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Scientific letter

Evidence Update on the Efficacy of Cytisinicline by Treatment Regimen: A Rapid Review

Actualización de la evidencia sobre la eficacia de la citisiniclina por régimen de tratamiento: una revisión rápida

Dear Editor,

Cytisinicline, a partial agonist of α4β2 nicotinic receptors, is a plant-derived alkaloid that has been used for smoking cessation in Eastern Europe for over six decades.[1] Despite this long-standing use, evidence remains limited.[2] This study summarizes recent clinical trial data on its efficacy and dosing strategies.

A rapid literature review was conducted in December 2024 across PubMed, ScienceDirect, EMBASE, Scopus, and the Cochrane Library using the terms "cytisine OR cytisinicline", limited to clinical trials published within the previous 10 years. Eleven clinical trials were identified, all of which had the primary objective of evaluating the efficacy of cytisinicline for smoking cessation. Overall, 4978 participants were treated with cytisinicline, and 4510 were controls who received varenicline, nicotine replacement therapy (NRT), nortriptyline, placebo or brief advice. Seven studies applied the standard 25-day descending-dose regimen (STGR), with 100 tablets of 1.5 mg,[3-10] while four used alternative schedules. Walker et al.[11] extended the STGR by continuing 2 tablets daily up to day 84; Pastorino et al.[12] compared 165 tablets over 40 days and 274 tablets over 84 days versus brief advice. Nides et al.[5] included the STGR arm and compared it with three alternative regimens, consisting of 1.5 mg three times daily (TID), 3 mg TID, and 3 mg in descending doses. Rigotti et al.[13] compared 3 mg TID for 6 and 12 weeks, both versus placebo.

The trial arms were disaggregated, resulting in 16 cytisinicline intervention groups that were analyzed separately (Fig. 1). Data were analyzed using SPSS© version 26 and the meta-analysis was performed using Epidat 3.1. No individual patient data were collected, analyzed, or used at any stage of this review.

Weighted mean abstinence rates were calculated for the intervention arms, taking into account the relative sample sizes of each study.

At the 3-month follow-up, abstinence was 23.2% with a standard deviation (SD) of 1.7 with the STGR (4 studies, 844 participants) versus 30% (SD 6.5) for alternative schedules (6 studies, 1028 participants).

At 6 months, abstinence rates were 22.3% (SD 8.4) for the STGR (7 studies, 3429 participants) vs. 15.4% (SD 3.9) for alternative regimens (3 studies, 876 participants).

At 12 months (3 studies each), abstinence rates were 20.8% (SD 5.8) with the STGR (1846 participants) vs 25.6% (SD 8.5; 807 participants).

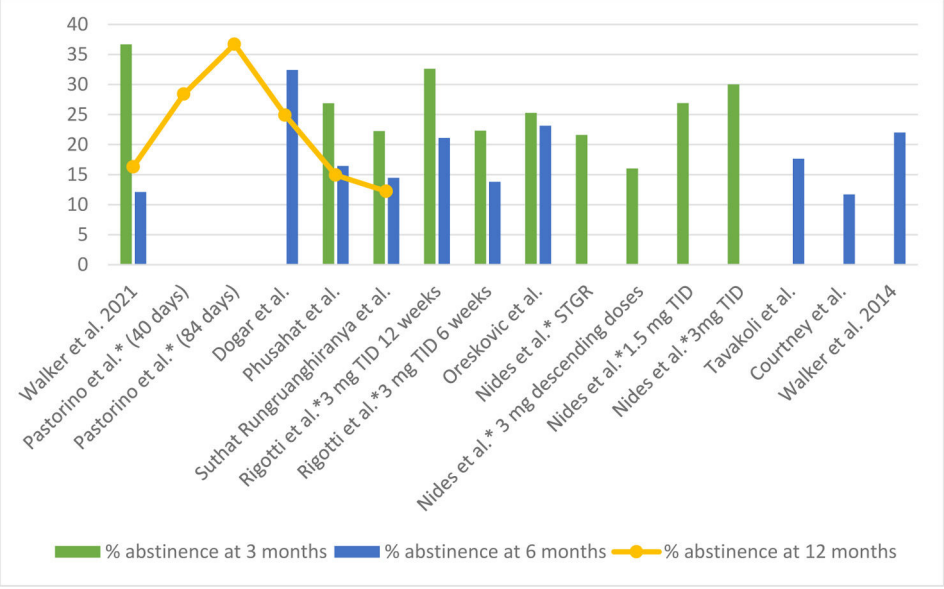

Fig. 1. Abstinence rates at 3, 6, and 12 months in clinical trials evaluating the efficacy of cytisinicline (2014–2024). Disaggregated trial arms using different cytisinicline regimens within the same study. STGR: standard 25-day descending-dose regimen; TID: three times daily.

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Differences were not statistically significant (Mann–Whitney U test at 3 months, $p = 0.26$; at 6 months, $p = 0.38$, at 12 months, $p = 0.20$).

A meta-analysis of 10 studies reporting 6-month abstinence (supplementary online material) found significant heterogeneity (Cochran's $Q = 48.7$, $p < 0.001$; $I^2 = 81.5\%$). The pooled relative risk of cytisinicline versus all comparators was 1.38 (95% CI: 1.06–1.77; random-effects model).

Differences in study design (e.g., non-inferiority trials by Oreskovic et al.,[8] Courtney et al.,[6] and Walker et al.[3,11]), dosing regimens, and control groups contribute to heterogeneity. Results should therefore be interpreted with caution and, where relevant, stratified by comparison type. Our limitations include the lack of a formal bias assessment.

Two systematic reviews published in 2023 concluded that cytisinicline was superior to placebo at 6 months, with moderate certainty: Ofori et al.[14] reported an RR of 2.25 (95% CI: 1.13–4.47) and the Cochrane review by Livingstone-Banks et al.[2] reported an RR of 1.30 (95% CI: 1.15–1.47). Differences in inclusion criteria explain variations to some extent. Livingstone-Banks et al.[2] required studies to report abstinence outcomes at ≥6 months and accepted self-reported abstinence, although biochemical verification was preferred. Ofori et al.[14] included only biochemically verified outcomes in the primary analysis, although they used self-reported data for the secondary objectives.

Compared to NRT monotherapy, cytisinicline has shown superior efficacy, although with low certainty[2,3]; and no recent trials have compared it directly with bupropion.

Regarding varenicline, the studies included in both reviews (Walker et al.[11] and Courtney et al.[6]) failed to confirm the non-inferiority of cytisinicline compared to varenicline. While cytisinicline appears less effective than varenicline in clinical trials, the reviews published in 2023[2,14] suggest that the smoking cessation benefit of both drugs may be comparable [Ofori et al.,[14] RR 1.13 (95% CI: 0.65–1.95); Livingstone-Banks et al.,[2] RR 1.00 (95% CI: 0.79–1.26)]. However, the evidence supporting this conclusion remains limited.

Oreskovic et al.[8] also compared cytisinicline and varenicline but this study was not included in either review. Although it reported only self-reported abstinence, its findings remain relevant as it was conducted in primary care settings in countries more comparable to our own.

Our analysis summarizes the most recent evidence on cytisinicline efficacy. Several studies were not included in the 2023 systematic reviews due to differences in inclusion criteria or publication timing. Rungruanghiranya et al.,[10] Tavakoli et al.[9] (psychiatric population), Phusahat et al.[7] and Rigotti et al.,[13] for example, were published after the Cochrane review[2] began in April 2022. The study of Nides et al.,[5] who reported 3-month outcomes, was excluded by Livingstone-Banks,[2] but included by Ofori et al.[14] as a secondary outcome and by Rigotti et al.[13] in their primary analysis.

We did not find significant differences in abstinence rates between standard and alternative cytisinicline regimens. Nevertheless, studies by Nides et al.[5] and Rigotti et al.[13] using 3 mg TID showed higher abstinence rates, which may have clinical relevance. Moreover, prolonged treatment increases withdrawal rates.[13]

Notably, cytisinicline has a much shorter plasma half-life than varenicline and minimal metabolism. It is renally eliminated, with 90%–95% of the drug being excreted unchanged in the urine[1] and offers advantages that could enhance its real-world effectiveness.[15] Cytisinicline is better tolerated, showing fewer adverse effects (mostly soft and gastrointestinal symptoms) than varenicline,[2,6,8,11,14] with no increase in safety concerns with increasing drug doses.[5,13] In addition, cytisinicline has better adherence.[2,14]

In clinical practice, the funding of cytisinicline has increased its use in attempts to quit smoking and it has been used in adults over 65.[16] Further research is needed in special populations, including older adults and those with hepatic or renal impairment. Evaluating alternative regimens and combination strategies may help optimize the therapeutic potential of cytisinicline. Given its favorable pharmacological profile and the emerging clinical data, cytisinicline represents a promising alternative for smoking cessation. However, its role in treatment guidelines remains limited, pending more consistent and robust evidence from future trials.

Ethical considerations

In this paper we have analysed results from selected studies, ensuring that no direct patient data were collected, analyzed, or utilized at any stage of the research.

Declaration of generative AI and AI-assisted technologies in the writing process

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

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Authors' contributions

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.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.opresp.2025.100472.

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