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Scientific Letter

Effectiveness of Cytisinicline Treatment in Hospital Smoking Units

Efectividad del tratamiento con citisiniclina en unidades de tabaquismo hospitalarias

Dear Editor,

Smoking is a chronic physical and psychological addictive disease, associated with learned behavior and social dependence. Comprehensive smoking cessation intervention is needed to help patients overcome nicotine addiction, unlearn a behavior, and modify environmental influences.[1] Pharmacological treatment for smoking cessation must be administered in the framework of a comprehensive intervention that offers cognitive-behavioral interventions and regular follow-up.[2]

Cytisinicline has been used in Eastern Europe since the second half of the 20th century,[3] while in Spain it has been available in an unfunded form since 2021 and in a funded form from 2023. It is safe and more effective than placebo in aiding smoking cessation, with a 1b level of evidence.[4,5]

Nineteen observational studies on the effectiveness of cytisinicline for nicotine dependence in patients treated in hospital smoking units were presented at the 56th and 57th Congresses of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Observational research under real-world conditions is essential and complements experimental trials.[6] Our aim was to synthesize and analyze these findings.

Five studies were excluded from the selection. Two did not report the duration of abstinence and 3 were preliminary or partial studies using data from studies already included in the selected papers. The 14 selected studies provided abstinence outcomes at 1, 3, 6 or 12 months and included a total of 1136 patients receiving standard cytisinicline treatment[7] (Landin Rey et al.,[8] Mata Calderón et al.,[8] Torba Kordyukova et al.,[8] Pou Álvarez et al.,[9] Lago Lagunas et al.,[9] 3 studies by Ignacio Expósito et al.,[9] Juarros Martínez et al.,[9] Fontoba Díaz et al.,[9] Cañón Barroso et al.,[9] Vaquero Lozano et al.,[9] Cristóbal Fernández et al.,[9] García Pulido et al.[9]). Some patients also received different treatments: 97 received bupropion, 36 received combined nicotine replacement therapy (NRT), 3 received fast-acting NRT, 1 received nicotine patches, 24 received cytisinicline with fast-acting NRT, 23 followed a sequential regimen starting with cytisinicline the NRT, while 14 received no drug therapy.

Seven of the studies were prospective and 7 were retrospective. A study by Ignacio Expósito et al.[9] compared the effectiveness of unfunded and funded cytisinicline, and reported no significant difference between them. We disaggregated these reports into 2 different studies, so the analysis presented here was performed on 15 studies. Since authors provided the data, the results of their study and those of Cañón Barroso et al.[9] were recalculated using an intention-to-treat approach. Fig. 1 shows abstinence rates at 3 and 6 months. Data were analyzed using SPSS© version 26. Ethical considerations: This study strictly adhered to ethical guidelines by ensuring that no direct patient data were collected, analyzed, or utilized at any stage of the research.

Weighted mean abstinence was calculated, considering methodological heterogeneity and the relative weights of each study.

The weighted mean abstinence at 1 month (8 studies, 544 participants) was 78.3% with a standard deviation (SD) of 19.4. At the 3-month follow-up (13 studies, 486 participants), abstinence was 49.7% (SD 12.4). For abstinence at the 6-month follow-up (12 studies, 332 participants), a weighted mean of 38.2% (SD 13.8) was obtained. Only 3 studies involving 65 participants provided data at the 12-month follow-up, with a weighted mean smoking cessation rate of 27% (SD 15).

The non-parametric Mann–Whitney *U* test did not show statistically significant differences between prospective and retrospective studies for continued abstinence at 1 month ($p = 0.43$), at 3 months ($p = 0.28$), or at 6 months ($p = 0.46$).

Three studies specified in the article that they used it for biochemical verification of abstinence. There is no difference in the rates of self-reported or unspecified reports of abstinence at 3 months ($p = 0.15$) and at 6 months ($p = 0.67$).

No significant difference was found between cytisinicline and bupropion (Pou Álvarez et al.[9]), though higher abstinence rates were seen with combined NRT (Juarros Martínez et al.,[9] Fontoba Díaz et al.[9]). The sequential regimen starting with cytisinicline followed by NRT showed higher abstinence rates at both 3 months (45.4% vs 28.5%) and 6 months (73.9% vs 53.8%) compared to cytisinicline alone; however, no statistically significant difference was found (Fontoba Díaz et al.[9]).

Ten studies reported adverse events (16.2% weighted mean incidence, SD 16) that were mostly mild and included gastrointestinal symptoms, headache, insomnia, and weight gain.

The observational studies analyzed at the SEPAR Congresses provide valuable information, showing high effectiveness rates with cytisinicline.

Compared with efficacy results from clinical trials, such as the Phusahat et al.[10] study, which examined the standard 25-day descending schedule of cytisinicline plus 5 sessions of health counseling, abstinence rates of 26.9%, 16.4% and 14.9% were obtained at 12, 24 and 48 weeks of follow-up, respectively. In contrast, Courtney et al.,[11] using the standard schedule, achieved an abstinence of 11.7% at 7 months of follow-up.

We also have evidence using different treatment regimens. Pastorino et al.[12] employed 2 experimental arms: one received cytisinicline for 40 days (165 tablets) and the other for 84 days (274 tablets). This study reported a 1-year smoking cessation rate of

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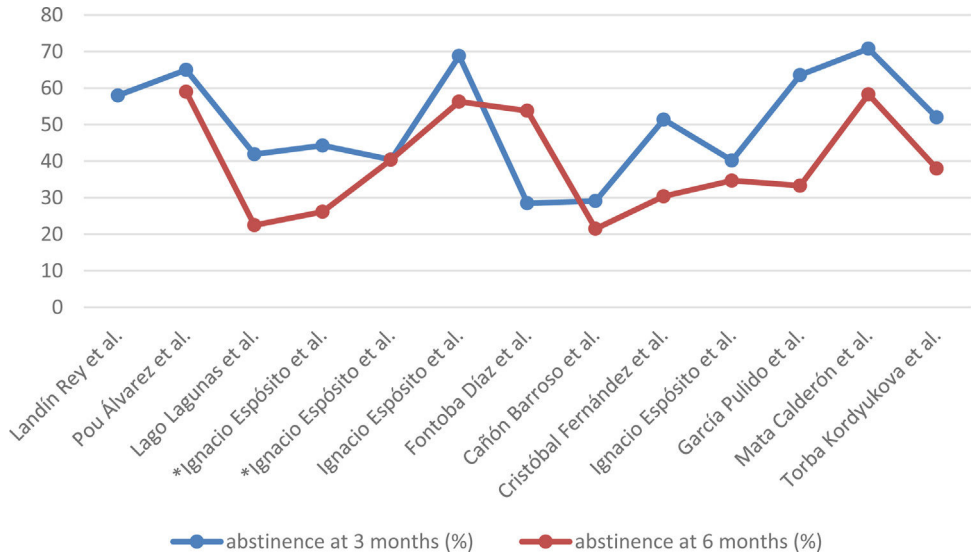

Fig. 1. Abstinence rates at 3 and 6 months. Studies from the SEPAR specialist smoking areas published at the 56th and 57th SEPAR Congresses. *Study comparing effectiveness of funded vs. unfunded cytisinicline, data disaggregated into 2 studies. These results, along with those of Cañón Barroso et al. were recalculated using an intention-to-treat approach.

32.1%, slightly higher than the 27% observed in the studies analyzed here. Walker et al.[13] provided an extended treatment regimen with 2 tablets daily from day 26 to 84. This study found a 6-month abstinence rate of 12.2%. In contrast, Rigotti et al.[14] studied the effect of 3 mg cytisinicline tablets 3 times a day for 6 and 12 weeks. Abstinence rates at 9 and 12 weeks (22.3% and 32.6%) were lower than those reported at 3 months in the hospital-based smoking cessation studies. By 24 weeks, rates had further declined to 13.8% and 21.1%.

Our findings should be interpreted with caution, as they represent a synthesis of studies presented at congresses and subsequently published in a peer-reviewed and indexed supplement of Open Respiratory Archives. While these studies exhibit methodological heterogeneity, they provide valuable real-world insights that complement clinical trials.

Pending U.S. Food and Drug Administration approval, cytisinicline achieved abstinence rates of 49.7% and 38.2% at 3 and 6 months, respectively, in combination with psychological support. Further trials are needed to evaluate varied dosing regimens which could enhance its real-world effectiveness.

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Authors' contributions

Original editor: Raúl Majo García. Andrea Crespo and Esther collaborated in the revision and selection of the articles, Guadalupe Espinosa proposed the methodology, María Nélida Fernández and Daniel Fernández collaborated reviewing the statistics and methodology.

Conflicts of interest

María Guadalupe Espinosa Villoria declares that she received support from Roche Diagnostics SLU in the form of reagent kit supplies, in support of her study 'SARS-CoV-2 Vaccine: The challenge of durable immunity'. The other authors declare no conflicts of interest that might influence the content of the manuscript directly or indirectly.

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