

misconosciute della N-Acetilcisteina nella bronchite cronica e nella BPCO in smoking cessation.

Prof. M. Baraldo, MD
Università degli Studi di Udine

Ambulatorio Tabagismo
SOC Ist. Farmacologia Clinica
Az. Ospedaliero Universitaria Friuli Centrale

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Dichiarazione di conflitto d’interessi

Questa relazione presenta del materiale informativo sul tabagismo, proveniente da Corsi, bibliografia nazionale e internazionale, che non ha conflitto d’interessi con l’industria del tabacco ed i prodotti ad essa correlati.

N-Acetilcisteina: PK

ASSORBIMENTO: dopo somministrazione orale, preferibilmente a digiuno, (Cmax) in circa 2 ore.

METABOLISMO: **parziale de-acetilazione nel fegato** e nella **parete intestinale**, convertendosi nel **metabolita attivo Cys**, precursore del **GSH**.

DISTRIBUZIONE: legame con le proteine plasmatiche è di circa il 78%.

ELIMINAZIONE: NAC e metaboliti sono eliminati principalmente attraverso l'urina.
La Cl renale rappresenta circa il 30% della clearance totale.

emivita: circa **6.25 ore**

Clin Pharmacokinet.1991;20(2):123–34
Papi A, et al. Adv Ther 2021;38:468–78 3;
Sjödin K, et al. Biochem Pharmacol 1989;38:3981-85.

TOX: LD50 os ratti: **6000 mg/kg** vs nicotina: **0.8mg/kg** [*Antioxidants 2024, 13, 832*].

NAC: POTENZIALITA’ CONOSCIUTE

FREE RADICAL RESEARCH
2018, VOL. 52, NO. 7, 751–762
https://doi.org/10.1080/10715762.2018.1468564

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REVIEW ARTICLE

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N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why

Giancarlo Aldini[a], Alessandra Altomare[a], Giovanna Baron[a], Giulio Vistoli[a], Marina Carini[a], Luisa Borsani[b] and Francesco Sergio[c]

[a]Department of Pharmaceutical Sciences, Università degli Studi di Milano, Milan, Italy; [b]Global Medical Information, Zambon S.p.A., Bresso, Italy; [c]Global Respiratory Medical Affairs, Zambon S.p.A., Bresso, Italy

ABSTRACT

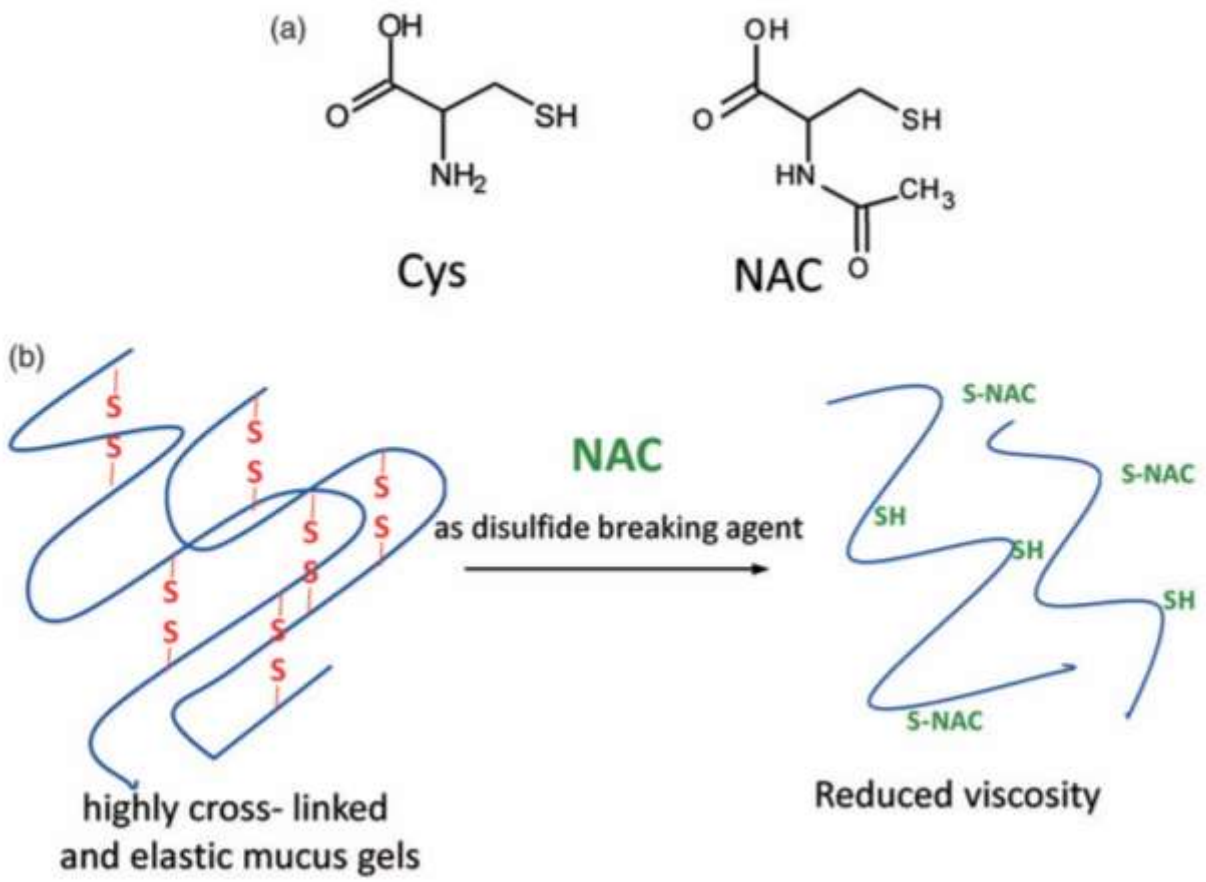
The main molecular mechanisms explaining the well-established antioxidant and reducing activity of N-acetylcysteine (NAC), the *N*-acetyl derivative of the natural amino acid L-cysteine, are summarised and critically reviewed. The antioxidant effect is due to the ability of NAC to act as a reduced glutathione (GSH) precursor; GSH is a well-known direct antioxidant and a substrate of several antioxidant enzymes. Moreover, in some conditions where a significant depletion of endogenous Cys and GSH occurs, NAC can act as a direct antioxidant for some oxidant species such as NO_2 and HOX. The antioxidant activity of NAC could also be due to its effect in breaking thiolated proteins, thus releasing free thiols as well as reduced proteins, which in some cases, such as for mercaptoalbumin, have important direct antioxidant activity. As well as being involved in the antioxidant mechanism, the disulphide breaking activity of NAC also explains its mucolytic activity which is due to its effect in reducing heavily cross-linked mucus glycoproteins. Chemical features explaining the efficient disulphide breaking activity of NAC are also explained.

ARTICLE HISTORY
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KEYWORDS
Antioxidant; disulphide breaking agent; glutathione precursor; N-acetylcysteine; oxidative stress

N-Acetilcisteina: PD

1. Fin dagli anni '60, la N-acetilcisteina (NAC), è stata ampiamente prescritta come **agente mucolitico**.



L'azione mucolitica è dovuta alla capacità del NAC di **rompere i ponti disolfuro** nelle **glicoproteine** ad alto peso molecolare del muco, **riducendone la viscosità**

N-Acetilcisteina: PD

2. Agisce come precursore del **GLUTATIONE (GSH)** che è un dei più **potenti antiossidanti endogeni.**

Proteggendo le cellule e tessuti dallo stress ossidativo.

Dal **1980,** il NAC è stato anche proposto per il **trattamento di malattie** in cui lo **stress ossidativo** è considerato coinvolto **nell'insorgenza e nella progressione dello stato patologico .**

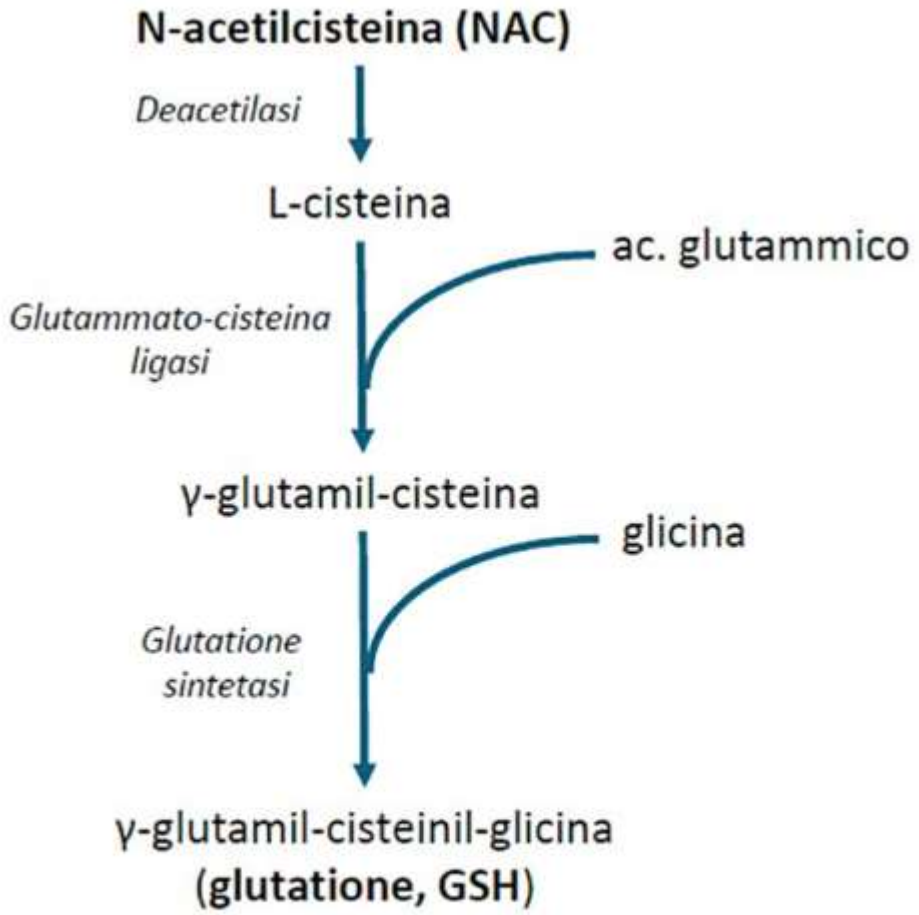


Figura 1 - Via metabolica attraverso la quale la NAC è utilizzata per la sintesi del glutatione

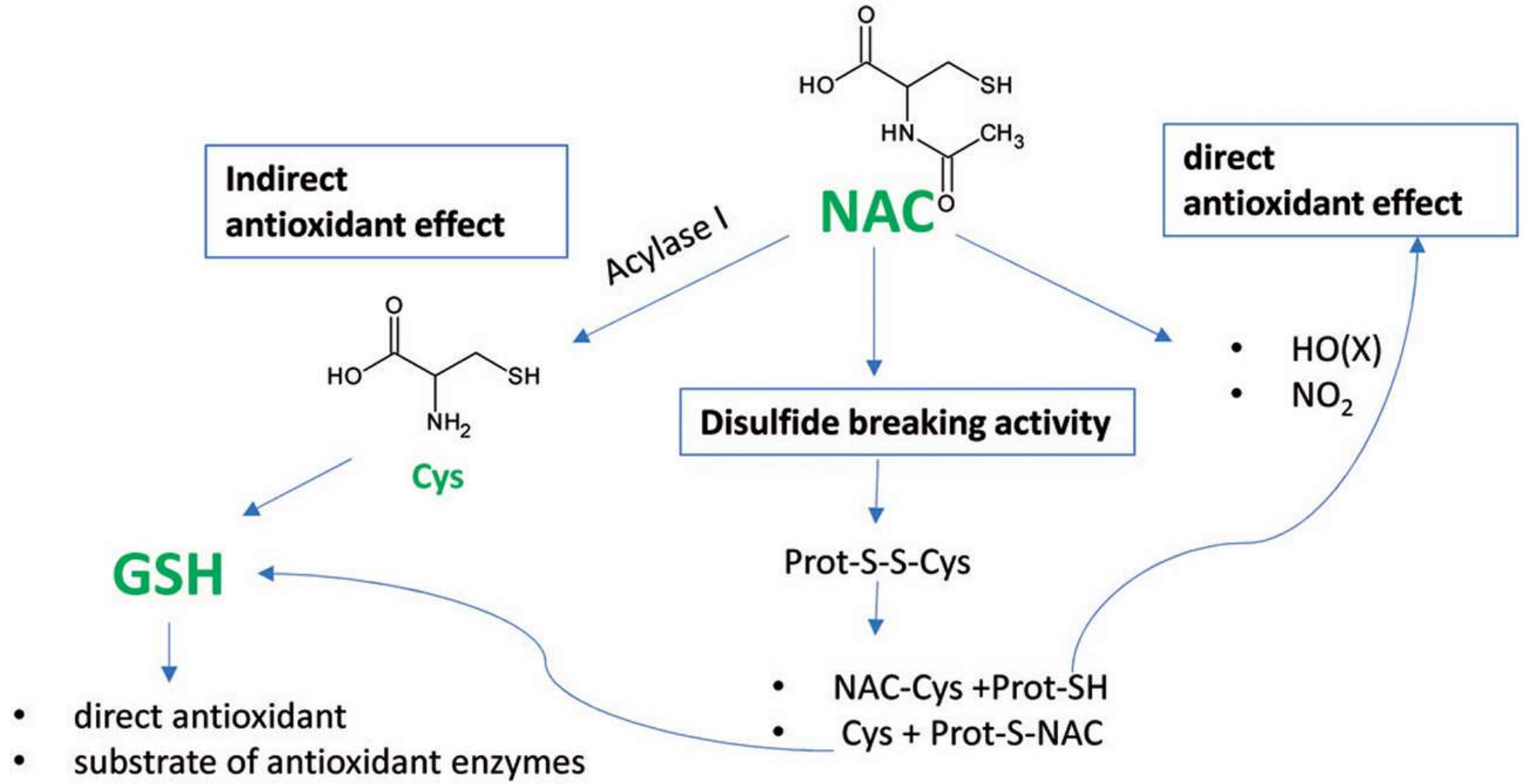


Figure 3. Overview of the antioxidant action of NAC. The antioxidant effect is due to indirect (GSH synthesis) and direct antioxidant activity, as well as disulphide breaking activity. The indirect activity refers to the ability of NAC to act as a GSH precursor, which in turn is a well-known direct antioxidant and a substrate of several antioxidant enzymes. When an oxidative stress status depletes the SH pools, NAC can act as direct scavenger of some oxidants such as NO(X) and NO_2. NAC breaks thiolated proteins thus releasing free thiols, which have a better antioxidant activity than NAC and boost the synthesis of GSH and reduced proteins, which in some cases, such as for mercaptoalbumin, have an important direct antioxidant activity.

bronchite e BPCO

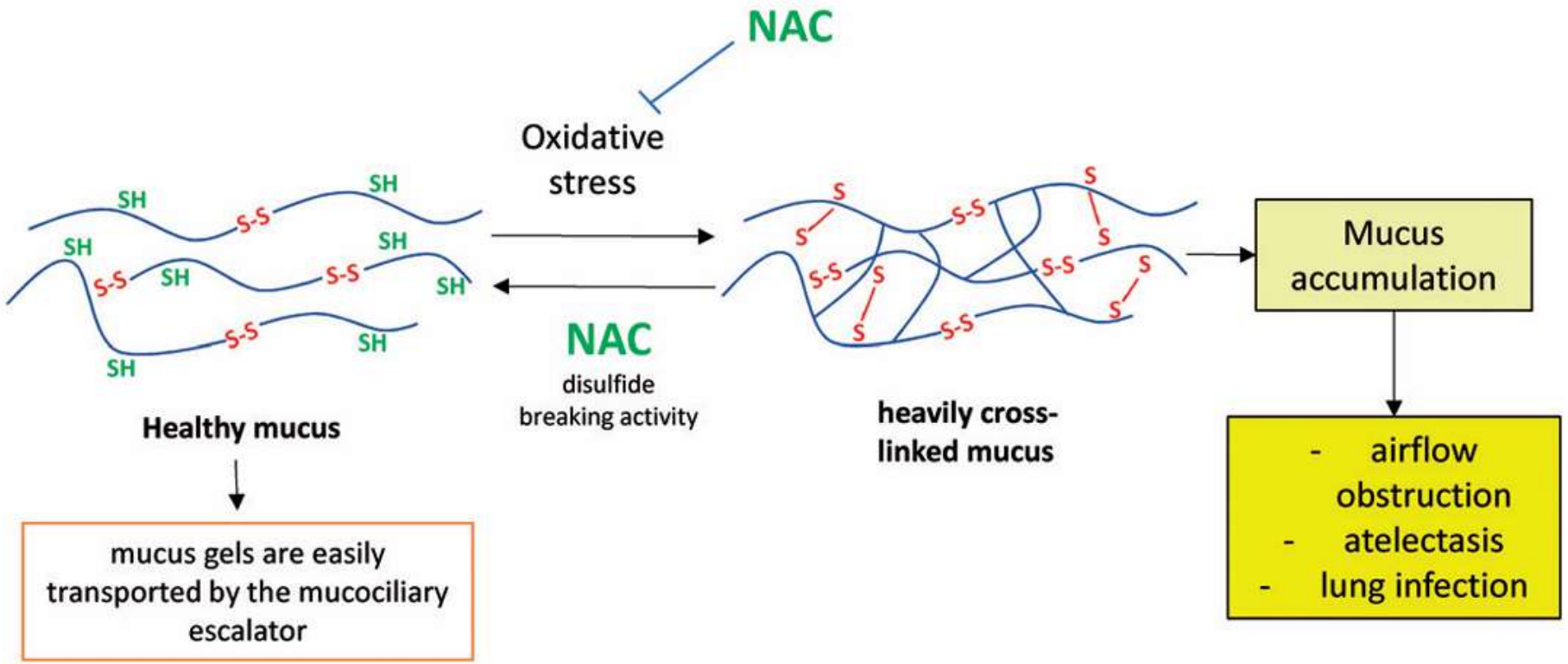


Figure 2. Antioxidant and disulphide breaking activity of NAC in lung disease characterised by an inflammatory condition. The oxidative burst causes the oxidation of internal cysteine of mucins, generating disulphide cross-links between internal cysteine domains. The resulting heavily cross-linked mucus is not easily transported and accumulates to cause airflow obstruction, atelectasis, and lung infection [24]. NAC is a mucolytic agent able to reduce the heavily cross-linked mucus. When Cys and GSH are depleted following the inflammatory condition, NAC can act as a direct antioxidant of some oxidant species such as HOX and NO_2.

N-Acetilcisteína e BPCO



Proposed Taxonomy (Etiotypes) for COPD — Figure 1.3

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

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N-acetylcysteine prevents cigarette smoke induced small airways alterations in rats

M.L. Rubio*, M.V. Sanchez-Cifuentes*, M. Ortega*, G. Peces-Barba*, J.D. Escolar**, S. Verbanck[#], M. Paiva[##], N. González Mangado*

N-*acetylcysteine prevents cigarette smoke induced small airways alterations in rats. M.L. Rubio, M.V. Sanchez-Cifuentes, M. Ortega, G. Peces-Barba, J.D. Escolar, S. Verbanck, M. Paiva, N. González Mangado.* ©*ERS Journals Ltd 2000.*

ABSTRACT: This study investigated the effect of cigarette smoke exposure and the potential protection *N*-acetylcysteine (NAC) in rat lungs.

Forty-eight rats were exposed to cigarette smoke (CS) for 10 weeks, without (CS group) or with (CS+NAC group) oral intake of NAC 200 mg·rat^{-1}·day^{-1}, or to fresh air (Control). All rat lungs were assessed in terms of lung function, ventilation distribution (nitrogen, helium and sulphur hexafluoride phase III slopes), and morphometry (airway wall thickening of small, medium and large bronchi).

The small bronchi, defined as the airways with an internal perimeter <1,000 μm showed significantly thicker airway walls in the CS than in the Control group. By contrast, no airway wall thickening was observed in the CS+NAC group with respect to Control. Except for decreased lung volumes and compliance in CS and CS+NAC groups, which were entirely attributable to smaller body weight gain, lung function was indistinguishable from Control. Phase III slopes were significantly increased only in the CS group.

In conclusion, smoke-induced alterations in the rat lungs were reflected in wall thickening of the small bronchi and increased ventilation maldistribution. These smoke-induced morphometric and ventilation distribution alterations were prevented by *N*-acetylcysteine.

Eur Respir J 2000; 15: 505–511.

*Lab. Fisiopatologá Respiratoria Experimental, Servicio de Neumologia, Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain. **Dpto. CC Morfológicas, Universidad de Medicina, Zaragoza, Spain. [#]Akademisch Ziekenhuis, Vrije Universiteit, Brussels, Belgium. [##]Biomedical Physics Lab, Université Libre de Bruxelles, Brussels, Belgium.

Correspondence: N. González Mangado, Servicio de Neumologá, Fundación Jiménez Díaz, Avda. Reyes Católicos, 2 28040-Madrid, Spain. Fax: 34 1550495.

Keywords: Cigarette smoke exposure, gas mixing, helium, *N*-acetylcysteine, rat, sulphur hexafluoride

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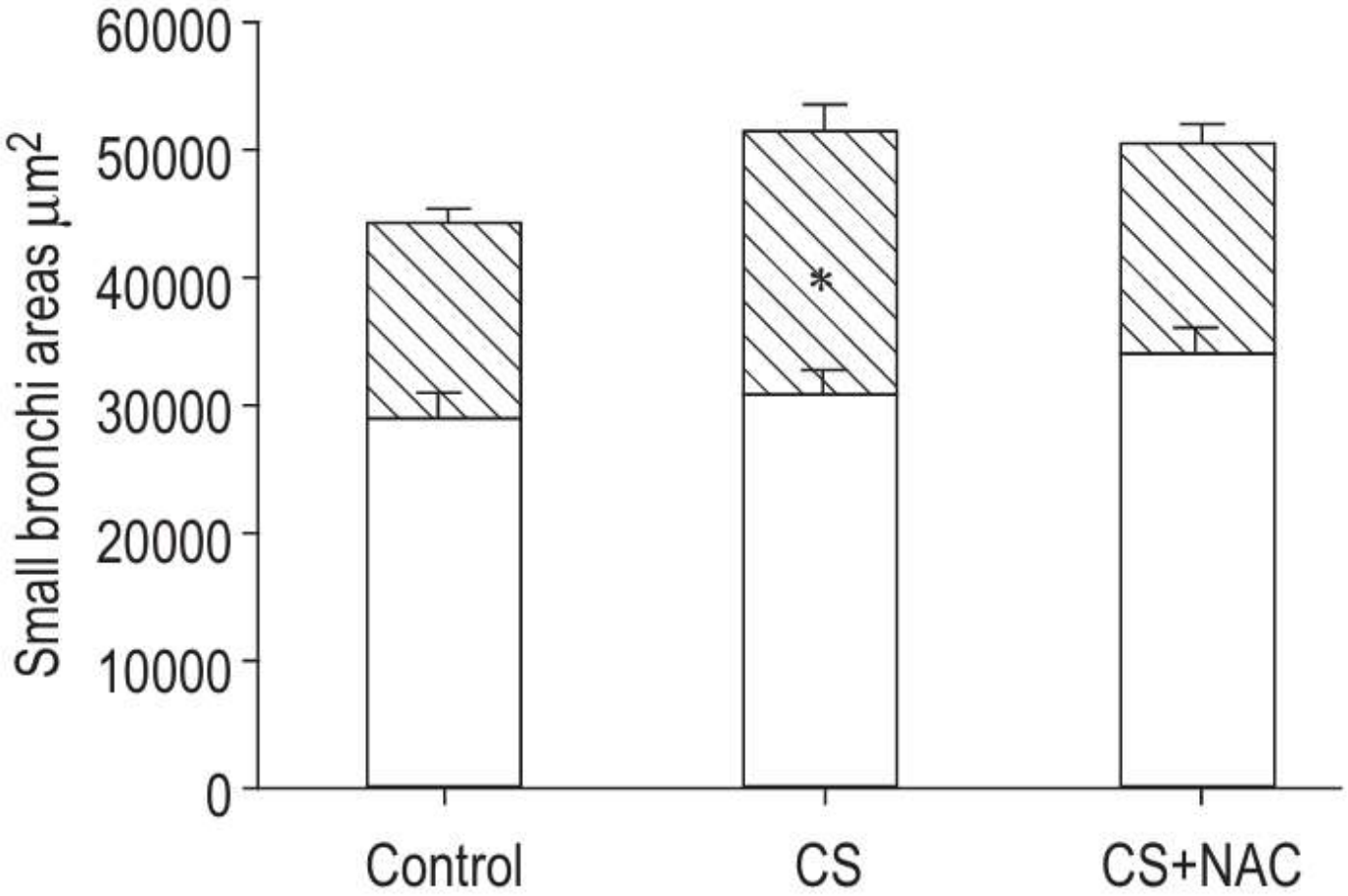


Fig. 4. – Lumen area (□; mean±SEM) and wall area (▨; mean±SEM) of small bronchi (*i.e.*, internal perimeter <1,000 µm) for the three groups under study. *: wall area of cigarette smoke (CS) group was significantly different from that of control group ($p<0.05$). NAC: *N*-acetylcysteine. All data are expressed in μm^2.

BMC Pulmonary Medicine 2004, 4:13 BioMed Central

Research article

Open Access

Randomised, controlled trial of N-acetylcysteine for treatment of acute exacerbations of chronic obstructive pulmonary disease [ISRCTN21676344]

Peter N Black*, Althea Morgan-Day, Tracey E McMillan, Phillippa J Poole and Robert P Young

High-Dose N-Acetylcysteine in Patients with Exacerbations of Chronic Obstructive Pulmonary Disease

Original Research Article | Published: 28 August 2012

Volume 25, pages 401–408 (2005) Cite this article

Il trattamento con **NAC 1200 mg/giorno** ha migliorato i marcatori biologici e gli esiti clinici nei pazienti con esacerbazioni di BPCO.

Eur Respir Rev 2015; 24: 451–461

Influence of *N*-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis

Mario Cazzola[1], Luigino Calzetta[1], Clive Page[2], Josè Jardim[3], Alexander G. Chuchalin[4], Paola Rogliani[1] and Maria Gabriella Matera[5]

1. I pazienti trattati con NAC hanno avuto significativamente e costantemente meno riacutizzazioni di bronchite cronica o BPCO
2. **NAC, a dosi elevate,** ha avuto un effetto significativo, non solo nei pazienti con bronchite cronica, ma anche in quelli con BPCO.
3. **La NAC ad alta dose è caratterizzata da un rapporto rischio-beneficio favorevole.**

nature communications (2024) 15:8468

Article https://doi.org/10.1038/s41467-024-51079-1

Effect of high-dose *N*-acetylcysteine on exacerbations and lung function in patients with mild-to-moderate COPD: a double-blind, parallel group, multicentre randomised clinical trial

1. **La differenza tra il gruppo trattato con N-acetilcisteina e il gruppo placebo** nel tasso annuale **di esacerbazioni totali non era significativa** (0,65 vs. 0,72 per paziente-anno; rischio relativo [RR], 0,90; intervallo di confidenza [IC] al 95%, 0,80–1,02; P= 0,10).
2. Non c'era una differenza significativa nel FEV1 prima dell'uso di broncodilatatori a 24 mesi.

Il trattamento a lungo termine con alte dosi di NAC non ha né ridotto significativamente il tasso annuale di esacerbazioni totali né migliorato la funzione polmonare nei pazienti con BPCO da lieve a moderata.

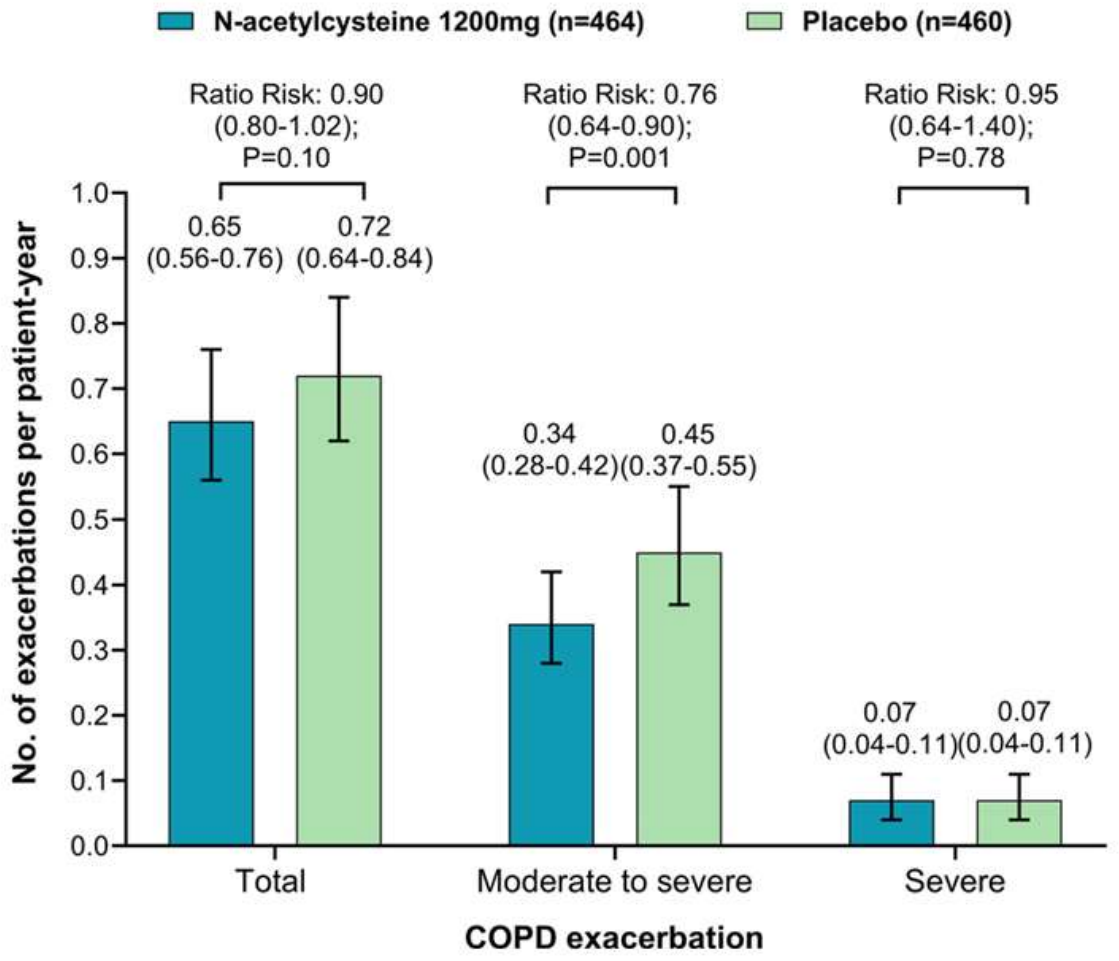


Fig. 2 | Acute exacerbation of COPD during the study (full analysis set for exacerbation). Data are mean ± standard error. COPD=chronic obstructive pulmonary disease. The relative risk was calculated using Poisson regression, with correction for exposure to the trial regimen, overdispersion, age, sex, body mass index, smoking status, COPD exacerbations in the previous year, COPD treatment at baseline and center. The error bars indicate 95% confidence intervals.

NAC: POTENZIALITA’ MISCONOSCIUTE

smoking cessation

Tabaccologia 3-2016 Review article 29

Una review della letteratura sull'uso della N-Acetil Cisteina nella prevenzione delle ricadute nel tabagismo

Quando la cura è a portata di mano

Daniel L. Amram, Vincenzo Zagà, Massimo Baraldo

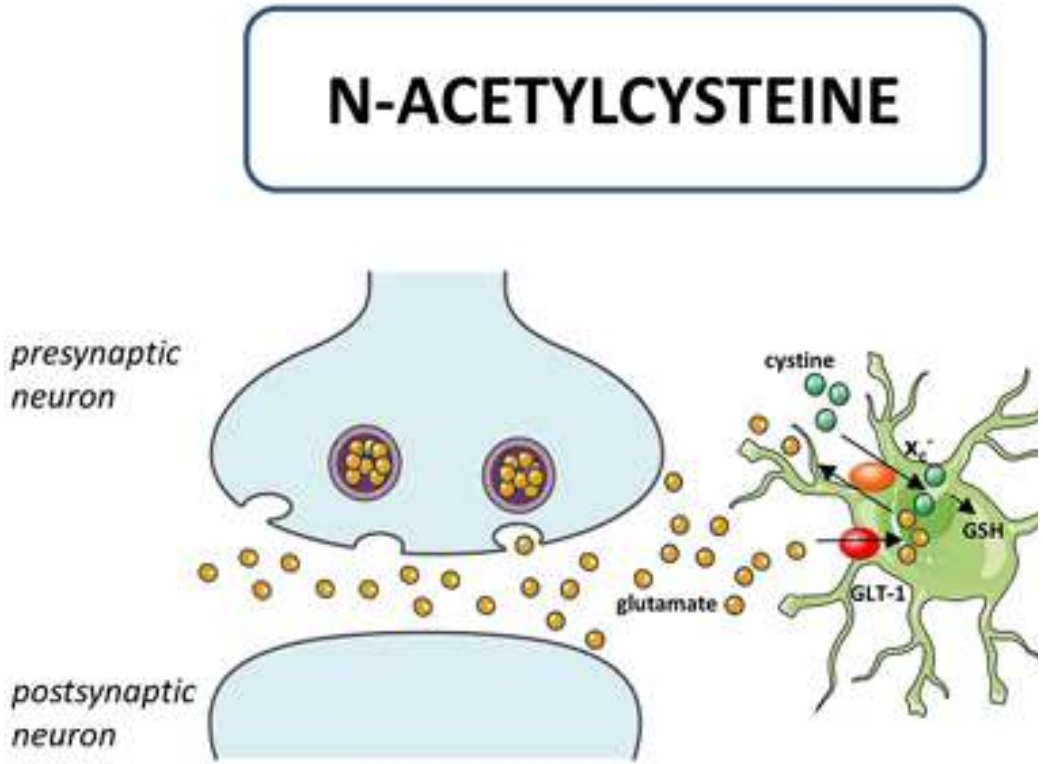
1. **ANTIOSSIDANTE DELL'ORGANISMO.**
2. **MODULA IL SISTEMA GLUTAMMATERGICO CHE REGOLA LE DIPENDENZE.**
3. **RIDUCE IL DESIDERIO ED I RISCHI DI RICADUTA NEL TABAGISMO.**

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https://doi.org/10.1007/s43440-021-00283-7

REVIEW

N-acetylcysteine in substance use disorder: a lesson from preclinical and clinical research

Irena Smaga[1] · Małgorzata Frankowska[1] · Małgorzata Filip[1]



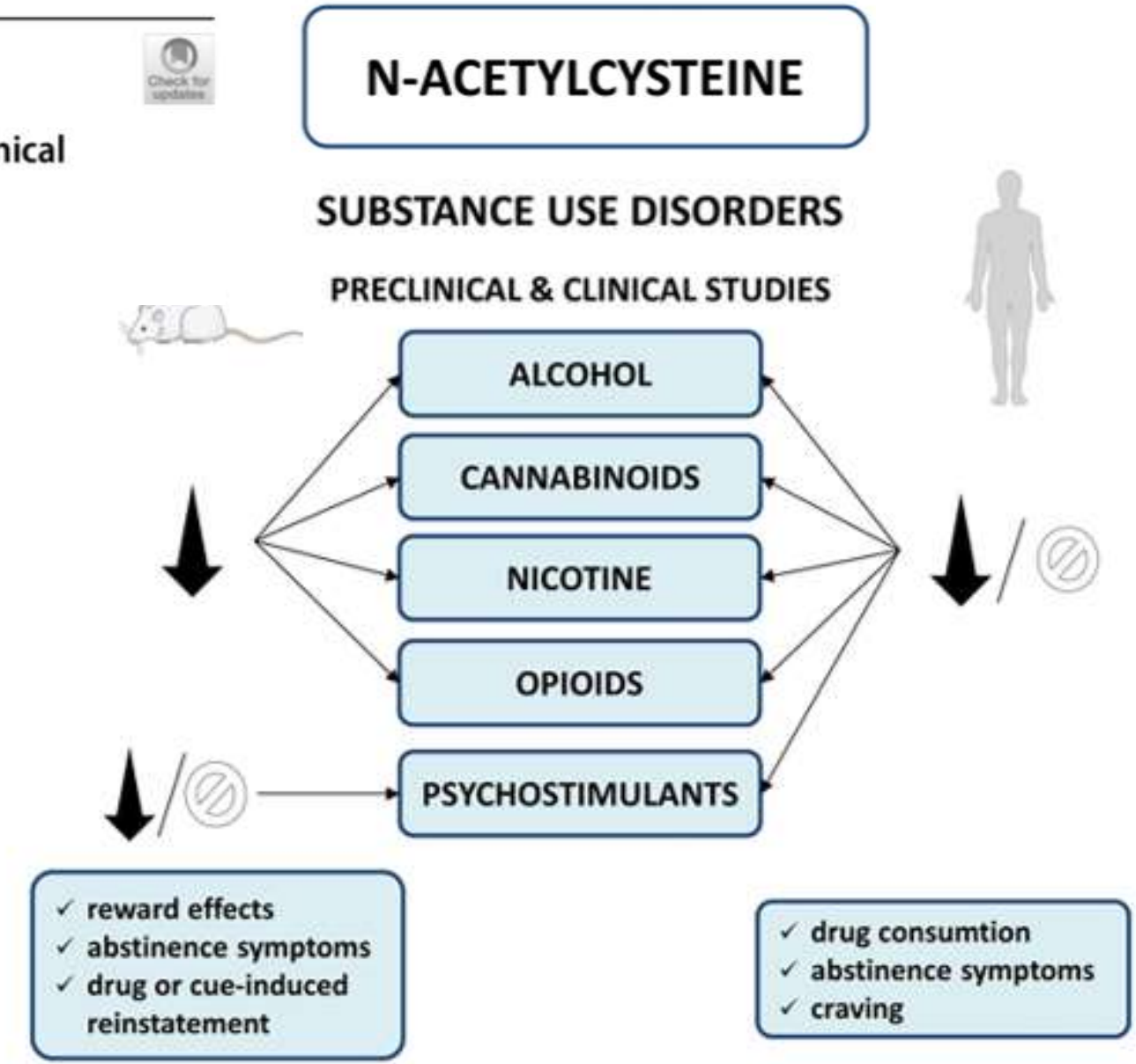


Fig. 1 Mechanism of action and summary of N-acetylcysteine effects in preclinical and clinical studies. ∅ no changed, ↓ decreased, *GLT-1* glutamate transporter 1, *GSH* glutathione, *system* x_c^- cystine/glutamate antiporter

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Biol Psychiatry. 2009 May 15; 65(10): 841–845. doi:10.1016/j.biopsych.2008.10.040.

The Role of Cystine-Glutamate Exchange in Nicotine Dependence in Rats and Humans

Lori A. Knackstedt[1,*], **Steven LaRowe**[2,*], **Pascale Mardikian**[2], **Robert Malcolm**[2], **Himanshu Upadhyaya**[2], **Sarra Hedden**[2], **Athina Markou**[3], and **Peter W Kalivas**[1]

[1] Department of Neurosciences, Medical University of South Carolina, Charleston

[2] Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston

[3] Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, CA 92093-0603

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An open-label pilot trial of *N*-acetylcysteine and varenicline in adult cigarette smokers

Erin A. McClure, Ph.D.[1], **Nathaniel L. Baker, M.S.**[2], **Cassandra D. Gipson, Ph.D.**[3], **Matthew J. Carpenter, Ph.D.**[1], **Amanda P. Roper, M.D.**[1], **Brett E. Froeliger, Ph.D.**[3], **Peter W. Kalivas, Ph.D.**[3], and **Kevin M. Gray, M.D.**[1]

[1] Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina

[2] Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina

[3] Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina

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The effects of *N*-Acetylcysteine on frontostriatal resting-state functional connectivity, withdrawal symptoms and smoking abstinence: A double-blind, placebo-controlled fMRI pilot study*

B. Froeliger[1,2,**], **P.A. McConnell**[1], **N. Stankeviciute**[1], **E.A. McClure**[3], **P.W. Kalivas**[1], and **K.M. Gray**[3]

[1]Department of Neuroscience, Medical University of South Carolina

[2]Hollings Cancer Center, Medical University of South Carolina

[3]Department of Psychiatry, Medical University of South Carolina

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Brazilian Psychiatric Association

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ORIGINAL ARTICLE

N-acetylcysteine as an adjunctive treatment for smoking cessation: a randomized clinical trial

Regina C.B.R. **Machado**,[1,2] Heber O. **Vargas**,[1,3] Marcela M. **Baracat**,[2] Mariana R. **Urbano**,[2,4] Waldiceu A. **Verri Jr**,[2,5] Mauro **Porcu**,[1,2] Sandra O.V. **Nunes**[1,2,3]

[1]*Centro de Referência de Abordagem e Tratamento do Tabagismo, Hospital Universitário, Universidade Estadual de Londrina (UEL), Londrina, PR, Brazil.* [2]*Programa de Pós-Graduação em Ciências da Saúde, Centro de Ciências da Saúde (CCS), UEL, Londrina, PR, Brazil.* [3]*Departamento de Medicina Clínica, Unidade de Psiquiatria, Hospital Universitário, CCS, UEL, Londrina, PR, Brazil.* [4]*Departamento de Estatística, Centro de Ciências Exatas, UEL, Londrina, PR, Brazil.* [5]*Departamento de Patologia, Centro de Ciências Biológicas, UEL, Londrina, PR, Brazil.*

Arancini *et al. Trials* (2019) 20:555
https://doi.org/10.1186/s13063-019-3628-5

Trials

STUDY PROTOCOL Open Access

N-acetylcysteine for cessation of tobacco smoking: rationale and study protocol for a randomised controlled trial

Lauren Arancini[1*], Chiara C. Bortolasci[2], Seetal Dodd[1,3,4,5], Olivia M. Dean[1,3,4,6] and Michael Berk[1,3,4,5,6]

NAC potrebbe rappresentare un trattamento sicuro, nuovo ed efficace per smettere di fumare, a basso costo.

La tollerabilità e la sicurezza del NAC potrebbero avere **vantaggi in popolazioni speciali** rispetto ad altre farmacoterapie per la cessazione del fumo.

NAC potrebbe essere subito applicato nella pratica e diventare un nuovo trattamento per smettere di fumare.

NAC ha un meccanismo d'azione nell'addiction chiaramente chiarito.

smoking cessation

HHS Public Access

Author manuscript

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Evaluating *N*-acetylcysteine for early and end-of-treatment abstinence in adult cigarette smokers

Punti salienti

1. La **NAC è stata valutata per l'astinenza precoce** e **sostenuta e per la prevenzione delle ricadute**.

2. La NAC è stata sicura e ben tollerata negli adulti fumatori abituali.

3. **La NAC non ha promosso una maggiore astinenza né ha ritardato il tempo di ricaduta.**

4. **È improbabile che la NAC abbia successo come monoterapia per fumatori adulti**

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Karen K .Szumlinski,
University of California, Santa Barbara,
United States

REVIEWED BY
Steven L. Batki,
University of California, San Francisco,
United States
Terril Verplaetse,
Yale University, United States

*CORRESPONDENCE
Giuseppina Cantarella,
gcantare@unict.it

†These authors have contributed equally to this work and share senior authorship

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Effect of N-acetylcysteine on craving in substance use disorders (SUD): a meta-analysis of randomized controlled trials

Micol Cuocina[1,2†], Giuseppe Aiello[1,2†], Pierfelice Cutrufelli[3], Martina Rampello[3], Laura Rapisarda[1,2], Alessandro Rodolico[4], Giuseppina Cantarella[1*], Maria Salvina Signorelli[3] and Renato Bernardini[1,2]

[1]Department Biomedical and Biotechnological Sciences (BIOMETEC), Section of Pharmacology, University of Catania, Catania, Italy, [2]Clinical Toxicology Unit, University Hospital of Catania, Catania, Italy, [3]Psychiatry Unit, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy, [4]Technical University of Munich, TUM School of Medicine and Health, Department of Psychiatry and Psychotherapy, Munich, Germany

Conclusione: sembra che il **NAC riduca la voglia di consumo nei pazienti con SUD, ma le prove sono deboli**. Servono più studi per confermare questo risultato.

10.3389/fphar.2024.1462612

ALCOOL

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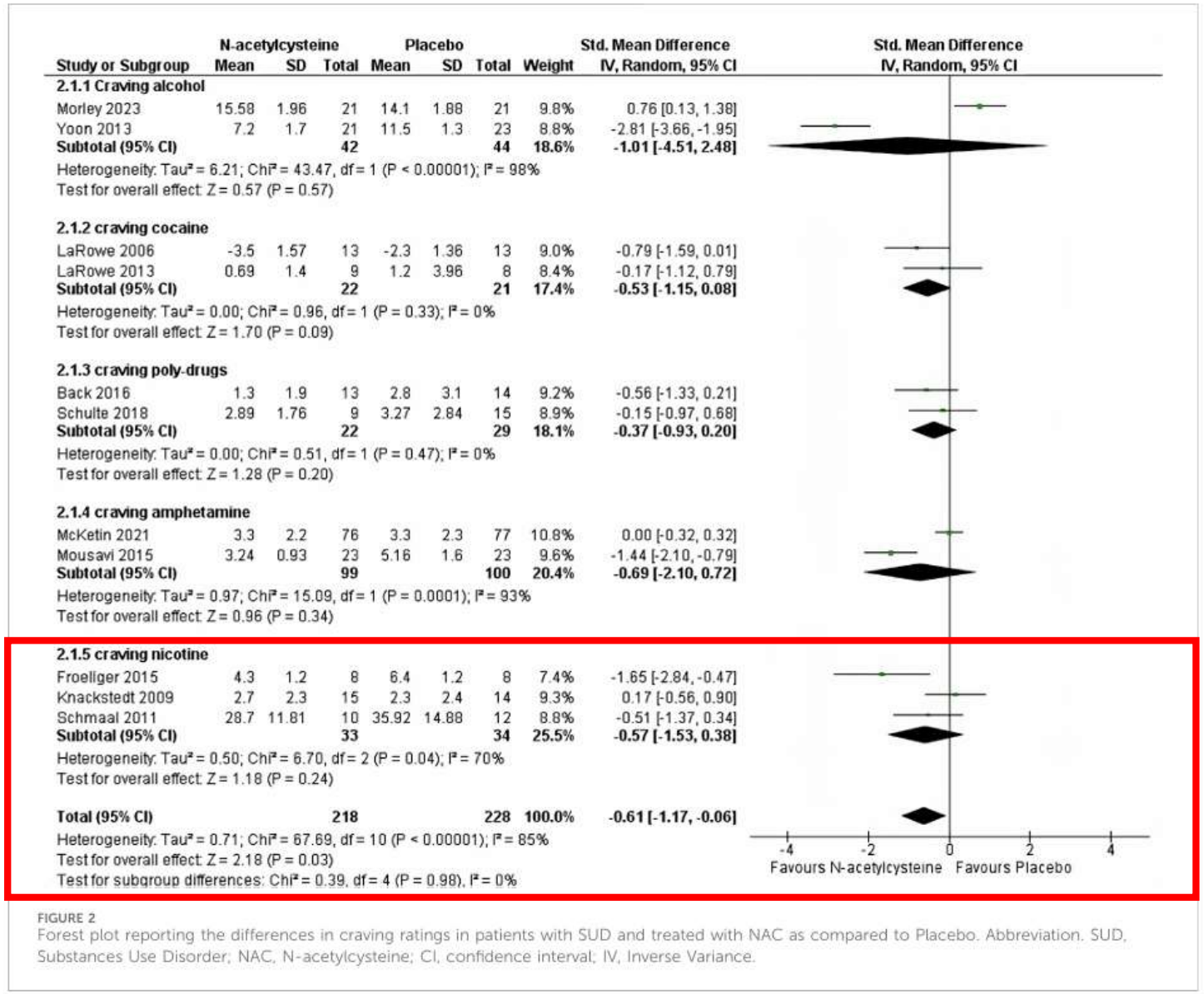


FIGURE 2
Forest plot reporting the differences in craving ratings in patients with SUD and treated with NAC as compared to Placebo. Abbreviation. SUD, Substances Use Disorder; NAC, N-acetylcysteine; CI, confidence interval; IV, Inverse Variance.

The Role of Twice-Daily N-acetylcysteine (NAC) 2400 mg in Smoking Cessation: A Randomized, Placebo-Controlled Trial in Indonesia

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Review ended 02/11/2024
Published 02/16/2024

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Annisa D. Harlivasari [1], Agus D. Susanto [1], Feni F. Taufik [1], Tribowo T. Ginting [2]

1. Pulmonology and Respiratory Medicine, Rumah Sakit Umum Pusat Persahabatan, Jakarta, IDN 2. Psychiatry, Rumah Sakit Umum Pusat Persahabatan, Jakarta, IDN

Corresponding author: Annisa D. Harlivasari, harlivasari@gmail.com

Questo studio controllato con placebo è stato condotto in Indonesia e ha mostrato che il **NAC, insieme al supporto comportamentale, è un farmaco efficace e ben tollerato per smettere di fumare.** Sono necessari **ulteriori studi randomizzati multicentrici per confermare** il tasso di astinenza sostenuto del **NAC**.

Conclusioni

1. NAC: mucolitico, antiossidante ed epatoprotettore (**conosciuto**);
2. NAC contrasta lo stress ossidativo e l'infiammazione polmonare indotta dal fumo di sigaretta (**conosciuto**);
3. NAC controlla la regolazione del glutammato: il glutammato è coinvolto nei meccanismi di dipendenza (**misconosciuto**);
4. NAC e regolazione glutammato: il glutammato diminuisce il *craving* (**misconosciuto**);
5. NAC come farmaco per smettere di fumare (**misconosciuto**);
6. NAC + trattamenti standard aiuta a ridurre il n. di sgt/die (**misconosciuto**).

Il NAC nella bronchite cronica e BPCO è un farmaco adiuvante al trattamento farmacologico e cognitivo-comportamentale.

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GRAZIE PER L'ATTENZIONE

Prof. M. Baraldo, MD

Università degli Studi di Udine

Ambulatorio Tabagismo

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