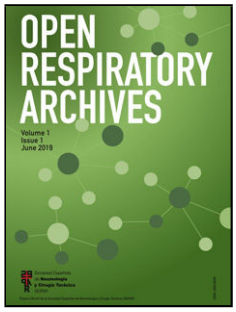

Do observational studies overestimate the effectiveness of cytisinicline?

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Letters to the Editor:

Do observational studies overestimate the effectiveness of cytisinicline?

¿Los estudios observacionales sobreestiman la eficacia de la citisiniclina?

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Dear Editor,

A recent Cochrane meta-epidemiological review found little discrepancy between estimates of treatment effects in observational studies and randomized controlled trials (RCTs)[1]. Particularly valuable for real-life clinical situations, observational studies often shows wide heterogeneity and limited internal validity. Reporting methodological details and potential sources of bias helps improve the interpretability of these findings[2].

Previously, we synthesized observational studies assessing the effectiveness of cytisinicline for smoking cessation in hospital-based smoking cessation units[3]. The reproducibility of results observed in those analyses has now been supported by new data presented at the 58th SEPAR Congress[4], where seven studies evaluated cytisinicline's real-world effectiveness in a total of 763 patients (Table 1). One study co-administered fast-acting nicotine replacement therapy (NRT) together with cytisinicline to 65% of its sample. In another work, the population consisted of smokers over 65 years of age.

Weighted mean abstinence was calculated, considering methodological heterogeneity and the relative weights of each study, Data were analysed using SPSS© version 26. Ethical considerations: This study strictly adhered to ethical guidelines by ensuring that no direct patient data were colllected, analyzed, or utilized at any stage of the research.

We observed abstinence rates of 78% at one month, 54.2% at three months, 42.9% at six months, and 34.1% at one year (Table 1).

Patients older than 65 years achieved lower abstinence rates at both, one and three months. This may be due to their greater physical dependence and complexity, as well as the presence of comorbidities. In contrast, co-administration of fast-acting NRT achieved higher success rates compared with the average of the other studies. These results are consistent with those found in our preceding work[3]. Furthermore, given the evidence of the superiority of combined treatment with NRT and varenicline[5], this therapy could have significant clinical relevance.

Taking all of the above into account, it should be noted that abstinence rates hardly differ from those achieved in ours previous syntesis[3]**.** Nevertheless, caution is warranted when interpreting these findings, given the inherent methodological limitations of observational designs.

On the other hand, higher effectiveness estimates compared with RCTs (gold standard) are not necessarily due to bias. It is worth considering the significant effect of the structured behavioral support, continuous follow-up, and adherence control typically provided in specialized smoking cessation units.

A large-scale multicentre randomized clinical trial, similar to an EAGLES-type design, is warranted to clarify the true magnitude of cytisinicline's effectiveness in real-world settings, including heterogeneous populations and different dosing regimens. Such evidence would help consolidate its role within evidence-based smoking cessation strategies, relative to other available pharmacotherapies.

Compulsory final declaration section:

Funding of the research:

We declare that this work did not receive any specific grant from funding agencies in the public, comercial, or not-for profit sectors.

Authors' contribution:

All authors were involved in study conception and design, data acquisition, analysis, interpretation, and drafting and revising the article.

Conflicts of interest:

Raúl Majo García has received speaker fees from Chiesi and funding from Adamed to attend conferences. Sheila María Martínez Tahoces has received speaker fees from GlaxoSmithKline (GSK) for scientific and educational lectures, unrelated to the present work.

Participation of artificial intelligence:

None of the materials has been produced partially or totally with the help of any artificial intelligence software or tool.

Ethical considerations

In this paper we have analysed results from selected studies, not using patient data.

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Table 1.

Study (first author), page(s) of the publication in the journal: Open Respir Arch. 2025; 7(S1): S1–641.	Mean age (years), cytisinicline-treated population (n)	Smoking abstinence rate (%) (months)	Methodology / Comments
Vargas Espinal et al. (p 556)	57.1 (127)	36.2 (12 months)	
Martínez Martínez et al. (pp 557-558)	56 (110)	74.3 (1 month) 53.3 (3 months) 37.4 (6 months)	Compares cytisinicline vs. varenicline. Higher abstinence rate with varenicline, not statistically significant.
Ruiz Amat et al. (pp 560-561)	57.5 (41)	70.7 (1 month) 51.2 (3 months) 39 (6 months) 24.4 (12 months)	
San Juan Redondo et al. (p 561)	57 (203)	63 (3 months) 54 (6 months)	Cytisinicline + fast-acting NRT (65% of patients). Results not stratified by co-administration of NRT.
Villar Laguna et al. (pp 561-562)	54.8 (171)	91.2 (1 month) 51.4 (3 months) 30.4 (6 months)	
Martín Gallego et al. (p 564)	60 (70)	52.8 (1 month) 34.3 (3 months) 27.1 (6 months)	Results recalculated using the intention-to-treat approach.
Segura Romero et al. (p 570)	69 (41)	43.9 (1 month) 24.4 (3 months)	>65 years population No adverse events were observed.
Weighted mean abstinence rates			

	No. of studies	Weighted means (SD)	Methodology	Results by different methodology	p value
1 month	5	78% (15.2)	STGR standard population vs. >65 years	80% vs.43.9%	p<0.001[a]
3 months	6	54.2% (9.4)	STGR vs. NRT co-administration vs. STGR > 65 years	49.8% vs. 63% vs. 24.4%	p<0.001[b] p<0.002[c]
6 months	5	42.9% (10.9)	STGR vs. NRT co-administration	33.1% vs. 54%	p<0.001[a]
12 months	2	34.1% (4.6)	STGR		

Table 1: Study design and abstinence cytisinicline rates. Studies from the specialist smoking area, published at the 58th SEPAR Congresses[4]. SD: standard deviation; [a]: Mann-Whitney U test; [b]: Kruskal-Wallis test; [c]: Bonferroni correction applied to post hoc pairwise comparisons (Dunn's test); NRT: nicotine replacement therapy; STGR: standard 25-day descending-dose regimen