Varenicline as first aid to treat nicotine dependence in smokers with high prevalence of co-morbidities

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Abstract: Varenicline is a first line smoking cessation pharmacotherapy. Smokers with comorbidities are prevalent in our center. The aim of the study was to assess efficacy and safety of varenicline in current practice of a smoking cessation center treating smokers with high prevalence of concomitant disorders. 98 smokers with concurrent stable respiratory, cardiovascular, digestive and psychiatric disorders (study group) and 116 healthy smokers (control group) were treated with varenicline in a 12 weeks cure to quit smoking. Primary end point was carbon monoxide confirmed continuous abstinence rate in the study group at weeks 9B 12. Secondly, varenicline safety, discontinuation profile and compliance to treatment were monitored. 41.8% smokers with comorbidities (25/52 cardiovascular, 9/26 respiratory, 4/13 digestive, 3/7 psychiatric) and 40.5% healthy smokers successfully quit smoking. Withdrawal symptoms and adverse effects picture did not differ significantly between groups. Varenicline is an effective and highly compliant therapy for smoking cessation in smokers with comorbidities. Safety profile of varenicline is comparable in healthy smokers and smokers with stable comorbidities.

Key words: smoking cessation, Varenicline, comorbidities, nicotine dependence, safety, compliance

1. Introduction

Smoking is a major cause of premature morbi-mortality in the world. Moreover, tobacco use is recognized as the most important avoidable such risk factor, as life expectancy of smokers is, in average, with 5 - 8 years shorter than in never smokers, even if smoking related diseases do not intervene. Nearly one of every 5 deaths in the U.S.A. is due to cigarette smoking. [1]

Despite continuous tobacco control measures implemented in the last decades, tobacco consumption is still a current practice for about one third of globe’s population. Nowadays, 12% of women and 42% of men worldwide use tobacco [1]. Three out of 10 EU citizens aged 15 and over say they smoke: a quarter (26%) smoke daily and 5% occasionally. Most daily smokers are men, 25-54 year-olds and manual workers [2]. The percentage of smokers is the highest in Greece (42%), followed by Bulgaria (39%), Latvia (37%), Romania, Hungary, Lithuania, the Czech Republic and Slovakia (all 36%). [3]

Tobacco exposure influences almost every organ in the human body of active smokers and it has also negative effects over pregnancy and delivery in smoking women, as well as in passively tobacco smoke exposed individuals. All this happens because cigarette smoke contains 4800 identified chemical compounds, among which 250 cause cancer or are toxic in other ways [1]. It is estimated that 61 chemicals in tobacco smoke cause cancer, with polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines being major contributors. Carbon monoxide and other chemicals in tobacco smoke contribute to processes leading to cardiovascular disease, such as endothelial injury and dysfunction, atherosclerosis, platelet aggregation, thrombosis, low-grade inflammation, and increased levels of carboxyhemoglobin. Active smoking induces processes of oxidative stress, inflammation and protease–antiprotease imbalances that injure airways and alveoli and if sustained, conduct to chronic obstructive pulmonary disease.

As a consequence, chronic tobacco consumption is a main cause for many diseases, if we refer here just to cancers, chronic obstructive pulmonary disease (COPD), cardiovascular diseases, sudden death, cataract,
respiratory infections, gastric ulcer, etc. Quite often, in long time life smokers, several conditions alike may co-exist and smoking induced co-morbidities can become a real health burden. Chronic tobacco use is responsible not only for the above-mentioned diseases but also for exacerbations of many other conditions like asthma and diabetes, it compromises wound or post surgery healing and reduces efficacy of diseases’ treatment, if patients don’t quit smoking.

Furthermore, smoking defined as chronic use of any type of tobacco product (cigarette, cigar, pipe, narguile, bidis, snus, etc.) represents also a disease per se. Thus, it is listed in all disease classification manuals as a psychiatric disorder and defined as nicotine dependence. Because they contain nicotine, all tobacco products produce addiction. The pharmacologic and behavioral processes that determine addiction to tobacco products are similar to those that determine addiction to illicit drugs such as heroin or cocaine, this is why nicotine addiction must be regarded as seriously as any heavy drug addiction. Nicotine is an alkaloid component of tobacco that has addictive capacities as it is a psycho-active substance acting especially through reward (satisfaction) and memory systems.

Nicotine introduced in the body by smoking has the capacity to bind to specific nicotinic acetylcholine receptors found both in the central and peripheral nervous system. Thus, nicotine binding leads to opened ion channels (nicotinic receptors are ligand-gated to), allowing depolarisation and release of neurotransmitters, particularly dopamine. Addiction process in smokers is linked mainly to the binding of nicotine to α4 β2 nicotinic acetylcholine receptors in the ventral tegmental area, causing the release of dopamine in the nucleus accumbens [4].

The intensity of nicotine dependence is very high, by comparison to other illicit drugs.

On a progressive dependence scale from 5 to 1, nicotine dependence is scored to 1 > heroine (2) > cocaine (3) > alcohol (4) > caffeine (5). [5] In addition, natural bioavailability and reinforcing properties of nicotine can be influenced by industrial process of tobacco products fabrication, which makes this substance even more dangerous. [6] Yet, it appears hard to explain why tobacco, even if demonstrated that it harms every person exposed to and it kills approximately 50% of those who use it, still can be easily purchased and consumed everywhere in the world and still remains the single lethal product legally commercialized.

So far, and despite actual international regulations, smoking is still worldwide spread, especially because of poor education of population regarding risks over health and insufficient access to smoking cessation therapy.

Current smoking cessation guidelines recommend unanimously as efficient both smoking prevention programs in all categories of population and smoking cessation pharmacotherapy and counseling in current smokers. [5] Any intervention towards stopping smoking is welcomed in respect to the following basic principles: evaluation of smoking status for every patient at each medical visit, encouraging all smokers to stop smoking, underlining tobacco exposure risks for non-smokers, providing counseling and pharmacotherapy (nicotinic substitutes, bupropion, varenicline, etc.) to smokers willing to quit.

2. Profile of smokers with co-morbidities

In current practice, it appears more easy to treat nicotine dependence in “healthy” smokers compared to smokers with co-morbidities. Most frequent smoking related disorders are chronic respiratory or cardiovascular conditions. Psychiatric, digestive and oncologic disorders are frequently associated to chronic smoking. Also, elderly, HIV positive and diabetes mellitus smokers represent a population that experiences difficulties to stop smoking. Usually, smokers with chronic diseases smoke more, are more heavily addicted to nicotine, less educated and less willing to quit. As well, due to related diseases, probability of cessation therapy side effects or drug interactions is more frequently encountered in ill smokers.

On the other hand, such patients should be more vulnerable, more aware of the important health benefit smoking cessation could bring for their treatment outcomes and disease progression, thus more compliant to cessation interventions.
Smoking cessation is beneficial any time for human health, but it is the most urgent elementary medical gesture when smokers develop smoking related morbidity conditions. Most often, it is respiratory and cardiovascular health that is affected in chronic smokers. Continuing smoking has very harmful influence in onset and progression of chronic respiratory and cardiovascular disorders, either alone or in association.

Patients with respiratory disease have greater and urgent need to stop smoking than the average smoker, achieving beneficial improvement of their respiratory condition and of treatment outcomes. Data overview has shown that stopping smoking reduces risk of accelerated decline of FEV1 approximately to that of a never smoker [7] and risk of subsequent mortality and further cardiac events among patients with cardiovascular disease as well, by almost 50% [8].

However, speed and magnitude of cardiovascular mortality risk reduction when a smoker quits is still under debate. If some studies have found considerable risk reduction after 2-3 years, other estimate still risk exists even in 20 years quitters, by comparison to life-long no smokers [9, 10].

All these data sustain necessity to provide smoking cessation as precociously as possible in all categories of smokers, whether smoking related diseases developed or not, giving priority to those smokers at cardiovascular risk. [8]

Some particular aspects of nicotine dependence pharmacotherapy should be taken in consideration when treating smokers with chronic airway obstruction and inflammation, psychiatric disorders or poor prognosis conditions:

- Carbon monoxide assessment in exhaled air of COPD or asthmatic smokers may be related both to tobacco exposure and to chronic airway inflammation.
- Nicotine spray is not allowed in asthmatics
- Smokers with cancer are more depressive, less motivated to quit and require especially designed smoking cessation approach
- In smokers with psychiatric conditions, alcoholics and drug consumers, a more severe withdrawal syndrome is described. These individuals smoke more and need more intensive behavioral interventions added to pharmacotherapy. Sometimes, drug interactions require supplementary action taken.

3. Problem formulation

Smoking cessation is known to be less effective in patients with concomitant chronic disorders by comparison to „healthy smokers”. Yet, if a “healthy smoker” is diagnosed with a chronic or severe disease, it is expectable his motivation to quit will increase. [11]

Currently available medications to treat nicotine dependence in Romania are: nicotine gum 2 and 4 mg concentrations, nicotine patches 5, 10 and 15 mg dosage, bupropion and varenicline, as first line therapies. Except nicotine substitutes, all other medications are available under prescription. Moreover, Varenicline, Bupropion and nicotine patches are provided free of charge within a national health program, since 2007.

In our one decade experience with treating smokers to quit, highest abstinence rates were due to free of charge effective pharmacotherapy. [11]. In the same time, evidence show that Varenicline is the most efficient smoking cessation medication, with high levels of safety in various co-morbidities. [12]. Thus, we formulated the hypothesis that free of charge therapy with Varenicline is the best option for smokers with concomitant chronic disorders.

As prevalence of smokers with co-morbidities addressed to our smoking cessation center is high, we conducted a study to assess efficacy and safety of varenicline in current practice, when delivered to treat smokers with chronic concomitant disorders compared to „healthy” smokers. The primary end point of the study was abstinence rates at 9-12 weeks of treatment in the study group vs. control group, while secondary end-point refered to abstinence rates at 12 months follow-up.

4. Material and method

Study population was made of 214 smokers, adult patients divided in two groups: Group 1 represented by healthy smokers (control group) and Group 2 (smokers with concurrent stable respiratory, cardiovascular, digestive and psychiatric disorders (study group).

The following inclusion criteria applied:
- current smoker, >10 cigarettes/day in the past 12 months
- age > 18 yrs
- stable chronic: respiratory, psychiatric, cardiovascular, digestive disease
- compliance to 12 months follow-up assessment either by office visit during 12 weeks treatment, either by telephone visit at final evaluation

Exclusion criteria were:
never or former smokers
- current smokers with unstable chronic disease
- pregnancy
- < 18 yrs old
- recent (< 1 month) quit smoking attempts
- lost in follow up patient (> 2 absences at follow-up visits)

All 214 patients were evaluated at inclusion for:
- Smoking status as revealed by a validated questionnaire referred to chronic tobacco consumption (the number of packs-year = nr of years of smoking x average nr. of cigarettes smoked daily), recent tobacco consumption (daily cigarettes consumption in the past 12 months), nicotine dependence score (established by the Fagerstrom nicotine dependence test), motivational interview, previous quit attempts history.
- Any evidence of chronic respiratory, cardio-vascular, digestive or psychiatric disorders, as revealed from medical records and our hospital’s database.

Before treatment initiation, all smokers received brief advice to quit smoking (3-5 minutes short advice to quit smoking together with medical information about harmful effects of smoking and health benefits of stopping tobacco use). Also smokers were asked to answer a validated smoking cessation motivational interview (SCMI) - see Fig. 1.

1. Do you want to give up smoking now?
2. Do you have health concerns in relation to your ongoing diseases?
3. If answering yes to question 2, which is your major health concern?
   a) Respiratory   b) Cardiovascular
   c) Digestive     d) Psychiatric
4. Do you feel that smoking will affect your health status?
   a) Yes          b) No
5. Do you agree to receive smoking cessation pharmacological therapy?
   a) Yes          b) No

Both study groups were treated by free of charge smoking cessation counseling and pharmacotherapy with varenicline in a 12 weeks first treatment cure to quit smoking.

Standard 3 months smoking cessation program was structured in 4-6 sessions to provide smokers with cognitive-behavioral smoking cessation counseling +/- medication upon request - as 12 weeks varenicline daily (0.5 mg in days 1-3, 0.5 mg x 2 in days 4-7 and 1 mg x 2 till end of cure)

All subjects were asked to attend the center for several follow-up visits, at 2, 4, 8 and 9-12 week treatment stage. Each visit consisted of smoking status, withdrawal symptoms and standard dose therapy side effects clinical evaluation. A final 12 months evaluation was done by telephone contact.

Smoking status was assessed by initial and follow-up questionnaire at 0, 2, 4, 8, 12 treatment weeks and at 12 months follow-up visit when information collected either by phone, either by face to face interview. Smoking abstinence was defined as “0-5 cigarettes daily smoking patient with 0-6 ppm carbon monoxide levels in exhaled air, at successive follow-up visits, in the next 6 months after quitting smoking” [8]. This parameter was both recorded in medical files and validated by carbon monoxide determination in exhaled air at office visits.

Carbon monoxide concentration in exhaled air was monitored on regular basis at each office visit, as primary end point of the study was carbon monoxide confirmed continuous abstinence rate in the study group at weeks 9-12. Secondary end point (abstinence rates at 12 months follow-up) was validated by telephone visits.

5. Problem solution

5.1. Results

Subjects were divided into Group 1 (n= 98) and Group 2 (n=116), with subgroups 2a (n = 26 chronic respiratory disorders), 2 b (n = 52 chronic cardiovascular disorders), 2 c (n = 12 chronic digestive diseases), 2 d (n = 8 psychiatric chronic conditions).

Profile of smokers included in the study is shown in Table 1:

Fig. 1: Smoking cessation motivational interview (SCMI)
Continuous smoking abstinence was achieved in 41.8% of Group 2 and in 40.5% of Group 1. (Fig. 2)

Dinamic evaluation (Fig. 4) of abstinence rates at 12 weeks end of treatment and 12 months follow-up revealed a very positive cessation impact in Subgroup 2b, a modest impact in both subgroup 2a & Group 1 and a less satisfactory/almost insignificant impact in subgroups 2c and 2d.

Table 1: Demographic and smoking variables in the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2 a</th>
<th>Group 2 b</th>
<th>Group 2 c</th>
<th>Group 2 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>38.6</td>
<td>46.2</td>
<td>59</td>
<td>48.7</td>
<td>42.5</td>
</tr>
<tr>
<td>Recent tobacco consumption &gt; 20 cigs/day (%)</td>
<td>10</td>
<td>18.5</td>
<td>50</td>
<td>25</td>
<td>36.5</td>
</tr>
<tr>
<td>No packs-yrs (average)</td>
<td>18</td>
<td>20</td>
<td>38</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Nicotine dependence score &gt; 7 (%)</td>
<td>20</td>
<td>33</td>
<td>42.8</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>&gt;5 years of medical history (%)</td>
<td>Not applicable</td>
<td>25</td>
<td>36</td>
<td>50</td>
<td>20</td>
</tr>
</tbody>
</table>

Overall cessation rate was higher in Group 2, compared to group 1, yet not as much as expected. Details on cessation rates of subgroups 2a, 2b, 2c and 2d are represented in Fig.3 and give additional data about cessation outcomes according to type of co-morbidity. The highest percentage of quitters was obtained in smokers with concomitant cardiovascular impairment.

Abstinence rates among healthy smokers in Group 1 at 12 weeks end of treatment registered an expected value (40.5%), in relation to our center’s experience and to scientific evidence. [12] By comparison, we expected lower abstinence rates in Group 2, if considering literatute findings about difficulties in approaching smokers with co-morbidities and as primary such experience in our center.

Yet, we noticed a satisfactory compliance to office visits in 12 weeks treatment follow-up, especially in smokers from Group 2. Study group registered higher attendance rates than control group (Fig.5), especially during 9-12 weeks of therapy, fact which is predictory for high cessation success rates [13].

5.2. Discussions

Overview of recently published data show Varenicline as an efficient and safe therapy for smoking cessation in smokers with stable cardiovascular chronic disorders and COPD as well as low incidence of adverse psychiatric events in smokers treated with Varenicline. [12] Our study took in charge smokers with various respiratory, cardiovascular, digestive and psychiatric diseases, aiming to check in current practice such recent data about efficacy vs. safety benefits of varenicline as single therapy for quitting smoking. In our previous practice (2000-2007), we have treated in majority of cases only „healthy smokers”; both with varenicline and other available therapies such as bupropion and nicotine patch/gum.

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When separate analysis of cessation outcomes in subgroups 2 a-d done, our results overlap actual knowledge for cessation rates in smokers classified as in subgroups 2 b and 2 d. Thus, it is well recognized that cardiovascular smokers are much more compliant to quitting and psychiatric smokers are more heavily addicted to nicotine, find more difficult to quit, experience a severe withdrawal syndrome and relapse more often [14, 15].

Furthermore, medication side effects can be exagerately perceived in smokers with digestive and psychiatric disorders and this reason can be used to abandon cessation therapy [16].

The picture of all adverse effects of varenicline reported in our study population is shown in Fig. 6.

![Compliance to follow-up](image)

**Fig.5. Compliance to follow-up**

Comments on end-points of the study allow remarks such as abstinence rates at both 12 weeks end of treatment visit and 12 months follow-up proved superior in the group of patients diagnosed with cardiovascular co-morbidity. More detailed analysis to explain this finding suggest that high nicotine dependence, heavy tobacco consumption especially in the past 12 months, elderly and old history severe cardiovascular condition had a major impact on motivation to quit smoking in subgroup 2 c. Finally, spectrum of varenicline safety in our study was reproducible with literature data and did not determine treatment discontinuation but in only 12 cases (3 cases in subgroup 2 c, 2 cases in subgroup 2 d and 7 cases in Group 1).

### 6. Conclusions

Varenicline is an effective and highly compliant therapy for smoking cessation in smokers with co-morbidities. Safety profile of varenicline is comparable in healthy smokers and smokers with stable co-morbidities, with focus on cardiovascular disorders.

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