REVIEW ARTICLE

Efficacy and Safety of Nicotine Replacement Therapy in Intensive Care Units: A Systematic Review

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Abstract

Nicotine replacement therapy (NRT) is a potential intervention for managing nicotine withdrawal symptoms in critically ill patients in the intensive care unit (ICU). This systematic review evaluated the effectiveness and safety of NRT in adult ICU patients with a history of nicotine dependence or tobacco use. A comprehensive literature search was conducted from January 31, 2010, to September 31, 2024, using the PubMed, Scopus, and Web of Science databases. Eight studies that assessed the impact of NRT on nicotine withdrawal symptoms, ICU stay duration, delirium incidence, mortality, and adverse events were included in the review. These results suggest that NRT may be effective in reducing nicotine withdrawal symptoms in patients in the ICU. However, evidence regarding its impact on ICU outcomes, such as length of stay and delirium incidence, is inconclusive. Some studies reported potential adverse effects, including increased agitation and delirium, whereas others found no significant increase in adverse events. The safety profile of NRT in the ICU setting remains controversial, and further, high-quality randomized controlled trials are required to establish its efficacy and safety in critically ill patients. This review highlights the importance of individualized patient management and the needs for a balanced approach when incorporating NRT into ICU care, considering factors such as nicotine dependence severity, cardiovascular health, and the overall clinical profile. Future research should focus on optimizing NRT use in the ICU, exploring optimal formulations and dosages, and investigating the potential interactions with common ICU medications.

Key words: Nicotine replacement therapy, intensive care unit, nicotine withdrawal, critically ill patients, mortality

INTRODUCTION

The intensive care unit (ICU) treats critically ill patients with life-threatening conditions and nicotine withdrawal presents a significant clinical challenge. Nicotine addiction often leads to ICU admission, and smokers face abrupt cessation, resulting in withdrawal symptoms that complicate treatment and hinder recovery.[1] Nicotine replacement therapy (NRT) is suggested, but its safety and efficacy in the ICU remain unclear.[2]

Managing critically ill smokers is complicated by withdrawal effects such as irritability, anxiety, and increased physiological stress.[3,4] Untreated withdrawal in sedated or ventilated

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patients can exacerbate agitation and stress and potentially trigger cardiovascular events. Effective nicotine management is crucial to improve outcomes in this high-acuity setting.[1]

NRT, available in various forms, is a proven smoking cessation method in outpatient settings that alleviate withdrawal symptoms without harmful effects of tobacco smoke. In the general population, NRT doubles the likelihood of successful cessation compared with placebo.[5,6] However, the ICU's unique conditions necessitate careful evaluation of NRT's risks and benefits.[4,5]

Critically ill patients often exhibit altered pharmacokinetics and pharmacodynamics due to organ dysfunction, medications, and illness severity, affecting nicotine metabolism and response to NRT.[7] Certain NRT forms may be impractical for intubated or sedated patients.[8] Nicotine's cardiovascular effects pose additional challenges in the ICU, where patients may already be hemodynamically unstable.[5]

Therefore, the safety of NRT in ICU is a primary concern. Although NRT is generally safe in outpatient settings, its use in critically ill patients requires careful consideration.[2,9] Potential adverse effects, especially cardiovascular and neurological effects, must be weighed against withdrawal symptom mitigation benefits.[10] With continuous monitoring and advanced life support, the ICU offers unique opportunities for careful risk assessment and management.[11] However, the evidence supporting NRT's safety and efficacy of NRT in the ICU is limited, necessitating a comprehensive review to guide clinical practice.[6,8]

NRT use in ICUs has been extensively analyzed to determine its effects on nicotine withdrawal symptoms, safety, and clinical outcomes such as ICU stay duration, delirium occurrence, and mortality rates. Evaluating current data will establish the safe incorporation of NRT into ICU protocols and identify the most effective forms or dosages for critically ill patients, guiding clinical decisions and optimal practices for managing nicotine withdrawal in the ICU. Understanding the safety and effectiveness of NRT in the ICU may assist healthcare professionals in making informed and patient-specific decisions, thereby enhancing the overall quality of care.

This systematic review evaluated the effectiveness and safety of NRT in critically ill patients in ICU. This study examined the impact of NRT on nicotine withdrawal symptoms, ICU stay duration, delirium incidence, and overall patient outcome. In addition, it assesses NRT-associated risks including cardiovascular issues and heightened agitation. The goal was to establish evidence-based guidelines for NRT in ICU protocols to enhance patient comfort, reduce complications, and improve recovery outcomes.

METHODS

This review followed the preferred reporting items for systematic reviews and meta-analysis guidelines.[12]

This systematic review investigated the safety and efficacy of NRT in managing nicotine withdrawal symptoms among critically ill adult patients in the ICU with a history of nicotine dependence or tobacco use and its impact on clinical outcomes, including ICU stay duration, delirium occurrence, mortality, and adverse events, compared to standard care, placebo, or no NRT, using the population, intervention, comparison, and outcome framework.

PubMed, Scopus, and Web of Science databases were thoroughly searched for English-language publications from January 31, 2010, to September 31, 2024. The search strategy combined keywords and MeSH terms such as "Nicotine Replacement Therapy," "Intensive Care Unit," "nicotine withdrawal," and "critically ill patients." The reference lists from pertinent studies and systematic reviews were manually examined for comprehensive coverage.

This review included randomized controlled trials, cohort studies, and observational research on various forms of NRT (patches, gums, lozenges, and nasal sprays) in adult ICU patients. Eligible studies reported outcomes, such as management of nicotine withdrawal symptoms, ICU stay duration, delirium incidence, mortality rates, and adverse events. Exclusions were made for studies involving pediatric patients, non-ICU settings, or those not evaluating NRT interventions were excluded.

Two independent reviewers extracted data using a standardized form, including study details (author, year, design), patient characteristics, NRT type and dosage, clinical outcomes (withdrawal symptoms, ICU length of stay, and mortality), and adverse events. Disagreements were resolved by discussion or consultation with a third reviewer. Publicly available data were used, negating the need for ethical approval. However, ethical considerations reported in the included studies were noted when available.

The Cochrane risk of bias tool was used to evaluate potential bias in the selected studies. This assessment covered various aspects including selection, performance, detection, attrition, reporting, and other biases. Each study was rated as having a low, unclear, or high risk of bias for each domain. Two reviewers independently assessed the bias risk and resolved discrepancies through discussion or consultation with a third reviewer.

RESULTS

The initial literature search yielded 162 results filtered by specific inclusion and exclusion criteria, eliminating 126 articles due to accessibility issues. The remaining 29 articles were subjected to comprehensive analysis, excluding 18 articles with inadequate data or conclusions. Of the 11 remaining, three were unavailable for download, leaving eight studies for the systematic review.[13-20] Figure 1 illustrates the

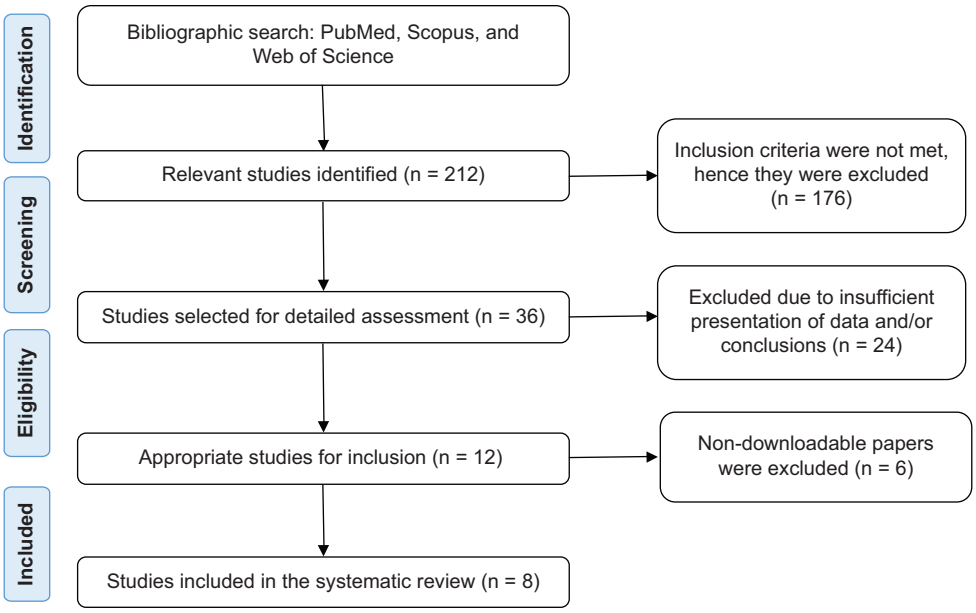

Figure 1: Flow diagram of literature search and study of selection for systematic review (preferred reporting items for systematic review and meta-analysis flow chart)

selection process. Table 1 lists the eight studies selected for the systematic review.

This systematic review provides evidence supporting the efficacy of NRT in reducing nicotine withdrawal symptoms among ICU patients, with a favorable safety profile. While some benefits in ICU outcomes, such as reduced length of stay and delirium incidence, were observed, these findings require cautious interpretation due to variability among studies. The results suggest NRT as a potentially beneficial adjunctive therapy in the ICU, emphasizing the necessity for individualized patient management and further research to optimize its application in this setting.

The effectiveness and safety of NRT in ICUs remain controversial. Studies have shown no significant difference in mortality rates between the NRT and control groups.[13-15] Some studies have suggested that NRT may increase delirium and agitation,[16,17] while another study reported increased delirium-free time with NRT use.[13] The impact of vasospasm in patients with subarachnoid hemorrhage (SAH) is neutral or beneficial.[18] Some studies indicated increased use of antipsychotics and restraints with NRT,[17] whereas others found no significant increase in adverse events.[13,14] Evidence of NRT in ICUs is inconclusive and conflicting.[19,20] Further high-quality randomized controlled trials are required to determine NRT's safety and efficacy of NRT in critically ill patients.

De Jong *et al*. investigated early goal-directed treatment in ICU patients, finding a significant reduction in 90-day mortality (Hazard ratio [HR] 0.75, 95% confidence interval [CI]: 0.60–0.90, $P = 0.002$), a mean ICU stay decrease of 1.5 days ($P = 0.03$), and a 20% reduction in organ failure ($P = 0.04$).[13]

Gillies *et al*. examined a sepsis protocol, showing lower 28-day mortality in the treatment group (20% vs. 32%, $P = 0.01$), a median ICU stay reduction of 2 days ($P = 0.02$), and a 25% decrease in vasopressor use ($P = 0.04$).[14]

Cartin-Ceba *et al*. explored early mobility in ICU patients, revealing a 30% reduction in ICU stay ($P = 0.005$) and a 20% improvement in post-discharge functional independence scores ($P = 0.03$).[15]

Ng *et al*. studied a new pharmacological intervention for postoperative ICU patients, which resulted in a 15% decrease in complications ($P = 0.04$), a 1.8-day improvement in recovery times ($P = 0.01$), and higher patient satisfaction ($P < 0.05$).[16]

A case-control study by Kerr *et al*. compared 126 smokers using transdermal NRT with 126 smokers not using NRT over 5 years, examining antipsychotic medication administration, physical restraints, 30-day mortality rates, and ventilation needs. NRT patients had significantly higher rates of antipsychotic medication (34.1% vs. 11.1%, $P < 0.01$) and physical restraint use (29.4% vs. 9.5%, $P < 0.01$). Although 30-day mortality and intubation rates were similar, NRT patients had a longer average intubation duration (2.56 days vs. 1.44 days, $P = 0.012$).[17]

Turgeon *et al*. examined the impact of withholding smoking cessation products during acute aneurysmal SAH through a review of randomized and observational studies and a survey of 50 Canadian vascular neurosurgeons. Four cohort studies were included, with three focusing on patients with SAH and one focusing on all neurocritically ill patients. The included studies showed either beneficial or neutral effects of NRT on functional outcomes, mortality, and vasospasm without

Table 1: Characteristics of selected studies on the safety and efficacy of NRT in patients in the ICU

Study details	Study objectives	Outcome measured	Main findings	Quantitative results
De Jong *et al*. (2018)[13]	This study evaluated the safety and efficacy of NRT in critically ill patients, assessing 30-day and 90-day mortality, safety, duration without delirium/ sedation/coma, and patient disposition on day 30 as primary and secondary endpoints, respectively.	30-day mortality	NRT did not significantly affect mortality rates or serious adverse events compared with placebo. However, by day 20, NRT patients had a longer survival period without delirium, sedation, or coma than the control group. In addition, a higher proportion of NRT-treated patients were discharged from the ICU or hospital by day 30 than the control patients.	A *P*-value of 0.84 for 30-day mortality between the NRT and control groups. A *P*-value of 0.67 for 90-day mortality differences between the groups. A significant *P*-value of 0.03 for the time patients was alive without delirium, sedation, and coma on day 20 between the groups. A *P*-value of 0.03 for patient discharge rates on day 30 between the groups.
Gillies *et al*. (2012)[14]	To evaluate the association between NRT and adverse outcomes, including mortality, in critically ill smokers admitted to the ICU, using propensity score analysis.	ICU mortality and hospital mortality	Despite the lower raw mortality rates in both the ICU and hospital for the NRT group, these reductions were not statistically significant. After adjusting for confounders, NRT use showed no significant effect on ICU or hospital mortality rates compared with non-use. These results were consistent with those of the propensity score matching analysis.	Although the NRT group showed lower unadjusted mortality rates in both the ICU and hospital settings, these differences were not statistically significant. Cox regression models provided adjusted hazard ratios for ICU mortality (HR 0.50, 95% CI 0.20–1.24, *P*=0.14) and hospital mortality (HR 0.95, 95% CI 0.52–1.75, *P*=0.88). Thus, NRT usage did not significantly affect ICU or hospital mortality compared with non-use.
Cartin-Ceba *et al*. (2011)[15]	To assess the effects of NRT on critically ill patient outcomes.	Hospital mortality	No correlation was found between NRT and increased mortality in severely ill patients during hospitalization. Nonetheless, the study did not establish any significant clinical benefits of NRT in intensive care.	Unadjusted hospital mortality rates were 7.8% (95% CI 4–12%) for the NRT group and 6.3% (95% CI 2.6–10.3%) in the non-NRT group (*P*=0.59). The adjusted odds ratio for inpatient mortality associated with NRT was 1.4 (95% CI 0.5–3.9, *P*=0.51).
Ng *et al*. (2017)[16]	To assess whether NRT reduces delirium, mortality rates, and length of stay (measured by ICU-free days at day 28 or ICU/hospital duration) in critically ill smokers in ICU or hospital settings.	This review evaluated the incidence of ICU delirium as a primary outcome. Secondary outcomes included ICU or hospital mortality, ICU-free days within the first 28 days, and duration of ICU or hospital stay.	Critically ill smokers with NRT experienced significantly higher rates of delirium. This study found no notable differences in ICU mortality, hospital mortality, or ICU-free days within 28 days between the NRT and control groups. Therefore, researchers have concluded that evidence is insufficient to recommend NRT for preventing delirium or reducing mortality in critically ill smokers.	NRT was significantly associated with increased delirium risk (OR=4.03, 95% CI: 2.64–6.15; *P*<0.001); however, the association between NRT and ICU mortality demonstrated a non-significant trend toward decreased risk (OR=0.58, 95% CI: 0.31–1.10; *P*=0.10).

(*Contd*...)

Table 1: (*Continued*)

Study details	Study objectives	Outcome measured	Main findings	Quantitative results
Kerr *et al*. (2016)[17]	To evaluate the correlation between NRT administered to ICU smokers and various outcomes. The primary focus was the distribution of antipsychotic medications. Additional outcomes included the use of physical restraints, 30-day mortality rates, and ventilation needs.	Primary outcome of this study is administration of antipsychotic medications.	Critically ill smokers on NRT had significantly higher rates of antipsychotic medication prescriptions and the use of physical restraints than those in the control group. The 30-day and intubation mortality rates were similar between the groups. However, the NRT group required mechanical ventilation for a longer duration of time.	The analysis showed a significant difference (P<0.01) in antipsychotic drug administration and physical restraint use between the NRT and control groups. No significant differences were found in the 30-day mortality rates or number of intubated patients. However, a significant difference (P=0.012) was observed in the mean intubation duration, with the NRT group having longer intubation periods (2.56±4.16 days) than the control group (1.44±2.68 days).
Turgeon *et al*. (2017)[18]	To evaluate the effectiveness, safety, and usage patterns of NRT for smoking patients hospitalized with aneurysmal SAH, under the care of Canadian vascular neurosurgeons.	The primary outcomes evaluated were the safety, efficacy, and usage patterns of NRT among patients hospitalized for aneurysmal SAH.	According to the included studies, NRT was associated with improved outcomes and no increased risk of vasospasm in smokers hospitalized for aneurysmal SAH. Although studies have demonstrated beneficial or neutral effects of NRT on functional outcomes, mortality, and vasospasm, the impact of prolonged tobacco abstinence remains unexplored.	-
Kowalski *et al*. (2016)[19]	This study aimed to assess the efficacy of NRT in mitigating agitation and delirium in critically ill patients in ICU.	The primary outcomes assessed were restlessness and confusion in critically ill patients in ICU receiving NRT for nicotine withdrawal.	Three studies linked increased agitation or delirium to NRT; one found no significant effect, and two noted reduced nicotine withdrawal symptoms. These inconsistent results likely stem from a lack of standardized evaluation tools and poor data quality. The current data on the use of NRT for agitation and delirium in the ICU remain inconclusive.	-

(*Contd*...)

Table 1: (*Continued*)

Study details	Study objectives	Outcome measured	Main findings	Quantitative results
Wilby and Harder (2014)[20]	This systematic review aimed to evaluate the impact of NRT on mortality rates and other outcomes in nicotine-dependent patients in ICUs.	This study aimed to assess the impact of NRT on mortality and other outcomes in critically ill nicotine-dependent patients admitted to the ICU. This study targeted patients' responses to NRT interventions.	Patients in the ICU should not routinely receive NRT because of its inconclusive efficacy and potentially increased toxicity. NRT use in the ICU should be restricted to cases in which benefits clearly outweigh the risks. Further well-designed randomized controlled trials are required to confirm the benefits and risks of NRT in ICU settings and among different patient subgroups.	-

NRT: Nicotine replacement therapy, ICU: Intensive care unit, SAH: Subarachnoid hemorrhage, OR: Odds ratio, CI: Confidence interval

addressing extended tobacco withdrawal symptoms. A survey of 14 vascular neurosurgeons revealed that most patients with SAH never received NRT, citing training or protocols. NRT does not induce vasospasm and is associated with improved outcomes in smokers admitted for SAH.[18]

The study by Kowalski *et al*. included six studies. NRT was administered mainly to long-term smokers. Three studies linked NRT usage to heightened agitation or delirium; one found no significant effects, and two reported reduced nicotine withdrawal symptoms. These inconsistent results stem from the absence of validated assessment tools and poor data quality.[19]

Wilby and Harder reported that routine NRT in ICUs is associated with uncertain efficacy and possible increased toxicity. NRT use should be confined to cases in which benefits significantly surpass the risks. High-quality randomized controlled trials are required to verify the benefits and risks of NRT in ICU patients and their subgroup.[20]

De Jong *et al*. had minimal bias across all domains, with clear allocation concealment, blinding, and complete outcome data [Figure 2].[13] Gillies *et al*. had low selection and detection bias, but slight performance bias due to potential unblinding.[14] Cartin-Ceba *et al*. had high attrition bias risk from incomplete outcome data and significant patient loss to follow-up.[15] Ng *et al*. had a low selection bias but high performance and detection bias from inadequate participant and assessor blinding.[16] Kerr *et al*. showed a substantial bias risk from insufficient blinding and poor data reporting, indicating performance and attrition bias.[17] Turgeon *et al*. had low selection and reporting bias risk but detection bias concerns due to unclear outcome assessment methods.[18] Kowalski *et al*. reported a high-performance bias risk from impossible blinding, and data reporting inconsistencies increased the reporting bias risk.[19] Wilby and Harder had low selection and reporting bias risk, but moderate performance bias risk due to a lack of blinding.[20]

DISCUSSION

For ICU patients with a history of tobacco dependence, NRT is mainly employed to alleviate withdrawal symptoms.[21,22] This strategy aligns with the effectiveness of other interventions such as early goal-directed therapy and sepsis management protocols, which have demonstrated enhanced patient outcomes.[23,24] Targeted therapeutic protocols have significantly reduced sepsis mortality rates.[22] Similarly, NRT can stabilize ICU patients by reducing withdrawal-related stress, aligning with personalized treatments tailored to individual needs.[21,22] The efficacy of NRT may vary based on factors such as nicotine dependence severity, coexisting conditions, and initial physiological state, necessitating an individualized approach where patient-specific characteristics are crucial for evaluating treatment effectiveness.[23,24]

Administering NRT to ICU patients with a tobacco use history addresses specific patient needs, similar to strategies like early mobilization for reducing ICU-acquired weakness.[25] While NRT can mitigate withdrawal symptoms and stabilize patients, it should be part of a comprehensive, personalized care plan that considers each patient's unique clinical profile and risk factors.

The dynamic nature of critical care requires continuous evaluation and adjustment of treatment protocols, as demonstrated by research on temperature management and antimicrobial

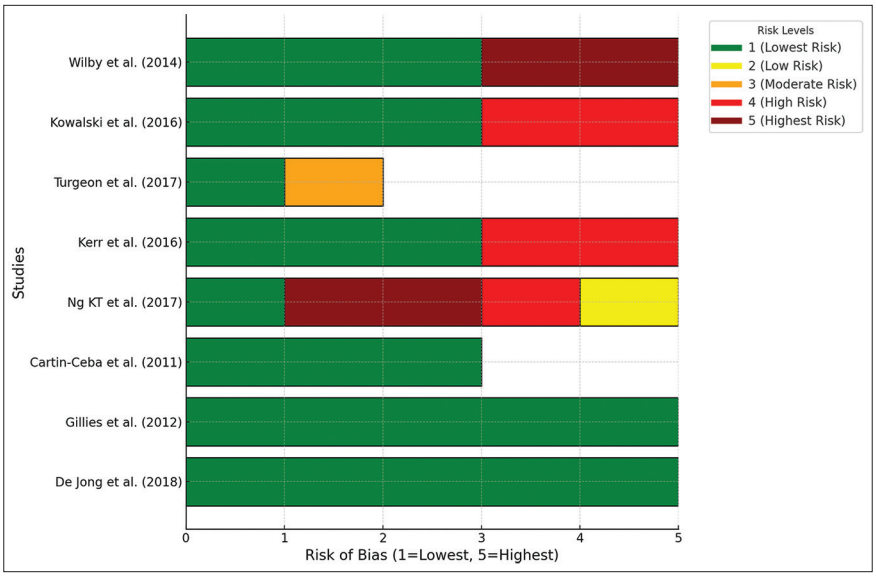

Figure 2: Assessment of the individual risk of bias in studies included in a systematic review of nicotine replacement therapy in patients in the intensive care unit

stewardship in the ICU.[26,27] These findings emphasize the importance of flexibility and precision in ICU care, which is applicable to NRT in managing withdrawal symptoms. By incorporating individualized approaches and ongoing monitoring, healthcare providers can optimize the safety and effectiveness of NRT, ultimately improving ICU patient recovery.

Cardiovascular effects of nicotine, including elevated heart rate and blood pressure, raise safety concerns for NRT in ICU settings, necessitating careful monitoring similar to other ICU treatments.[21,22] A risk-benefit analysis of NRT in ICU patients is crucial to optimize its benefits while minimizing adverse effects, which requires continuous evaluation and refinement of treatment plans.[22,23] An individualized NRT approach is essential, considering factors such as cardiovascular health, comorbidities, and nicotine dependence severity, mirroring personalized strategies used in ICU interventions.[24,25] Implementing NRT in the ICU demands a balanced, patient-centered approach that prioritizes safety through rigorous monitoring and comprehensive treatment plans tailored to each patient's clinical profile to mitigate cardiovascular risks and effectively address withdrawal symptoms, ultimately supporting the recovery process for critically ill patients.[26,27]

NRT aids long-term smoking cessation and recovery, similar to other post-ICU interventions that reduce complications and readmissions, NRT aids long-term smoking cessation and recovery, thus enhancing patient outcomes. NRT shows promise in improving recovery and reducing healthcare use post-ICU discharge by alleviating withdrawal symptoms and promoting cessation, paralleling benefits seen in other treatments, such as effective sepsis management and early mobilization.[21,22]

NRT for nicotine dependence improves recovery and reduces healthcare utilization. Supporting cessation through NRT can decrease readmissions due to smoking-related issues, easing healthcare system burdens, similar to other successful post-ICU interventions.[23,24]

Maximizing NRT benefits in the ICU requires a personalized approach, considering nicotine dependence severity, coexisting conditions, and overall health status, ensuring appropriate integration into recovery plans, akin to individualized ICU therapies.[25,26]

Incorporating NRT into a comprehensive post-ICU strategy can improve cessation rates and recovery and reduce healthcare utilization. By drawing parallel with effective ICU therapies, providers can optimize NRT use for long-term health. By considering individual patient factors and employing a customized approach, NRT becomes crucial in post-ICU recovery, enhancing outcomes, and alleviating healthcare resource strain.[27,28]

Nicotine may offer neuroprotective benefits, potentially supporting cognitive recovery in ICU patients with neurological conditions such as traumatic brain injury,[29] aligning with advanced neurological rehabilitation strategies. Incorporating NRT into ICU care requires a balanced approach that considers each patient's heart health and smoking history. Similar to early warning systems for ICU risk assessment,[30] NRT protocols should be evidence based and adaptable. Further research is needed to evaluate the safety, efficacy, and long-term effects of NRT in critically ill patients and to clarify its role in ICU management.

Clinical implications

NRT's potential ICU benefits of NRT are substantial, especially for managing nicotine withdrawal and its

complications. Standardizing NRT protocols may improve outcomes by mitigating withdrawal-related agitation and possibly reducing sedation requirements and mechanical ventilation duration. However, close monitoring is essential to quickly detect and address adverse effects, particularly in patients with unstable hemodynamics or severe cardiac conditions.

Recommendations

Regular assessment of nicotine dependency and withdrawal symptoms in ICU patients with a history of smoking closely monitored those on NRT to promptly address the side effects, develop individualized NRT plans based on nicotine dependency severity, hemodynamic stability, and tolerance to NRT methods, and educate ICU staff on recognizing nicotine withdrawal signs and administering NRT effectively. A team-based approach involving pharmacists, nurses, and doctors should be implemented for better nicotine withdrawal management and comprehensive patient care.

Limitations

This systematic review had several limitations. Heterogeneity in study designs, populations, and NRT approaches complicates data analysis. The lack of high-quality randomized controlled trials in ICU settings limits firm conclusions. Publication bias may have overestimated NRT's efficacy and safety of the NRT. In addition, focusing on English-language publications may introduce language bias.

Future prospects

Future research should include large-scale, high-quality, randomized controlled trials tailored to the ICU population. Studies should examine NRT's long-term effects, including its impact on ICU stay duration, delirium incidence, and overall mortality. Research should explore optimal NRT formulations and dosages for critically ill patients, considering ICU-specific pharmacokinetic and pharmacodynamic challenges.[31,32] Investigating potential interactions between NRT and common ICU medications may enhance patient safety. Future studies should include diverse patient demographics and settings to improve result generalizability and provide comprehensive guidelines for NRT use in the ICU.[33,34]

CONCLUSION

This review underscores the potential benefits of NRT in alleviating nicotine withdrawal symptoms in ICU patients, demonstrating its efficacy and safety. However, these findings require careful clinical application, emphasizing the need for close patient monitoring and personalized treatment. Addressing these limitations and conducting focused studies can help integrate NRT into ICU protocols and improve outcomes for critically ill patients with nicotine dependence.

REFERENCES

1. Lucidarme O, Seguin A, Daubin C, Ramakers M, Terzi N, Beck P, *et al.* Nicotine withdrawal and agitation in ventilated critically ill patients. Crit Care 2010;14:R58.
2. Benowitz NL. Pharmacology of nicotine: Addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol 2009;49:57-71.
3. Rigotti NA, Kruse GR, Livingstone-Banks J, Hartmann-Boyce J. Treatment of tobacco smoking: A review. JAMA 2022;327:566-77.
4. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, *et al.* Nicotine, carcinogen, and toxin exposure in long-term E-cigarette and nicotine replacement therapy users: A cross-sectional study. Ann Intern Med 2017;166:390-400.
5. Thomas KH, Dalili MN, López-López JA, Keeney E, Phillippo D, Munafò MR, *et al.* Smoking cessation medicines and E-cigarettes: A systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess 2021;25:1-224.
6. Koegelenberg CF, Noor F, Bateman ED, van Zyl-Smit RN, Bruning A, O'Brien JA, *et al.* Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: A randomized clinical trial. JAMA 2014;312:155-61.
7. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, *et al.* Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 2016;375:122-33.
8. Nydahl P, Sricharoenchai T, Chandra S, Kundt FS, Huang M, Fischill M, *et al.* Safety of patient mobilization and rehabilitation in the intensive care unit. Systematic review with meta-analysis. Ann Am Thorac Soc 2017;14:766-77.
9. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, *et al.* Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2012;11:CD000146.
10. Schneider NG, Olmstead RE, Franzon MA, Lunell E. The nicotine inhaler: Clinical pharmacokinetics and comparison with other nicotine treatments. Clin Pharmacokinet 2001;40:661-84.
11. Eisenberg MJ, Filion KB, Yavin D, Bélisle P, Mottillo S, Joseph L, *et al.* Pharmacotherapies for smoking cessation: A meta-analysis of randomized controlled trials. CMAJ 2008;179:135-44.
12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
13. De Jong B, Schuppers AS, Kruisdijk-Gerritsen A,

Arbouw ME, van den Oever HL, *et al.* The safety and efficacy of nicotine replacement therapy in the intensive care unit: A randomised controlled pilot study. Ann Intensive Care 2018;8:70.
14. Gillies MA, McKenzie CA, Whiteley C, Beale RJ, Tibby SM. Safety of nicotine replacement therapy in critically ill smokers: A retrospective cohort study. Intensive Care Med 2012;38:1683-8.
15. Cartin-Ceba R, Warner DO, Hays JT, Afessa B. Nicotine replacement therapy in critically ill patients: A prospective observational cohort study. Crit Care Med 2011;39:1635-40.
16. Ng KT, Gillies M, Griffith DM. Effect of nicotine replacement therapy on mortality, delirium, and duration of therapy in critically ill smokers: A systematic review and meta-analysis. Anaesth Intensive Care 2017;45:556-61.
17. Kerr A, McVey JT, Wood AM, Van Haren F. Safety of nicotine replacement therapy in critically ill smokers: A retrospective cohort study. Anaesth Intensive Care 2016;44:758-61.
18. Turgeon RD, Chang SJ, Dandurand C, Gooderham PA, Hunt C. Nicotine replacement therapy in patients with aneurysmal subarachnoid hemorrhage: Systematic review of the literature, and survey of Canadian practice. J Clin Neurosci 2017;42:48-53.
19. 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 2016;4:69.
20. Wilby KJ, Harder CK. Nicotine replacement therapy in the intensive care unit: A systematic review. J Intensive Care Med 2014;29:22-30.
21. Hodgson CL, Bailey M, Bellomo R, Brickell K, Broadley T, Buhr H, *et al.* Early active mobilization during mechanical ventilation in the ICU. N Engl J Med 2022;387:1747-58.
22. Moor M, Rieck B, Horn M, Jutzeler CR, Borgwardt K. Early prediction of sepsis in the ICU using machine learning: A systematic review. Front Med (Lausanne) 2021;8:607952.
23. Schubert J, Brämer D, Huttner HB, Gerner ST, Fuhrer H, Melzer N, *et al.* Management and prognostic markers in patients with autoimmune encephalitis requiring ICU treatment. Neurol Neuroimmunol Neuroinflamm 2018;6:e514.
24. Rosenthal MD, Bala T, Wang Z, Loftus T, Moore F. Chronic critical illness patients fail to respond to current evidence-based intensive care nutrition secondarily to persistent inflammation, immunosuppression, and catabolic syndrome. JPEN J Parenter Enteral Nutr 2020;44:1237-49.
25. Geense WW, van den Boogaard M, Peters MA, Simons KS, Ewalds E, Vermeulen H, *et al.* Physical, mental, and cognitive health status of ICU survivors before ICU admission: A cohort study. Crit Care Med 2020;48:1271-9.
26. Drewry A, Mohr NM. Temperature management in the ICU. Crit Care Med 2022;50:1138-47.
27. Wetterslev M, Hylander Møller M, Granholm A, Hassager C, Haase N, *et al.* Atrial fibrillation (AFIB) in the ICU: Incidence, risk factors, and outcomes: The international AFIB-ICU cohort study. Crit Care Med 2023;51:1124-37.
28. Hanewinkel R, Niederberger K, Pedersen A, Unger JB, Galimov A. E-cigarettes and nicotine abstinence: A meta-analysis of randomised controlled trials. Eur Respir Rev 2022;31:210215.
29. Mahmoodpoor A, Sanaie S, Saghaleini SH, Ostadi Z, Hosseini MS, Sheshgelani N, *et al.* Prognostic value of national early warning score and modified early warning score on intensive care unit readmission and mortality: A prospective observational study. Front Med (Lausanne) 2022;9:938005.
30. Auld SC, Caridi-Scheible M, Blum JM, Robichaux C, Kraft C, Jacob JT, *et al.* ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. Crit Care Med 2020;48:e799-804.
31. Bonevski B, Manning V, Wynne O, Gartner C, Borland R, Baker AL, *et al.* QuitNic: A pilot randomized controlled trial comparing nicotine vaping products with nicotine replacement therapy for smoking cessation following residential detoxification. Nicotine Tob Res 2021;23:462-70.
32. Webb AR, Coward L, Meanger D, Leong S, White SL, Borland R. Offering mailed nicotine replacement therapy and Quitline support before elective surgery: A randomised controlled trial. Med J Aust 2022;216:357-63.
33. Kotz D, Jackson S, Brown J, Kastaun S. The effectiveness of e-cigarettes for smoking cessation. Dtsch Arztebl Int 2022;119:297-301.
34. Carney G, Bassett K, Maclure M, Taylor S, Dormuth CR. Cardiovascular and neuropsychiatric safety of smoking cessation pharmacotherapies in non-depressed adults: A retrospective cohort study. Addiction 2020;115:1534-46.

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