Nocturnal oxygen therapy in patients with chronic obstructive pulmonary disease: A survey of Canadian respirologists

Yves Lacasse MD MSc, Frédéric Sériès MD, Sylvie Martin MSc, François Maltais MD

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BACKGROUND: Current evidence does not clearly support the provision of nocturnal oxygen therapy in patients with chronic obstructive pulmonary disease (COPD) who desaturate during sleep but who would not otherwise qualify for long-term oxygen therapy (LTOT).
OBJECTIVES: To characterize the perception and clinical practice of Canadian respirologists regarding the indications and prescription of nocturnal oxygen therapy in COPD, and to determine what Canadian respirologists consider an important treatment effect of nocturnal oxygen therapy in a randomized, placebo-controlled trial.
METHODS: A mail survey of all the respirologists registered in the 2006 *Canadian Medical Directory* was conducted.
RESULTS: A total of 543 physicians were surveyed. The response rate was 60%, and 99% of the respondents indicated that the problem of nocturnal oxygen desaturation is clinically relevant. Eighty-two per cent interpret oximetry tracings themselves, and 87% have access to a sleep laboratory. Forty-two per cent believe that all COPD patients with significant nocturnal desaturation should have a polysomnography to rule out sleep apnea, and 41% would prescribe nocturnal oxygen therapy to active smokers. Assuming a risk of death or progression to LTOT of 40% over a three-year period, the respirologists indicated that to declare nocturnal oxygen therapy effective in reducing the rate of major clinical events in a clinical trial, the minimal absolute risk difference of death or progression to LTOT between oxygen and room air breathing should be 14%.
CONCLUSIONS: Canadian respirologists are interested in the issue of nocturnal oxygen desaturation in COPD. There is variation in clinical practices among Canadian respirologists in several aspects of the management of this problem.

Key Words: *COPD; Mail questionnaire; Oxygen therapy; Survey*

L'oxygénothérapie nocturne chez les personnes atteintes d'une maladie pulmonaire obstructive chronique : une enquête auprès des pneumologues canadiens

HISTORIQUE : Les données probantes courantes n'étayent pas clairement l'administration d'oxygénothérapie nocturne chez les personnes atteintes d'une maladie pulmonaire obstructive chronique (MPOC) qui désaturent pendant leur sommeil mais qui ne seraient pas autrement admissibles à une oxygénothérapie à long terme (OTLT).
OBJECTIFS : Caractériser la perception et la pratique clinique des pneumologues canadiens au sujet des indications et de la prescription d'oxygénothérapie nocturne en cas de MPOC et déterminer ce que les pneumologues canadiens considéreraient comme un effet important du traitement par oxygénothérapie nocturne dans le cadre d'un essai aléatoire contrôlé contre placebo.
MÉTHODOLOGIE : Les auteurs ont mené une enquête postale auprès de tous les pneumologues inscrits dans le *Canadian Medical Directory* de 2006.
RÉSULTATS : Au total, 543 médecins ont été sondés. Le taux de réponse était de 60 %, et 99 % des répondants ont indiqué que le problème de désaturation nocturne en oxygène était pertinent d'un point de vue clinique. Quatre-vingt-deux pour cent interprétaient eux-mêmes le tracé d'oxymétrie, et 87 % avaient accès à un laboratoire du sommeil. Quarante-deux pour cent étaient d'avis que toutes les personnes atteintes de MPOC présentant une importante désaturation nocturne devraient subir une polysomnographie pour écarter la possibilité d'apnée du sommeil, et 41 % prescriraient une oxygénothérapie nocturne aux fumeurs actifs. En postulant un risque de décès ou d'évolution vers l'OTLT de 40 % sur trois ans, les pneumologues ont indiqué que pour déclarer l'oxygénothérapie nocturne efficace à réduire le taux d'événements cliniques majeurs dans le cadre d'un essai clinique, la différence minimale de risque absolu de décès ou d'évolution vers l'OTLT entre la respiration d'oxygène et celle d'air ambiant devrait s'élever à 14 %.
CONCLUSIONS : Les pneumologues canadiens s'intéressent à la question de l'oxygénothérapie nocturne en cas de MPOC. On remarque une variation de la pratique clinique des pneumologues canadiens à l'égard de divers aspects de la prise en charge de ce problème.

Long-term oxygen therapy (LTOT) is the only component of the management of chronic obstructive pulmonary disease (COPD) that improves survival in patients with severe daytime hypoxemia (defined as an arterial oxygen pressure [PaO_2] measured in the stable state of 55 mmHg or lower, or in the range of 56 mmHg to 59 mmHg when clinical evidence of pulmonary hypertension or polycythemia are noted) (1,2). Several studies (3-11) have demonstrated oxygen desaturation during sleep in patients with COPD. The earliest studies that described this phenomenon included patients with marked daytime hypoxemia qualifying for LTOT. Conventional LTOT, given 15 h/day to 18 h/day, compulsorily includes sleep time and therefore corrects sleep-related hypoxemia. However, sleep-related oxygen desaturation often occurs in patients not qualifying for LTOT. Sleep-related oxygen desaturation is considered by many physicians as an indication for providing nocturnal oxygen therapy in patients who would not otherwise qualify for LTOT. This perceived indication stems from the suggestion that the natural progression of COPD to its end stages of chronic pulmonary hypertension, severe hypoxemia,

Centre de recherche, Hôpital Laval, Institut universitaire de cardiologie et de pneumologie de l'Université Laval, Sainte-Foy, Québec
Correspondence: Dr Yves Lacasse, Centre de Pneumologie, Hôpital Laval, 2725 Chemin Sainte-Foy, Sainte-Foy, Québec G1V 4G5.
Telephone 418-656-4747, fax 418-656-4762, e-mail Yves.Lacasse@med.ulaval.ca

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right heart failure and death is dependent on the severity of desaturation occurring during sleep (12,13).

Despite the lack of clear guidance by scientific societies regarding the indications for and use of nocturnal oxygen therapy in COPD patients not qualifying for conventional LTOT, a number of patients are currently treated with nocturnal oxygen (14). This is occurring even after two small randomized, controlled trials (15,16) and their meta-analysis (17) do not clearly support this clinical practice. Further research is warranted in this area.

We report the results of a mail survey of Canadian respirologists that was conducted with the primary objective of characterizing their perception and clinical practice regarding the indications and prescription of nocturnal oxygen therapy in patients with COPD. Our secondary objective was to determine what Canadian respirologists consider as an important treatment effect of nocturnal oxygen therapy in a placebo-(room air) controlled clinical trial. The present study is as an important preliminary step in our planning of a national multicentre, randomized, controlled trial of oxygen therapy in patients with COPD, in which the primary outcome is a composite of all-cause mortality or progression to LTOT.

METHODS

Study population

A total of 543 respirologists who were registered in the 2006 *Canadian Medical Directory*, which lists more than 90% of the physicians currently licensed in the country, were surveyed.

Questionnaire

The mail survey was organized into four sections. The first section was designed to collect general information about the respondents, including sex, year of graduation, clinical experience with the management of COPD, and their involvement in the organization and/or delivery of home oxygen therapy services in their area. The second section related to the diagnosis and treatment of nocturnal desaturation. In this section, the questionnaire included four short scenarios to examine the perceived indications for nocturnal home oximetry in specific clinical circumstances.

The third section of the questionnaire was to determine what Canadian respirologists consider as a minimal important treatment effect of nocturnal oxygen therapy on mortality or disease progression. Such information has important implications for sample-size calculation in randomized trials (18). The following background information was provided:

Although nocturnal oxygen is often prescribed in patients with COPD, the magnitude of its treatment effect (if any) remains unknown. From the current literature, we know that, over a three-year period: the mortality of patients with moderate-to-severe COPD not qualifying for LTOT but who desaturate overnight is about 20%; and an additional 20% will be prescribed LTOT because of disease progression. Therefore, the three-year major clinical event rate (including progression to severe hypoxaemia necessitating LTOT or death) in this group of patients is roughly 40%.

The supporting references (16,19) were not cited in the questionnaire. The minimal important difference was determined using two different questions. The first one addressed the issue of benefit of nocturnal oxygen in terms of absolute risk reduction ("To what proportion would you like to see nocturnal oxygen therapy decrease this event rate before declaring it to be clinically effective?"). The second question directly elicited a number needed to treat (NNT) ("To consider nocturnal oxygen therapy effective in patients with COPD, to how many patients would you be willing to administer nocturnal oxygen to prevent one patient from a major clinical event (ie, death or progression to LTOT) over a 3-year period?").

In the final section of the questionnaire, the respondents were invited to inform the authors about their potential interest in participating in a future randomized trial of nocturnal oxygen therapy in COPD patients. The French version of the questionnaire was pilot-tested on five respirologists and translated into English after modifications and clarifications were made. Five minutes were sufficient to complete the questionnaire.

Survey

The survey was conducted in April and May 2006 according to the 'total design method' described by Dillman (20). Each respirologist was mailed a package containing a cover letter, a questionnaire in his/her language (French or English) and a prepaid reply envelope. Each questionnaire was numbered and coded for identification, and to protect confidentiality. This first shipping was then followed after one week by a reminder postcard. Four weeks later, those who had not responded to the initial questionnaire were sent a second package that was identical to the first one, except for the cover letter mentioning that their questionnaire had not yet been received.

Statistics

Response rate: The response rate was calculated as the ratio of analyzable responses over the number of eligible physicians that were reached (21):

$$\text{Response rate} = \frac{\text{Number of respondents contributing to the analysis}}{\text{Number of questionnaires sent} - (\text{Noneligible} + \text{Nonreachable})}$$

Physicians who returned their questionnaire indicating that they do not see patients presenting with COPD in their practice were designated 'noneligible'. Physicians whose first package was returned to us were designated 'nonreachable'. Newfoundland and Labrador, Nova Scotia, Prince Edward Island and New Brunswick were analyzed as the 'Atlantic provinces', and Alberta, Saskatchewan and Manitoba as the 'Prairies'. The other provinces (Ontario, Quebec and British Columbia) were analyzed separately. A response rate of 60% was predicted a priori (21).

Analysis: Descriptive statistics (proportions and means ± SDs when appropriate) were used to characterize the respondents and to report the results of the survey. For each respondent, the absolute risk difference corresponding to the minimal important difference in major event rate between treated patients and untreated patients was calculated by subtracting the expected event rate in the treated group (elicited by the questionnaire) from the estimated event rate in the untreated group (which was assumed to be 40%). From this absolute risk difference, the corresponding NNT was computed (computed NNT=1/absolute risk difference). Finally, the concordance between the computed NNT and the elicited NNT using the intraclass correlation coefficient was examined (22).

RESULTS

Respondents

Five hundred forty-three respirologists were sent the questionnaire, and 332 replied. Of these respondents, 280 completed

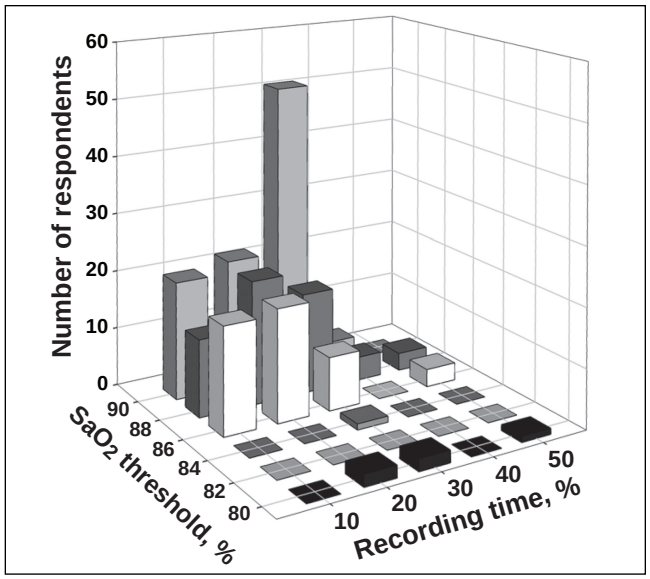

Figure 1) *Definition of 'significant nocturnal oxygen desaturation' (215 respondents; four outliers do not appear on the graph) expressed in terms of percentage of the recording time spent below a given threshold saturation. SaO_2 Arterial oxygen saturation*

the questionnaire and 52 indicated that they are not involved in the care of patients with COPD. Twenty-three packages were returned by the post office as undeliverable. Therefore, the response rate among potentially eligible respondents was (332–52)/(543–[52+23]), or 60%.

All the regions of the country were represented, with response rates ranging from 80% in the Atlantic provinces to 49% in the Prairies. Twenty-three per cent of the respondents were female. On average, the respondents were in clinical practice for 23±9 years. A significant proportion of the respondents' clinical practice was dedicated to the care of patients with COPD (mean 30±17%). One hundred fifty respirologists (54%) indicated that they are involved in the organization and/or delivery of home oxygen therapy in their area.

Diagnosis and treatment of nocturnal desaturation

Only four respondents (1%) indicated that the problem of nocturnal oxygen desaturation in patients with COPD should not be considered. These respondents were instructed not to go further in the questionnaire and to return it as is.

Among the other 276 respondents, 87% indicated that they have already prescribed nocturnal oxygen; 97% have access to pulse oximeters, and 82% interpret oximetry tracings themselves. In addition, 87% of the respondents have access to a sleep laboratory in their institution. For 42% of the respondents, a full sleep study was deemed necessary in all cases to rule out sleep apnea. Fifty-seven per cent of the respondents indicated that one abnormal recording is sufficient to prescribe nocturnal oxygen; two abnormal recordings are necessary for 35% of the respondents. Forty-one per cent of the respondents would prescribe home oxygen (either LTOT or nocturnal oxygen only) to active smokers.

The question related to the definition of 'significant nocturnal oxygen desaturation' generated a wide range of responses. The vast majority (95%) indicated that the time spent below a given threshold is an important factor defining nocturnal oxygen desaturation. However, both the time and the threshold varied considerably among respondents (Figure 1). Approximately one-third of the respondents (34%) also considered the average saturation over the entire recording time to be important. The average saturation (88±2%) was quite similar among respondents (n=90). Finally, the lowest saturation (79±5%) reached during the night was also important for 25% of the respondents (n=62). Sixty-three respondents identified other factors defining 'significant nocturnal desaturation', the most frequent being polycythemia, cor pulmonale, symptoms of left heart failure at night, ventricular cardiac arrhythmias and unstable ischemic heart disease.

TABLE 1
Perceived indications of nocturnal home oximetry in specific clinical circumstances (n=276)

Clinical scenario	Number (%) of respondents who would request a nocturnal oximetry
Scenario #1 Mr W is a 63-year-old patient with severe chronic obstructive pulmonary disease (COPD). He has been stable during the previous year. His resting oxygen saturation is 93%.	48 (17.4)
Scenario #2 Mrs X is a patient with physical signs of right heart failure who otherwise does not qualify for long-term oxygen therapy.	269 (97.5)
Scenario #3 Mrs Y was hospitalized two months ago for an acute exacerbation of COPD that was complicated by severe hypoxemia. She then left the hospital with a new prescription of home oxygen. Upon re-evaluation, her resting PaO_2 (at room air) is now 65 mmHg.	138 (50.0)
Scenario #4 Mr Z is a 74-year-old patient with severe COPD (FEV_1, 36% predicted) who snores and complains of mild daytime sleepiness.	269 (97.5)

FEV_1 Forced expiratory volume in 1 s; PaO_2 Arterial oxygen pressure

The clinical scenarios and the associated responses are presented in Table 1. Clearly, the respondents would not screen for nocturnal oxygen desaturation in patients with stable COPD (scenario #1). Physical signs of right heart failure without severe daytime hypoxemia would prompt most respondents to look for nocturnal oxygen desaturation (scenario #2). The finding of an adequate PaO_2 at the time of re-evaluation, following an acute exacerbation complicated by severe hypoxemia, was seen as an indication of looking for nocturnal desaturation in one-half of the respondents (scenario #3). Finally, the vast majority of respondents would look for sleep apnea even in elderly patients with severe COPD (scenario #4).

Determination of the minimal clinically important difference

The absolute risk difference considered as minimal to declare nocturnal oxygen therapy effective in reducing the rate of major clinical events compared with room air breathing was 14±6%. The mean computed NNT was 9. When directly elicited by the questionnaire, the mean NNT was 13±12. No concordance was found between the computed NNT and the NNT directly elicited by the questionnaire (intraclass correlation coefficient of 0.0; Figure 2).

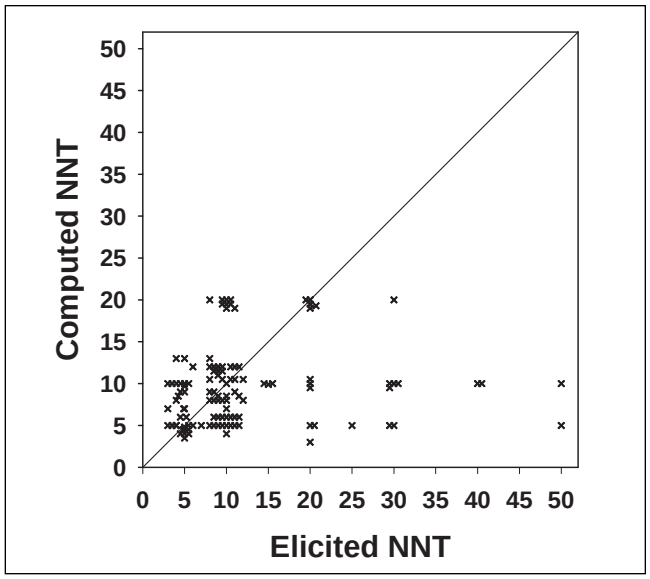

Figure 2) *Lack of concordance between the computed number needed to treat (NNT) and the elicited NNT*

Interest in participating in a future randomized trial

One hundred eight respondents (39%) from all regions of Canada indicated that they would be interested in participating in a randomized trial of nocturnal oxygen therapy in patients with COPD.

DISCUSSION

The response rate we obtained (60%) was typical of physicians' reply to mailed surveys, which usually averages 50% to 55% (21). We attempted to investigate the potential for nonrespondent bias by making a priori predictions on the response rate, and by examining the representation in the survey of physicians from all the regions in the country. The overall response rate met our a priori prediction. Also, all parts of Canada were represented in the survey.

Why should respirologists be interested in nocturnal oxygen desaturation? COPD clearly represents a significant burden of health care systems wherever it has been assessed (23). Home oxygen therapy comes in second place (only after hospitalizations) among the most expensive health care resources for COPD (24). In the Canadian cohort of the Confronting COPD survey (24) (3265 individuals; mean age of 63 years; 44% female), outpatient treatment for COPD accounted for over 30% of total direct costs, the majority of which was for home oxygen therapy. Overall, home oxygen therapy accounted for almost 20% of the entire annual direct costs for COPD (24). Informal surveys among respiratory home care programs in Quebec indicate that 15% to 20% of those who receive home oxygen therapy through these programs have been prescribed oxygen for nocturnal use only. Given the resources allocated to nocturnal oxygen therapy, its prescription should therefore be justifiable by demonstrating an improvement in clinical outcomes other than the mere correction of nocturnal oxygen desaturation.

However, the current evidence that nocturnal oxygen therapy prolongs survival comes only from the indirect comparison of the results of the British Medical Research Council Study (1) with those of the Nocturnal Oxygen Therapy Trial of the National Heart, Lung, and Blood Institute (2), and these results apply only to severely hypoxemic patients with COPD, ie, those with a diurnal PaO_2 of 55 mmHg or lower. To date, only two randomized trials directly addressed the issue of nocturnal oxygen therapy in patients with COPD with significant nocturnal oxygen desaturation who would not otherwise qualify for LTOT (15,16). The recent meta-analysis by Cranston et al (17) concluded that nocturnal oxygen has no effect on survival (pooled OR 0.97; 95% CI 0.41 to 2.31). However, the authors did not comment on the lack of precision in the effect estimate.

TABLE 2
Key elements of the upcoming Canadian Nocturnal Oxygen (CANOX) trial

Study population
Patients with chronic obstructive pulmonary disease fulfilling the definition of nocturnal oxygen desaturation, ie, 30% or more of the recording time with transcutaneous arterial oxygen saturation lower than 90% on two consecutive recordings. Patients with sleep apnea were excluded.
Intervention
Nocturnal oxygen therapy delivered overnight to allow the oxygen saturation to be higher than 90%; placebo (room air) delivered by a defective concentrator (sham concentrator).
Outcome
Composite of either all-cause mortality or requirement for long-term oxygen therapy.
Design
Three-year multicentre, placebo-controlled, randomized trial.

Among the recent COPD treatment guidelines (25-28), only the Canadian document (28) addressed the issue of nocturnal oxygen therapy, albeit in vague terms. Two recent workshops of the National Heart, Lung, and Blood Institute identified nocturnal oxygen therapy as a research priority in COPD (25,29). This situation stimulated our planning of a randomized trial of nocturnal oxygen therapy in patients with COPD, the Canadian Nocturnal Oxygen (CANOX) trial, in which the ultimate objective would be to examine the effect of nocturnal oxygen on mortality and disease progression requiring LTOT (Table 2).

The design of a randomized controlled trial of nocturnal oxygen raises important methodological problems in the choice of the primary outcome. In such a trial, whatever the treatment received, the condition of participants may deteriorate to the point that LTOT is required. This situation is particularly problematic because LTOT compulsorily includes sleep time (and therefore nocturnal oxygen therapy). LTOT would thus represent an important contaminant and a threat to the validity of the trial. Therefore, a composite of mortality or progression to LTOT would constitute the primary outcome of the trial. The choice of a composite outcome requires that its components are of similar importance, occur with similar frequency and have similar RR reduction (30). Whether disease progression requiring LTOT has the same weight as death for patients with severe COPD is debatable. However, we know that the prescription of LTOT is a marker of disease progression and a strong predictor of mortality (31-33). It is also associated with poor functional status, impaired quality of life and depression (34). Of note, in a trial by Chaouat et al (16), mortality and progression to LTOT were well balanced in proportion, and moved in the same direction.

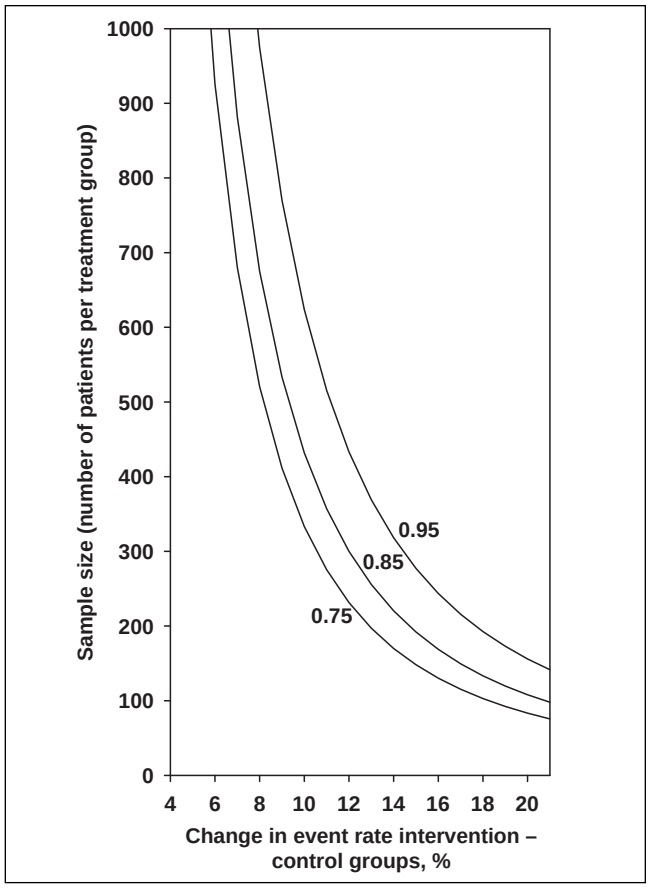

Figure 3) *Sample sizes (number of patients per group) required to detect absolute risk differences between treated and untreated patients, with two-sided significance level of 0.05 and varying study powers (0.75, 0.85 and 0.95). The risk of a major clinical event in the untreated group is assumed to be 40%*

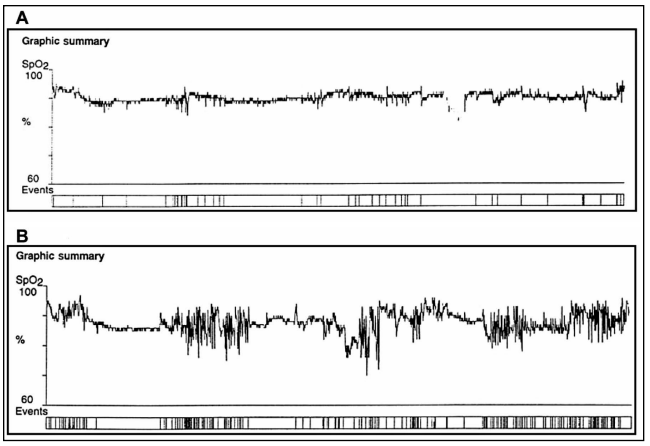

Figure 4) *Nocturnal oximetry tracings in patients with chronic obstructive pulmonary disease not qualifying for long-term oxygen therapy.* **A** *Nocturnal oxygen desaturation (30% or more of the recording time with an oxygen saturation lower than 90%) with nonperiodical variation in saturation throughout sleep. This tracing is not suggestive of sleep apnea.* **B** *Nocturnal oxygen desaturation with cyclical changes in saturation suggesting sleep apnea. SpO_2 Arterial oxygen saturation*

The results of our survey provided useful information for the planning of the CANOX trial. We were particularly interested in determining what Canadian respirologists consider as the minimal important difference in major event rate (ie, mortality or progression to LTOT) between untreated patients (room air) and treated patients (nocturnal oxygen). Our finding of a poor concordance between the computed NNT and that directly elicited by the questionnaire was of no surprise. Previous studies (21,35,36) also suggested that physicians' enthusiasm for therapy varies when the data are presented with the NNT compared with the absolute risk reduction. Assuming a major event rate of 40% in the untreated group, we determined that 221 patients per group were needed to demonstrate a 14% difference in event rates between the two study groups (power 85%; alpha error 5%, two-sided) (37). If the sample size was increased to 300 patients per group, the difference to be detected is 12%. Figure 3 illustrates that small changes in the difference to be detected have a huge impact on the needed sample size.

We clarified other components of the CANOX trial's protocol from the results of the present survey. The first one relates to the diagnosis of sleep apnea in patients with severe COPD and the routine use of polysomnography in such patients. Approximately 60% of the respondents would accept to confidently diagnose nocturnal oxygen desaturation alone on the basis of oximetry tracings only. Given the limited access to diagnostic facilities for patients with suspected sleep apnea in Canada (38), this argues in favour of a pragmatic approach for the inclusion of patients in the study on the basis of the pretest probability of sleep apnea and the results of oximetry tracings (Figure 4). The second issue relates to the inclusion of active smokers in the trial. Forty-one per cent of the respondents would prescribe nocturnal oxygen therapy to active smokers. Although less than desirable (39), this situation is a reflection of current practices in Canada that are not about to change. The current version of the study protocol does not exclude current smokers from the trial. A stratified randomization process should be used to ensure that smokers are equally distributed in treated and untreated patients.

Finally, that 108 respirologists expressed their willingness to participate in a multicentre trial of nocturnal oxygen therapy is very supportive and clearly demonstrates the interest raised by the problem of nocturnal oxygen desaturation in COPD patients. Our finding of variations in clinical practices in several aspects of the management of nocturnal oxygen desaturation is also an indication that further research is warranted. The present survey provided important information for the planning of a national randomized, placebo-controlled trial of nocturnal oxygen therapy in COPD.

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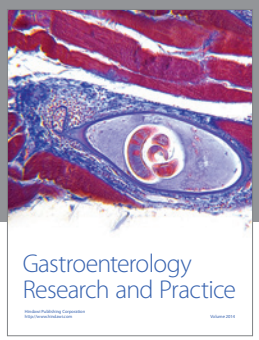

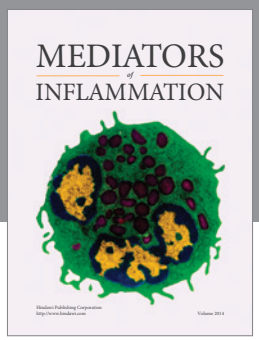

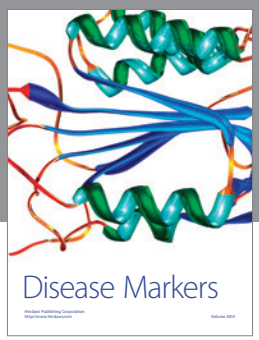

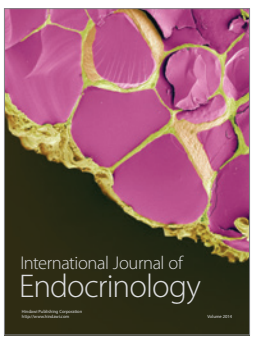

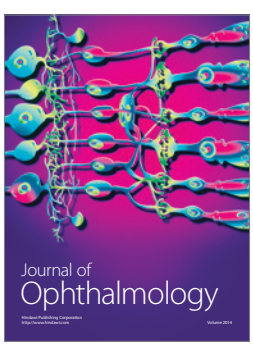

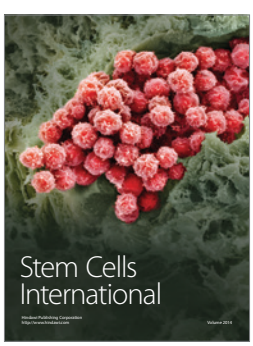

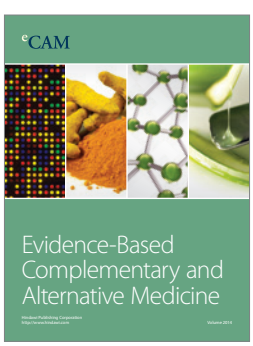

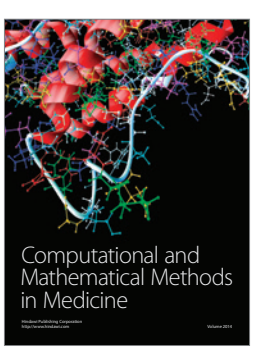

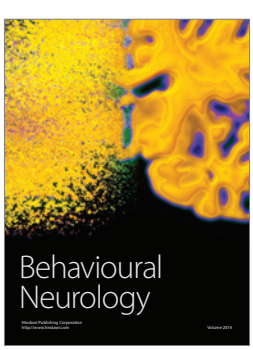

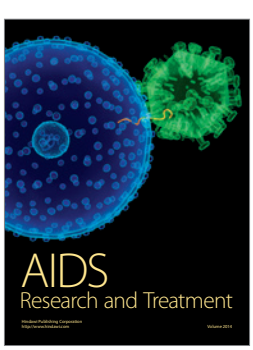

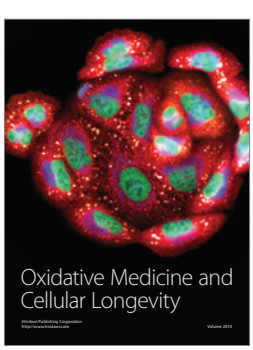

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