Os resultados dos 33 artigos selecionados foram organizados de acordo com as diferentes vias de como o tabaco pode afectar o sono e permitiram-nos estabelecer uma relação entre as queixas subjetivas e as alterações objectivas do sono nos fumadores. Os fumadores para além de referirem sintomas como sonolência diurna, mais frequentemente, também apresentam uma diminuição do tempo total de sono, maior latência para adormecer e ainda uma padrão de registo polissonográfico alterado (com diminuição de sono de ondas lentas, um aumento da latência para iniciar sono REM, um aumento de frequências α e diminuição de frequências δ), quando comparados com indivíduos não fumadores. A esmagadora maioria destas alterações foi também encontrada aquando a administração de pensos de nicotina de libertação prolongada (24 horas) em não fumadores (impossibilitando a existência de efeito agudo de abstinência) e após a exclusão de distúrbios respiratórios, que pudessem pôr em causa, por si só, a continuidade do sono.

Conclusão: As alterações do sono em fumadores são principalmente causadas pelo efeito direto da nicotina nos neurónios reguladores do sono. Futuramente, devem ser

levados a cabo estudos que procurem esclarecer a influência da nicotina nos circuitos neuronais relacionados com o comportamento e o ritmo biológico.

IMPLICATIONS

Despite being a controversial topic, sleep disturbance in smokers is consistently reported in the literature. However, information regarding this subject has been poorly discussed in a comprehensive manner and this investigation aims to fill that gap. This report aims to not only summarise the state of the art, but also to point out the mechanism that most likely explains how cigarette smoking affects sleep. In fact, the conclusions of our study may support a different course of action for physicians manage patients with insomnia combined with a nicotine addiction. It is also noteworthy the fact that nicotine affects sleep in a different pattern in depressed individuals. Further investigations regarding nicotine influence on patients with susceptibility for mental illness should be conducted.

INTRODUCTION

Cigarette smoking is the most preventable cause of death in the world. In the 20th century, the tobacco epidemic killed 100 million people worldwide. It mainly affects cardiovascular and respiratory systems.[1]

Most of people are aware of the physical health risks of smoking tobacco, but usually have no idea of its association with mental health. There is no evidence that, in the long-term, heavy smoking leads to any kind of mental illness symptoms. But, on the other hand, we know that cigarette smoking is a very prevalent addiction in people with mental illness. Few studies have proved the existence of this association but it is still dubious whether smoking is a cause of mental disease or, otherwise, if people with mental problems are likely to become smokers.

Using the U.S.A. as a statistical example (where 1 out of each 5 adults have some form of mental illness):

- 36% of people with mental illness smoke, while only 21% of adults without mental illness do so;
- 31% of all cigarettes are smoked by adults with mental illness;
- 40% of men and 34% of women with mental illness smoke;
- 48% of people with mental illness, who live below the poverty level, smoke, compared to 33% of those with mental illness who lived above the poverty level.[2]

As any other drug of abuse, nicotine artificially improves our reward system and stimulates many others neural circuits in the brain. This could explain why people with mental health problems abuse tobacco in an effort to reduce their symptoms:

- patients with schizophrenia may use nicotine to reduce cognitive deficits and negative symptoms or neuroleptic side effects. The prevalence of cigarette smoking amongst these subjects is still higher than in any other mental illness: 60-90% of patients with schizophrenia smoke.[3]

- patients with depression are twice more likely to be smokers. Nicotine stimulates the release of dopamine and serotonin, which is involved in triggering positive feelings. These neurotransmitters, like many others, are often found to be low amongst people with depression, who may then use cigarettes as a way of temporarily increasing their dopamine and serotonin supply. However, smoking encourages the brain to switch off its own mechanism for producing them so, in the long-term, the supply decreases, which in turn prompts people to smoke even more.[4]
- patients with anxiety are also commonly smokers. Nicotine creates an immediate sense of relaxation so, people smoke believing that it reduces stress and anxiety, but this feeling is temporary and soon gives way to withdrawal symptoms and increased craving.[4]

Most people start to smoke before they show signs of mental illness so, it remains unclear whether smoking leads to mental illness or mental illness encourages people to start smoking. The most likely explanation is that there is a complex relationship between the two. Although being hard to prove that cigarette smoking is a direct cause of major mental disorder, we cannot ignore the evidence of its influence upon the balance of Central Nervous System (CNS). One of the most significant proofs of it is how cigarette smoking affects sleep architecture. The correlation of it as an impact on mental health comes naturally.

Evidence shows that sleep is essential to help maintaining the mood, memory, and cognitive performance. Sleep is a dynamic behavior, which consists in a special activity of the brain controlled by elaborate and precise mechanisms. Using these mechanisms, we depress few brain functions sequentially. Consequently, it is not a surprise that sleep problems may increase the risk of developing particular mental illnesses, as well as a result from such disorders.[5] More recently, neuroimaging and neurochemistry studies suggest that a good night's sleep helps foster both mental and

emotional resilience, while chronic sleep disruptions set the stage for negative thinking and emotional vulnerability.[6] Last but not least, sleep disturbance can also affect physical health. Actually, sleep loss does far more than make us grumpy and groggy. It influences negatively our immune, cardiovascular and endocrine systems, as well as contributing to serious diseases such as obesity, diabetes, and hypertension.

For instance, let's take Americans as a sample population example. Actually, they represent industrialized society very well in this context. In a 2002 epidemiological study concerning sleep, 74% of respondents experienced at least one symptom of a sleep disorder a few nights a week or more.[7] Concerning chronic sleep problems, these affect between 10% and 18% of adults in the general U.S. population.[6] Despite this fact, more than 60% of adults have never been asked about the quality of their sleep by a physician, and fewer than 20% ever initiated a discussion about it.[8] The latest research has shown that symptoms related to sleep are even more common among smokers when compared with the general population.

Cigarette smoking can affect sleep through three different mechanisms:

- nicotine can stimulate the release of several neurotransmitters that collectively participate in regulating the sleep-wake cycle;
- regular smokers often experience acute withdrawal as the nicotine concentration in plasma is decreased during sleep;
- smoke impact on airways can lead to sleep-related breathing disorders, such as apnea, whish consequently disrupt sleep continuity.

Moreover, these hypothesized causal mechanisms are not mutually exclusive. In fact, some sleep disturbances may result from complex interactions among the stimulant effects of nicotine, nicotine withdrawal, and the respiratory effects of smoking. Based on that, this review aims to provide an overview of investigations on cigarette smoking and its effect on sleep.

METHODOLOGY

Using *Pubmed* as database we started our search with the following query: ("sleep"[MeSH] AND "smoking"[MeSH]). We got 446 articles.

Then we used 2 additional filters:

- articles written:

1. in English; (410)
2. after 1998, including; (279)

After that, we analysed all abstracts of these 279 articles and used, as an excluding factor, the fact of that article doesn't have the relation between "sleep" and "cigarette smoking" as a main subject. With that analysis we ended up with 21 articles. Three of them were rejected because the sample was not significant to our study (21-3=18).

Then we realised that, few studies couldn't use "cigarette smoking" terminology and instead of it, explore the specific effect of nicotine. Hence we made a second query: ("sleep"[MeSH] AND "nicotine"[MeSH]), and used the same additional filters: we got 54 articles. After using the same excluding factors as we did previously, we obtained a total of 20 articles. Five of them had appeared in previous search. Therefore, we conclude our search with 15 new articles to add to our research database, which ended up with a literary basis of 33 articles.

RESULTS

The articles we found were heterogeneous, therefore we organized the information in reports according to their different contents. Based on this we will be able to write a more methodical discussion.

Cigarette smoking is in fact a predictive factor for the development of sleep disturbances. However, tobacco is not usually the exclusive sleep-affecting habit in smokers: they also tend to make other unhealthy lifestyle choices, such as frequent use of alcohol and caffeine. On the other hand, the prevalence of self-reported cardiovascular and pulmonary disease was higher among current smokers than never smokers. A vast majority of the studies we selected tried to control these several confounding factors by performing a multivariate analysis. Finally, depression and use of psychotropic medication was also partly taken into account.[9-14] All the summarised information in the next chapters presents statistically significant differences that were found.

Epidemiology

Sleep complaints

Smokers have nearly double the risk of experiencing sleep disturbances, manifested primarily as difficulties falling asleep and daytime sleepiness. Thus, current smokers report greater difficulty than never smokers not only in initiating sleep, but also in maintaining it. Other symptoms of poor nocturnal sleep quality, including nocturnal awakenings, non-restorative sleep and difficulty in morning awakening are also more common in smokers.[9,10,12,14-16]

Polysomnography pattern

Even though subjective reports provide a convenient means for assessing sleep disturbance in field studies, they cannot characterize the range of physiologic

disturbances that may be detected with overnight polysomnography. Besides, current investigations show that the sleep architecture of smokers and non-smokers actually differs. Recent data have shown that smokers have less total sleep time (TST), lower sleep efficiency (ratio of total sleep time to the total amount of time spent in bed) and longer latency to sleep onset.[9,10,17]

Tobacco also affects the pattern of sleep stages. Sleep pattern in smokers generally has:

- increase of stage 1 and 2 with a concomitant decrease in slow wave sleep (SWS – formed by stage 3 and 4);[9,10]
- extension of REM sleep latency;[9,10,17]
- temporal alterations of REM sleep was not evident in any of the studies – see chapter "nicotine in sleep-wake cycle neuromodulation");[9,10,17,18]
- increase of α-frequencies and reduction of δ-frequencies, which is most pronounced at the beginning of the sleep period.[9,10,17,18]

Cigarette smoking has also been related with alteration of activity during the day and of circadian rhythm, which is measured by a method called actigraphy. Actually, smoking is associated with less interdaily stability and more intradaily variability of the rhythm. Moreover, these variations typically occur in subjects who also have extended sleep onset latency and less total sleep time.[12]

Former smoker vs Current smoker

None of the studies showed significant differences between former and never smokers regarding sleep parameters. This suggests that smoking cessation can reverse the disturbances in nocturnal sleep.[9]

Etiopathology

Nicotine in sleep-wake cycle neuromodulation

Given the effects of nicotine on the central nervous system (CNS), the high prevalence of sleep disturbances in smokers is not surprising. Nicotine, the primary pharmacologically active component of cigarette smoke, acts centrally by stimulating nicotine-acetylcholine receptors. It does so by binding itself to the β2 subunit of the nAch receptors. These receptors are widely distributed in presynaptic neurons located in areas such as the anterior hypothalamus and the brainstem reticular formation. Activation of nicotinic receptors leads to the release of several neurotransmitters, including acetylcholine, dopamine, serotonin, norepinephrine, and gamma-amino butyric acid. The action of nicotine in sleep depends on interactive effects of these neurotransmitters on the central mechanisms that regulate the sleep-wake cycle, which can be delineated by oscillations between two opponent processes, one promoting sleep and the other promoting wakefulness.[9,10,19,20] Studies in rats have shown that administration of mecamylamine (antagonist of nAch receptors) supresses the effects on sleep produced by nicotine.[21] However, nicotine interferes with the sleep-wake cycle neuromodulation in a totally different way in non-REM sleep and REM sleep.

Regulation of non-REM sleep depends on a decrease in aminergic neuronal activity within the locus coeruleus and dorsal ralph. By stimulating the release of aminergic neurotransmitters, nicotine may disturb the normal regulation of non-REM (NREM) sleep and shift the distribution of sleep architecture toward lighter stages of sleep. This extended state of arousal also explains the increase in sleep latency.[9,10]

The ponto-geniculo-occipital (PGO) spikes, which are a specific characteristic of REM sleep in polysomnography in animals, are generated by cholinergic projections from pedunculo-pontine tegmental (PPT) and latero-dorsal (LDT) neurons.

Investigations in vivo have shown a dose-dependent suppression of the PGO spikes by nicotine. High levels of nicotine lead to stimulation of serotoninergic neurons of the dorsal raphe nucleus (DRN), which will have an inhibitory effect on LDT and PPT neurons.[10] Studies in rats show that nicotine increases discharge in serotoninergic neurons in the DRN specifically during REM sleep. At least in the DRN, this discharge stimulated by nicotine, only has a statistically significant increment during REM sleep and NREM-REM sleep transition.[22]

Additionally, studies have proved that nicotine inhibits sleep-promoting neurons in the ventrolateral preoptic area (VLPO) through a muscarinic postsynaptic action and nicotinic presynaptic action on noradrenergic terminals. This area, whose nucleus is located in the anterior hypothalamus, contains GABA, which is responsible for this mechanism of inhibition. These VLPO neurons constitute the majority of the projections to the dorsal raphe nucleus (DRN), the locus coeruleus and the interneurons of (LDT/PPT) region, so this can be related with the basis of neuronal circuit alterations described above.[23,24]

We cannot forget that before the secondary regulation of REM sleep by serotoninergic neurons, the PGO spikes are generated by cholinergic neurons (located in the reticular formation[21]), which are directly sensible to nicotine action. Hence, studies also suggest that in lower doses, nicotine stimulates REM sleep. This might explain why alterations in REM-sleep in smokers are not consistent. Despite not been taken into account in all studies, it will always depend on the smoking status of each participant. In summary, data suggests dose-dependent effects of nicotine on REM sleep, i.e., lower doses stimulating REM sleep and higher doses supressing it.[10]

This complex duality can explain why REM sleep alterations are not statistical significant in any of the studies. It would depend on the smoking status of each subject, which directly affects nicotine plasma levels before sleep.

Sleep apnea in smokers

Sleep-related breathing disorders represent another possibility of how cigarette smoking affects sleep. There seems to be a synergistic effect between smoking and sleep apnea syndrome (SAS), causing increased cardiovascular morbidity combined, than each of them isolated.[25] SAS is characterised by the interruption of breathing during sleep leading to a decrease of oxygen saturation. Occurrence of apnea leads to serious sleep fragmentation with frequent arousals and sleep stage changes and usually to daytime sleepiness.

Prevalence of SAS among smokers is almost 40 times higher in smokers.[10] It seems to be mainly caused by other substances in tobacco smoke other than nicotine (although one report describes a possible direct effect of nicotine in upper airway muscles[26]). There also seems to be an acute effect of these irritant substances on the pharynx mucosa. Actually, former smokers showed no increased risk of impaired breathing during sleep after controlling for other risk factors, such as coffee consumption, body mass index, etc.[10,26,27]

Pathophysiology of SAS caused by cigarette smoke includes upper airway inflammation and decreased hypoxia sensitivity (which facilitates longer durations of apnea with saturation). This inflammation results in increased surface adhesive forces at the level of pharyngeal mucosa promoting upper airway collapse, obstruction and consequently snoring. Another explanation, could be the levels of plasma orexin-A, a neuropeptide involved in the regulation of food intake and the sleep-wake cycle, which is diminished in SAS patients and even more in SAS patients who smoke.[10,20,26-29] Finally, when we only analyse studies where smoker participants with significant respiratory disturbances events were excluded, we realize that, in general, the main parameters of sleep pattern keep altered in the same way as others studies. For this reason, even though SAS influences sleep in smokers, it is not the most

significant cause of sleep disturbances in smoker population.

Nicotine withdraw during sleep

With sleep onset, blood nicotine levels gradually decrease and induce a state of nicotine withdrawal that can modify sleep continuity. This is obviously more preponderant when nicotine levels are higher during the day, which occurs among heavy smokers. Actually, few studies have observed nightly awakening due to nicotine craving in 20% of heavy smokers. Nevertheless, the arousals caused by craving would not be enough to wake up, but they still influence sleep architecture by subtle changes in temporal distribution of non-REM and REM sleep. [9,10]

Nicotine administration in healthy non-smokers

Transdermal nicotine application in non-smokers results in a dose-dependent reduction of REM sleep, increased sleep stage 2, decreased TST with earlier awakening times and an increase in sleep latency. When nicotine is being administrated transdermally by 13-hour or 16-hour patches, instead of 24-hours patches, REM suppression is followed by a REM sleep rebound during withdrawal. This data is consistent with effects of smoked cigarettes, which supports the direct influence of nicotine in the CNS, which remains the main explanation to sleep disturbances in smokers. As a matter of fact, these studies show that nicotine administration was continuous and the participants were all non-smokers, hence none of them could feel nicotine withdrawal during night and the proportion of obstructive respiratory problems was equal between them and controls.[10,30]

Sleep disturbance and cigarette abstinence

Chronic tobacco consumption is usually coupled with physical and psychological dependence. Withdrawal symptoms include the craving for cigarettes, dysphoria, fear,

anhedonia, irritability or restless and increased appetite[10,20,31] In addition to these depressive symptoms, there is sleep disturbance: insomnia complaints during nicotine withdrawal are reported in up to 39% cases.[10] There are also few studies talking about a possible relationship between insomnia complaints and relapse rates.[9,10,32,33]

Although subjective impairments of sleep during nicotine withdrawal were reported in all studies, polysomnography information did not consistently reproduce these findings and were contradicting regarding sleep duration, sleep efficiency, frequency of sleep stage changes and arousal frequency. This can be explained by the fact that sleep disturbance during withdrawal appears as a secondary effect of a state of depression. Similar to what happens in others kinds of depression, symptoms are very diverse among different subjects. No one feels depression the same way.

Anyway, in most of the cases, this insomnia is temporary. Actually, the initial daytime sleepiness gradually decreased over 20 days. After 1 month, sleep architecture is comparable to the sleep of a never smoker.[9,10]

In the particular case of heavy smokers, polysomnography data is more concordant with self-rating scales, i.e., in these cases, nicotine withdrawal has shown an increased sleep fragmentation.[33,34] Some authors do indeed suggest that these patients, during smoking cessation, could benefit of a transition period provided by a transdermal nicotine patch that delivers nicotine to the blood at a slow constant rate through topical application on the skin. Specifically, the patches applied for 24-hour are more likely to protect against effects of abrupt nicotine withdrawal in sleep[34-36] and to alleviating morning smoking urges.[36] But even with 24-hour nicotine replacement therapy, the subjective complaints remain, probably related with a state of depression associated with a behavioral component of addiction (they are not using cigarette to get nicotine into plasma).[34] Besides, if we use these patches in smokers who continue to smoke, that extra increment of nicotine, contrarily to the effect in smokers during

cessation process, results in an increase of sleep fragmentation.[37]

Less sleep, more cigarettes – a vicious cycle

Attention, decision-making and executive functioning are few examples of cognitive capacities, which are impaired by extended periods of wakefulness. On the other hand, during sleep deprivation, the nucleus accumbens becomes selectively more active. This area in the brain is not only responsible for the process of pleasure obtained in a present activity, but it is also involved with the anticipation of reward. Being selectively more active, it results in an elevation of the expectation of gains and a diminution of the effects of one's losses following risky decisions. So, it seems logical that impaired attention and a deficit of inhibitory control combined, could increase cigarette smoking by smokers with sleep deprivation.

In fact, a study suggests that sleep loss increases the likelihood of smoking during an abstinence period of 48h. However, this increase was not related with measures of inhibition and attention. They concluded that sleep deprivation increases smoking, probably because smokers expect a decrease of sleepiness with it. Another possibility pointed by this study is that measures of impulsivity/inhibition weren't sensitive enough to the effects of sleep deprivation and, therefore, increases of smoking through aspect of decision-making could not detected.[38] Besides, impulsivity is much more complex to measure than self-reported fatigue.

Sleep disturbance in depression – role of nicotine

Sleep parameters of depressed patients are quite different from those of healthy individuals. They typically have decreased TST and sleep efficiency and significant decrements in stages 1, 3 and 4. Finally, total REM sleep duration is greater in depressed patients compared to healthy subjects, associated to a shortened REM sleep

latency. REM sleep disinhibition at the beginning of the night is one of the most frequently described biologic features of depressive disorders. This feature results from a cholinergic neuronal overactivity and also poor releases of serotonin by the dorsal ralph. As we already know, acetylcholine is a facilitator of REM-sleep, and serotonin, a neurotransmitter that is clearly diminished in depressed brains, is an inhibitor of REM-sleep.

Two studies have shown that long-term administration of transdermal nicotine improve mood and sleep in depressed patients. This alteration seems to extend throughout the nicotine withdrawal period. Contrarily to healthy subjects (see chapter "Nicotine administration in healthy non-smokers"), nicotine administration in depressed people seems to improve sleep parameters such as an increment in REM sleep latency and an increased slow wave sleep, TST, and sleep efficiency.

The increase in REM sleep latency was accompanied by a significant decrease in the score of the Hamilton rating scale for depression. Thus, nicotine in depression not only improves sleep, but also mood. Actually the two features seem to be etiologically related. Serotonin plays a modulatory role in sleep-wake cycle and mood. Tryptophan, a serotonin precursor, increases slow-wave sleep, reduces REM sleep and awake time during the night. Patients with major depression have a significant lower tryptophan/competing amino acids ratio than healthy individuals. So, it appears that major depression and related sleep disorders are associated with diminished serotonin synthesis in the brain. It is thus conceivable that nicotine's action on sleep and mood is indirectly exerted through the serotonin system. The fact that during withdrawal of nicotine these patients maintained REM sleep latency values close to normal and showed sustained mood improvement may be related to equilibrium between cholinergic and serotoninergic activities. In the future, it would be of interest to determine if administration of transdermal nicotine modifies the actions of

antidepressants, and if it could be used in treatment-resistant depression.[39,40] Actually, one of these studies shows an equivalent antidepressant efficacy between nicotine and fluoxetine,[40] and a similar effect on sleep; however fluoxetine produces a greater increment in REM sleep latency.[40,41]

We cannot forget that both studies were conducted with a small sample of non-smokers and nicotine administration was going to be reduced along a few months and stopped after 9/10 months (depending on the study). By the way, this fact doesn't contradict that depression in smokers doesn't have a better outcome. We are just discussing an eventual benefice of temporary nicotine administration in the rebalance of neurotransmitters in depression.

DISCUSSION

Although the influence of cigarette smoking in sleep is still very controversial, we have tried to focus on the most significant and concordant data that we found. Nonetheless, the complexity of the topic is not the only limitation. Most of the studies, at least the ones conducted with humans, did not take into account variables such as:

- serum nicotine concentrations among subjects;
- menstrual cycle in females;
- precise smoking pattern (smoking status was based on self-report without corroborating objective documentation).

It is clear now, that acetylcholine plays a role in regulating sleep, and all kinds of nicotine administration influences this control by stimulating nAch receptors. This direct influence is, in our point of view, the most preponderant way in which cigarette smoking affects sleep. As proof of that, main alterations of sleep found in smokers (such as decreased TST, increased REM sleep latency and sleep latency and less SWS) were concordant with changes found in studies where nicotine was administered continuously by patches in healthy subjects. On the other hand, differences found in electroencephalographic (EEG) activity between smokers and non-smokers were greatest in the early part of the sleep period. Facts that remove importance from the other two possible causes of how tobacco could affect sleep are: respiratory diseases (insignificant in healthy non-smokers groups) and nicotine withdrawal during the night (inexistent in a continuous nicotine administration). This influence is diminished in repeated administrations (studies in rats[21]) as we can see in chronic smokers (when comparing with acute administrations on healthy non-smokers). Sleep modification should be attenuated by compensatory mechanisms triggered by chronic treatment. However, an absolute reverse can only take place after

a period of totally nicotine abstinence. This fact also reinforces the idea that sleep disturbance in smokers is mainly caused by direct influence of nicotine present in plasma, and once removed, the effect is over. At this point we can extrapolate few guides for practical medicine on two types of patients:

- a smoker patient who suffers insomnia should be informed that tobacco has a harmful influence on sleep and should therefore be motivated to quit or reduce;
- a smoker who wants to quit, should notice that he will probably experience insomnia, but it will be gradually diminished during the first month of abstinence and after that he will have a better sleep quality than he has as a smoker (reinforcing patient will).

Like what happens in most of medical topics, “each case is a case”. Nicotine administration, even when temporary, is prejudicial to sleep architecture with practical consequences (for example: daytime sleepiness) in mental healthy subjects. On the other hand it could be useful to revert sleep disturbance in depressed patients. Anyway, we can now safely conclude that nicotine has a significant impact in neural circuits homeostasis, and sleep disturbance probably is just one single proof of many more. Finally, further investigations targeting a better understanding of how nicotine could affect neural basis of behaviour and biological rhythms are needed.

FUNDING

None declared.

DECLARATION OF INTEREST

None declared.

ACKNOWLEDGEMENTS

We are thankful to José Miguel Barreto Bernardo, a colleague from Faculty of Medicine, University of Porto, for the careful English language correction.

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8. When you are satisfied with the uploaded manuscript proof, click on **Next**, which will take you to the **Review & Submit** screen. The system will check that you have completed all the mandatory fields and that you have viewed your manuscript proof. It will also present you with a summary of all the information you have provided and give you a final chance to edit it. If there is a red cross next to any section, this will indicate that not all the fields have been filled in correctly. You may either go back to the relevant page or click the nearest **Edit** button.

9. When you have finished reviewing this information, press **Submit**. It is not until this button is pushed that the manuscript and all of the associated information (i.e., contributing authors, institutions, etc.) is linked together and the manuscript is given a manuscript number. Once the manuscript is submitted, it is not possible to undo the submission.

10. After the manuscript has been submitted, you will see a confirmation screen and receive an email confirmation stating that your manuscript has been successfully submitted. This will also give the assigned manuscript number, which is used in all correspondence during peer review. If you do not receive this, your manuscript will not have been successfully submitted to the journal and the paper cannot progress to peer review. If this is the case, your manuscript will still be sitting in the **Unsubmitted Manuscripts** section of your **Author Center** awaiting your attention.

11. If you return to your **Author Center**, you will notice that your newly submitted manuscript can be found in the **Submitted Manuscripts** area. The **Status** section provides information on the status of your manuscript as it moves through the review process.

D. Submitting a Revised Manuscript

Log on to the online submission site as before and, in the **Author Center**, click on **Manuscripts with Decisions**. At the bottom of the screen, you will see those manuscripts that require a revision (or that have been revised). Create a revision of this manuscript by clicking on **Create a Revision** under **Actions**. You will now be able to see the editor and reviewer comments and will be able to respond to these.

You will need to upload the files that constitute your revised manuscript. To facilitate the production process, it is essential that you upload your revised manuscript as a .doc, .rtf, or .tex file, and not in .pdf format. If you wish to finish this another time, you will find the manuscript in your 'Revised manuscripts in draft' list.

If you click on **View comments/respond** you will see the editor's letter to you together with the referees' comments. You may cut and paste your responses into the text areas at the bottom of the screen.

E. Figure Files

Your images are required as high-resolution .tif files (1200 dpi for line drawings and 300 dpi for colour and half-tone artwork). For useful information on preparing your figures for publication, go to http://art.cadmus.com/da/index.jsp. **Please note that publication of your manuscript will not proceed until figures suitable for reproduction are received.**

F. Getting Help

If you experience any problems during the online submission process please consult the Author's User Guide, which provides more detailed submission instructions and 'movie tutorials' explaining how to submit your paper. Alternatively, please contact the journal editorial office who will be pleased to assist you.

III. FIGURE GUIDELINES

A. Preparing Figures

This information is also available online here.

1. **Why use a figure?** Do not include a figure unless it is the best way to present information. Tables and text description take less space, and often are a simpler way to present findings. Limit the use of multiple-pane figures and complex figures.

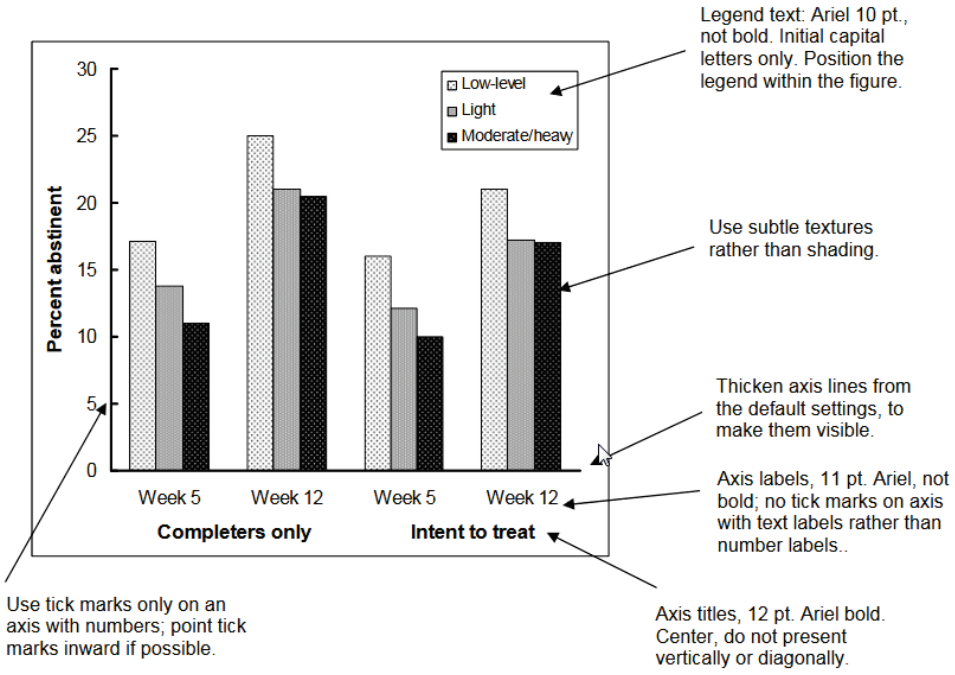
2. **Follow the instructions.** Figures must conform to the journal's guidelines before a manuscript can be accepted in final form and sent to production. Submitting figures in a nonpreferred format will delay or prevent publication. The acceptance date will reflect any delays related to unacceptable figure file.

3. **Create or reuse?** Authors submitting a figure simply copied from a PowerPoint presentation or a poster most likely will be asked to re-create the figure for publication, resulting in delays in acceptance and publication. The journal editors recommend that you create a figure specifically for submission to *Nicotine & Tobacco Research*, based on these guidelines.

4. **Colour or black/white?** Figures can be colour or black/white. Figures published in color in the print version of the paper will incur a publishing cost to the authors ($600.00 per figure). Figures can be published in black/white in print but in colour online at no cost to authors. In this case, the downloadable PDF of the published article will include colour figures. A colour figure also should be understandable in grayscale (that is, in pure black and white or with gray shades), since the article is likely to be photocopied or printed in grayscale.

B. Figure Preferences

The below figure will reproduce well.



C. Excel Figures

Creating your figures in Excel helps ensure that they will be reproduced correctly and legibly. Do not copy your Excel figures into the Word document of your manuscript. Instead, provide figures in a separate Excel file, with each figure in a separate worksheet. The worksheet labels for the figures should be: Figure 1, Figure 2...

Do not simply use the Excel defaults for creating a figure. You will need to make changes in the figure to make it clear and easy to follow:

1. Remove the gridlines.
2. Consider adding data labels if the data are not included in a table. Make the background white.
3. Remove the "border" around the chart area, so that only the x and y axes remain.
4. Thicken the axis lines so that they are at least three times as thick as the default lines.
5. Thicken any plotted lines so that they are at least as thick as the axis lines. Point the tick marks inward rather than outward, if possible.
6. Do not use gradations of shading; instead, use fine-lined textures.
7. Do not use tick marks on an axis with text labels rather than numbers.
8. If your x-axis data labels are lengthy or numerous, do not use angled labels. Instead, consider reversing the axes so that the labels are horizontal on the y-axis.

D. Other Graphic Programs

If you create figures in a program such as SigmaPlot or CorelDraw, you must export the file as .TIF or another file format listed below. The typesetters can work with figures in the following formats:

- .**TIF** (Tagged Image Format File)
- .**DOC** (Microsoft Word document)
- .**XLS** (Microsoft Excel)
- .**PPT** (Microsoft PowerPoint)
- .**PDF** (Portable document format, Adobe)
- .**AI** (Adobe Illustrator)
- .**WMF** (Windows metafile)
- .**PNG** (Portable Network Graphics)

The journal or publisher editors may request that you redraw the figure and export it again. Please follow the preferred style example and the guidelines under "Excel figures."

E. Order the Figures

Number all figures consecutively, as they should appear in the text.

F. Separate Files

Submit a figure as a separate file; do not embed it in the main manuscript document.

G. Figure Size

Size the figure to the column or page width of the journal and set the resolution at 300 dpi or greater for color and grayscale and 600 dpi for pure black and white

H. Microcharts

The Journal encourages the use of microcharts (also called sparklines) where appropriate. They can save considerable space and can include data and a graphic element. Shareware software for microcharts is available at http://www.bestshareware.net/download/microcharts-professional.htm.

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IV. COMPETING INTERESTS

Declarations of Funding and Competing Interest for *Nicotine & Tobacco Research*

Please visit the updated Declaration of Funding and Competing Interest here.

V. TRANSPARENCY AND OPENNESS GUIDELINES

The Transparency and Openness Guidelines can be downloaded as a PDF here.

VI. OFFPRINT ORDER FORM

The Offprint Order Form can be downloaded as a PDF here.

VII. OTHER RESOURCES

1. Archived SRNT Trainee Network webinars are limited to society members, but everyone can now access the slides and handouts from two key presentations:
    a. **"An Introduction to Writing Scientific Articles on Tobacco Use,"** presented by SRNT Past President John Hughes and Saul Shiffman. Access the slides from their 2013 webinar.
    b. **"Getting Published in N&TR,"** presented by Editor-in-Chief Marcus Munafò and Managing Editor Margaret Searle. Access the slides and handout from their 2015 webinar.
2. **Terminology**
   The International Society of Addiction Journal Editors recommends against the use of terminology that can stigmatize people who use alcohol, drugs, other addictive substances or who have an addictive behavior. Click here for more information.

VIII. EDITORIAL OFFICE CONTACTS

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