MIKOŁAJCZYK, Oskar, SUCHOŁBIAK, Aleksandra, MAŁACHOWSKI, Aleksander, SERAFIN, Aleksandra, NAJA, Katarzyna, BARAN, Karolina, ZWARDON, Jakub, SAŁATA, Julia and BRACICHOWICZ, Filip. Expanding Horizons - A Broad-Spectrum Review of Emerging Medical Applications of N-Acetylcysteine. Quality in Sport. 2025;43:62333. eISŠN 2450-3118.

https://doi.org/10.12775/QS.2025.43.62333 https://apcz.umk.pl/QS/article/view/62333

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences). Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Zalącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). The Authors 2025.
This article is published with open access under the License Open Journal Systems of Nicolaus Copernicus University in Torun, Poland. Open Access: This article is distributed under the terms of the Creative Compone Literature (Institution Naudana) and provided the original authority and process are accepted. This is no new parts and process provided the original authority and process are accepted.

Commons Attribution Noncommercial License, which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non-commercial Share Alike License (http://creativecommons.org/licenses/by-nc-sa/4,0/), which permits unrestricted, non-commercial use,

distribution, and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interest regarding the publication of this paper.

Received: 15.06.2025. Revised: 05.07.2025. Accepted: 05.07.2025. Published: 09.07.2025.

Expanding Horizons - A Broad-Spectrum Review of Emerging Medical Applications of **N-Acetylcysteine**

Authors: Mikołajczyk Oskar, Suchołbiak Aleksandra, Małachowski Aleksander, Serafin Aleksandra, Sałata Julia, Baran Karolina, Naja Katarzyna, Zwardoń Jakub, Bracichowicz Filip

Oskar Mikołajczyk

Faculty of Medicine at The Medical University of Warsaw

Żwirki i Wigury 61, 02-091 Warsaw, Poland

oskrmikol@gmail.com

https://orcid.org/0009-0006-8470-6845

Aleksandra Suchołbiak

Faculty of Medicine at The Medical University of Warsaw

Żwirki i Wigury 61, 02-091 Warsaw, Poland

al.sucholbiak@gmail.com

https://orcid.org/0009-0001-2931-157X

Aleksander Małachowski MD

S.P.Z.O.Z. w Mińsku Mazowieckim,

Szpitalna 37, 05-300 Mińsk Mazowiecki, Poland

alek.m1999@gmail.com

https://orcid.org/0000-0002-4924-0000

Aleksandra Serafin

Faculty of Medicine at The Medical University of Warsaw

Żwirki i Wigury 61, 02-091 Warsaw, Poland

o.serafin75@gmail.com

https://orcid.org/0009-0002-2573-0811

Julia Sałata

COPERNICUS sp.z.o.o. Szpital im. M. Kopernika

Nowe Ogrody 1/6, 80-803, Gdańsk

Juliasalata@gmail.com

https://orcid.org/0009-0001-7905-9157

Karolina Baran

Faculty of Medicine at The Medical University of Warsaw

Żwirki i Wigury 61, 02-091 Warsaw, Poland

karolina.ba01@gmail.com

https://orcid.org/0009-0006-3076-2892

Katarzyna Naja

Faculty of Medicine at The Medical University of Warsaw

Żwirki i Wigury 61, 02-091 Warsaw, Poland

Katarzynanaja99@gmail.com

https://orcid.org/0009-0008-6513-6984

Jakub Zwardoń

Faculty of Medicine at The Medical University of Warsaw

Żwirki i Wigury 61, 02-091 Warsaw, Poland

Jak.zwa@gmail.com

https://orcid.org/0009-0005-3944-2943

Filip Bracichowicz

Military Institute of Aviation Medicine

Krasińskiego 54/56, 01-755 Warsaw, Poland

filip.bracichowicz@gmail.com

https://orcid.org/0009-0008-6661-5450

Abstract:

N-acetyl-l-cysteine is a thiol-containing compound widely recognized for its antioxidant, mucolytic, and glutathione-replenishing properties. Historically established for use in acetaminophen toxicity and respiratory diseases, n-acetyl-l-cysteine has garnered growing interest for its broad therapeutic potential across diverse medical domains. This narrative review synthesizes evidence from meta-analyses published from January 2024 onwards,

3

sourced from PubMed, to present emerging clinical applications of n-acetyl-l-cysteine. Findings suggest promising roles for n-acetyl-l-cysteine as an adjunctive therapy in managing rheumatoid arthritis, improving reproductive outcomes in women with polycystic ovary syndrome, and enhancing recovery following physical exertion by reducing oxidative stress and inflammation. While results for substance use disorders remain mixed, n-acetyl-l-cysteine's modulation of glutamatergic and antioxidant pathways warrants further investigation. Nonetheless, n-acetyl-l-cysteine's favorable safety profile and multifaceted biological actions underscore its potential in various clinical contexts. This review highlights medical areas of growing evidence on n-acetyl-l-cysteine's efficacy while identifying gaps that necessitate further well-designed trials. Its aim is to inform about new research directions.

Keywords: N-acetylcysteine, N-acetyl-l-cysteine, Rheumatoid Arthritis, Polycystic ovary syndrome, physical exertion recovery

1. Introduction

N-acetyl-l-cysteine (NAC) has become a compound of undeniable clinical importance. It is stocked in virtually every hospital and is the most popular antioxidant used in laboratory experiments (Herzenberg, 2019; Suzuki, 2009). It is also commercially very popular, sold as an over-the-counter supplement in pharmacies, health food stores, and online platforms in many countries including the United States, Canada, and Australia (Šalamon et al., 2019). Its story starts in the second half of the 20th century. Patented in 1960, NAC was first brought to the market three years later in September of 1963 after FDA approval (Schwalfenberg et al., 2021; Kobylarz et al., 2023). NAC has two main areas with historically most established clinical utility: first as an effective mucolytic agent, employed since 1969 in conditions such as cystic fibrosis and chronic obstructive pulmonary disease, then since 1977 as the antidote for acetaminophen (paracetamol) overdose, where it leverages its ability to replenish hepatic glutathione (Schwalfenberg et al., 2021; Syiem et al., 2024; Tieu et al., 2023). The profound impact of NAC in mitigating acetaminophen-induced liver injury further led to its global recognition culminating in its inclusion on the World Health Organization's (WHO) Model List of Essential Medicines (Šalamon et al., 2019).

Chemically NAC is a sulfhydryl-containing N-acetylated derivative of the amino acid L-cysteine (Tenório et al., 2021). While its precursor L-cysteine can be found in abundance in foods such as meat, grains, and dairy, NAC itself exists in nature only in trace amounts inside some fruits and vegetables, such as asparagus or tomatoes (Mokhtari et al., 2017; Demirkol et al., 2004).

Its current fundamental medical significance stems from its role as a precursor to L-cysteine, which is crucial for the synthesis of intracellular glutathione, the body's primary endogenous antioxidant (Atkuri et al., 2007). NAC also directly exerts antioxidant effects by scavenging reactive oxygen species (ROS) via its free thiol group and can act as a disulfide-breaking agent (Kalyanaraman, 2022). Despite having historically well-established applications, there is a rapidly increasing interest in exploring new therapeutic applications for NAC, driven by a deeper understanding of its diverse mechanisms of action beyond simple antioxidant and mucolytic effects (Pedre et al., 2021). These include modulation of inflammatory pathways, regulation of glutamatergic neurotransmission, neurotrophic effects, and potential benefits in conditions involving mitochondrial dysfunction (Tardiolo et al., 2018; Xiao et al., 2016; Ooi et al., 2018) The compound's favorable safety profile, general tolerability even at high doses, and cost-effectiveness further encourage its investigation as an adjunctive or primary therapy across a wide spectrum of medical conditions (Tenório et al., 2021; Ooi et al., 2018; Joshy et al., 2023)

This review aims to synthesize and critically evaluate the current clinical evidence supporting emerging uses of NAC. The significance of this review lies in providing a holistic overview of NAC's clinical potential. By identifying existing knowledge gaps, and highlighting areas in need for further investigation, this work seeks to inform readers about potential future research directions and pave the way for broader clinical understanding of this versatile compound.

2. Research materials and methods

A comprehensive narrative review was conducted by searching PubMed for meta-analytical studies on NAC published between January 1, 2024, and May 10, 2025. The search strategy used terms including "N-acetylcysteine," "NAC," "meta-analysis," and "systematic review," with filters applied for English language and human studies. Inclusion criteria were meta-analyses and systematic reviews with quantitative synthesis evaluating NAC in human subjects across various clinical indications. Titles and abstracts were screened independently with full texts assessed for eligibility. Data extracted from eligible studies included study

design, number of participants, NAC dosing and administration (if mentioned), interventions, outcomes measured, and key results. The synthesis focused on summarizing the main findings of the meta-analyses, providing an overview of NAC's therapeutic potential across diverse health conditions.

3. Research results

3.1. NAC in substance use disorders

The meta-analysis by Winterlind et al. (2024) evaluated the efficacy of NAC in reducing cravings among individuals with substance use disorders. The study addressed inconsistencies in prior findings (Greenberg et al. 2022; Winterlind et al., 2024). Winterlind et al. (2024) identified nine randomized controlled trials (RCTs) which assessed NAC in 623 participants addicted to various substances. The duration of the analysed studies ranged from 3 days to 12 weeks. The cravings were measured via self-report tools (see Table 1). Some trials included behavioral or psychosocial co-interventions (see Table 2). Pooled results showed no significant reduction in cravings with NAC versus placebo (SMD = 0.189, 95% CI = -0.015to 0.393) (Winterlind et al., 2024). These findings differ from earlier meta-analyses that reported significant effects (Chang et al., 2021; Duailibi et al., 2017; Winterlind et al., 2024). The reason for that might be due to the fact that the meta-analysis by Winterlind et al. (2024) included additional, more recent, larger trials. However, the authors underline that there are still some limitations, which include small number of trials analyzed, high heterogeneity across trials (I2 = 99.26%), potential variability in NAC product quality and focus only on assessing craving. In order to draw definitive conclusions, further research on NAC in substance use disorders should assess broader clinical outcomes, such as abstinence and relapse (Winterlind et al., 2024).

Table 1. Summary of trials included in meta-analysis by Winterlind et al. (2024).

Study (first author, year)	Substance(s)	Baseline (N=NAC/N =Placebo	Craving Measure(s)
Schmaal et al. (2011)	Tobacco	10/12	QSU-B (subscales and total score)
Yoon (2013)	Alcohol	22/24	PACS, OCDS (total scores)
Roten et al. (2013)	Cannabis	45/44	MCQ-SF (subscales and total score)
Back et al. (2016)	Multiple	13/14	VAS (three subscales)
Schulte et al. (2017)	Tobacco	24/24	QSU, VAS (total scores)
Back et al. (2021)	Multiple	49/41	OCDS (total score)
McKetin et al. (2021)	МЕТН	76/77	CEQ (total score)
Back et al. (2023)	Alcohol	93/89	OCDS (two subscales)
Morley et al. (2023)	Alcohol	21/21	PACS (total score)

CEQ – Craving Experiences Questionnaire, MCQ-SF – Marijuana Craving Questionnaire – Short Form, METH – Methamphetamine, NAC – N-acetylcysteine, OCDS – Obsessive Compulsive Drinking Scale, PACS – Penn Alcohol Craving Scale, QSU-B – Questionnaire of Smoking Urges – Brief, VAS – Visual Analogue Scale

Source: Data from Winterlind et al. (2024).

Table 2. Summary of interventions applied in trials included in meta-analysis by Winterlind et al. (2024).

Study (first author, year)	NAC dosage	Co-Intervention in study and placebo groups	
Schmaal et al. (2011)	3 days 1800 mg 2x/day and 1 day 1800 mg 1x/day	None reported	
Yoon (2013)	900 mg/day x 1 week; 1800 mg/day x 1 week, 2,700 mg/day x 1 week; 3,600 mg/day x 5 weeks	None reported	
Roten et al. (2013)	2400 mg/day x 8 weeks	Contingency management + cessation counseling x 8 weeks	
Back et al. (2016)	2400 mg/day x 8 weeks	CBT x 8 weeks	
Schulte et al. (2017)	2400 mg/day x 2 weeks	None reported	
Back et al. (2021)	2400 mg/day x 8 weeks	CBT x 8 weeks	
McKetin et al. (2021)	2400 mg/day x 12 weeks	None reported	
Back et al. (2023)	2400 mg/day x 12 weeks	CBT x 12 weeks	
Morley et al. (2023)	2400 mg/day x 4 weeks	None reported	
second trial; CBT – C	second trial; CBT – Cognitive Behavioral Therapy		

Source: Data from Winterlind et al. (2024).

3.2. NAC in physical excertion

NAC is considered to show prominent results in reducing fatigue and muscle damage caused by physical exertion (Sadowski et al., 2024; Sakelliou et al., 2016; Kerksick et al., 2010; Michailidis et al., 2013; Cobley et al., 2011).

The systematic review and meta-analysis by Sadowski et al. (2024) evaluated the effects of NAC on biomarkers of oxidative stress, inflammation, lactate metabolism, and muscle damage after exercise (Sadowski et al., 2024). The summary of the analysed studies is depicted in Table 3 below. The study analysed twenty RCTs involving a total of 266 healthy adults. It examined oral or intravenous NAC supplementation. Intervention durations ranged from 3 to 30 days. NAC significantly increased reduced glutathione levels (p < 0.00001), reduced lipid peroxidation measured by thiobarbituric acid reactive substances (p = 0.02) and decreased inflammatory interleukin-6 (p = 0.03). It also lowered post-exercise blood lactate (p = 0.03), muscle soreness twenty-four hours post-exercise (p = 0.001) and muscle soreness

after exercise, regardless of the time (p = 0.03). No significant changes were found in oxidized glutathione, tumor necrosis factor-alpha and creatine kinase (Sadowski et al., 2024).

According to the recent meta-analysis, NAC seems to enhance antioxidant capacity, reduce inflammatory and fatigue-related biomarkers, and support recovery post-exercise (Sadowski et al., 2024) which is not in line with the previous findings that NAC did not prove to be beneficial for sports performance (Rhodes & Braakhuis 2017). However, the previous meta-analysis focused on performance and side effects of NAC supplementation, rather than specifically on the biomarker outcomes in response to physical exertion like the newest meta-analysis by Sadowski et al., 2024. Nevertheless, there are still some limitations to the study by Sadowski et al. (2024) which include small sample sizes, limited search databases, heterogeneity in participant training levels, inability to differentiate effects by exercise type (aerobic vs. anaerobic), lack of studies on immune response, missing 72-hour comparative data, and diversity in biological materials used across studies (Sadowski et al., 2024).

Table 3. Summary of trials included in systematic review and meta-analysis by Sadowski et al. (2024).

Study (first author, year)	Sample size (n)	NAC dose & schedule; duration	Measured outcomes
Bailey et al. (2011)	8	IV 125 mg/kg b.w./h for 15 min before exercise, 25 mg/kg b.w./h throughout exercise; acute	Lactate
Christensen et al. (2019)	11	Oral 20 mg/kg b.w.; acute before excersise	Lactate
Cobley et al. (2011)	12	Oral 2 × 50 mg/kg b.w; chronic for 6 days + pre-exercise bolus.	CK, Muscle soreness
Ferreira et al. (2011)	17	Study 1 – Oral 2 × 300 or 2 × 600 mg (9 or 18 mg/kg b.w.); acute Study 2 – Oral 35, 70, or 140 mg/kg b.w.; acute	GSH, GSSG
Kelly et al. (2009)	9	Oral 1 800 mg, acute: 45 min before exercise	GSH, Lactate
Kerksick et al. (2010)	30	Oral 1 800 mg; chronic for 14 days	CK, TNF-α, Muscle soreness
Leelarungrayu b et al. (2011)	29	Oral 2 × 600 mg day; chronic for 7 days	Lactate, TNF-α, CK
Medved et al. (2004)	8	IV 125 mg/kg b.w./h for 15 min, 25 mg/kg/h for 20 min prior to and throughout exercise; acute	GSH, GSSG
Merry et al. (2010)	9	IV 125 mg/kg/h for 15 min, then 25 mg/kg/h for 20 min prior to and throughout exercise;	GSH, GSSG, Lactate

		acute	
Michailidis et al. (2013)	10	Oral 20 mg/kg b.w.; chronic for 7 days after training	GSH, GSSG, TBARS, IL-6, TNF-α, CK, Muscle soreness
Moraes et al. (2018)	20	Oral 2 × 600 mg/day; chronic for 7 days	GSH, TBARS, CK
Nielsen et al (2001)	19	Oral 6 g/day; chronic for 3 days before exercise	GSH, Lactate
Paschalis et al. (2018)	36	Oral 2 × 600 mg/day; chronic for 30 days	GSH
Rhodes et al. (2019)	17	Oral 1 g/day; chronic for 6 days	Muscle soreness
Sakelliou et al. (2016)	10	Oral 20 mg/kg/day; chronic for 8 days	GSH, GSSG, TBARS, IL-6, CK, Muscle soreness
Sen et al. (1994)	9	Oral 4 × 200 mg/day; chronic for 3 days	GSH, GSSG, TBARS
Silva et al. (2008)	29	Oral NAC (10 mg/kg b.w.) for 21 days or NAC plus placebo (14-day NAC + 7-day placebo); chronic	TNF-α, Muscle soreness
Slattery et al. (2014)	8	Oral 2 × 600 mg/day; chronic for 9 days	GSH, GSSG, TBARS, IL-6
Trewin et al. (2013)	9	Oral 5 × 100 mg/kg; acute: before excersise	GSH, GSSG, TBARS, Lactate
Trewin et al. (2015)	7	IV Initial loading dose of 62.5 mg/kg/h for the first 15 min, followed by a constant infusion of 25 mg/kg/h for the next 80 min; acute	GSH, GSSG, IL-6

b.w.— body weight; **CK** — creatine kinase; **GSH** — reduced glutathione; **GSSG** — oxidized glutathione; **IL-6** — interleukin-6; **IV** — intravenous; **NAC** — N-acetylcysteine; **TBARS** — thiobarbituric acid reactive substances.

Source: Data from Sadowski et al. (2024).

3.3. NAC in Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease driven by inflammation and oxidative stres (Han et al., 2024; He et al., 2024). Despite standard disease-modifying antirheumatic drugs (DMARDs) therapy, some patients do not respond sufficiently to the first-line treatment (Hofman et al., 2025; He et al., 2024). Since NAC exhibits antioxidant and anti-inflammatory properties, it has been proposed as a potential adjunct therapy in RA (He et al., 2024).

The recent systematic review and meta-analysis by He et al. (2024) included four RCTs comparing NAC plus DMARDs to placebo plus DMARDs. The total number of participants

from analyzed RCTs was 204, all in active state of disease. Outcomes analyzed included disease activity, measured by DAS28-ESR and global health; number of tender and swollen joints; inflammatory markers, including ESR and CRP; oxidative stress (TAC, MDA, NO); and adverse events (He et al., 2024). The summary of the analysed trials is depicted in Table 4 below.

NAC significantly improved global health scores (p = 0.03), and reduced ESR (p = 0.02), CRP (p = 0.03), number of tender joints (p = 0.03) and swollen joints (p = 0.003). However, it did not significantly reduce disease activity or affect oxidative stress markers (all p > 0.05). Adverse effects were mild and comparable between groups, indicating good tolerability (He et al., 2024).

The meta-analysis by He et al. (2024) suggested that NAC's potential benefits in RA appear to be driven by anti-inflammatory rather than antioxidant mechanisms. Despite promising effects, the authors reported limitations that include small sample size and uniform dosing (He et al., 2024).

Table 4. Summary of trials included in systematic review and meta-analysis by He et al. (2024).

Study (first author, year)	Sample Size (N=NAC/N=P lacebo)	Study duration	NAC Dosage	Measured outcomes
Batooei et al. (2018)	27/24	12 weeks	600 mg 2x/day	DAS28-ESR, Global Health, number of tender joints, number of swollen joints, ESR
Hashemi et al. (2019)	23/19	12 weeks	600 mg 2x/day	ESR, CRP, TAC, MDA, NO
Jamali et al. (2021)	22/19	8 weeks	600 mg 2x/day	DAS28-ESR, Global Health, number of tender joints, number of swollen joints, ESR
Esalatmanes h et al. (2022)	34/36	3 months	600 mg 2x/day	DAS28-ESR, ESR, CRP, TAC, MDA, NO

CRP – C-reactive protein; DAS28-ESR – Disease Activity Score 28 - erythrocyte sedimentation rate; ESR – erythrocyte sedimentation rate; GH – Global Health; MDA – malondialdehyde; NAC – N-acetylcysteine; NO – nitric oxide; TAC – total antioxidant capacity

Source: Data from He et al. (2024).

3.4. NAC in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by hormonal imbalance, insulin resistance, and infertility (Dilliyappan et al., 2024; Viña et al., 2025). The management of PCOS is challenging due to its complex pathogenesis. Letrozol, lomiphene citrate (CC) and metformin are the drugs that were suggested for managing infertility in women with PCOS. However, the results, especially concerning CC and metformin, are inconclusive (Sharpe et al., 2019; Hoeger et al., 2021).

The recent systematic review and meta-analysis by Viña et al. (2025) assessed NAC as a potential therapy for infertility in women with PCOS. Twenty-two studies, including eighteen RCTs, with a total of 2,515 participants were analyzed. The meta-analysis did not present the information on dosages of NAC and duration of the trials. The trials compared NAC, alone or with clomiphene citrate (CC), letrozole, or laparoscopic ovarian drilling to different combinations of placebo, CC, metformin, 1-carnitine, letrozole and laparoscopic ovarian drilling. Outcomes included levels of progesterone, LH, FSH, estradiol (E2), total testosterone (TT), sex hormon binding globulin (SHBG), endometrial thickness, and follicle count (Viña et al., 2025). The summary of the analysed trials is depicted in Table 5 below.

NAC significantly increased progesterone levels (p=0.02) and endometrial thickness (p=0.02) compared to the placebo and other interventions. The study reported also an increase in LH compared to metformin (p=0.003). No significant effects were found for FSH, E2, TT, or SHBG. NAC showed trends toward improving follicle count, but results were inconsistent. Limitations of the study include: high heterogeneity, small number of studies for some outcomes, and publication bias which was assessed only through visual inspection (Viña et al., 2025).

According to the meta-analysis, NAC, due to its antioxidant and insulin-sensitizing properties, may be a valuable adjunctive therapy, particularly for women with thin endometrium or low progesterone levels (Viña et al., 2025). This study strengthens the findings from previous meta-analysis that NAC may be an alternative supplement instead of metformin in women with PCOS (Song et al., 2020).

Table 5. Summary of trials included in systematic review and meta-analysis by Viña et al. (2025).

Study (first author, year)	Study design	Intervention	Sample size (N)
Mostajeran et al.,	RCT	Letrozole + NAC	65
2018	RCI	Letrozole + placebo	61
No. of al. 2010	RCT	LOD + NAC	30
Nasr et al., 2010		LOD + placebo	30
Do down at al. 2007	Cross-over trial	CC + NAC	210
Badawy et al., 2007	Cross-over trial	CC	260
V" as at al. 2015	Clinical trial	PCOS + NAC	17
Köse et al., 2015		PCOS	17
On an at al. 2011	RCT	NAC	45
Oner et al., 2011	RCI	Metformin	30
Kilic-Okman et al., 2004	Clinical trial	NAC	20
El Sharkwy et al.,	DOT	CC + NAC	82
2019	RCT	CC + 1-carnitine	80
C1 1: , 1 2016	D.C.T.	NAC	15
Cheraghi et al., 2016	RCT	Placebo	15
Fulghesu et al., 2002	Prospective analysis	NAC	37
	DOT	CC	40
Maged et al., 2015	RCT	CC + NAC	40
II 1: 4 1 2010	RCT	NAC + CC	95
Hashim et al., 2010		Metformin + CC	97
D' 1 1 . 2005	RCT	NAC	75
Rizk et al., 2005		CC + placebo	75
C 1 1 4 1 2012	RCT	CC + NAC	82
Salehpour et al., 2012		CC + placebo	85
Javanmanesh et al.,	DCT	NAC	46
2015	RCT	Metformin	48
Cl	D CIT	Clomiphene + NAC	33
Ghomian et al., 2019	RCT	Clomiphene	33
Nemati et al., 2017	RCT	CC + NAC	54
		CC + Metformin	54
Elgindy et al., 2010	RCT	Long IVF protocol + NAC	38
		Long IVF protocol	38
Taim avail at -1 2021	RCT	Letrozole + NAC	158
Teimouri et al., 2021		Letrozole	159
Carratui -t -1 2010	D.C.T.	NAC	50
Gayatri et al., 2010	RCT	Metformin	50

Chandil at al. 2010	RCT	NAC	45
Chandil et al., 2019		Metformin	45
Elnashar et al., 2007	RCT	NAC	30
		Metformin	31
11 4 1 2010	RCT	CC + NAC	150
Hassan et al., 2019		CC + placebo	150

CC – clomiphene citrate; LOD – laparoscopic ovarian drilling; NAC – N-acetyl-cysteine; RCT – randomised controlled trial

Source: Data from Viña et al. (2025) and Ghomian et al. (2019).

4. Discussion

The compiled meta-analyses on NAC across various conditions highlight its broad therapeutic potential (see Table 6). NAC demonstrates promising effects in RA, PCOS and exercise-induced oxidative stress and fatigue (He et al., 2024; Viña et al., 2025; Sadowski et al., 2024).

In the context of substance addiction, NAC's glutamatergic modulation and antioxidant properties were associated with reductions in cravings for different substances (Winterlind et al., 2024). While some meta-analyses reported a statistically significant reduction in cravings, others find no clear evidence for NAC's efficacy (Chang et al., 2021; Duailibi et al., 2017; Winterlind et al., 2024). The findings of NAC in substance use disorders remain insufficient and assessment of broader clinical outcomes is needed in order to draw definite conclusions (Winterlind et al., 2024).

Some studies suggest the possible utility of metformin in PCOS, but its role remains limited (Hoeger et al., 2021). Based on the meta-analytical findings by Viña et al. (2025), we suggest that in PCOS, NAC, an alternative to metformin, might be a valuable adjunctive therapy to letrozol, the drug that is currently considered the first-line treatment of infertility in PCOS (Song et al., 2020; Wang et al., 2019; Hoeger et al., 2021; Yifu, 2024).

Since NAC shows potential in reducing inflammatory mediators, possibly through mechanisms involving glutathione restoration and NF-κB inhibition (He et al., 2024; Verhasselt et al., 1999), it might be a valuable adjunct to DMARDs in RA (He et al., 2024).

In sport, NAC has been investigated for its role in mitigating exercise-induced oxidative damage and improving recovery (Devrim-Lanpir et al., 2021; Sadowski et al., 2024). Meta-analysis suggests that NAC supplementation can lower several biomarkers associated with exercise-induced oxidative stress and fatigue (Sadowski et al., 2024). Nevertheless, its effect on performance outcomes, such as time-to-exhaustion or peak power, appears minimal or

inconsistent (Rhodes & Braakhuis 2017). We suggest that future studies should focus on measuring both biomarkers and performance outcomes.

Across all studies, heterogeneity in study design—including NAC dosing, duration of supplementation, and outcome assessment methods—limits the ability to draw definitive conclusions. While meta-analyses attempt to account for this variability through subgroup and sensitivity analyses, the high heterogeneity values in several analyses underscore the need for more standardized, high-quality RCTs. Furthermore, while NAC's safety profile is generally favorable (Adil et al., 2018), many studies did not report adverse events systematically, leaving potential tolerability concerns underexplored.

Table 6. Summary of meta-analyses discussed in results.

Study	Utility of NAC analysed	Conclusions
Viña et al., 2025	Infertility in PCOS	Significant effect on progesterone, endometrial thickness and LH levels
Winterlind et al., 2024	Craving management for SUD	Limited impact on substance craving
He et al., 2024	RA	Reduction of inflammatory markers, improvement joint tenderness, and swelling
Sadowski et al., 2024	Reduction of fatigue and muscle damage caused by physical exertion	Promising results for reducing muscle soreness, lactate, TBARS and IL-6 concentrations and increasing GSH level following physical exertion

GSH – Glutathione; IL-6 – Interleukin 6; LH – Luteinizing Hormone; NAC – N-Acetylcysteine; PCOS – Polycystic Ovary Syndrome; RA – Rheumatoid Arthritis; SUD – Substance Use Disorder; TBARS – Thiobarbituric Acid Reactive Substances

Data from: (He et al., 2024; Viña et al., 2025; Sadowski et al., 2024; Winterlind et al., 2024).

5. Conclusions

In summary, meta-analytical evidence suggests that NAC, due to its antioxidant properties and modulation of inflammatory and neurotransmitter pathways, holds therapeutic promise across many different conditions. However, to establish its clinical utility more firmly, further research is needed -particularly large, well-designed randomized controlled trials with standardized dosing protocols, broader outcome measures, and robust reporting of clinical endpoints and adverse events.

Disclosure: Author's Contribution Statement:

Conceptualization: Oskar Mikołajczyk, Aleskandra Suchołbiak, Aleksander Małachowski

Methodology: Aleksandra Serafin, Aleksander Małachowski

Software: Aleksander Małachowski, Filip Bracichowicz

Check: Julia Sałata, Karolina Baran

Formal analysis: Aleskandra Suchołbiak, Julia Sałata

Investigation: Oskar Mikołajczyk, Aleksandra Serafin

Resources: Aleksandra Serafin, Karolina Baran

Data curation: Aleksandra Serafin, Aleksander Małachowski, Karolina Baran

Writing-rough preparation: Oskar Mikołajczyk, Aleskandra Suchołbiak

Writing-review and editing: Jakub Zwardoń, Katarzyna Naja, Filip Bracichowicz

Visualization: Aleskandra Suchołbiak

Supervision: Oskar Mikołajczyk, Aleskandra Suchołbiak

Project administration: Oskar Mikołajczyk

Receiving funding: None

Funding Statement: The study did not receive special funding of any kind.

Conflict of Interest Statement: All authors state no conflict of interest.

All authors have read and agreed with the published version of the manuscript.

Declaration of the use of AI and AI-assisted technologies in the writing process:

Artificial intelligence (AI) tools such as ChatGPT and ANARA were employed in this research solely to assist in refining the academic English language of the manuscript. Their purpose was to ensure clarity, consistency, and adherence to scientific writing standards. AI tools were used strictly for additional linguistic polishing-focused on proper grammar, style, and clarity of the text in presenting the results. Importantly, these tools were used only as support under the direct supervision of the authors. All final interpretations, classification of findings, and conclusions were determined exclusively by human experts with formal training in clinical medicine. The role of AI was limited to enhancing the efficiency of language refinement, pattern recognition, and data processing, and it did not replace human judgment in the analytical process.

References:

Adil, M., Amin, S. S., & Mohtashim, M. (2018). N-acetylcysteine in dermatology. *Indian Journal of Dermatology, Venereology and Leprology*, 84(6), 652–659.

https://doi.org/10.4103/ijdvl.IJDVL 33 18

Atkuri, K. R., Mantovani, J. J., Herzenberg, L. A., & Herzenberg, L. A. (2007). Nacetylcysteine—a safe antidote for cysteine/glutathione deficiency. *Current Opinion in Pharmacology*, 7(4), 355–359. https://doi.org/10.1016/j.coph.2007.04.005

Chang, C. T., Hsieh, P. J., Lee, H. C., Lo, C. H., Tam, K. W., & Loh, E. W. (2021). Effectiveness of N-acetylcysteine in treating clinical symptoms of substance abuse and dependence: A meta-analysis of randomized controlled trials. *Clinical Psychopharmacology and Neuroscience*, 19(2), 282. https://doi.org/10.9758/cpn.2021.19.2.282

Cobley, J. N., McGlory, C., Morton, J. P., & Close, G. L. (2011). N-acetylcysteine's attenuation of fatigue after repeated bouts of intermittent exercise: Practical implications for tournament situations. *International Journal of Sport Nutrition and Exercise Metabolism*, 21(6), 451–461. https://doi.org/10.1123/ijsnem.21.6.451

Demirkol, O., Adams, C., & Ercal, N. (2004). Biologically important thiols in various vegetables and fruits. *Journal of Agricultural and Food Chemistry*, 52(26), 8151–8154. https://doi.org/10.1021/jf040266f

Devrim-Lanpir, A., Hill, L., & Knechtle, B. (2021). How N-acetylcysteine supplementation affects redox regulation, especially at mitohormesis and sarcohormesis level: Current perspective. *Antioxidants*, 10(2), 153. https://doi.org/10.3390/antiox10020153

Dilliyappan, S., Kumar, A. S., Venkatesalu, S., et al. (2024). Polycystic ovary syndrome: Recent research and therapeutic advancements. *Life Sciences*, *359*, 123221. https://doi.org/10.1016/j.lfs.2024.123221

Duailibi, M. S., Cordeiro, Q., Brietzke, E., et al. (2017). N-acetylcysteine in the treatment of craving in substance use disorders: Systematic review and meta-analysis. *American Journal of Addiction*, 26(7), 660–666. https://doi.org/10.1111/ajad.12620

Ghomian, N., Khadem, N., Moeindarbari, S., & Abdolrazagh, A. (2019). Comparison of pregnancy rate in patients with polycystic ovary syndrome treated with clomiphene alone and

in combination with N-acetyl cysteine: A randomized clinical trial. *International Journal of Women's Health and Reproduction Sciences*, 7, 185–189. https://doi.org/10.15296/ijwhr.2019.31

Greenberg, N. R., Farhadi, F., Kazer, B., Potenza, M., & Gustavo, A. A. (2022). Mechanistic effects and use of N-acetylcysteine in substance use disorders. *Current Behavioral Neuroscience Reports*, *9*(4), 124–143. https://doi.org/10.1007/s40473-022-00250-3

Han, H., Zhang, G., Zhang, X., & Zhao, Q. (2024). Nrf2-mediated ferroptosis inhibition: A novel approach for managing inflammatory diseases. *Inflammopharmacology*, 32(5), 2961–2986. https://doi.org/10.1007/s10787-024-01519-7

He, T., Ren, K., Xiang, L., Yao, H., Huang, Y., & Gao, Y. (2024). Efficacy of N-acetylcysteine as an adjuvant therapy for rheumatoid arthritis: A systematic review and meta-analysis of randomized controlled trials. *British Journal of Hospital Medicine*, 85(11), 1–16. https://doi.org/10.12968/hmed.2024.0560

Herzenberg, L. A. (2018). History of N-acetylcysteine. In *The therapeutic use of N-acetylcysteine (NAC) in medicine* (pp. 1–15). Springer. https://doi.org/10.1007/978-981-10-5311-5

Hoeger, K. M., Dokras, A., & Piltonen, T. (2021). Update on PCOS: Consequences, challenges, and guiding treatment. *Journal of Clinical Endocrinology & Metabolism*, 106(3), e1071–e1083. https://doi.org/10.1210/clinem/dgaa839

Hofman, Z. L. M., Roodenrijs, N. M. T., Nikiphorou, E., et al. (2025). Difficult-to-treat rheumatoid arthritis: What have we learned and what do we still need to learn? *Rheumatology*, 64(1), 65–73. https://doi.org/10.1093/rheumatology/keae544

Joshy, A., Thomas, A., Baby, E., Biju, S., Mishra, B., & Jose, N. (2023). Pharmacological applications and pharmacokinetic modifications of N-acetylcysteine. *International Journal of*

Pharmaceutics and Drug Analysis, 17–30. https://doi.org/10.47957/ijpda.v11i1.535

Kalyanaraman, B. (2022). NAC, NAC, knockin' on heaven's door: Interpreting the mechanism of action of N-acetylcysteine in tumor and immune cells. *Redox Biology*, *57*, 102497. https://doi.org/10.1016/j.redox.2022.102497

Kerksick, C. M., Kreider, R. B., & Willoughby, D. S. (2010). Intramuscular adaptations to eccentric exercise and antioxidant supplementation. *Amino Acids*, 39(1), 219–232. https://doi.org/10.1007/s00726-009-0432-7

Kobylarz, D., Noga, M., Frydrych, A., et al. (2023). Antidotes in clinical toxicology—Critical review. *Toxics*, 11(9), 723. https://doi.org/10.3390/toxics11090723

Michailidis, Y., Karagounis, L. G., Terzis, G., et al. (2013). Thiol-based antioxidant supplementation alters human skeletal muscle signaling and attenuates its inflammatory response and recovery after intense eccentric exercise. *American Journal of Clinical Nutrition*, 98(1), 233–245. https://doi.org/10.3945/ajcn.112.049163

Mokhtari, V., Afsharian, P., Shahhoseini, M., Kalantar, S. M., & Moini, A. (2017). A review on various uses of N-acetyl cysteine. *Cell Journal*, 19(1), 11–17. https://doi.org/10.22074/cellj.2016.4872

Ooi, S. L., Green, R., & Pak, S. C. (2018). N-acetylcysteine for the treatment of psychiatric disorders: A review of current evidence. *BioMed Research International*, 2018, 2469486. https://doi.org/10.1155/2018/2469486

Pedre, B., Barayeu, U., Ezeriņa, D., & Dick, T. P. (2021). The mechanism of action of N-acetylcysteine (NAC): The emerging role of H₂S and sulfane sulfur species. *Pharmacology & Therapeutics*, 228, 107916. https://doi.org/10.1016/j.pharmthera.2021.107916

Rhodes, K., & Braakhuis, A. (2017). Performance and side effects of supplementation with N-acetylcysteine: A systematic review and meta-analysis. *Sports Medicine*, 47(8), 1619–1636. https://doi.org/10.1007/s40279-017-0677-3 Sadowski, M., Zawieja, E., & Chmurzynska, A. (2024). The impact of N-acetylcysteine on lactate, biomarkers of oxidative stress, immune response, and muscle damage: A systematic review and meta-analysis. *Journal of Cellular and Molecular Medicine*, 28(23), e70198. https://doi.org/10.1111/jcmm.70198

Sakelliou, A., Fatouros, I. G., Athanailidis, I., et al. (2016). Evidence of a redox-dependent regulation of immune responses to exercise-induced inflammation. *Oxidative Medicine and Cellular Longevity*, 2016, 2840643. https://doi.org/10.1155/2016/2840643

Schwalfenberg, G. K. (2021). N-acetylcysteine: A review of clinical usefulness (an old drug with new tricks). *Journal of Nutrition and Metabolism*, 2021, 9949453. https://doi.org/10.1155/2021/9949453

Sharpe, A., Morley, L. C., Tang, T., Norman, R. J., & Balen, A. H. (2019). Metformin for ovulation induction (excluding gonadotrophins) in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews, 12*, CD013505. https://doi.org/10.1002/14651858.CD013505

Song, Y., Wang, H., Huang, H., & Zhu, Z. (2020). Comparison of the efficacy between NAC and metformin in treating PCOS patients: A meta-analysis. *Gynecological Endocrinology*, 36(3), 204–210. https://doi.org/10.1080/09513590.2019.1689553

Suzuki, K. (2009). Anti-oxidants for therapeutic use: Why are only a few drugs in clinical use? *Advanced Drug Delivery Reviews*, 61(4), 287–289. https://doi.org/10.1016/j.addr.2009.03.002

Šalamon, Š., Kramar, B., Marolt, T. P., Poljšak, B., & Milisav, I. (2019). Medical and dietary uses of N-acetylcysteine. *Antioxidants*, 8(5), 111. https://doi.org/10.3390/antiox8050111

Syiem, R. P., Wahlang, J. B., R. K., Kalyan, P. B., Nahakpam, D., & Langstieh, A. J. (2024). Exploring the novel therapeutic potential of N-acetylcysteine in depression, bipolar disorders and anxiety. *Journal of Pharmacology and Pharmacotherapeutics*, 15(2), 133–141. https://doi.org/10.1177/0976500X241246402

Tardiolo, G., Bramanti, P., & Mazzon, E. (2018). Overview on the effects of N-acetylcysteine in neurodegenerative diseases. *Molecules*, 23(12), 3305. https://doi.org/10.3390/molecules23123305

Tenório, M. C. D. S., Graciliano, N. G., Moura, F. A., Oliveira, A. C. M., & Goulart, M. O. F. (2021). N-acetylcysteine (NAC): Impacts on human health. *Antioxidants*, 10(6), 967. https://doi.org/10.3390/antiox10060967

Tieu, S., Charchoglyan, A., Paulsen, L., et al. (2023). N-acetylcysteine and its immunomodulatory properties in humans and domesticated animals. *Antioxidants*, 12(10), 1867. https://doi.org/10.3390/antiox12101867

Verhasselt, V., Vanden Berghe, W., Vanderheyde, N., Willems, F., Haegeman, G., & Goldman, M. (1999). N-acetyl-L-cysteine inhibits primary human T cell responses at the dendritic cell level: Association with NF-κB inhibition. *Journal of Immunology*, *162*(5), 2569–2574.

Viña, I., Viña, J. R., Carranza, M., & Mariscal, G. (2025). Efficacy of N-acetylcysteine in polycystic ovary syndrome: Systematic review and meta-analysis. *Nutrients*, *17*(2), 284. https://doi.org/10.3390/nu17020284

Wang, R., Li, W., Bordewijk, E. M., et al. (2019). First-line ovulation induction for polycystic ovary syndrome: An individual participant data meta-analysis. *Human Reproduction Update*, 25(6), 717–732. https://doi.org/10.1093/humupd/dmz029

Winterlind, E. L., Malone, S. G., Setzer, M. R., Murphy, M. A., Saunders, D., & Gray, J. C. (2024). N-acetylcysteine as a treatment for substance use cravings: A meta-analysis. *medRxiv*. https://doi.org/10.1101/2024.05.13.24306839

Xiao, H., Wu, M., Shao, F., et al. (2016). N-acetyl-L-cysteine protects the enterocyte against oxidative damage by modulation of mitochondrial function. *Mediators of Inflammation*, 2016, 8364279. https://doi.org/10.1155/2016/8364279

Yifu, P. (2024). A review of antioxidant N-acetylcysteine in addressing polycystic ovary syndrome. *Gynecological Endocrinology,* 40(1), 2381498. https://doi.org/10.1080/09513590.2024.2381498