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ERS STUDY PROTOCOLS

CEASE (Collaborative European Anti-Smoking Evaluation): a challenging multicentre trial organized by the European Respiratory Society

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Smoking has recently been confirmed by PETO *et al.* [1] as one of the major causes of death in the developed countries. According to the estimates of these authors, by the end of this century about 30% of all deaths in the age range 35–69 yrs and 14% of deaths in the more elderly will be caused by cigarette smoking in developed countries. Unfortunately, despite determined efforts to reduce the number of smokers, 30 to 50% of the adult population in Europe is still smoking [2].

Addiction to smoking is multifactorial, varying with individuals and changing with time. Two important factors are the psychological component and the nicotine addiction [3–5]. With regard to nicotine dependence, the US Surgeon General in 1988 stated that "nicotine is a highly addictive substance comparable in its psychological and physiological properties to other substances of abuse" [6]. The statement clearly pointed out the importance of nicotine replacement therapy in smoking cessation programmes. Chewing gum, followed by transdermal patches, were the first available tools for delivering nicotine; recently a report on nasal sprays has also been published [7–11].

15 years of research on the pharmacological effects of nicotine [12], has led to the performance, over the last few years, of large clinical trials designed to assess the success rate for different methods of nicotine delivery in assisting smoking cessation. Most of these studies showed a success rate of 15–35% after one year [8–10].

Despite having improved our knowledge about nicotine replacement therapy, we still need to answer many basic questions on such points as duration of the treatment, optimal nicotine dose, and relative efficacy of the different forms of nicotine administration and their possible combinations. Also, we need to focus on relapse and causes for relapse, as 60–75% of participants in smoking cessation trials are "failures" after one year [7–10].

Nevertheless, we believe that it is now time to promote the rationale and the practical aspects of nicotine replacement therapy among European pulmonary physicians. With this background in mind, the Scientific Assembly on Epidemiology, Occupational-Environmental Medicine and Health Education of the European Respiratory Society (ERS) decided to organize a European multicentric study to investigate additional aspects of nicotine replacement therapy. We have selected the nicotine patch for its ease of use, being less dependent on adequate instructions than nicotine chewing gums. In contrast to the gum, the patch delivers nicotine at a constant rate of about 1 $mg \cdot hour^{-1}$, with no possibility to selftitrate the dose. A multicentre study based on 900 smokers in the US reported a dose-response effect on success rate for three different nicotine patch doses, using a 24 hour patch [10]. We feel it is important to try to confirm these findings in Europe using a 16 hour patch, which avoids nicotine replacement during sleep, testing different doses and duration for treatment. A large clinical trial, conducted on behalf of the ERS, will not only provide vital scientific information but also promote the concept of nicotine replacement therapy among chest physicians in Europe.

The ERS Collaborative European Anti-Smoking Evaluation (CEASE) will be based on a randomized, double-blind, parallel group design in order to compare: 1) different dosages of nicotine replacement therapy and 2) a different duration of the treatment. Three thousand (3000) smokers will be enrolled from selected Pulmonary Divisions in the following countries: Norway, Sweden, Denmark, Finland, The Netherlands, Belgium, France, Ireland, United Kingdom, Germany, Italy, Spain, Greece, Austria, Switzerland, and Portugal. Smokers, enrolled in the study by standard advertising methods following local laws, will be evaluated for: 1) presence of respiratory symptoms (by standard questionnaire); 2) forced spirometry (forced vital capacity and derived expiratory flows); 3) psychological status (motivation to quit smoking, familial background, anxiety, depression, *etc.*); 4) nicotine and cotinine plasma concentrations; 5) nicotine dependency (FAGERSTRÖM questionnaire) [13]; 6) expired carbon monoxide level; 7) body weight; and 8) medical history and physical examination including systemic blood

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pressure. During the full dose treatment, nicotine and cotinine plasma values will be measured at regular intervals, in order to evaluate the efficacy of the nicotine replacement therapy in terms of substitution and, later, for checking the compliance of treatment and the consistency of the smoking status. The end-point evaluation will be the smoking status after 12 months; additional assessments at 18 and 24 months will be performed. Smoking reduction will also be considered in the final analysis, although it must not be considered as a "success". Finally, lung function and the presence of respiratory symptoms will be reassessed to provide objective measurements of the beneficial effects of quitting cigarette smoking. The success rate in the different treatment groups (different doses, durations, and placebo) will be evaluated in relation to basal nicotine/cotinine plasma values during smoking, nicotine dependency, gender, age, number of quit attempts, psychological status and other factors.

An interesting and innovative aspect of CEASE will be the organization of the data collection. Data will be collected using a computerized system in order to save time and reduce errors, both at the time of collection and during the process of transferring data to a "magnetic support". Thus, all parameters will be automatically checked for consistency. All centres will use a personal computer with a special data-base system which will facilitate both the organization of the visits for each subject and the progressive collection of the information. Each centre will be connected through a special network to the main centre for statistical analysis. During the collection phase, data from each centre will be checked on line by the main centre. Nicotine/cotinine plasma values will be the only off-line parameters. Using this system, data will be checked and updated on a daily basis and thus be rapidly available for partial analyses. All centres will receive the protocol and instructions in their native language. However, the data-base will be structured in English, which is the official common language of our Society.

One of the main objectives of the European Respiratory Society is the promotion of research in pulmonary medicine. The implementation of a trial on smoking cessation allows the ERS to take a major step forward. Indeed, this clinical trial may provide information to aid development of programmes for the prevention of lung diseases, such as lung cancer and chronic obstructive pulmonary disease (COPD).

The study is fully sponsored by Kabi-Pharmacia (Sweden), a pharmaceutic company which has been involved in the field of smoking cessation from many years. Kabi-Pharmacia will support all the computerized systems for the centres, the medication, CO analyzers, *etc.* However, the ERS is responsible for the scientific control of the study. The Scientific Assembly on Epidemiology, Occupational-Environmental Medicine and Health Education has appointed a Steering Committee (made up of experts in the field of smoking cessation, epidemiologists, statisticians and lung physicians) with the specific task to design the study protocol and the instruction for all the centres. A Scientific Committee has also been appointed with the aim of critically reviewing the work of the Steering Committee in order to guarantee the scientific quality of the trial. Finally, a Safety Committee has been nominated to evaluate possible unethical and risk aspects of the study.

Another further aspect of interest is the great effort involved in running a standardized research protocol in different countries with different languages, laws and cultural background. This follows a recent decision by the ERS to endorse and support multicentric trials of major general interest, such as the ongoing "EUROSCOP" [14] designed to assess the efficacy of inhaled steroids in the prevention of the decline of lung function in patients with COPD. It is heartening to report that, during the development of this project, Europe acted as a unit without barriers, regardless of the recent difficult economical and political events.

In conclusion, CEASE may be the proof that it is possible to develop effective research projects by the conjunction of motivated researchers from different countries supported by enlightened pharmaceutical industrial groups which understand the importance of focusing on specific research questions without stressing the marketing aspects. We hope to be able to pursue smoking cessation - inclusive of nicotine replacement therapy - in the daily work of the European chest physicians, thus underlining the importance of prevention in this area of health care.

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