

Nicotine Withdrawal, the Role of NRT in Hospitalised Smoker Patients and its Implications for Covid-19

Sudhanshu Patwardhan* and Ira Banerjee

Centre for Health Research and Education, University of Southampton Science Park, Chilworth, Hampshire, UK

*Correspondence to:

Dr. Sudhanshu Patwardhan
Director, Centre for Health Research and
Education University of Southampton Science
Park Chilworth, Hampshire, UK
E-mail: sud@chre-uk.com

Received: April 27, 2020

Accepted: May 06, 2020

Published: May 08, 2020

Citation: Patwardhan S, Banerjee I. 2020. Nicotine Withdrawal, the Role of NRT in Hospitalised Smoker Patients and its Implications. *J Addict Sci* 6(S1): S1-S4.

Copyright: © 2020 Patwardhan and Banerjee. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY) (<http://creativecommons.org/licenses/by/4.0/>) which permits commercial use, including reproduction, adaptation, and distribution of the article provided the original author and source are credited.

Published by United Scientific Group

Abstract

Nicotine withdrawal may commonly manifest amongst hospitalised smokers under emergency; it has the potential to be underdiagnosed, and worse still, under-treated. This perspective piece reviews the sparse literature around the issue. The challenges posed by nicotine withdrawal amongst hospitalised smokers are highlighted and it explores how they may become increasingly relevant throughout Covid-19. Here we discuss what the emerging data on nicotine use, Covid-19 incidence, and proposed studies with NRT during Covid-19 may suggest for the adoption of nicotine replacement for future in-patient settings to manage nicotine withdrawal.

Keywords

Smoking, ICU, Nicotine withdrawal, Nicotine replacement, Smoking cessation, Tobacco harm reduction

Introduction

In the UK, the smoking rate amongst the adult population is at 14%, a significant decline over the past five decades [1]. Nicotine replacement therapy (NRT) medications are now widely allowed for general sales (i.e. can be sold in convenience stores, not just pharmacies) and stop smoking services are available in the community. The emergence of innovative nicotine delivery products such as e-cigarettes and nicotine pouches have made nicotine replacement even more accessible, affordable and available.

Smoking is banned in all hospital sites including mental health facilities across the UK. Patients and hospital workers now don't have access to an on-premises smoking site, and instead would have to leave the premises in order to smoke. In the absence of pro-active smoking cessation support on most hospital sites, hospitalisations remain to be 'untapped' teachable moments [2] by not introducing smoking cessation to clinical practice. This isn't good news for heavy and/or regular smokers who are admitted to hospitals, especially in emergency or unplanned circumstances.

Nicotine Withdrawal in Hospitalised Patients

It has long been established that nicotine withdrawal can often mimic symptoms similar to that of mental health illnesses. The conditions surrounding smoking cessation and ways to limit withdrawal symptoms are usually well explored when linked to supporting those actively trying to quit- i.e. those enrolled in quit smoking programmes and having access to community-based stop smoking services. Patients admitted into hospital without any prior

warning are at high risk for their withdrawal symptoms to be misdiagnosed and inaccurately attributed to the condition that they were admitted for. Many less frequent nicotine withdrawal symptoms such as delirium [3] and general agitation can be easily blurred with mental health symptoms and therefore go untreated. This clearly has the potential to be very unpleasant for the patient and can potentially extend their hospitalisation. In some circumstances, it may even negatively impact their treatment outcome.

It is still yet to be *completely* determined whether active smokers face adverse clinical symptoms from an immediate nicotine 'cold turkey' in an intensive care setting. Nicotine withdrawal symptoms such as agitation and delirium are vague and often caused by a multitude of conditions, making the allocation of these symptoms difficult. We reviewed whether negative treatment outcomes are more pronounced due to nicotine withdrawal amongst smoker critical care patients, or whether these outcomes are primarily dependent on the critical condition they are being treated for.

A Brief Review of Existing Literature

The role of acute nicotine withdrawal in outcomes amongst hospitalised smokers and particularly those treated in intensive care has been a focal point for a few studies, showing a mixed bag of results.

Luciderme et al. [4] suggested that nicotine withdrawal was associated with agitation and higher morbidities in critically ill patients on mechanical ventilation. The study included patients with primary diagnosis of septic shock (14/44) and respiratory disease (15/44). Chronic alcoholism was a confounding factor among many cases in this study (30/44). Nicotine withdrawal was identified as risk factor of agitation, but not delirium, in multivariate and matched case-control analyses adjusted for confounding factors. Agitation was associated with a higher adverse-event rate, such as accidental self-removal of tubes and catheters, and the need for new interventions including supplemental sedation and physical restraint.

Almeida et al. [5] also suggested worse outcomes for those suffering from nicotine withdrawal. The incidence of agitation in the first 7 days after admission to the intensive care unit was higher amongst active smokers. Agitated patients had fewer ventilator-free days in the first 7 days, suggesting the nicotine withdrawal has the potential to lead to longer hospitalisation. Lim et al. [6] studied symptoms in stroke cases, and they concluded that abrupt cigarette cessation was in fact detrimental and increased the risk of post-stroke delirium. This was further confirmed by Mayer et al. [7] who reported that by providing NRT, conditions of 5 patients who had undergone serious brain injuries improved, suggesting that the nicotine withdrawal was in fact the cause of the worsened conditions prior to NRT. Tran-van et al. [8] reached the same conclusion when testing on a singular nicotine dependent woman. Improvements in restlessness and mechanical ventilation were achieved when a transdermal nicotine patch was applied. De Jong et al. [9] showed that time alive without delirium, sedation and coma amongst an ICU cohort at day 20 in NRT

patients was longer than in control patients.

There is also conflicting, strong evidence from a number of studies, suggesting that perhaps no certain link can be determined just yet. Current evidence for the use of NRT in agitation and delirium management in the ICU was deemed to be inconclusive by Kowalski et al. [10]. They observed 6 studies and found no statistical evidence to suggest that NRT could improve or alleviate any symptoms. Better quality of recording and analysing results was recommended by them in subsequent studies. This corresponded with Hseih et al's conclusions after reviewing 14 studies on the matter. It was concluded that there was insufficient evidence between NRT and symptom alleviation amongst active smoker patients [11]. Briefly discussed in Luciderme's study above [4], smoker patients may also be facing alcohol withdrawal when admitted into an ICU setting. It could be beneficial for those aforementioned studies discounting nicotine withdrawal as a risk factor for delirium, to test for its dependence on alcohol withdrawal instead.

There are some studies that go one step further and suggest that the introduction of NRTs could actually be a direct threat to the critically ill. For example, those suffering from cardiac arrest were shown by Paciullo et al to be at greater risk of morbidity if NRTs were introduced into their treatment [12]. In order to account for all variables, Wilby et al. [13] concluded after an extensive literature review on the topic that NRT should not be routinely prescribed to patients admitted to intensive care settings. With only ambiguous evidence of efficacy, they felt that its use should be limited to selected patients where the potential benefit clearly outweighs the risk.

Despite the abundance of active smokers being hospitalised, this paucity of data describing nicotine withdrawal during their hospital stay [14], and its prevention and treatment options in the critically ill is worrying. Also, there are guidelines in place at the level of individual hospital trusts in the UK that aim to address the nicotine withdrawal in hospitalised patients by providing access to NRT [15]. However, there is no published research or audit on their implementation or success.

Covid-19 and Hospital Admissions

Covid-19 has the potential to exacerbate the unresolved issue of nicotine withdrawal in intensive care. The epidemic has resulted in a large short-term increase in ICU demand, faced by hospitals all over the world. The respiratory attacking nature of SARS-coV-2 (the virus responsible for Covid-19) particularly puts active smokers at risk of facing more serious health symptoms. Initial studies from China showed that a history of smoking may increase the likelihood of SARS-coV-2 developing into Covid-19 pneumonia [16]. One study suggested that smokers or those with a history of smoking were 2.4 times more likely to get admitted into the ICU with Covid-19 related complications [17]. Other researchers are looking at the emerging data from around the world, e.g. from France and the US, and are attempting to identify any correlation between nicotine use and incidence of Covid-19-related hospitalisation. A French study [18] found that the rate

of current daily smokers were significantly lower in Covid-19 outpatients and inpatients, as compared to the general population. The authors suggest that nicotine in cigarettes may exert a protective effect against SARS-coV-2. Analysis of the US CDC data by Miyara et al. [18] and Chinese data by Farsalinos et al. [19] also goes against assumptions that current smoking is a risk factor for hospitalization for Covid-19. Instead, based on the low prevalence of current smoking among Covid-19 patients in the US (1.3%), it was postulated that nicotine may have beneficial effects on Covid-19. A hypothesis has been put forward that attributes a protective role to nicotine, due to its immunomodulatory effects and its interaction with the renin-angiotensin system [20]. They propose a clinical trial that will involve using nicotine (and other nicotinic agents) patches or other delivery methods (like sniffing/chewing) in hospitalized patients and in the general population to prevent the infection and the retro-propagation of the virus through the central nervous system [18, 20].

Discussion

To Patch or Not To Patch

As the Covid-19 pandemic rages on and is likely to continue bringing patients with lung complications for intensive care in the coming months [21], intensivists and hospital staff involved in patient care worldwide would benefit from clear guidance on nicotine withdrawal management.

Nicotine is the main addictive component of tobacco. Nicotine is also on the WHO Essential Medicines list to be used for nicotine replacement therapy for achieving smoking cessation [22]. Medicinal nicotine is available in the form of gums, patches and mouth spray etc., made from pharmaceutical grade nicotine. Even nicotine used in e-cigarettes and nicotine pouches may be of pharmaceutical grade, in countries where the regulation requires so and/or where the manufacturers voluntarily use that quality in manufacturing. It is well established that the majority of harm from smoking cigarettes comes from the smoke toxicants formed as a product of the combustion of tobacco. It follows that using clean nicotine from well-regulated delivery systems (those that do not involve inhaling smoke) can be used to achieve tobacco harm reduction [23]. The UK medicines agency, MHRA, has licensed NRT for tobacco harm reduction [24]. The National Health Service (NHS) guidance for smokers identifies the biggest problems with NRT: that people *don't use enough of it for long enough*. The NHS Quit Smoking website clearly states that "It is important to use your nicotine replacement for as long as you need to stop you going back to smoking" [25]. Allowing for dosing nicotine adequately, often in the form of dual therapy, combining short and long acting forms of nicotine, can be more successful in helping smokers quit and prevent relapse to smoking [26].

For long, the risks and harms from nicotine and tobacco smoke have been conflated. Nicotine illiteracy is rampant even among healthcare professionals [27], thus likely leading to poorer prescription of nicotine replacement in a clinical environment, including hospitals. Subsequently, healthcare

professionals may be missing out on leveraging potential 'teachable moments' during consultation that are often the first step in smoking cessation.

The application of the tobacco harm reduction principle in a hospital setting needs to be assessed. Current literature and indeed clinical practice lack deep insights on patients who are forced into an acute nicotine withdrawal as a result of emergency hospitalisation.

The Covid-19 crisis brings a sharp focus on a potential role of nicotine in offering a possible protective effect in Covid-19 infection and disease progression. One thing worth remembering is how the data of smoker patients is collected. It relies on both patient accounts and the doctor's ability to record accurate patient history, both of which may be compromised in the stressful environment of a bustling Covid-19 ward. There may be other factors, yet unexplained, as to why the incidence of Covid-19 and related hospital admissions may be disproportionately lower among current smokers compared to the general population. It would be hasty for the authors to propose or support a protective potential effect of nicotine based on the current sparse data on Covid-19 epidemiology. The desperate stockpiling of NRT among the French following the publication of the single study [18] should act as a reminder of the risks of extrapolating without enough robust assessment and approval by regulatory agencies.

The opportunity however presents itself to study the topic in more detail using rigorously designed clinical studies. It would be beneficial to focus on the nicotine withdrawal policies of hospitals for emergency admissions. Policies should be put in place to administer adequate NRTs for hospitalised smokers depending on their daily cigarette consumption, so as to pre-empt nicotine withdrawal, and to monitor mental and physical health outcomes as a result.

Conclusions

Smoking remains a leading preventable cause of disease and early death globally. Efforts to help smokers quit in the community and during a hospital stay should continue and in fact, accelerate.

An interest in nicotine's potential protective effect for Covid-19 presents an opportunity to also better understand the routinely missed nicotine withdrawal diagnoses and management in clinical practice.

Based on clinical judgement and the absence of any contraindications for the use of NRTs, nicotine replacement treatment amongst emergency-care smoker patients should be routinely considered. To be able to do so, robust multi-centre and randomized controlled clinical trials will be needed to control for any confounding factors for nicotine withdrawal and to arrive at the right dosing regimens. Special attention will need to be paid to specific sub-populations and demographics, e.g. smoker pregnant women admitted for emergency procedures and smoker mental health patients.

By identifying Covid-19 patients' smoking status upon

arrival into ICU, healthcare professionals could put in treatment plans which allow smoker patient's access to NRTs as appropriate. Their symptoms could be monitored over time, potentially leading to:

- The alleviation of patients' nicotine withdrawal symptoms.
- A better understanding of nicotine withdrawal symptoms when paired with Covid-19 pneumonia.
- Serve as the first step to an inexpensive, easily implemented smoking cessation programme that can be embedded into routine practice beyond its application to Covid-19.

Hospital admissions can be life changing and often are considered good teachable moments. Starting nicotine replacement treatments and providing evidence-based support in a hospital setting may inspire smokers to continue their smoke cessation journey beyond their hospital stay.

Conflict of Interest

SP is the paid Director of the Centre for Health Research and Education, UK (CHRE). IB is the Communications Manager at CHRE. SP, IB or CHRE do not receive any funding from tobacco, electronic cigarette or pharmaceutical companies.

References

1. ASH-Smoking statistics. (Accessed: May 06, 2020)
2. McBride CM, Emmons KM, Lipkus IM. 2003. Understanding the potential of teachable moments: the case of smoking cessation. *Health Educ Res* 18(2): 156-170. <https://doi.org/10.1093/her/18.2.156>
3. Dinesh K, Ankit G, Sucheta T, Prerna K. 2019. Delirium and nicotine withdrawal. In: Preedy VP (ed) *Neuroscience of nicotine: mechanisms and treatment* pp 221-228.
4. Lucidarme O, Seguin A, Daubin C, Ramakers M, Terzi N, et al. 2010. Nicotine withdrawal and agitation in ventilated critically ill patients *Crit Care* 14(2): R58.
5. Almeida TM, Azevedo LC, Nosé PM, Freitas FG, Machado FR. 2016. Risk factors for agitation in critically ill patients. *Rev Bras Ter Intensiva* 28(4): 413-419. <https://doi.org/10.5935/0103-507X.20160074>
6. Lim TS, Lee JS, Yoon JH, Moon SY, Joo IS, et al. 2017. Cigarette smoking is an independent risk factor for post-stroke delirium. *BMC Neurol* 17(1): 56. <https://doi.org/10.1186/s12883-017-0840-3>
7. Mayer SA, Chong JY, Ridgway E, Min KC, Commichau C, et al. 2001. Delirium from nicotine withdrawal in neuro-ICU patients. *Neurology* 57(3): 551-553. <https://doi.org/10.1212/wnl.57.3.551>
8. Tran-Van D, Hervé Y, Labadie P, Derouilhe G, Avarguès P. 2004. Agitation en réanimation: penser au syndrome de sevrage nicotinique. *Ann Fr Anesth Reanim* 23(6): 604-606. <https://doi.org/10.1016/j.annfar.2004.02.046>
9. de Jong B, Schuppers AS, Kruisdijk-Gerritsen A, Arbouw MEL, van den Oever HLA, et al. 2018. The safety and efficacy of nicotine replacement therapy in the intensive care unit: a randomised controlled pilot study. *Ann Intensive Care* 8(1): 70. <https://doi.org/10.1186/s13613-018-0399-1>
10. Kowalski M, Udy AA, McRobbie HJ, Dooley MJ. Nicotine replacement therapy for agitation and delirium management in the intensive care unit: a systematic review of the literature. *J Intensive Care* 4: 69. <https://doi.org/10.1186/s40560-016-0184-x>
11. Hsieh SJ, Shum M, Lee AN, Hasselmark F, Gong MN. 2013. Cigarette smoking as a risk factor for delirium in hospitalized and intensive care unit patients. *Ann Am Thorac Soc* 10(5): 496-503. <https://doi.org/10.1513/AnnalsATS.201301-001OC>
12. Paciullo CA, Short MR, Steinke DT, Jennings HR. 2009. Impact of nicotine replacement therapy on postoperative mortality following coronary artery bypass graft surgery. *Ann. Pharmacother* 43(7-8): 1197-1202. <https://doi.org/10.1345/aph.1L423>
13. Wilby KJ, Harder CK. 2014. Nicotine replacement therapy in the intensive care unit: a systematic review. *J Intensive Care Med* 29(1): 22-30. <https://doi.org/10.1177/0885066612442053>
14. Afessa B, Keegan MT. 2010. Critical care support of patients with nicotine addiction. *Crit Care* 14(3): 155. <https://doi.org/10.1186/cc8955>
15. NHS Foundation Trust. 2018. Nicotine Replacement Therapy Inpatient Prescribing Guideline. 1-14.
16. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, et al. 2020. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J (Engl)* 133(9):1032-1038. <https://doi.org/10.1097/CM9.0000000000000775>
17. Vardavas CI, Nikitara K. 2020. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis* 18: 20. <https://doi.org/10.18332/tid/119324>
18. Miyara M, Tubach F, POURCHER V, Morelot-Panzini C, Pernet J, et al. 2020. Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19. *Qeios*. <https://doi.org/10.32388/WPP19W.3>
19. Farsalinos K, Barbouni A, Niaura R. 2020. Smoking, vaping and hospitalization for COVID-19. *Qeios*. <https://doi.org/10.32388/Z69O8A.13>
20. Changeux JP, Amoura Z, Rey F, Miyara M. 2020. A nicotinic hypothesis for Covid-19 with preventive and therapeutic implications. *Qeios*. <https://doi.org/10.32388/FXGQSB.2>
21. Data-Driven Prediction of COVID-19 Pandemic End Dates. (Accessed: May 06, 2020)
22. Nicotine replacement therapy on the Essential Medicines List. (Accessed: May 06, 2020)
23. Tobacco Advisory Group of the Royal College of Physicians. 2007. Harm reduction in nicotine addiction-Helping people who can't quit.
24. Nicotine replacement therapy and harm reduction.
25. 10 myths about stop smoking treatments.
26. Burch J, Tort S. 2019. How does combination nicotine replacement therapy (NRT) compare with monotherapy for people trying to quit smoking? *Cochrane Clinical Answers*.
27. Patwardhan SR, Murphy MA. 2013. Survey of GPs' understanding of tobacco and nicotine products. *Drugs Alcohol Today* 13(2): 119-150. <https://doi.org/10.1108/DAT-02-2013-0010>