The therapeutic use of nicotine in narcolepsy

Aleksandros Makris and Carolina Diamandis

Affiliations

Lazar Research Consortium
A non-profit entity
Established by Dr. Marius Lazar

Corresponding Author

LCG Greece
Dr. Carolina Diamandis
Lazar Group Non-profit Research Consortium
Kifissias 16, Athina, 115 26
Hellenic Republic
LazarClinicGroup@post.com

Abstract

Nicotine is best known for its troublesome role in tobacco addiction. However, in small doses, it is actually quite a potent and safe stimulant. Based on significant reports about a positive role of nicotine on narcoleptic seizures, we searched the medical literature for signals to better understand the opportunities and risks of medical nicotine use in patients with any severe form of narcolepsy.

Introduction

Stimulants (wakefulness-promoting drugs) have long been used to treat excessive daytime sleepiness. In many countries, two agents, modafinil and methylphenidate, are currently approved for the treatment of daytime sleepiness in narcolepsy. Since 2007, sodium oxybate has also been available for the treatment of daytime sleepiness in narcolepsy. It is used when severe cataplexies or cataplexies and interrupted night sleep are present in addition to daytime sleepiness. In principle, all substances that suppress REM sleep are effective against cataplexy, but this leads to the paradoxical situation that night sleep, which is disturbed in narcoleptics, is also affected. Therefore, sedatives are often prescribed for the night. In other words, it is treated as if a car driver is on the accelerator and brake pedal at the same time. It is obvious even to the medical layman that this situation is not very satisfactory. A possible breakthrough could be achieved in the medium to long term with orexin, the production of which is reduced in narcoleptics due to irreversible cell damage. Hypocretin and orexin act as neurotransmitters (messengers in the brain) via specific binding sites (receptors).

In contrast to the hypocretin/orexin-producing cells, the receptors are intact in narcolepsy patients. Therapeutically, therefore, the possibility of replacing the missing neurotransmitter seems promising. However, hypocretin/orexin as a protein body would be immediately destroyed if absorbed via the gastrointestinal tract and would thus be ineffective. If it were delivered directly through the systemic circulation (parenterally), this could be avoided. The difficulty, however, is in crossing the blood-brain barrier, i.e. orexin cannot readily enter the brain. Further trials with an application via the nasal mucosa (intranasal) only showed an improvement in olfactory function. Initial studies on this have already been conducted, but therapeutic success with the core symptoms of narcolepsy described above has not yet been demonstrated. The treatment options for narcolepsy with and without cataplexy are thus strongly limited at present. This makes it all the more important to follow a lead that the physicians of our research consortium were put on by affected patients themselves. The patients were three males, aged 29 to 43, suffering from narcolepsy with cataplexy, who independently used nicotine patches as part of an experimental self-treatment - with apparent success. The patients reported sporadic use on particularly seizure-prone days with nicotine patches at 14-21mg/24h. Subjectively, there was a good one-third improvement in symptoms with fewer imperative sleep attacks per day. Since all three patients are non-smokers, the patch was removed in each case upon the occurrence of subjectively unpleasant side effects (mainly hot flushes and a noticeably accelerated heart rate). The treating physicians advised the patients of the risks and side effects of any nicotine use, but remained neutral toward the self-initiated treatment attempt, since nicotine patches are freely available in the respective countries and patients, as adults and informed persons, have the right to legal self-treatment. However, we used these reports as an opportunity to evaluate nicotine as a treatment for narcolepsy based on existing knowledge.

For details about narcolepsy with cataplexy please read our open access paper:

Carolina Diamandis, David Seideman, Jacob S Adams: Narcolepsy with Cataplexy - What we know about it in 2021. Authorea Publishing. 2021. doi: 10.22541/au.162074600.01266148/v1

Nicotine

Most people are familiar with nicotine as an addictive toxin present in cigarettes. In fact, however, nicotine is a psychotropic substance like many others. In the brain, nicotine binds to acetylcholine receptors, which are binding sites on cells specialized for certain biochemical signaling processes. For example, it stimulates increased dopamine production, which is associated with an immediate feeling of well-being or calming. In addition to stimulating this process in the so-called "reward center" of the brain, nicotine also has a stimulating effect on brain areas responsible for alertness and increasing attention.[15]

The processes taking place in the brain ultimately trigger activation of both, the sympathetic and parasympathetic systems. Any stimulation of the parasympathetic nervous system leads to an increase in gastric juice production, as well as increased intestinal activity, thus stimulating digestion. Activation of the sympathetic nervous system leads to the release of adrenaline and thus to an increase in heart rate and increased breakdown of fats and glycogen (blood sugar). This also causes ingested food to be metabolized more rapidly, resulting in increased energy expenditure. In addition, nicotine acts on the so-called "vomiting center", i.e. it reduces appetite and causes nausea.[16]

The release of vasopressin triggered by nicotine causes blood vessels to constrict, which subsequently contributes to an increase in blood pressure. In addition, vasopressin has an antidiuretic effect, meaning that it reduces urine production and the urge to urinate. Nicotine also promotes the blood's tendency to clot, which increases the risk of thrombosis. Nicotine causes an increase in respiratory rate and, due to the over-excitation of pressure and pain receptors, also an increased sensitivity to pain. After it has taken effect, nicotine is broken down in the liver, oxidizing nicotine to cotinine, which is eventually excreted through the bladder.[15-17]

The half-life of nicotine in the body is only about 2 hours, a fact that will be of utmost importance later in this article. Already during nicotine depletion, smokers develop a renewed desire to smoke in order to supply the receptors in the brain with replenishment and thus achieve the desired feeling of well-being. If this supply is missing for too long, unpleasant withdrawal symptoms arise, such as restlessness, irritability, lack of concentration and many other undesirable effects.[16,17]

Nicotine in narcolepsy

The effects reported by the three patients with narcolepsy mentioned above are not surprising. It has long been known that inhalant cigarette smokers with narcolepsy experience a worsening of their condition when they stop smoking. There are even credible anecdotal reports that the effect of nicotine on sleep attacks also applies to secondhand smokers and cannabis users who smoke their drug with more tobacco than cannabis. We also know from other conditions that affect the brain, such as schizophrenia, that tobacco use and cravings for tobacco products are very common in this patient population. Given all these anecdotal reports, one might wonder why nicotine has not long since found its place as a mild stimulant in the treatment of narcolepsy. Its risk of addiction is not any higher than that of other stimulants, nor are its undesirable side effects. In particular, its half-life of only 2 hours is a powerful argument for nicotine as an adjunctive, experimental treatment for narcolepsy. The short half-life is crucial because it allows the use of a short-acting sedative for nighttime use. A "gas pedal and brake pedal at the same time effect" can be easily avoided. In a systematic search, we did only find two papers that looked neutrally at nicotine as a regular treatment option for narcolepsy.[9,13,14] We suspect that nicotine's poor image as an ingredient in toxic cigarette smoke contributes to a reluctance to use this easily manageable stimulant as a fast-acting, relatively safe, and readily available medication for patients >18 years of age for days of very high to extreme symptom burden.[18]

Of even greater importance is the fact that many patients with secondary narcolepsy are already taking many medications. Rapid intervention with a skin patch containing a drug that has a half-life of only 2 hours is highly desirable for this subset of patients many of whom have varying degrees of brain damage due to their underlying disease. This is by no means the first time that a promising medical drug has not been thoroughly researched, despite endless anecdotal evidence suggesting that it may be helpful for certain seriously ill patients. Cannabis might be the most prominent "victim" among drugs that are shunned for broad medical use because of their stigma as (formerly) illegal psychotropic drugs. As a stimulant alkaloid naturally occurring in the tobacco plant, but also in other nightshade plants, nicotine has potent effects even in small quantities, making it highly attractive for the treatment of narcolepsy. So does its ability to easily cross the blood-brain barrier, even when absorbed slowly through the skin. Nicotine activates so-called nicotinic acetylcholine receptors in the nervous system by binding to them. These are actually stimulated by the neurotransmitter acetylcholine. Nicotinic ACh-receptors are located primarily at motor endplates, where signals are transmitted from nerve cells to muscles. In the brain, the receptors are located on the downstream sympathetic and parasympathetic nerve cells, among others. This part of the autonomic nervous system controls unconscious processes such as alertness, intestinal activity, heartbeat, secretion activity of many glands and much more. Since nicotine acts similarly to the actual messenger substance, the human body practically never reacts with an allergic

reaction to nicotine. As soon as nicotine has bound to the ACh-receptor, various messenger substances such as dopamine, adrenaline, noradrenaline and serotonin as well as hormones such as cortisol are released. While acetylcholine is quickly broken down again, nicotine binds to the receptors over a somewhat longer period of time. As a result, the excitation of the respective cell lasts longer. This is of considerable importance in the context of the presumed pathomechanism of narcolepsy. However, as with other stimulants, there is a tendency for tolerance to develop as the effect wears off.[1-7,16-19]

In the long term, cells adapt to this mechanism and incorporate additional receptors into the cell membrane. If nicotine is missing, there are suddenly too many free receptors, and the downstream nerve cells can no longer be stimulated to the extent they should. Dopamine levels drop, and cravings for new and higher doses develop. For clinical use in the context of narcolepsy, this means that nicotine should only be used sporadically; for example, on days with particularly high symptom burden. However, as an acute medication only, this effect should be negligible and the benefits far outweigh the risks.[12-15]

This is because nicotine undoubtedly has a stimulating effect through the increased release of norepinephrine, epinephrine and vasopressin. The heart beats faster, blood pressure rises, blood vessels constrict and vigilance increases significantly at daily doses between 14 mg and 21 mg percutaneously. This leads to better mental performance and alertness. Nicotine also causes the amount of glucose in the blood to increase, thereby dampening the craving for food. However, the stimulant effects occur only at the low doses already mentioned. High doses of nicotine paradoxically have a sedative, sometimes even paralyzing effect. This explains why many people find smoking relaxing. On the other hand, the stimulating effect at low doses and the fact that nicotine is broken down so quickly are the reasons why the first cigarette of the day has the strongest effect.[1,2,12,14,15,18,19]

After that, the addicted smoker is only concerned with maintaining a constant nicotine level. In sporadic use associated with narcolepsy, correctly dosed nicotine causes the release of the neurotransmitter dopamine in the nucleus accumbens (brain) and interacts with orexin receptors and orexin as such in a variety of ways, many of which are still being explored. However, it is already apparent that nicotine and orexin are interwoven in the cells and receptors of the human brain in a variety of ways. Since orexin is one of the targets in narcolepsy research, it is not in the least surprising that these two agents metaphorically "play on the same field." The medical literature abounds with such indirect evidence that nicotine may be useful as an effective stimulant for acute use in narcoleptic patients with high symptom burden. It is difficult to find a reputable study that describes nicotine as more dangerous than currently used medications in all forms of narcolepsy. It is therefore justifiable to tolerate patients trying to control their narcolepsy now and then with low-dose nicotine patches.[3-7]

Conclusion

We found evidence that nicotine, administered as a dermal patch at a dosage of 14 mg to 21 mg per 24 hours, is a fast-acting and relatively safe drug to relieve the symptom burden of severely affected patients suffering from all types of narcolepsy. Like most stimulants, nicotine is highly addictive and its use should be limited to a maximum of 5 days per month in nonsmokers. Further research, especially a well-designed prospective study, is recommended.

Conflicts of interest

None.

Ethical standards and patient's rights

This article is about scientific facts based on research literature. It is not reporting on a clinical trial, especially not a prospective one. Our research work is always conducted in accordance with the Declaration of Helsinki.

References

1. Carolina Diamandis, David Seideman, Jacob S Adams. Narcolepsy with Cataplexy: What we know about it in 2021. Authorea Publishing, 2021. doi: 10.22541/au.162074600.01266148/v1

2. Carolina Diamandis, David Seideman, Balaskas, Anastasios Papadopoulos, Riku Honda. Prevalence of narcolepsy in patients with H63D syndrome. Researchsquare, 2021. doi: 10.21203/rs.3.rs-507295/v1

2. al'Absi M, Lemieux A, Hodges JS, Allen S. Circulating orexin changes during withdrawal are associated with nicotine craving and risk for smoking relapse. Addict Biol. 2019 Jul;24(4):743-753. doi: 10.1111/adb.12643. Epub 2018 Aug 16. PMID: 30117237; PMCID: PMC7263380.

3. Pasumarthi RK, Reznikov LR, Fadel J. Activation of orexin neurons by acute nicotine. Eur J Pharmacol. 2006 Mar 27;535(1-3):172-6. doi: 10.1016/j.ejphar.2006.02.021. Epub 2006 Mar 6. PMID: 16545369.

4. Barson JR, Leibowitz SF. Orexin/Hypocretin System: Role in Food and Drug Overconsumption. Int Rev Neurobiol. 2017;136:199-237. doi: 10.1016/bs.irn.2017.06.006. Epub 2017 Aug 8. PMID: 29056152; PMCID: PMC5820772.

5. von der Goltz C, Koopmann A, Dinter C, Richter A, Rockenbach C, Grosshans M, Nakovics H, Wiedemann K, Mann K, Winterer G, Kiefer F. Orexin and leptin are associated with nicotine craving: a link between smoking, appetite and reward. Psychoneuroendocrinology. 2010 May;35(4):570-7. doi: 10.1016/j.psyneuen.2009.09.005. Epub 2009 Oct 13. PMID: 19828259.

6. Adeghate E, Lotfy M, D'Souza C, Alseiari SM, Alsaadi AA, Qahtan SA. Hypocretin/orexin modulates body weight and the metabolism of glucose and insulin. Diabetes Metab Res Rev. 2020 Mar;36(3):e3229. doi: 10.1002/dmrr.3229. Epub 2020 Jan 16. PMID: 31655012.

7. Khoo SY, McNally GP, Clemens KJ. The dual orexin receptor antagonist TCS1102 does not affect reinstatement of nicotine-seeking. PLoS One. 2017 Mar 15;12(3):e0173967. doi: 10.1371/journal.pone.0173967. PMID: 28296947; PMCID: PMC5351999.

8. Morgan RE, Crowley JM, Smith RH, LaRoche RB, Dopheide MM. Modafinil improves attention, inhibitory control, and reaction time in healthy, middle-aged rats. Pharmacol Biochem Behav. 2007 Mar;86(3):531-41. doi: 10.1016/j.pbb.2007.01.015. Epub 2007 Jan 23. PMID: 17328945.

9. Bagai K, Malow BA. A novel approach to treating morning sleep inertia in narcolepsy. J Clin Sleep Med. 2010 Feb 15;6(1):77-8. PMID: 20191943; PMCID: PMC2823281.

10. Sienkiewicz-Jarosz H, Zatorski P, Korkosz A, Ryglewicz D, Swiecicki L, Bienkowski P, Scinska A. Disruption of nicotine addiction associated with paroxysmal hypersomnia. J Neuropsychiatry Clin Neurosci. 2009 Summer;21(3):342. doi: 10.1176/jnp.2009.21.3.342. PMID: 19776317.

11. Thorpy MJ, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. Sleep Med. 2015 Jan;16(1):9-18. doi: 10.1016/j.sleep.2014.10.002. Epub 2014 Oct 16. PMID: 25458251.

12. Corrigall WA. Hypocretin mechanisms in nicotine addiction: evidence and speculation. Psychopharmacology (Berl). 2009 Sep;206(1):23-37. doi: 10.1007/s00213-009-1588-2. Epub 2009 Jun 16. PMID: 19529922.

13. Ebben MR, Krieger AC. Narcolepsy with cataplexy masked by the use of nicotine. J Clin Sleep Med. 2012 Apr 15;8(2):195-6. doi: 10.5664/jcsm.1780. PMID: 22505866; PMCID: PMC3311418.

14. Krahn LE, Martin KA, Silber MH. Narcoleptic patients' perceptions of nicotine. J Clin Sleep Med. 2009 Aug 15;5(4):390. PMID: 19968021; PMCID: PMC2725262.

15. Prochaska JJ, Benowitz NL. Current advances in research in treatment and recovery: Nicotine addiction. Sci Adv. 2019;5(10):eaay9763. Published 2019 Oct 16. doi:10.1126/sciadv.aay9763

16. Allenby CE, Boylan KA, Lerman C, Falcone M. Precision Medicine for Tobacco Dependence: Development and Validation of the Nicotine Metabolite Ratio. J Neuroimmune Pharmacol. 2016;11(3):471-483. doi:10.1007/s11481-016-9656-y

17. Moerke MJ, McMahon LR, Wilkerson JL. More than Smoke and Patches: The Quest for Pharmacotherapies to Treat Tobacco Use Disorder. Pharmacol Rev. 2020;72(2):527-557. doi:10.1124/pr.119.018028

18. Unpublished data of LCG Research Greece

19. Boggs DL, Carlson J, Cortes-Briones J, Krystal JH, D'Souza DC. Going up in smoke? A review of nAChRs-based treatment strategies for improving cognition in schizophrenia. Curr Pharm Des. 2014;20(31):5077-5092. doi:10.2174/1381612819666131216121019